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Composite Metabolic Indices for Incident Cardiometabolic Multimorbidity: Evidence from the CHARLS and ELSA Cohorts

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Abstract

Background Cardiometabolic multimorbidity (CMM) is increasingly common and reflects the accumulation of metabolic and cardiovascular disorders. Composite metabolic indices integrating glucose-lipid metabolism and obesity-related phenotypes may improve risk assessment, but their comparative performance across populations remains unclear. We evaluated five composite metabolic indices in relation to incident CMM in two prospective cohorts from China and the UK.

Methods Baseline data were obtained from the China Health and Retirement Longitudinal Study (CHARLS) and the English Longitudinal Study of Ageing (ELSA). Five composite indices were examined: TyG-WHtR, TyG-BRI, AIP-WHtR, AIP-BRI, and the integrated cardiometabolic risk score (ICMRS). Multivariable Cox proportional hazards models were used to assess associations with incident CMM. Restricted cubic spline, discrimination, Kaplan-Meier cumulative incidence, subgroup, sensitivity, and pooled cohort interaction analyses were performed.

Results A total of 8,682 participants from CHARLS and 2,422 from ELSA were included, among whom 1,471 and 540 incident CMM cases occurred during follow-up, respectively. In CHARLS, all five indices were associated with incident CMM, and the strongest association was observed for TyG-WHtR (HR 3.18, 95% CI 2.70-3.74). In ELSA, significant associations were observed for TyG-WHtR, TyG-BRI, AIP-WHtR, and ICMRS, whereas AIP-BRI was not statistically significant. Across both cohorts, TyG-WHtR and ICMRS showed the most consistent performance. Pooled interaction analyses suggested heterogeneity in effect estimates between cohorts, with stronger associations in CHARLS than in ELSA.

Conclusions Composite metabolic indices were associated with incident CMM in both cohorts, although the magnitude and consistency of associations differed across indices and populations. TyG-WHtR and ICMRS showed the most stable overall performance, supporting their potential value in assessing cardiometabolic risk burden across populations.

Keywords: cardiometabolic multimorbidity; metabolic risk; obesity phenotypes; TyG-WHtR; ICMRS; cohort study.

Introduction

With the acceleration of global population aging and profound changes in lifestyle, the coexistence of multiple chronic non-communicable diseases is becoming increasingly prominent[1]. Cardiometabolic multimorbidity (CMM) refers to the co-occurrence of two or more cardiometabolic diseases in an individual, such as hypertension, type 2 diabetes, coronary heart disease, and stroke[2, 3]. Compared with a single disease, patients with CMM face higher mortality risk, poorer functional status, and a heavier medical burden, making it a core issue in public health in aging societies[4-6]. Therefore, identifying robust metabolic risk markers has important clinical and public health relevance for understanding and potentially reducing the burden of CMM in ageing populations.

The occurrence of CMM is not driven by a single risk factor, but rather the result of long-term accumulation and interaction of multiple cardiac metabolic abnormalities. Previous studies have indicated that central obesity, glucolipid metabolic disorders, insulin resistance, and chronic low-grade inflammation can collectively promote the clustering of cardiometabolic diseases such as diabetes, coronary heart disease, and stroke through pathways including vascular endothelial dysfunction, atherosclerosis, β-cell dysfunction, and cardiovascular remodeling[7-10]. Although traditional single indicators such as fasting glucose or triglycerides can partially reflect certain metabolic dimensions, they are insufficient to comprehensively capture an individual's overall cardiometabolic risk burden. In recent years, the triglyceride-glucose index (TyG)[11] and the atherogenic index of plasma (AIP) [12] have received widespread attention as reliable surrogate markers of insulin resistance and dyslipidemia[13, 14]. The atherogenic index of plasma reflects atherosclerotic dyslipidemia through the TG/HDL-C ratio and has been confirmed to be associated with cardiovascular disease risk in middle-aged and elderly populations[15]. The waist-to-height ratio (WHtR) [16] and the body roundness index (BRI)[17] can better reflect central obesity and body fat distribution characteristics. Combining TyG or AIP with WHtR and BRI can construct composite indicators such as TyG-WHtR, TyG-BRI, AIP-WHtR, and AIP-BRI, which integrate information on glucose metabolism, lipid metabolism, and central obesity within a single index. Recent studies have shown that TyG-WHtR is closely associated with the risk of CMM[18], but a systematic comparison of the relative performance and external generalizability of different composite metabolic indicators across multinational aging

populations is still lacking. Meanwhile, the integrated cardiometabolic risk score (ICMRS), which summarizes multidimensional metabolic information, may provide a broader estimate of overall cardiometabolic risk burden than single-component markers; however, its performance in predicting incident CMM across different cohorts still requires further validation[19].

Existing research has confirmed that composite indices such as TyG-WHtR are significantly associated with the risk of developing type 2 diabetes, cardiovascular diseases, and strokes[20-22]. For instance, a prospective study based on the Japanese population indicated that TyG-WHtR ratio index has good predictive value for long-term type 2 diabetes risk, outperforming the individual TyG index or WHtR[23]. Moreover, recent studies have begun to focus on the value of combining TyG with traditional or novel obesity indices in assessing CMM risk, suggesting that the integration of metabolic and body shape indicators may help improve CMM risk stratification[24]. However, existing studies predominantly concentrate on single race or cohorts, mainly revolving around TyG-related indices; there is still a lack of systematic comparisons regarding the relative performance and external generalizability of TyG/AIP combined with different body shape indices for predicting newly developed CMM risk in aging populations across countries. China and the UK exhibit significant differences in population structure, dietary patterns, obesity phenotypes, and chronic disease management systems, which may lead to varying predictive performances of the same indices in the two cohorts. Therefore, such studies are crucial for evaluating the cross-population applicability of these indices and for screening more robust risk identification tools.

To address this gap, we used data from two large prospective ageing cohorts, CHARLS and ELSA, to systematically evaluate and compare the associations of five composite metabolic indices—TyG-WHtR, TyG-BRI, AIP-WHtR, AIP-BRI, and ICMRS—with incident CMM. These indices may provide useful information for identifying individuals at higher risk of cardiometabolic multimorbidity using routinely available clinical measures. Unlike prior studies that mainly focused on a single index within a single population, our study directly compared the relative performance, stability, and cross-cohort heterogeneity of multiple composite metabolic indices in Chinese and UK ageing populations. We further assessed these associations using Cox regression, restricted cubic spline analysis, ROC analyses,

Kaplan-Meier cumulative incidence analysis, cohort interaction analysis, subgroup analysis, and sensitivity analysis.

Methods

Data sources and study population

This study was based on two prospective ageing cohorts, the China Health and Retirement Longitudinal Study (CHARLS)[25] and the English Longitudinal Study of Ageing (ELSA)[26]. In the CHARLS cohort, Wave 3 (2015–2016) was selected as the baseline assessment due to its comprehensive biochemical and anthropometric datasets, which are essential for deriving the TyG-WHtR, TyG-BRI, AIP-WHtR, AIP-BRI, and ICMRS indices. This selection also facilitates the tracking of incident CMM in subsequent waves. Similarly, ELSA utilized Wave 6 as the starting point, motivated by the concurrent availability of crucial exposure variables and longitudinal follow-up records. Standardizing these initial time points across both populations ensured methodological uniformity in cohort assembly and enhanced the comparability of findings. To maintain the prospective nature of the study, the analysis was limited to individuals without prevalent CMM at enrollment who also had complete follow-up data.

In CHARLS, the baseline sample for Wave 3 consisted of 21,097 individuals. After excluding 4,235 individuals aged under 50 years, 16,862 individuals remained. Further exclusion of 6,052 individuals with missing key exposure variables resulted in a complete exposure sample of 10,810 individuals. Following the exclusion of 1,580 individuals with pre-existing CMM at baseline, the final baseline sample comprised 9,230 individuals. After excluding 548 individuals without follow-up information, a total of 8,682 individuals were included in the analysis.

In ELSA, the baseline sample for Wave 6 consisted of 10,601 individuals, with successful matching of 8,054 individuals to the Wave 6 nurse data. After excluding 30 individuals aged under 50 years, 8,024 individuals remained. Further exclusion of 5,233 individuals with missing key exposure variables resulted in a complete exposure sample of 2,791 individuals. Following the exclusion of 11 individuals with pre-existing CMM at

baseline, the final baseline sample comprised 2,780 individuals. After excluding 358 individuals without follow-up information, a total of 2,422 individuals were included in the analysis. The inclusion and exclusion process of the study subjects is shown in Figure 1.

Definition and calculation of composite metabolic indices

These composite indices were selected because they combine complementary dimensions of cardiometabolic risk. TyG reflects insulin resistance and glucose-lipid metabolic dysfunction, AIP reflects atherogenic dyslipidemia, whereas WHtR and BRI reflect central obesity and body fat distribution. Therefore, combining TyG or AIP with WHtR or BRI may better capture the joint contribution of metabolic dysfunction and adiposity to incident CMM than any single component alone.

The following formulas were used to calculate the basic indicators[27-29].

$$TyG=ln\left(\frac{TG\times FPG}{2}\right)$$

$$AIP=log_{10}\left(\frac{TG}{HDL\text{-}C}\right)$$

$$WHtR=WC(cm)/Height(cm)$$

$$BRI=364.2-365.5\times\sqrt{1-(WC/(2\pi)/0.5\times Height)^2}$$

The composite indices were then defined as follows[30-33]:

$$TyG\text{-}WHtR=TyG\times WHtR$$

$$TyG\text{-}BRI=TyG\times BRI$$

$$AIP\text{-}WHtR=AIP\times WHtR$$

$$AIP\text{-}BRI=AIP\times BRI$$

ICMRS was constructed as an equal-weight sum of standardized TyG, BRI, and AIP values, with standardization performed separately within each cohort.

$$Z_{TyG}=\frac{TyG-\mu TyG}{\sigma TyG}$$

$$Z_{BRI}=\frac{BRI-\mu BRI}{\sigma BRI}$$

$$Z_{AIP}=\frac{AIP-\mu AIP}{\sigma AIP}$$

$$ICMRSeq=Z_{TyG}+Z_{BRI}+Z_{AIP}$$

Here, μ and σ represent the mean and standard deviation of the corresponding indicators within the research sample, respectively. Standardization was performed within

each cohort separately. In subsequent analyses, this indicator is uniformly referred to as ICMRS in the paper, while the data processing variable is named *ICMRSeq*.

Outcome definition

The primary outcome of this study was incident cardiometabolic multimorbidity (CMM), identified during follow-up among participants who were free of CMM at baseline. CMM was defined as the coexistence of at least two cardiometabolic diseases, including diabetes, heart disease, and stroke[34]. The diagnosis of heart disease and stroke is based on self-reported data collected during baseline and follow-up surveys, or relevant medication usage. An individual is diagnosed with diabetes if any of the following criteria are met: (1) self-reported diabetes ("Has your doctor diagnosed you with diabetes or hyperglycemia?"); (2) current use of hypoglycemic medications; (3) FBG $\geqslant$ 126 mg/dL; or (4) hemoglobin A1c (HbA1c) $\geqslant$6.5%. For secondary outcomes, we conducted further analyses on diabetes, heart disease, and stroke separately. Our CMM diagnostic criteria are consistent with previous literature based on CHARLS data[35].

Covariates

Potential confounding factors were selected on the basis of prior literature and data availability and were included in the multivariable analyses: (1) Demographic data: baseline age (years, continuous variable), sex (female and male), marital status (married and others), education level (illiterate, junior high school and below, and junior high school and above), and place of residence (rural villages and urban communities). (2) Lifestyle data: smoking status (never and others), alcohol consumption status (current and others). (3) Medical history (present or absent): hypertension, cancer. (4) Physical measurements: systolic blood pressure (SBP) and diastolic blood pressure (DBP). (5) Laboratory test data: total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). The determination of hypertension is based on SBP$\geqslant$ 140 mmHg or DBP $\geqslant$90 mmHg, or a previous history of hypertension, or the use of antihypertensive medications[36]. The determination of dyslipidemia is based on self-reported dyslipidemia or the use of lipid-lowering treatment. This study considers the aforementioned variables as potential confounders, and in both CHARLS and ELSA, the main models adopt a covariate adjustment

strategy that is as consistent as possible to enhance the comparability of results between the two cohorts.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation, while categorical variables are represented as counts and percentages. Based on whether new cases of CMM occurred during the follow-up period, the study subjects were divided into a non-incident CMM group and an incident CMM group. The comparison of continuous variables between the two groups was conducted using t-tests or Wilcoxon rank-sum tests, while categorical variables were compared using x^2 tests.

To assess the association between five composite metabolic indicators and the risk of incident CMM, this study employed the Cox proportional hazards model[37] to calculate the hazard ratios (HR) and 95% confidence intervals (95% CI). Each composite indicator was categorized into quartiles, with the lowest quartile (Q1) serving as the reference group for comparing the risk of incident CMM in Q2, Q3, and Q4, along with trend tests. Additionally, each indicator was standardized to further evaluate the association of a one-standard-deviation increase with the risk of incident CMM.

Three progressively adjusted Cox models were fitted. Model 1 was adjusted for age and gender; Model 2 was additionally adjusted for education, marital status, smoking, and drinking. Model 3 was further adjusted for hypertension, cancer history, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) based on Model 2. The fully adjusted model (Model 3) was used as the main model in the primary analyses.

To investigate the dose-response relationship between five composite metabolic indicators and the risk of incident CMM, this study employed a restricted cubic spline (RCS) model to evaluate potential nonlinear associations[38], adjusting for covariates in Model 3. To further explore the potential threshold effects suggested by the RCS curves, we applied a piecewise Cox regression model for threshold effect analysis specifically for TyG-WHtR and ICMRS, determining the optimal threshold point using the maximum likelihood method. To

assess the discriminative ability of each indicator, we compared the predictive performance for incident CMM using traditional ROC curves, time-dependent ROC curves[39], and Harrell's C-index[40]. Kaplan – Meier cumulative incidence curves were plotted to describe the cumulative incidence of incident CMM across ICMRS quartiles, and log-rank tests were used to compare differences among groups. All primary analyses were first conducted separately in the CHARLS and ELSA cohorts. We then pooled the two cohorts and introduced an interaction term between cohort and each standardized composite index to test whether the strength of association differed between CHARLS and ELSA. Subgroup analyses and sensitivity analyses were subsequently performed to assess the robustness of the main findings. The subgroup analyses were stratified by sex, age, BMI, alcohol consumption, and smoking status; the sensitivity analyses included complete case analysis and repeated analysis after excluding early events. All statistical analyses were conducted using *R software (version 4.5.1)* and *Stata 17*. A two-tailed P value < 0.05 was considered statistically significant.

Results

Baseline Characteristics of the study participants

A total of 8,682 participants from CHARLS and 2,422 participants from ELSA were included in the final analyses. Participants in each cohort were classified into incident CMM and non-incident CMM groups according to whether CMM occurred during follow-up. The participant selection process is shown in Figure 1.

In the CHARLS cohort, 1,471 (16.9%) participants developed incident CMM during follow-up. Compared with those without incident CMM, participants with incident CMM were older and had higher levels of systolic blood pressure, diastolic blood pressure, HbA1c, total cholesterol, triglycerides, and LDL-C, but lower HDL-C levels (all P<0.05). They were also more likely to be female, less educated, unmarried, current non-drinkers, and current non-smokers. In addition, the prevalence of hypertension, diabetes, heart disease, and stroke were 48.25%, 9.86%, 17.35%, and 4.69%, respectively in the incident CMM group, all of which were significantly higher than those non-incident CMM group(all P<0.05), whereas cancer did not differ significantly between groups (P=0.713) (Table 1).

Table 1 Baseline characteristics of CHARLS participants according to incident CMM status

Variable	Total (n=8682)	No incident CMM (n=7211)	Incident CMM (n=1471)	P value
Age, years	62.23 ± 8.45	61.92 ± 8.50	63.72 ± 8.04	<0.001
Sex				<0.001
0	4500 (51.83)	3660 (50.76)	840 (57.10)	
1	4182 (48.17)	3551 (49.24)	631 (42.90)	
Education				0.001
Primary school or below	3976 (45.86)	3260 (45.27)	716 (48.74)	
Primary school	2061 (23.77)	1691 (23.48)	370 (25.19)	
Middle school	1745 (20.13)	1502 (20.86)	243 (16.54)	
High school or above	888 (10.24)	748 (10.39)	140 (9.53)	
Marital status				<0.001
Other	1185 (13.65)	938 (13.01)	247 (16.79)	
Married	7496 (86.35)	6272 (86.99)	1224 (83.21)	
Smoking				<0.001
No	5554 (64.07)	4543 (63.11)	1011 (68.78)	
Yes	3115 (35.93)	2656 (36.89)	459 (31.22)	
Drinking				<0.001
No	6143 (70.84)	5017 (69.64)	1126 (76.70)	
Yes	2529 (29.16)	2187 (30.36)	342 (23.30)	
Hypertension				<0.001
No	5897 (74.72)	5248 (79.06)	649 (51.75)	
Yes	1995 (25.28)	1390 (20.94)	605 (48.25)	
Diabetes				<0.001
No	7549 (96.03)	6425 (97.14)	1124 (90.14)	
Yes	312 (3.97)	189 (2.86)	123 (9.86)	
Heart disease				<0.001
No	7198 (91.38)	6169 (93.02)	1029 (82.65)	
Yes	679 (8.62)	463 (6.98)	216 (17.35)	
Stroke				<0.001
No	7723 (97.23)	6503 (97.60)	1220 (95.31)	
Yes	220 (2.77)	160 (2.40)	60 (4.69)	
Cancer				0.713
No	7823 (98.70)	6561 (98.72)	1262 (98.59)	
Yes	103 (1.30)	85 (1.28)	18 (1.41)	
SBP, mmHg	126.64 ± 19.35	124.88 ± 18.96	135.36 ± 18.91	<0.001
DBP, mmHg	74.63 ± 11.51	73.91 ± 11.40	78.20 ± 11.37	<0.001
HbA1c, %	5.93 ± 0.87	5.83 ± 0.68	6.40 ± 1.40	<0.001
TC, mg/dL	184.98 ± 36.13	184.22 ± 36.15	188.75 ± 35.81	<0.001
TG, mg/dL	138.46 ± 86.53	134.76 ± 84.38	156.58 ± 94.35	<0.001
LDL-C, mg/dL	103.35 ± 28.69	102.88 ± 28.59	105.68 ± 29.09	0.001
HDL-C, mg/dL	51.83 ± 11.77	52.19 ± 11.95	50.08 ± 10.67	<0.001
FBG, mg/dL	101.57 ± 30.98	98.95 ± 25.84	114.44 ± 46.83	<0.001
Waist circumference, cm	84.72 ± 12.92	83.94 ± 12.58	88.50 ± 13.88	<0.001
Height, m	1.58 ± 0.10	1.58 ± 0.10	1.57 ± 0.09	0.190
BMI, kg/m²	24.19 ± 15.97	23.99 ± 17.30	25.18 ± 6.10	0.009
TyG	16.06 ± 0.62	16.01 ± 0.59	16.27 ± 0.67	<0.001
AIP	0.37 ± 0.28	0.36 ± 0.28	0.44 ± 0.28	<0.001
WHtR	0.540 ± 0.096	0.535 ± 0.096	0.564 ± 0.094	<0.001
BRI	4.32 ± 2.71	4.22 ± 2.81	4.81 ± 2.10	<0.001
ICMRS_eq	0.00 ± 2.35	-0.16 ± 2.31	0.78 ± 2.35	<0.001

Abbreviations: CMM cardiometabolic multimorbidity; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1C, glycated hemoglobin; FBG, fasting blood glucose; WC, waist measurements; TyG, triglyceride-glucose; WHtR, waist height ratio; TyG-WHtR, triglyceride glucose-waist

height ratio index; AIP,atherogenic index of plasma; BRI, body roundness index;ICMRS_eq,Integrated Cardiometabolic Risk Score.

In the ELSA cohort, 540 individuals (22.3%) developed incident cardiometabolic multimorbidity (CMM) during follow-up. Compared with those without incident CMM, participants with incident CMM were older and had higher HbA1c and triglyceride levels, but lower diastolic blood pressure, total cholesterol, LDL-C, and HDL-C levels (all $P<0.05$). Systolic blood pressure did not differ significantly between the two groups ($P=0.560$). In categorical analyses, the incident CMM group included a higher proportion of males, whereas education level, current alcohol consumption, current smoking, and hypertension did not differ significantly. The prevalence of diabetes, heart disease and stroke was higher in the incident CMM group(all $P<0.05$), whereas current smoking($P=0.528$), drinking($P=0.836$), and the prevalence of hypertension($P=0.360$) and cancer ($P=0.463$) was not significantly different between the two groups (Table 2).

Collectively, participants with incident CMM in both cohorts demonstrated less favorable cardiometabolic profiles, including older age, greater metabolic abnormalities, and a heavier burden of pre-existing cardiometabolic diseases. Compared with ELSA, intergroup differences in CHARLS were more evident across blood pressure, lipid-related variables, and lifestyle factors.

Table 2 Baseline characteristics of ELSA participants according to incident CMM status

Variable	Total (n=2422)	No incident CMM (n=1882)	Incident CMM (n=540)	P value
Age, years	64.63 ± 7.09	64.25 ± 7.14	65.97 ± 6.74	<0.001
Sex				0.001
Female	1418 (58.55)	1134 (60.26)	284 (52.59)	
Male	1004 (41.45)	748 (39.74)	256 (47.41)	
Education				0.437
Below high school	575 (25.66)	441 (25.26)	134 (27.07)	
High school/vocational training	526 (23.47)	422 (24.17)	104 (21.01)	
Higher education	629 (28.07)	491 (28.12)	138 (27.88)	
	511 (22.80)	392 (22.45)	119 (24.04)	
Marital status				0.892
Married/partnered	1734 (71.62)	1347 (73.01)	387 (71.67)	
Separated	24 (0.99)	20 (1.06)	4 (0.74)	
Divorced	290 (11.98)	223 (11.85)	67 (12.41)	
Widowed	227 (9.38)	180 (9.56)	47 (8.70)	
Never married	146 (6.03)	111 (5.90)	35 (6.48)	
Smoking				0.528
No	2185 (90.21)	1694 (77.53)	491 (22.47)	
Yes	237 (9.79)	188 (79.32)	49 (20.68)	

Variable	Total (n=2422)	No incident CMM (n=1882)	Incident CMM (n=540)	P value
Drinking				0.836
No	186 (8.14)	146 (78.49)	40 (21.51)	
Yes	2098 (91.86)	1633 (77.84)	465 (22.16)	
Hypertension				0.360
No	1698 (70.11)	1328 (78.21)	370 (21.79)	
Yes	724 (29.89)	554 (76.52)	170 (23.48)	
Diabetes				<0.001
No	2397 (98.97)	1881 (78.47)	516 (21.53)	
Yes	25 (1.03)	1 (4.00)	24 (96.00)	
Heart disease				<0.001
No	2266 (93.56)	1875 (82.74)	391 (17.26)	
Yes	156 (6.44)	7 (4.49)	149 (95.51)	
Stroke				0.030
No	2384 (98.43)	1858 (77.94)	526 (22.06)	
Yes	38 (1.57)	24 (63.16)	14 (36.84)	
Cancer				0.463
No	2182 (90.09)	1700 (77.91)	482 (22.09)	
Yes	240 (9.91)	182 (75.83)	58 (24.17)	
SBP, mmHg	130.85 ± 16.80	130.92 ± 16.86	130.59 ± 16.60	0.560
DBP, mmHg	75.21 ± 9.84	75.48 ± 9.72	74.26 ± 10.18	0.007
HbA1c, mmol/mol	39.16 ± 5.08	38.66 ± 4.02	40.90 ± 7.45	<0.001
TC, mmol/L	5.76 ± 1.12	5.82 ± 1.10	5.54 ± 1.18	<0.001
TG, mg/dL	119.05 ± 64.38	117.63 ± 63.19	124.01 ± 68.19	0.027
LDL-C, mmol/L	3.43 ± 1.00	3.48 ± 0.98	3.26 ± 1.04	<0.001
HDL-C, mmol/L	1.72 ± 0.47	1.74 ± 0.47	1.65 ± 0.47	<0.001
Fasting glucose, mmol/L	5.33 ± 0.81	5.25 ± 0.68	5.60 ± 1.12	<0.001
Waist circumference, cm	62.74 ± 14.67	62.07 ± 12.26	65.09 ± 20.86	<0.001
Height, cm	166.21 ± 9.21	165.90 ± 9.13	167.29 ± 9.39	0.002
BMI, kg/m²	27.69 ± 4.80	27.49 ± 4.71	28.36 ± 5.05	<0.001
TyG	8.53 ± 0.48	8.51 ± 0.47	8.61 ± 0.51	<0.001
AIP	-0.14 ± 0.28	-0.15 ± 0.28	-0.10 ± 0.28	<0.001
WHtR	0.378 ± 0.089	0.375 ± 0.077	0.389 ± 0.121	<0.001
BRI	1.53 ± 4.57	1.44 ± 4.06	1.84 ± 6.01	0.072
ICMRS_eq	0.00 ± 2.27	-0.10 ± 2.19	0.37 ± 2.48	<0.001

Abbreviations: CMM cardiometabolic multimorbidity; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1C, glycated hemoglobin; FBG, fasting blood glucose; WC, waist measurements; TyG, triglyceride-glucose; WHtR, waist height ratio; TyG-WHtR, triglyceride glucose-waist height ratio index; AIP,atherogenic index of plasma; BRI, body roundness index;ICMRS_eq,Integrated Cardiometabolic Risk Score.

Associations of five composite metabolic indices with incident CMM

In both cohorts, higher quartiles of the five composite metabolic indices were generally associated with higher risks of incident CMM.

In the CHARLS cohort, the average follow-up time was 4.66 years, with a minimum of 3 years and a maximum of 5 years. Cox proportional hazards models showed that all five composite indices were significantly associated with incident CMM in the fully adjusted

model. Compared with the lowest quartile, the highest quartile of TyG-WHtR, TyG-BRI, AIP-WHtR, AIP-BRI, and ICMRS was associated with a higher risk of incident CMM, and all trend tests were statistically significant (all P <0.001) (Table 3). Among these indices, TyG-WHtR showed the strongest risk stratification, followed by TyG-BRI and ICMRS.

Table 3 Associations of five composite indices with incident cardiometabolic multimorbidity in CHARLS under different adjustment models

Indicator	Model 1 Q2 vs Q1 HR (95%CI)	Model 1 Q3 vs Q1 HR (95%CI)	Model 1 Q4 vs Q1 HR (95%CI)	Model 2 Q2 vs Q1 HR (95%CI)	Model 2 Q3 vs Q1 HR (95%CI)	Model 2 Q4 vs Q1 HR (95%CI)	Model 3 Q2 vs Q1 HR (95%CI)	Model 3 Q3 vs Q1 HR (95%CI)	Model 3 Q4 vs Q1 HR (95%CI)	P for trend
TyG-WHtR	1.32 (1.10–1.59)	1.87 (1.57–2.22)	3.25 (2.76–3.83)	1.32 (1.10–1.59)	1.87 (1.57–2.22)	3.24 (2.75–3.82)	1.30 (1.09–1.57)	1.84 (1.54–2.18)	3.18 (2.70–3.74)	<0.001
TyG-BRI	1.36 (1.14–1.63)	1.80 (1.52–2.14)	3.14 (2.67–3.70)	1.36 (1.14–1.63)	1.80 (1.52–2.14)	3.13 (2.66–3.69)	1.34 (1.12–1.61)	1.78 (1.49–2.11)	3.06 (2.60–3.61)	<0.001
AIP-WHtR	1.04 (0.88–1.23)	1.49 (1.27–1.74)	2.12 (1.83–2.46)	1.04 (0.88–1.23)	1.49 (1.27–1.74)	2.12 (1.83–2.46)	1.04 (0.88–1.23)	1.47 (1.26–1.72)	2.10 (1.81–2.44)	<0.001
AIP-BRI	1.09 (0.92–1.30)	1.56 (1.33–1.83)	2.38 (2.05–2.77)	1.09 (0.92–1.30)	1.56 (1.33–1.83)	2.38 (2.04–2.76)	1.09 (0.92–1.30)	1.55 (1.32–1.81)	2.35 (2.02–2.74)	<0.001
ICMRS	1.21 (1.02–1.44)	1.76 (1.49–2.07)	2.59 (2.22–3.03)	1.21 (1.01–1.44)	1.76 (1.49–2.07)	2.59 (2.21–3.02)	1.20 (1.01–1.43)	1.75 (1.48–2.06)	2.57 (2.20–3.00)	<0.001

Abbreviations: HR, hazard ratio; CI, confidence interval; TyG, triglyceride-glucose index; BRI, body roundness index; WHtR, waist-to-height ratio; AIP, atherogenic index of plasma; ICMRS, integrated cardiometabolic risk score; CMM, cardiometabolic multimorbidity.

Notes:Model 1 was adjusted for age and sex. Model 2 was additionally adjusted for education, marital status, smoking, and drinking. Model 3 was further adjusted for hypertension, history of cancer, SBP, DBP, TC, HDL-C, and LDL-C. CHARLS main fully adjusted models included 8,651 participants and 1,466 incident events.

In the ELSA cohort, the average follow-up period was approximately 2.83 wave units. The highest quartiles of TyG-WHtR, TyG-BRI, AIP-WHtR, and ICMRS were also associated with higher risks of incident CMM in the fully adjusted model, whereas AIP-BRI did not reach statistical significance (P for trend = 0.077) (Table 4). Among these indices, ICMRS showed the strongest association in ELSA.

Table 4 Associations of five composite indices with incident cardiometabolic multimorbidity in ELSA under different adjustment models

Indicator	Model 1 Q2 vs Q1 HR (95%CI)	Model 1 Q3 vs Q1 HR (95%CI)	Model 1 Q4 vs Q1 HR (95%CI)	Model 2 Q2 vs Q1 HR (95%CI)	Model 2 Q3 vs Q1 HR (95%CI)	Model 2 Q4 vs Q1 HR (95%CI)	Model 3 Q2 vs Q1 HR (95%CI)	Model 3 Q3 vs Q1 HR (95%CI)	Model 3 Q4 vs Q1 HR (95%CI)	P for trend
TyG-WHtR	1.00 (0.77–1.30)	1.18 (0.91–1.52)	1.48 (1.16–1.89)	1.00 (0.77–1.30)	1.18 (0.91–1.52)	1.48 (1.16–1.89)	1.03 (0.78–1.36)	1.18 (0.89–1.55)	1.49 (1.14–1.95)	0.001
TyG-BRI	0.99	1.19	1.39	0.99	1.19	1.39	1.05	1.19	1.42	0.006

Indicator	Model 1 Q2 vs Q1 HR (95%CI)	Model 1 Q3 vs Q1 HR (95%CI)	Model 1 Q4 vs Q1 HR (95%CI)	Model 2 Q2 vs Q1 HR (95%CI)	Model 2 Q3 vs Q1 HR (95%CI)	Model 2 Q4 vs Q1 HR (95%CI)	Model 3 Q2 vs Q1 HR (95%CI)	Model 3 Q3 vs Q1 HR (95%CI)	Model 3 Q4 vs Q1 HR (95%CI)	P for trend
AIP-WHtR	1.01 (0.78–1.31)	1.16 (0.90–1.49)	1.43 (1.12–1.83)	1.01 (0.78–1.31)	1.16 (0.90–1.49)	1.42 (1.11–1.82)	1.11 (0.85–1.45)	1.16 (0.89–1.52)	1.41 (1.08–1.84)	0.012
AIP-BRI	0.98 (0.76–1.28)	1.04 (0.80–1.35)	1.29 (1.01–1.65)	0.98 (0.76–1.27)	1.04 (0.80–1.35)	1.29 (1.01–1.65)	0.94 (0.72–1.22)	0.99 (0.76–1.30)	1.25 (0.97–1.61)	0.077
ICMRS	0.96 (0.73–1.27)	1.30 (1.00–1.68)	1.48 (1.15–1.90)	0.96 (0.73–1.27)	1.30 (1.00–1.68)	1.48 (1.15–1.90)	0.97 (0.73–1.29)	1.33 (1.02–1.73)	1.52 (1.17–1.98)	<0.001

Abbreviations: HR, hazard ratio; CI, confidence interval; TyG, triglyceride-glucose index; BRI, body roundness index; WHtR, waist-to-height ratio; AIP, atherogenic index of plasma; ICMRS, integrated cardiometabolic risk score; CMM, cardiometabolic multimorbidity.

Notes: Model 1 adjusted for age and sex; Model 2 adjusted for age, sex, marital status, education level, smoking status, and alcohol consumption status; Model 3 further adjusted for hypertension, dyslipidemia, and cancer history, as well as systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) based on Model 2. ELSA main fully adjusted models included about 2,117 participants and 464 incident events.

Cross-cohort comparison of effect estimates

Although the overall directions of association were generally consistent across the two cohorts, the effect estimates were stronger in CHARLS than in ELSA, particularly for TyG-WHtR, TyG-BRI, and ICMRS. For instance, the HR for TyG-WHtR in CHARLS for Q4 quartile compared to the Q1 quartile was 3.18 (95% CI: 2.70 – 3.74), while in ELSA it was 1.49 (95% CI: 1.14 – 1.95); the corresponding HR for ICMRS in the two cohorts were 2.57 (95% CI: 2.20 – 3.00) and 1.52 (95% CI: 1.17 – 1.98), respectively. Notably, AIP-BRI remained significantly associated with incident CMM in CHARLS but did not reach statistical significance in ELSA(*P*=0.077) (Supplementary Table S1, Figure 2). Overall, the five composite indicators showed clearer risk gradients in CHARLS, suggesting stronger risk stratification in the Chinese cohort than in the UK cohort .

Further analyses based on per-1-standard deviation increases showed that the directions of association for the five indices were generally consistent across the two cohorts, but the effect sizes were overall stronger in CHARLS. In CHARLS, the HRs for the risk of incident CMM corresponding to an increase of one standard deviation in TyG-WHtR, TyG-BRI, AIP-WHtR, AIP-BRI, and ICMRS were 1.22 (95% *CI*: 1.18 – 1.25), 1.08 (95% *CI*: 1.06 –

1.11), 1.31 (95% *CI*: 1.25 – 1.38), 1.13 (95% *CI*: 1.11 – 1.16), and 1.27 (95% *CI*: 1.23 – 1.31), respectively. In ELSA, the corresponding *HRs* (95% *CI*) were 1.15 (1.06 – 1.25), 1.13 (1.04 – 1.23), 1.12 (1.02 – 1.21), 1.08 (0.99 – 1.17), and 1.17 (1.08 – 1.28) (Table 5). Notably, AIP-BRI did not reach statistical significance in ELSA. These findings were consistent with the quartile-based analyses (Table 5).

Table 5 Per-1-SD increase and incident CMM in CHARLS and ELSA

Indicator	CHARLS HR (95%*CI*)	CHARLS *P* for trend	ELSA HR (95%*CI*)	ELSA *P* for trend
TyG-WHtR	1.22 (1.18–1.25)	<0.001	1.15 (1.06–1.25)	0.001
TyG-BRI	1.08 (1.06–1.11)	<0.001	1.13 (1.04–1.23)	0.006
AIP-WHtR	1.31 (1.25–1.38)	<0.001	1.12 (1.02–1.21)	0.012
AIP-BRI	1.13 (1.11–1.16)	<0.001	1.08 (0.99–1.17)	0.077
ICMRS	1.27 (1.23–1.31)	<0.001	1.17 (1.08–1.28)	<0.001

Notes: Results were from fully adjusted Cox proportional hazards models (Model 3). Model 3 was adjusted for age, sex, education, marital status, smoking, drinking, hypertension, history of cancer, systolic blood pressure, diastolic blood pressure, total cholesterol, HDL-C, and LDL-C.

Dose-response relationships

Restricted cubic spline(RCS) analyses were performed to further evaluate the dose-response relationships between the five composite metabolic indices and incident CMM. The results showed that in the CHARLS cohort, TyG-WHtR, TyG-BRI, AIP-WHtR, AIP-BRI, and ICMRS were all significantly associated with the risk of incident CMM, and nonlinear dose-response relationships were observed for all five indices(all $P < 0.05$; P for nonlinearity were <0.0001, <0.0001, 0.0063, <0.0001, and <0.0001, respectively)(Figure 3A). Overall, the risk of incident CMM increased progressively with higher levels of the indices, with TyG-WHtR, AIP-BRI, and ICMRS showing steeper increases at moderate to high levels.

In ELSA, the overall associations of all five indices with incident CMM were statistically significant (all $P < 0.05$), and nonlinear relationships were observed for TyG-WHtR(P=0.0134), TyG-BRI(P=0.00060), AIP-WHtR(P=0.0138), and AIP-BRI(P=0.0045), whereas the nonlinear test for ICMRS was not statistically significant(P for nonlinearity = 0.1251) (Figure 3B). Compared with CHARLS, the increase in risk associated with higher levels of the indices was generally less pronounced in ELSA.

To further explore potential threshold effects, two-piecewise Cox regression analyses were conducted for TyG-WHtR and ICMRS, the two indices showed the most stable overall

performance in the main analyses. The results indicated that the optimal thresholds for TyG-WHtR and ICMRS in the CHARLS cohort were 10.878 and 4.008, respectively; while in the ELSA cohort, the corresponding thresholds were 4.187 and 2.311. In both cohorts, higher levels of TyG-WHtR and ICMRS were associated with higher risks of incident CMM. The overall association of ICMRS with CMM in the ELSA cohort was statistically significant, yet the nonlinear trend is not significant (*P* for nonlinearity = 0.1251), suggesting potential differences in risk patterns between the cohorts. The threshold analyses should therefore be interpreted as exploratory findings (Supplementary Figure S2).

Discriminative performance of the five indices

The discriminative performance of the five composite metabolic indices was further assessed using Harrell's C-index, conventional ROC analysis, and time-dependent ROC analysis. Across both cohorts, ICMRS achieved the highest Harrell's C-index, measuring 0.6379 for CHARLS and 0.6057 for ELSA, suggesting the best overall discriminative performance. Whereas, TyG-WHtR (0.6355 and 0.6024) and AIP-WHtR(0.6249 and 0.5992) performed particularly well in conventional ROC and time-dependent ROC analyses(Table 6).

Table 6 Predictive performance of five composite indices for incident CMM in CHARLS and ELSA

Indicator	CHARLS C-index	ELSA C-index	CHARLS ROC AUC	ELSA ROC AUC	CHARLS time-dependent AUC	ELSA time-dependent AUC
TyG-WHtR	0.6355	0.6024	0.6458	0.5668	0.654	0.625
TyG-BRI	0.6029	0.5952	0.6399	0.5618	0.648	0.618
AIP-WHtR	0.6249	0.5992	0.5978	0.545	0.603	0.577
AIP-BRI	0.6177	0.5929	0.6106	0.5259	0.617	0.539
ICMRS	0.6379	0.6057	0.6217	0.5589	0.628	0.601

Note: The C-index refers to the Harrell's concordance index, while AUC represents the area under the traditional ROC curve, and time-dependent AUC denotes the area under the time-dependent ROC curve. A higher value indicates better discriminative ability.

Overall, the discriminative performance of all five indices was stronger in CHARLS than in ELSA. In conventional ROC analyses, the AUC of TyG-WHtR was the highest (0.6458), followed by TyG-BRI (0.6399) and ICMRS (0.6217) in CHARLS(Figure S1 A). In ELSA, TyG-WHtR also had the highest AUC (0.5668), while AIP-BRI had the lowest (0.5259)(Figure S1 B). The results of the time-dependent ROC analysis were generally

consistent with the aforementioned findings. In CHARLS, the time-dependent AUCs for TyG-WHtR, TyG-BRI, AIP-WHtR, AIP-BRI, and ICMRS were 0.654, 0.648, 0.603, 0.617, and 0.628, respectively; in ELSA, they were 0.625, 0.618, 0.577, 0.539, and 0.601, respectively. Overall, TyG-WHtR demonstrated relatively superior time-dependent discriminative ability in both cohorts, whereas AIP-BRI showed the weakest performance in ELSA(Table 5，Figure 4A and 4B). Time-dependent ROC analyses yielded similar patterns, further supporting the relative stability of TyG-WHtR and ICMRS across the two cohorts.

Cohort interaction analysis

To formally assess cross-cohort heterogeneity, interaction analyses were conducted in the pooled dataset after the two cohorts had been analyzed separately Significant interactions with cohort were observed for TyG-WHtR, AIP-WHtR, AIP-BRI, and ICMRS,(*P* for interaction < 0.001, < 0.001, 0.001, and < 0.001, respectively), indicating that the strength of association differed between CHARLS and ELSA for these indices.In contrast, the interaction for TyG-BRI was not statistically significant (*P* for interaction = 0.101)(Figure 5, and Supplementary Table 2).These findings supported the between-cohort differences observed in the main analyses.

Subgroup Analysis

Subgroup analyses were conducted on TyG-WHtR and ICMRS to assess the consistency of the main results across various demographic and clinical groups. Generally, the subgroup analyses aligned well with the primary findings from both the CHARLS and ELSA cohorts, although certain selected subgroups displayed some variations in results.

Within the CHARLS study, the relationship between TyG-WHtR and the occurrence of CMM remained fairly stable when evaluated by sex and age categories, without any notable interactions. On the other hand, significant interactions were noted regarding obesity status (*P*< 0.001) and smoking (*P*=0.048), indicating that the association's strength differed among various BMI categories and smoking classifications (Figure 6A). For the ICMRS analysis, significant interactions were noted in relation to obesity status (*P*< 0.001) and diabetes

(*P*=0.023), while the interactions concerning sex, age, alcohol consumption, and smoking were found to be statistically insignificant (see Figure 6B).

In the ELSA cohort, the overall directions of association for TyG-WHtR and ICMRS were similar to those in CHARLS, but the effect sizes were weaker. No statistically significant subgroup interactions were observed for TyG-WHtR or ICMRS in ELSA, suggesting that their associations with incident CMM were relatively stable across the examined subgroups (Figure 6C and 6D).

Taken together, the subgroup analyses supported the robustness of the main findings while also suggesting potential heterogeneity in certain metabolism-related subgroups, particularly in CHARLS.

Sensitivity Analysis

Sensitivity analyses yielded results that were broadly consistent with the primary analyses. In CHARLS, the associations of the five composite indices with incident CMM remained materially unchanged when hypertension was included in the definition of CMM, when participants who developed outcome events during the first follow-up interval were excluded, and when the analysis was restricted to participants with complete covariate data. In ELSA, analyses that excluded early events and complete-case analyses also produced results comparable to those of the main analyses. Overall, these findings support the robustness of the primary results (Table 7; Supplementary Tables S2 and S3).

Table 7 Summary of sensitivity analyses: comparison of the highest versus lowest quartile of five composite indices in CHARLS and ELSA

Cohort	Sensitivity analysis	TyG-WHtR	TyG-BRI	AIP-WHtR	AIP-BRI	ICMRS
CHARLS	Hypertension included	3.07 (2.65–3.55)	3.03 (2.61–3.51)	2.13 (1.86–2.44)	2.38 (2.07–2.73)	2.52 (2.19–2.90)
CHARLS	Excluding early events	2.89 (2.19–3.81)	2.84 (2.14–3.75)	1.86 (1.45–2.39)	2.08 (1.62–2.68)	2.34 (1.81–3.04)
CHARLS	Complete-case analysis	3.18 (2.70–3.74)	3.07 (2.61–3.62)	2.10 (1.81–2.44)	2.34 (2.02–2.73)	2.57 (2.20–3.00)
ELSA	Excluding early events	1.49 (1.14–1.95)	1.42 (1.08–1.86)	1.41 (1.08–1.84)	1.25 (0.97–1.61)	1.52 (1.17–1.98)
ELSA	Complete-case analysis	1.49 (1.14–1.95)	1.42 (1.08–1.86)	1.41 (1.08–1.84)	1.25 (0.97–1.61)	1.52 (1.17–1.98)

Abbreviations: HR, hazard ratio; CI, confidence interval; CMM, cardiometabolic multimorbidity; TyG, triglyceride-glucose index; WHtR, waist-to-height ratio; BRI, body roundness index; AIP, atherogenic index of plasma; ICMRS, integrated cardiometabolic risk score.

Notes: This summary table presents the associations for the highest quartile versus the lowest quartile from fully adjusted Cox models across sensitivity analyses. The overall direction and magnitude of associations

were largely consistent with those observed in the primary analyses, supporting the robustness of the main findings.

Kaplan–Meier Cumulative Incidence Analysis

Kaplan–Meier cumulative incidence curves were constructed to compare the incidence of CMM across ICMRS quartiles in the CHARLS and ELSA cohorts. In both cohorts, the incidence of CMM differed significantly across the ICMRS quartiles (log-rank tests, both $P < 0.001$). Overall, higher ICMRS quartiles were associated with progressively higher cumulative incidences of CMM, with the highest cumulative incidence observed in Q4 and the lowest in Q1 (Figure 7A and 7B). Notably, the separation of the curves was more pronounced in the CHARLS cohort than in the ELSA cohort, which was consistent with the stronger associations observed in the fully adjusted Cox models and the results of the cohort interaction analyses.

Discussion

Principal findings

In this study, we systematically compared five composite metabolic indices in relation to incident cardiometabolic multimorbidity (CMM) across two prospective cohorts of older adults, CHARLS and ELSA. Several key findings emerged. First, all five indices were positively associated with incident CMM overall, although the strength of association varied across indices and cohorts. However previous studies have largely focused on the association of single indicators (such as the TyG index or AIP) with individual cardiovascular diseases or diabetes [13, 20], or have only examined the cross-sectional characteristics of metabolic syndrome[7]. Second, TyG-WHtR and ICMRS showed the most stable overall performance across the two cohorts, with TyG-WHtR showning relatively stronger discrimination in ROC analyses and ICMRS yielding the highest Harrell's C-index. Compared to previous studies based solely on single-country populations[22, 41], this research reveals the differences in effect sizes of composite metabolic indicators across different population backgrounds through cross-cohort comparisons, filling the knowledge gap in this field regarding the lack of cross-national external validation.Third, the associations and discriminative performance of these indices were generally stronger in CHARLS than in ELSA, suggesting cross-cohort heterogeneity. Finally, subgroup analyses and sensitivity analyses broadly supported the robustness of the main findings.

Possible explanations for the observed associations

The occurrence of CMM is not driven by a single metabolic abnormality. Rather, it reflects the long-term accumulation and interaction of multiple adverse cardiometabolic processes, including insulin resistance, dyslipidemia, central adiposity, and chronic low-grade inflammation. In this context, composite indices that integrate metabolic and anthropometric information may better capture the overall cardiometabolic burden than single markers alone.

Among the five indices, TyG-WHtR demonstrated particularly consistent performance in both cohorts. This observation is biologically reasonable since TyG is commonly viewed as a practical indicator of insulin resistance, while WHtR signifies central adiposity and fat distribution. Therefore, their combined use might more accurately represent the coexistence of metabolic dysfunction and abdominal obesity, which are both critical in the clustering of diabetes, heart disease, and stroke. Furthermore, WHtR is straightforward to compute and does not necessitate sex-specific cutoffs, which may partially account for its practical application in population-based risk stratification[24, 42].

In contrast, ICMRS appeared to excel in overall discrimination, as indicated by the highest Harrell’s C-index in both cohorts. This assessment is also valid because ICMRS was developed to summarize the multidimensional burden of cardiometabolic factors rather than reflect a single metabolic pathway. Collectively, these findings imply that TyG-WHtR might be more appealing as a simple screening-focused index, while ICMRS may serve better when a broader, integrated evaluation of cardiometabolic risk is required.

Why were the associations stronger in CHARLS than in ELSA?

A notable finding of this study was that the effect sizes of the composite indices were generally larger in CHARLS than in ELSA. This pattern was observed not only in the quartile-based analyses, but also in the per-1-standard deviation analyses. The interaction analyses further supported this cohort difference, as significant interactions with cohort were observed for TyG-WHtR, AIP-WHtR, AIP-BRI, and ICMRS.

Several factors may explain this difference. First, Chinese and UK older populations differ in dietary patterns, obesity phenotypes, healthcare access, chronic disease management, and baseline cardiometabolic risk distribution. These differences may influence both the biological relevance and the epidemiological performance of the same composite index across

cohorts. Second, although we harmonized the overall analytic framework, the two cohorts differ in follow-up structure, variable measurement, and disease ascertainment, which may also contribute to differences in effect estimates. Third, some indices may be more population-sensitive than others. For example, AIP-BRI remained significantly associated with incident CMM in CHARLS but did not reach statistical significance in ELSA, suggesting that not all composite indices are equally generalizable across settings. This interpretation is further supported by the cohort interaction analyses, in which TyG-WHtR, AIP-WHtR, AIP-BRI, and ICMRS showed significant interactions with two cohort.

The Kaplan–Meier cumulative incidence analyses were consistent with this interpretation. In both cohorts, incident CMM differed significantly across ICMRS quartiles, but the gradient was more pronounced in CHARLS, in line with the stronger associations observed in the fully adjusted Cox models.

Clinical and public health implications

From a practical perspective, the findings of this study are clinically relevant because all five indices are derived from routinely available anthropometric and laboratory measurements. This makes them potentially useful for population-level risk assessment and cardiometabolic risk stratification in settings where metabolic abnormalities and obesity-related phenotypes need to be identified efficiently.

These indices may help identify individuals with a higher burden of metabolic dysfunction and a greater likelihood of developing cardiometabolic multimorbidity[22]. TyG-WHtR may be particularly attractive because of its simplicity, whereas ICMRS may be more useful when a broader summary of cardiometabolic risk burden is needed[41]. Furthermore, the observed effect sizes in the CHARLS cohort were generally stronger than those in ELSA, suggesting that these composite indicators may have greater utility for cardiometabolic risk stratification in the Chinese population, which has direct public health implications for a country facing an increasing burden of CMM[5, 43]. ncorporating TyG-WHtR and ICMRS into population-level risk assessment frameworks may facilitate earlier identification of high-risk individuals and support more targeted intervention strategies, thereby helping to reduce the burden of CMM.

Given the growing burden of CMM, early identification of individuals at elevated risk may help target lifestyle intervention, risk factor management, and closer follow-up. In this sense, our results support the potential use of composite metabolic indices for cardiometabolic risk stratification rather than as replacements for comprehensive clinical assessment.

Strengths and limitations

This study has several advantages. First, it included two large prospective ageing cohorts from different countries, which allowed not only within-cohort evaluation but also cross-cohort comparison of the predictive performance of the five indices. Second, rather than focusing on a single indicator, we systematically compared five composite metabolic indices, providing a broader assessment of their relative utility. Third, we used a relatively comprehensive analytical framework, including Cox regression, restricted cubic spline analysis, ROC and time-dependent ROC analyses, Kaplan–Meier cumulative incidence analysis, cohort interaction analysis, subgroup analysis, and sensitivity analysis, which strengthened the overall robustness of the findings

Several limitations should also be acknowledged. Initially, this analysis, being an observational study, cannot establish a causal relationship, and the potential for residual confounding remains despite adjustments for multiple variables. Furthermore, the two cohorts displayed differences in their follow-up structures, methods of variable measurement, and disease identification, which may have affected the direct comparability of the effect sizes. Although the indices exhibited overall acceptable performance, their discriminative ability was moderate rather than exceptional, indicating they should be regarded as practical risk markers rather than standalone diagnostic instruments. Lastly, trajectory-based analyses were not performed due to insufficient synchronization of repeated measurements of key biomarkers and anthropometric indicators across follow-up waves in CHARLS and ELSA. Given that previous studies have suggested that long-term metabolic trajectories may be relevant to CMM risk[44]. Future studies with more complete and cross-cohort comparable repeated measurements should further examine whether trajectories of TyG-WHtR, ICMRS, and related indices in order to provide additional prognostic information. Finally, although the overall direction of the findings was consistent, some cohort-specific differences suggest that further validation in other ethnic and healthcare settings is still needed.

Conclusion

In summary, this multinational cohort study demonstrates that the five composite metabolic indicators, namely TyG-WHtR, TyG-BRI, AIP-WHtR, AIP-BRI, and ICMRS, are independent predictors of newly developed cardiac metabolic comorbidities. Among which TyG-WHtR and ICMRS showed the most stable overall performance across the CHARLS and ELSA cohorts. Overall, these indices demonstrated stronger risk stratification and discrimination in CHARLS than in ELSA. As a simple, low-cost, and relatively stable index, TyG-WHtR may be particularly useful for early risk identification of CMM, whereas ICMRS may be more useful when a more integrated summary of cardiometabolic burden is needed. Further validation in other populations is warranted before broader clinical application.

Abbreviations

AIP: Atherogenic index of plasma
AIP-BRI: Atherogenic index of plasma-body roundness index
AIP-WHtR: Atherogenic index of plasma-waist-to-height ratio
AUC: Area under the curve
BMI: Body mass index
BRI: Body roundness index
CI: Confidence interval
CHARLS: China Health and Retirement Longitudinal Study
CMM: Cardiometabolic multimorbidity
DBP: Diastolic blood pressure
ELSA: English Longitudinal Study of Ageing
FPG: Fasting plasma glucose
HbA1c: Glycated hemoglobin
HDL-C: High-density lipoprotein cholesterol
HR: Hazard ratio
ICMRS: Integrated cardiometabolic risk score
LDL-C: Low-density lipoprotein cholesterol
Q: Quartile
RCS: Restricted cubic spline
ROC: Receiver operating characteristic
SBP: Systolic blood pressure
TC: Total cholesterol
TG: Triglycerides
TyG: Triglyceride-glucose index

TyG-BRI: Triglyceride-glucose-body roundness index
TyG-WHtR: Triglyceride-glucose-waist-to-height ratio
WHtR: Waist-to-height ratio

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Not applicable.

Data availability

The data supporting the results of this study can be found on CHARLS (https://charls.pku.edu.cn/) , and ELSA (https://www.elsa-project.ac.uk/) websites.

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Declaration

Ethics approval and consent to participate

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and relevant institutional guidelines and regulations. The original China Health and Retirement Longitudinal Study (CHARLS) was approved by the Biomedical Ethics Review Committee of Peking University (approval number: IRB00001052-11015). The English Longitudinal Study of Ageing (ELSA) Wave 6 was approved by the National Research Ethics Service Committee South Central–Berkshire (approval number: 11/SC/0374), and the subsequent waves were approved by the relevant research ethics committees. Written informed consent was obtained from all participants by the original cohort study teams. The present study involved a secondary analysis of de-identified data from the CHARLS and ELSA databases, with no new participant recruitment or intervention.

Clinical trial number: not applicable.

Competing interests

No potential conflicts of interest relevant to this study were reported.

Author contributions

XYJ designed the study and wrote and the manuscript. HZC analyzed the data. JGL and JD assisted with data collection and interpretation. XL and WMX were responsible for manuscript review and supervised the study. All authors read and approved of the final manuscript.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work, the authors used ChatGPT only for language editing and improvement of readability. After using this tool, the authors carefully reviewed and revised the manuscript and take full responsibility for the content of the published article.

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Figure Legends

Figure 1 Flowchart of inclusion and exclusion criteria for subjects in the CHARLS and ELSA cohort studies

Figure 2 Comparison of fully adjusted associations between five composite indices and incident CMM in CHARLS and ELSA. Forest plots showed hazard ratios (HRs) and 95% confidence intervals (CIs) for the highest versus lowest quartiles (Q4 vs Q1) of TyG-WHtR, TyG-BRI, AIP-WHtR, AIP-BRI, and ICMRS in the two cohorts. Estimates were derived from the fully adjusted Cox models.

Figure 3 Restricted cubic spline analyses of five composite indices and incident CMM in CHARLS and ELSA (The solid line represents the fully adjusted HR, and the shaded area indicates the 95% CI. The median value of each index was used as the reference. Results were from fully adjusted covariates(Models 3).Models 3 were adjusted for age, sex, education, marital status, smoking, drinking, hypertension, history of cancer, SBP, DBP, TC, HDL-C, and LDL-C.)

Figure 4 Predictive performance of five composite indices for incident CMM in CHARLS and ELSA(A. Time-dependent ROC curves in CHARLS; B. Time-dependent ROC curves in ELSA)

Cohort interaction analysis

Figure 5 Cohort-specific associations of five standardized composite indices with incident CMM in the pooled CHARLS and ELSA analysis. (Points represent hazard ratios per 1 standard deviation increase, and horizontal lines indicate 95% confidence intervals. CHARLS and ELSA were shown separately for each composite index. P for interaction was obtained by testing the interaction between each standardized composite index and cohort indicator in the pooled fully adjusted Cox proportional hazards model.)

Figure 6 Subgroup analyses of TyG-WHtR and ICMRS for incident CMM in CHARLS and ELSA. (A) TyG-WHtR in CHARLS; (B) ICMRS in CHARLS; (C) TyG-WHtR in ELSA; and (D) ICMRS in ELSA. Subgroup analyses were performed according to sex, age, obesity status, diabetes, drinking status, and smoking status. Points indicate HRs per 1-SD increase, and horizontal lines indicate 95% CIs. The red dashed line indicates HR = 1. P for interaction was calculated by testing the interaction between each standardized index and the corresponding subgroup variable in fully adjusted Cox models.

Figure 7 Kaplan–Meier cumulative curves for incident CMM according to exposure categories in CHARLS and ELSA (A) CHARLS cohort; (B) ELSA cohort. Participants were grouped according to baseline ICMRS quartiles. Q1 indicates the lowest quartile and Q4 indicates the highest quartile. The log-rank test was used to compare differences across quartiles.

CHARLS cohort

Wave 3 baseline sample
(2015-2016)
N = 21,097

Excluded:
age < 50 years
n = 4,235

After excluding age < 50 years
N = 16,862

Excluded:
missing key exposures
n = 6,052

Exposure-complete sample
N = 10,810

Excluded:
prevalent CMM at baseline
n = 1,580

Baseline eligible sample
(excluding prevalent CMM)
N = 9,230

Excluded:
without follow-up
n = 548

Final analytic sample
N = 8,682

ELSA cohort

Wave 6 main sample
N = 10,601

Matched with Wave 6 nurse data
N = 8,054

Excluded:
age < 50 years
n = 30

After excluding age < 50 years
N = 8,024

Excluded:
missing key exposures
n = 5,233

Exposure-complete sample
N = 2,791

Excluded:
prevalent CMM at baseline
n = 11

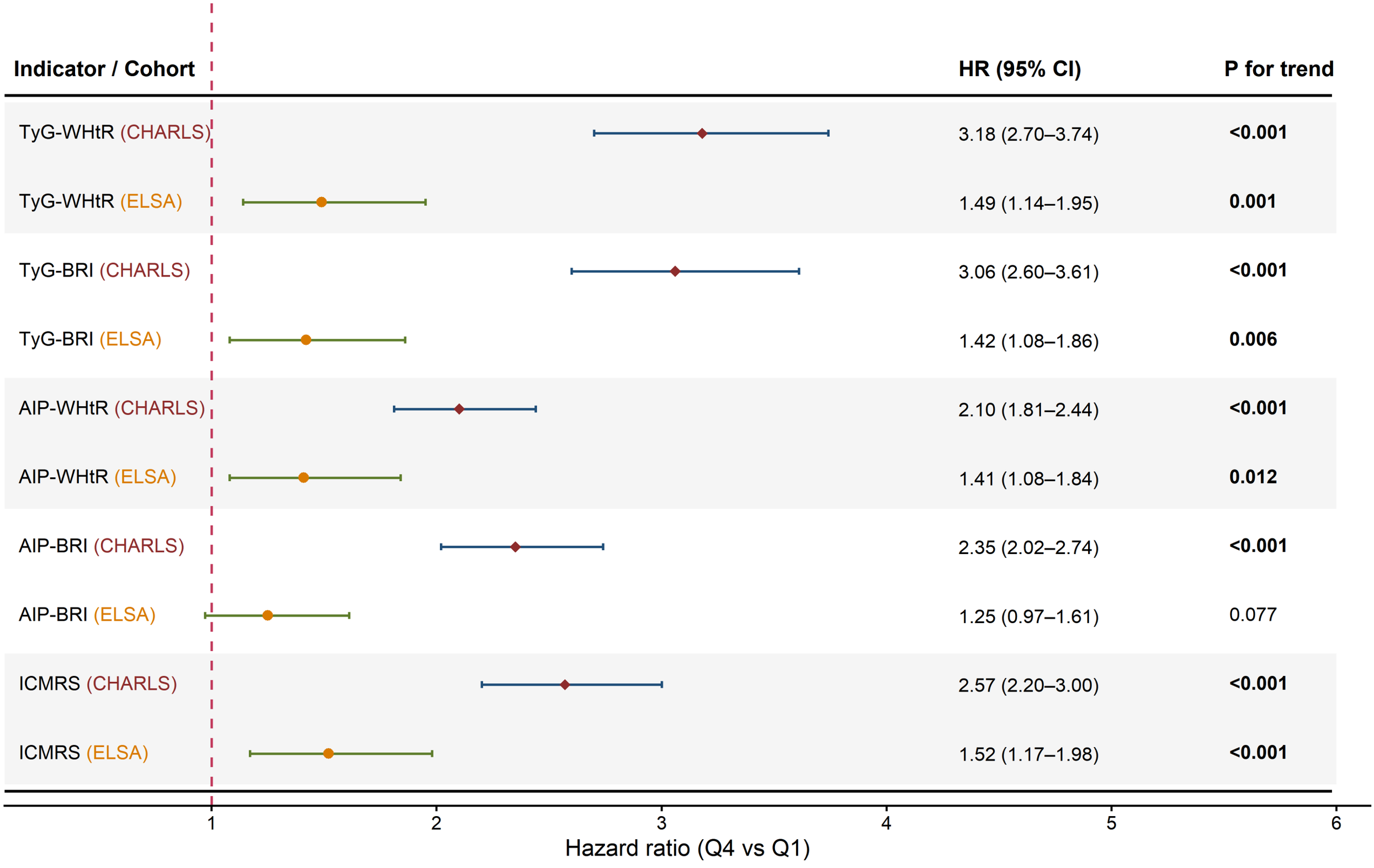
Baseline eligible sample
(excluding prevalent CMM)
N = 2,780

Excluded:
without follow-up information
n = 358

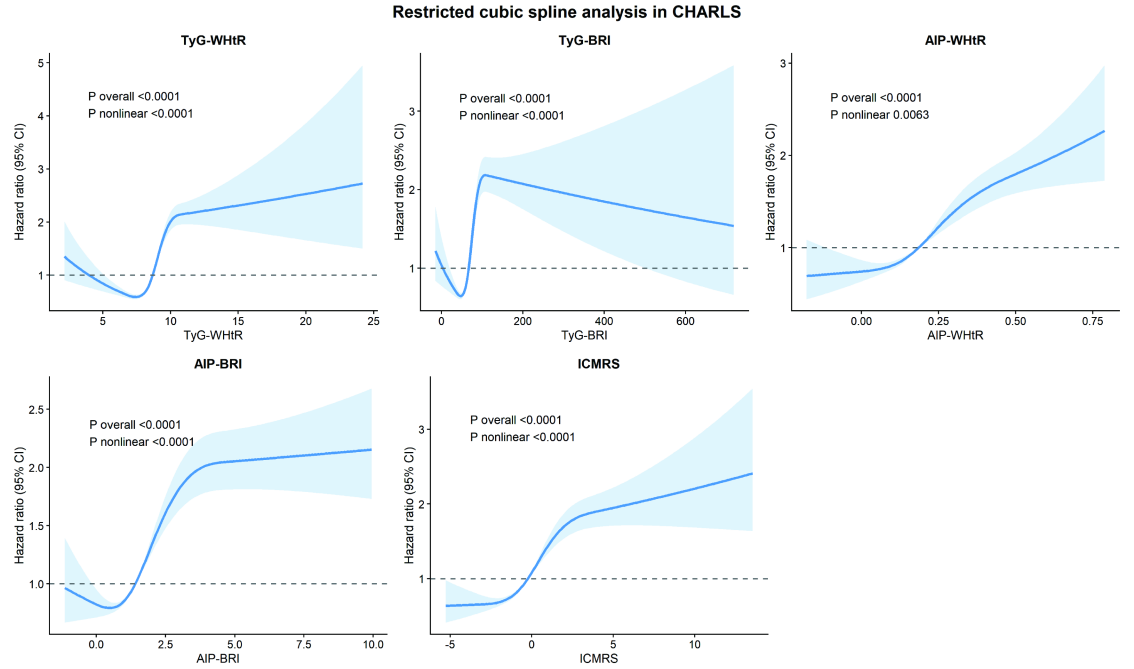
Final analytic sample
N = 2,422

Comparison of associations of five composite indices with incident CMM

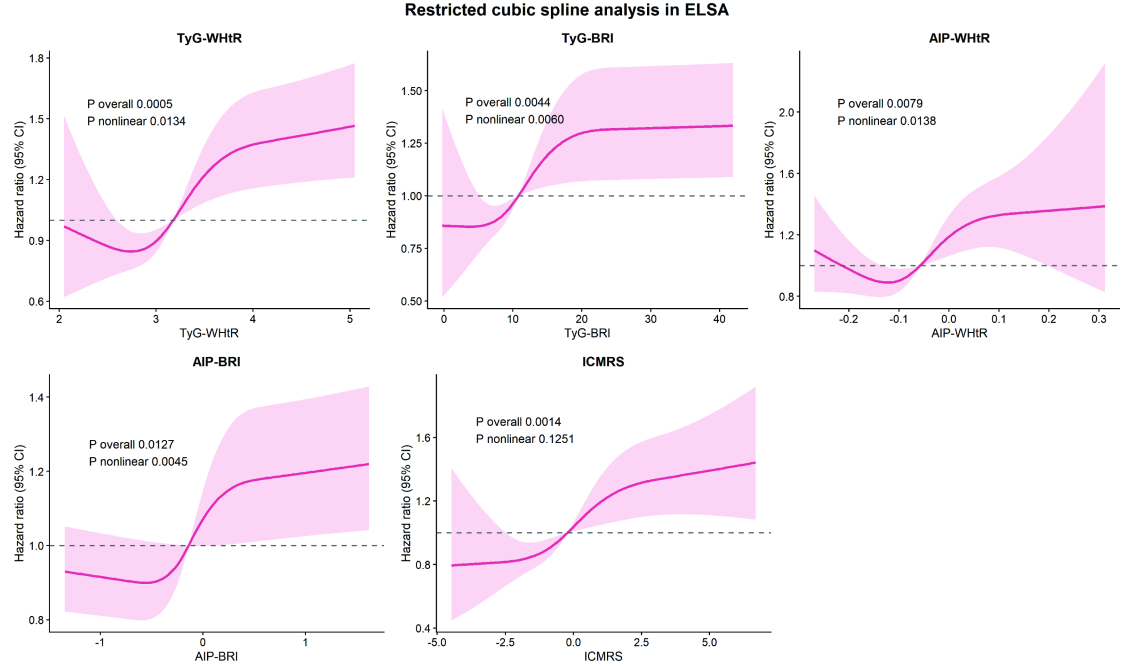
Indicator / Cohort	HR (95% CI)	P for trend
TyG-WHtR (CHARLS)	3.18 (2.70–3.74)	**<0.001**
TyG-WHtR (ELSA)	1.49 (1.14–1.95)	**0.001**
TyG-BRI (CHARLS)	3.06 (2.60–3.61)	**<0.001**
TyG-BRI (ELSA)	1.42 (1.08–1.86)	**0.006**
AIP-WHtR (CHARLS)	2.10 (1.81–2.44)	**<0.001**
AIP-WHtR (ELSA)	1.41 (1.08–1.84)	**0.012**
AIP-BRI (CHARLS)	2.35 (2.02–2.74)	**<0.001**
AIP-BRI (ELSA)	1.25 (0.97–1.61)	0.077
ICMRS (CHARLS)	2.57 (2.20–3.00)	**<0.001**
ICMRS (ELSA)	1.52 (1.17–1.98)	**<0.001**



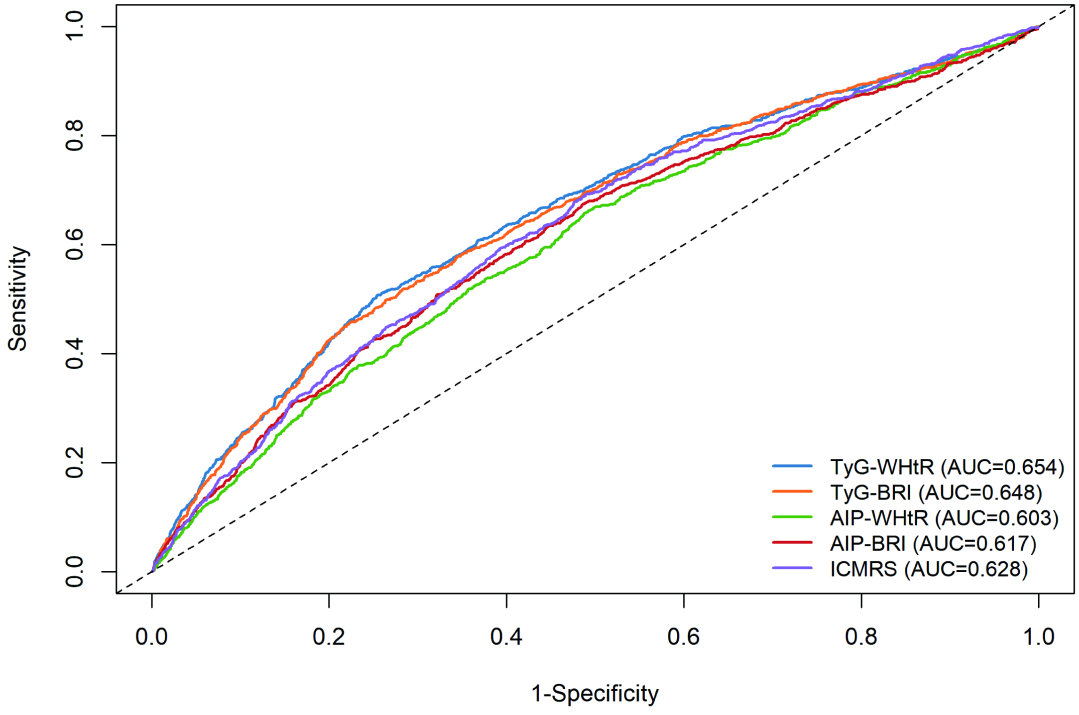
A


Restricted cubic spline analysis in CHARLS
TyG-WHtR
P overall <0.0001
P nonlinear <0.0001
Hazard ratio (95% CI)
TyG-WHtR
TyG-BRI
P overall <0.0001
P nonlinear <0.0001
Hazard ratio (95% CI)
TyG-BRI
AIP-WHtR
P overall <0.0001
P nonlinear 0.0063
Hazard ratio (95% CI)
AIP-WHtR
AIP-BRI
P overall <0.0001
P nonlinear <0.0001
Hazard ratio (95% CI)
AIP-BRI
ICMRS
P overall <0.0001
P nonlinear <0.0001
Hazard ratio (95% CI)
ICMRS

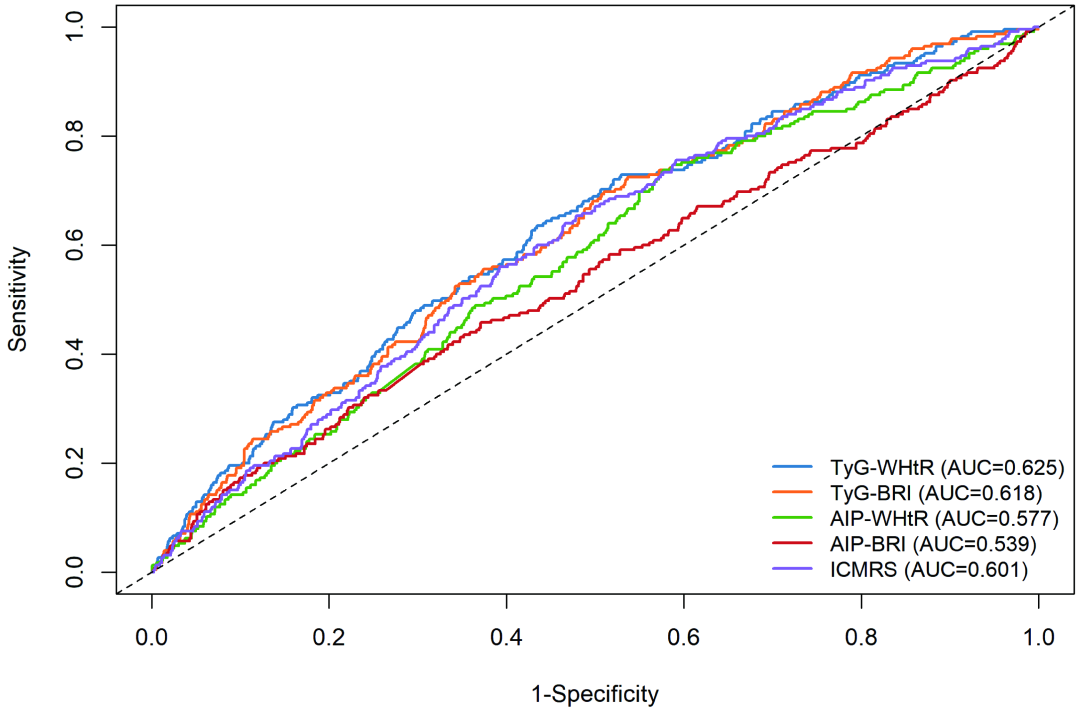
B

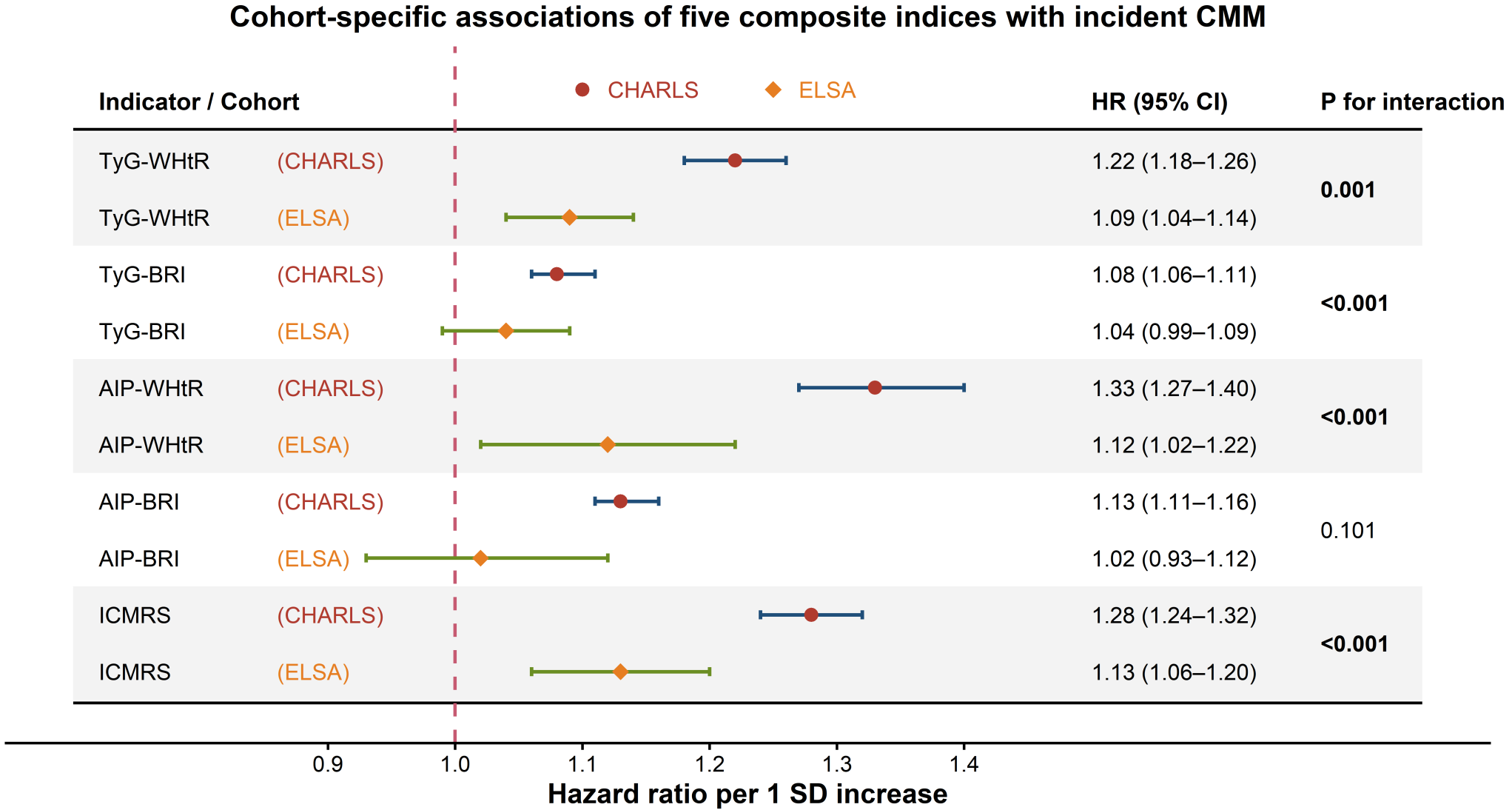

Restricted cubic spline analysis in ELSA
TyG-WHtR
P overall 0.0005
P nonlinear 0.0134
Hazard ratio (95% CI)
TyG-WHtR
TyG-BRI
P overall 0.0044
P nonlinear 0.0060
Hazard ratio (95% CI)
TyG-BRI
AIP-WHtR
P overall 0.0079
P nonlinear 0.0138
Hazard ratio (95% CI)
AIP-WHtR
AIP-BRI
P overall 0.0127
P nonlinear 0.0045
Hazard ratio (95% CI)
AIP-BRI
ICMRS
P overall 0.0014
P nonlinear 0.1251
Hazard ratio (95% CI)
ICMRS

A


CHARLS: Time-dependent ROC curves at 4 years
Sensitivity
1-Specificity
0.0
0.2
0.4
0.6
0.8
1.0
TyG-WHtR (AUC=0.654)
TyG-BRI (AUC=0.648)
AIP-WHtR (AUC=0.603)
AIP-BRI (AUC=0.617)
ICMRS (AUC=0.628)

B


ELSA: Time-dependent ROC curves at 2.5 years
Sensitivity
1-Specificity
0.0
0.2
0.4
0.6
0.8
1.0
TyG-WHtR (AUC=0.625)
TyG-BRI (AUC=0.618)
AIP-WHtR (AUC=0.577)
AIP-BRI (AUC=0.539)
ICMRS (AUC=0.601)

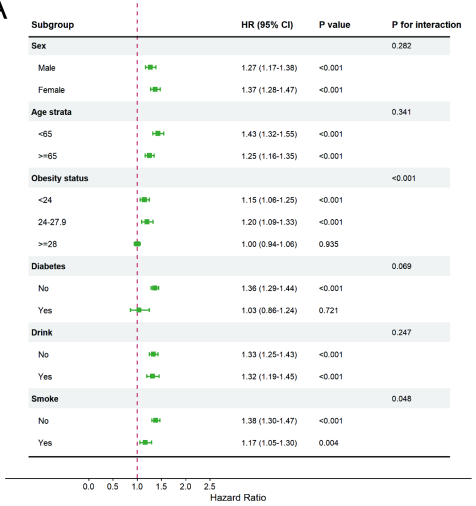

Cohort-specific associations of five composite indices with incident CMM
Indicator / Cohort
CHARLS
ELSA
HR (95% CI)
P for interaction
TyG-WHtR (CHARLS)
1.22 (1.18–1.26)
0.001
TyG-WHtR (ELSA)
1.09 (1.04–1.14)
TyG-BRI (CHARLS)
1.08 (1.06–1.11)
<0.001
TyG-BRI (ELSA)
1.04 (0.99–1.09)
AIP-WHtR (CHARLS)
1.33 (1.27–1.40)
<0.001
AIP-WHtR (ELSA)
1.12 (1.02–1.22)
AIP-BRI (CHARLS)
1.13 (1.11–1.16)
0.101
AIP-BRI (ELSA)
1.02 (0.93–1.12)
ICMRS (CHARLS)
1.28 (1.24–1.32)
<0.001
ICMRS (ELSA)
1.13 (1.06–1.20)
0.9
1.0
1.1
1.2
1.3
1.4
Hazard ratio per 1 SD increase

Subgroup analyses of TyG-WHtR and ICMRS for incident CMM in CHARLS and ELSA

A

CHARLS: TyG-WHtR

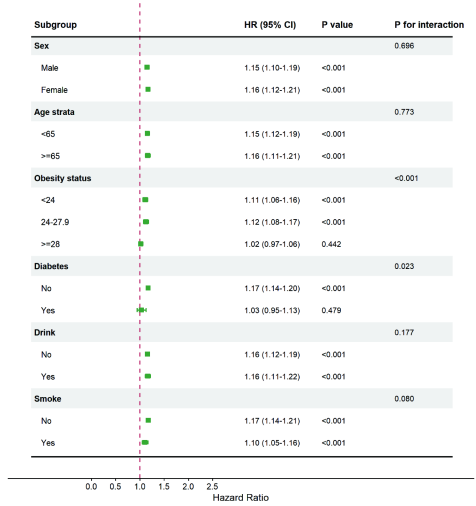
Subgroup	HR (95% CI)	P value	P for interaction
Sex			0.282
Male	1.27 (1.17-1.38)	<0.001	
Female	1.37 (1.28-1.47)	<0.001	
Age strata			0.341
<65	1.43 (1.32-1.55)	<0.001	
>=65	1.25 (1.16-1.35)	<0.001	
Obesity status			<0.001
<24	1.15 (1.06-1.25)	<0.001	
24-27.9	1.20 (1.09-1.33)	<0.001	
>=28	1.00 (0.94-1.06)	0.935	
Diabetes			0.069
No	1.36 (1.29-1.44)	<0.001	
Yes	1.03 (0.86-1.24)	0.721	
Drink			0.247
No	1.33 (1.25-1.43)	<0.001	
Yes	1.32 (1.19-1.45)	<0.001	
Smoke			0.048
No	1.38 (1.30-1.47)	<0.001	
Yes	1.17 (1.05-1.30)	0.004	



B

CHARLS: ICMRS

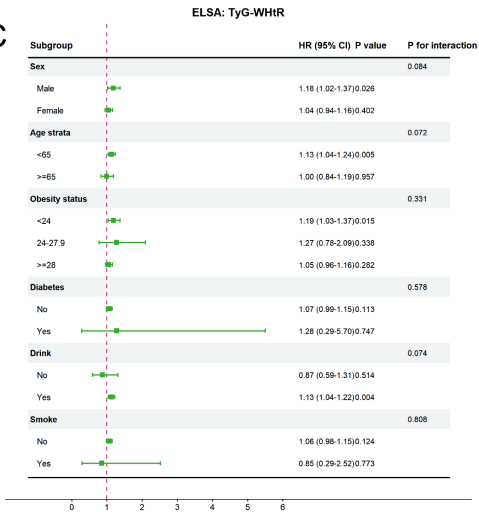
Subgroup	HR (95% CI)	P value	P for interaction
Sex			0.696
Male	1.15 (1.10-1.19)	<0.001	
Female	1.16 (1.12-1.21)	<0.001	
Age strata			0.773
<65	1.15 (1.12-1.19)	<0.001	
>=65	1.16 (1.11-1.21)	<0.001	
Obesity status			<0.001
<24	1.11 (1.06-1.16)	<0.001	
24-27.9	1.12 (1.08-1.17)	<0.001	
>=28	1.02 (0.97-1.06)	0.442	
Diabetes			0.023
No	1.17 (1.14-1.20)	<0.001	
Yes	1.03 (0.95-1.13)	0.479	
Drink			0.177
No	1.16 (1.12-1.19)	<0.001	
Yes	1.16 (1.11-1.22)	<0.001	
Smoke			0.080
No	1.17 (1.14-1.21)	<0.001	
Yes	1.10 (1.05-1.16)	<0.001	



C

ELSA: TyG-WHtR

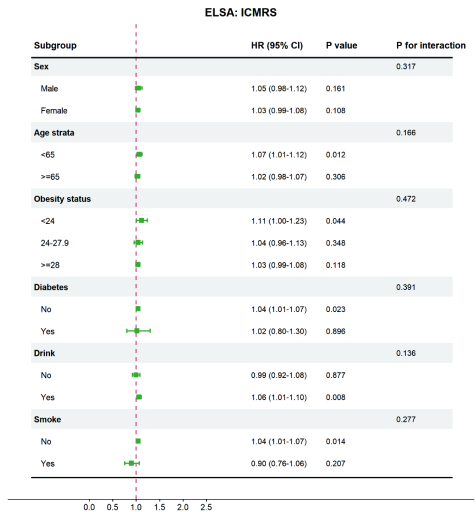
Subgroup	HR (95% CI)	P value	P for interaction
Sex			0.084
Male	1.18 (1.02-1.37)	0.026	
Female	1.04 (0.94-1.16)	0.402	
Age strata			0.072
<65	1.13 (1.04-1.24)	0.005	
>=65	1.00 (0.84-1.19)	0.957	
Obesity status			0.331
<24	1.19 (1.03-1.37)	0.015	
24-27.9	1.27 (0.78-2.09)	0.338	
>=28	1.05 (0.96-1.16)	0.282	
Diabetes			0.578
No	1.07 (0.99-1.15)	0.113	
Yes	1.28 (0.29-5.70)	0.747	
Drink			0.074
No	0.87 (0.59-1.31)	0.514	
Yes	1.13 (1.04-1.22)	0.004	
Smoke			0.808
No	1.06 (0.98-1.15)	0.124	
Yes	0.85 (0.29-2.52)	0.773	



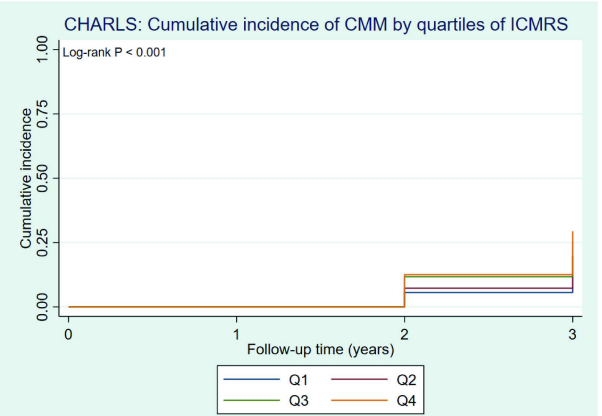
D

ELSA: ICMRS

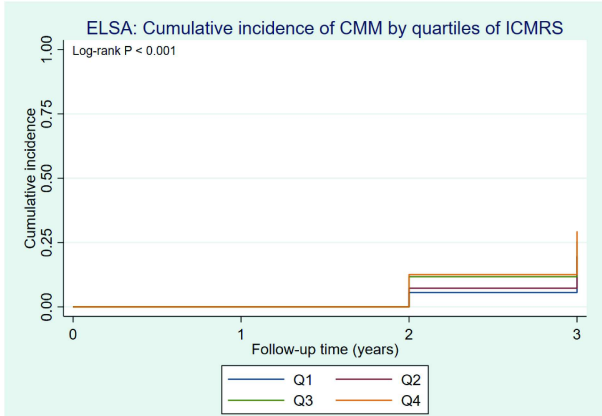
Subgroup	HR (95% CI)	P value	P for interaction
Sex			0.317
Male	1.05 (0.98-1.12)	0.161	
Female	1.03 (0.99-1.08)	0.108	
Age strata			0.166
<65	1.07 (1.01-1.12)	0.012	
>=65	1.02 (0.98-1.07)	0.306	
Obesity status			0.472
<24	1.11 (1.00-1.23)	0.044	
24-27.9	1.04 (0.96-1.13)	0.348	
>=28	1.03 (0.99-1.08)	0.118	
Diabetes			0.391
No	1.04 (1.01-1.07)	0.023	
Yes	1.02 (0.80-1.30)	0.896	
Drink			0.136
No	0.99 (0.92-1.06)	0.877	
Yes	1.06 (1.01-1.10)	0.008	
Smoke			0.277
No	1.04 (1.01-1.07)	0.014	
Yes	0.90 (0.76-1.06)	0.207	



A


CHARLS: Cumulative incidence of CMM by quartiles of ICMRS
Log-rank P < 0.001
Cumulative incidence
0.00
0.25
0.50
0.75
1.00
0
1
2
3
Follow-up time (years)
Q1
Q2
Q3
Q4

B


ELSA: Cumulative incidence of CMM by quartiles of ICMRS
Log-rank P < 0.001
Cumulative incidence
0.00
0.25
0.50
0.75
1.00
0
1
2
3
Follow-up time (years)
Q1
Q2
Q3
Q4

Composite Metabolic Indices for Predicting Incident Cardiometabolic Multimorbidity



Study design

Two prospective ageing cohorts



CHARLS
Wave 3 baseline
n = 8,682 Incident CMM = 1,471



ELSA
Wave 6 baseline
n = 2,422
Incident CMM = 540



Five indices

Five composite metabolic indices



TyG-WHtR



TyG-BRI



AIP-WHtR



TyG-BRI



TyG-BRI

Based on glucose, lipid, and anthropometric measures

Key Findings



All five indices predicted incident CMM



TyG-WHtR and ICMRS showed the most stable performance



TyG-WHtR and ICMRS showed the most stable performance

TyG-WHtR may be a simple and practical tool for early CMM risk identification

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryMaterialTableS1S4andFigureS1S2.docx