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Association between the Single-Point Insulin Sensitivity Estimator and Future Cardiovascular Disease Risk in a Population with Cardiovascular-Kidney-Metabolic Syndrome Stage 0 - 3: A Nationwide Prospective Cohort Study

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Abstract

Objective: The concept of cardiovascular-kidney-metabolic (CKM) syndrome has been proposed to highlight the complex interplay among metabolic disorders, kidney disease, and cardiovascular disease (CVD). We investigated the association between the single-point insulin sensitivity estimator (SPISE), an insulin resistance (IR) marker, and future CVD risk in individuals with CKM stages 0 - 3. **Method:** Based on data from the China Health and Retirement Longitudinal Study (CHARLS), a total of 6887 participants were included. Kaplan Meier analysis and multivariable Cox proportional hazards models were used to evaluate the association between the SPISE and the CVD incidence. Restricted cubic spline (RCS) models were applied to explore potential non-linear relationships. Subgroup analyses were performed to assess consistency across subgroups. **Results:** Over a median follow-up of 6.7 years, 1453 CVD events occurred. Higher SPISE was independently associated with lower CVD risk (HR 0.95, 95% CI 0.92 - 0.97). Participants in the highest quartile (Q4) had a 28% lower risk versus the lowest (Q1) (HR 0.72, 95% CI 0.61 - 0.85). RCS showed a linear negative dose – response relationship. Notably, significant interactions were observed for sex (P = 0.021), indicating that the protective association was more robust in men. **Conclusions:** Higher SPISE levels are significantly associated with reduced CVD risk in CKM stages 0 - 3. SPISE may serve as a valuable marker for early risk identification in these populations.

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Keywords

SPISE, Cardiovascular-Kidney-Metabolic Syndrome, CVD

1. Introduction

Recognizing the intricate interplay between metabolic disorders, cardiovascular disease (CVD), and chronic kidney disease (CKD), the American Heart Association (AHA) introduced the Cardiovascular-Kidney-Metabolic (CKM) syndrome framework. This concept highlights the synergistic, multi-directional links among metabolic risks, renal function, and cardiovascular health, which collectively precipitate poor cardiovascular prognoses and systemic organ dysfunction [1] [2]. As metabolic disorders and obesity become increasingly widespread globally, the incidence of CKM syndrome has risen in parallel, highlighting it as a major and expanding threat to global public health [3]. Given the disproportionate CVD burden across CKM stages, it is essential to view the metabolic, renal, and cardiovascular systems as an interconnected triad [4]-[6]. Accordingly, the AHA emphasizes that interventions for individuals in the pre-clinical or early phases of CKM stages 0 - 3 should prioritize the prevention of CVD onset [1].

Within the multifactorial pathogenesis of CKM syndrome, Insulin Resistance (IR) acts as a central driver of metabolic dysregulation. By promoting atherosclerosis, exacerbating renal impairment, and driving systemic inflammation, IR serves as a potent independent predictor of adverse CVD outcomes [1]. While the hyperinsulinemic-euglycemic clamp (HIEC) remains the gold standard for diagnosing IR [7], its invasive nature and high cost render it impractical for large-scale epidemiological surveys. Similarly, the utility of HOMA-IR for broad population screening is often constrained by logistical and financial burdens [8]. Although the triglyceride-to-HDL cholesterol (TG/HDL) ratio offers better accessibility [9], its clinical application is hindered by significant ethnic variability in diagnostic thresholds [10]. To address these limitations, the Single Point Insulin Sensitivity Estimator (SPISE) has emerged as a robust and practical surrogate. By integrating body mass index (BMI), HDL cholesterol, and triglycerides, SPISE provides a novel, non-invasive approach to effectively quantify IR [11].

While the CVD implications of SPISE are acknowledged, existing literature remains fragmented and confined to narrow cohorts—primarily elderly men or individuals with type 2 diabetes—and restricted to isolated endpoints such as heart failure (HF) or coronary heart disease (CHD) [12]-[14]. Critically, a systematic evaluation of the association between SPISE and broad CVD risk within the specific context of CKM stages 0 - 3 is currently lacking. To bridge this gap, we leveraged data from the China Health and Retirement Longitudinal Study (CHARLS) to examine the predictive value of the SPISE index for incident CVD in this understudied demographic.

2. Methods

2.1. Study Design and Study Population

We analyzed data from the CHARLS, a nationally representative longitudinal survey of Chinese adults aged 45 years or older. CHARLS recruited participants from 28 provinces and 150 counties across China [15]. Data were collected through face-to-face interviews by trained fieldworkers using standardized instruments. The study was conducted in accordance with the Declaration of Helsinki and approved by the Peking University Institutional Review Board (IRB00001052-11015). All participants provided written informed consent. The 2011-2012 wave was treated as the baseline, with follow-up surveys conducted in 2013, 2015 and 2018.

A total of 11,847 participants with available blood test results were initially identified from Wave 1. To ensure data quality and cohort homogeneity, we applied the following exclusion criteria: (1) participants with missing data on CVD status across Waves 1 - 4 (n = 2170); (2) individuals aged < 45 years at baseline (n = 206); (3) those with insufficient data to calculate the baseline SPISE index (n = 1528); and (4) participants with a history of CVD diagnosed prior to 2011 (n = 1056). Consequently, the final analytical sample comprised 6887 participants (Figure 1).

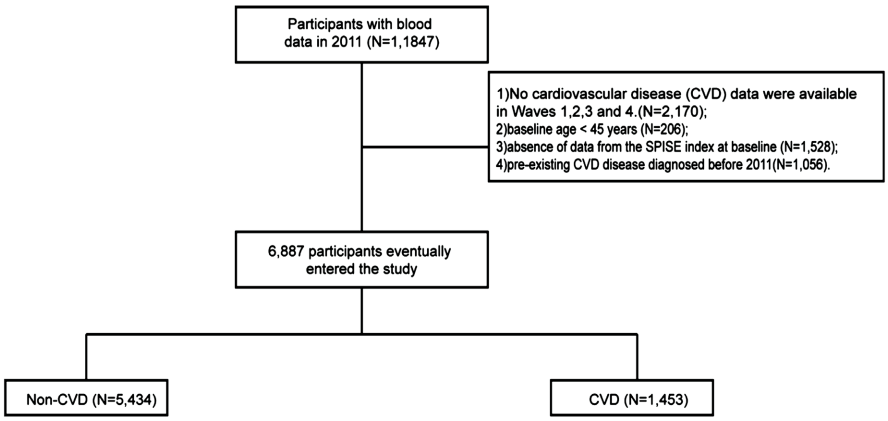

Figure 1. Flowchart of participant selection in the CHARLS cohort.

2.2. Definition of CKM Syndrome Stages 0 to 3

We categorized CKM Syndrome into stages 0 through 3, adhering to the criteria outlined in the AHA Presidential Advisory [1]. The stages were defined as follows: Stage 0, absence of CKM risk factors; Stage 1, presence of excess or dysfunctional adiposity; Stage 2, metabolic risk factors or chronic kidney disease (CKD); and Stage 3, subclinical CVD. To identify subclinical CVD equivalents for Stage 3, very high-risk CKD was defined as stages G4-G5 (eGFR < 30 mL/min/1.73m^2). Additionally, a high 10-year predicted cardiovascular disease (CVD) risk was determined using the Framingham risk score, with cut-off values of ≥ 21.6 for males and ≥ 21.5 for females [16]. The estimated glomerular filtration rate (eGFR) was

calculated using the Chinese Modification of Diet in Renal Disease (C-MDRD) equation [17], with CKD staging determined according to the KDIGO guidelines [1]. The detailed criteria for each stage are summarized in **Table S1**.

2.3. Assessment of Cardiovascular (CVD) and Computation of the Single-Point Insulin Sensitivity Estimator (SPISE)

We defined CVD as the primary outcome, comprising both heart disease and stroke events. Heart disease status was determined by an affirmative answer to the question: "Has your doctor ever told you that you were diagnosed with a heart attack, angina pectoris, coronary heart disease, heart failure, or other heart problems?" Stroke was identified through the question: "Has your doctor ever told you that you were diagnosed with a stroke?" Thus, CVD was characterized by a self-reported diagnosis of heart disease and/or stroke, aligning with the diagnostic criteria used in prior CHARLS research [18] [19]. For the longitudinal analysis spanning the 2011-2020 follow-up period, the occurrence time of a newly diagnosed CVD event was defined as the interview date of the survey wave in which the participant first reported the diagnosis. Participants who died or were lost to follow-up during the observation period were excluded from the analytical cohort. For individuals who remained free of CVD throughout the study period, their follow-up time was right-censored at the date of their final completed interview.

In this study, the SPISE index was used as the predictor and was calculated as in previous research [11], using the following formula: $600 \times \text{high-density lipoprotein cholesterol [mg/dL]}^{0.185} / (\text{triglycerides [mg/dL]}^{0.2} \times \text{body mass index [kg/m}^2\text{]}^{1.338})$.

2.4. Covariables

To control for potential confounding factors, we included covariates based on previous studies [18]-[20]. Demographic covariates included age (years), sex ("Female" and "Male"), education level ("Primary or below" and "Other"), marital status ("Married" and "Other"), and area of residence ("Rural" and "Other"). Behavioral and anthropometric indicators included smoking status ("Smoker" or "Non-smoker"), drinking status ("Yes" or "No"), systolic blood pressure (SBP, mmHg), diastolic blood pressure (DBP, mmHg), and body mass index (BMI, kg/m^2). Laboratory tests included white blood cell count (WBC, 10^9/L), mean corpuscular volume (MCV, fL), platelets (10^9/L), hematocrit (%), blood urea nitrogen (BUN, mg/dL), glucose (mg/dL), serum creatinine (Scr, mg/dL), total cholesterol (mg/dL), triglycerides (mg/dL), high-density lipoprotein cholesterol (HDL, mg/dL), low-density lipoprotein cholesterol (LDL, mg/dL), C-reactive protein (CRP, mg/L), glycated hemoglobin (HbA_{1c}, %), and serum uric acid (SUA, mg/dL). Health status and medical history encompassed hypertension status ("Yes" or "No"), dyslipidemia ("Yes" or "No"), diabetes status ("Normoglycemia", "Prediabetes", or "Diabetes"), Treated for Hypertension ("Yes" or "No"). To address partial data missing in the CHARLS database, this study used the multiple imputation method based on chained equations to process the missing values, ensuring the accuracy of the analysis [21].

2.5. Statistical Analysis

We compared baseline characteristics between participants with and without incident CVD using the independent-samples t-test for continuous variables and the chi-square test for categorical variables. Data are reported as mean ± SD for continuous metrics and counts (percentages) for categorical measures. To investigate the association between the SPISE index and CVD incidence among participants with CKM syndrome stages 0 - 3, we generated Kaplan-Meier survival curves and employed multivariable Cox proportional hazards regression models. The proportional hazards assumption was verified using Schoenfeld residuals, with no significant violations detected. In the fully adjusted model, covariates were selected based on clinical relevance and prior literature. To explicitly mitigate confounding bias related to baseline disease severity, the baseline CKM syndrome stage was incorporated as an adjusting covariate. Furthermore, to rule out potential multicollinearity between the SPISE index and other metabolic parameters, we calculated the variance inflation factor (VIF) for all candidate variables prior to inclusion, setting a VIF threshold of ≥ 5 as the criterion for variable exclusion. Ultimately, all covariates yielded a VIF of less than 5, indicating the absence of severe multicollinearity; thus, no variables were excluded from the final model. Additionally, restricted cubic spline (RCS) analysis with four knots was utilized to explore potential dose-response patterns, and non-linear relationships were evaluated using the P-value for non-linearity. Subgroup analyses were conducted to evaluate the generalizability and robustness of the findings across different strata. All statistical analyses were performed using R software (version 4.2), with a two-sided p-value < 0.05 considered statistically significant.

3. Results

3.1. Baseline Characteristics of Participants by Incidence of Cardiovascular Disease

A total of 6887 participants with CKM syndrome stages 0 - 3 were included in this study, with a mean (SD) age of 58.37 (8.77) years and a female proportion of 54.20%. The mean (SD) SPISE for the entire cohort was 7.47 (2.15). During a median follow-up of 6.7 years, 1453 incident CVD events were identified. As shown in Table 1, participants who developed incident CVD were significantly older and exhibited lower SPISE levels than those without CVD. In terms of sociodemographic and clinical profiles, those who developed CVD were more likely to be presented with significantly higher levels of BMI, SBP, DBP, WBC, platelets, glucose, total cholesterol and CRP. Furthermore, a higher prevalence of hypertension, pre-diabetes, and CKM stage 3 was observed in the incident CVD group than in the non-CVD group.

3.2. Association of SPISE with Incident Cardiovascular Disease

Figure 2 demonstrates the Kaplan-Meier survival curve analysis investigating the impact of SPISE on the incidence of CVD. The results revealed that as the SPISE

increased, the incidence of CVD decreased significantly. A statistically significant difference was observed between the survival curves of the different SPISE quartiles (log-rank P < 0.001).

Table 1. Baseline characteristics of participants with incident cardiovascular disease measured.

Variables	Total (n = 6887)	Non-CVD (n = 5434)	CVD (n = 1453)	P
SPISE, Mean ± SD	7.47 ± 2.15	7.57 ± 2.15	7.13 ± 2.14	<0.001
AGE, Mean ± SD	58.37 ± 8.77	57.83 ± 8.70	60.40 ± 8.73	<0.001
SEX, n (%)				<0.001
Female	3733 (54.20)	2877 (52.94)	856 (58.91)	
Male	3154 (45.80)	2557 (47.06)	597 (41.09)	
Education Level, n (%)				0.365
Primary or below	4801 (69.71)	3774 (69.45)	1027 (70.68)	
other	2086 (30.29)	1660 (30.55)	426 (29.32)	
Marital Status, n (%)				<0.001
Married	6187 (89.84)	4918 (90.50)	1269 (87.34)	
other	700 (10.16)	516 (9.50)	184 (12.66)	
Area, n (%)				<0.001
Rural	5887 (85.48)	4690 (86.31)	1197 (82.38)	
Other	1000 (14.52)	744 (13.69)	256 (17.62)	
Smoking status, n (%)				0.117
Non-smoker	4267 (61.96)	3341 (61.48)	926 (63.73)	
Smoker	2620 (38.04)	2093 (38.52)	527 (36.27)	
Drinking status, n (%)				<0.001
No	4546 (66.01)	3515 (64.69)	1031 (70.96)	
Yes	2341 (33.99)	1919 (35.31)	422 (29.04)	
BMI, Mean ± SD	23.51 ± 3.87	23.34 ± 3.75	24.17 ± 4.22	<0.001
SBP, Mean ± SD	129.26 ± 20.76	127.94 ± 20.18	134.17 ± 22.11	<0.001
DBP, Mean ± SD	75.38 ± 11.89	74.88 ± 11.69	77.24 ± 12.44	<0.001
WBC, Mean ± SD	6.23 ± 1.85	6.20 ± 1.83	6.33 ± 1.91	0.013
MCV, Mean ± SD	90.39 ± 8.66	90.35 ± 8.62	90.53 ± 8.79	0.487
Platelets, Mean ± SD	211.96 ± 72.47	210.23 ± 70.82	218.45 ± 78.04	<0.001
Hematocrit, Mean ± SD	41.52 ± 6.20	41.51 ± 6.25	41.55 ± 6.04	0.825

Continued

BUN, Mean ± SD	15.68 ± 4.38	15.73 ± 4.39	15.48 ± 4.34	0.059
Glucose, Mean ± SD	109.35 ± 34.53	108.53 ± 32.80	112.38 ± 40.22	<0.001
Scr, Mean ± SD	0.77 ± 0.18	0.77 ± 0.18	0.77 ± 0.18	0.836
TC, Mean ± SD	193.74 ± 38.61	193.13 ± 38.65	196.01 ± 38.36	0.012
Triglycerides, Mean ± SD	132.94 ± 112.85	131.88 ± 115.46	136.89 ± 102.48	0.133
HDL, Mean ± SD	51.45 ± 15.31	51.73 ± 15.31	50.43 ± 15.27	0.004
LDL, Mean ± SD	116.30 ± 34.88	115.67 ± 34.62	118.66 ± 35.74	0.004
CRP, Mean ± SD	2.49 ± 6.87	2.40 ± 6.71	2.82 ± 7.45	0.039
HbA_{1c}, Mean ± SD	5.25 ± 0.77	5.23 ± 0.74	5.33 ± 0.87	<0.001
SUA, Mean ± SD	4.40 ± 1.22	4.41 ± 1.21	4.37 ± 1.25	0.296
Hypertension Status, n (%)				<0.001
No	4348 (63.13)	3626 (66.73)	722 (49.69)	
Yes	2539 (36.87)	1808 (33.27)	731 (50.31)	
Dyslipidemia, n (%)				0.002
No	5201 (75.52)	4148 (76.33)	1053 (72.47)	
Yes	1686 (24.48)	1286 (23.67)	400 (27.53)	
Diabetes Status, n (%)				<0.001
Diabetes	1058 (15.36)	774 (14.24)	284 (19.55)	
Prediabetes	3042 (44.17)	2405 (44.26)	637 (43.84)	
Normoglycemia	2787 (40.47)	2255 (41.50)	532 (36.61)	
Treated for Hypertension, n (%)				<0.001
No	5825 (84.58)	4765 (87.69)	1060 (72.95)	
Yes	1062 (15.42)	669 (12.31)	393 (27.05)	
CKM stages, n (%)				<0.001
0	999 (14.51)	856 (15.75)	143 (9.84)	
1	2399 (34.83)	1926 (35.44)	473 (32.55)	
2	1392 (20.21)	1109 (20.41)	283 (19.48)	
3	2097 (30.45)	1543 (28.40)	554 (38.13)	

Mean ± SD for continuous variables; n (%) for categorical variables. Abbreviation: SPISE, single-point insulin sensitivity estimator; BMI, body mass index; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; WBC, White Blood Cell; MCV, Mean Corpuscular Volume; BUN, Blood Urea Nitrogen; Scr, Serum Creatinine; TC, Total cholesterol; HDL, High-Density Lipoprotein Cholesterol; LDL, Low-Density Lipoprotein; CRP, C-reactive protein; HbA1c, Glycosylated hemoglobin; SUA, Serum Uric Acid; CKM, cardiovascular-kidney-metabolic syndrome.

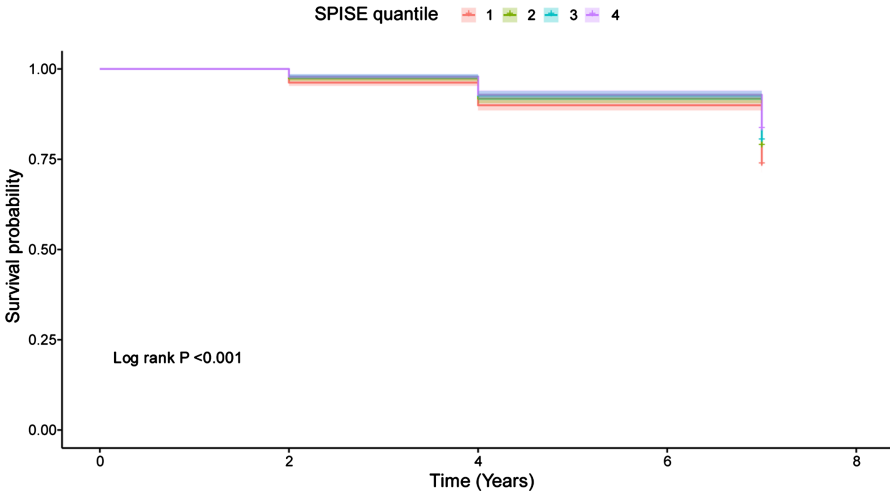

Figure 2. Kaplan-Meier curves for incident cardiovascular disease according to SPISE quantile.

Table 2 shows the association between SPISE levels and the risk of CVD. Multivariate Cox regression analyses showed that SPISE levels were significantly associated with the risk of CVD in both the crude model (Model 1) and the model adjusted for age and sex (Model 2). In the fully adjusted model (Model 3), the inverse correlation remained significant (HR = 0.95; 95% CI: 0.92 - 0.97; P < 0.001). Furthermore, when participants were categorized into quartiles based on SPISE levels, the association remained statistically significant (P for trend < 0.05). Compared to the lowest quartile (Q1), those in the highest quartile (Q4) exhibited a 28% lower risk of CVD (HR = 0.72; 95% CI: 0.61 - 0.85; P < 0.001). The RCS curve (Figure 3) analysis of the fully adjusted model (Model 3) further demonstrated an inverse correlation between SPISE and the risk of CVD incidence.

Table 2. Association of SPISE with incident cardiovascular disease.

Variables	Model 1		Model 2		Model 3	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
SPISE	0.92 (0.90 - 0.94)	<0.001	0.91 (0.88 - 0.93)	<0.001	0.95 (0.92 - 0.97)	<0.001
SPISE quantile						
1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
2	0.79 (0.69 - 0.91)	<0.001	0.78 (0.68 - 0.90)	<0.001	0.86 (0.74 - 0.99)	0.041
3	0.73 (0.64 - 0.84)	<0.001	0.70 (0.61 - 0.81)	<0.001	0.84 (0.72 - 0.98)	0.028
4	0.61 (0.53 - 0.71)	<0.001	0.56 (0.48 - 0.65)	<0.001	0.72 (0.61 - 0.85)	<0.001

HR: Hazard Ratio, CI: Confidence Interval. Model1: Crude. Model2: Adjust: SEX, AGE. Model3: Adjust: SEX, AGE, SBP, WBC, MCV, Plt, HCT, BUN, Glu, Scr, LDL, CRP, Hba1c, SUA, Education Level, Marital Status, Area, Dyslipidemia, Smoking status, Drinking status, Diabetes Status, Treated for Hypertension.

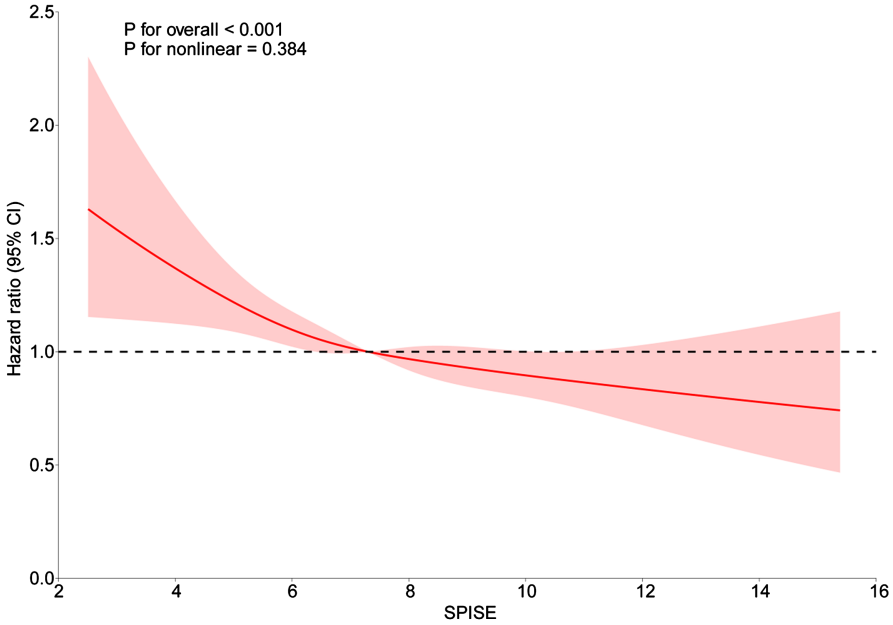

Figure 3. Dose-response relationship between SPISE and incident cardiovascular disease.

3.3. Subgroup Analyses

To evaluate whether the association between SPISE levels and incident CVD varied across subgroups, analyses were conducted using the fully adjusted model (Model 3) (Figure 4). Interaction tests were performed for sex, marital status,

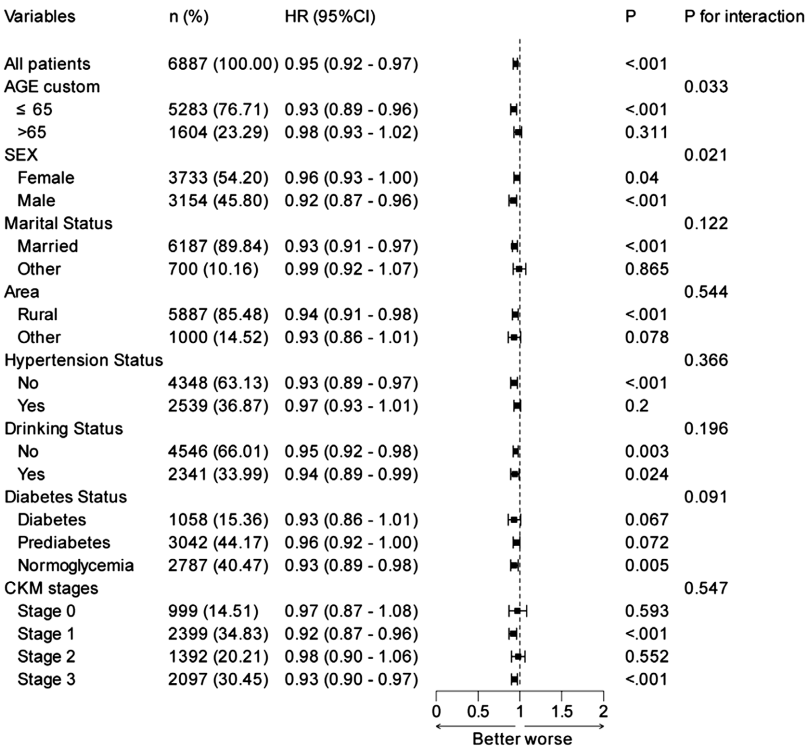

Figure 4. Subgroup analyses of the association between SPISE and incident cardiovascular disease.

area, hypertension status, drinking status, diabetes status and CKM stages. A significant interaction was observed for sex (P for interaction = 0.021), indicating that the association differed between men and women. The inverse association was more pronounced in men (HR 0.92, 95% CI 0.87 - 0.96) than in women (HR 0.96, 95% CI 0.93 - 1.00). No significant interactions were detected for the other subgroups (all P for interaction > 0.05), suggesting that the association between SPISE and CVD risk was generally consistent across most demographic and clinical characteristics.

4. Discussion

In this prospective cohort study of 6887 individuals from a representative population with CKM stages 0 - 3, we found that the SPISE index was an independent predictor of CVD. A significant inverse association was observed between SPISE and the risk of incident CVD. Notably, subgroup analyses indicated that this inverse association was more pronounced in men.

Developed from a European cohort of 1300 adults, the SPISE was derived from oral glucose tolerance and euglycemic-hyperinsulinemic clamp test data. Paulmichl *et al.* [11]. refined this index using computer-assisted mathematical modeling. Compared to the clamp test cut-off for IR (M-value < 4.7 mg/kg/min), SPISE demonstrates superior sensitivity and specificity over traditional indices. Furthermore, recent evidence in younger populations indicates that SPISE outperforms the Triglyceride-Glucose index in predicting IR, reinforcing its utility as a reliable surrogate marker for IR in this group [22].

To our knowledge, this is the first study to show that a higher SPISE index is significantly associated with a reduced risk of incident CVD among middle-aged and older adults with CKM stages 0 - 3. Our findings are consistent with several prior investigations that underscore the prognostic value of SPISE across diverse cohorts. A study targeting obese Korean adults demonstrated that individuals in the lowest SPISE tertile exhibited significantly elevated triglyceride levels (P < 0.001) and a higher proportion of small dense low-density lipoprotein particles (P < 0.001), both of which are markers associated with an increased risk of CVD [23]. Research by Correa-Burrows *et al.* in 2020 identified a substantial inverse correlation between the SPISE index and cardiometabolic risk, noting that values lower than 6.0 in women and 5.0 in men were associated with poorer metabolic outcomes [24]. A large cohort study involving middle-aged and older populations in China and the UK reported that higher SPISE levels are associated with a reduced prevalence of CVD [20]. Additionally, recent research indicates that elevated SPISE levels are associated with a stepwise reduction in the risk of future CVD events among patients with type 2 diabetes [14]. Collectively, these findings are consistent with our results and support the relevance of SPISE as a marker for CVD risk assessment.

Subgroup analysis results revealed a significant interaction between sex and the SPISE index (P for interaction = 0.021), indicating that the inverse association

between higher SPISE levels and a reduced risk of incident CVD was more pronounced among male patients with CKM stages 0 - 3. This finding aligns with the trend observed by Correa-Burrows *et al.* (2020), who noted that SPISE serves as a precise diagnostic tool for predicting IR in males, whereas its performance in females is less than optimal [24]. This discrepancy reflects the inherent sexual dimorphism in the incidence, age of onset, and progression of most cardiometabolic diseases, with men typically exhibiting more adverse metabolic profiles. It is well-established that sex significantly influences body fat distribution, ectopic fat accumulation, insulin signaling, glucose homeostasis, and lipid metabolism [25]-[28]. Consequently, these inherent biological discrepancies likely explain the sex-specific performance of the SPISE index in CVD risk prediction.

Although the exact molecular mechanisms underlying the association between elevated SPISE scores and reduced CVD risk in patients with CKM syndrome remain to be elucidated, this index—given its status as an established surrogate marker for IR—may comprehensively reflect the complex pathophysiological evolution unique to this specific population. The molecular landscape of CKM syndrome is characterized by a multifaceted interplay of systemic and cellular derangements. These range from metabolic and hormonal imbalances (such as hyperglycemia and RAAS hyperactivation) to cellular-level insults, including oxidative stress, lipotoxicity, and mitochondrial failure, alongside compromised calcium signaling and persistent low-grade inflammation [29]. In CKM syndrome, IR-mediated dysregulation of the PI3K/Akt and MAPK pathways leads to diminished nitric oxide bioavailability and elevated endothelin-1, thereby triggering endothelial dysfunction and myocardial injury [30]-[32]. Concurrently, IR-driven hyperglycemia and dyslipidemic profiles (elevated TG/reduced HDL) intensify oxidative stress and lipotoxicity, thereby fueling vascular remodeling and atherogenesis [33]-[36]. Furthermore, the interplay between RAAS hyperactivation and adipocyte dysfunction triggers a systemic release of pro-inflammatory cytokines and free fatty acids, extending damage to cardiorenal tissues [37] [38]. These insults are further exacerbated by mitochondrial failure and disrupted calcium homeostasis, ultimately culminating in significant myocardial damage [39] [40]. Since SPISE is intrinsically derived from BMI and lipid profiles, its decline effectively mirrors the aggravation of these lipotoxic and inflammatory cascades, bridging the gap between metabolic dysregulation and overt CVD pathology Nonetheless, further mechanistic studies are warranted to delineate how higher SPISE reduces CVD risk in patients with CKM syndrome.

The clinical utility of SPISE is underscored by its practical advantages over alternative methods. Unlike the "gold standard" HIEC [7], which is labor-intensive and technically demanding , SPISE offers a simplified approach. Furthermore, compared to traditional indices such as HOMA-IR that necessitate insulin assays [8], SPISE relies solely on routine clinical parameters (TG, HDL, and BMI). By eliminating the need for fasting insulin measurement, this index significantly reduces diagnostic costs and laboratory requirements, making it a more accessible

and feasible tool for large-scale clinical screening and routine patient monitoring, especially in resource-limited settings.

This study has several strengths. First, it focuses on the clinically important yet understudied CKM stages 0 - 3 population and provides the first evaluation of SPISE in assessing CVD risk in this group. Second, using nationally representative survey data and rigorous screening criteria, we analyzed 6887 eligible participants, ensuring the robustness of our findings. Finally, this study is the first to systematically demonstrate the association between SPISE levels and CVD incidence across CKM stages 0 - 3, offering new insights for future research and cardiovascular risk stratification.

Meanwhile, several limitations of this study should be acknowledged. First, the study population consisted exclusively of middle-aged and elderly Chinese individuals, which may limit the generalizability of the findings to other ethnic groups and age ranges. Second, CVD status was determined based on self-reported information, potentially introducing misclassification bias. Specifically, undiagnosed or unreported cases could lead to an underestimation of CVD prevalence, which might attenuate the observed associations. Third, the application of strict exclusion criteria and loss to follow-up resulted in a substantial reduction in sample size, from 11,847 participants at baseline to 6887 in the final analysis. This may have induced selection bias, as the remaining participants were likely to be healthier and more compliant, potentially leading to conservative estimates of the actual risk. Future studies with larger sample sizes, objective disease ascertainment, more frequent biomarker assessments, and extended follow-up periods are warranted to further validate our findings.

5. Conclusion

Our findings suggest that a higher SPISE index is associated with a lower risk of incident CVD in individuals with CKM stages 0 - 3. As an easily obtainable biomarker, SPISE may be a promising marker for CVD risk stratification and warrants further investigation in future studies.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Appendix

Table S1. Methods for evaluating CKM stages 0 - 3.

CKM stages	Threshold for CKM conditions
Stages 0	All criteria are met: 1) BMI < 23 kg/m^2 2) Waist circumference < 80/90 cm in female/male 3) Fasting blood glucose < 100 mg/dL and HbA1c < 5.7% and without self-reported diagnosis of diabetes, use of insulin, or oral hypoglycemic agents. 1) SBP < 130 mm Hg and DBP < 80 mm Hg without self-reported diagnosis of hypertension or use of antihypertensive medications. 2) HDL-C ≥ 50/40 mg/dL in female/male 3) TG < 150 mg/dL 4) eGFR ≥ 60 ml/min/1.73m^2 and without self-reported diagnosis of CKD 5) No Subclinical CVD and clinical CVD Any of the three criteria is met: 1) Overweight/obesity 2) Abdominal obesity 3) Prediabetes
Stages 1	All criteria are met: a) SBP < 130 mmHg and DBP < 80 mmHg without self-reported diagnosis of hypertension or use of anti-hypertensive medications. b) HDL-C < 50/40 mg/dL in female/male c) TG < 150 mg/dL d) eGFR ≥ 60 ml/min/1.73m^2 and without self-reported diagnosis of CKD e) No Subclinical CVD and clinical CVD
Stages 2	Any of the five criteria is met: 1) Hypertriglyceridemia 2) Hypertension 3) Diabetes 4) metabolic syndrome 5) eGFR: 30 - 60 ml/min/1.73m^2 and/or with self-reported diagnosis of CKD All criteria are met: 1) No Subclinical CVD and clinical CVD
Stages 3	Any of the two criteria is met: 1) eGFR < 30 ml/min/1.73m^2 2) Subclinical CVD Any of the eight criteria is met: 1) Overweight/obesity 2) Abdominal obesity 3) Prediabetes 4) Hypertriglyceridemia 5) Hypertension 6) diabetes 7) metabolic syndrome 8) eGFR: 30 - 60 ml/min/1.73m^2 and/or with self-reported diagnosis of CKD The criterion is met: 1) No clinical CVD

Abbreviations: CVD: cardiovascular diseases; CKM: Cardio-Kidney-Metabolic Syndrome; CKD: chronic kidney disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; LDL: low-density lipoprotein cholesterol; eGFR: estimated glomerular filtration rate; TC: total cholesterol; HDL: high-density lipoprotein cholesterol; TG: triglyceride; BMI: body mass index.