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Relationships of triglyceride-glucose-related indices with colorectal cancer incidence and mortality in an American population: a dose-response meta-analysis and cohort study

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Abstract

Background The degree to which the triglyceride-glucose (TyG) index might interact with colorectal cancer (CRC) incidence and mortality is undefined. This systematic analysis was conducted through meta-analyses and large-scale databases.

Methods A meta-analysis was conducted through database search up to April 1, 2025, and articles investigating the incidence of CRC with clearly reported TyG index values, focusing on their dose-response relationship, were included. To validate the findings, data from the 1999–2018 National Health and Nutrition Examination Survey (NHANES) were utilized to explore links of TyG levels with CRC-linked mortality. Analyses involving restricted cubic splines (RCSs), weighted logistic regression (WLR), and multivariate Cox proportional hazards models were performed. Receiver operating characteristic (ROC) analyses explored predictive potential. Subgroup evaluation was subsequently conducted for detecting the susceptible populations.

Results Multivariate logistic regression showcased a greater CRC incidence among individuals in quartiles two, three, and four of TyG and TyG-body mass index (TyG-BMI) (95% confidence intervals (CIs): 1.14–1.5, 1.07–1.45; 1.39–1.83, 1.11–1.64; and 1.60–2.12, 1.19–1.93, respectively; $P < 0.001$). In contrast, multivariate Cox regression indicated a significant increase in CRC-related mortality only in the second quartile of TyG (95% CI: 1.22–7.47; $P < 0.05$). Analysis of the RCS curves demonstrated that the incidence of CRC displayed a nonlinear association with TyG ($P = 0.045$ for nonlinearity) but a positive linear association with TyG-BMI ($P = 0.385$ for nonlinearity). The TyG and associated indices did not exhibit any obvious dose-response association with CRC-related mortality ($P > 0.05$). ROC analyses exploring CRC risk revealed that TyG-BMI outperformed all indicators (area under the curve (AUC) = 0.71). Subgroup analysis revealed statistically significant links of CRC incidence with both TyG-BMI and female sex.

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Conclusion TyG and TyG-BMI may function as dependable markers for predicting CRC likelihood, and TyG-BMI outperformed all other predictors considered herein. However, TyG and associated indices showed no significant interrelationships with the mortality of CRC.

Keywords Colorectal neoplasms, Insulin resistance, Incidence, Mortality, Triglyceride-glucose index, Meta-analysis, National health and nutrition examination survey

Introduction

Colorectal cancer (CRC), a malignancy that develops in the colon or rectum, was the third most frequent cancer in 2022, comprising 9.6% of all new cases globally (approximately 1.93 million). Worldwide, CRC was a chief source of cancer-related mortality, representing 9.3% of deaths (around 904,000), second only to lung cancer (18.7%). The global incidence of CRC and associated fatalities are expected to rise markedly by 2050, posing a significant global economic burden [1]. It is therefore urgently essential to identify the risk factors and modifiable determinants of CRC for lowering disease incidence. CRC exhibits an intricate pathogenicity and is strongly associated with numerous factors, including genetics, lifestyle, metabolic status, and others. However, approximately 60–65% of the cases of CRC are sporadic and not associated with genetic factors [2].

Hyperinsulinemia is a characteristic feature of insulin resistance (IR), which contributes to the pathophysiological mechanisms underlying metabolic disorders [3]. Nevertheless, the benchmark for diagnosing IR is intricate and costly, thereby restricting its implementation in clinics [4]. As a straightforward and affordable metabolic parameter relevant to IR, the triglyceride-glucose (TyG) index is determined through fasting blood glucose (FBG) and fasting triglyceride (FTG) levels [5, 6]. Recent research has highlighted obesity as a driver behind numerous cancers [7–9]. Dimensions like waist-to-height ratio (WHtR), waist circumference (WC), and body mass index (BMI) are commonly utilized to assess central obesity. When combined with the TyG index, these anthropometric indicators may offer a novel composite marker for assessing IR [10]. Current reports demonstrate an interrelationship between TyG and the incidence and prognostic characteristics of various malignancies, including malignancies of the female reproductive system, lungs, pancreatic ducts, and stomach, among others [11–14]. Some reports have indicated favorable linkages between the TyG index and CRC risk [15–19]. However, potential relationships of CRC risk with composite TyG-related indices have not been fully investigated. A previous study [20] demonstrated that TyG-waist-to-height ratio (TyG-BMI) provides superior prediction accuracy—compared with the TyG index—in estimating liver fibrosis presence and associated factors, suggesting that it also differs in predictive power for CRC risk. Moreover, the relationships of CRC-related mortality risk with TyG-related indices have not been investigated.

Previous studies offer controversial views on the nonlinearity [16] and linearity [19] of the interrelationships of TyG with the likelihood of CRC. Additionally, few reports [16–18] have investigated the dose-effect interrelationships of TyG with the likelihood of CRC. A prior study [21] highlighted the potential of a hybrid measure comprising C-reactive protein levels and the TyG index as a possible indicator for CRC outcomes. Nonetheless, the prognostic utility of the TyG index alone warrants further validation. Accordingly, a retrospective meta-analysis of previous studies was conducted herein. The investigation was extended by analyzing associations of TyG-related indices and various clinical parameters with CRC incidence and mortality, using the extensive U.S. National Health and Nutrition Examination Survey (NHANES) dataset for the years 1999 to 2018.

Materials and methods

Analytical protocol and information acquisition

NHANES was launched in the 1960s as a comprehensive survey intended to explore the well-being and dietary profiles of U.S. children and adults, and the data are primarily gathered through questionnaires and health assessments. Since 1999, the NHANES has been conducted every 2 years, enrolling approximately 5000 participants annually for data collection. The ethical conduct of NHANES was reviewed and approved by the Institutional Review Board within the National Center for Health Statistics (NCHS). Additionally, documented agreements are acquired from the enrolled individuals prior to inclusion. The NHANES dataset contains various data types, including data pertaining to demographics, dietary information, test results, laboratory data, questionnaires, and limited access data. Managed by the NCHS, the NHANES dataset provides comprehensive information regarding Americans' dietary habits, chronic disease history, lifestyle factors, environmental exposures, and other metrics. The 1999–2018 NHANES dataset contains data from 118,687 enrolled individuals. Individuals under 20 years of age or lacking TyG index data, CRC-related information, or pregnancy status were excluded, leaving 25,163 subjects for further studies (Fig. 1).

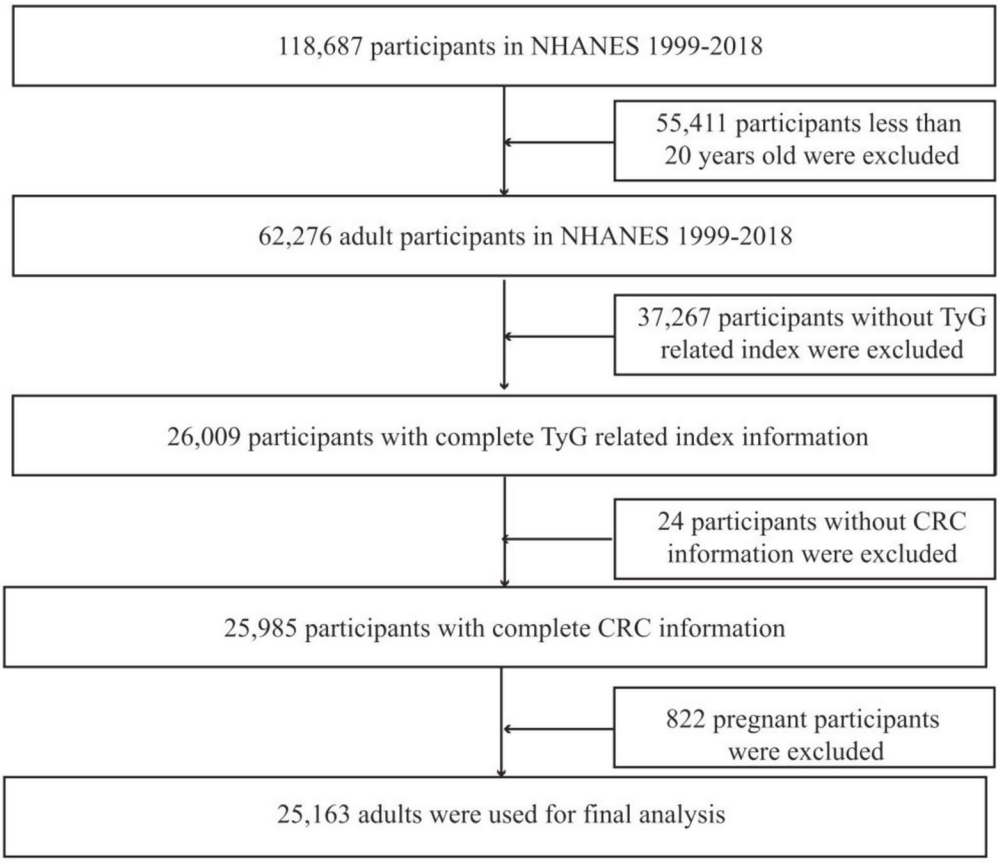

Fig. 1 Schematic depicting the protocol for the inclusion of research subjects

Predictors and endpoints

The current investigation selected the TyG and its three related indices as key predictive metrics. Serum FTG concentrations were quantified via biochemical analysis machines: the Roche Hitachi 717 and 912 series, Roche/Hitachi Cobas 6000 system, and Roche Modular P Chemistry platform. Levels of FBG were detected with the Roche C501 and Roche C311, in 2007–2016 and 2016, respectively. The use of separate analyzers for determining the levels of the aforementioned parameters was not essential as per the analytical guidelines of NHANES. The body weights, heights, WC, and blood pressure of the research subjects were measured by trained healthcare professionals during physical assessments, and a recorder was used to document the measurements. Primarily utilized to assess IR, the TyG index is a metric originating from serum FBG and FTG levels [22]. Additional TyG-related indices—TyG-BMI, TyG-waist circumference (TyG-WC), and TyG-waist-to-height ratio (TyG-WHtR) [23]—integrate various obesity-related parameters to comprehensively evaluate IR and its health implications. The main outcomes included the incidence and mortality associated with CRC. A diagnosis of CRC was confirmed if a subject responded "yes" to the query "Has any healthcare professional or doctor ever told you that you have CRC?" The data from different groups were subjected to Survival analysis was conducted across distinct participant groups to evaluate relationships between of all-cause mortality risk among individuals with CRC and the following predictors: TyG index, TyG-related indices, and other TyG-related variables that showed any associations in individuals with and without CRC. The endpoints and follow-up data pertaining to the participants were retrieved by associating their information with the open-access National Death Index file (https://www.cdc.gov/nchs/data-linkage/mortality.htm), using information up to December 31, 2019. Mortality tracking and duration since initial examination were monitored using the variables "Mortality status (MORTSTAT)" and "Person-Months of Follow-Up from Examination Date (PERMTH_EXM)", respectively.

Covariates

All the participants provided information pertaining to CRC status, age, sex, race/ethnicity, academic credentials (including lower than, equal to, or higher than high school level), smoking behavior (including current, former, or never smokers), drinking behavior (including current or never drinkers), marriage situation, medical

insurance, energy consumption, household poverty income ratio, and leisure time physical activity (LTPA). BMI was calculated as weight (kg) divided by (height (m)2) [24]. Serum samples were collected from participants during their visit to the mobile health assessment facility; these samples were used to derive laboratory values. The collection vials were maintained at suitable freezing conditions until transportation to the NCHS for subsequent assessment. The diagnosis of hypertension required: (1) diastolic or systolic blood pressure ≥ 90 or ≥ 140 mmHg, respectively; (2) subjects who answered "yes" to the question inquiring whether medical professionals had informed them of their hypertension status; or (3) if a subject was presently receiving antihypertensive medications [25]. A diagnosis of diabetes was confirmed if a study subject met one of the following criteria: (1) concentration of hemoglobin A1C ≥ 6.5%; (2) FBG level ≥ 126 mg/dL; (3) self-disclosed utilization of antidiabetics; or (4) if diabetes was previously diagnosed.

Meta-analyses

This conduct of this study followed guidance outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework. While it was not formally registered in the International Prospective Register of Systematic Reviews (PROSPERO) database, the protocol was developed a priori and strictly followed throughout the research process. A systematic search was implemented across the PubMed, Scopus, and Web of Science databases, with inclusion threshold set at April 1, 2025. The objective was to examine linkages between the TyG index and incidence or risk of CRC, including any dose-response patterns. Methodological quality appraisal incorporated the Newcastle-Ottawa Scale (NOS). Data extraction was independently performed by two researchers (LL and ZL), and any discrepancies were settled by consensus. The methodology is described in detail in the Supplementary Methods section.

The effects across different groups were depicted using forest plots; effects of continuous changes in the TyG index were visualized by dose-response curves.

Statistical analyses

A meta-analysis was performed on previous studies, and the heterogeneity was assessed using the I^2 statistic, where $I^2 > 50\%$ denotes significant heterogeneity. The effects of the respective reports on the overall pooled effect size were evaluated by "leave-one-out" sensitivity analyses. Any bias in the selected publications was investigated by Egger's and funnel plot analyses. Both standard and dose-response meta-analyses were conducted utilizing the "meta" and "dosresmeta" packages within the R statistical environment. The "WTSAF2YR" variable was implemented as the weighting variable in the cross-sectional study, and denotes the sample weighting code for the fasting sub-samples in the 1999–2018 dataset. Participants were stratified into CRC and non-CRC groups based on CRC presence or absence. Categorical factors were presented in terms of frequencies (percentages) and comparatively evaluated by Pearson's chi-square method. For numerical variables, mean ± standard deviation values were reported; either Wilcoxon rank-sum tests or t-tests were employed for comparisons, as appropriate. Evaluation of TyG-related indices in relation to CRC risk involved univariate and multivariate weighted logistic regression (WLR) analyses; findings were output in the form of odds ratios (ORs) with 95% confidence intervals (CIs). Further assessment comprised determining associations between the TyG index—with its companion indices—and CRC-related mortality among individuals with or without CRC were estimated using weighted univariate and multivariate Cox regression models. Relationships were conveyed as hazard ratios (HRs) and 95% CIs. Nonlinear connection patterns were identified through restricted cubic spline (RCS) models based on multivariate logistic regression outputs. To mitigate the impact of possible confounding variables, a tiered modeling strategy was adopted: Model 1 included no adjustment layers; Model 2 incorporated demographic and socioeconomic variables such as (e.g., age, sex, racial groups, BMI, academic qualification, marital status, and health insurance); and Model 3 integrated smoking and drinking behavior, energy intake, LTPA, and medical history of hypertension or diabetes, along with the components of Model 2. Covariates considered in these models were selected based on the findings of clinically relevant studies and supported by existing literature. The usefulness of TyG-related metrics in forecasting CRC risk entailed receiver operating characteristic (ROC) analysis; diagnostic performance was further quantified through calculation of area under the curve (AUC) values. Detection of susceptible populations required subset evaluation. Two-sided $P < 0.05$ indicated statistical significance, and R (v4.4.0) was used for statistical analyses.

Results

Meta-analyses of TyG index and analysis of CRC risk

A total of five studies [15–19] and approximately 536,953 research subjects were selected for the meta-analyses (Supplementary Table 5). Upper TyG index quartiles were significantly linked to increased CRC risk and exhibited a potential a dose-response relationship (Fig. 2A). Further analyses revealed that the risks of CRC increased by 23% (HR = 1.23 [1.14, 1.33], $P < 0.01$) for a single unit elevation in the TyG index (Fig. 2B), which aligned with the observations of quartile analysis. Meta-analyses of the dose-effect interrelationships between TyG and the incidence of CRC revealed an approximately linear relationship

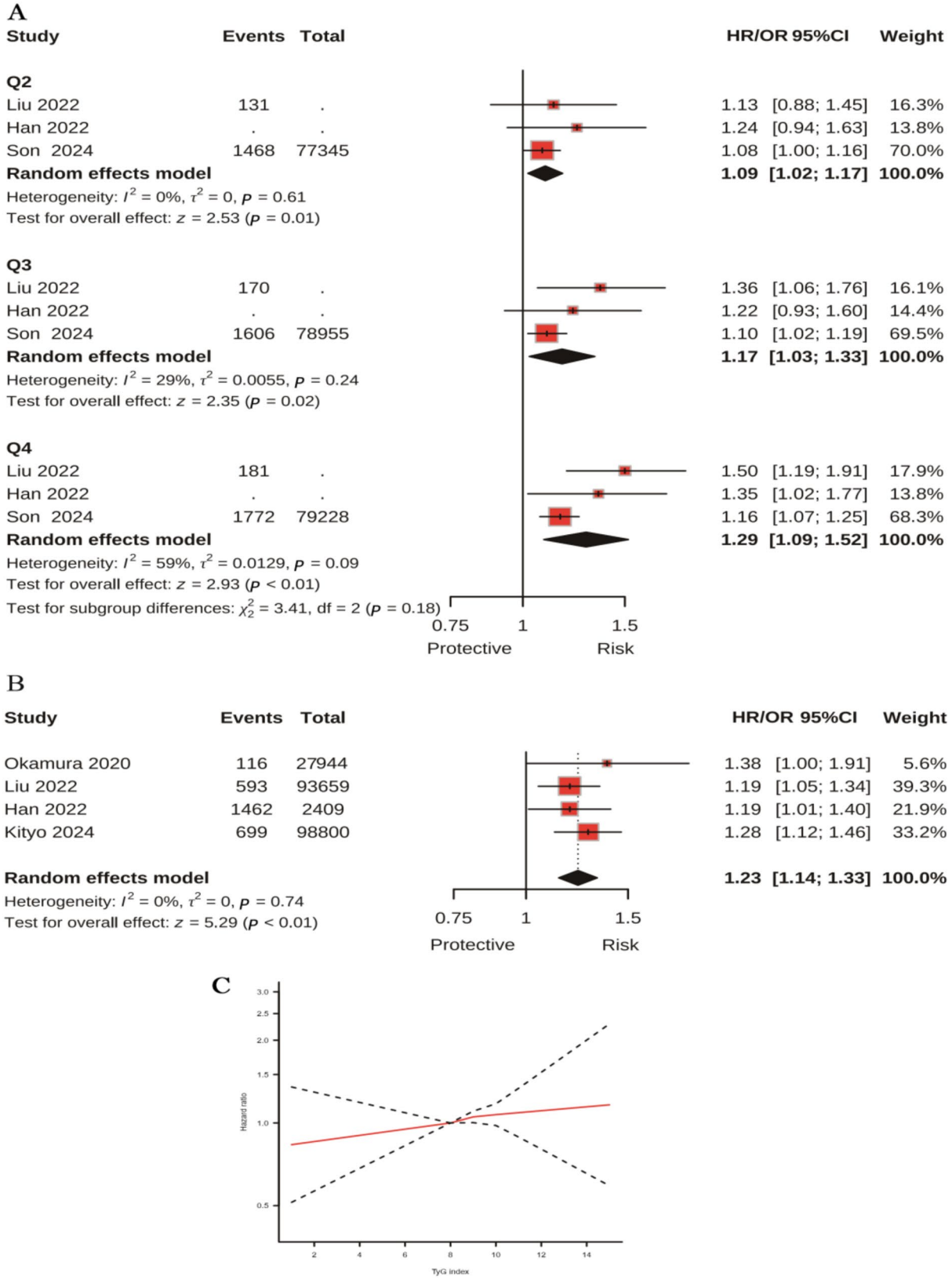

Fig. 2 Meta-analysis of CRC risk across TyG index quartiles (**A**). Assessment of linearity in the TyG–CRC interrelationship (**B**). Graphical dose-response representation evaluating the TyG index and its connection with CRC incidence (**C**)

($P > 0.05$ for nonlinearity; Fig. 2C), implying that the TyG index lacks a safe cutoff regarding CRC incidence. Altogether, the findings indicated a close-to-linear association, consistent with previously published evidence. Evaluation of the funnel plots revealed the absence of a publication bias in the selected references (Supplementary Fig. 2).

NHANES 1999–2018 dataset: participant baseline characteristics

The investigation included 25,163 participants, comprising 12,686 men and 12,477 women, of which approximately 0.58% (147) were diagnosed with CRC. In particular, the majority of individuals with CRC were older, inactive, and active drinkers, and were found to have lower education levels and higher BMIs. Additionally, individuals with CRC generally exhibited higher TyG values, elevated TyG-related indices, and a greater incidence of cardiovascular abnormalities. Supplementary Table 1 presents all participants'baseline features, stratified according to TyG index level and CRC status. Supplementary Table 2 outlines baseline survival and mortality data for all individuals with CRC, also grouped by TyG index.

TyG-related indices: associations with CRC mortality and incidence

As illustrated in Fig. 3, the TyG index and its derivative metrics appeared independent of one another across all individuals and showed no correlations. Although TyG-WC and TyG-WHtR did not display any significant positive correlations with CRC risk, both TyG and TyG-BMI demonstrated strong positive links with CRC risk: after adjusting for covariates, the incidence of CRC gradually increased in the second, third, and fourth quartiles ($P < 0.001$ for all) compared to that of the reference cohort (quartile 1), as depicted in Table 1. On the other hand, no compelling associations were found concerning CRC-related mortality and the derivative metrics. The likelihood of CRC-related mortality was elevated in quartile 2 of the TyG index, as indicated in Table 2. Figures 4 and 5 present RCS curves that depict dose-response relationships of the TyG index and its derivative metrics with CRC incidence and associated mortality. As depicted in Fig. 4, the findings revealed that the risk of CRC exhibited a nonlinear association with the TyG index ($P = 0.045$ for nonlinearity); it featured a positive linear association with TyG-BMI ($P = 0.385$ for nonlinearity). As depicted in Fig. 5, the risk of mortality associated with CRC exhibited a somewhat inverted U-shaped relation with the TyG index; however, no significant differences and no obvious dose-response relationships were observed for the other three indicators. Figure 6 displays ROC curves that highlight the degree to which TyG-related indices could estimate CRC risk. The findings further highlighted that TyG-BMI outperformed the other predictors in estimating the likelihood of CRC, as indicated by an AUC of 0.71. Subgroup analysis based on clinical characteristics (Fig. 7) indicated that both female sex and the TyG-BMI index exhibited significant associations with CRC incidence. It was observed that women, individuals with a BMI below 25, non-smokers, non-drinkers, those who did not exercise, and who were not diagnosed with diabetes, were found to be more susceptible to elevated TyG-BMI.

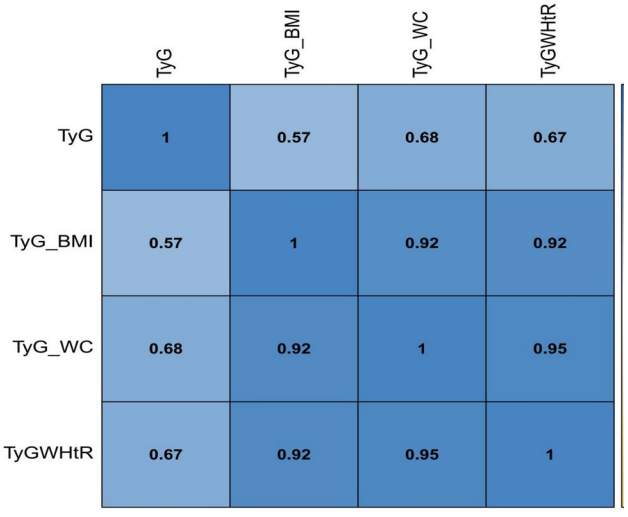

Fig. 3 Heat map showing no correlations among TyG-related indices, indicating independence

Discussion

Using both conventional and dose-response meta-analyses, this investigation identified a close-to-linear association involving the TyG index and CRC risk. These findings, along with associations of CRC risk and mortality with the TyG-related indices, were further substantiated using NHANES 1999–2018 data. The analyses uncovered that while the TyG index was nonlinearly connected to CRC incidence, TyG-BMI exhibited a positive linear trend with CRC risk. Notably, TyG-BMI demonstrated predictive superiority compared with the TyG index. Furthermore, subgroup analysis revealed that sex, especially women, and TyG-BMI displayed significant associations with the likelihood of CRC.

Five relevant articles exploring linkages involving the TyG index and CRC risk were retrieved via literature search. These included four cohort studies conducted prospectively and one cross-sectional investigation, all of which reported positive linkages concerning elevated TyG levels and CRC risk. However, there has been evidence of discrepancies regarding linearity or nonlinearity between the TyG index and CRC risk. For example, Liu et al. [16] identified a nonlinear relationship, suggesting

Table 1 Associations between CRC risk and TyG-related indices

Index	Evaluation Setup: Model 1		Evaluation Setup: Model 2		Evaluation Setup: Model 3	
	OR and 95% CI	*P* value	OR and 95% CI	*P* value	OR and 95% CI	*P* value
TyG index						
Continuous	1.76 (1.67, 1.85)	< 0.001	1.57 (1.47, 1.68)	< 0.001	1.47 (1.37, 1.58)	< 0.001
TyG group						
Group 1 (Reference Quartile)	1 (Ref)		1 (Ref)		1 (Ref)	
Group 2 (Second Quartile)	1.88 (1.66, 2.12)	< 0.001	1.35 (1.17, 1.55)	< 0.001	1.30 (1.14, 1.50)	< 0.001
Group 3 (Third Quartile)	2.52 (2.25, 2.83)	< 0.001	1.69 (1.48, 1.94)	< 0.001	1.59 (1.39, 1.83)	< 0.001
Group 4 (Highest Quartile)	3.32 (2.97, 3.72)	< 0.001	2.09 (1.82, 2.40)	< 0.001	1.84 (1.60, 2.12)	< 0.001
TyG-BMI index						
Continuous	1.01 (1.00, 1.01)	0.008	1.04 (1.02, 1.05)	< 0.001	1.03 (1.02, 1.04)	< 0.001
TyG-BMI group						
Group 1 (Reference Quartile)	1 (Ref)		1 (Ref)		1 (Ref)	
Group 2 (Second Quartile)	1.42 (1.28, 1.57)	< 0.001	1.27 (1.09, 1.48)	0.002	1.25 (1.07, 1.45)	0.004
Group 3 (Third Quartile)	1.31 (1.18, 1.45)	< 0.001	1.45 (1.20, 1.76)	< 0.001	1.34 (1.11, 1.64)	0.003
Group 4 (Highest Quartile)	1.24 (1.12, 1.38)	< 0.001	1.77 (1.40, 2.24)	< 0.001	1.52 (1.19, 1.93)	0.001
TyG-WC index						
Continuous	1.22 (1.12, 1.33)	< 0.001	1.11 (0.95, 1.29)	0.174	1.10 (0.94, 1.29)	0.231
TyG-WC group						
Group 1 (Reference Quartile)	1 (Ref)		1 (Ref)		1 (Ref)	
Group 2 (Second Quartile)	1.67 (0.94, 3.05)	0.086	0.93 (0.49, 1.78)	0.818	0.90 (0.48, 1.74)	0.757
Group 3 (Third Quartile)	2.68 (1.59, 4.73)	< 0.001	1.22 (0.62, 2.45)	0.566	1.18 (0.60, 2.39)	0.637
Group 4 (Highest Quartile)	2.85 (1.70, 5.01)	< 0.001	1.17 (0.54, 2.58)	0.685	1.10 (0.50, 2.47)	0.805
TyG-WHtR index						
Continuous	1.44 (1.25, 1.65)	< 0.001	1.11 (0.85, 1.42)	0.433	1.08 (0.82, 1.41)	0.570
TyG-WHtR group						
Group 1 (Reference Quartile)	1 (Ref)		1 (Ref)		1 (Ref)	
Group 2 (Second Quartile)	2.36 (1.29, 4.57)	0.007	1.19 (0.62, 2.38)	0.615	1.12 (0.58, 2.25)	0.743
Group 3 (Third Quartile)	3.30 (1.86, 6.24)	< 0.001	1.27 (0.62, 2.70)	0.514	1.18 (0.58, 2.53)	0.652
Group 4 (Highest Quartile)	3.88 (2.22, 7.27)	< 0.001	1.20 (0.54, 2.76)	0.660	1.08 (0.48, 2.52)	0.854

Model 1: Unadjusted

Model 2: Incorporated age, sex, racial groups, BMI, academic qualification, marital status, and health insurance

Model 3: Model 2 + integration of smoking and drinking behavior, energy intake, LTPA, and history of hypertension and diabetes

a safety threshold for the TyG index at or below 8.19. Son et al. [18]also reported a nonlinear association, identifying a safety threshold below 8.67. In contrast, Kityo et al. [19] documented a linear increase in CRC risk at higher TyG index values, indicating no apparent safety threshold. In the present study, meta-analysis findings supporting a proportional relationship between TyG levels and CRC risk. These results suggest that physicians should exercise greater caution when evaluating CRC risk among individuals with elevated TyG values, potentially conducting more frequent screenings. Conversely, our analyses of the 1999–2018 NHANES dataset revealed a nonlinear association, likely shaped by sample size, ethnicity, geographic region, and other factors. Collectively, the findings emphasize the need for extensive, multicenter prospective studies involving broader participant pools to clarify the linear or nonlinear nature of the TyG–CRC relationship and to establish safety thresholds. Such evidence would enable physicians to more accurately assess CRC risk and develop personalized preventive and intervention strategies for high-risk populations.

The interrelationship of TyG-BMI with the probability of CRC remains to be elucidated to date. A recent case-control investigation [26] involving Chinese adults revealed a positive linkage between TyG-BMI and non-small cell lung cancer (NSCLC) incidence, demonstrating that it can serve as an effective predictor of the likelihood of NSCLC. Yang et al. [27] explored how surrogate IR markers affect the likelihood of esophageal cancer. In their study, TyG and TyG-BMI were positively linked to esophageal adenocarcinoma risk. The current study is among the earliest to explore how TyG-BMI influences CRC risk. The findings indicated that TyG-BMI provided greater CRC forecasting accuracy compared with the TyG index and followed a linear trend with CRC incidence, which aligns with the fact that CRC is connected to obesity. Furthermore, a recent meta-analysis [28] of randomized controlled trials demonstrated that probiotic and prebiotic interventions significantly reduced

Table 2 Associations between CRC-related mortality and TyG-related indices

Index	Evaluation Setup: Model 1		Evaluation Setup: Model 2		Evaluation Setup: Model 3	
	HR and 95% CI	*P* value	HR and 95% CI	*P* value	HR and 95% CI	*P* value
TyG index						
Continuous	0.68 (0.44, 1.03)	0.071	1.04 (0.65, 1.69)	0.858	1.11 (0.63, 1.96)	0.714
TyG group						
Group 1 (Reference Quartile)	1 (Ref)		1 (Ref)		1 (Ref)	
Group 2 (Second Quartile)	1.50 (0.78, 2.87)	0.225	2.67 (1.18, 6.06)	0.019	3.02 (1.22, 7.47)	0.017
Group 3 (Third Quartile)	0.88 (0.44, 1.79)	0.729	2.03 (0.86, 4.83)	0.108	2.39 (0.94, 6.08)	0.068
Group 4 (Highest Quartile)	0.68 (0.33, 1.41)	0.301	1.06 (0.44, 2.56)	0.889	1.07 (0.39, 2.94)	0.897
TyG-BMI index						
Continuous	0.44 (0.26, 0.73)	0.002	1.88 (0.59, 6.00)	0.284	1.95 (0.55, 6.98)	0.303
TyG-BMI group						
Group 1 (Reference Quartile)	1 (Ref)		1 (Ref)		1 (Ref)	
Group 2 (Second Quartile)	0.94 (0.52, 1.71)	0.842	1.08 (0.49, 2.36)	0.855	1.08 (0.46, 2.52)	0.86
Group 3 (Third Quartile)	0.54 (0.28, 1.03)	0.06	1.61 (0.54, 4.78)	0.39	2.18 (0.62, 7.66)	0.223
Group 4 (Highest Quartile)	0.25 (0.11, 0.59)	0.001	1.03 (0.19, 5.57)	0.977	0.93 (0.14, 6.09)	0.937
TyG-WC index						
Continuous	0.83 (0.70, 0.98)	0.032	1.02 (0.75, 1.40)	0.880	0.97 (0.67, 1.40)	0.877
TyG-WC group						
Group 1 (Reference Quartile)	1 (Ref)		1 (Ref)		1 (Ref)	
Group 2 (Second Quartile)	0.71 (0.38, 1.34)	0.288	0.72 (0.28, 1.88)	0.508	0.73 (0.26, 2.05)	0.554
Group 3 (Third Quartile)	0.51 (0.27, 0.97)	0.039	0.69 (0.24, 1.96)	0.481	0.67 (0.22, 2.07)	0.49
Group 4 (Highest Quartile)	0.36 (0.17, 0.78)	0.01	0.93 (0.22, 3.84)	0.919	0.98 (0.20, 4.89)	0.982
TyG-WHtR index						
Continuous	0.69 (0.51, 0.92)	0.013	1.15 (0.69, 1.93)	0.585	1.10 (0.62, 1.96)	0.751
TyG-WHtR group						
Group 1 (Reference Quartile)	1 (Ref)		1 (Ref)		1 (Ref)	
Group 2 (Second Quartile)	0.74 (0.40, 1.37)	0.337	0.48 (0.22, 1.07)	0.073	0.52 (0.23, 1.21)	0.13
Group 3 (Third Quartile)	0.62 (0.32, 1.22)	0.166	2.16 (0.75, 6.25)	0.155	2.13 (0.63, 7.23)	0.224
Group 4 (Highest Quartile)	0.41 (0.19, 0.87)	0.021	1.27 (0.40, 3.97)	0.683	1.22 (0.34, 4.33)	0.76

Model 1: Unadjusted

Model 2: Incorporated age, sex, ethnic group, BMI, academic qualification, marital status, and health insurance

Model 3: Model 2 + integration of smoking and drinking behavior, energy intake, LTPA, and history of hypertension and diabetes

serum triglyceride levels, suggesting that the consumption of probiotics and prebiotics exerts a beneficial role in modulating lipid metabolism. Therefore, in addition to lifestyle modifications, probiotic or prebiotic supplementation may be considered as a potential adjunct therapy for reducing CRC incidence among individuals with elevated TyG or TyG-BMI values. These findings also underscore the notion that the TyG index and TyG-BMI can be incorporated into early CRC screening and risk stratification.

The TyG index is gaining momentum for use in predicting outcomes across various malignancies. For instance, Song et al. [13] documented that the TyG index peaks in early-phase pancreatic ductal adenocarcinoma (PDAC) and decreases in the advanced stages of the disease. This suggests that early pancreatic cancer, which is driven by prolonged hyperinsulinemia, is associated with an elevated TyG index, and establishes a new metabolic balance that contributes to disease progression to advanced stages. This indicates that higher TyG index levels may contribute to tumor progression and are significantly associated with poor prognostic outcomes in PDAC. A prospective multi-center cohort [14] study explored the prognostic significance of IR and widespread inflammatory response in subjects with gynecological cancers. Elevated TyG index levels have been linked to worse cancer prognoses. Although numerous reports suggest that elevated values of the TyG index suggest poor clinical outlook for patients suffering from cancer, some investigations have presented contradictory findings. For instance, a prospective cohort [29] analysis examined the interrelationships of TyG concerning all- and specific-cause mortality, it displayed an inverse linear trend involving TyG levels and cancer-related mortality. In another study, Cai et al. [12] explored how the TyG index influenced prognosis in patients who had undergone radical gastrectomy for stomach cancer. The results showed that patients with higher TyG index values experienced significantly longer overall survival relative to those with lower values. These data suggest that the TyG

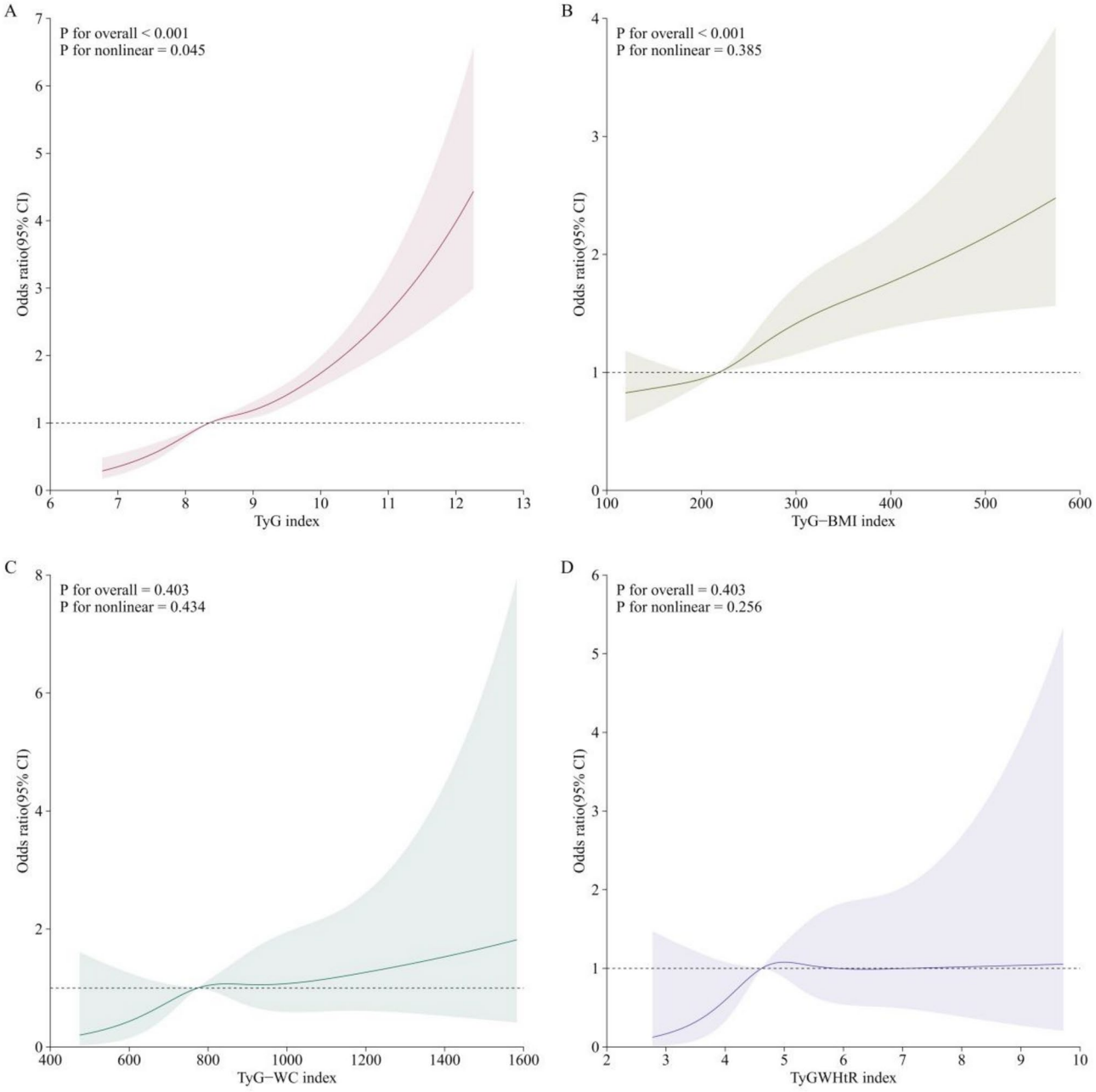

Fig. 4 Restricted cubic spline (RCS) curves illustrating relationships between each TyG-related metric and CRC incidence

index may act independently as a forecasting marker for postoperative outcomes in gastric cancer cases. Based on these reports, it is suggested that there are discrepancies pertaining to the interrelationship of the TyG index with the prognostic outlook of malignancies. The studies additionally established that the TyG index displays complex linkages with cancer-related mortality. However, the interrelationship of IR with the prognosis of CRC remains to be elucidated to date. This current investigation additionally showed no significant associations between CRC-related mortality and any of the indices examined. Large prospective investigations with extensive cohorts are critical for exploring the associations between IR and CRC-related mortality in future.

Although prior research has shown that CRC incidence is higher in males than females [1], the present investigation identified female sex and elevated TyG-BMI as significant contributors to higher CRC risk. This suggested that women are more likely to be affected by an increase in TyG-BMI than men, resulting in a higher risk of CRC among women, and it is considered that this may be related to estrogen. Among the participants in

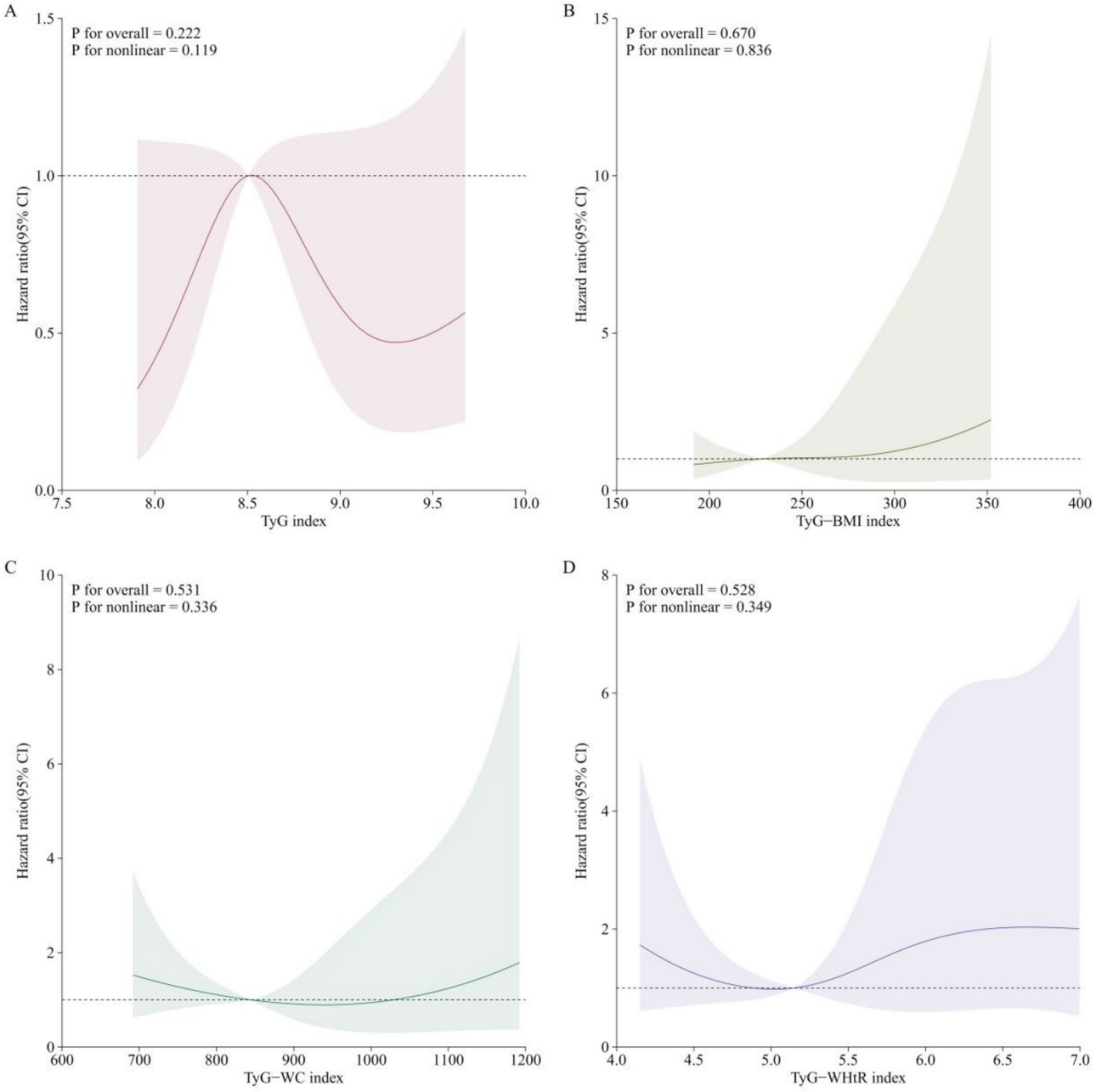

Fig. 5 RCS curves illustrating relationships between each TyG-related metric and CRC-related mortality

this study, 21.8% of the women were aged 45–64 years, while 75.5% were aged over 65 years, and the majority were in the post-menopausal period with estrogen deficiency. Circulating estradiol levels typically span between 2000 and 15,000 pg/mL in premenopausal women; these values sharply decline to approximately 10 pg/mL after menopause [30]. This endocrine transition predisposes postmenopausal populations to various metabolic derangements, including dysregulated lipid metabolism, increased visceral adiposity, and altered fatty acid metabolism [31–33], thereby contributing to elevated TyG-BMI values through mechanistic pathways. Previous epidemiological studies and randomized controlled trials have revealed that CRC incidence is substantially lower in hormone replacement therapy-treated post-menopausal women relative to untreated age-matched women [34, 35]. Some studies have further revealed that post-menopausal estrogen deficiency may worsen the overall survival of elderly women with CRC than in elderly men [36]. This indicates that estrogen may confer protection against the development of CRC, and the potential mechanisms are primarily associated with the functions

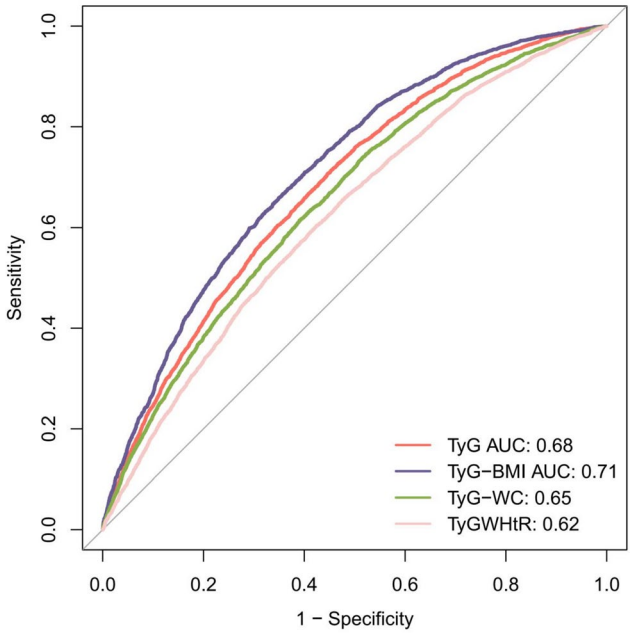

Fig. 6 Receiver operating characteristic (ROC) diagram illustrating the extent to which each TyG-related metric can detect CRC risk

of estrogen receptors and the modulation of related signaling pathways [37]. Therefore, the values of TyG-BMI require stringent monitoring in postmenopausal women. Elevated TyG-BMI values may warrant the implementation of comprehensive lifestyle modifications and the intensification of targeted screening protocols in this population. Additionally, estrogen supplementation could represent a viable approach for reducing CRC risk in postmenopausal women with elevated TyG-BMI.

Strengths and limitations

The research draws its merits from analyzing an extensive American population, which enhanced the robustness of the data obtained herein. However, the investigation is subject to certain limitations, which are discussed hereafter. First, although many confounding parameters were accounted for, unmeasured or residual confounding factors may have subtly influenced connections of TyG-related indices with CRC risk cannot be entirely excluded. Second, the incidence of CRC was analyzed retrospectively, which only allowed for the identification of correlations but not causal relationships. Third, the study focused on the American population and is based on the NHANES dataset, which limits the universality of the observations to cohorts in other countries and areas. Fourth, despite strict adherence to quality control in the NHANES questionnaire, the validity of the findings might be compromised by potential inaccuracies in self-reported information and possible errors of misclassification. Finally, the reliance on all-cause mortality as a surrogate endpoint may have underestimated the actual magnitude of connection involving the TyG index and CRC-specific mortality in this study. Therefore, future studies with more precise cause-of-death data are necessary for validating these findings.

Conclusion and outlook

TyG-related indices may constitute effective predictors of the likelihood of CRC and exhibit significant dose-response associations with the incidence of CRC. TyG-BMI outperformed all the other indicators considered in this study, and it can help preemptively identify people with a higher likelihood of developing CRC, implement personalized intervention measures, and assist doctors in determining which populations would need to undergo colonoscopy screening. This may help avoid unnecessary examinations and reducing economic, physical, and psychological burdens. Nevertheless, none of the examined indices showed a significant relationship with CRC-related mortality. It was observed that the sex, especially women, and TyG-BMI displayed significant associations with the incidence of CRC, given that over 75.5% of the participants in this study were post-menopausal women, for post-menopausal women with elevated TyG-BMI, estrogen supplementation might potentially reduce CRC incidence. However, it still requires analysis of the pros and cons. Lifestyle intervention remains the fundamental measure for preventing CRC.

Variable	Count	Percent	OR and 95%CI	*P* value	*P* for interaction
Sex					0.002
Men	12686	50.4	1.00 (0.71, 1.41)	0.987	
Women	12477	49.6	2.00 (1.51, 2.66)	<0.001	
Age					0.619
20−44	10971	43.6	0.53 (0.10, 2.83)	0.458	
45−64	8397	33.4	1.22 (0.76, 1.96)	0.418	
≥ 65	5795	23	1.11 (0.82, 1.51)	0.488	
Ethnic group					0.882
Mexican American	4246	16.9	1.75 (0.88, 3.51)	0.112	
Other Hispanic	1987	7.9	1.44 (0.69, 3.02)	0.33	
Non−Hispanic White	11785	46.8	1.35 (1.02, 1.79)	0.038	
Non−Hispanic Black	5045	20	1.76 (1.03, 2.99)	0.038	
Other Race − Including Multi−Racial	2100	8.3	1.15 (0.39, 3.39)	0.805	
Education level					0.519
<High school	6288	25	1.18 (0.78, 1.78)	0.439	
High school graduate	5683	22.6	1.21 (0.77, 1.91)	0.401	
Some college	7374	29.3	1.62 (1.11, 2.36)	0.012	
College graduate or above	5818	23.1	1.77 (1.01, 3.10)	0.047	
Marital status					0.271
Married	13342	53	1.26 (0.90, 1.76)	0.17	
Widowed	1920	7.6	1.26 (0.74, 2.13)	0.395	
Divorced	2508	10	1.35 (0.82, 2.21)	0.235	
Separated	823	3.3	1.19 (0.44, 3.16)	0.734	
Never married	4614	18.3	2.36 (1.03, 5.40)	0.041	
Living with partner	1956	7.8	0.09 (0.01, 1.29)	0.076	
PIR					0.333
<1.35	7521	29.9	1.50 (1.06, 2.13)	0.022	
1.35−3.00	7573	30.1	1.14 (0.79, 1.65)	0.487	
≥ 3.00	10069	40	1.70 (1.13, 2.57)	0.011	
BMI					0.177
Under 25	7810	31	2.11 (1.30, 3.42)	0.002	
25−30.0	8617	34.2	1.28 (0.89, 1.85)	0.186	
30.0 and over	8736	34.7	1.21 (0.84, 1.74)	0.318	
Smoking					0.187
Current smoker	5327	21.2	1.49 (0.82, 2.71)	0.194	
Ex−smoker	6339	25.2	1.08 (0.75, 1.55)	0.69	
Never smoker	13497	53.6	1.67 (1.23, 2.29)	0.001	
Drinking					0.267
Drinker	19184	76.2	1.30 (0.99, 1.71)	0.059	
Non−drinker	5979	23.8	1.68 (1.18, 2.39)	0.004	
Covered by health insurance					0.887
Yes	19864	78.9	1.45 (1.16, 1.83)	0.001	
No	5299	21.1	1.37 (0.60, 3.13)	0.459	
Energe intake					0.298
adequate	10236	40.7	1.24 (0.87, 1.76)	0.238	
high	4697	18.7	2.44 (1.16, 5.13)	0.018	
low	10230	40.7	1.45 (1.07, 1.96)	0.016	
LTPA					0.703
active	8678	34.5	1.32 (0.86, 2.02)	0.201	
inactive	16485	65.5	1.45 (1.13, 1.87)	0.004	
Hypertension					0.382
No	16630	66.1	1.40 (0.96, 2.04)	0.084	
Yes	8533	33.9	1.13 (0.85, 1.51)	0.403	
Diabetes					0.052
No	22277	88.5	1.50 (1.14, 1.96)	0.003	
Yes	2886	11.5	0.88 (0.56, 1.40)	0.596	

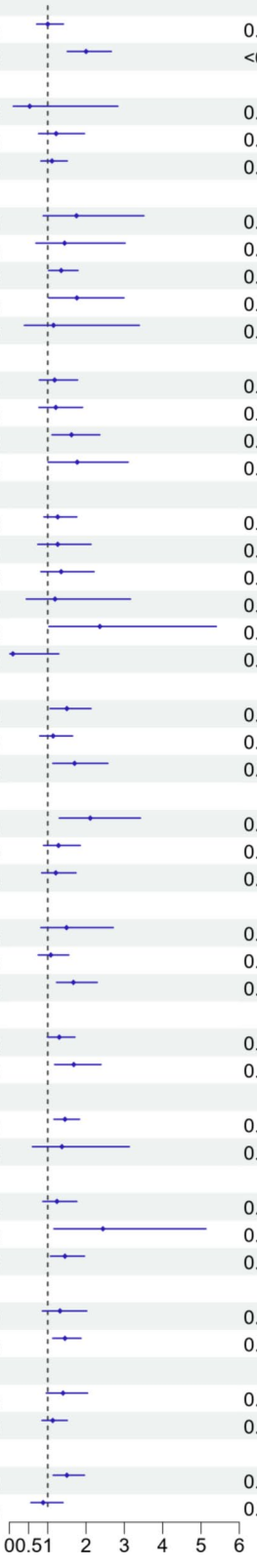

Fig. 7 Subgroup analysis based on relevant clinical characteristics revealed that both the sex (women) and TyG-BMI exhibited significant associations with the incidence of CRC

Abbreviations

AUC	Area under the curve
BMI	Body mass index
CI	Confidence intervals
CRC	Colorectal cancer
FBG	Fasting blood glucose
FTG	Fasting triglyceride
HRs	Hazard ratios
IR	Insulin resistance
LTPA	Leisure time physical activity
MORTSTAT	Mortality status
NCHS	National Center for Health Statistics
NHANES	National Health and Nutrition Examination Survey
NOS	Newcastle-Ottawa scale
OR	Odds ratio
PERMTH_EXM	Person-Months of Follow-Up from Examination Date
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
RCS	Restricted cubic spline
ROC	Receiver operating characteristic
TyG	Triglyceride glucose
TyG-BMI	TyG-body mass index
TyG-WC	TyG-waist circumference
TyG-WHtR	TyG-waist-to-height ratio
WC	Waist circumference
WHtR	Waist-to-height ratio
WLR	Weighted logistic regression

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-025-02574-x.

Supplementary Material 1

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Author contributions

WWOY: study conception and design; LL: manuscript preparation and statistical analyses; LL and ZL: data extraction. QG, JF, and LYW: article refinement and evaluation of records. All the authors have review and endorsed the article for publication.

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Data availability

This work incorporated datasets taken from open-access resources managed by the CDC (https://www.cdc.gov/nchs/nhanes/index.htm) alongside relevant peer-reviewed literature.

Declarations

Ethics approval and consent to participate

The ethical conduct of NHANES was reviewed and approved by the Ethics Review Board under the NCHS. Written documentation of consent was obtained from every participant.

Consent for publication

Irrelevant.

Competing interests

The authors declare no competing interests.

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