

Association between insulin resistance surrogate indices and incident chronic kidney disease among the population with cardiovascular-kidney-metabolic syndrome stage 0-3: a cohort study

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Research Article

Keywords: surrogate indices of insulin resistance, cardiovascular-kidney-metabolic syndrome, chronic kidney disease, prospective cohort study, CHARLS

Posted Date: October 20th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11158090/v1>

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Additional Declarations: No competing interests reported.

Abstract

Background

Insulin resistance (IR) is central to the cardiovascular-kidney-metabolic (CKM) syndrome. Routine-biochemistry surrogate indices of IR are widely used, but prospective evidence that they identify high-renal-risk individuals within the CKM staging framework is lacking. We compared six such indices for association with new-onset chronic kidney disease (CKD) in middle-aged and older adults at CKM stage 0–3.

Methods

From the 2011 and 2015 waves of the China Health and Retirement Longitudinal Study we included 4,068 adults aged ≥ 45 years at CKM stage 0–3 with blood data in both waves, excluding baseline eGFR < 60 mL/min/1.73 m², CKM stage 4, and missing or implausible key values. Incident CKD was defined as an eGFR ≥ 60 mL/min/1.73 m² in 2011 and an eGFR < 60 mL/min/1.73 m² in 2015 (2021 CKD-EPI creatinine equation). Six indices (TyG, cumulative TyG, TyG-WC, TyG-WHtR, TyG-BMI, METS-IR) entered logistic regression per 1-SD increase and in tertiles, with stepwise adjustment (M1 demographic and behavioural factors; M2 plus blood pressure, LDL-C, uric acid and BUN; M3 plus baseline creatinine, hypertension and diabetes). Restricted cubic splines, ROC analysis (DeLong), eight-subgroup interaction tests and three sensitivity analyses were performed.

Results

Over four years, 120 participants developed CKD (2.9%). All six indices were higher at baseline in incident cases ($P = 0.048$ to < 0.001); incidence was highest in the top tertile for all, with significant trends for five (TyG-WHtR 2.14% to 4.20%, $P = 0.001$). Per-SD odds ratios (ORs) were 1.19–1.42 in crude and M1 models. TyG and cumulative TyG lost significance in M2, whereas the four composite indices remained significant after full adjustment: TyG-WC 1.27 (95% CI 1.03–1.56), TyG-WHtR 1.28 (1.03–1.59), TyG-BMI 1.28 (1.04–1.58) and METS-IR 1.26 (1.03–1.54). No non-linearity was detected ($P = 0.087$ –0.948) and AUCs were 0.563–0.592. Cumulative TyG and METS-IR associations were stronger at BMI < 24 kg/m² (interaction $P = 0.035$, 0.043); composite-index associations were confined to non-drinkers (interaction $P = 0.016$ –0.041). Excluding BMI ≥ 28 kg/m² or removing uric acid did not change composite-index significance.

Conclusions

In CKM stage 0–3, composite indices (especially TyG-BMI and TyG-WHtR) were more robustly associated with incident CKD than TyG alone, while all indices showed limited discrimination. These low-

cost indices may complement CKM staging in identifying subgroups needing eGFR monitoring.

BACKGROUND

Chronic kidney disease (CKD) is a major global public health challenge. Recent estimates from the Global Burden of Disease study indicate that the number of adults with CKD worldwide continued to expand between 1990 and 2023, with accumulating deaths attributed to hyperglycaemia, hypertension and abnormal renal haemodynamics, and CKD has evolved from a little-known "silent disease" into one of the leading burdens of chronic disease [1]. The situation in China is particularly serious. A national cross-sectional survey covering more than 500,000 adults in 13 provinces around 2010 first revealed a CKD prevalence of 10.8% among Chinese adults, corresponding to nearly 120 million patients, with awareness below 15% [2]. The sixth China Chronic Disease and Risk Factor Surveillance, covering 176,874 adults across 31 provinces, estimated a CKD prevalence of 8.2% in 2018–2019, comprising 2.2% with reduced kidney function and 6.7% with albuminuria [3]; 73.3% of patients remained at stage 1–2 with an awareness of only 10.0%, and prevalence was markedly higher among elderly, obese, hypertensive, diabetic and dyslipidaemic subgroups [3]. An analysis of the national China Health and Retirement Longitudinal Study (CHARLS) sample found that only 8.7% of patients were aware of their diagnosis and 4.9% were receiving treatment [4]. Screening tools remain limited relative to this large patient base: because of the compensatory capacity of the kidneys, serum creatinine often stays within the "normal" range until glomerular filtration is substantially lost, so early detection depends heavily on active screening of high-risk groups. Urinary albumin is sensitive to early glomerular injury but has limited sampling compliance and is affected by infection, fever and metabolic fluctuation [5], while glycated haemoglobin reflects recent glucose exposure rather than kidney function. By contrast, the combination of triglycerides and fasting glucose carries metabolic information on both the glucose and lipid pathways. Whether routinely available glucose, lipid and anthropometric measures can identify individuals at high renal risk is therefore a question of practical importance.

The cardiovascular-kidney-metabolic (CKM) syndrome is a disease state characterised by interlinked metabolic risk factors (including diabetes and obesity), CKD and cardiovascular disease [6], with metabolic disturbance as its core pathology [7]. The American Heart Association proposed the CKM construct in 2023 and stratified the population into stages 0–4 according to the sequence of systemic adipose dysfunction, metabolic risk factors, subclinical cardiovascular disease and clinical cardiovascular events [8]; in 2026, a joint AHA/ACC/ADA/ASN clinical practice guideline systematically revised and promoted this framework, specifying screening intensity, intervention targets and management pathways for each stage [6]. CKM is highly prevalent worldwide, particularly in Southeast Asia and the Western Pacific [9]. In China, the prevalence of CKM syndrome rose from 77.1% in 2010 to 83.7% in 2019, and 23.6% of individuals already had organ involvement or cardiovascular events corresponding to CKM stages 3–4 [10, 11]. With population ageing and nutritional transition proceeding in parallel, the burden concentrated in the stage 0–3 population without clinical events will continue to grow. Pathophysiologically, CKM ultimately reflects excess and dysfunctional adipose tissue, especially visceral fat [6]; hypertrophic and hypoxic adipocytes recruit macrophages and sustain chronic low-grade

inflammation, adiponectin deficiency coexists with leptin resistance, and ectopic lipid deposition in liver and muscle impairs insulin signalling through intermediaries such as ceramide, producing insulin resistance (IR) [6, 12]. In the kidney, IR activates the intrarenal renin-angiotensin system, constricts afferent arterioles and raises glomerular pressure, and lipid accumulation in tubular epithelial cells triggers oxidative stress, mitochondrial dysfunction and tubulointerstitial fibrosis, so-called renal lipotoxicity [12, 13]. Early cohort evidence indicates that higher IR predicts incident CKD even among people without diabetes [14], and IR is closely linked to cardiovascular events and mortality in CKD patients [15]. Identifying IR status early therefore has clear value for early CKD detection.

Direct measurement of IR by the hyperinsulinaemic-euglycaemic clamp is impractical in large populations. In 2008, Simental-Mendía et al. proposed the triglyceride-glucose (TyG) index, the logarithm of the product of fasting triglycerides and glucose, as a simple surrogate marker of IR [16], and subsequent validation studies against the clamp confirmed acceptable sensitivity and specificity [17]. The TyG index relies only on routine biochemistry and is well suited to large population studies. Building on the TyG index, a family of composite indices incorporates anthropometric information: cumulative TyG characterises long-term exposure [18]; the products of TyG with body mass index, waist circumference and waist-to-height ratio (TyG-BMI, TyG-WC and TyG-WHtR) integrate fat distribution into the IR measure; and the metabolic score for insulin resistance (METS-IR), constructed from triglycerides, glucose, BMI and HDL-C, was designed to capture both glycolipid burden and visceral fat [19]. Six indices in total are considered here, five of which are TyG-based.

Existing evidence does not agree on which index is most closely related to CKD. Meta-analytic evidence indicates that higher TyG is positively associated with incident CKD, with reproducible dose-response relations across independent cohorts [20], and prospective analyses of cumulative TyG-BMI report clear positive associations [21]. METS-IR has been shown to be independently associated with CKD and albuminuria in Chinese populations [22]. In a Chinese comparison, discrimination was best for TyG-WHtR whereas association strength was highest for TyG [23]; in NHANES data, TyG showed the strongest association with CKD prevalence while TyG-WHtR led in discrimination and mortality prediction [24, 25]; and in a population without diabetes both the association and discrimination rankings were led by METS-IR [26], so the expectation that composite indices are always superior does not hold. Moreover, the population-level evidence remains incomplete: some studies prospectively predicted cardiovascular events in CKM stage 0–3 populations [27], others used the rate of kidney function decline as the renal endpoint [28], and others did not stratify by CKM stage at all [29]. Whether and how strongly the TyG-based indices relate to incident CKD in Chinese middle-aged and older adults at CKM stage 0–3 therefore remains uncertain.

Using CHARLS wave 1 (2011) as baseline and wave 3 (2015) as the follow-up endpoint, this study compared six IR surrogate indices (TyG, cumulative TyG, TyG-WC, TyG-WHtR, TyG-BMI and METS-IR) in relation to incident CKD among adults at CKM stage 0–3, evaluated the dose-response relation and the linearity assumption of each index, examined discrimination, and tested robustness through multiple

sensitivity analyses, in order to provide a basis for selecting a simple and scalable marker for early CKD screening and risk stratification in CKM populations.

METHODS

Study design and data source

This study used data from CHARLS, a nationally representative longitudinal survey directed by the National School of Development of Peking University [30]. CHARLS uses multistage stratified probability-proportional-to-size sampling covering 150 counties and 450 villages or communities in 28 provincial administrative regions, and enrolls residents aged 45 years and older. The baseline survey was conducted in 2011 with follow-up every two to three years; each wave includes household and individual questionnaires, physical examination and venous blood testing, with blood samples cold-chain transported to a central laboratory for uniform assay under standardised quality control [30]. Wave 1 (2011; fieldwork extended into 2012, referred to hereafter as the 2011 baseline) served as baseline and wave 3 (2015) as the follow-up endpoint, giving a four-year interval. The CHARLS survey was conducted in accordance with the Declaration of Helsinki, approved by the Biomedical Ethics Review Committee of Peking University (IRB00001052-11015), and all participants provided written informed consent. The present secondary analysis of de-identified CHARLS data followed the CHARLS data use agreement.

Participants

From the 17,708 participants in the 2011 baseline survey, exclusions were applied in the following sequence (flow diagram in Additional file 7): (1) age younger than 45 years or missing age, or inconsistent sex records between the two waves ($n = 486$; 32 participants verified as cross-wave household identifier mismatches had their sex corrected from household registry and relationship information); (2) incomplete 2011 blood tests or physical measurements, or unmet fasting requirements ($n = 8,728$); (3) loss to follow-up in 2015, incomplete 2015 blood tests, or unmet fasting requirements ($n = 3,593$); (4) baseline CKD, defined as an eGFR below $60 \text{ mL/min/1.73 m}^2$, or CKM stage 4, i.e. pre-existing clinical cardiovascular disease such as heart disease or stroke ($n = 717$); and (5) implausible biochemistry or anthropometric values ($n = 116$). The remaining 4,068 participants (23.0% of the baseline survey) constituted the analytical sample; the representativeness implications are addressed in the Discussion. Self-reported kidney disease was not used as an exclusion criterion or for outcome definition because of its very poor agreement with objective kidney function in CHARLS (see Results).

Exposure assessment

Venous blood was collected by trained nurses after at least 8 hours of fasting. Serum triglycerides (TG), fasting blood glucose (FBG), glycated haemoglobin, total cholesterol (TC), HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), blood urea nitrogen (BUN), uric acid (UA), serum creatinine (SCr) and cystatin C were

measured with standardised methods and quality control; serum creatinine by the enzymatic method and cystatin C by immunoturbidimetry, with consistent assays and quality control across the 2011 and 2015 waves. FBG and SCr are reported in mg/dL and TG in mmol/L, with conversion applied where formulae require.

Six IR surrogate indices were computed at the 2011 baseline:

(1) $TyG = \ln[TG \text{ (mg/dL)} \times FBG \text{ (mg/dL)} / 2]$

(2) cumulative TyG = $(TyG_{2011} + TyG_{2015}) / 2 \times 4$ years, approximating the four-year area under the exposure curve (unit: index-years; used only for ranking and per-SD comparison, with no directly interpretable clinical scale)

(3) $TyG-WC = TyG \times \text{waist circumference (cm)}$

(4) $TyG-WHtR = TyG \times \text{waist-to-height ratio}$

(5) $TyG-BMI = TyG \times BMI$, where $BMI = \text{weight (kg)} / \text{height (m)}^2$

(6) $METS-IR = \ln[(2 \times FBG \text{ (mg/dL)} + TG \text{ (mg/dL)}) \times BMI \text{ (kg/m}^2) / \ln(HDL-C \text{ (mg/dL)})]$, after Bello-Chavolla et al. [19] Waist circumference was measured at the umbilical level in the standing position, height and weight with calibrated instruments, and blood pressure as the mean of three seated readings.

Outcome assessment

eGFR was estimated with the 2021 CKD-EPI creatinine equation without a race coefficient [31]: $eGFR = 142 \times \min(SCr/\kappa, 1)^\alpha \times \max(SCr/\kappa, 1)^{-1.200} \times 0.9938^{\text{age}} \times (1.012 \text{ if female})$, where SCr is serum creatinine (mg/dL), κ is 0.7 mg/dL in women and 0.9 mg/dL in men, and α is -0.241 in women and -0.302 in men. Incident CKD was defined as a baseline (2011) eGFR of at least 60 mL/min/1.73 m² followed by a 2015 eGFR below 60 mL/min/1.73 m².

CKM staging

CKM stages 0–4 were assigned following the AHA staging framework combined with the assessment pathway of the Chinese expert consensus [6–8] (stage 0: no CKM risk factors, i.e. BMI < 23 kg/m² using the Asian cutoff [32], normal waist circumference, normal blood pressure, glucose and lipids, and no CKD or cardiovascular disease; stage 1: overweight, obesity or central obesity, i.e. BMI ≥ 23 kg/m² or waist circumference above the cutoff; stage 2: metabolic risk factors, i.e. hypertension, hypertriglyceridaemia, diabetes or metabolic syndrome, or moderate-to-high-risk CKD; stage 3: subclinical cardiovascular disease or very-high-risk status). Because participants with baseline eGFR below 60 mL/min/1.73 m² were excluded at the outset, the eGFR < 30 mL/min/1.73 m² criterion was not applied to stage assignment. Very-high-risk status was defined by the simplified CKM2S2-BAG risk score of the Chinese

consensus, which predicts ten-year cardiovascular disease risk from age (1 point per 10 years), male sex (2 points), current smoking (2 points), systolic blood pressure (1 point per 10 mmHg), fasting glucose (1 point per 10 mg/dL), non-HDL cholesterol (1 point per 10 mg/dL) and eGFR (1 point per 10 mL/min/1.73 m² decrease); scores of 0–4, 5–9 and ≥ 10 indicate low, moderate and high risk, and high-risk participants were assigned to CKM stage 3 [7].

Hypertension was defined as self-reported physician diagnosis, current antihypertensive medication, or mean systolic blood pressure ≥ 140 mmHg and/or mean diastolic blood pressure ≥ 90 mmHg. Diabetes was defined as self-reported physician diagnosis, current glucose-lowering medication, FBG ≥ 7.0 mmol/L (126 mg/dL), or glycated haemoglobin $\geq 6.5\%$.

Covariates

Sociodemographic and behavioural covariates came from the questionnaires: age, sex, education, marital status (married/partnered versus other) and residence (rural versus urban hukou), ever-smoking (former or current versus never) and drinking (any alcohol in the past year versus none). Education was recorded on the original nine-level scale (1 illiterate, 2 not completing primary school but able to read and write, 3 private-school schooling, 4 primary school, 5 junior middle school, 6 senior middle school, 7 vocational/technical school, 8 associate degree, 9 bachelor degree or above; valid records for 4,067 participants: 1,165, 767, 16, 927, 821, 272, 51, 43 and 5 across levels 1–9, one missing) and entered models as a continuous ordinal term. Physician-diagnosed hypertension, diabetes and other chronic diseases were self-reported.

Statistical analysis

Baseline characteristics were described by incident CKD status: normally distributed continuous variables as mean (SD) with two-sided t tests, skewed variables as median (interquartile range) with tie-corrected Mann-Whitney U tests (Z statistic), and categorical variables as n (%) with chi-square tests. Missing data were handled by complete-case analysis within each model: the crude model included n = 4,068 (120 events); M1 excluded 7 participants with missing education (1), residence (2) or smoking (4), giving n = 4,061 (119 events); M2 and M3 further excluded 7 participants with missing LDL-C, giving n = 4,054 (118 events); 14 participants (0.3%) and 2 events were lost in total.

Each index was analysed (a) as a per-1-SD increase after Z standardisation, with the SD taken from the full sample (n = 4,068) so that indices are comparable, and (b) in tertiles split at the 33.3% and 66.7% percentiles of the total population (approximately 1,356 per tertile), with the lowest tertile as reference and linear trend tested by entering the tertile ordinal (1–3) as a continuous term. Associations were estimated with logistic regression in three adjustment levels: M1 included age, sex, education, marital status, residence, smoking and drinking; M2 further included systolic and diastolic blood pressure, LDL-C, uric acid and BUN; M3 further included baseline creatinine, hypertension and diabetes (fully adjusted). The same covariate set was used for all six indices within each level, without exposure-specific additional adjustment. Because CHARLS provides kidney function only at discrete waves, no reliable

survival time can be constructed; odds ratios (ORs) are therefore interpreted as associations with CKD status at the end of follow-up rather than instantaneous hazard ratios.

Multiple collinearity was assessed with variance inflation factors (VIF), with $VIF < 5$ considered acceptable. Dose-response relations were modelled with three-knot restricted cubic splines (RCS) placed at the 10th, 50th and 90th percentiles of each index, fully adjusted as in M3, referenced to the 50th percentile, with the x-axis trimmed to the 5th-95th percentile range; the non-linearity P value (likelihood-ratio test of the spline model, containing one non-linear term, against the linear model) is shown in the figure. Discrimination was assessed by ROC analysis for each index as the single unadjusted predictor, with AUCs and 95% CIs by the DeLong method and tested against $AUC = 0.5$; cumulative TyG was excluded because its computation window overlaps the prediction window (its results remain in the association tables for comparability across the six indices but are interpreted in the position of a sensitivity analysis). Crude incidence rates are reported with Wilson 95% CIs, and tertile incidence trends were tested with the Cochran-Armitage chi-square test (unadjusted).

Subgroup analyses covered eight strata (age < 60 or ≥ 60 years, sex, BMI < 24 or ≥ 24 kg/m², hypertension, diabetes, residence, smoking and drinking); within each stratum the fully adjusted model was fitted with the stratifying variable removed from the covariates, and effect modification was tested by the Wald test of the exposure-by-stratum interaction (product term) in the full-sample M3 model. Three sensitivity analyses were performed: (1) repeating the M2 and M3 models after excluding participants with BMI ≥ 28 kg/m² (Chinese obesity standard, WS/T 428–2013); (2) stratifying by uric acid and removing uric acid from the stratum models, with the split at the sample median because events were too few below the clinical cutoff (< 15 in the high-uric-acid group); and (3) removing uric acid from the fully adjusted model to test its influence. The variance inflation factors are reported in Additional file 3 (Table S3), the subgroup analyses in Table 5, the BMI-based and uric-acid sensitivity analyses in Additional files 2, 4, and 5, and the agreement analysis for self-reported kidney disease in Additional file 1 (Table S1).

Agreement between self-reported kidney disease and objectively defined CKD (eGFR < 60 mL/min/1.73 m²) was evaluated in CHARLS participants with valid creatinine or cystatin C, age and sex information, using sensitivity, specificity, positive predictive value, negative predictive value and Kappa.

All tests were two-sided, with $P < 0.05$ considered statistically significant. Analyses were performed in R version 4.6.1. During manuscript preparation, a large language model was used to translate the manuscript from Chinese into English. All AI-assisted text was reviewed and verified by the authors, who take full responsibility for the work.

RESULTS

Baseline characteristics

Of 4,068 participants (mean age 58.55 ± 8.53 years; 2,214 women [54.4%]; 89.4% married or partnered; 1,529 ever-smokers [37.6%]; 1,068 drinkers [26.3%]), 120 developed CKD over the four-year follow-up, a cumulative incidence of 2.9% (Table 1). Compared with non-incident participants, incident cases were older (63.42 ± 9.00 versus 58.40 ± 8.48 years, $P < 0.001$), had lower baseline eGFR (85.78 ± 15.91 versus 97.96 ± 11.60 mL/min/1.73 m², $P < 0.001$), higher systolic blood pressure (135.84 ± 25.44 versus 129.10 ± 20.56 mmHg, $P < 0.001$), a higher prevalence of hypertension (52.5% versus 37.4%, $P = 0.001$) and a lower proportion married or partnered (81.7% versus 89.6%, $P = 0.008$). Incident cases also had higher waist circumference (87.65 versus 85.18 cm, $P = 0.006$), waist-to-height ratio (0.56 versus 0.54, $P < 0.001$), median triglycerides (1.37 versus 1.15 mmol/L, $P = 0.013$), total cholesterol (201.60 ± 49.43 versus 194.20 ± 37.59 mg/dL, $P = 0.036$), uric acid (4.81 ± 1.24 versus 4.33 ± 1.20 mg/dL, $P < 0.001$), serum creatinine (0.86 ± 0.20 versus 0.75 ± 0.16 mg/dL, $P < 0.001$) and cystatin C. All six IR indices were higher at baseline in incident cases, with the largest between-group difference for TyG-WHtR. BMI, diastolic blood pressure, fasting glucose, LDL-C, diabetes, smoking and drinking did not differ between groups ($P > 0.05$).

Table 1
Baseline characteristics of participants by incident CKD status

Variable	Overall (n = 4,068)	No incident CKD (n = 3,948)	Incident CKD (n = 120)	Statistic	P
Age (years)	58.55 (8.53)	58.40 (8.48)	63.42 (9.00)	t = -6.38	< 0.001
Women (%)	2214 (54.4)	2146 (54.4)	68 (56.7)	$\chi^2 = 0.17$	0.684
Married/cohabiting (%)	3637 (89.4)	3539 (89.6)	98 (81.7)	$\chi^2 = 7.00$	0.008
Smoking (%)	1529 (37.6)	1488 (37.7)	41 (34.5)	$\chi^2 = 0.39$	0.53
Drinking (%)	1068 (26.3)	1040 (26.4)	28 (23.3)	$\chi^2 = 0.41$	0.524
Body mass index (kg/m ²)	23.49 (3.52)	23.48 (3.52)	24.06 (3.37)	t = -1.80	0.072
Waist circumference (cm)	85.25 (9.75)	85.18 (9.70)	87.65 (10.97)	t = -2.74	0.006
Waist-to-height ratio	0.54 (0.06)	0.54 (0.06)	0.56 (0.07)	t = -3.41	< 0.001
Systolic blood pressure (mmHg)	129.30 (20.75)	129.10 (20.56)	135.84 (25.44)	t = -3.51	< 0.001
Diastolic blood pressure (mmHg)	75.49 (11.98)	75.50 (11.96)	75.22 (12.71)	t = 0.26	0.797
Mean arterial pressure (mmHg)	93.43 (13.90)	93.37 (13.83)	95.42 (15.79)	t = -1.60	0.11
Fasting blood glucose (mg/dL)	102.24 (94.50-111.42)	102.24 (94.50-111.42)	102.33 (95.40-112.55)	Z = 0.88	0.378
Triglycerides (mmol/L)	1.16 (0.83-1.68)	1.15 (0.82-1.67)	1.37 (0.96-1.77)	Z = 2.50	0.013
Total cholesterol (mg/dL)	194.42 (38.01)	194.20 (37.59)	201.60 (49.43)	t = -2.10	0.036
HDL-C (mg/dL)	51.56 (15.05)	51.62 (15.04)	49.45 (15.06)	t = 1.56	0.119
LDL-C (mg/dL)	117.98 (33.90)	117.85 (33.79)	122.18 (37.25)	t = -1.37	0.17
HbA1c (%)	5.20 (4.90-5.40)	5.20 (4.90-5.40)	5.20 (4.90-5.50)	Z = 1.07	0.285
C-reactive protein (mg/L)	0.99 (0.54-2.02)	0.98 (0.54-2.01)	1.09 (0.68-2.80)	Z = 1.72	0.085
Uric acid (mg/dL)	4.34 (1.20)	4.33 (1.20)	4.81 (1.24)	t = -4.33	< 0.001

Variable	Overall (n = 4,068)	No incident CKD (n = 3,948)	Incident CKD (n = 120)	Statistic	P
Blood urea nitrogen (mg/dL)	15.49 (4.27)	15.47 (4.26)	16.10 (4.67)	t = -1.59	0.111
Serum creatinine (mg/dL)	0.76 (0.16)	0.75 (0.16)	0.86 (0.20)	t = -7.27	< 0.001
Cystatin C (mg/L)	0.97 (0.85–1.10)	0.96 (0.85–1.10)	1.07 (0.90–1.31)	Z = 5.32	< 0.001
eGFR (mL/min/1.73 m ²)	97.60 (11.93)	97.96 (11.60)	85.78 (15.91)	t = 11.18	< 0.001
Hypertension (%)	1540 (37.9)	1477 (37.4)	63 (52.5)	$\chi^2 = 10.64$	0.001
Diabetes (%)	567 (13.9)	546 (13.8)	21 (17.5)	$\chi^2 = 1.02$	0.313
Self-reported kidney disease (%)	226 (5.6)	216 (5.5)	10 (8.3)	$\chi^2 = 1.31$	0.252
CKM stage 3, high risk (%)	632 (15.5)	586 (14.8)	46 (38.3)	$\chi^2 = 47.20$	< 0.001
TyG	8.65 (0.63)	8.65 (0.63)	8.79 (0.67)	t = -2.40	0.016
Cumulative TyG (index-years)	34.63 (2.21)	34.62 (2.21)	35.02 (2.27)	t = -1.97	0.048
TyG-WC	739.48 (114.74)	738.50 (114.26)	771.73 (125.66)	t = -3.13	0.002
TyG-WHtR	4.69 (0.74)	4.68 (0.74)	4.94 (0.84)	t = -3.69	< 0.001
TyG-BMI	203.90 (37.98)	203.65 (37.97)	212.04 (37.76)	t = -2.39	0.017
METs-IR	35.37 (7.65)	35.32 (7.64)	37.05 (8.04)	t = -2.44	0.015

Note: Values are mean (SD), median (IQR), or n (%); comparisons by two-sided t test, tie-corrected Mann-Whitney U test (Z), or chi-square test. All blood measures are 2011 baseline values. Smoking was missing for 4 participants (1 incident case); percentages use valid denominators. Incident CKD: eGFR at least 60 mL/min/1.73 m² in 2011 and below 60 mL/min/1.73 m² in 2015 (2021 CKD-EPI creatinine equation). CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; CKM, cardiovascular-kidney-metabolic.

Incidence by exposure tertile

For all six indices, incidence increased across baseline tertiles (each n = 1,356) and was highest in the top tertile (Fig. 1): TyG rose from 2.29% to 3.83% (P for trend = 0.017), cumulative TyG from 2.36% to 3.69% (P = 0.041), TyG-WC from 2.43% to 3.98% (P = 0.017), TyG-WHtR from 2.14% to 4.20% (P = 0.001), TyG-BMI from 2.21% to 3.83% (P = 0.013) and METS-IR from 2.51% to 3.76% (P = 0.054). Trends were

significant for all indices except METS-IR. The gradient was steepest for TyG-WHtR, whose top-tertile incidence was approximately 1.96 times that of the bottom tertile, with the smallest trend P value among the six indices.

Associations with incident CKD

In per-SD models (Table 2), all six indices were positively associated with incident CKD in the crude model (ORs 1.19–1.37, all $P < 0.05$), most strongly for TyG-WHtR (OR = 1.37, 95% CI 1.16–1.63, $P < 0.001$). After M1 adjustment, associations strengthened for all indices (ORs 1.25–1.42): cumulative TyG 1.25 (1.04–1.49, $P = 0.015$), TyG 1.28 (1.08–1.52, $P = 0.005$), TyG-WC 1.40 (1.17–1.67, $P < 0.001$), TyG-WHtR 1.41 (1.17–1.69, $P < 0.001$), TyG-BMI 1.42 (1.19–1.70, $P < 0.001$) and METS-IR 1.40 (1.18–1.66, $P < 0.001$). With further M2 adjustment, cumulative TyG (OR = 1.12, 95% CI 0.92–1.36, $P = 0.270$) and TyG (OR = 1.17, 95% CI 0.97–1.42, $P = 0.108$) lost statistical significance, whereas TyG-WC (OR = 1.27, 95% CI 1.05–1.54, $P = 0.016$), TyG-WHtR (OR = 1.27, 95% CI 1.04–1.55, $P = 0.021$), TyG-BMI (OR = 1.29, 95% CI 1.06–1.57, $P = 0.012$) and METS-IR (OR = 1.27, 95% CI 1.05–1.54, $P = 0.014$) remained significant. In the fully adjusted M3 model, the four composite indices all remained significant: TyG-WC 1.27 (95% CI 1.03–1.56, $P = 0.026$), TyG-WHtR 1.28 (95% CI 1.03–1.59, $P = 0.028$), TyG-BMI 1.28 (95% CI 1.04–1.58, $P = 0.019$) and METS-IR 1.26 (95% CI 1.03–1.54, $P = 0.027$). TyG (OR = 1.15, 95% CI 0.92–1.43, $P = 0.226$) and cumulative TyG (OR = 1.09, 95% CI 0.88–1.36, $P = 0.437$) retained positive point estimates with confidence intervals crossing 1.

In tertile models (Table 3), the top tertile carried the excess risk in every index. In M1, top-tertile ORs versus the bottom tertile ranged from 1.73 (cumulative TyG, 95% CI 1.09–2.75) to 2.55 (TyG-BMI, 95% CI 1.56–4.16), with intermediate tertiles indistinguishable from the reference and trend P values between < 0.001 and 0.018. In M2, the top tertile remained significant for TyG-WHtR (OR = 1.78, 95% CI 1.06–3.01, $P = 0.031$), TyG-BMI (OR = 2.11, 95% CI 1.26–3.55, $P = 0.005$) and METS-IR (OR = 1.72, 95% CI 1.05–2.82, $P = 0.031$), while TyG and TyG-WC (both OR = 1.55) lost significance ($P = 0.079$ and 0.080). In M3, only TyG-BMI retained a top-tertile risk of approximately twofold (OR = 1.99, 95% CI 1.16–3.40, $P = 0.012$; P for trend = 0.011), with TyG-WHtR (OR = 1.69, 95% CI 0.98–2.91, $P = 0.060$) and METS-IR (OR = 1.61, 95% CI 0.97–2.67, $P = 0.066$) borderline.

All covariates in the six fully adjusted models had VIF values below 5, with the highest for systolic blood pressure (3.29), indicating no collinearity requiring remedy (Additional file 3: Table S3).

Dose-response relation

In RCS models (Fig. 2), no statistically significant non-linearity was detected for any index (non-linearity P values 0.087–0.948). ORs of TyG-WC, TyG-WHtR, TyG-BMI and METS-IR increased across the exposure range: for TyG-WC and TyG-WHtR the lower confidence bound exceeded 1 from the 75th percentile onwards and remained above 1 at the 95th percentile (ORs 1.55 and 1.57), while TyG-BMI and METS-IR reached ORs of 1.27 at the 75th percentile (lower bounds above 1) and 1.45 and 1.40 at the 95th percentile with confidence intervals again including 1. The curves of TyG and cumulative TyG were flat

across percentiles, with confidence intervals including 1 throughout; the corresponding per-SD association P values in the fully adjusted model were 0.226 and 0.437 (Table 2).

Table 2
Associations of insulin resistance surrogate indices with incident chronic kidney disease (per 1-SD increase)

Exposure	Unadjusted OR (95% CI), P	M1 OR (95% CI), P	M2 OR (95% CI), P	M3 OR (95% CI), P
TyG	1.23 (1.04–1.45), 0.016*	1.28 (1.08–1.52), 0.005**	1.17 (0.97–1.42), 0.108	1.15 (0.92–1.43), 0.226
Cumulative TyG	1.19 (1.00–1.41), 0.049*	1.25 (1.04–1.49), 0.015*	1.12 (0.92–1.36), 0.270	1.09 (0.88–1.36), 0.437
TyG-WC	1.31 (1.11–1.56), 0.002**	1.40 (1.17–1.67), < 0.001***	1.27 (1.05–1.54), 0.016*	1.27 (1.03–1.56), 0.026*
TyG-WHtR	1.37 (1.16–1.63), < 0.001***	1.41 (1.17–1.69), < 0.001***	1.27 (1.04–1.55), 0.021*	1.28 (1.03–1.59), 0.028*
TyG-BMI	1.23 (1.04–1.46), 0.017*	1.42 (1.19–1.70), < 0.001***	1.29 (1.06–1.57), 0.012*	1.28 (1.04–1.58), 0.019*
METs-IR	1.23 (1.04–1.45), 0.015*	1.40 (1.18–1.66), < 0.001***	1.27 (1.05–1.54), 0.014*	1.26 (1.03–1.54), 0.027*

*Note: ORs are per 1-SD increase, SDs from the full sample (n = 4,068). Crude: n = 4,068 (120 events). M1: age, sex, education, marital status, residence, smoking, drinking (n = 4,061; 119 events). M2: M1 plus SBP, DBP, LDL-C, uric acid and BUN (n = 4,054; 118 events). M3: M2 plus baseline creatinine, hypertension and diabetes. * P < 0.05, ** P < 0.01, *** P < 0.001.*

Table 3
Association of insulin resistance surrogate indices with incident CKD by baseline tertiles (T1 as reference)

Exposure	Model	n	T2 OR	T2 95% CI	T2 P	T3 OR	T3 95% CI	T3 P	P for trend
TyG	M1	4061	1.23	0.75–2.01	0.418	1.88	1.18–3.00	0.008**	0.007**
TyG	M2	4054	1.16	0.70–1.91	0.560	1.55	0.95–2.53	0.079	0.071
TyG	M3	4054	1.08	0.65–1.80	0.755	1.37	0.82–2.29	0.230	0.216
Cumulative TyG	M1	4061	1.19	0.73–1.94	0.476	1.73	1.09–2.75	0.021*	0.018*
Cumulative TyG	M2	4054	1.09	0.66–1.79	0.742	1.37	0.84–2.24	0.205	0.190
Cumulative TyG	M3	4054	1.04	0.63–1.72	0.882	1.22	0.73–2.03	0.446	0.431
TyG-WC	M1	4061	1.08	0.66–1.78	0.752	1.91	1.21–3.02	0.006**	0.004**
TyG-WC	M2	4054	1.01	0.61–1.68	0.958	1.55	0.95–2.53	0.080	0.067
TyG-WC	M3	4054	1.01	0.61–1.69	0.960	1.46	0.87–2.43	0.149	0.134
TyG-WHtR	M1	4061	1.27	0.76–2.13	0.356	2.18	1.33–3.58	0.002**	0.001**
TyG-WHtR	M2	4054	1.17	0.69–1.96	0.563	1.78	1.06–3.01	0.031*	0.025*
TyG-WHtR	M3	4054	1.16	0.69–1.98	0.572	1.69	0.98–2.91	0.060	0.053
TyG-BMI	M1	4061	1.62	0.98–2.66	0.060	2.55	1.56–4.16	< 0.001***	< 0.001***
TyG-BMI	M2	4054	1.46	0.88–2.42	0.147	2.11	1.26–3.55	0.005**	0.004**
TyG-BMI	M3	4054	1.39	0.83–2.33	0.208	1.99	1.16–3.40	0.012*	0.011*
METs-IR	M1	4061	1.27	0.78–2.07	0.345	2.09	1.31–3.34	0.002**	0.002**
METs-IR	M2	4054	1.17	0.71–1.93	0.538	1.72	1.05–2.82	0.031*	0.028*

Exposure	Model	n	T2 OR	T2 95% CI	T2 P	T3 OR	T3 95% CI	T3 P	P for trend
METs-IR	M3	4054	1.11	0.67– 1.84	0.685	1.61	0.97– 2.67	0.066	0.062

Tertiles were formed from the 33.3rd and 66.7th percentiles of the full sample; T1 is the reference. P for trend was obtained by entering the ordinal tertile number (1–3) as a continuous term. Model definitions as in Table 2; outcome as in Table 2; n = model-specific complete cases. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Discrimination

AUCs of the five single-measurement indices were all above 0.5 (Table 4, Fig. 3): TyG-WHtR was highest (AUC = 0.592, 95% CI 0.538–0.646, $P < 0.001$), followed by TyG-WC (0.578, 95% CI 0.525–0.631, $P = 0.004$), TyG (0.570, 95% CI 0.520–0.620, $P = 0.007$), TyG-BMI (0.566, 95% CI 0.515–0.617, $P = 0.011$) and METS-IR (0.563, 95% CI 0.511–0.616, $P = 0.018$). The AUCs fell within a narrow band of 0.563–0.592, indicating limited discrimination when the indices were used alone.

Subgroup analyses

Across 48 exposure-by-subgroup interaction tests (Table 5), 42 were non-significant ($P = 0.058$ – 0.994) and 6 reached nominal significance: cumulative TyG-by-BMI ($P = 0.035$), METS-IR-by-BMI ($P = 0.043$), TyG-WC-by-drinking ($P = 0.016$), TyG-WHtR-by-drinking ($P = 0.037$), TyG-BMI-by-drinking ($P = 0.027$) and METS-IR-by-drinking ($P = 0.041$). The two BMI interactions pointed in the same direction: associations of cumulative TyG (OR 1.20 versus 0.91) and METS-IR (OR 1.55 versus 0.97) were larger at BMI < 24 kg/m² than at BMI ≥ 24 kg/m², with significance within the BMI < 24 stratum for METS-IR (OR = 1.55, 95% CI 1.01–2.38, $P = 0.043$). The four drinking interactions were likewise consistent: associations of TyG-WC, TyG-WHtR, TyG-BMI and METS-IR were confined to non-drinkers (ORs 1.41, 1.39, 1.39 and 1.37, all $P < 0.05$), with point estimates near 1 among drinkers. In stratum-specific models, TyG-WHtR was nominally significant among men (OR = 1.45, 95% CI 1.02–2.07), participants without hypertension (OR = 1.45, 95% CI 1.06–2.00), rural residents (OR = 1.30, 95% CI 1.03–1.64), non-drinkers (OR = 1.39, 95% CI 1.08–1.79) and ever-smokers (OR = 1.55, 95% CI 1.05–2.31). Event counts varied across strata (diabetes 20, urban 14, drinking 28), so the corresponding estimates are imprecise and require cautious interpretation.

Table 4
ROC analysis of five IR surrogate indices for predicting
incident CKD

Exposure	AUC	95% CI	P (vs AUC = 0.5)
TyG	0.570	0.520–0.620	0.007**
TyG-WC	0.578	0.525–0.631	0.004**
TyG-WHtR	0.592	0.538–0.646	< 0.001***
TyG-BMI	0.566	0.515–0.617	0.011*
METs-IR	0.563	0.511–0.616	0.018*

AUC, area under the curve; ROC, receiver operating characteristic; CKD, chronic kidney disease. An ROC curve was drawn for each indicator as the single predictor of 4-year incident CKD; AUCs and 95% CIs were estimated by DeLong's non-parametric method, and P from the test against AUC = 0.5 (n = 4,068). Cumulative TyG was not included because its computation window overlaps the follow-up period. Model definitions as in Table 2; outcome as in Table 2. * P < 0.05, ** P < 0.01, *** P < 0.001.

Table 5
Subgroup analyses of the associations between the six IR indices and incident CKD

Exposure	Subgroup	Subgroup 1 OR (95% CI), P [n, events]	Subgroup 2 OR (95% CI), P [n, events]	P for interaction
TyG	Age < 60 vs ≥ 60	1.40 (0.98–1.99), 0.062 [2292, 40]	1.03 (0.77–1.38), 0.838 [1762, 78]	0.479
TyG	Male vs Female	1.26 (0.89–1.78), 0.184 [1848, 52]	1.08 (0.80–1.44), 0.617 [2206, 66]	0.991
TyG	BMI < 24 vs ≥ 24	1.19 (0.88–1.62), 0.252 [2415, 61]	1.02 (0.73–1.42), 0.910 [1639, 57]	0.102
TyG	No hypertension vs Hypertension	1.25 (0.92–1.71), 0.158 [2523, 57]	1.09 (0.79–1.50), 0.596 [1531, 61]	0.830
TyG	No diabetes vs Diabetes	1.08 (0.84–1.39), 0.552 [3493, 98]	1.43 (0.91–2.24), 0.118 [561, 20]	0.421
TyG	Rural vs Urban	1.17 (0.93–1.48), 0.178 [3489, 104]	0.77 (0.34–1.75), 0.535 [565, 14]	0.363
TyG	Never smoked vs Former/current smoker	1.07 (0.81–1.41), 0.631 [2528, 77]	1.35 (0.92–1.98), 0.125 [1526, 41]	0.991
TyG	Non-drinker vs Drinker	1.19 (0.92–1.54), 0.178 [2989, 90]	1.06 (0.67–1.65), 0.809 [1065, 28]	0.192
Cumulative TyG	Age < 60 vs ≥ 60	1.28 (0.90–1.81), 0.163 [2292, 40]	1.01 (0.76–1.36), 0.929 [1762, 78]	0.615
Cumulative TyG	Male vs Female	1.19 (0.85–1.68), 0.313 [1848, 52]	1.02 (0.76–1.36), 0.888 [2206, 66]	0.983
Cumulative TyG	BMI < 24 vs ≥ 24	1.20 (0.88–1.63), 0.242 [2415, 61]	0.91 (0.65–1.26), 0.561 [1639, 57]	0.035
Cumulative TyG	No hypertension vs Hypertension	1.19 (0.87–1.63), 0.280 [2523, 57]	1.05 (0.77–1.44), 0.751 [1531, 61]	0.957
Cumulative TyG	No diabetes vs Diabetes	1.02 (0.79–1.31), 0.879 [3493, 98]	1.38 (0.88–2.17), 0.164 [561, 20]	0.350
Cumulative TyG	Rural vs Urban	1.13 (0.89–1.42), 0.310 [3489, 104]	0.84 (0.38–1.83), 0.652 [565, 14]	0.283
Cumulative TyG	Never smoked vs Former/current smoker	1.02 (0.78–1.33), 0.910 [2528, 77]	1.30 (0.88–1.91), 0.190 [1526, 41]	0.994
Cumulative TyG	Non-drinker vs Drinker	1.17 (0.91–1.50), 0.215 [2989, 90]	0.87 (0.54–1.40), 0.565 [1065, 28]	0.059
TyG-WC	Age < 60 vs ≥ 60	1.22 (0.86–1.74), 0.271 [2292, 40]	1.34 (1.02–1.76), 0.036 [1762, 78]	0.262

Exposure	Subgroup	Subgroup 1 OR (95% CI), P [n, events]	Subgroup 2 OR (95% CI), P [n, events]	P for interaction
TyG-WC	Male vs Female	1.35 (0.97–1.88), 0.073 [1848, 52]	1.22 (0.93–1.62), 0.156 [2206, 66]	0.750
TyG-WC	BMI < 24 vs ≥ 24	1.21 (0.85–1.74), 0.291 [2415, 61]	1.13 (0.78–1.64), 0.514 [1639, 57]	0.272
TyG-WC	No hypertension vs Hypertension	1.44 (1.06–1.95), 0.018 [2523, 57]	1.14 (0.85–1.54), 0.386 [1531, 61]	0.711
TyG-WC	No diabetes vs Diabetes	1.19 (0.94–1.51), 0.141 [3493, 98]	1.61 (0.98–2.64), 0.058 [561, 20]	0.441
TyG-WC	Rural vs Urban	1.29 (1.03–1.60), 0.025 [3489, 104]	0.84 (0.38–1.85), 0.670 [565, 14]	0.618
TyG-WC	Never smoked vs Former/current smoker	1.20 (0.92–1.56), 0.174 [2528, 77]	1.48 (1.03–2.14), 0.036 [1526, 41]	0.797
TyG-WC	Non-drinker vs Drinker	1.41 (1.10–1.79), 0.006 [2989, 90]	0.91 (0.58–1.43), 0.674 [1065, 28]	0.016
TyG-WHtR	Age < 60 vs ≥ 60	1.33 (0.92–1.94), 0.128 [2292, 40]	1.32 (0.99–1.75), 0.057 [1762, 78]	0.822
TyG-WHtR	Male vs Female	1.45 (1.02–2.07), 0.041 [1848, 52]	1.19 (0.89–1.58), 0.233 [2206, 66]	0.887
TyG-WHtR	BMI < 24 vs ≥ 24	1.27 (0.87–1.84), 0.211 [2415, 61]	1.08 (0.73–1.60), 0.695 [1639, 57]	0.148
TyG-WHtR	No hypertension vs Hypertension	1.45 (1.06–2.00), 0.021 [2523, 57]	1.13 (0.83–1.55), 0.435 [1531, 61]	0.921
TyG-WHtR	No diabetes vs Diabetes	1.21 (0.95–1.55), 0.123 [3493, 98]	1.54 (0.92–2.58), 0.102 [561, 20]	0.467
TyG-WHtR	Rural vs Urban	1.30 (1.03–1.64), 0.025 [3489, 104]	0.81 (0.35–1.87), 0.629 [565, 14]	0.674
TyG-WHtR	Never smoked vs Former/current smoker	1.19 (0.91–1.56), 0.200 [2528, 77]	1.55 (1.05–2.31), 0.029 [1526, 41]	0.984
TyG-WHtR	Non-drinker vs Drinker	1.39 (1.08–1.79), 0.011 [2989, 90]	0.93 (0.57–1.52), 0.781 [1065, 28]	0.037
TyG-BMI	Age < 60 vs ≥ 60	1.35 (0.96–1.92), 0.087 [2292, 40]	1.22 (0.93–1.61), 0.156 [1762, 78]	0.647
TyG-BMI	Male vs Female	1.55 (1.10–2.18), 0.013 [1848, 52]	1.14 (0.87–1.50), 0.327 [2206, 66]	0.719
TyG-BMI	BMI < 24 vs ≥ 24	1.53 (0.95–2.48), 0.083 [2415, 61]	1.07 (0.72–1.60), 0.723 [1639, 57]	0.058

Exposure	Subgroup	Subgroup 1 OR (95% CI), P [n, events]	Subgroup 2 OR (95% CI), P [n, events]	P for interaction
TyG-BMI	No hypertension vs Hypertension	1.48 (1.10–1.99), 0.010 [2523, 57]	1.16 (0.85–1.56), 0.347 [1531, 61]	0.612
TyG-BMI	No diabetes vs Diabetes	1.27 (1.00–1.60), 0.048 [3493, 98]	1.40 (0.83–2.34), 0.207 [561, 20]	0.957
TyG-BMI	Rural vs Urban	1.28 (1.02–1.59), 0.029 [3489, 104]	0.99 (0.46–2.11), 0.978 [565, 14]	0.879
TyG-BMI	Never smoked vs Former/current smoker	1.21 (0.94–1.56), 0.145 [2528, 77]	1.50 (1.03–2.20), 0.035 [1526, 41]	0.756
TyG-BMI	Non-drinker vs Drinker	1.39 (1.10–1.76), 0.006 [2989, 90]	0.89 (0.54–1.48), 0.659 [1065, 28]	0.027
METs-IR	Age < 60 vs ≥ 60	1.16 (0.82–1.65), 0.393 [2292, 40]	1.32 (1.00–1.72), 0.047 [1762, 78]	0.187
METs-IR	Male vs Female	1.50 (1.09–2.06), 0.013 [1848, 52]	1.11 (0.84–1.46), 0.466 [2206, 66]	0.604
METs-IR	BMI < 24 vs ≥ 24	1.55 (1.01–2.38), 0.043 [2415, 61]	0.97 (0.66–1.43), 0.889 [1639, 57]	0.043
METs-IR	No hypertension vs Hypertension	1.28 (0.95–1.71), 0.099 [2523, 57]	1.28 (0.95–1.72), 0.106 [1531, 61]	0.694
METs-IR	No diabetes vs Diabetes	1.23 (0.98–1.55), 0.078 [3493, 98]	1.38 (0.85–2.24), 0.194 [561, 20]	0.798
METs-IR	Rural vs Urban	1.25 (1.00–1.54), 0.045 [3489, 104]	1.05 (0.50–2.23), 0.897 [565, 14]	0.900
METs-IR	Never smoked vs Former/current smoker	1.21 (0.93–1.56), 0.152 [2528, 77]	1.40 (0.99–1.99), 0.060 [1526, 41]	0.705
METs-IR	Non-drinker vs Drinker	1.37 (1.08–1.72), 0.009 [2989, 90]	0.91 (0.56–1.49), 0.709 [1065, 28]	0.041

*Note: Within each stratum the fully adjusted (M3) model was fitted with the stratifying variable removed; interaction P from the exposure-by-stratum product term (Wald test, full-sample M3 model); ORs per 1-SD increase (SD from the full sample). Square brackets: stratum n and events. Exploratory analysis; interaction P values are nominal. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.*

Sensitivity analyses

After excluding 446 participants with BMI ≥ 28 kg/m² (17 events), the subset of 3,611 participants (102 events) yielded fully adjusted ORs of 1.30 (95% CI 1.01–1.67, $P = 0.040$) for TyG-WC, 1.30 (95% CI 1.00–1.68, $P = 0.048$) for TyG-WHtR, 1.38 (95% CI 1.03–1.83, $P = 0.029$) for TyG-BMI and 1.37 (95% CI 1.04–1.79, $P = 0.024$) for METS-IR, close to the full-sample estimates, while cumulative TyG ($P = 0.416$) and

TyG ($P = 0.208$) remained non-significant; M2 results were consistent (four composite indices $P = 0.009–0.029$) (Additional file 2: Table S2).

In uric-acid-stratified models (Additional file 4: Table S4), all six interaction tests were non-significant ($P = 0.185–0.985$). Within the high-uric-acid group, TyG-BMI ($OR = 1.31$, 95% CI 1.01–1.69, $P = 0.040$) and METS-IR ($OR = 1.35$, 95% CI 1.05–1.73, $P = 0.017$) were significant, whereas no index was significant within the normal-uric-acid group.

Removing uric acid from the fully adjusted model changed ORs by + 0.3% to + 0.9%, with slightly smaller P values for the four composite indices (0.015–0.022), indicating that the association estimates were not materially affected by adjustment for uric acid (Additional file 5: Table S5).

Agreement of self-reported kidney disease with objective CKD

Self-reported kidney disease agreed poorly with objectively defined CKD (Additional file 1: Table S1). Referenced to $eGFR < 60$ mL/min/1.73 m², the 2011 creatinine-based evaluation ($N = 11,489$) yielded a sensitivity of 15.7% (95% CI 11.9–20.4), specificity 93.5%, positive predictive value 5.7% (4.3–7.6) and Kappa 0.050; the corresponding 2015 creatinine-based values were 12.0%, 94.2%, 8.5% and 0.052 ($N = 13,202$), and the 2015 cystatin-C-based values were 10.4%, 94.2%, 9.9% and 0.045 ($N = 13,198$). Both under-reporting and over-reporting were present. Self-reported kidney disease was therefore not used as an exclusion criterion or for outcome definition.

DISCUSSION

In this four-year prospective cohort of 4,068 Chinese adults at CKM stage 0–3, all six IR surrogate indices were associated with incident CKD in crude and demographically adjusted models, but the associations diverged as adjustment deepened: TyG and cumulative TyG lost significance beyond M2, whereas the four composite indices incorporating adiposity information remained significant under full adjustment, with TyG-BMI and TyG-WHtR showing the most robust and complementary performance. These findings suggest that within a stage 0–3 CKM population, composite IR indices carry renal risk information beyond simple glycaemic-lipid measures, while their discrimination when used alone remains limited.

In shallowly adjusted models the present results align with prior evidence in direction and magnitude. Meta-analytic evidence supports a positive TyG-CKD association with reproducible dose-response patterns [20]; a functional-community cohort found higher CKD incidence among people with persistently high TyG [18]; and prospective analyses of cumulative TyG-BMI reported clear positive associations [21]. Our M1 estimates for TyG ($OR 1.28$, 95% CI 1.08–1.52) and cumulative TyG (1.25, 1.04–1.49) are of the same order, and top-tertile risks in M1 ranged from 1.73 to 2.55 times the reference. This concordance attenuated with deeper adjustment, which has two non-exclusive readings. Adjustment for hypertension and diabetes, which lie downstream of IR, can be seen as blocking part of

the mediated pathway; single indices carry a narrower glycolipid signal that downstream phenotypes largely absorb, whereas composite indices additionally encode fat distribution and body size and retain residual information after such adjustment. Alternatively, composite indices may relate to CKD through pathways less readily absorbed by metabolic history. Either way, the judgement of an "independent association" depends on the adjustment strategy, and cross-study comparisons must check the covariate sets. We also observed that demographic adjustment strengthened rather than attenuated the associations (M1 above crude). Age is a strong CKD risk factor whose correlation with the indices was not formally examined here; the strengthening suggests masking by the demographic composition, and crude models alone should not be taken as unbiased estimates.

Which index performs best remains unsettled in the literature, consistent with the divergence observed here. TyG-WHtR showed the strongest predictive value for kidney function decline in elderly hypertensive populations [33]. In the UK Biobank, insulin resistance mediated part of the association between adiposity markers and incident chronic kidney disease [34]. NHANES analyses reported non-monotonic relations of TyG and TyG-WHtR with CKD prevalence, turning positive above thresholds of 9.05 and 4.3 respectively [25]. Chinese comparisons have variously favoured TyG-WHtR for discrimination and TyG for association strength [23], with NHANES data likewise indicating differing cardiorenal patterns of TyG and composite indices [24]. Our within-cohort comparison under identical conditions adds CKM-framework evidence to this question. The construct differences offer one reading: TyG captures only the glycolipid environment, the TyG-adiposity products integrate fat distribution, and METS-IR additionally incorporates HDL-C, so the indices carry different information. The divergence of our cumulative TyG results from studies using longer cumulative exposure windows [18, 21] may reflect the limited information in only two measurements, the overlap of the computation window with the follow-up endpoint, and the restricted variability of the indices within a stage 0–3 population; our results therefore do not refute the cumulative exposure hypothesis, and for practical purposes the single-measurement composite indices are already usable, with repeated measurement a more promising route to precision than switching indices.

Placing the renal endpoint within the CKM staging framework is the main feature distinguishing this work. Longitudinal evidence links TyG to kidney function worsening in CKM populations [35], TyG relates to cardiovascular outcomes in a stage-dependent manner [36], and atherogenic-index-of-plasma and TyG relate to renal decline in early CKM populations [28]; TyG also modifies CKD renal trajectories through pulse pressure and hypertension [37], and systemic inflammatory indices show independent associations with renal worsening in CKM populations [38], consistent in direction with the non-significant elevation of C-reactive protein among incident cases here ($P = 0.085$). IR indices have been used to prospectively predict cardiovascular events in CKM stage 0–3 populations [27]; the present study extends the same framework to a renal endpoint. Within our cohort, CKM stage 3 accounted for 15.5% of participants but 38.3% of incident cases. This concentration is a descriptive, unadjusted result, and because stage assignment includes age, staging and age structure are entangled; the IR indices provide continuous glycolipid information beyond the staging elements, but we did not formally decompose the increments of staging and indices, and the safer reading is complementarity rather than

independence. Previous CHARLS-based work on IR indices and multimorbidity [39] and on the CRP-TyG index across cardiovascular risk stages [40] points the same way.

Mechanistically, the IR-to-kidney-damage pathway is well described in three strands: haemodynamic (hyperinsulinaemia activating the intrarenal renin-angiotensin system, sodium retention, sympathetic activation and reduced nitric oxide bioavailability, producing glomerular hypertension) [12, 15]; metabolic (ectopic lipid accumulation in tubular epithelial cells with ceramide-mediated oxidative stress, mitochondrial dysfunction and interstitial fibrosis) [12]; and hyperfiltration (higher renal plasma flow and filtration fraction in central obesity, driving glomerular hypertrophy towards focal segmental sclerosis). Central obesity amplifies all three strands, and the waist-to-height ratio is its surface marker, consistent with the retention of TyG-WHtR and TyG-BMI under full adjustment here [33]. Adipokine disturbance accompanies all strands, and visceral adipose dysfunction is the starting point of the AHA staging. Conversely, kidney damage itself aggravates metabolic disturbance and raises cardiovascular mortality risk [41], further supporting the incorporation of renal outcomes into the CKM framework. These readings are literature-inferred; this study performed no mediation decomposition, and the relative contribution of each pathway awaits data.

The AUCs of 0.563–0.592 indicate that none of the single-measurement indices is sufficient for screening on its own. Association and discrimination are different questions, and this study answers only the former; comparable IR indices achieve AUCs around 0.7 for hypertension prediction [42], discrimination of such indices is generally moderate across outcomes [43], and because we did not test the increment of IR indices over traditional risk factors, the reported predictive gains in the literature are neither confirmed nor excluded here. TyG-based indices are not kidney-specific markers, being associated also with outcomes such as depression [44], which plausibly limits standalone discrimination for renal endpoints. The practical value of the composite indices lies in accessibility rather than discrimination: their components (fasting glucose, triglycerides, waist circumference, height or weight) are routine primary-care items with near-zero incremental cost, so a reasonable application is to use the better-performing composite indices as continuous variables alongside CKM staging and eGFR in risk evaluation, rather than as standalone screening tools. Subgroup and interaction findings should be treated as hypothesis-generating, as all interaction P values are nominal; for example, the TyG-WHtR association among rural residents (OR = 1.30, 95% CI 1.03–1.64) was not supported by effect modification (interaction P = 0.674) and the urban stratum had only 14 events with a wide interval (0.35–1.87). Two further boundaries apply: the population is aged 45 years or older, and lipid- or glucose-lowering treatment alters index values, so cross-time comparisons should account for medication.

This study has limitations. First, exposure was measured at only two waves: cumulative TyG approximates the exposure curve from two points and its window overlaps the endpoint, and the five single-measurement indices rest on one baseline blood draw, so within-person variation of triglycerides and glucose will misclassify exposure and dilute associations. Second, the outcome was a single eGFR threshold without albuminuria, confirmation of persistence over three months, or eGFR slope; participants near the threshold at baseline are more likely to cross it during follow-up, and transient

declines can create false positives while recovery can mask true cases, so misclassification arose in both directions. Albuminuria testing rates remain low among high-risk populations in real-world practice [45]. Third, only 120 events occurred (118 in fully adjusted models); the borderline significance of the composite indices ($P = 0.019\text{--}0.028$) and the small strata (14–28 events) call for replication in larger samples. Fourth, as an observational analysis, residual confounding cannot be excluded: smoking, drinking and diagnoses were self-reported, blood pressure was measured on one day, and diet, physical activity and medication were not modelled; CHARLS has a complex sampling design with same-household members, and no survey weights or cluster-robust standard errors were used; and the analytical sample retained 23.0% of the baseline survey, so population-level generalisation requires caution. Future analyses using the later CHARLS waves can extend the cumulative exposure window and separate the exposure and outcome windows, and composite renal endpoints combining albuminuria with eGFR change, together with net reclassification and integrated discrimination analyses over traditional risk factors, would answer the increment question left open here; calibration of screening cutoffs in sensitivity, specificity and absolute-risk terms is a prerequisite for primary-care implementation.

Conclusions

Among middle-aged and older Chinese adults at CKM stage 0–3, associations of the six IR surrogate indices with four-year incident CKD diverged with adjustment depth: TyG and cumulative TyG lost significance under comprehensive adjustment, whereas TyG-WC, TyG-WHtR, TyG-BMI and METS-IR remained significant, with TyG-BMI and TyG-WHtR the most robust in complementary ways (TyG-BMI with the smallest P values in M2, M3 and the no-uric-acid model; TyG-WHtR leading in crude association, incidence gradient and AUC). Discrimination of all single-measurement indices was limited (AUC 0.563–0.592). The composite indices may serve as a low-cost complement to CKM staging for identifying subgroups who need eGFR monitoring, pending verification of their incremental value over existing risk information.

Abbreviations

AIP

atherogenic index of plasma

AUC

area under the curve

BAG

the risk score in the Chinese CKM2S2-BAG system

BMI

body mass index

BUN

blood urea nitrogen

CHARLS

China Health and Retirement Longitudinal Study
CKD
chronic kidney disease
CKD-EPI
Chronic Kidney Disease Epidemiology Collaboration
CKM
cardiovascular-kidney-metabolic
CRP
C-reactive protein
CysC
cystatin C
DBP
diastolic blood pressure
eGFR
estimated glomerular filtration rate
FBG
fasting blood glucose
HDL-C
high-density lipoprotein cholesterol
IR
insulin resistance
LDL-C
low-density lipoprotein cholesterol
METS-IR
metabolic score for insulin resistance
OR
odds ratio
RCS
restricted cubic spline
ROC
receiver operating characteristic
SBP
systolic blood pressure
SCr
serum creatinine
SD
standard deviation
TC
total cholesterol
TG

triglyceride
TyG
triglyceride-glucose
TyG-BMI
TyG-body mass index
TyG-WC
TyG-waist circumference
TyG-WHtR
TyG-waist-to-height ratio
UA
uric acid
VIF
variance inflation factor
WC
waist circumference
WHtR
waist-to-height ratio

Declarations

Ethics approval and consent to participate

The CHARLS survey was approved by the Biomedical Ethics Review Committee of Peking University (IRB00001052-11015) and conducted in accordance with the Declaration of Helsinki; all participants provided written informed consent. The present secondary analysis used de-identified CHARLS data under the CHARLS data use agreement.

Consent for publication

Not applicable.

Availability of data and materials

The CHARLS data analysed in this study are publicly available from the CHARLS official data website (<https://charls.charlsdata.com>) upon registration and acceptance of the data use agreement. No new datasets were generated.

Competing interests

The authors declare that they have no competing interests.

Funding

This research received no specific funding from any public, commercial, or not-for-profit funding agency.

Authors' contributions

JW: conceptualization, methodology, formal analysis, investigation, data curation, visualization, writing – original draft. ML: methodology, writing – review and editing. XT: conceptualization, methodology, supervision, writing – review and editing. YC: conceptualization, methodology, supervision, writing – review and editing. XT and YC jointly supervised this work. XT is responsible for correspondence during submission and peer review on behalf of all authors. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

Authors' information

Not applicable.

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Figures

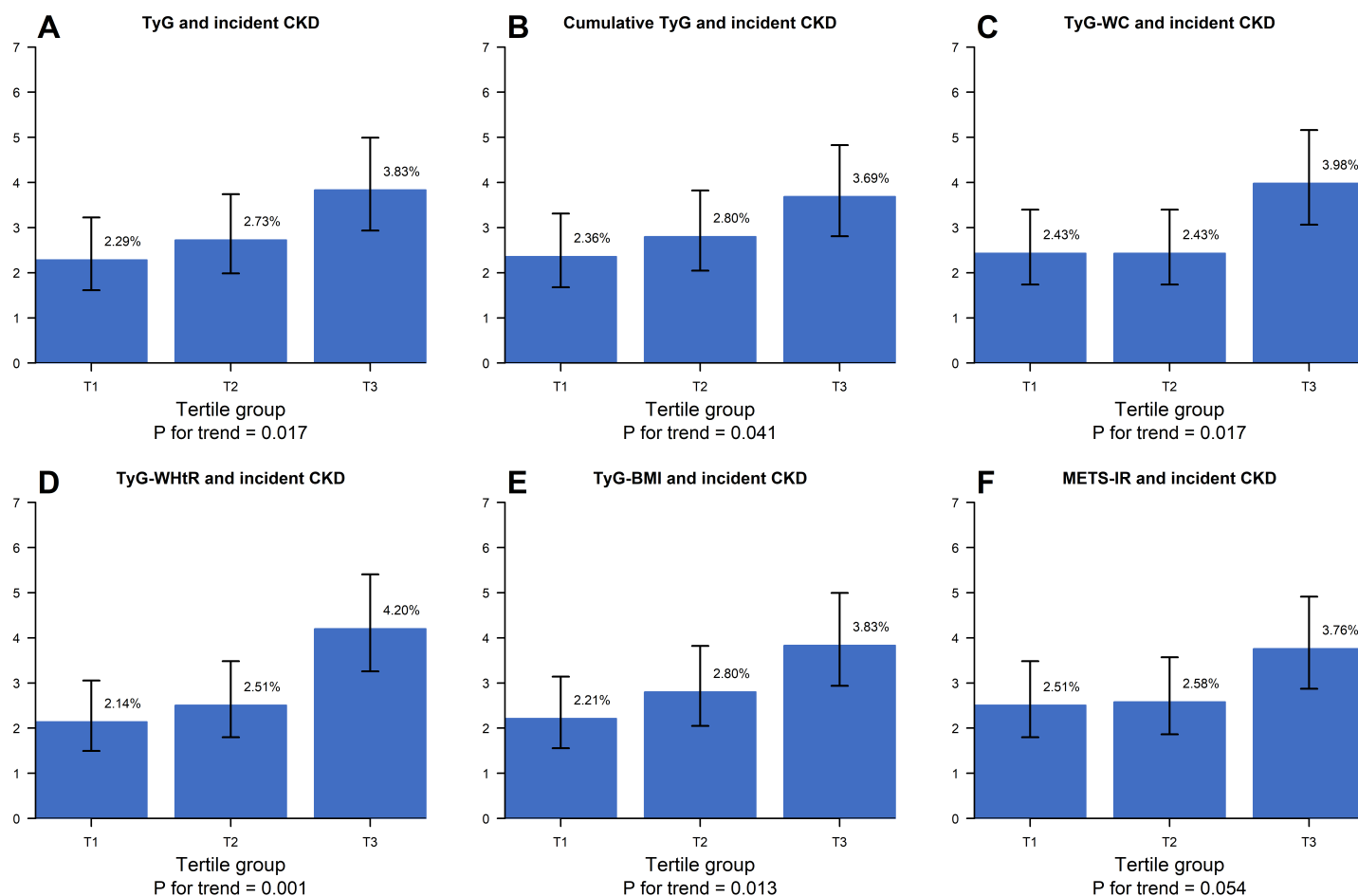


Figure 1

Incidence of new-onset CKD by baseline tertile of the six IR surrogate indices. Error bars are Wilson 95% confidence intervals; P for trend from the Cochran-Armitage chi-square test (unadjusted); n=1,356 per tertile.

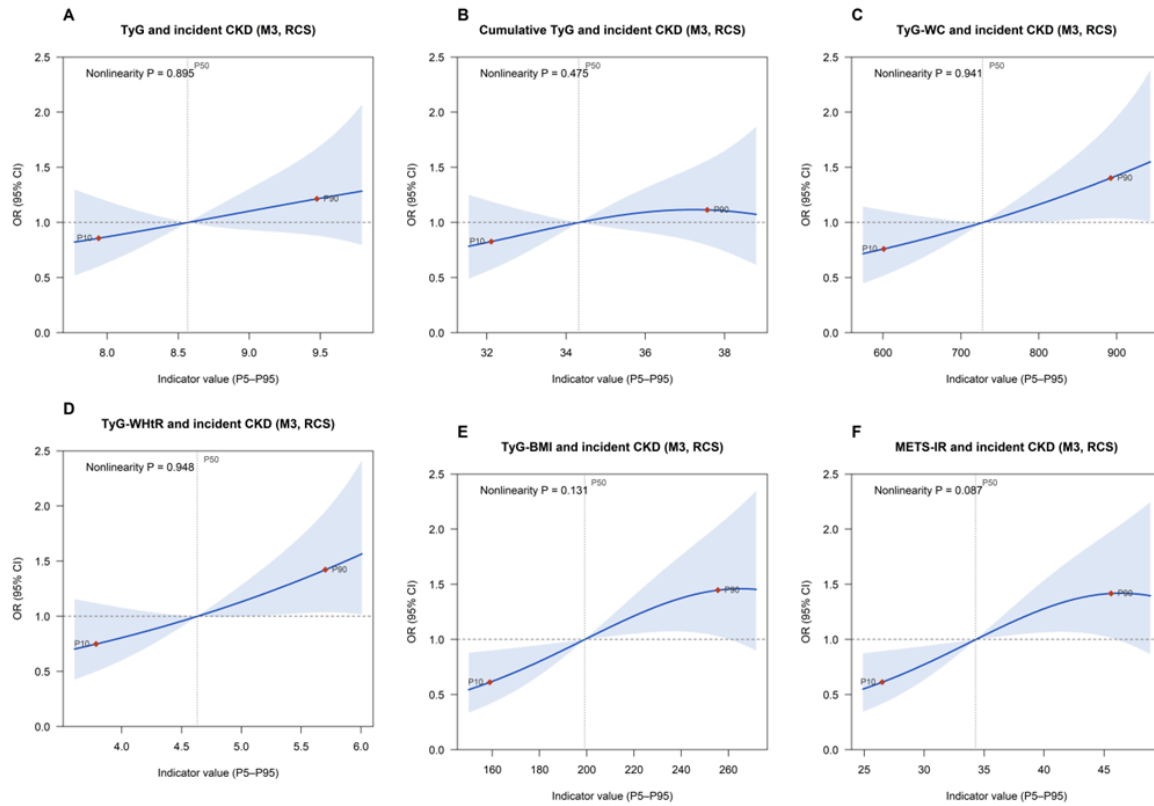


Figure 2

Dose-response associations of the six IR surrogate indices with new-onset CKD from restricted cubic spline models. Three knots placed at the 10th, 50th and 90th percentiles of each index, referenced to the 50th percentile (OR=1), with the x-axis trimmed to the 5th-95th percentile range. Models fully adjusted as in M3 (Table 2). Non-linearity P from the likelihood-ratio test of the spline model (one non-linear term) against the linear model; analysis set n=4,054 with 118 events.

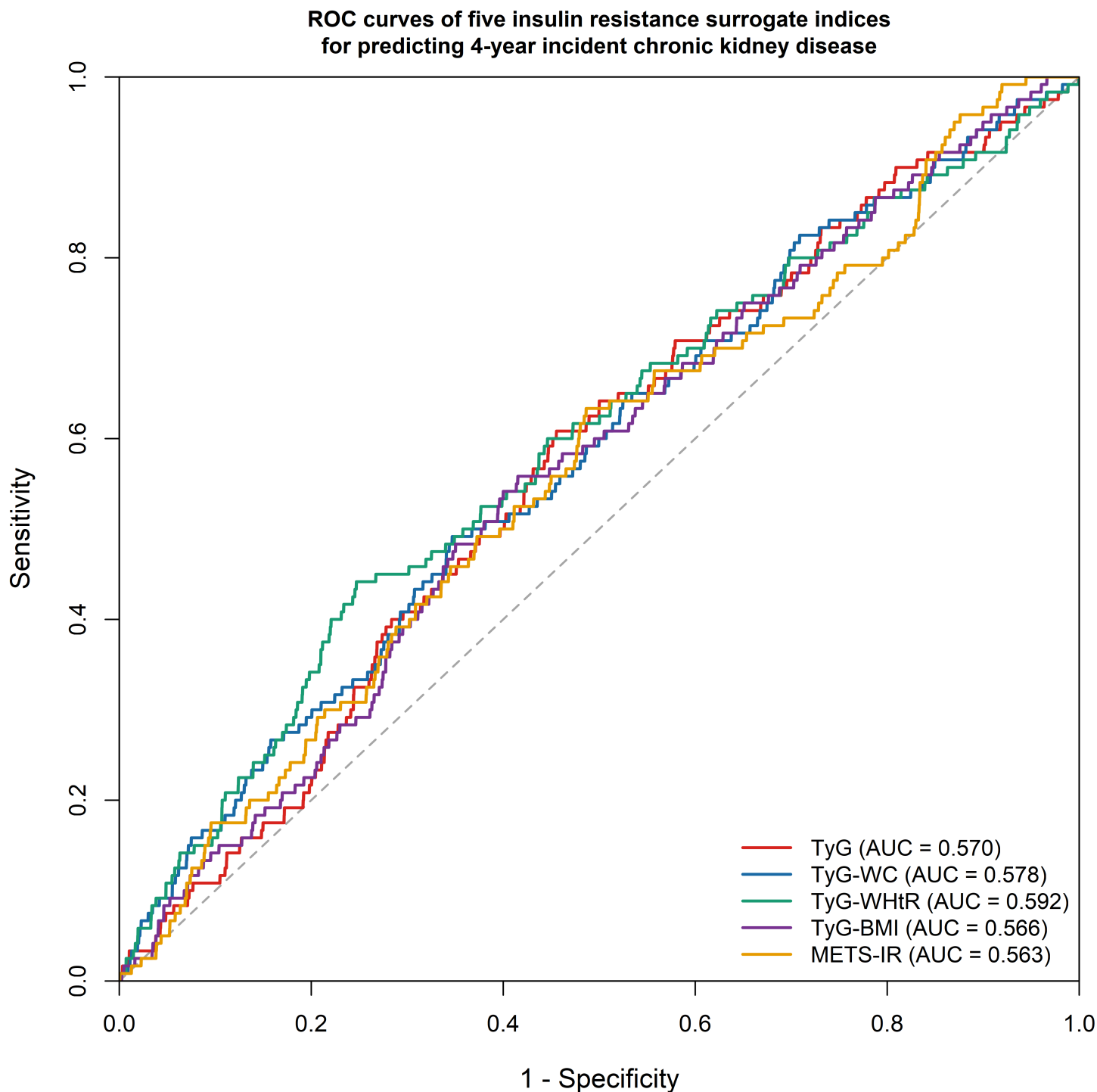


Figure 3

Receiver operating characteristic curves of the five single-measurement IR indices for new-onset CKD. AUCs and 95% CIs by the DeLong method; diagonal dashed line is the no-discrimination reference. n=4,068, 120 events. Cumulative TyG is not shown (see Table 4 footnote).

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