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Triglyceride–glucose index and its derived anthropometric indices: a comparative analysis for mortality prediction in the population cohort of the URRAH study

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ABSTRACT

Background and aims: The triglyceride–glucose (TyG) index is an established surrogate marker of insulin resistance and has been consistently associated with adverse cardiovascular outcomes. Composite indices combining TyG with anthropometric measures, such as body mass index (BMI) and waist circumference (WC), have been proposed to enhance risk prediction. However, their incremental prognostic value remains uncertain. This study aimed to compare the predictive performance of TyG, BMI, and WC with that of their derived multiplicative indices (TyG-BMI and TyG-WC) for all-cause and cardiovascular mortality.

Methods and results: Data were analysed from the multicentre URRAH cohort, including 17,742 participants for the evaluation of TyG-BMI and a sub-analysis of 7052 individuals for TyG-WC. Over a median follow-up of 11.7 years, 2650 all-cause deaths occurred, including 1158 cardiovascular deaths. The TyG index showed a strong and independent association with both outcomes. Although TyG-BMI and TyG-WC were significantly associated with mortality, their risk patterns largely reflected those of their individual components. In multivariable models, inclusion of the derived indices did not meaningfully improve model fit, discrimination, individual risk prediction, or clinical usefulness.

Conclusion: In this large general cohort, the TyG index was confirmed as a robust predictor of all-cause and cardiovascular mortality. In contrast, derived indices combining TyG with BMI or WC did not confer meaningful incremental prognostic value beyond modelling TyG and anthropometric measures separately, supporting the use of TyG as a simple and clinically informative marker for mortality risk stratification.

1. Introduction

Insulin resistance (IR) is a pivotal pathophysiological mechanism linking metabolic abnormalities to cardiovascular disease and mortality [1]. Through its effects on glucose and lipid metabolism, IR promotes endothelial dysfunction, chronic low-grade inflammation, neurohormonal activation, and adverse vascular and cardiac remodelling, thereby accelerating atherosclerotic processes and increasing cardiovascular vulnerability [2,3]. Because IR often precedes overt diabetes and manifests sub-clinically for long periods, its early identification is particularly relevant for cardiovascular risk stratification in population-based and primary prevention settings.

Despite its clinical importance, direct assessment of IR remains unrealistic in routine care and large epidemiological studies. Gold-standard techniques are resource-intensive, and surrogate indices requiring insulin measurement are limited by cost, analytical variability, and availability [4]. Against this background, the triglyceride–glucose (TyG) index has emerged as a simple and accessible marker of IR, derived from fasting triglyceride and glucose concentrations routinely measured in clinical practice [5]. Experimental and observational evidence suggests that TyG reflects both hepatic and peripheral IR and captures key metabolic disturbances relevant to cardiovascular risk [6].

A growing body of epidemiological evidence has linked higher TyG values to adverse outcomes, including all-cause mortality [7–9], cardiovascular mortality [7,8,10], and cardiovascular risk factors [11–18]. These associations have been reported across heterogeneous populations and clinical contexts, often persisting after adjustment for traditional cardiovascular risk factors [19,20]. Collectively, these findings support TyG as a pragmatic indicator of long-term cardio-metabolic risk. However, some variability in the methodological implementation of the TyG index across studies should be acknowledged [6]. Differences in formula presentation and analytical handling may affect comparability and the definition of shared thresholds, particularly when TyG is incorporated into derived indices. In parallel with the expanding use of TyG, composite indices combining TyG with anthropometric measures, most notably body mass index (BMI) and waist circumference (WC), have been proposed. These derived indices, such as TyG-BMI and TyG-WC, aim to integrate metabolic dysfunction with overall or central adiposity. Although pooled analyses showed a significant predictive role of these indices [21,22], the single data on the comparison with TyG are heterogeneous, with reported improvements often modest, outcome-specific, or methodologically limited [23–27]. Moreover, combining a non-standardised marker such as TyG with anthropometric measures may amplify variability, generating indices that are more difficult to interpret and less generalisable. Whether these composite measures capture true biological synergy or largely re-scale information already conveyed by TyG or adiposity remains unclear.

Taken together, these considerations underscore the need for a rigorous evaluation of TyG-derived anthropometric indices, focusing on their incremental prognostic value, interpretability, and clinical usefulness, particularly for hard endpoints such as all-cause and cardiovascular mortality.

Accordingly, the aim of the present study was to compare the prognostic performance of the TyG index and conventional anthropometric measures, namely BMI and WC, with that of their derived multiplicative indices (TyG-BMI and TyG-WC). Specifically, we examined whether these composite measures provide additional prognostic information beyond their individual components, characterised the shape of their associations with mortality outcomes, and quantified their

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incremental value in terms of model fit, discrimination, and clinical usefulness.

2. Methods

2.1. Study population

The URRAH database is a multicentre, retrospective, observational cohort study including participants recruited from all regions of Italy, with an age range of 18–95 years. A detailed description of the URRAH project design and methodology has been published elsewhere [28,29]. The present report was prepared in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [30] (Supplemental Table 1).

From a total of 27,078 participants, 17,742 were included for the evaluation of the TyG-BMI index for the current analysis. Participants were excluded if they had incomplete data, triglyceride levels >400 mg/dL, or fasting glucose levels <60 or >300 mg/dL, to minimise distortion of the TyG index distribution and ensure clinical interpretability. Individuals with a history of cardiovascular events were also excluded. In addition, a sub-analysis evaluating the TyG-WC index was conducted in 7052 participants, after further exclusion of individuals with missing WC measurements, applying the same eligibility criteria described above.

2.2. Data collection

The URRAH study procedures have been extensively described [28,29]. Body weight and height were measured on a standard beam balance scale with an attached ruler. BMI was calculated according to the formula weight (kg)/height^2 (m^2). WC was measured in cm at the level of the umbilicus with the subject standing erect with a flexible and inextensible plastic tape.

The indices were calculated using the following formula:

1. TyG: ln (TG-mg/dL x fasting glucose-mg/dL)/2;
2. TyG-BMI: TyG x BMI;
3. TyG-WC: TyG x WC.

2.3. Outcome

All-cause and cardiovascular mortality were evaluated at the end of the follow-up. Information on patients who had died was obtained from hospital records or death certificates. Mortality from cardiovascular disease was coded according to the International Classification of Diseases, Tenth Revision – ICD10 (i.e., myocardial infarction, heart failure, angina pectoris, transient ischemic attack, stroke, and hypertensive complications) [28].

2.4. Statistical analysis

The statistical analyses were performed using the statistical package R (The R Project for Statistical Computing, version 4.5.2) and STATA Corp. software (version 17). A two-sided P value < 0.05 was considered statistically significant.

Continuous variables were reported as means (and standard deviation - SD) and categorical variables as percentages. The functional form of the association between the TyG index, anthropometric measures (i.e., BMI, WC), and the derived multiplicative indices (TyG-BMI and TyG-WC) with mortality outcomes was first explored using restricted cubic spline (RCS) regression. Spline models were fitted using four knots placed at the 5th, 35th, 65th, and 95th percentiles of each predictor distribution, with the median value used as the reference point for hazard estimation and graphical representation. RCS analyses were used to assess overall associations and the presence of non-linear components and to guide the specification (linear vs non-linear) of predictors in subsequent regression models. Associations with all-cause mortality were examined using Cox proportional hazards regression, after verification of the proportional hazards assumption. Cardiovascular mortality was analysed using the competing risk regression (Fine-Gray sub-distribution hazard model). For each exposure (TyG, BMI, WC, TyG–BMI, and TyG–WC), we fitted univariate Cox models, models adjusted for age and sex, and fully adjusted models including age, sex, hypertension, diabetes, renal function (estimated glomerular filtration rate), smoking status, and total cholesterol. Fully adjusted models were complete-case analyses (9% and 3% sample reduction in the TyG-BMI and TyG-WC datasets, respectively). Multivariable models then included TyG and the corresponding anthropometric measure, parameterised according to the spline-derived functional form identified in the RCS analyses. To evaluate the incremental prognostic value of the derived indices, extended models including TyG-BMI or TyG-WC were compared with base models containing TyG and the respective anthropometric variable only.

For all-cause mortality, model performance was evaluated using likelihood-based χ^2 statistics, Harrell's concordance statistic (C-index) with 95% confidence intervals (CIs), and information criteria (Akaike Information Criterion-AIC and Bayesian Information Criterion-BIC). Discrimination was quantified as Harrell's C-index from Cox proportional hazards models. Ninety-five percent CIs for the C-index and for between-model differences (ΔC) were obtained using nonparametric bootstrap resampling (2000 iterations, percentile method) on a common analysis sample, with ties handled using the Breslow method. For competing-risk analyses, model comparisons relied primarily on information criteria and overall model fit, complemented by concordance of predicted risks and decision-curve analyses. Predicted risks were derived from each model using the linear predictor for Cox models and the cumulative incidence function for competing-risk models. Concordance between predicted risks from base and extended models was quantified using Pearson correlation coefficients to evaluate changes in individual risk estimates. Collinearity among predictors (i.e., TyG, BMI, TyG-BMI; TyG, WC, TyG-WC) was assessed using variance inflation factors (VIF). The clinical usefulness was examined using decision curve analysis (DCA), estimating the net benefit of each predictor across a range of clinically relevant threshold probabilities for 10-year all-cause and cardiovascular mortality.

3. Results

3.1. TyG, BMI, TyG-BMI

This analysis included a total of 17,742 participants, who at baseline had a mean age of 56.1 years and an almost equal sex distribution (49.8% men, 50.2% women) (Supplemental Table 2). The mean BMI was 26.4 kg/m^2, with 42.5% of individuals classified as overweight and 17.6% as obese. Hypertension was present in 69.8% of the cohort, diabetes mellitus in 10.8%, and 24.6% were current smokers. The baseline TyG index showed a mean value of 4.62 Unit (median 4.61).

Over a median follow-up of 11.7 years (140 months; 25th-75th: 74–190 months), 2650 deaths from all causes (14.9%) were observed, of which 1158 (43.7%) were due to cardiovascular causes.

As expected, the uncentred TyG–BMI product was highly collinear with its components (VIF >400), whereas mean-centring mitigated this issue (mean VIF = 1.21).

3.1.1. All-cause mortality

RCS analysis demonstrated a strong association between TyG and all-cause mortality (overall $\chi^2(3) = 271.1$; $P < 0.0001$), with clear evidence of non-linearity ($\chi^2 = 32.3$; $P < 0.0001$) (Fig. 1). BMI was also

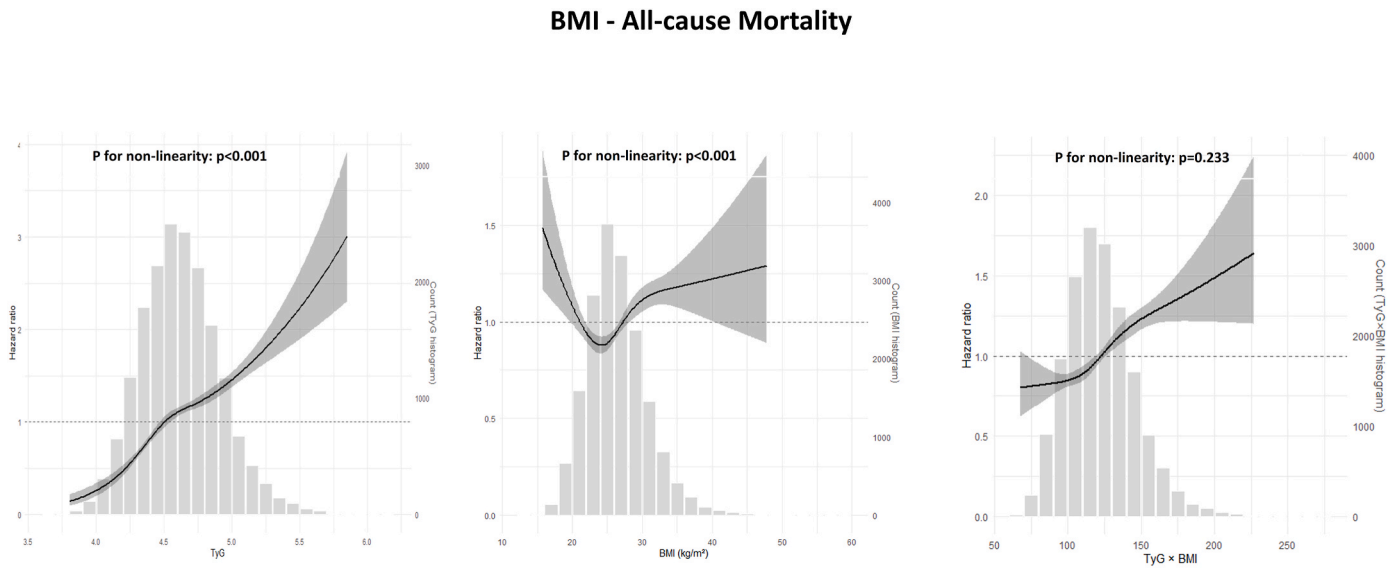

Fig. 1. TyG, BMI-related indices and all-cause mortality
Restricted cubic spline curves showing the association of the triglyceride–glucose (TyG) index, body mass index (BMI), and the TyG-BMI product with all-cause mortality. Hazard ratios and 95% confidence intervals were estimated using Cox proportional hazards models, with the median value of each exposure as reference. Histograms show the distribution of the predictors.

significantly associated with all-cause mortality (overall $\chi^2(3) = 29.9$; $P < 0.0001$), showing a non-linear relationship ($\chi^2 = 22.0$; $P < 0.0001$) characterised by a shallow U-shaped pattern, with higher risk at lower BMI values, a nadir in the normal-to-overweight range, and a modest increase at higher BMI levels (Fig. 1).

The TyG-BMI product was significantly associated with all-cause mortality (overall $\chi^2(3) = 65.6$; $P < 0.0001$); however, no evidence of non-linearity was observed ($\chi^2 = 2.9$; $P = 0.233$), indicating an essentially linear association. The spline curve closely mirrored the monotonic increase observed for TyG, suggesting that the combined index largely reflects the dominant contribution of TyG rather than generating a distinct risk pattern (Fig. 1).

In univariate Cox regression models, TyG emerged as the strongest predictor of all-cause mortality, with a highly significant global effect (overall χ^2 (3) = 271.1; $P < 0.0001$), compared with a markedly weaker association for BMI (overall χ^2 (3) = 29.8; $P < 0.0001$). The TyG–BMI product showed a significant global association when modelled with RCS (overall $\chi^2(3) = 65.6$; $P < 0.0001$), but remained inferior to TyG alone. Discrimination and information-criterion comparisons were concordant with these results and consistently favoured TyG over BMI and TyG–BMI (Tables 1 and 2). In fully adjusted Cox models including age, sex, estimated glomerular filtration rate, total cholesterol, smoking, diabetes, and hypertension, with RCS terms for TyG and BMI, the overall model association was strong (global Wald $\chi^2 = 2058$; df = 13; $P < 0.0001$). Adding the TyG–BMI product yielded only a modest improvement in likelihood-based fit (likelihood-ratio test χ^2 (1) = 4.80; $P = 0.0285$), without meaningful improvement in discrimination and with no consistent support from information criteria (Tables 1 and 2).

Predicted risks were almost perfectly correlated between the base and extended models ($r = 0.9988$).

DCA confirmed these findings, TyG consistently provided the greatest net benefit across clinically relevant threshold probabilities, whereas BMI showed limited utility. The TyG-BMI product did not improve decision-making, with a net benefit curve virtually overlapping that of TyG alone, confirming the absence of incremental clinical value (Supplemental Fig. 1).

3.1.2. *Cardiovascular mortality*

In competing risk models, TyG showed a strong association with cardiovascular mortality (overall $\chi^2(3) = 172.2$; $P < 0.0001$), with a significant non-linear component ($\chi^2 = 17.8$; $P = 0.00014$). The spline curve indicated a distinctly non-linear risk pattern, characterised by a progressively steeper increase in hazard at higher TyG values (Fig. 2).

BMI was also significantly associated with cardiovascular mortality (overall $\chi^2(3) = 16.7$; $P = 0.0008$), displaying a non-linear relationship ($\chi^2 = 10.6$; $P = 0.005$). The analysis showed that cardiovascular risk increased predominantly at higher BMI levels, consistent with a curvilinear or plateau-shaped pattern rather than a uniform risk gradient across the BMI distribution (Fig. 2).

The TyG-BMI product was significantly associated with cardiovascular mortality (overall $\chi^2(3) = 45.9$; $P < 0.0001$); however, spline modelling provided no evidence of non-linearity ($P = 0.27$), indicating an essentially linear association. The risk profile closely followed that of TyG and did not introduce additional curvature beyond that captured by TyG and BMI modelled separately, suggesting limited incremental information conveyed by the derived index (Fig. 2).

In univariate competing-risk analyses, TyG was the most informative predictor of cardiovascular mortality, showing a strong and highly significant global effect (overall $\chi^2(3) = 172.2$; $P < 0.0001$), whereas BMI displayed a markedly weaker association (overall χ^2 (3) = 16.7; $P = 0.0008$). The TyG–BMI product showed intermediate performance (overall $\chi^2(3) = 45.9$; $P < 0.0001$), but remained inferior to TyG alone. Information-criterion comparisons (AIC/BIC) consistently supported these patterns and are reported in Table 2.

In multivariable competing-risk models including non-linear terms for TyG and BMI and the main covariates, the overall model association was strong (global Wald χ^2: 1274.3 in the base model vs 1277.4 in the extended model). Adding TyG–BMI did not improve model fit, and information criteria did not support the more complex specification (Table 2).

Predicted cardiovascular risk scores were virtually identical between the base and extended models ($r = 0.9978$), supporting the absence of meaningful incremental prognostic value.

Table 1
C-index for TyG, BMI, and their derived indices (TyG–BMI and TyG–WC) in predicting mortality risk.

TyG, BMI, TyG-BMI		
	C-index	95% CI
Univariate Model		
TyG (non-linear)	0.5909	0.5798 to 0.6018
BMI (non-linear)	0.5127	0.5023 to 0.5247
TyG-BMI (linear)	0.5401	0.5282 to 0.5515
ΔC: TyG vs BMI	0.0782	0.0639 to 0.0910
ΔC: TyG vs TyG-BMI	0.0508	0.0402 to 0.0613
ΔC: BMI vs TyG-BMI	−0.0274	−0.0312 to −0.0195
Multivariate Model		
Model 1: Age, Sex, TyG, BMI, GFR, total Cholesterol, smoke, diabetes, hypertension	0.8219	0.8145 to 0.8297
Model 2: Model 1 + TyG-BMI	0.8222	0.8147 to 0.8299
ΔC: Model 2 vs Model 1	0.0003	−0.0001 to 0.0009
TyG, WC, TyG-WC		
	C-index	95% CI
Univariate Model		
TyG (linear)	0.5919	0.5680 to 0.6154
WC (linear)	0.5943	0.5710 to 0.6191
TyG-WC (non-linear)	0.6050	0.5839 to 0.6302
ΔC: TyG vs WC	−0.0024	−0.0317 to 0.0253
ΔC: TyG vs TyG-WC	−0.0131	−0.0366 to 0.0062
ΔC: WC vs TyG-WC	−0.0107	−0.0222 to −0.0021
Multivariate Model		
Model 1: Age, Sex, TyG, WC, GFR, total cholesterol, smoking, diabetes, hypertension	0.8046	0.7904 to 0.8210
Model 2: Model 1 + TyG-WC	0.8049	0.7911 to 0.8214
ΔC: Model 2 vs Model 1	0.0003	−0.0003 to 0.0029

BMI: body mass index; CI: confidence interval; TyG: triglyceride-glucose; WC: waist circumference.

DCA for 10-year cardiovascular mortality further supported these results: TyG consistently yielded the highest net benefit across clinically relevant threshold probabilities, whereas BMI contributed minimally. The TyG-BMI product did not enhance decision utility, with a net benefit curve closely overlapping that of TyG throughout the examined range. Collectively, these findings indicate that TyG provides superior clinical usefulness for cardiovascular risk prediction, while the derived index offers no incremental value (Supplemental Fig. 1).

3.2. TyG, WC, TyG-WC

This analysis included a total of 7052 participants, who at study entry had a mean age of 54.5 years and a modest predominance of men (53.8%) (Supplemental Table 2). Adiposity measures indicated a mean BMI of 26.5 kg/m^2, with 41.1% of individuals classified as overweight and 19.1% as obese, and a mean WC of 90.6 cm. Cardio-metabolic risk factors were common, with hypertension present in 51.4% of participants, diabetes mellitus in 11.7%, and current smoking in 23.9%. The baseline TyG index averaged 4.58 Unit (median: 4.57).

During a median follow-up of 12.0 years (144 months; 25th-75th: 81–163 months), 553 deaths from all causes (7.8%) occurred, including 184 cardiovascular deaths (33.3%).

As expected, the product term showed structural multicollinearity when modelling with TyG and WC simultaneously (VIF> 350), which was largely mitigated by mean-centring of the component terms (mean VIF = 1.37).

3.2.1. *All-cause mortality*

In this sub-dataset, TyG was significantly associated with all-cause mortality (overall $\chi^2(3) = 54.2$; $P < 0.0001$), with no evidence of non-linearity ($\chi^2 = 2.46$; $P = 0.293$), indicating an essentially linear and monotonically increasing relationship with mortality risk (Fig. 3). WC was likewise significantly associated with all-cause mortality (overall $\chi^2(3) = 57.4$; $P < 0.0001$), and the absence of a significant non-linear component ($\chi^2 = 5.74$; $P = 0.0566$) supported a predominantly linear risk gradient across the WC distribution (Fig. 3).

The TyG-WC product showed a strong overall association with all-cause mortality (overall $\chi^2(3) = 72.4$; $P < 0.0001$) and, in contrast to TyG and WC considered individually, exhibited a significant non-linear component ($\chi^2 = 10.8$; $P = 0.0045$). The resulting spline curve suggested a curved risk profile largely driven by the progressively increasing pattern of WC rather than by a distinct synergistic interaction between the two components (Fig. 3).

In univariate Cox regression analyses, TyG and WC were both significantly associated with all-cause mortality (overall $\chi^2(3) = 54.2$ and 57.4, respectively; both $P < 0.0001$), while the TyG–WC product showed the strongest global association (overall χ^2 (3) = 72.4; $P < 0.0001$). Discrimination and information-criterion comparisons are reported in Tables 1 and 2 and were consistent with these findings. However, inspection of the spline profile suggested that the apparent advantage of the product term primarily reflected the dominant contribution of WC rather than a distinct synergistic effect. In fully adjusted Cox models including age, sex, estimated glomerular filtration rate, total cholesterol, smoking, diabetes, and hypertension, with TyG and WC modelled as linear terms, adding the TyG–WC product (modelled with RCS) did not improve model fit (likelihood-ratio test $\chi^2(3) = 4.38$; $P = 0.2234$). Discrimination and information-criterion results similarly did not support the more complex specification and are detailed in Tables 1 and 2

In an exploratory analysis, WC was positively associated with TyG ($\beta = 0.00599$, $P < 0.001$). However, adjustment for TyG did not attenuate the association between WC and all-cause mortality, as the WC coefficient moved slightly further from the null (from −0.00547 to −0.00654).

Predicted risk scores remained highly concordant between the base and extended models ($r = 0.9976$), indicating only minimal changes in individual risk estimates. DCA for 10-year all-cause mortality further supported these findings: the TyG-WC product did not improve decision utility, as its net benefit curve overlapped those of TyG and WC and never exceeded them across the examined range. Overall, these results indicate that the combined index offers no incremental clinical value beyond TyG and WC when used separately (Supplemental Fig. 2).

3.2.2. *Cardiovascular mortality*

In competing risk models, TyG was significantly associated with cardiovascular mortality (overall $\chi^2(3) = 21.4$; $P < 0.0001$), with no evidence of non-linearity ($\chi^2 = 0.06$; $P = 0.97$), indicating a fully linear relationship across the TyG distribution (Fig. 4). WC was likewise significantly associated with cardiovascular mortality (overall $\chi^2(3) = 23.9$; $P < 0.0001$), and the absence of a significant non-linear component ($\chi^2 = 2.15$; $P = 0.34$) supported an essentially linear risk gradient across WC values (Fig. 4). The TyG-WC product was also significantly associated with cardiovascular mortality (overall $\chi^2(3) = 27.7$; $P < 0.0001$); however, spline modelling did not demonstrate a statistically

Table 2
Akaike information criterion (AIC) and Bayesian information criterion (BIC) for TyG, BMI, and their derived indices (TyG–BMI and TyG–WC) in predicting mortality risk.

TyG, BMI, TyG-BMI							
All-cause mortality							
Univariate Model							
	AIC	**ΔAIC (vs best)**			**BIC**	**ΔBIC (vs best)**	
TyG	49026	best			49049	best	
BMI	49305	+279			49328	+279	
TyG-BMI	49269	+243			49277	+228	
Multivariate models							
	AIC (Base)		**AIC (Extended)**	**ΔAIC (Extended vs Base)**	**BIC (Base)**	**BIC (Extended)**	**ΔBIC (Extended vs Base)**
Base (TyG + BMI + covariates)	40198	**Extended** (Base + TyG-BMI)	40194	−4	40297	40302	+5
Cardiovascular mortality							
Univariate Model							
	AIC	**ΔAIC (vs best)**			**BIC**	**ΔBIC (vs best)**	
TyG	21626	best			21650	best	
BMI	21806	+180			21830	+180	
TyG-BMI	21779	+153			21787	+137	
Multivariate models							
	AIC (Base)		**AIC (Extended)**	**ΔAIC (Extended vs Base)**	**BIC (Base)**	**BIC (Extended)**	**ΔBIC (Extended vs Base)**
Base (TyG + BMI + covariates)	18226	**Extended** (Base + TyG-BMI)	18228	+2	18325	18335	+10
TyG, WC, TyG-WC							
All-cause mortality							
		AIC	**ΔAIC (vs best)**		**BIC**	**ΔBIC (vs best)**	
Univariate Model							
TyG		9345	+25		9352	+12	
WC		9342	+22		9349	+10	
TyG-WC		9320	best		9340	best	
Multivariate models							
	AIC (Base)		**AIC (Extended)**	**ΔAIC (Extended vs Base)**	**BIC (Base)**	**BIC (Extended)**	**ΔBIC (Extended vs Base)**
Base (TyG + WC + covariates)	8402	**Extended** (Base + TyG-WC)	8404	+2	8464	8486	+22
Cardiovascular mortality							
		AIC	**ΔAIC (vs best)**		**BIC**	**ΔBIC (vs best)**	
Univariate Model							
TyG		3120	+12		3127	+12	
WC		3113	+5		3120	+7	
TyG-WC		3108	best		3115	best	
Multivariate models							
	AIC (Base)		**AIC (Extended)**	**ΔAIC (Extended vs Base)**	**BIC (Base)**	**BIC (Extended)**	**ΔBIC (Extended vs Base)**
Base (TyG + WC + covariates)	2754	**Extended** (Base + TyG-WC)	2755	+1	2815	2823	+8

BMI: body mass index; CI: confidence interval; TyG: triglyceride-glucose; WC: waist circumference.
Covariates: age, sex, estimated glomerular filtration rate, total cholesterol, smoking, diabetes, hypertension.

significant non-linear component ($\chi^2 = 5.16$; $P = 0.076$), indicating a predominantly linear association. The shape of the risk curve closely resembled that of its individual components, particularly WC, and did not introduce meaningful deviations beyond those captured by TyG and WC modelled separately (Fig. 4).

In univariate competing-risk analyses, TyG and WC were significantly associated with cardiovascular mortality when modelled with RCS (overall $\chi^2(3) = 21.4$ and 23.9, respectively; both $P < 0.0001$). The TyG–WC product also showed a significant global association when modelled with RCS (overall $\chi^2(3) = 27.7$; $P < 0.0001$). Information-criterion comparisons are reported in Table 2 and showed only a modest advantage for the derived product. However, this pattern was consistent with the dominant risk contribution of WC rather than a genuine gain in prognostic information.

In fully adjusted competing-risk models including the main covariates, with TyG and WC modelled as linear terms, adding the TyG–WC product did not improve model fit. The global association statistic decreased slightly (global Wald χ^2: 290.54 in the base model vs 284.67 in the extended model), and information criteria did not support the more complex specification (Table 2).

Similarly, in competing-risk analysis for cardiovascular mortality, adjustment for TyG did not attenuate the association with WC, as the WC

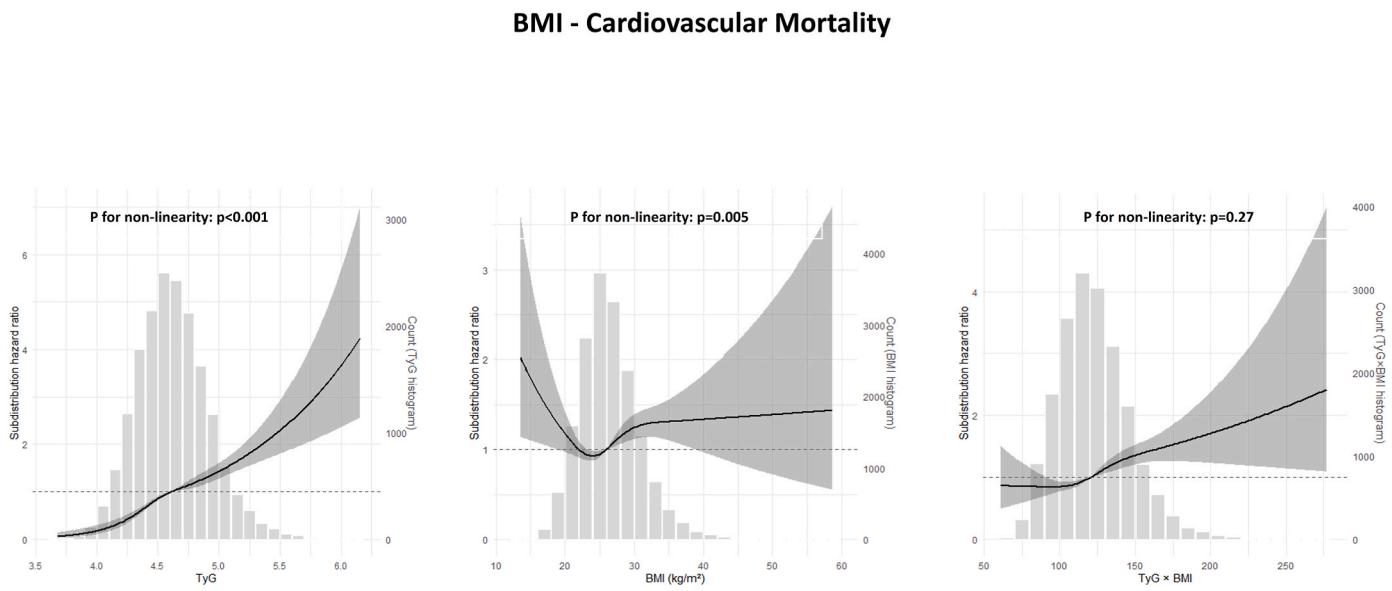

Fig. 2. TyG, BMI-related indices and cardiovascular mortality
Restricted cubic spline curves showing the association of the triglyceride–glucose (TyG) index, body mass index (BMI), and the TyG-BMI product with cardiovascular mortality. Subdistribution hazard ratios and 95% confidence intervals were obtained from competing risk regression, using the median value of each exposure as reference. Histograms show the distribution of the predictors.

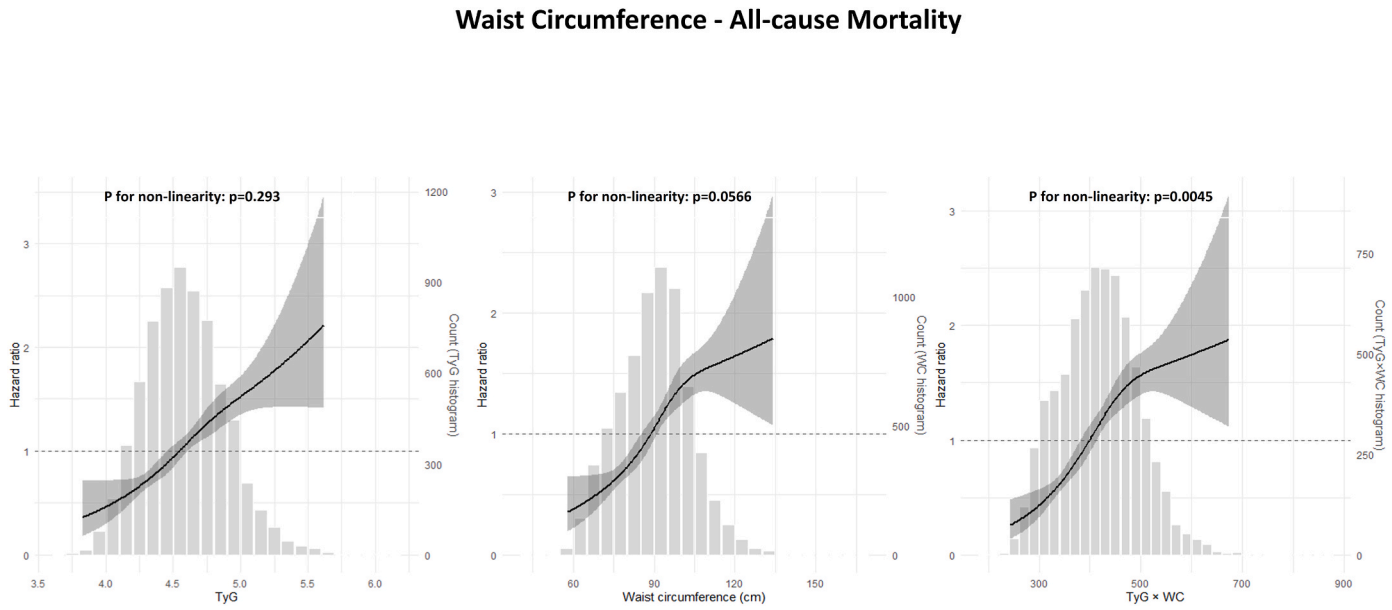

Fig. 3. TyG, waist circumference–related indices and all-cause mortality
Restricted cubic spline curves depicting the association of the triglyceride–glucose (TyG) index, waist circumference (WC), and the TyG-WC product with all-cause mortality. Hazard ratios and 95% confidence intervals were estimated using Cox proportional hazards models, with the median exposure as reference. Histograms show the distribution of the predictors.

coefficient moved slightly further from the null (from −0.00099 to −0.00129).

Predicted cardiovascular risk scores were strongly concordant between the base and extended models (r = 0.9987), indicating that the product induced only minimal changes in individual risk estimates. DCA for 10-year cardiovascular mortality further corroborated these findings: the TyG-WC product did not improve decision utility, as its net benefit curve closely overlapped those of TyG and WC and never exceeded them across the examined range. Overall, these results indicate that the combined metric offers no incremental value over TyG or WC for competing risk–adjusted cardiovascular mortality prediction (Supplemental Fig. 2).

4. Discussion

In this large multicentre observational cohort, our findings strengthen evidence from the URRAH population by supporting the TyG index as a strong and consistent predictor of both all-cause and cardiovascular mortality. TyG showed graded associations across the primary and secondary analyses, with clear dose–response relationships and, for

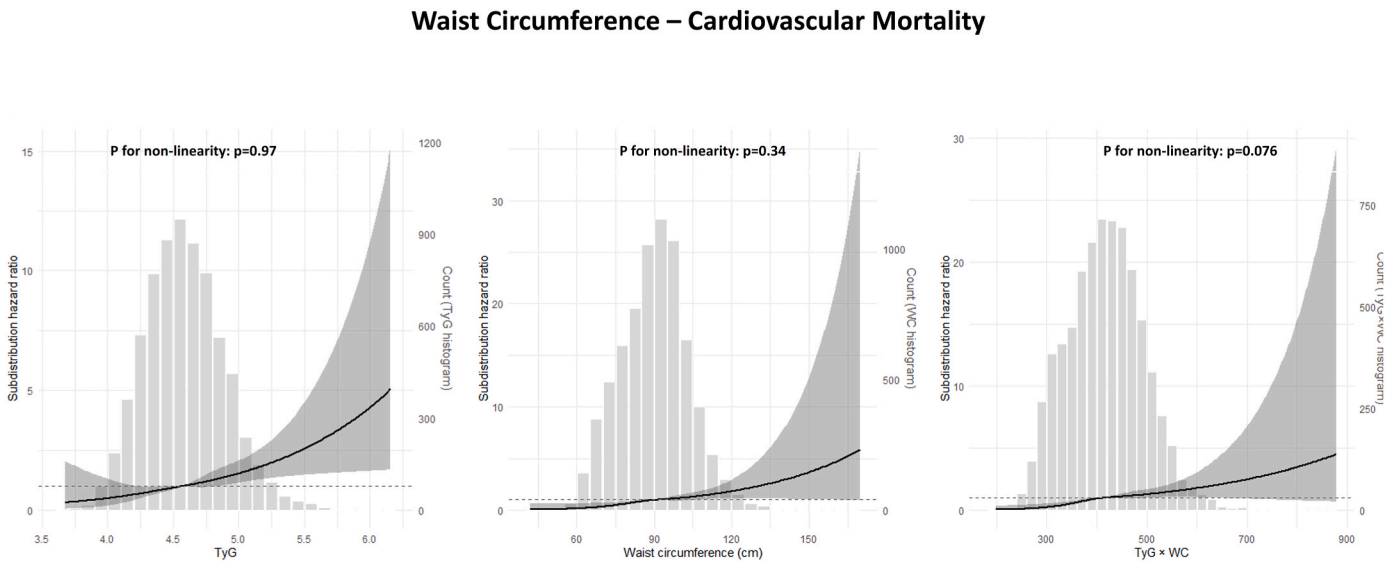

Fig. 4. TyG, Waist circumference–related indices and cardiovascular mortality
Restricted cubic spline curves showing the association of the triglyceride–glucose (TyG) index, waist circumference (WC), and the TyG-WC product with cardiovascular mortality. Subdistribution hazard ratios and 95% confidence intervals were estimated using competing risk regression, with the median exposure as reference. Histograms show the distribution of the predictors.

cardiovascular mortality, a marked non-linear increase in risk at higher values. In contrast, BMI displayed weaker and more heterogeneous associations, often with non-linear or threshold-type patterns that varied by outcome. In the WC sub-analysis, WC showed univariate discrimination comparable to TyG, but contributed limited incremental information once TyG was included in multivariable models.

Although indices combining TyG with BMI or WC were statistically associated with mortality, their risk profiles closely mirrored those of their dominant components. TyG-BMI largely tracked the monotonic gradient of TyG, whereas TyG-WC predominantly followed the WC pattern, indicating that these multiplicative indices did not capture meaningful additional prognostic information beyond modelling the components separately. Consistently, TyG–WC ranked best by information criteria in univariate models, but this apparent advantage was not retained in multivariable comparisons and was accompanied by negligible changes in discrimination and predicted risks, supporting a WC-driven pattern rather than incremental prognostic content. This interpretation is consistent with the model-comparison results: for all-cause mortality, adding TyG–BMI improved model fit statistically, but the magnitude of improvement was small and was not accompanied by better discrimination or more favourable information criteria; predicted risks were virtually unchanged between base and extended models.

The prognostic performance of TyG is biologically plausible, given its ability to reflect IR–related metabolic perturbations linked to cardiovascular risk [6]. By comparison, BMI and WC provide more distal proxies of metabolic risk and contributed limited independent information once TyG was included, particularly when non-linear terms were used to capture their risk shapes.

Recent evidence also supports the clinical relevance of the TyG index in patients with chronic kidney disease, in whom higher TyG values have been associated with a more adverse metabolic profile and poorer cardiovascular prognosis [31,32]. These findings are broadly consistent with our results. In our cohort, however, adjustment for renal function did not materially change the observed associations. Nevertheless, comparisons with chronic kidney disease-specific populations should be interpreted cautiously, since renal dysfunction may substantially affect metabolic and cardiovascular risk pathways. As expected, the uncentred product terms exhibited marked structural multicollinearity with their component variables (high VIFs), whereas mean-centring TyG and BMI/WC reduced residual multicollinearity to negligible levels (mean VIF: 1.2–1.4), indicating that the lack of incremental prognostic value is unlikely to be an artefact of residual collinearity but rather reflects substantial informational overlap. Because strong structural multicollinearity and non-linear specifications render the product-term coefficient difficult to interpret and potentially unstable, any incremental value was therefore appraised primarily through overall model performance (discrimination, information criteria, and concordance of predicted risks). Taken together, these results suggest that TyG captures most of the IR–related risk gradient, while anthropometric measures add only modest information, and that joint effects are predominantly additive rather than multiplicative in terms of risk prediction.

Consistently, exploratory analyses assessing whether adjustment for TyG attenuated the association between WC and the study outcomes showed no evidence of attenuation for either all-cause or cardiovascular mortality, which does not support a substantial mediating role of TyG in this dataset.

The limited incremental prognostic value of TyG-derived anthropometric products may reflect both a true lack of biological synergy and methodological features of these indices. Because multiplicative terms mainly re-scale their components, they tend to track the dominant risk gradient rather than add distinct prognostic information. Moreover, using single baseline measurements may further dilute any additional signal, given within-person changes in metabolic status and adiposity over follow-up.

Evidence from meta-analyses indicates that TyG-derived indices are associated with incident cardiovascular outcomes. A recent meta-analysis of cohort studies reported a significant and largely linear association between higher TyG-BMI levels and the incidence of cardiovascular disease in populations free of cardiovascular disease at baseline [21]. However, this evidence was based mainly on analyses of incident events and categorical comparisons and did not assess whether TyG-BMI provides incremental prognostic information beyond the TyG index for mortality outcomes, limiting direct comparability with the present findings. Similarly, another meta-analysis of prospective cohorts showed that higher TyG-BMI and TyG-WC levels were associated with an increased risk of incident stroke [22], although substantial between-study heterogeneity was observed and neither non-linear risk patterns nor incremental prognostic value over TyG were formally evaluated. Findings from large population-based cohorts further highlight variability across settings. Analyses conducted in NHANES

populations showed that TyG-BMI and TyG-WC were associated with cardiovascular mortality but did not consistently demonstrate higher predictive performance compared with the TyG index alone [23]. Differences in outcome definition, population characteristics, and the limited range of comparative performance metrics used in those analyses should be considered when relating these findings to the present study, which applied a broader modelling framework. In another NHANES-based cohort with extended follow-up, both TyG and TyG-BMI were independently associated with all-cause and cardiovascular mortality, with TyG showing the highest discriminative ability for all-cause mortality [24]. However, the absence of an analysis including TyG-WC and the predominant reliance on ROC-based measures constrain direct comparison with our results. Additional heterogeneity is observed in the UK Biobank data. In that cohort, TyG-BMI did not show a consistent association with mortality after multivariable adjustment, whereas TyG-WC exhibited a more apparent relationship with risk [25]. Moreover, differences in the functional form of the associations were observed, with TyG-BMI showing relatively flat or irregular risk patterns, in contrast to the monotonic associations identified in our spline analyses. These differences in the shape of association, together with the focus on association and discrimination metrics rather than formal assessments of incremental prognostic value, further limit direct comparability across studies. Other investigations have addressed different clinical contexts. Studies conducted in Chinese populations focused primarily on incident ischemic stroke or incident cardiovascular disease and mainly evaluated TyG-BMI, without directly comparing its predictive performance with that of the TyG index alone [26,27]. Variations in outcome definition, population characteristics, and analytical approaches may therefore partly explain the heterogeneity observed across studies and underscore the need for cautious interpretation when comparing results.

4.1. Strengths and limitations

The strengths of this study include the large sample size, the long duration of follow-up, and the availability of both all-cause and cardiovascular mortality outcomes. In addition, the use of advanced statistical approaches allowed a detailed assessment of non-linear associations, incremental prognostic value, and model performance across multiple complementary metrics, thereby providing a comprehensive evaluation of the predictive role of TyG and its derived indices.

Several limitations should also be acknowledged. The analyses relied on single baseline measurements, which do not account for longitudinal changes in metabolic status over time. Moreover, insulin concentrations were not available, preventing direct comparisons with insulin-based indices of IR. In the cardiovascular mortality sub-analysis (i.e., TyG, WC, and TyG-WC), the relatively limited number of events may have reduced the stability of spline-based estimates at the extremes of the exposure distributions, and these results should therefore be interpreted with caution. Finally, the study population consisted predominantly of Caucasian individuals, which may limit the generalisability of the findings to other ethnic groups. In particular, variations in visceral adiposity at similar BMI or WC levels across populations may partly affect the relative prognostic performance of TyG-derived indices.

5. Conclusions

The present findings indicate that multiplicative indices derived from the TyG index do not meaningfully improve mortality risk prediction compared with modelling TyG and anthropometric measures separately. Increasing index complexity, therefore, does not appear to translate into clearer prognostic insights and may reduce interpretability without providing tangible advantages in risk stratification.

From a practical perspective, the TyG index represents a simple and practical marker for large-scale epidemiological risk assessment, as it relies on routinely available laboratory parameters and does not require insulin measurement. At the same time, established anthropometric indices such as BMI and WC retain independent clinical and epidemiological relevance and should not be disregarded, as they capture complementary aspects of cardio-metabolic risk. This is consistent with the WC sub-analysis, where WC performed comparably in univariate models, yet multiplicative TyG–WC combinations did not yield incremental gains once TyG and WC were modelled jointly. In contrast, the routine use of TyG-derived anthropometric indices should be approached with caution, particularly in large-scale settings where standardisation and interpretability are essential and where any increase in complexity should be justified by clear and consistent gains across discrimination, information criteria, and decision utility.

Future research should prioritise the standardisation of TyG definitions, assess the prognostic relevance of longitudinal changes in TyG, and evaluate its performance across diverse populations and clinical contexts. Importantly, before TyG-derived anthropometric indices are adopted in epidemiological or clinical frameworks, their ability to provide superior and consistent prognostic information compared with TyG alone, and beyond that offered by conventional anthropometric measures, should be clearly demonstrated. Such efforts may help consolidate the role of TyG as a practical tool for large-scale cardiovascular risk stratification while avoiding unnecessary complexity.

Authors' contributions

Conceptualization: Lanfranco D'Elia, Agostino Virdis, Claudio Borghi, and Ferruccio Galletti; Data curation: Edoardo Casiglia and Valerie Tikhonoff; Formal analysis: Lanfranco D'Elia and Ferruccio Galletti; Funding acquisition: Agostino Virdis, Claudio Borghi, Valerie Tikhonoff, Edoardo Casiglia; Investigation: all authors; Methodology: Lanfranco D'Elia and Ferruccio Galletti; Project administration: Agostino Virdis, Claudio Borghi, Valerie Tikhonoff, Edoardo Casiglia; Resources: Agostino Virdis, Claudio Borghi, Edoardo Casiglia, Valerie Tikhonoff; Software: Lanfranco D'Elia, Valerie Tikhonoff, Edoardo Casiglia; Supervision: Ferruccio Galletti; Validation: Ferruccio Galletti; Visualization: Claudio Borghi, Edoardo Casiglia, Valerie Tikhonoff, Lanfranco D'Elia; Writing – original draft, Lanfranco D'Elia and Ferruccio Galletti; Writing – review & editing: all authors.

Ethics approval and consent to participate

The URRAH study was performed according to the Declaration of Helsinki for Human Research (41st World Medical Assembly, 1990). Approval was sought from the Ethics Committee of the 7 coordinating center at the Division of Internal Medicine of the University of Bologna (no. 77/2018/Oss/AOUBo). Informed consent was obtained from all subjects included in the study.

Data availability statement

Some or all datasets generated during and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Use of AI and AI-assisted technologies statement

During the preparation of this work, the authors did not use any automated authoring tools or services.

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Conflict of interest

Borghi C. has received research grant support from Menarini Corporate and Novartis Pharma; has served as a consultant for Novartis Pharma, Alfasigma, Grunenthal, Menarini Corporate, and Laboratoires Servier; and received lecturing fees from Laboratoires Servier, Takeda, Astellas, Teijin, Novartis Pharma, Berlin Chemie, and Sanofi. Volpe M. has received honoraria for speakers' bureau or advisory boards from Menarini Int., Astra Zeneca, Sanofi, Servier and Polpharma and is supported by a grant of Italian Ministry of Health ("Ricerca Corrente"). The remaining authors have no disclosures to report.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2026.104726.

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