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Weight-adjusted waist index outperforms other obesity indices for cardiovascular disease prediction in cardiovascular-kidney-metabolic syndrome: insights from UK biobank

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Abstract

Background Cardiovascular-kidney-metabolic (CKM) syndrome, a systemic disorder often initiated by adipose tissue dysfunction, is an emerging concept for integrated risk assessment. Although the link between obesity and cardiovascular disease (CVD) is established, the optimal anthropometric index for predicting CVD risk across different stages of CKM syndrome remains undetermined.

Methods This prospective cohort study utilized data of individuals with CKM syndrome in stages 0–3 from UK Biobank. Cox proportional hazards models with multi-variable adjustment were used to assess the associations of nine obesity-related indices—weight-adjusted waist index (WWI), cardiometabolic index (CMI), waist-to-height ratio (WHtR), conicity index (CI), relative fat mass (RFM), visceral adiposity index (VAI), body mass index (BMI), waist circumference (WC), and lipid accumulation product (LAP) with incident CVD risk. Potential non-linear associations were examined through restricted cubic spline (RCS) modeling. The discriminative capacity of the nine indicators was further quantified using receiver operating characteristic (ROC) analysis. Moreover, subgroup analyses and interaction tests were carried out for the indicator with the strongest predictive performance to explore its relationship with CVD risk across diverse population subgroups.

Results A total of 13,064 participants, including 55.2% males, were enrolled in this study. During a median follow-up period of 15.4 years, 2,537 (19.42%) of them developed CVD. Multivariable Cox proportional hazards analyses revealed that WWI, CMI, WHtR, CI, RFM, VAI, and BMI were all significantly linked to an elevated risk of CVD in participants with CKM syndrome at stages 0–3. Of these indices, WWI exhibited the strongest correlation with CVD, with an adjusted hazard ratio (HR) of 1.33 and 95% confidence intervals (95% CIs) of 1.06–1.59, followed by CMI (HR: 1.27,

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95% CIs: 1.08–1.51). Nonlinear thresholds were identified at CMI (1.63), WHtR (0.49), VAI (0.65) and BMI (24.88). ROC analysis demonstrated that WWI exhibited the highest discriminatory power in predicting CVD among these indices. Subgroup analyses further revealed that the association between WWI and CVD risk was most pronounced in participants under 60 years old and those with diabetes, hypercholesterolemia, or metabolic syndrome.

Conclusion Among various obesity indices, WWI showed the strongest association with incident CVD among individuals with CKM syndrome stages 0–3 and may serve as a superior simple anthropometric indicator for initial risk stratification compared with traditional measures.

Keywords Cardiovascular-kidney-metabolic syndrome, Obesity, Cardiovascular disease, Screening indicators

Introduction

Cardiovascular-kidney-metabolic (CKM) syndrome has been recently conceptualized to frame the integrated pathophysiology connecting metabolic risk factors, chronic kidney disease (CKD), and cardiovascular disease (CVD) [1]. The American Heart Association (AHA) has officially recognized CKM syndrome as a clinically relevant systemic condition, emphasizing its role in increasing the risk of multiorgan dysfunction and unfavorable cardiovascular outcomes [2]. Individuals with CKM syndrome face an elevated risk of experiencing various cardiovascular events, resulting from the confluence of metabolic abnormalities such as diabetes and obesity, CKD and underlying cardiovascular dysfunction [3, 4]. The CKM syndrome staging framework (stages 0–4) provides a practical tool for risk stratification: stage 0 denotes the absence of CKM health risk factors; stage 1 reflects excess and/or dysfunctional adiposity; stage 2 is characterized by metabolic risk factors and/or chronic kidney disease; stage 3 indicates subclinical cardiovascular disease in the context of CKM abnormalities; and stage 4 corresponds to overt clinical cardiovascular events [5]. The risk of CVD escalates with advancing stage, underscoring the need for early and accurate risk identification [6].

Obesity, particularly central adiposity, is a cornerstone of CKM syndrome pathophysiology and a well-established independent risk factor for CVD [7]. However, traditional anthropometric indices, including body mass index (BMI) and waist circumference (WC), are constrained by their inability to differentiate fat from lean mass and to capture the distribution of visceral adiposity, a critical determinant of metabolic dysfunction [8]. Consequently, numerous novel indices such as weight-adjusted waist index (WWI), waist-to-height ratio (WHtR), relative fat mass (RFM), conicity index (CI) and cardiometabolic index (CMI), have been developed to more accurately quantify adiposity and its metabolic consequences [9–13]. The visceral adiposity index (VAI) and lipid accumulation product (LAP) are specific to abdominal obesity and lipid accumulation, offering valuable insights into metabolic risk profiles [14, 15].

Despite the proliferation of these indices, their comparative prognostic utility for incident CVD has not been systematically evaluated within the specific context of the CKM syndrome framework. Therefore, this study aimed to conduct a head-to-head comparison of nine traditional and novel obesity-related indices in a large, prospective cohort to identify the most effective measure for CVD risk stratification in the CKM syndrome population.

Methods

Study design and population

This study was a prospective analysis of data from the UK Biobank, a large, population-based cohort that recruited 503,317 participants aged 40 to 69 years from across the United Kingdom between 2006 and 2010 [16, 17]. In accordance with UK Biobank procedures, data for participants who subsequently withdrew consent or whose records were no longer provided are removed from the UK Biobank Research Analysis Platform (UKB-RAP), such that 502,424 participants were available in the UKB-RAP dataset and formed the starting cohort.

For this analysis, we included participants classified into CKM syndrome stages 0 to 3. Participants were excluded if they: (1) were not in a fasting state at blood collection ($n = 481,082$); (2) had insufficient data for CKM syndrome staging ($n = 6,383$); (3) had a baseline diagnosis of CVD, including coronary heart disease (CHD), cardiac arrhythmia, cerebrovascular disease (CBVD), or heart failure (HF) ($n = 1,879$); (4) lacked information on covariates ($n = 16$). After applying these criteria, the final analytical cohort consisted of 13,064 participants. Figure 1 depicts the selection process.

Exposure and outcome ascertainment

Exposures included nine screening measures associated with obesity include: WWI, CMI, WHtR, CI, RFM, VAI, BMI, WC and LAP. The formulas for each index are provided in Fig. 2.

The outcome was the first incidence of CVD, identified by ICD-10 codes I20-I26 (CHD), I44-I49 (cardiac arrhythmia), I50 (HF), I60-I69 (CBVD) [18]. For each participant, follow-up time was calculated from the date of the baseline UK Biobank assessment (between 2006

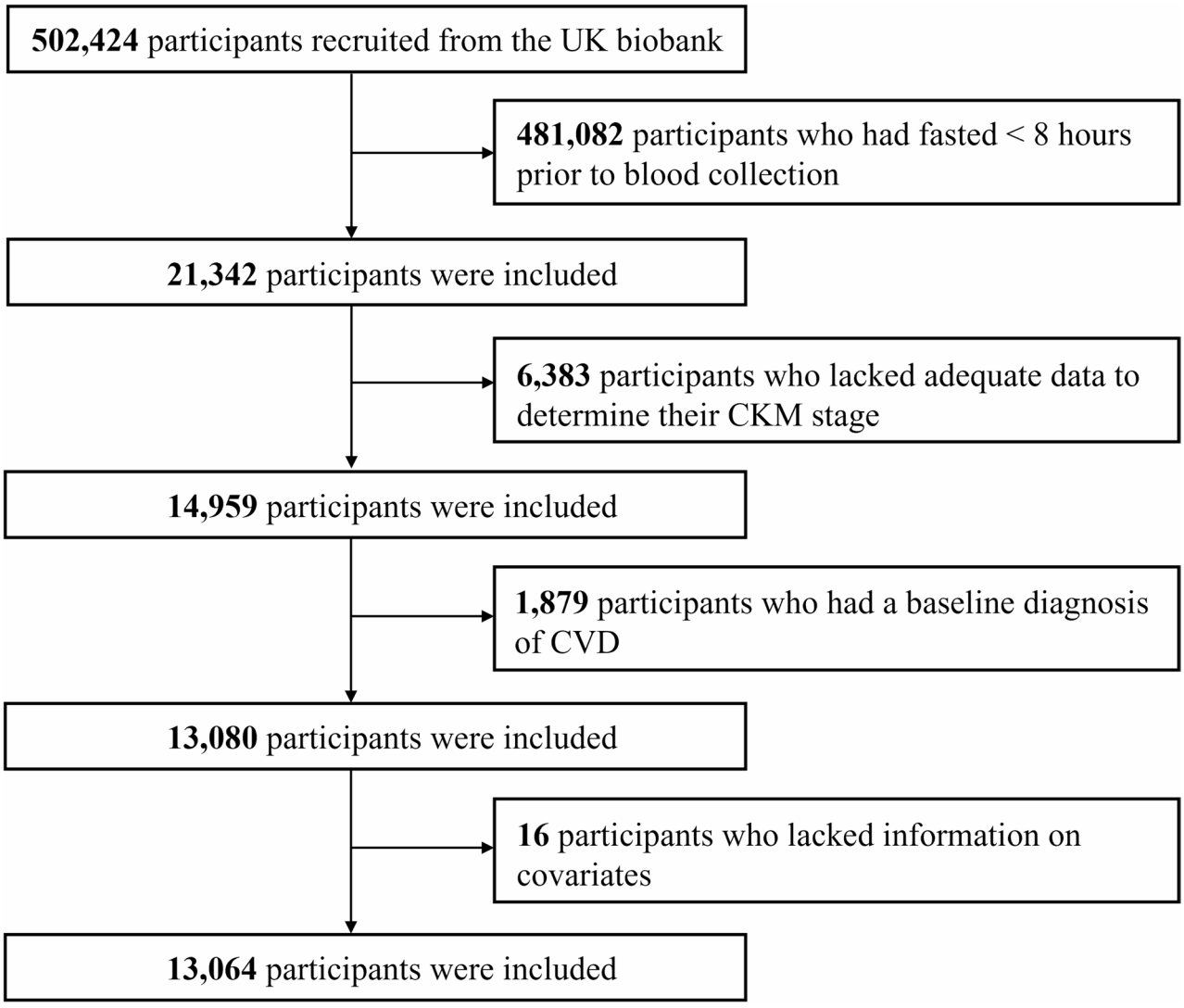

Fig. 1 Flowchart of participant selection

and 2010) to the first occurrence of CVD, death, loss to follow-up, or the end of the data ascertainment period (1 September 2024), whichever came first, resulting in a median follow-up duration of 15.4 years.

Definition of CKM syndrome stages 0–3

According to the American Heart Association Presidential Advisory Statement [19], CKM syndrome stages 0–3 are specified as follows: stage 0: no CKM health risk factors; stage 1: excess and/or dysfunctional adiposity; stage 2: metabolic risk factors and CKD; stage 3: subclinical CVD in CKM. CKD was classified based on the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, using estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (UACR) [20]. The estimated glomerular filtration rate (eGFR) was derived using the 2021 creatinine-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [21]. The detailed definition of disease and specific staging criteria are provided in Supplementary Table S1, S2.

Covariates

In this study, several confounders were incorporated as covariates. Demographic information included: age, sex, and the Townsend deprivation index, an area-level measure of socioeconomic deprivation derived from participants' residential postcode [22]. For smoking status, we categorized them into three groups: no, only occasionally and on most or all days. Alcohol consumption was categorized as: never, previous and current. Laboratory testing data included: low-density lipoprotein cholesterol (LDL-C) and eGFR. Clinical variables included hypertension, diabetes, hypercholesterolemia and metabolic syndrome (MetS).

$$\text{WC} = \text{Horizontal circumference around the umbilicus (cm)}$$

$$\text{BMI} = \frac{\text{Weight(kg)}}{[\text{Height(m)}]2}$$

$$\text{WWI} = \frac{\text{WC(cm)}}{[\text{Weight(kg)}]^{0.5}}$$

$$\text{WHtR} = \frac{\text{WC(cm)}}{\text{Height(cm)}}$$

$$\text{CI} = \frac{\text{WC(m)}}{0.109} / [\frac{\text{Weight(kg)}}{\text{Height(cm)}}]^{0.5}$$

$$\text{RFM: Males} = 64 - [20 * \frac{\text{Height(m)}}{\text{WC(m)}}]$$

$$\text{Females} = 76 - [20 * \frac{\text{Height(m)}}{\text{WC(m)}}]$$

$$\text{CMI} = \frac{\text{TG(mmol/L)}}{\text{HDL−C(mmol/L)}} * \frac{\text{WC(cm)}}{\text{Height(cm)}}$$

$$\text{LAP: Males} = [\text{WC(cm)-65)}] * \text{TG(mmol/L)}$$

$$\text{Females} = [\text{WC(cm)-58)}] * \text{TG(mmol/L)}$$

$$\text{VAI: Males} = \frac{\text{WC(cm)}}{39.68+1.88*\text{BMI(kg/m}^2)} * \frac{\text{TG(mmol/L)}}{1.03} * \frac{1.08}{\text{HDL−C(mmol/L)}}$$

$$\text{Females} = \frac{\text{WC(cm)}}{36.58+1.89*\text{BMI(kg/m}^2)} * \frac{\text{TG(mmol/L)}}{0.81} * \frac{1.52}{\text{HDL−C(mmol/L)}}$$

Fig. 2 Formulas for nine different obesity-based screening indicators. *WC* Waist circumference, *BMI* Body mass index, *WWI* Weight-adjusted waist index, *WHtR* Waist-to-height ratio, *CI* Conicity index, *RFM* Relative fat mass index, *CMI* Cardiometabolic index, *LAP* Lipid accumulation product, *VAI* Visceral adiposity index, *TG* Triglyceride, *HDL-C* High-density lipoprotein cholesterol

Statistical analysis

Continuous variables are presented as mean (standard deviation, SD), and categorical variables as counts (%). The distribution of each continuous variable was examined using histograms and Q-Q plots. Variables that were approximately normally distributed were compared between groups using Student's t-test, whereas variables with evident skewness were compared using the Mann-Whitney test. Given the large sample size and to facilitate interpretation, all continuous variables are reported as mean (SD) in Table 1, even when mildly skewed, while the choice of parametric or non-parametric test was determined by their empirical distribution. Categorical

Table 1 Baseline characteristics of participants by CVD status

Variables	Total	Non-CVD	CVD	*P*-value
	N **= 13,064**	***N*** **= 10,527 (80.58%)**	***N*** **= 2537(19.42%)**	
Age	53.6 (7.96)	52.7 (7.76)	57.4 (7.63)	< 0.001
Sex				< 0.001
Male	7217 (55.2%)	5508 (52.3%)	1709 (67.4%)	
Female	5847 (44.8%)	5019 (47.7%)	828 (32.6%)	
Townsend deprivation index	−0.330 (3.51)	−0.406 (3.48)	−0.0149 (3.60)	< 0.001
Smoking status				< 0.001
No	10,393 (79.6%)	8520 (80.9%)	1873 (73.8%)	
Only occasionally	526 (4.0%)	422 (4.0%)	104 (4.1%)	
On most or all days	2145 (16.4%)	1585 (15.1%)	560 (22.1%)	
Alcohol consumption				< 0.001
Never	715 (5.5%)	588 (5.6%)	127 (5.0%)	
Previous	575 (4.4%)	411 (3.9%)	164 (6.5%)	
Current	11,774 (90.1%)	9528 (90.5%)	2246 (88.5%)	
Diabetes				< 0.001
No	12,308 (94.2%)	10,033 (95.3%)	2275 (89.7%)	
Yes	756 (5.8%)	494 (4.7%)	262 (10.3%)	
Hypertension				< 0.001
No	2628 (20.1%)	2350 (22.3%)	278 (11.0%)	
Yes	10,436 (79.9%)	8177 (77.7%)	2259 (89.0%)	
Hypercholesterolemia				< 0.001
No	8109 (62.1%)	6715 (63.8%)	1394 (54.9%)	
Yes	4955 (37.9%)	3812 (36.2%)	1143 (45.1%)	
MetS				< 0.001
No	9442 (72.3%)	7863 (74.7%)	1579 (62.2%)	
Yes	3622 (27.7%)	2664 (25.3%)	958 (37.8%)	
CKM syndrome				< 0.001
Stage 0	967 (7.4%)	900 (8.5%)	67 (2.6%)	
Stage 1	919 (7.0%)	823 (7.8%)	96 (3.8%)	
Stage 2	8729 (66.8%)	7236 (68.7%)	1493 (58.8%)	
Stage 3	2449 (18.7%)	1568 (14.9%)	881 (34.7%)	
Height (cm)	169 (9.26)	169 (9.30)	170 (9.03)	< 0.001
Weight (kg)	80.8 (17.2)	79.9 (16.8)	84.3 (18.1)	< 0.001
SBP (mmHg)	139 (18.4)	137 (17.8)	145 (19.6)	< 0.001
DBP (mmHg)	85.0 (10.3)	84.6 (10.2)	86.9 (10.3)	< 0.001
FBG (mmol/L)	5.15 (1.11)	5.11 (0.977)	5.32 (1.51)	< 0.001
HbA1c (mmol/mol)	36.0 (6.99)	35.5 (6.21)	37.8 (9.35)	< 0.001
Creatinine (μmol/L)	73.0 (21.9)	72.2 (15.2)	76.3 (38.6)	< 0.001
eGFR(ml/min/1.73m^2)	89.2 (16.7)	89.4 (16.2)	88.5 (18.6)	0.040
TC (mmol/L)	5.82 (1.13)	5.83 (1.12)	5.82 (1.19)	0.975
TG (mmol/L)	1.53 (0.957)	1.49 (0.937)	1.68 (1.02)	< 0.001
HDL-C (mmol/L)	1.45 (0.392)	1.46 (0.389)	1.40 (0.404)	< 0.001
LDL-C (mmol/L)	3.70 (0.889)	3.70 (0.878)	3.71 (0.933)	0.983
WC (cm)	92.3 (13.9)	91.3 (13.7)	96.6 (14.2)	< 0.001
BMI	28.1 (5.15)	27.9 (5.05)	28.9 (5.47)	< 0.001
WWI	10.3 (0.769)	10.2 (0.759)	10.6 (0.756)	< 0.001
WHtR	0.545 (0.0771)	0.540 (0.0756)	0.567 (0.0798)	< 0.001
RFM	32.0 (6.96)	32.0 (6.98)	32.9 (6.89)	0.004
CI	123 (9.72)	122 (9.62)	126 (9.37)	< 0.001
VAI	1.83 (1.51)	1.78 (1.48)	2.04 (1.61)	< 0.001

Table 1 (continued)

Variables	Total	Non-CVD	CVD	*P*-value
	N = 13,064	*N* = 10,527 (80.58%)	*N* = 2537(19.42%)	
CMI	0.688 (0.632)	0.661 (0.616)	0.800 (0.685)	< 0.001
LAP	50.2 (44.0)	47.8 (42.3)	60.2 (49.2)	< 0.001

Data are presented as mean ± standard deviation or number (%)

MetS Metabolic syndrome, *CKM syndrome* Cardiovascular-kidney-metabolic syndrome, *SBP* Systolic blood pressure, *DBP* Diastolic blood pressure, *FBG* Fasting blood glucose, *HbA1c* Glycated hemoglobin A1c, *eGFR* Estimated glomerular filtration rate, *TC* Total cholesterol, *TG* Triglycerides, *HDL-C* High-density lipoprotein cholesterol, *LDL-C* Low-density lipoprotein cholesterol, *WC* Waist circumference, *BMI* Body mass index, *WWI* Weight-adjusted waist index, *WHtR* Waist-to-height ratio, *RFM* Relative fat mass, *CI* Conicity index, *VAI* Visceral adiposity index, *CMI* Cardiometabolic index, *LAP* Lipid accumulation product

variables were compared using Pearson's χ^2 test or Fisher's exact test, as appropriate.

We used Cox proportional hazards regression to estimate hazard ratio (HR) and 95% confidence intervals (95% CIs) for the association between each obesity index (analyzed as both a continuous variable and in quartiles) and incident CVD. Model 1 showed an unadjusted risk; Model 2 was adjusted for age, sex and Townsend deprivation index; Model 3 was further adjusted for LDL-C, eGFR, smoking status, alcohol consumption, hypertension, diabetes, hypercholesterolemia and MetS. The dose-response correlation of nine obesity-related screening indicators with CVD risk was analyzed by conducting restricted cubic splines (RCS) analysis (adjusted by Model 3). When evidence of non-linearity was observed, a threshold effect was further evaluated using a two-piecewise Cox proportional hazards model. The inflection point was determined by maximizing the model likelihood via a recursive algorithm. The adequacy of the segmented model over the linear Cox model was assessed using a likelihood ratio test, enabling distinct hazard ratio estimations on either side of the threshold.

Receiver operating characteristic (ROC) curves were generated, and the corresponding area under the curve (AUC) was calculated to evaluate the predictive performance of the various indicators. Subgroup analyses were further performed with the most predictive indicator to examine its association with CVD risk. A two-sided p-value < 0.05 was considered statistically significant. All statistical analyses were performed using R software (version 4.4.3).

Results

Baseline characteristics

Of the 13,064 participants (7,217 men and 5,847 women), 2,537 developed new-onset CVD. These individuals exhibited significant differences in baseline characteristics compared with participants who did not develop CVD. Table 1 presents the demographic and clinical characteristics of patients with CKM syndrome stages 0–3. Specifically, CVD cases demonstrated remarkably higher mean values of age, weight, systolic and diastolic blood pressure, fasting blood glucose (FBG), glycated hemoglobin A1c (HbA1c), creatinine, triglycerides (TG), and all nine obesity-based indices—namely WWI, CI, RFM, WHtR, BMI, VAI, CMI, WC, LAP ($P < 0.05$). In addition, they exhibited elevated rates of smoking, CKM syndrome stage 3, diabetes, hypertension, hypercholesterolemia and MetS. Conversely, high-density lipoprotein cholesterol (HDL-C) and eGFR were significantly lower among those who developed CVD ($P < 0.05$).

Association of nine obesity-based screening indicators and risk of CVD

Cox proportional hazards models with multi-model adjustment were employed to examine the association of nine obesity-based screening indicators and risk of CVD in patients with CKM syndrome stages 0–3. All indices were significantly associated with CVD risk in both Model 1 and Model 2. After full adjustment in Model 3, seven indices—WWI, CMI, WHtR, CI, RFM, VAI and BMI remained significantly and positively associated with CVD. Of these indices analyzed as continuous variables, WWI exhibited the strongest correlation with CVD, with an adjusted HR of 1.33 and 95% CIs of 1.06–1.59, followed by CMI (HR: 1.27, 95% CIs: 1.08–1.51). In analyses using categorical variables, WWI also demonstrated the strongest association with CVD risk (HR = 1.40, 95% CIs: 1.19–1.64). It was followed by CMI (HR = 1.31, 95% CIs: 1.10–1.46), CI (HR = 1.30, 95% CIs: 1.11–1.41), VAI (HR = 1.28, 95% CIs: 1.03–1.43), WHtR (HR = 1.25, 95% CIs: 1.04–1.52), RFM (HR = 1.21, 95% CIs: 1.02–1.38), and BMI (HR = 1.11, 95% CIs: 1.03–1.26). The relationships between all nine indices and CVD risk across the three models and both variable types are visually summarized in Fig. 3, with more detailed data available in Table S3. Importantly, the associations between WWI and incident CVD remained significant after adjusting for hypertension, diabetes, hypercholesterolemia, MetS and lifestyle factors in Model 3, demonstrating that WWI captures cardiometabolic risk beyond these traditional determinants.

Nonlinear associations between nine indicators and CVD

RCS analyses were used to assess potential nonlinear associations between nine indices and new-onset CVD in patients with CKM syndrome stages 0–3. As illustrated in Fig. 4, CMI, WHtR, VAI and BMI exhibited

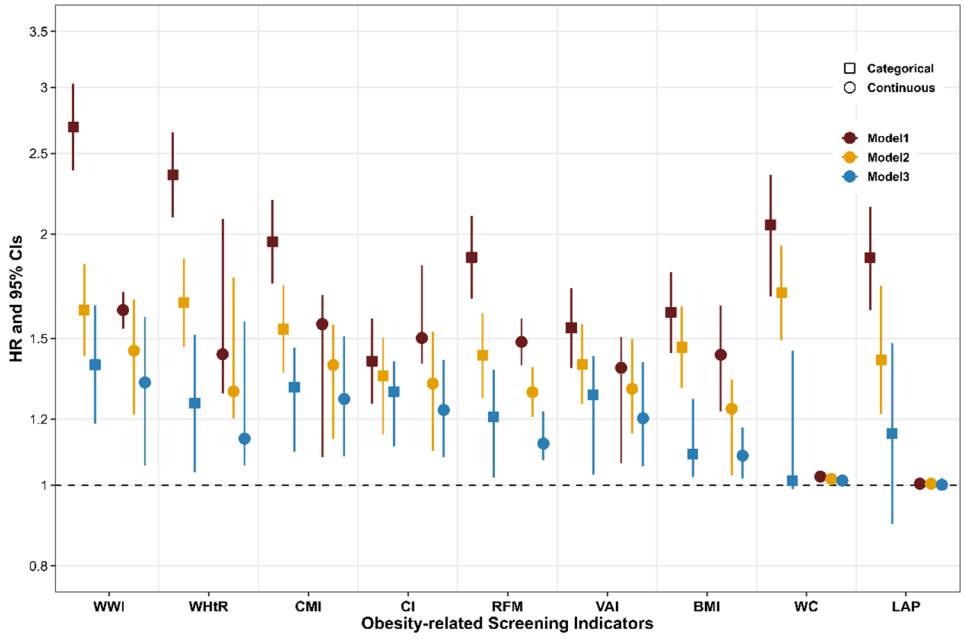

Fig. 3 Relationship between nine obesity-related indicators and CVD in different models. Model 1: non-adjusted; Model 2: adjusted for age, sex and Townsend deprivation index; Model 3: further adjusted for LDL-C, eGFR, smoking status, alcohol consumption, hypertension, diabetes, hypercholesterolemia and MetS. The nine indices were entered into the models both as continuous and categorical variables. When analyzed categorically, HR values were derived by comparing the highest quartile against the lowest quartile. *WWI* Weight-adjusted waist index, *WHtR* Waist-to-height ratio, *CMI* Cardiometabolic index, *CI* Conicity index, *RFM* Relative fat mass index, *BMI* Body mass index, *VAI* Visceral adiposity index, *WC* Waist circumference, *LAP* Lipid accumulation product, *LDL-C* Low-density lipoprotein cholesterol, *eGFR* Estimated glomerular filtration rate, *MetS* Metabolic syndrome

significant nonlinear relationships with CVD risk (P for nonlinearity < 0.05).

Due to the observed nonlinearity, we performed an analysis of threshold effects employing a two-segment Cox proportional hazards model. For CMI, a threshold was identified at 1.63. Above this value, no significant association with CVD risk was observed (HR = 0.95, 95% CIs: 0.84–1.06, $P = 0.331$). Below the threshold, however, each unit increase in CMI was significantly associated with elevated CVD risk (HR = 1.39, 95% CIs: 1.12–1.81, $P < 0.001$). The two-piecewise model demonstrated a significantly better fit than the linear Cox model, as indicated by the log-likelihood ratio test ($P = 0.039$). Detailed results of other indices are presented in Table 2.

Predictive value of nine indicators for CVD

Figure 5; Table 3 present AUC values and corresponding 95% CIs for the nine adiposity indices in screening CVD in patients with CKM syndrome stages 0–3. WWI demonstrated the highest discriminative ability for CVD (AUC = 0.63), closely followed by WHtR (AUC = 0.60) and RFM (AUC = 0.59). The optimal diagnostic thresholds for these indicators were determined to be 10.49, 0.55 and 50.03, respectively. Based on DeLong's test for comparing ROC curves (Table S4), the difference in AUC values between WWI and all other obesity-related indices was statistically significant ($P < 0.05$).

Subgroup and sensitivity analyses

As presented in Fig. 6, significant positive associations were consistently demonstrated across most subgroups stratified by age, sex, smoking status, alcohol consumption, hypertension, diabetes, hypercholesterolemia, MetS and CKM syndrome stage. Furthermore, WWI demonstrated particularly strong associations in participants aged under 60 years, as well as in those with diabetes, hypercholesterolemia, and MetS (all $P < 0.05$; P for interaction < 0.05). These findings suggest that WWI helps to differentiate higher-risk individuals not only across CKM stages but also within strata defined by conventional risk factors, and may therefore reflect subclinical cardio-metabolic abnormalities that precede overt CVD events.

Several sensitivity analyses were conducted to assess the reliability of our study. First, we conducted an additional analysis by excluding the new-onset CVD that occurred during the first 90 days of follow-up (Table S5). In addition, given that participants classified as stage 0 may exhibit minimal cardiovascular risk factors or may fall below clinically significant thresholds, we performed a sensitivity analysis that excluded these individuals (Table S6). The findings above remained consistent with those of the primary analysis, reinforcing the robustness of our results.

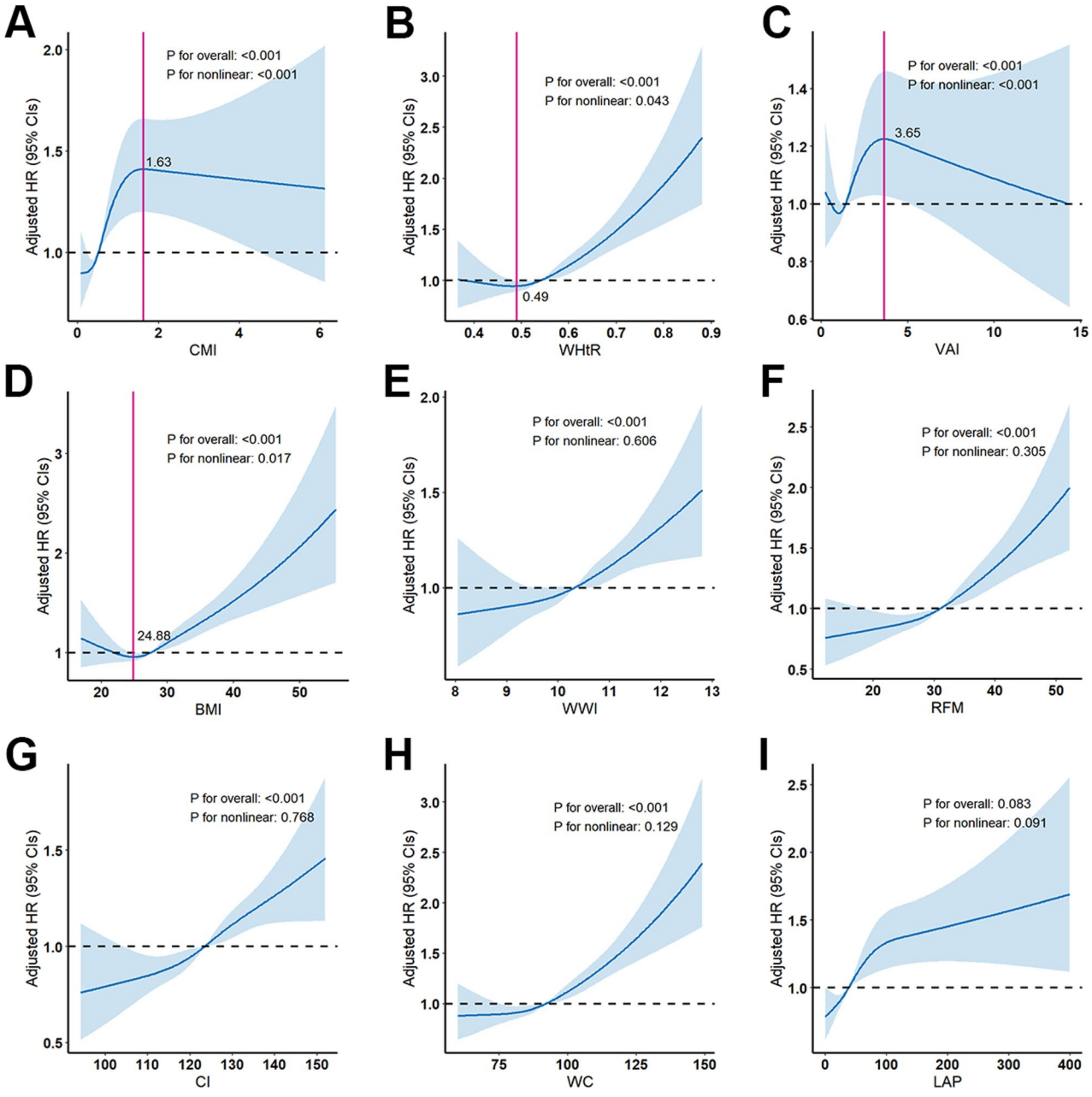

Fig. 4 RCS analysis between nine obesity-based indicators and CVD incidence. The model was adjusted for age, sex, Townsend deprivation index, LDL-C, eGFR, smoking status, alcohol consumption, hypertension, diabetes, hypercholesterolemia and MetS. **A** CMI, (**B**) WHtR, (**C**) VAI, (**D**) BMI, (**E**) WWI, (**F**) RFM, (**G**) CI, (**H**) WC and (**I**) LAP

Discussion

In this large, prospective cohort study of individuals stratified by CKM syndrome stage, we conducted a comprehensive comparison of nine obesity-related indices for the prediction of incident CVD. Our principal finding is that while several indices were independently associated with CVD risk, WWI demonstrated the strongest and most consistent association.

Specifically, we found that seven indices—WWI, CMI, WHtR, CI, RFM, VAI, and BMI—were independently associated with future CVD events in patients with CKM syndrome stages 0–3, while WC and LAP demonstrated weaker associations after multivariable adjustment. Among these indices, WWI showed the strongest predictive performance, with an adjusted HR of 1.33 (95% CIs: 1.06–1.59), outperforming more traditional measures such as BMI and WC. Non-linear analyses identified threshold effects for CMI (1.63), WHtR (0.49), VAI (0.65) and BMI (24.88), suggesting that subtle variations around these cut-points may translate into disproportionate

Table 2 Threshold effect analysis of obesity-related indices on new-onset CVD using a two-piecewise linear regression model

CVD risk	Adjusted HR (95% CIs)	*P*-value
CMI		
Fitting by the standard linear model	1.27 (1.08,1.69)	< 0.001
Fitting by the two-piecewise linear model		
Inflection point	1.63	
CMI < 1.63	1.39 (1.12,1.81)	< 0.001
CMI ≥ 1.63	0.95 (0.84,1.06)	0.331
P for Log-likelihood ratio		0.039
WHtR		
Fitting by the standard linear model	1.14 (1.06,1.57)	< 0.001
Fitting by the two-piecewise linear model		
Inflection point	0.49	
WHtR < 0.49	0.187 (0.013, 1.177)	0.217
WHtR ≥ 0.49	1.36 (1.07,1.63)	< 0.001
P for Log-likelihood ratio		0.041
VAI		
Fitting by the standard linear model	1.20 (1.05,1.41)	< 0.001
Fitting by the two-piecewise linear model		
Inflection point	0.65	
VAI < 0.65	0.98 (0.94,1.03)	0.513
VAI ≥ 0.65	1.32 (1.27,1.40)	< 0.001
P for Log-likelihood ratio		0.028
BMI		
Fitting by the standard linear model	1.14 (1.06,1.57)	< 0.001
Fitting by the two-piecewise linear model		
Inflection point	24.88	
BMI < 24.88	0.97 (0.94,1.01)	0.131
BMI ≥ 24.88	1.26 (1.03,1.58)	< 0.001
P for Log-likelihood ratio		0.003

The model was adjusted for age, sex, Townsend deprivation index, LDL-C, eGFR, smoking status, alcohol consumption, hypertension, diabetes, hypercholesterolemia and MetS

CMI Cardiometabolic index, *WHtR* Waist-to-height ratio, *VAI* Visceral adiposity index, *BMI* Body mass index, *LDL-C* Low-density lipoprotein cholesterol, *eGFR* Estimated glomerular filtration rate

elevations in CVD risk. ROC analyses further confirmed the superior discriminative ability of WWI, highlighting its potential clinical applicability as a simple and reliable marker. Subgroup analyses showed that the predictive value of WWI was particularly pronounced in younger individuals (< 60 years), as well as those with diabetes, hypercholesterolemia and MetS, indicating that WWI may capture the synergistic impact of multiple metabolic derangements and identify individuals at an earlier stage of the disease continuum where adverse changes in body composition begin to exert a synergistic effect on vascular health.

The potential superiority of WWI may be attributable to its unique ability to capture the high-risk phenotype of sarcopenic obesity. Unlike BMI, which cannot differentiate between fat and lean mass [23], WWI standardizes WC by total body weight, penalizing individuals with disproportionately large waists relative to their body mass, thereby providing a more accurate reflection of central adiposity and fat distribution [24]. This characteristic enables WWI to serve as a practical proxy for an unfavorable body composition phenotype, defined by excessive visceral adiposity in conjunction with reduced muscle mass. Such sarcopenic obesity is metabolically detrimental, promoting pronounced insulin resistance, persistent inflammation, and endothelial dysfunction [25, 26]—all core pathophysiologic mechanisms in the progression of CKM syndrome and atherosclerosis [27]. Excess visceral fat promotes secretion of pro-inflammatory cytokines and free fatty acids, aggravates dyslipidemia, and drives oxidative stress and vascular remodeling [28–32]. These processes not only accelerate atherosclerosis but also exacerbate the cardio-renal-metabolic feedback loops central to CKM syndrome [33, 34]. The non-linear associations identified in our analyses suggest that once adiposity reaches critical thresholds, pathological processes may escalate rapidly, which is consistent with earlier observations that abdominal fat accumulation disproportionately increases CVD risk [35].

Although WWI demonstrated statistical superiority in direct comparisons with other single indicators, its clinical utility should be interpreted with caution. An AUC of 0.63 reflects only modest predictive performance, far below that of established multivariable risk scores such as the ASCVD Pooled Cohort Equations or SCORE2. Thus, WWI should not be viewed as a replacement for comprehensive risk assessment tools. Instead, its value may lie in its simplicity and cost-free applicability as an initial screening measure to improve early risk stratification. In particular, WWI and other novel indices (CMI, WHtR, CI, RFM, and VAI) appear to outperform conventional anthropometric measures such as BMI and WC in identifying individuals at elevated CVD risk. This may be especially relevant in metabolically vulnerable CKM syndrome populations, where early detection could facilitate timely intervention. For example, individuals exceeding threshold values for WWI may benefit from more intensive lifestyle counseling, cardiometabolic evaluation and targeted pharmacotherapy. Furthermore, the stronger associations observed among younger adults and those with multiple metabolic abnormalities highlight the potential of WWI to help prioritize preventive strategies in subgroups where traditional risk scores may underestimate vascular risk.

From a broader public health perspective, WWI may also have implications beyond individual clinical decision-making. Because WWI requires only weight and waist circumference, it can be easily obtained in community settings, primary care clinics, and low-resource

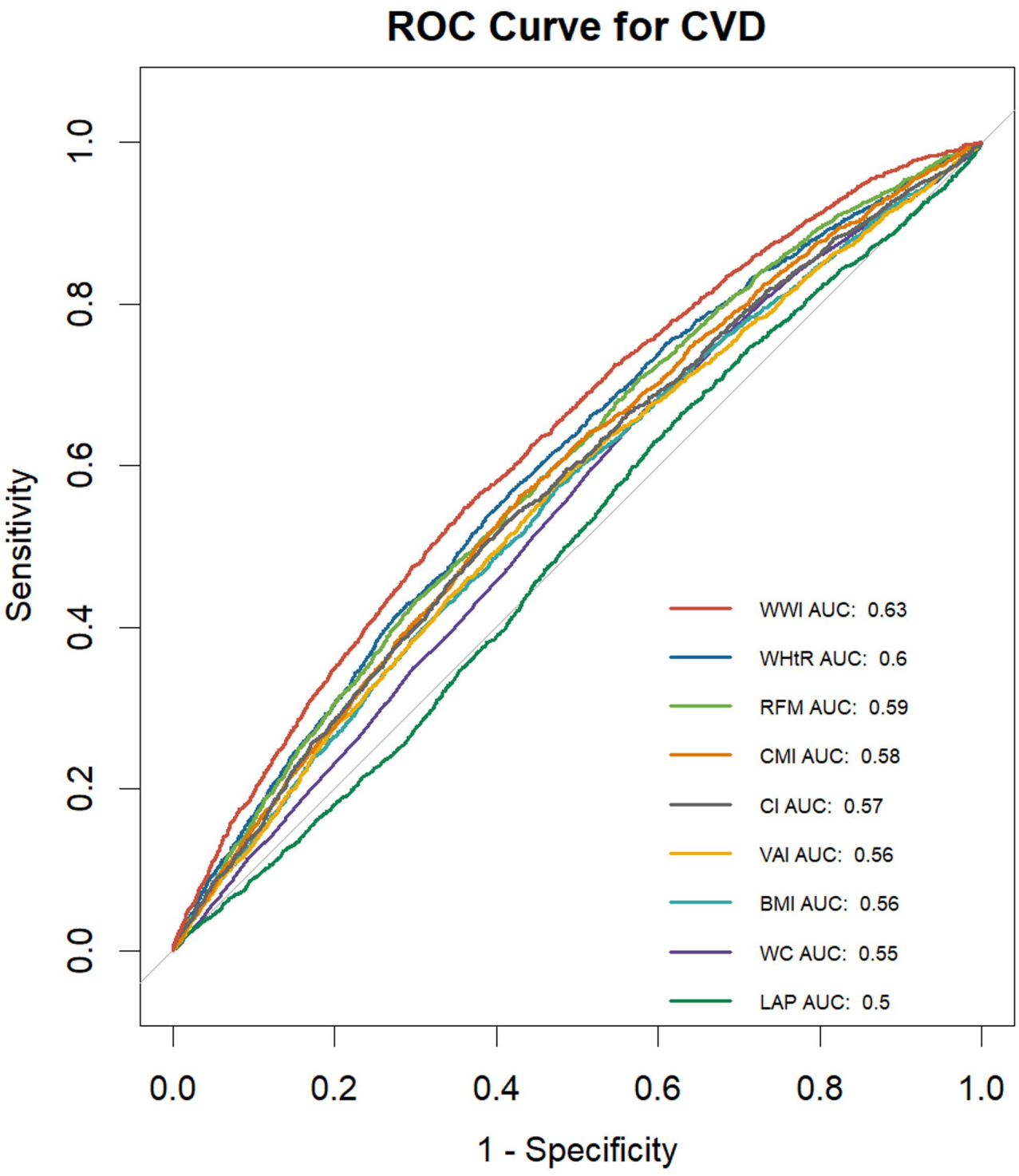

Fig. 5 ROC curves of nine indices for CVD screening in patients with CKM syndrome stages 0–3

environments without additional laboratory testing. Incorporating WWI into population-level screening programs for CKM syndrome could help flag individuals at elevated cardiovascular risk earlier in the disease continuum and at minimal cost. In health systems facing constrained resources, WWI-based thresholds might be used to prioritize more intensive cardiometabolic assessment, lifestyle counseling, and pharmacologic prevention for those with CKM syndrome and high WWI, while reserving more resource-intensive evaluations for those most likely to benefit. If validated in diverse populations, such a tiered approach could inform health policy and

Table 3 Results of ROC analysis of nine screening tools

	AUC	95%CI low	95%CI up	Best threshold	Specificity	Sensitivity	Accuracy	PPV	NPV
WWI	0.63	0.60	0.64	10.49	0.64	0.55	0.62	0.27	0.85
WHtR	0.60	0.59	0.61	0.55	0.58	0.56	0.58	0.25	0.85
RFM	0.59	0.58	0.60	50.03	0.70	0.43	0.65	0.26	0.84
CMI	0.58	0.57	0.59	0.69	0.53	0.60	0.54	0.23	0.84
CI	0.57	0.56	0.58	123.68	0.62	0.49	0.59	0.24	0.83
VAI	0.57	0.55	0.57	1.83	0.53	0.58	0.54	0.23	0.84
BMI	0.56	0.55	0.57	28.46	0.52	0.57	0.53	0.22	0.84
WC	0.55	0.53	0.58	93.56	0.57	0.55	0.56	0.23	0.84
LAP	0.50	0.49	0.51	33.53	0.37	0.66	0.43	0.20	0.82

AUC Area under the curve, *PPV* Positive predictive value, *NPV* Negative predictive value, *WWI* Weight-adjusted waist index, *WHtR* Waist-to-height ratio, *RFM* Relative fat mass, *CMI* Cardiometabolic index, *CI* Conicity index, *WC* Waist circumference, *BMI* Body mass index, *VAI* Visceral adiposity index, *LAP* Lipid accumulation product

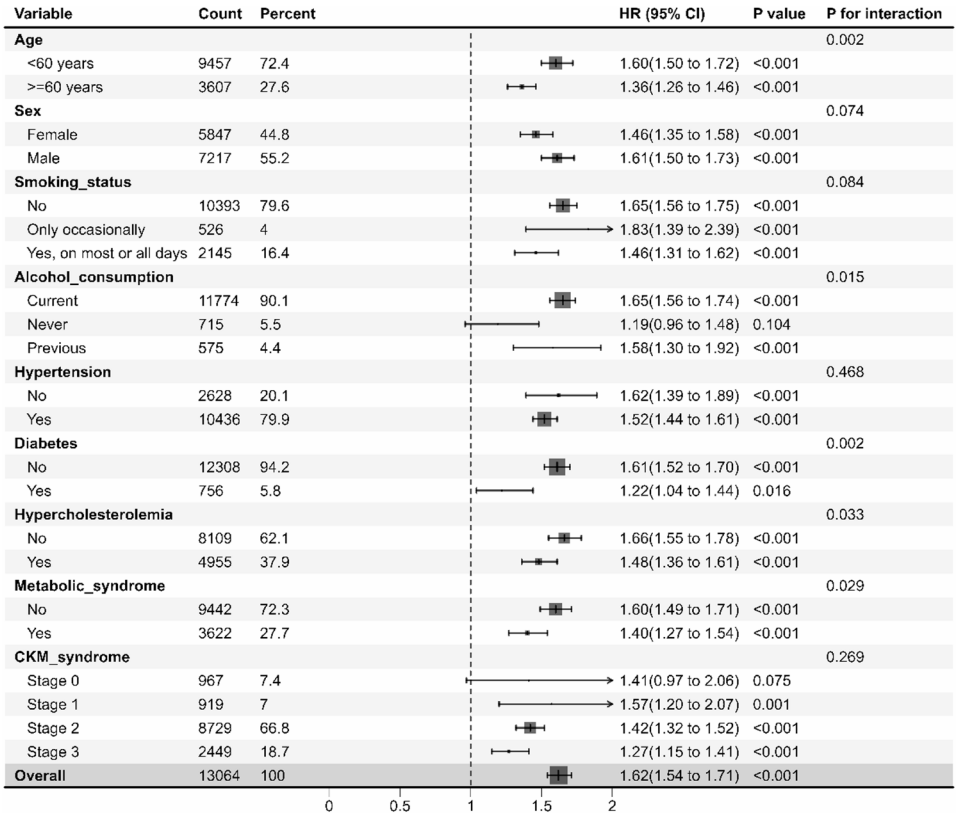

Fig. 6 Subgroup and interaction analyses of the association between WWI and CVD incidence in patients with CKM syndrome stages 0–3

resource allocation by integrating a simple anthropometric index into CKM-focused prevention strategies.

In the context of the CKM staging framework, our findings also suggest that WWI may complement, rather than replace, existing stage definitions. CKM stages 0–3 capture progressive clustering of metabolic, renal, and subclinical cardiovascular abnormalities, yet there remains substantial heterogeneity in risk within each stage. In our subgroup analyses stratified by CKM stage, WWI retained a positive association with incident CVD, indicating that it provides incremental prognostic information beyond stage assignment alone. This raises the possibility that WWI could be used to refine risk stratification within a given CKM stage—for example, to identify higher-risk phenotypes among individuals classified as CKM stages 1–3 who might warrant earlier or more intensive preventive intervention.

Moreover, our ROC analysis yielded an optimal WWI threshold for incident CVD in this CKM population (10.49 in the present cohort). While this cut-off should be interpreted cautiously and requires external validation, it illustrates how WWI-based thresholds might eventually be integrated into the CKM framework—for instance, as stage-specific modifiers or subcategories to distinguish individuals at particularly high short-term cardiovascular risk. Future work should formally evaluate whether

adding WWI thresholds to CKM staging criteria meaningfully improves discrimination, calibration, and reclassification compared with the current staging system alone, and whether such refinements translate into better clinical and public health outcomes.

Strengths and limitations

Our results are in line with previous studies showing the predictive value of novel indices such as RFM and CI for cardiovascular outcomes [36, 37]. However, our study extends prior work in three important ways. First, we excluded participants who were not fasting when the blood sample was collected, trying to remove the interference of dietary factors on blood biochemistry and classification of CKM syndrome stages as much as possible. Second, we simultaneously compared nine indices within the same CKM syndrome population, providing head-to-head evidence of their relative predictive performance. Third, by incorporating restricted cubic spline analyses, we identified clinically meaningful non-linear thresholds, which have not been systematically reported in the context of CKM syndrome. These innovations strengthen the case for adopting WWI and related indices as refined tools for risk stratification beyond conventional indices.

Nevertheless, several limitations should be acknowledged. First, despite adjustment for major covariates, residual confounding like physical activity and dietary patterns cannot be fully excluded. Second, as the study was based on UK Biobank participants, who tend to be healthier and less socioeconomically diverse than the general population [38, 39], caution is needed in extrapolating our findings to other ethnic or demographic groups. Third, the cohort is predominantly of White European ancestry, so the results may not be applicable to other ethnic groups. Fourth, although CKM syndrome stages were defined based on available data, some subclinical markers may have been underrepresented, potentially leading to misclassification. Finally, we did not directly compare WWI-augmented models with established multivariable CVD risk scores or with models including only classical risk factors, and thus the incremental gain in discrimination, calibration, and risk reclassification attributable to WWI could not be quantified in this study. Future work should formally assess the added value of WWI on top of existing risk equations.

Conclusion

In a large cohort of individuals across the spectrum of CKM syndrome stages 0–3, WWI was the most robust simple anthropometric predictor of incident CVD. While its absolute predictive ability is modest and it should not replace comprehensive risk algorithms, WWI may be a clinically useful, accessible tool for enhancing initial risk stratification beyond traditional measures like BMI. Future studies should not only validate these findings across diverse populations and further elucidate the underlying biological mechanisms, but also evaluate WWI-guided, risk-stratified interventions and implementation strategies in real-world clinical and community settings to determine whether its use can improve CKM management and reduce CVD events.

Abbreviations

AHA	American Heart Association
AUC	Area under the curve
BMI	Body mass index
CBVD	Cerebrovascular disease
CHD	Coronary heart disease
CI	Conicity index
CIs	Confidence intervals
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CKM	Cardiovascular-kidney-metabolic
CMI	Cardiometabolic index
CVD	Cardiovascular disease
eGFR	Estimated glomerular filtration rate
FBG	Fasting blood glucose
HbA1c	Glycated hemoglobin A1c
HDL-C	High-density lipoprotein cholesterol
HF	Heart failure
HR	Hazard ratio
KDIGO	Kidney Disease Improving Global Outcomes
LAP	Lipid accumulation product
LDL-C	Low-density lipoprotein cholesterol
MetS	Metabolic syndrome
RCS	Restricted cubic splines
RFM	Relative fat mass
ROC	Receiver operating characteristic
SD	Standard deviation
TG	Triglycerides
UACR	Urine albumin-to-creatinine ratio
UKB-RAP	UK Biobank Research Analysis Platform
VAI	Visceral adiposity index
WC	Waist circumference
WHtR	Waist-to-height ratio
WWI	Weight-adjusted waist index

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-025-25830-2.

Supplementary Material 1.

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Authors' contributions

TYW and LXZ conceived and designed the study, performed data analysis and interpretation. PFC and CC drafted the manuscript. LX and MG critically reviewed the manuscript and contributed important intellectual content. All authors read and approved the final version of the manuscript.

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Data availability
The datasets generated and analyzed during the current study are available from the UK Biobank repository (https://www.ukbiobank.ac.uk).

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval for the UK Biobank was granted by the UK National Health Service's National Research Ethics Service (reference 11/NW/0382). Our research was conducted using data from UK Biobank under application number 105474. All participants provided written informed consent prior to participation.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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