Cardiovascular Diabetology

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Insulin resistance-related indices, genetic risk, and the risk of cardiovascular disease in individuals with preclinical or clinical obesity: a large prospective cohort study in the UK biobank

Jinling Hu[1†], Cong Shang[1†], Yueqing Huang[2*], Chaonan Sun[3*] and Jing Zhang[1*]

Abstract

Background Insulin resistance (IR)-related indices are validated prognostic markers in metabolic disorders, but have not been applied to preclinical or clinical obesity. This study aimed to investigate the relationship between IR-related indices and cardiovascular disease (CVD) incidence, considering genetic factors and biomarkers.

Methods This prospective study analyzed 112,866 UK Biobank participants with preclinical or clinical obesity. IR-related indices were evaluated: triglyceride-glucose (TyG) index, TyG-body mass index (TyG-BMI), TyG-waist circumference (TyG-WC), and TyG-waist-to-height ratio (TyG-WHtR). Genetic risk was estimated using the polygenic risk score. Outcomes, including total CVD, coronary artery disease (CAD), and stroke, were ascertained through medical records linkage. Cox proportional hazard models were used to evaluate the associations and modification effects of genetic risk. Incremental predictive value was assessed by net reclassification index (NRI) and integrated discrimination improvement index (IDI). Mediation analyses explored the role of inflammatory, hepatic, and renal biomarkers.

Results Over a median follow-up period of 13.45 years, 21,601 total CVD, 11,942 CAD, and 3347 stroke cases were documented. Compared with the lowest quartile of IR-related indices, participants in the highest quartile presented increased CVD risk. For total CVD, hazard ratios (HRs) (95% confidence intervals, CIs) for the fourth versus the first quartiles were 1.33 (1.28–1.39) for TyG-BMI, 1.41 (1.34–1.48) for TyG-WC, and 1.25 (1.20–1.31) for TyG-WHtR. All IR-related indices demonstrated significant associations with CAD. Borderline significant associations were observed

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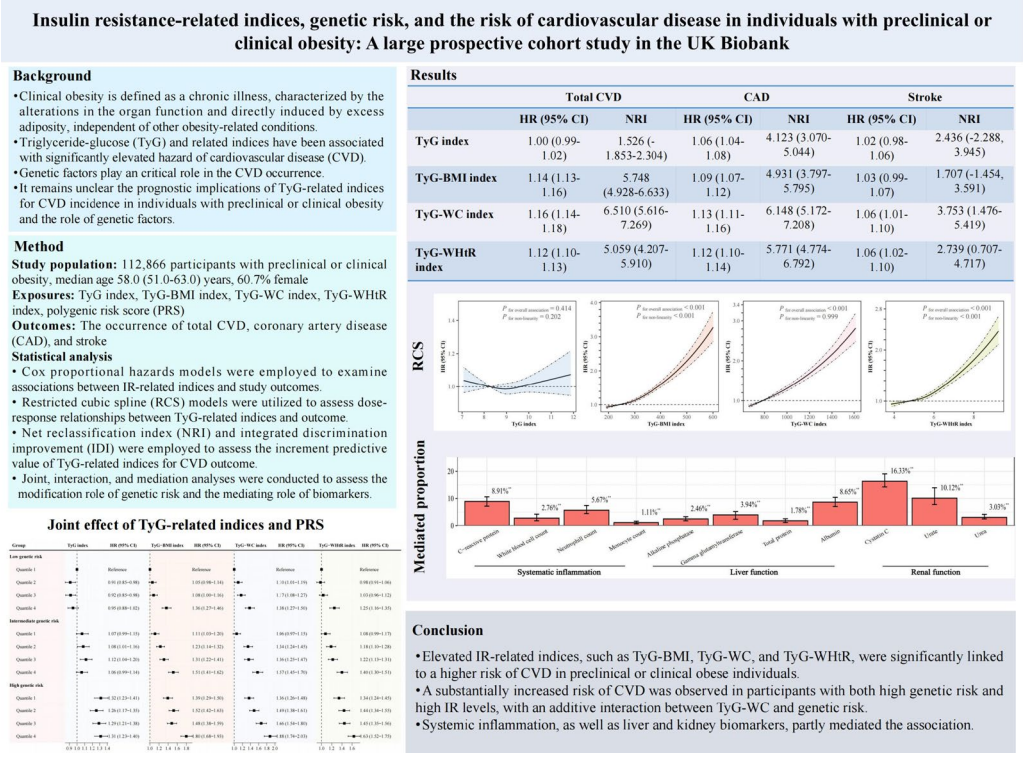
for stroke. Distinct dose-response association patterns with total CVD were observed: TyG-BMI and TyG-WHtR exhibited nonlinear relationships, while TyG-WC demonstrated a linear association. The CVD risk was highest in individuals with high genetic risk and high IR indices, with an additive interaction between TyG-WC and genetic risk being observed. Significantly higher NRI and IDI were observed for TyG-WC, TyG-BMI, and TyG-WHtR in predicting CVD, with TyG-WC achieving the highest performance. Mediation analyses indicated that inflammation, liver, and renal biomarkers might partially mediate the relationship.

Conclusion Elevated IR-related indices, particularly TyG-WC, were associated with increased total CVD and CAD risks in preclinical or clinical obesity. Additive effects of TyG-WC and genetic risk on CVD were revealed, with mediating biomarkers suggesting potential targeted interventions for CVD risk reduction.

Keywords Preclinical or clinical obesity, Insulin resistance, Triglyceride glucose, Cardiovascular disease, Genetic risk, Joint, Interaction, Biomarker, Mediation, Cohort study

Graphical abstract



Research Insights

What is currently known about this topic?

- Preclinical or clinical obesity is linked to higher CVD risk.
- Insulin resistance (IR)-related indices are established markers of CVD risk.
- These indices remain unexplored in preclinical or clinical obesity.

What is the key research question?

- What is the association of IR-related indices with CVD incidence in individuals with preclinical or clinical obesity?

What is new?

- IR-related indices, especially TyG-WC, are valid predictors of CVD prognosis in these patients.
- High genetic risk and IR indices jointly elevate CVD risk, with additive interactions for TyG-WC.
- Inflammatory, hepatic, and renal markers might mediate the observed associations.

How might this study influence clinical practice?

- IR-related indices may improve risk stratification and early detection in preclinical or clinical obese patients.

Introduction

Cardiovascular disease (CVD), particularly stroke and coronary artery disease (CAD), remains the leading cause of morbidity and mortality worldwide [1, 2]. In 2019, the global incidence of CVD exceeded 500 million cases, approximately double that reported in 1990 [2]. According to the 2019 Global Burden of Disease (GBD) report, cardiovascular-related deaths are projected to reach 35.6 million by 2050 [3]. Obesity, a major yet modifiable risk factor for CVD [4], has emerged as a critical public health concern, affecting more than 800 million adults globally in 2022 [5]. Although body mass index (BMI) remains the most widely used metric for diagnosing obesity and categorizing its severity, it does not to capture fat distribution characteristics, thereby limiting its ability to differentiate the metabolic activity of adipose tissue or assess the risk of obesity-related conditions [6]. Recently, *The Lancet Diabetes & Endocrinology* Commission emphasized that obesity should be regarded as a chronic disease entity rather than merely a risk factor, specifically highlighting that excessive fat accumulation can directly impair organ or system function [7]. The Commission proposed distinguishing between preclinical and clinical obesity based on the presence or absence of organ dysfunction: preclinical obesity refers to excess adiposity without major organ impariment, whereas clinical obesity is characterized by excess adiposity accompanied by organ dysfunction affecting physiological systems or limiting daily activities [7]. Incorporating assessments of organ function and activity into obesity evaluation may enhance disease risk stratification and address the limitations of BMI-based classifications. Therefore, identifying modifiable risk factors associated with cardiovascular outcomes in preclinical or clinical obese populations is essential for developing and implementing targeted prevention strategies.

Insulin resistance (IR), a central pathophysiological mechanism underlying clinical obesity [7], is characterized by reduced sensitivity to glucose utilization and plays a pivotal role in the development of CVD [8, 9]. However, its clinical assessment remains challenging. Although the hyperinsulinemic-euglycemic clamp is considered the gold standard for IR evaluation, its complexity and high cost limit routine applicability [10]. Consequently, attention has shifted toward surrogate markers that are simple, scalable, and cost-effective. Among these, the triglyceride-glucose (TyG) index and its derivatives—TyG-body mass index (TyG-BMI), TyG-waist circumference (TyG-WC), and TyG-waist-to-height ratio (TyG-WHtR)—have emerged promising alternatives for IR assessment [11–13]. Previous studies have demonstrated the prognostic value of these indices for cardiovascular events in populations with various metabolic disorders, including hypertension [14], diabetes mellitus [15], metabolic syndrome [16], cardiometabolic diseases [17], and metabolic dysfunction-associated fatty liver disease (MASLD) [18]. However, only a few investigations have explored their association with cardiovascular outcomes in obese populations [19–26]. Moreover, most available studies were conducted in U.S. cohorts [19–22], defined obesity solely using anthropometric measures [19–22], or focused on a single exposure or outcome [19–21, 23, 24]. Two studies have reported associations between TyG-related indices and early cardiovascular damage in overweight or obese individuals [25, 26]. Despite these advances, evidence remains lacking for preclinical and clinical obesity. Therefore, a large prospective cohort study is warranted to evaluate the prognostic implications of IR-related indices in individuals with preclinical or clinical obesity.

Increasing evidence emphasizes the contribution of genetic factors to CVD [27]. Genetic risk can be quantified using polygenic risk scores (PRS), which allow for the identification of individuals at elevated genetic risk to CVD [27]. Although some research suggests that favorable metabolic profiles may mitigate the deleterious effects of high genetic risk [28, 29], it remains unclear the role of genetic risk in the associations between IR-related indices and incident CVD in preclinical or clinical obesity. Additionally, early studies have established associations between IR-related indices and blood-based biomarkers reflecting liver function [30], renal function [31], and systemic inflammation [14, 32], all of which are mechanistically linked to cardiovascular events [33–35]. For example, a prospective cohort study has reported that inflammatory markers may partially mediate the relationship between TyG-related indices and adverse cardiovascular outcomes in hypertensive populations [14]. Nevertheless, whether similar mediation pathways exist in the context of preclinical or clinical obesity remains to be elucidated.

To address these knowledge gaps, this study aimed to: (1) examine the prospective associations between IR-related indices and the risk of incident CVD and its major subtypes in individuals with preclinical or clinical obesity; (2) evaluate the incremental predictive value of these indices for CVD outcomes; (3) investigate the joint associations and potential interactions between IR-related indices and genetic risk; and (4) assess the potential mediating roles of inflammatory, hepatic, and renal biomarkers.

Methods

Study design and participants

This study utilized data from the UK Biobank, a large, nationally representative, prospective cohort comprising over 500,000 individuals recruited from England, Scotland, and Wales between 2006 and 2010. Participants completed electronic questionnaires, underwent comprehensive physical examinations, and provided biological specimens. Detailed descriptions of the study design and cohort characteristics have been published elsewhere [36]. Ethical approval was obtained from the North West Multi-Centre Research Ethics Committee (MREC reference: 21/NW/0157), and all participants provided written informed consent. The present analysis was conducted under Application Number 104,283.

After sequentially excluding participants with missing IR-related indices ($n = 80,801$), those without obesity ($n = 293,717$), and those with a prior diagnosis of CVD ($n = 14,982$), the final analytic sample consisted of 112,866 individuals with preclinical or clinical obesity. A flowchart summarizing the participant selection process is presented in Fig. 1.

Assessment of preclinical or clinical obesity

This study adopted the diagnostic framework for preclinical or clinical obesity as proposed by the *Lancet Diabetes & Endocrinology* Commission [7]. Preclinical obesity was defined as the presence of excess adiposity, operationalized by a BMI ≥ 25 kg/m² in conjunction with a WC >88 cm for women or >102 cm for men, or assumed when BMI exceeded 40 kg/m², in the absence of any clinical signs or symptoms of organ dysfunction or obesity-related functional limitations [7, 37]. Clinical obesity, by contrast, was defined using the same anthropometric

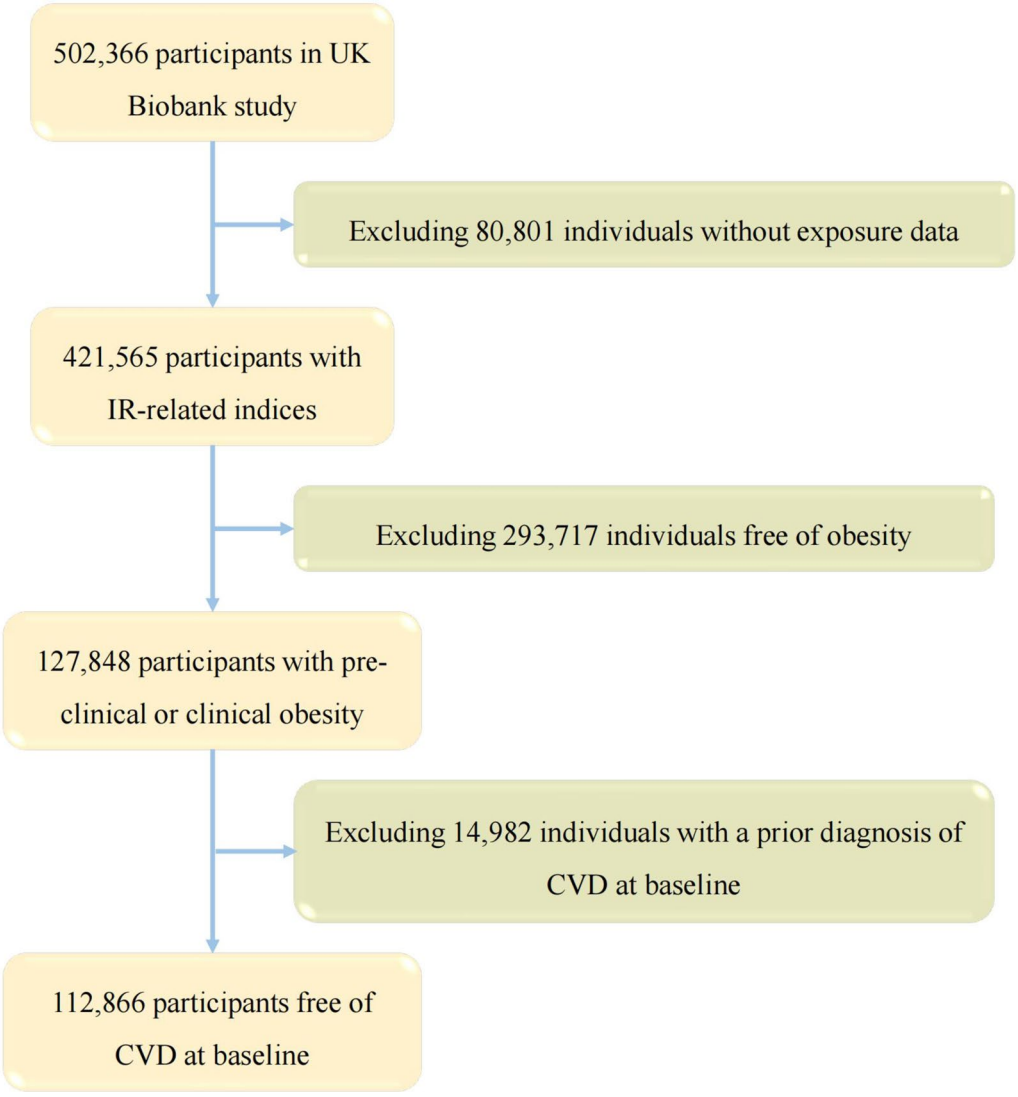


Fig. 1 Flowchart of selection process

thresholds; however, it required the presence of either evidence of organ dysfunction or substantial limitations in daily living activities attributable to obesity [7, 37].

Obesity-induced organ dysfunction was identified based on a predefined set of diagnostic criteria aligned with the Commission's framework [37]. Diagnoses were drawn from hospital inpatient records up to baseline, as coded in the 10th revision of the International Classification of Diseases (ICD-10), and supplemented by relevant self-reported baseline indicators. These criteria spanned dysfunction across multiple physiological systems. Neurological dysfunction included diagnoses G93.2 and H53.4; respiratory dysfunction included G47.3, J96.1, and R06.2; cardiovascular dysfunction was defined using I50, I48, I27, I26.9, and I10; metabolic dysfunction by E78; hepatic dysfunction by K76.0 and K74.0; renal dysfunction by N18.1-N18.5; urinary dysfunction by N39.4; reproductive dysfunction by N97.0, N91.3-N91.5, E28.2, and E29.1; and lymphatic dysfunction by I89.0. Musculoskeletal dysfunction was assessed through responses to the UK Biobank question: "*In the last month, have you experienced any of the following that interfered with your usual activities?*", specifically focusing on chronic and severe knee or hip pain. Mobility limitations attributable to obesity were identified using both ICD-10 codes—R29.6 (falls), R26.2 (impaired walking), and Z74.0 (need for assistance with personal care)—and self-reported indicators. These included shortness of breath, leg pain, or chest pain/discomfort during walking on level ground, based on the following UK Biobank questions: "*Do you get short of breath walking with people of your own age on level ground?*" (UK Biobank Field ID: 4717); "*Do you get pain when you walk at an ordinary pace on the level?*" (Field ID: 5485); and "*Do you get this pain or discomfort when you walk at an ordinary pace on the level?*" (Field ID: 3606), the latter of which followed a question about experiencing chest pain or discomfort. These measures were selected to operationalize the Commission's definition of obesity-related organ dysfunction as comprehensively as possible, leveraging all available data sources, in line with prior literature using UK Biobank data [37].

Assessment of exposures

Biochemical markers, including glucose, triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C), were measured from peripheral blood samples collected at baseline by the UK Biobank. These samples were obtained randomly, with informed consent from participants, processed by separating the components, and stored at − 80 °C. All assays were performed using a Beckman Coulter AU5800 automated chemistry analyzer at the UK Biobank central laboratory. Glucose and TG levels were determined enzymatically, and the results were reported in mmol/L. The detailed protocols for sample collection, processing, and quality control procedures are available via the UK Biobank online showcase (https://biobank.ndph.ox.ac.uk/showcase/refer.cgi?id=1227) and have been comprehensively described in earlier publications [36, 38].

For the calculation of the IR-related indices [14, 17, 34], the TyG index was derived using the formula TyG = ln [TG (mg/dL) × glucose (mg/dL) / 2]. The TyG-BMI was then computed by multiplying the TyG index by body mass index (BMI), as represented by TyG-BMI = TyG × [weight (kg) / height^2 (m^2)]. The TyG-WC was calculated by multiplying the TyG index by waist circumference (WC), i.e., TyG-WC = TyG × WC (cm). Lastly, the TyG-WHtR was derived by multiplying the TyG index by the ratio of waist circumference to height, or TyG-WHtR = TyG × [WC (cm) / height (cm)].

Assessment of potential mediating biomarkers

For this study, blood biomarkers were selected based on well-established biological pathways and validated through rigorous quality control procedures to evaluate their role in mediating the relationship between IR-related indices and cardiovascular outcomes [14, 30–35]. These biomarkers included markers of inflammation (C-reactive protein [CRP], white blood cell count [WBC], and counts for neutrophils, monocytes, lymphocytes, and platelets), liver function (alanine aminotransferase [ALT], alkaline phosphatase [ALP], aspartate aminotransferase [AST], gamma-glutamyltransferase [GGT], total bilirubin, total protein, and albumin), and renal function (cystatin C, creatinine, urate, and urea).

Assessment of outcomes

This study's primary outcome was the incidence of total CVD, comprising CAD and stroke, among individuals with preclinical or clinical obesity. Participants without CVD at baseline were prospectively followed from their initial assessment until the first occurrence of CAD or stroke, death, or the end of follow-up (November 30, 2022), whichever came first. CVD events were identified through linkage with hospital inpatient data, primary care records, and national mortality registries [28]. Diagnostic coding followed the ICD-10 system, with I20-I25 denoting CAD and I60-I64 for stroke [28]. Mortality information was sourced from the National Health Service (NHS) death registry.

Assessment of genetic risk

Blood samples were collected from participants for genotyping. The complete procedures for whole-genome genotyping and quality control have been described in detail previously [39]. Genotyping was conducted using either the UK Lung Exome Variant Evaluation (UK BiLEVE) array or the UK Biobank Axiom Array. PRS

obtained from the "Standard PRS" (Category 301) in the UK Biobank were used to quantify the genetic risk of each participant (https://biobank.ndph.ox.ac.uk/showcase/label.cgi?id=301). In line with prior publications [40], standard PRS for total CVD (Field ID: 26223), CAD (Field ID: 26227), and stroke (Field ID: 26248) were employed, all of which are derived from aggregated data across multiple external genome-wide association studies (GWAS). The UK Biobank team has released standard PRS for 53 diseases and quantitative traits, demonstrating strong capacity for risk stratification [41]. PRS were calculated using a Bayesian framework that integrates data across diverse ancestries and related traits, with adjustments for age, sex, and ancestry principal components [41]. Individuals with higher PRS tend to exhibit a greater genetic risk for developing diseases [27, 41]. Participants in this study were categorized into low, intermediate, and high genetic risk groups based on PRS tertiles.

Covariates

Variables associated with IR indices or CVD were included as potential covariates [14, 17, 18, 34]. These comprised sociodemographic factors: age (continuous, in years), sex, ethnicity (White vs. non-White), Townsend Deprivation Index (TDI; continuous, with higher scores indicating greater deprivation), employment status (employed vs. non-employed), educational attainment (college degree or above vs. others), and household income (<£18,000; £18,000–£51,999; ≥£52,000). Lifestyle factors included smoking status (never, ever, current), physical activity (adequate vs. inadequate), alcohol consumption frequency (never, 1–3 times/month, 1–2 times/week, 3–4 times/week, daily or almost daily), sleep duration (< 7, 7–8, or >8 h/day), and diet quality score (continuous). Biological variables encompassed systolic and diastolic blood pressure (SBP and DBP, continuous, mmHg) and glycated hemoglobin (HbA1c, continuous, mmol/mol). Self-reported histories of hypertension and diabetes, as well as the use of antihypertensive, hypoglycemic, and lipid-lowering medications, were also included. Adequate physical activity was defined as ≥ 75 min/week of vigorous activity, ≥ 150 min/week of moderate activity, or an equivalent combination [42]. The diet quality score was derived from seven dietary components, with higher scores indicating better dietary quality [42]. To maximize sample size, missing covariate values were imputed using a multiple imputation strategy based on random forest algorithms. Most of the covariates had missing rates below 5% (Table S1), which is generally considered acceptable for multiple imputation procedures [43].

Statistical analysis

Descriptive statistics

To describe the baseline profile, baseline characteristics of participants were summarized using descriptive statistics, stratified by TyG index quartiles (Quartiles, Q1–Q4) and by baseline obesity status (preclinical or clinical obesity). Continuous variables were expressed as mean (standard deviation, SD) for normally distributed data or median (interquartile range, IQR) for non-normal distributions. Categorical variables were presented as counts and proportions. Between-group comparisons were conducted using independent t-tests for normally distributed data, Kruskal-Wallis tests for skewed data, and Pearson's chi-square tests for categorical comparisons.

Primary association analyses

To assess the relationship between IR-related indices and cardiovascular outcomes, Cox proportional hazards models, with follow-up time as the time scale, were employed to examine associations between IR-related indices and the incidence of CVD, CAD, and stroke in participants with preclinical or clinical obesity. The proportional hazards assumption was assessed using Schoenfeld residuals, and no violations were detected in the Cox models for our primary exposures (all P >0.05; Table S2) [44]. Each IR-related index (TyG, TyG-BMI, TyG-WC, and TyG-WHtR) was analyzed in a separate model. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated per SD increase in continuous IR-related indices, as well as across quartiles (Q2–Q4), using Q1 as the reference. Three models were fitted: Model 0, which was unadjusted for covariates; Model 1, which adjusted for sociodemographic and lifestyle variables; and Model 2, which further adjusted for SBP, DBP, HbA1c, histories of hypertension and diabetes, relevant medication use (antihypertensive, hypoglycemic, lipid-lowering), and corresponding PRS. Besides, Kaplan-Meier (KM) survival curves, stratified by IR index quartiles, were plotted to assess cumulative CVD incidence and compared using log-rank tests. Restricted cubic spline (RCS) models based on Model 2 were used to assess dose-response relationships [45]. P values for the overall associations and tests of non-linearity in the RCS models were calculated using the log-likelihood ratio test [45]. If nonlinearity was observed, threshold values were determined by testing a range of possible values and selecting the one with the highest likelihood. Subsequently, two-piecewise Cox proportional hazard models were constructed on either side of the threshold for each TyG-related index to evaluate their associations with outcomes [15, 17].

Incremental predictive value

To evaluate whether IR-related indices provide added prognostic information, we constructed two comparative models following prior work [18, 46, 47]: a basic model and a novel model. The basic model incorporated adjusted risk factors from Model 2. The novel model expanded upon this by including the same variables plus IR-related indices—namely, TyG, TyG-BMI, TyG-WC, and TyG-WHtR. The incremental predictive value of the novel model was assessed using the net reclassification index (NRI) and integrated discrimination improvement (IDI), which quantified whether the novel model provided improved risk stratification [48]. In general, higher positive IDI values indicate greater average improvement in sensitivity, and an NRI >0 suggests enhanced risk reclassification; values around or above 0.1 are often interpreted as reflecting a clinically meaningful gain, though no absolute thresholds are universally endorsed [48]. To further validate the added value of the TyG-related indices, we conducted calibration curve analysis.

Joint association and interaction analyses

To explore the combined effects of genetic risk and IR-related indices, we examined the joint associations of IR-related indices and genetic risk categories with incident CVD, CAD, and stroke by constructing twelve unique exposure combinations, using participants with both low genetic risk and IR-related indices in Q1 as the reference group. Additionally, stratified analyses were performed to estimate the associations between IR-related indices and outcomes within different genetic risk categories. To assess potential effect modification by genetic risk, multiplicative interaction terms between IR indices and genetic risk were included in Cox models adjusted for Model 2 covariates [49]. The significance of these interactions was evaluated using the likelihood ratio test [49]. Furthermore, additive interactions were assessed by calculating the relative excess risk due to interaction (RERI), the attributable proportion due to interaction (AP), and the synergy index (SI) [49]. Evidence of additive interaction was indicated when the 95% confidence interval (CI) for RERI or AP excluded 0, or when the CI for SI excluded 1 [49].

Mediation analyses

To identify potential biological pathways linking IR-related indices and CVD risk, we conducted mediation analyses using the IR-related index that demonstrated the strongest predictive performance [34]. Consistent with previous studies [33, 34], we applied a two-step modeling approach to identify potential mediators. First, multivariable-adjusted linear regression models were used to assess the associations between the primary exposure and selected biomarkers. Second, multivariable-adjusted Cox proportional hazards models were employed to evaluate the associations between these biomarkers and incident CVD. Both models adjusted for covariates in Model 2. Biomarkers that were statistically significant and exhibited consistent effect directions in both models were considered potential mediators [50]. In line with prior research [50], mediation analyses were conducted using the *CMAverse* R package (https://bs1125.github.io/CMAverse/), which provides a standardized and reproducible counterfactual-based framework [51]. A regression-based approach under the Cox proportional hazards model was applied to estimate the total effect (TE), natural direct effect (DE), natural indirect effect (IE), and the proportion mediated (PM), with all effects expressed on the HR scale [51]. Non-parametric bootstrapping with 1000 resamples was used to obtain 95% CIs and *P* values. The TE represents the overall effect of the IR-related index on cardiovascular outcomes. The DE reflects the effect of the IR-related index on the outcome not operating through the mediator, while the IE quantifies the effect transmitted through the mediator. On the multiplicative scale, the effects satisfy $HR_{TE} \approx HR_{DE} \times HR_{IE}$ [50]. The PM was estimated as $HR_{DE} \times (HR_{IE} - 1)/(HR_{DE} \times HR_{IE} - 1)$ [50]. The PM is considered interpretable only when DE and IE point in the same direction [50]. Compared with the commonly used *Mediation* package, which is based on accelerated failure time models, the *CMAverse* package supports Cox regression-based mediation analyses and is therefore more suitable for this study [51]. All biomarker data were standardized prior to formal analysis.

Sensitivity and subgroup analyses

Several additional analyses were performed to evaluate the robustness of the observed associations. First, we reran the association analyses separately in preclinical or clinical obese populations. Second, to reduce potential reverse causation, participants who developed the study outcomes within the first two years of follow-up were excluded. Third, analyses were repeated after removing individuals with missing covariate data. Fourth, to address potential bias from competing risks of non-CVD-related deaths, we re-estimated associations using a competing risk model. Fifth, to address potential collinearity between exposures and the study population, we regressed the TyG index on each obesity indicator (BMI, WC, or WHtR) to obtain residuals, and subsequently assessed the association with CVD outcomes. Sixth, based on classification by tertiles or quintiles of TyG-related indices, association analyses were repeated. Furthermore, subgroup analyses were conducted stratified by age (<60 vs. ≥60 years), sex (female vs. male), smoking status (never vs. ever/current smoking), physical activity

(adequate vs. inadequate), and drinking frequency (< 3 times/week vs. ≥3 times/week).

All statistical analyses were performed using R software version 4.4.0 (R Foundation for Statistical Computing). Statistical significance was defined as a Benjamini-Hochberg false discovery rate (FDR)-corrected $P < 0.05$ for multiple comparisons, including biomarker analyses and indices-outcome association analyses, and two-sided $P < 0.05$ for other analyses.

Results

Baseline characteristics of the study population

Table 1 presents the baseline characteristics of 112,866 participants (median age (IQR): 58.0 (51.0, 63.0) years; 60.7% female) with preclinical or clinical obesity, stratified by quartiles of the TyG index. Compared to participants in the lower TyG index (Q1) group, those in the Q4 group were more likely to be male, unemployed, less educated, have a lower household income, live in socioeconomically deprived areas, be current smokers, be physically inactive, have unhealthy sleep durations, and be more likely to take glucose-lowering, antihypertensive, and lipid-lowering medications. Furthermore, they were more likely to have hypertension and diabetes at baseline, as well as develop CVD, CAD, and stroke during follow-up, and to have higher baseline levels of SBP, DBP, and HbA1c (all $P < 0.001$). Similar trends were observed in the baseline characterization stratified by obesity status (Table S3).

Associations between IR-related indices and incident CVD, CAD, and stroke

During a median follow-up of 13.45 years (IQR: 12.50–14.30), 21,601 (19.1%) incident CVD cases were recorded, including 11,942 (10.6%) cases of CAD and 3347 (3.0%) strokes. The KM curves indicated a significantly higher cumulative hazard of incident total CVD among participants in the highest quartile of the IR-related indices (e.g., TyG, TyG-BMI, TyG-WC, and TyG-WHtR) (all log-rank P values < 0.001; Fig. 2). Table 2 presents the associations between IR-related indices and the risk of incident overall CVD and its subtypes in patients with preclinical or clinical obesity. After full adjustment for covariates, each SD increase in the TyG index was associated with an 18% higher risk of CAD (HR = 1.06, 95% CI 1.04–1.08), while no statistically significant associations were observed for overall CVD and stroke. Compared with the lowest quartile (Q1), participants in the highest TyG quartile (Q4) had HRs of 0.98 (95% CI 0.94–1.02) for overall CVD, 1.18 (95% CI 1.11–1.24) for CAD, and 0.97 (95% CI 0.87–1.07) for stroke. Similar, but more pronounced, positive associations were observed for TyG-BMI, TyG-WC, and TyG-WHtR. In fully adjusted models, the HRs for overall CVD in the highest versus lowest quartile were 1.33 (95% CI 1.28–1.39) for TyG-BMI, 1.41 (95% CI 1.34–1.48) for TyG-WC, and 1.25 (95% CI 1.20–1.31) for TyG-WHtR (all FDR-corrected $P < 0.05$). For incident CAD, the HRs (95% CIs) for the fourth quartile versus the first quartile were 1.29 (95% CI 1.22–1.36) for TyG-BMI, 1.47 (95% CI 1.37–1.57) for TyG-WC, and 1.37 (95% CI 1.29–1.45) for TyG-WHtR (all FDR-corrected $P < 0.05$). A borderline significant positive association was observed for incident stroke, with HRs of 1.04 (95% CI 0.94–1.16), 1.12 (95% CI 0.99–1.26), and 1.14 (95% CI 1.02–1.27) for the fourth quartile versus the first quartile of TyG-BMI, TyG-WC, and TyG-WHtR, respectively. For each SD increase in these indices, a higher CAD risk was associated—HRs of 1.09 (95% CI 1.07–1.12) for TyG-BMI, 1.13 (95% CI 1.11–1.16) for TyG-WC, and 1.12 (95% CI 1.10–1.14) for TyG-WHtR (all FDR-corrected $P < 0.05$). Modestly elevated stroke risk was also noted, with HRs of 1.03 (95% CI 0.99–1.07), 1.06 (95% CI 1.01–1.10), and 1.06 (95% CI 1.02–1.10), respectively. When the study population was further categorized into preclinical or clinical obesity, we found similar patterns of associations (Tables S4 and S5). Overall, IR-related metrics were significantly associated with total CVD and CAD incidence in patients with preclinical or clinical obesity.

In Fig. 3, the RCS analysis reveals dose-response relationships between IR-related indices and the risks of total CVD, CAD, and stroke. In line with prior association analysis, no significant overall relationship was found between the TyG index and study outcomes ($P > 0.05$ for overall association; Fig. 3A, E and I). Except TyG-WC, which showed a linear association with total CVD (P for non-linearity > 0.05; Fig. 3C), both TyG-BMI and TyG-WHtR exhibited a significant nonlinear dose-response relationship with total CVD (P for non-linearity < 0.001; Fig. 3B and D). An L-shaped dose-response relationship between these metrics and CAD was also observed (P for non-linearity < 0.05; Fig. 3F, G, and H). In contrast, TyG-WC and TyG-WHtR exhibited more linear relationships with stroke, with non-linearity P-values > 0.05 (Fig. 3K and L). To account for the nonlinear relationships, we employed two-segmented Cox regression models stratified by the inflection points (Table S6). Both TyG-BMI (Inflection point = 307.41) and TyG-WHtR (6.00) were positively associated with CVD risk at either side of the inflection points. When these indices exceeded their respective inflection points, the association with CVD risk became steeper, and the risk increased more rapidly. Conversely, when the indices were below the threshold values, the risk increased more gradually, with the curve being flatter. Inflection points for TyG-BMI, TyG-WC, and TyG-WHtR were also identified for incident CAD. Overall, except for TyG-WC, which showed a linear association with total CVD, all other IR-related indices (TyG-BMI, TyG-WC, and TyG-WHtR) exhibited significant

Table 1 Baseline characteristics of included population stratified by baseline TyG level

Characteristics	Total population	TyG index				*P* value
		Quantile 1	Quantile 2	Quantile 3	Quantile 4	
n	112,866	28,217	28,215	28,217	28,217	
Age, years	58.0 (51.0, 63.0)	57.0 (49.0, 63.0)	59.0 (52.0, 64.0)	59.0 (52.0, 64.0)	59.0 (52.0, 63.0)	< 0.001
Sex						< 0.001
Female	68,498 (60.7)	20,099 (71.2)	18,309 (64.9)	16,558 (58.7)	13,532 (48.0)	
Male	44,368 (39.3)	8118 (28.8)	9906 (35.1)	11,659 (41.3)	14,685 (52.0)	
Ethnicity						< 0.001
Whites	106,062 (94.0)	25,421 (90.1)	26,781 (94.9)	26,960 (95.5)	26,900 (95.3)	
Non-Whites	6804 (6.0)	2796 (9.9)	1434 (5.1)	1257 (4.5)	1317 (4.7)	
Employment						< 0.001
Yes	102,213 (90.6)	25,658 (90.9)	25,802 (91.4)	25,652 (90.9)	25,101 (89.0)	
No	10,653 (9.4)	2559 (9.1)	2413 (8.6)	2565 (9.1)	3116 (11.0)	
Educational level						< 0.001
University or college	30,023 (26.6)	8089 (28.7)	7583 (26.9)	7336 (26.0)	7015 (24.9)	
Others	82,843 (73.4)	20,128 (71.3)	20,632 (73.1)	20,881 (74.0)	21,202 (75.1)	
TDI	− 1.9 (− 3.5, 1.0)	− 1.7 (− 3.4, 1.3)	− 2.0 (− 3.5, 0.9)	− 1.9 (− 3.5, 0.8)	− 1.8 (− 3.4, 1.1)	< 0.001
Family income						< 0.001
Low	32,399 (28.7)	7470 (26.5)	7952 (28.2)	8395 (29.8)	8582 (30.4)	
Middle	57,945 (51.3)	14,606 (51.8)	14,626 (51.8)	14,374 (50.9)	14,339 (50.8)	
High	22,522 (20.0)	6141 (21.8)	5637 (20.0)	5448 (19.3)	5296 (18.8)	
Physical activity						< 0.001
Inadequate	43,046 (38.1)	10,313 (36.5)	10,668 (37.8)	10,900 (38.6)	11,165 (39.6)	
Adequate	69,820 (61.9)	17,904 (63.5)	17,547 (62.2)	17,317 (61.4)	17,052 (60.4)	
Smoking status						< 0.001
Never smoking	58,436 (51.8)	15,752 (55.8)	14,934 (52.9)	14,287 (50.6)	13,463 (47.7)	
Ever smoking	43,076 (38.2)	10,151 (36.0)	10,694 (37.9)	11,016 (39.0)	11,215 (39.7)	
Current smoking	11,354 (10.1)	2314 (8.2)	2587 (9.2)	2914 (10.3)	3539 (12.5)	
Drinking status						0.012
Never	27,675 (24.5)	6875 (24.4)	6811 (24.1)	6825 (24.2)	7164 (25.4)	
1–3 times/month	14,598 (12.9)	3639 (12.9)	3661 (13.0)	3644 (12.9)	3654 (12.9)	
1–2 times/week	29,126 (25.8)	7248 (25.7)	7303 (25.9)	7366 (26.1)	7209 (25.5)	
3–4 times/week	22,112 (19.6)	5600 (19.8)	5651 (20.0)	5536 (19.6)	5325 (18.9)	
Daily or almost daily	19,355 (17.1)	4855 (17.2)	4789 (17.0)	4846 (17.2)	4865 (17.2)	
Sleeping duration						< 0.001
< 7 h/day	30,838 (27.3)	7893 (28.0)	7600 (26.9)	7539 (26.7)	7806 (27.7)	
7–8 h/day	71,841 (63.7)	18,088 (64.1)	18,199 (64.5)	18,083 (64.1)	17,471 (61.9)	
> 8 h/day	10,187 (9.0)	2236 (7.9)	2416 (8.6)	2595 (9.2)	2940 (10.4)	
Healthy diet score	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	< 0.001
SBP, mmHg	140.0 (129.0, 152.5)	137.0 (126.0, 150.0)	140.0 (129.0, 152.5)	141.0 (130.5, 153.5)	142.5 (131.5, 154.5)	< 0.001
DBP, mmHg	85.5 (79.0, 92.0)	84.5 (78.0, 91.0)	85.5 (79.0, 91.5)	85.5 (79.5, 92.0)	86.0 (79.5, 92.5)	< 0.001
HbA1C, mmol/mol	36.3 (33.7, 39.4)	35.2 (32.8, 37.8)	36.0 (33.5, 38.7)	36.6 (34.1, 39.5)	38.0 (34.9, 43.0)	< 0.001
Self-reported disease history						
Hypertension	43,991 (39.0)	9346 (33.1)	10,751 (38.1)	11,344 (40.2)	12,550 (44.5)	< 0.001
Diabetes	10,102 (9.0)	1326 (4.7)	1600 (5.7)	2284 (8.1)	4892 (17.3)	< 0.001
Use of medications						
Antihypertensive	34,499 (30.6)	6964 (24.7)	8223 (29.1)	8920 (31.6)	10,392 (36.8)	< 0.001
Antidiabetics	7151 (6.3)	904 (3.2)	1037 (3.7)	1527 (5.4)	3683 (13.1)	< 0.001
Lipid-lowering	23,680 (21.0)	4332 (15.4)	5235 (18.6)	6023 (21.3)	8090 (28.7)	< 0.001
CVD incidence	21,601 (19.1)	4636 (16.4)	5092 (18.0)	5622 (19.9)	6251 (22.2)	< 0.001
CAD incidence	11,942 (10.6)	2278 (8.1)	2692 (9.5)	3139 (11.1)	3833 (13.6)	< 0.001
Stroke incidence	3347 (3.0)	730 (2.6)	752 (2.7)	876 (3.1)	989 (3.5)	< 0.001

Data are presented as median (interquartile range) for continue variables and count (%) for categorical variables. TyG: triglyceride-glucose index; TDI: Townsend deprivation index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HbA1c: glycated hemoglobin; CVD: cardiovascular disease; CAD: coronary artery disease

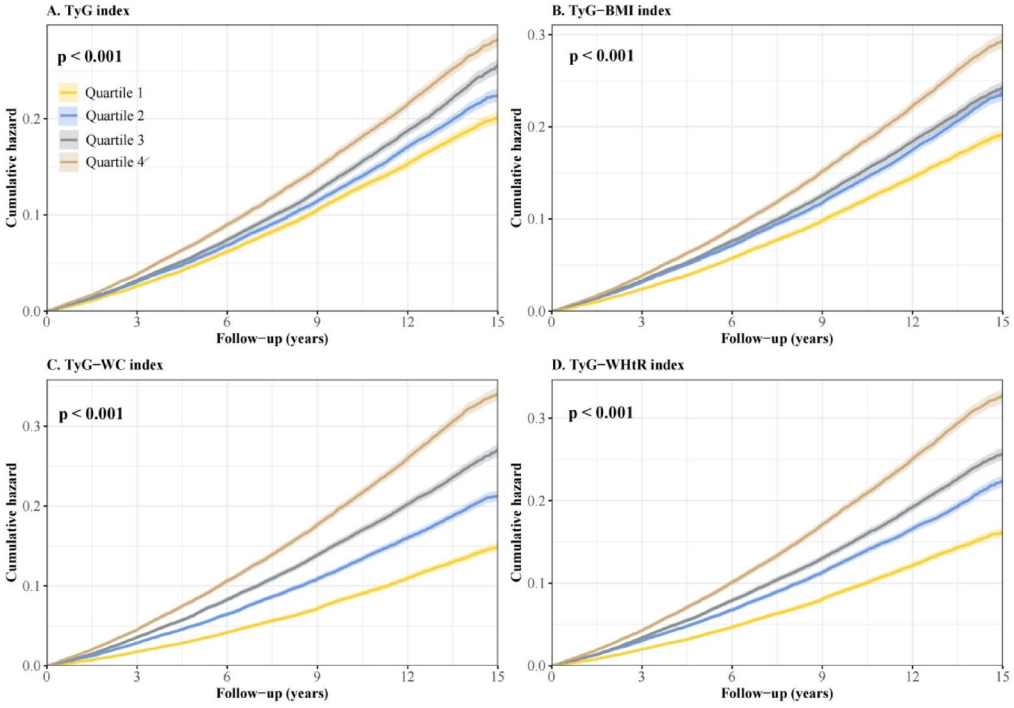


Fig. 2 Cumulative hazard of incident overall cardiovascular disease in individuals with preclinical or clinical obesity according to quantiles of TyG index. *Curves estimated from Cox proportional hazards models*
Abbreviations: TyG: triglyceride-glucose index; BMI: body mass index; WC: waist circumference; WHtR: weight-to-height ratio

non-linear dose-response relationships with total CVD and CAD.

Incremental predictive values of IR-related indices

We further assessed whether the addition of IR-related indicators to the basic model (Model 2) would enhance the predictive performance for the risks of incident CVD, CAD, and stroke. As shown in Table 3, incorporating these indicators significantly improved both IDI and NRI for the study outcomes, except for the TyG index in the CVD and stroke models. For total CVD incidence, the TyG-WC index provided the highest incremental predictive values [NRI: 6.510 (95% CI 5.616–7.269); IDI: 0.309 (95% CI 0.229–0.391)], followed by TyG-BMI [NRI: 5.748 (95% CI 4.928–6.633); IDI: 0.326 (95% CI 0.254–0.406)], and TyG-WHtR [NRI: 5.059 (95% CI 4.207–5.910); IDI: 0.210 (95% CI 0.152–0.277)]. For incident CAD, TyG-WC again exhibited the highest values [NRI: 6.148 (95% CI 5.172–7.208); IDI: 0.140 (95% CI 0.102–0.209)], followed by TyG-WHtR [NRI: 5.771 (95% CI 4.774–6.792); IDI: 0.139 (95% CI 0.092–0.190)], and TyG-BMI [NRI: 4.931 (95% CI 3.797–5.795); IDI: 0.099 (95% CI 0.059–0.143)]. Consistent findings were observed in the incident stroke model, where the TyG-WC index outperformed other indices. The calibration curve analysis further confirmed the incremental values of these indices (Fig. S1). Together, the addition of IR-related indices, especially TyG-WC, substantially improved risk prediction beyond conventional models, particularly for CVD and CAD.

Joint effects of IR-related indices and genetic risk on cardiovascular outcomes

Combining IR-related indices and genetic risk, quantified by PRS, we divided the study population into 12 groups. The joint associations of IR-related indices and genetic risk with CVD incidence exhibited a dose-response relationship (Fig. 4). Specifically, compared with participants in the Q1 of these indices and low genetic risk, those in the Q4 of these indices and high genetic risk had the highest risk of incident total CVD [TyG index: HR = 1.31 (95% CI 1.23–1.40); TyG-BMI: HR = 1.80 (95% CI 1.68–1.93); TyG-WC: HR = 1.88 (95% CI 1.74–2.03); and TyG-WHtR: HR = 1.63 (95% CI 1.52–1.75)]. Similar joint effects were observed for incident CAD and stroke outcomes (Figs. S2 and S3). Further analyses, stratified by genetic risk levels, showed that the associations between IR-related indices and the risk of CVD, CAD, and stroke were similar across genetic risk groups, with no significant multiplicative interactions (Table S7; all *P* for interaction > 0.05). In addition, the RERI, AP, and SI were statistically significant, indicating positive additive interactions between the TyG-WC index and genetic risk for CVD incidence (Table S8). Specifically, for individuals with a high TyG-WC index with high genetic risk, the RERI was 0.101

Table 2 Association between insulin resistance-related indices and risk of cardiovascular disease in individuals with preclinical or clinical obesity

Exposure	Total CVD				CAD				Stroke			
	Incidence rate	Model 0	Model 1	Model 2	Incidence rate	Model 0	Model 1	Model 2	Incidence rate	Model 0	Model 1	Model 2
Total CVD												
TyG index												
Each 1-SD increase		1.16 (1.14–1.17)**	1.06 (1.04–1.07)**	1.00 (0.99–1.02)		1.25 (1.23–1.27)**	1.15 (1.13–1.17)**	1.06 (1.04–1.08)**		1.17 (1.13–1.21)**	1.09 (1.05–1.13)**	1.02 (0.98–1.06)
Quartile 1	13.11	Reference	Reference	Reference	6.23	Reference	Reference	Reference	1.95	Reference	Reference	Reference
Quartile 2	14.56	1.11 (1.07–1.16)**	0.98 (0.94–1.02)	0.96 (0.92-1.00)	7.43	1.19 (1.13–1.26)**	1.07 (1.01–1.13)*	1.05 (0.99–1.11)	2.01	1.03 (0.93–1.14)	0.91 (0.82–1.01)	0.89 (0.80–0.98)
Quartile 3	16.2	1.24 (1.19–1.29)**	1.02 (0.98–1.06)	0.98 (0.94–1.02)	8.73	1.40 (1.33–1.48)**	1.18 (1.11–1.24)**	1.12 (1.06–1.18)**	2.35	1.21 (1.10–1.33) **	1.01 (0.91–1.11)	0.96 (0.87–1.06)
Quartile 4	18.34	1.41 (1.35–1.46)**	1.10 (1.06–1.15)**	0.98 (0.94–1.02)	10.86	1.75 (1.66–1.84)**	1.37 (1.30–1.45)**	1.18 (1.11–1.24)**	2.67	1.37 (1.25–1.51)**	1.11 (1.01–1.23)*	0.97 (0.87–1.07)
TyG-BMI index												
Each 1-SD increase		1.17 (1.16–1.19)**	1.20 (1.19–1.22)**	1.14 (1.13–1.16)**		1.18 (1.17–1.20)**	1.18 (1.16–1.20)**	1.09 (1.07–1.12)**		1.08 (1.05–1.12)**	1.11 (1.07–1.15)**	1.03 (0.99–1.07)
Quartile 1	12.42	Reference	Reference	Reference	6.17	Reference	Reference	Reference	2.04	Reference	Reference	Reference
Quartile 2	15.14	1.22 (1.17–1.27)**	1.12 (1.08–1.17)**	1.09 (1.04–1.13)**	8.12	1.32 (1.25–1.39)**	1.18 (1.12–1.25)**	1.14 (1.07–1.20)**	2.26	1.11 (1.01–1.23)*	1.04 (0.95–1.15)	1.00 (0.91–1.11)
Quartile 3	15.71	1.27 (1.22–1.32)**	1.18 (1.13–1.22)**	1.10 (1.06–1.15)**	8.68	1.41 (1.34–1.49)**	1.25 (1.19–1.33)**	1.15 (1.09–1.22)**	2.2	1.08 (0.98–1.19)	1.04 (0.94–1.15)	0.96 (0.86–1.06)
Quartile 4	18.96	1.54 (1.48–1.60)**	1.52 (1.46–1.58)**	1.33 (1.28–1.39)**	10.24	1.67 (1.58–1.76)**	1.54 (1.46–1.63)**	1.29 (1.22–1.36)**	2.47	1.22 (1.10–1.34)**	1.25 (1.13–1.38)**	1.04 (0.94–1.16)
TyG-WC												
Each 1-SD increase		1.35 (1.33–1.36)**	1.23 (1.21–1.25)**	1.16 (1.14–1.18)**		1.39 (1.37–1.42)**	1.24 (1.21–1.26)**	1.13 (1.11–1.16)**		1.23 (1.19–1.27)**	1.15 (1.11–1.20)**	1.06 (1.01–1.10)
Quartile 1	9.57	Reference	Reference	Reference	4.53	Reference	Reference	Reference	1.61	Reference	Reference	Reference
Quartile 2	13.77	1.45 (1.39–1.51)**	1.20 (1.14–1.25)**	1.15 (1.10–1.20)**	7.1	1.57 (1.48–1.67)**	1.28 (1.20–1.36)**	1.21 (1.14–1.29)**	2.15	1.34 (1.21–1.49)**	1.13 (1.02–1.26)*	1.07 (0.96–1.20)
Quartile 3	17.28	1.82 (1.75–1.90)**	1.32 (1.26–1.38)**	1.22 (1.17–1.28)**	9.38	2.08 (1.96–2.20)**	1.44 (1.35–1.53)**	1.31 (1.22–1.40)**	2.36	1.48 (1.33–1.64)**	1.13 (1.01–1.27)*	1.03 (0.92–1.16)
Quartile 4	22.08	2.34 (2.25–2.44)**	1.64 (1.56–1.72)**	1.41 (1.34–1.48)**	12.42	2.76 (2.61–2.92)**	1.80 (1.68–1.92)**	1.47 (1.37–1.57)**	2.87	1.80 (1.63–1.99)**	1.37 (1.22–1.54)**	1.12 (0.99–1.26)
TyG_WHtR												
Each 1-SD increase		1.29 (1.28–1.31)**	1.19 (1.17–1.20)**	1.12 (1.10–1.13)**		1.34 (1.32–1.36)**	1.22 (1.20–1.24)**	1.12 (1.10–1.14)**		1.24 (1.20–1.28)**	1.15 (1.11–1.19)**	1.06 (1.02–1.10)*
Quartile 1	10.49	Reference	Reference	Reference	4.89	Reference	Reference	Reference	1.57	Reference	Reference	Reference
Quartile 2	14.27	1.37 (1.31–1.43)**	1.09 (1.04–1.13)**	1.05 (1.01–1.10)**	7.5	1.54 (1.45–1.63)**	1.22 (1.15–1.29)**	1.17 (1.11–1.25)**	2.13	1.36 (1.22–1.51)**	1.11 (0.99–1.23)	1.07 (0.96–1.19)

Table 2 (continued)

Exposure	Total CVD				CAD				Stroke			
	Incidence rate	Model 0	Model 1	Model 2	Incidence rate	Model 0	Model 1	Model 2	Incidence rate	Model 0	Model 1	Model 2
Total CVD												
Quartile 3	16.53	1.59 (1.52–1.65)**	1.16 (1.11–1.21)**	1.08 (1.04–1.13)**	9.15	1.88 (1.78–1.99)**	1.35 (1.27–1.43)**	1.24 (1.17–1.32)**	2.41	1.53 (1.38–1.70)**	1.17 (1.05–1.30)**	1.07 (0.97–1.20)
Quartile 4	21.23	2.05 (1.97–2.13)**	1.45 (1.39–1.51)**	1.25 (1.20–1.31)**	11.84	2.44 (2.31–2.58)**	1.67 (1.57–1.76)**	1.37 (1.29–1.45)**	2.88	1.84 (1.67–2.04)**	1.37 (1.23–1.52)**	1.14 (1.02–1.27)

**FDR-*P* < 0.001, * FDR-*P* < 0.05. Results are shown as HRs with 95% CIs from Cox proportional hazards models, with each index fitted in a separate model. Incidence rates are expressed as cases per 1000 person-years, estimated through descriptive analysis by dividing the number of incident events by the total person-time at risk in the study population. Model 0 were unadjusted model. Model 1 were adjusted for age, sex, ethnicity, employed status, Townsend deprivation index, educational level, family income, smoking status, drinking frequency, sleep duration, physical activity, and diet quality. Model 2 were adjusted for age, sex, ethnicity, employed status, Townsend deprivation index, educational level, family income, smoking status, drinking frequency, sleep duration, physical activity, diet quality, systolic/diastolic blood pressure, glycated hemoglobin, self-reported history of hypertension and diabetes, use of antihypertensive, antidiabetic, lipid-lowering medications, and genetic risk. CVD: cardiovascular disease; CAD: coronary artery disease; HR: hazard ratio; CI: confidence interval; SD: standard deviation; TyG: triglyceride-glucose index; BMI: body mass index; WC: waist circumference; WHtR: weight-to-height ratio; FDR: false discovery rate

(95% CI 0.017–0.180), suggesting a 0.101 relative excess risk due to the additive interaction. Compared to the lowest risk group, the highest risk group (high TyG-WC index + high genetic risk) had a total CVD incidence rate of 25.19 per 1000 person-years, resulting in an absolute risk difference of 17.01 per 1000 person-years (Table S9). For the incidence of CAD, we also found similar additive interactions (Table S8). Overall, all IR-related indices, in combination with genetic risk, had joint effects on CVD risk, with TyG-WC showing the strongest joint effect and a significant additive interaction.

Mediating effects of blood biomarkers

Given that the TyG-WC index exhibited the superior incremental predictive performance for CVD among all IR-related indices, it was selected as the primary exposure for subsequent mediation analyses. As detailed in Table S10, multivariate-adjusted linear regression models revealed that, with the exception for creatinine, the TyG-WC index was significantly linked to all selected biomarkers (all FDR-corrected $P < 0.001$), with adjusted regression coefficients (95% CIs) ranging from −0.108 (− 0.115, − 0.100) for albumin to 0.270 (0.263, 0.276) for urate. The associations of selected biomarkers with incident overall CVD, CAD, and stroke are displayed in Table S11. Multivariate-adjusted Cox regression models indicated that 12 out of 17 selected biomarkers were significantly associated with total CVD occurrence (all FDR-corrected $P < 0.01$), with adjusted HRs (95% CIs) ranged from 0.93 (0.91–0.95) for albumin to 1.12 (1.10–1.13) for cystatin C. Accordingly, a total of 11 biomarkers, significant in both models with the same effect direction, were included in the mediation analyses. These biomarkers, reflecting systemic inflammation (CRP, WBC, neutrophil counts, monocyte counts), liver function (ALP, GGT, total protein, albumin), and kidney (cystatin C, urate, urea) function, demonstrated varying degrees of statistically significance (all $P < 0.001$, Fig. 5). The PM ranged from 1.11% (95% CI 0.67%–1.64%) for monocyte counts to 16.33% (95% CI 14.24%–19.04%) for cystatin C. Regarding incident CAD, we observed consistent mediating patterns (all $P < 0.001$, Fig. 5), with PM ranging from 1.28% (95% CI 0.41%–2.17%) for monocyte counts to 16.87% (95% CI 13.47%–21.88%) for cystatin C. Similar mediating patterns were detected for incident stroke (Fig. 5). Detailed mediation findings for selected biomarkers are summarized in Table S12. Together, systemic inflammation, liver function, and kidney function biomarkers partly mediated the associations between TyG-WC and cardiovascular outcomes, with cystatin C showing the strongest mediating role.

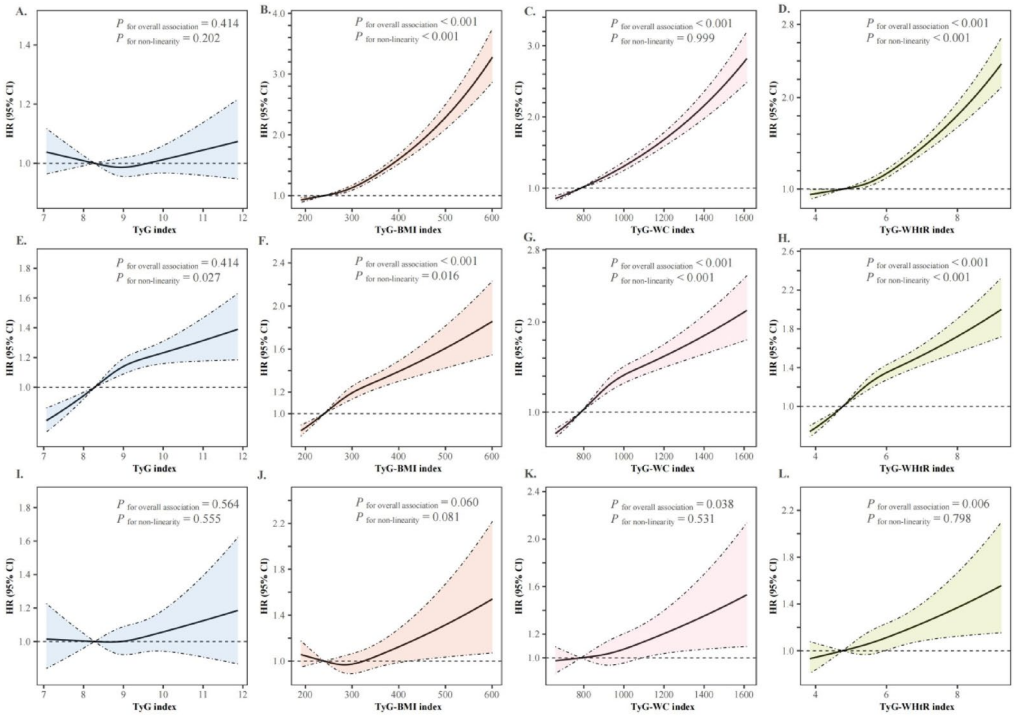


Fig. 3 Dose-response relationship of insulin resistance-related indices with risk of cardiovascular disease in individuals with preclinical or clinical obesity. *Associations were estimated using restricted cubic splines in multivariable Cox proportional hazards models.* **A**–**D** *for overall CVD*, **E**–**H** *for CAD*; **I**–**L** *for stroke*. All models were adjusted for age, sex, ethnicity, employed status, Townsend deprivation index, educational level, family income, smoking status, drinking frequency, sleep duration, physical activity, diet quality, systolic/diastolic blood pressure, glycated hemoglobin, self-reported history of hypertension and diabetes, use of antihypertensive, antidiabetic, lipid-lowering medications, and genetic risk. Abbreviations: CVD: cardiovascular disease; CAD: coronary artery disease; HR: hazard ratio; CI: confidence interval; SD: standard deviation; TyG: triglyceride-glucose index; BMI: body mass index; WC: waist circumference; WHtR: weight-to-height ratio

Table 3 Increment predictive values of insulin resistance-related indices in cardiovascular disease in individuals with preclinical or clinical obesity

	Overall CVD		CAD		Stroke	
	IDI	NRI	IDI	NRI	IDI	NRI
Basic model	Reference	Reference	Reference	Reference	Reference	Reference
Basic model + TyG index	− 0.001 (− 0.004, 0.006)	1.526 (− 1.853–2.304)	0.020 (0.001–0.041)	4.123 (3.070–5.044)	0.001 (− 0.001, 0.009)	2.436 (− 2.288, 3.945)
Basic model + TyG-BMI index	0.326 (0.254–0.406)	5.748 (4.928–6.633)	0.099 (0.059–0.143)	4.931 (3.797–5.795)	0.004 (− 0.000, 0.025)	1.707 (− 1.454, 3.591)
Basic model + TyG-WC index	0.309 (0.229–0.391)	6.510 (5.616–7.269)	0.140 (0.102–0.209)	6.148 (5.172–7.208)	0.007 (0.000-0.030)	3.753 (1.476–5.419)
Basic model + TyG-WHtR index	0.210 (0.152–0.277)	5.059 (4.207–5.910)	0.139 (0.092–0.190)	5.771 (4.774–6.792)	0.014 (0.001–0.037)	2.739 (0.707–4.717)

Results are based on NRI and IDI from multivariable Cox proportional hazards model. Basic models were developed using age, sex, ethnicity, employed status, Townsend deprivation index, educational level, family income, smoking status, drinking frequency, sleep duration, physical activity, diet quality, systolic/diastolic blood pressure, glycated hemoglobin, self-reported history of hypertension and diabetes, and the use of antihypertensive, antidiabetic, lipid-lowering medications. CVD: cardiovascular disease; CAD: coronary artery disease; NRI: net reclassification index, IDI: integrated discrimination improvement index; TyG: triglyceride-glucose index; BMI: body mass index; WC: waist circumference; WHtR: weight-to-height ratio

Sensitivity and subgroup analyses

Several additional analyses were performed to assess the robustness of the associations. Subgroup analyses stratified by age, sex, smoking status, drinking frequency, and physical activity yielded findings consistent with the primary analyses (Figs. S4–S8). Sensitivity analyses also produced similar findings after excluding participants who developed corresponding outcomes within the first two years of follow-up (Fig. S9), excluding those with missing covariate data (Fig. S10), and applying competing hazard models (Fig. S11). In the sensitive analysis using residual-based TyG indices as exposures, the associations with incident CVD remained statistically significant, though with somewhat attenuated effect sizes (Table S13).

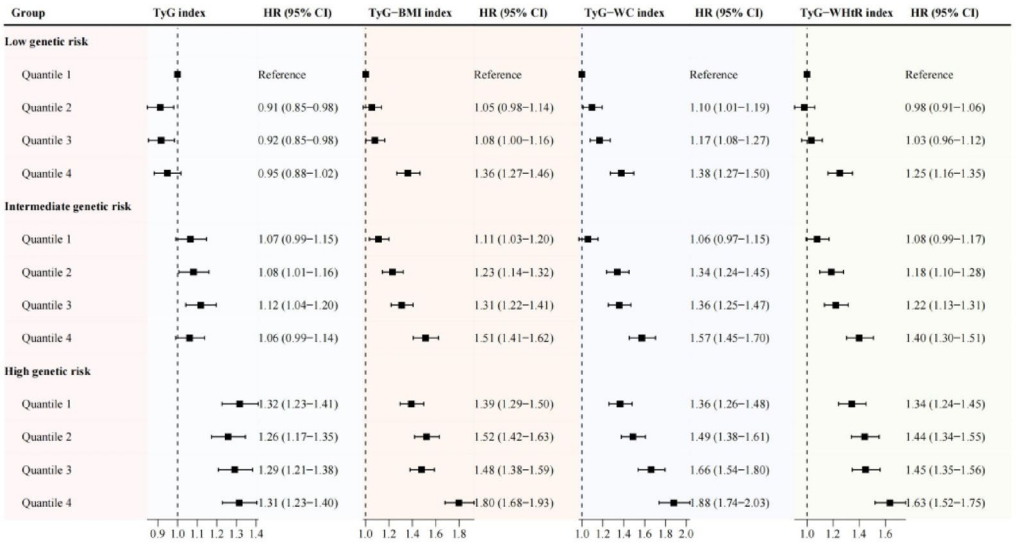


Fig. 4 Joint effect of insulin resistance-related indices and genetic risk with cardiovascular disease in individuals with preclinical or clinical obesity. *HRs with 95% CIs estimated using multivariable Cox proportional hazards models. Models were adjusted for age, sex, ethnicity, employed status, Townsend deprivation index, educational level, family income, smoking status, drinking frequency, sleep duration, physical activity, diet quality, systolic/diastolic blood pressure, glycated hemoglobin, self-reported history of hypertension and diabetes, and use of antihypertensive, antidiabetic, lipid-lowering medications*. Abbreviations: CVD: cardiovascular disease; CAD: coronary artery disease; HR: hazard ratio; CI: confidence interval; SD: standard deviation; TyG: triglyceride-glucose index; BMI: body mass index; WC: waist circumference; WHtR: weight-to-height ratio

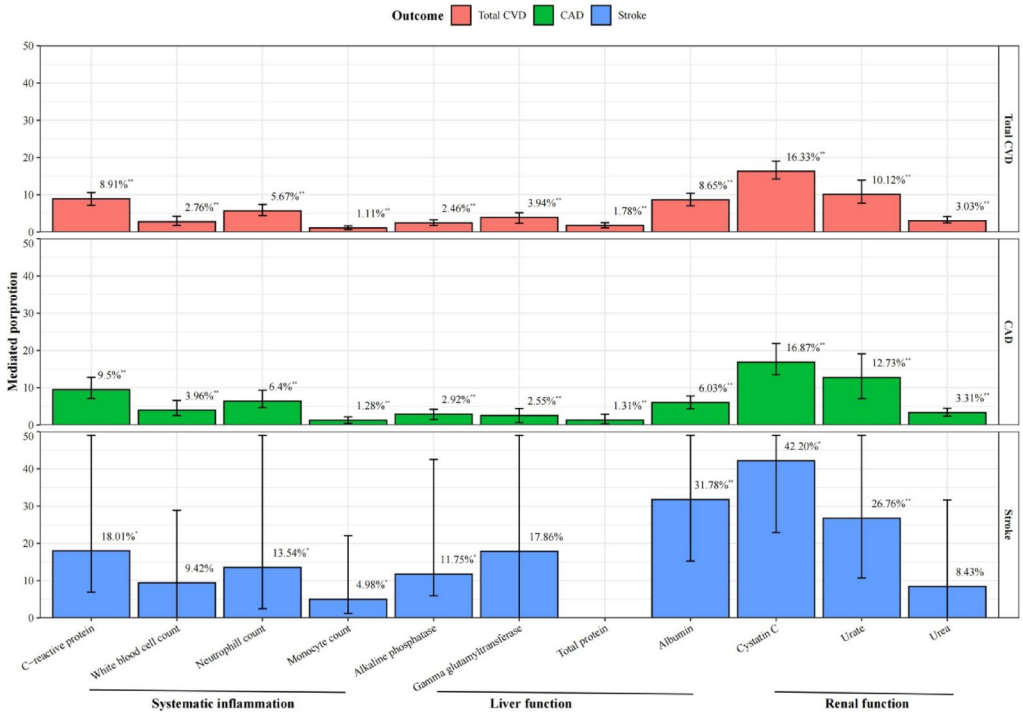


Fig. 5 Mediated proportion by selected biomarkers in the association between the TyG-WC index and risk of cardiovascular disease. *Proportions and confidence intervals were derived from mediation analyses based on multivariable linear regression models and Cox proportional hazards models. Bars represent mediated proportion, with error bars indicating 95% confidence intervals. *P < 0.05; **P < 0.001*. Models were adjusted for age, sex, ethnicity, employed status, Townsend deprivation index, educational level, family income, smoking status, drinking frequency, sleep duration, physical activity, diet quality, systolic/diastolic blood pressure, glycated hemoglobin, self-reported history of hypertension and diabetes, and the use of antihypertensive, antidiabetic, lipid-lowering medications. Abbreviations: CVD: cardiovascular disease; CAD: coronary artery disease; TyG: triglyceride-glucose index; WC: waist circumference

Sensitivity analyses using tertile or quintile categorizations of the exposures yielded similar findings to the primary analysis (Table S14). These consistent results across sensitivity and subgroup analyses reinforced the robustness of our primary findings.

Discussion

Leveraging data from a large prospective cohort with a median follow-up of 13.45 years, this study explored the associations between IR-related indices, specifically TyG, TyG-WC, TyG-WHtR, and TyG-BMI, and the incidence of CVD in 112,866 patients with preclinical or clinical obesity. Except for the TyG index, all IR-related indices were positively associated with an increased risk of incident total CVD. When examining specific CVD subtypes, all elevated IR-related indices were significantly associated with an increased risk of CAD. The robustness of these associations was supported by multiple sensitivity and subgroup analyses. Joint analyses incorporating genetic factors revealed that individuals with both high genetic risk and the highest quartile of these indices had the greatest CVD risk compared to the reference group. As well, our study provided quantitative data indicating that genetic risk interacts in an additive manner with individual IR indices, such as the TyG-WC index, to augment the risk of developing CVD. Notably, incorporating TyG-WC, TyG-WHtR, or TyG-BMI substantially enhanced the prognostic capacity for CVD risk assessment in patients with preclinical or clinical obesity. Of these indices, TyG-WC correlated most strongly with CVD risk with optimal incremental predictive value, where this effect was partially mediated through inflammatory, hepatic, and renal biomarkers.

Increasing studies have indicated that IR-related indices may serve as powerful markers of adverse cardiovascular prognosis in patients with various metabolic diseases [14–18, 47]. For example, Huang et al. found that elevated TyG-related indices were significantly associated with increased CVD risk in hypertensive patients [14]. A prospective cohort study based on 282,920 participants with cardiovascular-kidney-metabolic (CKM) syndrome reported that TyG-related markers were significantly and positively associated with increased risk of future CVD [47]. However, the role of these indices in cardiovascular prognosis in individuals with obesity remains poorly understood. Although several past studies have explored the relationship between IR-related measures and cardiovascular events in obese populations [19–26], several limitations remain to be addressed. First, existing studies on the topic have been conducted in the US or Asian populations [19–26], and the applicability of the findings to European obese populations (e.g., the UK) remains unknown. Second, most of these studies have limitations such as small sample sizes (n = 1028 to 8769) [19–23, 25, 26] or cross-sectional designs [21, 22, 25, 26] that potentially affect the statistical power of the results. Notably, most of these studies have used anthropometric measures [19–22, 25, 26], such as BMI, to define obese patients, but BMI does not take into account fat distribution or body composition, thus limiting its validity in evaluating the hazard of obesity-associated diseases [6]. The *Lancet Diabetes & Endocrinology Commission* recently introduced the concept of preclinical or clinical obesity that potentially ameliorates the limitations of traditional BMI-based categorization [7]. To our knowledge, no study has investigated the associations of IR-associated metrics with incident CVD in preclinical or clinical obese patients. Leveraging a large prospective cohort with a median follow-up of over 13 years, this study, involving more than 100,000 patients with preclinical or clinical obesity, is the first to demonstrate the positive association between IR-related metrics, specifically TyG-WC, TyG-WHtR, and TyG-BMI, and the incidence of CVD. These findings have significant clinical and public health implications, addressing existing knowledge gaps and extending the insights from previous research.

Although the effect of genetic risk on the risk of incident CVD has been described in prior studies [27–29], no study to date has evaluated the joint and interaction effects of genetic factors and IR-related indices on CVD incidence. Our study is the first to integrate genetic risk with IR-related indicators to examine their combined effects and interactions in relation to the risk of developing CVD. We found that individuals with high IR indices faced a similar increased risk of CVD across genetic risk groups, and no significant interactions were observed. Similar to our findings, a prospective study based on the UK Biobank concluded that lower HbA1c levels were associated with a significant reduction in CVD risk regardless of genetic risk [52]. Additionally, this study found that individuals co-exposed to high IR indices and high genetic risk faced the greatest risk of CVD, emphasizing the significance of jointly considering these factors in CVD risk assessment. Specifically, individuals with a high genetic risk of CVD should be more conscious of the dangers of elevated IR-related indices. Supporting our findings, Kim et al. also found that individuals with high glucose levels and high PRS were associated with the greatest risk of cardiovascular outcomes [52]. Similarly, Li et al. observed that participants who were metabolically healthy and at low genetic risk experienced the lowest risk of CVD morbidity compared to participants who were metabolically unhealthy and at high genetic risk [29]. Furthermore, the additive interaction between TyG-WC and genetic risk was identified in the current study. Approximately 10.1 of CVD risk could be explained by the additive effect of co-exposure to high TyG-WC and high genetic risk, meaning that the

combined effects of TyG-WC and genetic risk were much greater than simply adding the two effects together. The absolute risk difference for total CVD between the highest and lowest risk groups is approximately 17 cases per 1000 person-years. From a clinical standpoint, the modest absolute risk difference highlights the importance of considering the combined effect of TyG-WC and genetic risk in the broader context of patient management. While the absolute risk difference might appear small at an individual level, identifying high-risk individuals through this combined index could help clinicians prioritize preventive interventions for those at the greatest risk of CVD. This can lead to more effective targeting of resources and treatment plans, especially for individuals with both high TyG-WC and high genetic risk, who may benefit from early intervention strategies.

Overall, this study provides first-hand evidence that IR-related indices might contribute to the development of CVD in combination with genetic risk in preclinical or clinical obese patients. The integration of the TyG index with anthropometric measures, such as TyG-WC and TyG-WHtR, has consistently demonstrated superior predictive performance for CVD compared to the TyG index alone [12, 18, 34, 47, 53]. Supporting and expanding on previous findings [12, 18, 34, 47, 53], our study observed that incorporating TyG-WC, TyG-WHtR, and TyG-BMI significantly enhanced the incremental predictive value for CVD in individuals with preclinical or clinical obesity. For example, a prospective cohort study involving 97,331 MASLD patients reported that TyG-WC and TyG-WHtR were associated with significantly higher NRI and IDI in predicting CVD risk and mortality [18]. Similarly, a study by Hong et al., using data from 7364 individuals with CKM syndrome, demonstrated that TyG-WC, TyG-WHtR, and TyG-BMI outperformed the TyG index alone in predicting CVD incidence [53], while another cohort study encompassing 282,920 participants with CKM syndrome stages 0–3 yielded comparable results [47]. Notably, among all IR-related markers examined, TyG-WC exhibited the strongest predictive strength for CVD incidence, aligning with findings from Dang et al., who identified TyG-WC as most closely associated with overall CVD risk [12]. In the meanwhile, we observed a linear dose-response association between the TyG-WC index and overall CVD risk, indicating the need for tight control of this index in obese patients at preclinical or clinical stages. Alongside previous evidence, our results support that the IR-related indices, especially TyG-WC, could function as accessible and reliable indicators for stratifying CVD risk in preclinical or clinical obese populations.

Although the underlying mechanisms by which elevated IR-related indices elevate cardiovascular risk in preclinical or clinical obesity remain to be fully elucidated, we performed mediation analyses utilizing TyG-WC as a surrogate marker due to its superior predictive power. These analyses highlighted several potential biological mediators—particularly those related to inflammatory pathways and hepatic and renal function—that may account for the observed association. Systemic inflammatory markers, particularly CRP (PM = 8.91%), may partially mediate the relationship. Mechanistically, IR promotes the secretion of pro-inflammatory cytokines, triggering inflammatory responses and oxidative stress, thereby contributing to myocardial ischemic injury and the development of atherosclerosis, ultimately increasing CVD risk [54]. Supporting our findings, two large cohort studies have demonstrated that inflammatory factors may act as mediators between TyG-related indices and adverse cardiovascular outcomes [14, 34]. Moreover, previous studies have detected that IR-related indices are associated with liver function metrics [30, 55], which are recognized as potential risk factors for CVD [56, 57]. Extending and corroborating these findings, our mediation analyses implied that liver-related biomarkers, including ALP, GGT, total protein, and albumin, could explain 2.46%, 3.94%, 1.78%, and 8.65% of the association, respectively. Besides, our analysis identified a significant mediating role of renal function biomarkers, with cystatin C contributing the most substantial effect (PM = 16.33%), followed by urate (10.12%). IR-related indices were found to be associated with rapid kidney function decline [31]. Individuals with impaired renal function are at a higher risk for cardiovascular events [58, 59]. For example, a prospective cohort study with a 7-year follow-up showed a positive association between serum cystatin C and new-onset CVD [59]. Therefore, impaired renal function may serve as a plausible biological mechanism linking IR to an increased risk of CVD. Similar to our mediating findings, Tian et al. reported that these biomarkers reflecting liver and renal function might partially explain the association between elevated TyG-WC index and increased risk of cardiometabolic multimorbidity [34]. These mediation findings could provide preliminary evidence supporting targeted interventions on systemic inflammation and hepatic/renal function in preclinical or clinical obese populations as a potential strategy to reduce IR-induced CVD risk. Future well-controlled investigations are essential to validate these observations and to discover novel mediating mechanisms.

This study presented the first longitudinal evidence linking IR indices with CVD in preclinical or clinical obese populations. Its strengths included a large cohort, prolonged follow-up, thorough covariate adjustment (including genetic factors), precise variable measurements, and extensive sensitivity and subgroup analyses. Notably, we were the first to quantify the joint and interactive effects of IR indices and genetic risk on CVD. The

mediators identified may inform targeted intervention strategies. While this study provides important insights, several limitations should be considered. First, despite previous validation of risk factor analyses in the UK Biobank cohort [60], the "healthy volunteer" bias could limit the generalizability of the results [61]. Second, even with comprehensive covariate adjustments, the potential for residual confounding and reverse causality still exists, restricting the ability to make causal claims. Third, the predominantly White study population further limits the applicability of our findings, which emphasizes the need for validation of our findings in more ethnically diverse populations to better understand potential differences in cardiovascular risk across various ethnic groups. Fourth, the use of only baseline measurements of IR indices limits our ability to assess how these factors change over time. This highlights the need for future studies to incorporate repeated measurements and trajectory analyses to explore the potential differences in prognostic implications between "persistent" and "transient" hyperinsulinemia. Fifth, the partial overlap between the exposures and the study population may introduce collinearity, potentially overestimating the associations. While the residual-based sensitivity analyses reinforced the robustness of our findings, the possibility of partial inflation due to overlapping constructs cannot be fully excluded.

Conclusions

This prospective cohort study provided evidence that elevated IR-related indices, such as TyG-BMI, TyG-WC, and TyG-WHtR, were significantly linked to a higher risk of total CVD and CAD in preclinical or clinical obese individuals. For stroke, the associations were borderline significant. Among these, TyG-BMI and TyG-WHtR demonstrated non-linear associations with total CVD, whereas TyG-WC showed an approximately linear relationship and the strongest prognostic value, suggesting that monitoring TyG-WC may be particularly useful for early CVD prevention in preclinical or clinical obesity management. Moreover, we observed a substantially increased risk of CVD in participants with both high genetic risk and high IR levels, and additive interactions between TyG-WC and genetic risk, underscoring the importance of prioritizing individuals at high genetic risk in clinical management. Furthermore, systemic inflammation and liver and kidney biomarkers were identified as partial mediators, highlighting potential targets for future intervention strategies aimed at reducing CVD risk in individuals with high IR levels.

Abbreviations

CVD	Cardiovascular disease
IR	Insulin resistance
TyG	Triglyceride-glucose
BMI	Body mass index
WC	Waist circumference
WHtR	Waist-to-height ratio
CAD	Coronary artery disease
MASLD	Metabolic dysfunction-associated fatty liver disease
PRS	Polygenic risk scores
TG	Triglyceride
HDL-C	High-density lipoprotein cholesterol
ICD-10	International Classification of Diseases, Tenth Revision
CRP	C-reactive protein
WBC	White blood cell count
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
GGT	Gamma-glutamyltransferase
GWAS	Genome-wide association studies
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
TDI	Townsend Deprivation Index
HbA1c	Glycated hemoglobin
Q	Quartile
SD	Standard deviation
IQR	Interquartile ranges
HR	Hazard ratio
CI	Confidence interval
RCS	Restricted cubic spline
KM	Kaplan-Meier
NRI	Net reclassification index
IDI	Integrated discrimination improvement index
RERI	Relative excess risk due to interaction
AP	Attributable proportion due to interaction
SI	Synergy index
PM	Proportion mediated
FDR	False discovery rate
CKM	cardiovascular-kidney-metabolic

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02961-9.

Supplementary Material 1.

Supplementary Material 2.

Acknowledgements

We thank all participants and staff from the UK Biobank study. The current study was conducted using the UK Biobank resource under Application Number 104283.

Author contributions

JLH, CS, YQH, CNS, and JZ conceived and designed the research, JLH and CS performed the data analysis, JLH wrote the manuscript, JLH and CS interpreted the analyzed results, and YQH, CNS, and JZ revised the manuscript critically for important intellectual content. All authors contributed to the interpretations of the findings and reviewed the manuscript. All authors read and approved the final manuscript.

Funding

This research received no external funding.

Data availability

Data supporting the findings of this study from the UK Biobank team (http://www.ukbiobank.ac.uk/). The data and methods that support the findings of this study are available from the corresponding author on reasonable request. The primary analytic R codes are available in the Supplementary Materials.

Declarations

Ethics approval and consent to participate
The Northwest Multi-center Research Ethics Committee (MREC reference: 21/NW/0157) provided ethical approval for the UK Biobank project. All participants gave informed consent before being recruited.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 13 August 2025 / Accepted: 26 September 2025
Published online: 25 October 2025

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