Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Association of the modified cardiometabolic index with all-cause and cardiovascular mortality in individuals with cardiovascular-kidney-metabolic syndrome

Mengliu Wu
The Seventh Clinical Medical College, Guangzhou University of Chinese Medicine,
Yang Gao
The Seventh Clinical Medical College, Guangzhou University of Chinese Medicine,
Fan Xing
The Seventh Clinical Medical College, Guangzhou University of Chinese Medicine,
Yishan Zhou
The Seventh Clinical Medical College, Guangzhou University of Chinese Medicine,
Yihong Zou
The Seventh Clinical Medical College, Guangzhou University of Chinese Medicine,
Lili Chen
The Seventh Clinical Medical College, Guangzhou University of Chinese Medicine,
Xiaona Tang
The Seventh Clinical Medical College, Guangzhou University of Chinese Medicine,
Ying Pi
piying85@gzucm.edu.cn

The Seventh Clinical Medical College, Guangzhou University of Chinese Medicine,

Article

Keywords: MCMI, CKM syndrome, all-cause mortality, cardiovascular mortality, NHANES

Posted Date: June 17th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9738138/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background

Cardiovascular, kidney, and metabolic disorders frequently coexist and collectively contribute to adverse health outcomes. The modified cardiometabolic index (MCMI), which integrates lipid metabolism, glycemic status, and central adiposity, has emerged as a comprehensive marker of cardiometabolic risk. However, its prognostic value in individuals with cardiovascular–kidney–metabolic (CKM) syndrome remains unclear.

Methods

We included 7,554 adults with CKM syndrome from the National Health and Nutrition Examination Survey (NHANES) 2011–2018. MCMI was calculated using triglycerides, fasting plasma glucose, high-density lipoprotein cholesterol, and waist-to-height ratio, and categorized into tertiles. Mortality outcomes were determined through linkage with the National Death Index, with follow-up through December 31, 2019. Kaplan–Meier methods and weighted Cox proportional hazards models were used to evaluate associations.

Results

During a median follow-up of 4.8 years, 446 deaths occurred, including 134 from cardiovascular causes. In fully adjusted models, individuals in the highest MCMI tertile had a significantly increased risk of cardiovascular mortality compared with those in the lowest tertile (HR 2.59, 95% CI 1.26–5.32). No independent association was observed between MCMI and all-cause mortality. The association with cardiovascular mortality was more pronounced among individuals younger than 60 years (P for interaction < 0.001).

Conclusions

Higher MCMI is independently associated with increased cardiovascular mortality, but not all-cause mortality, in individuals with CKM syndrome. MCMI may serve as a practical and accessible marker for cardiovascular risk stratification, particularly in younger populations.

Introduction

The global burden of chronic diseases continues to rise, with multiple conditions frequently coexisting within individuals[1]. Cardiovascular, renal, and metabolic disorders are not isolated entities but are closely interconnected through shared risk factors and overlapping pathophysiological mechanisms.

These interactions often result in a compounded risk of adverse clinical outcomes, particularly increased mortality[2].

To better capture this interrelationship, the concept of cardiovascular-kidney-metabolic (CKM) syndrome has been proposed as an integrated framework linking metabolic dysfunction, kidney impairment, and cardiovascular disease. CKM syndrome follows a progressive trajectory, beginning with early metabolic abnormalities and potentially advancing to overt cardiovascular disease[3].Previous studies have demonstrated that individuals at more advanced CKM stages face a higher risk of adverse outcomes, especially cardiovascular mortality[4].

However, CKM staging alone may not fully explain the heterogeneity in clinical outcomes. Recent large-scale studies have indicated that there is no consistent graded relationship between CKM stages 1–4B and adverse clinical outcomes, and individuals within the same CKM stage may still exhibit substantial differences in prognosis[5]. This suggests that additional biomarkers are needed to improve risk stratification, and identifying simple, accessible, and integrative indicators of cardiometabolic health may provide incremental value in clinical assessment.

The modified cardiometabolic index (MCMI) is a composite indicator derived from triglycerides, fasting plasma glucose, high-density lipoprotein cholesterol, and central adiposity. By integrating these components, MCMI captures multiple dimensions of metabolic dysfunction in a single metric. Although previous population-based studies have demonstrated that the modified cardiometabolic index (MCMI) is closely associated with a spectrum of metabolic disorders, including type 2 diabetes, hypertension, dyslipidemia, and non-alcoholic fatty liver disease[6–8], its prognostic significance—particularly among individuals with cardiovascular-kidney-metabolic (CKM) syndrome—remains insufficiently explored.

Therefore, we aimed to examine the associations of MCMI with all-cause and cardiovascular mortality among adults with CKM syndrome in NHANES 2011–2018.

Methods

Data source and study population

Data for this study were derived from the National Health and Nutrition Examination Survey (NHANES) 2011–2018[9], which is a nationally representative survey of the U.S. population. The NHANES website provides open access to comprehensive details regarding the survey's design and data collection protocols[10]. As the dataset is publicly accessible and contains no identifiable personal information, the present analysis was exempt from additional ethical approval:www.cdc.gov/nchs/nhanes/.

To construct the study population, all participants from the selected survey cycles were first considered. Individuals were then gradually removed if key information was unavailable or if they did not meet the study requirements. Specifically, participants were excluded when CKM stage could not be determined, when they were younger than 18 years, or when pregnancy or lack of follow-up information could affect

outcome assessment. Additional exclusions were made for missing variables necessary for MCMI calculation, invalid sampling weights, or incomplete covariate data. After this screening process, 7,554 individuals remained and were included in the final analysis.

Sample size determination

Because this was a secondary analysis of a publicly available NHANES dataset, the sample size was determined by the number of participants who met the predefined inclusion and exclusion criteria, and no formal a priori sample size calculation was performed.

Ascertainment of exposure and outcome variables

In the present study, the modified cardiometabolic index (MCMI) was used as the exposure indicator to characterize cardiometabolic status. It was calculated based on triglycerides, fasting plasma glucose, high-density lipoprotein cholesterol, and waist-to-height ratio using the following formula[11]:

MCMI = log [(triglyceride × fasting plasma glucose) / high-density lipoprotein cholesterol] × (waist circumference / height)

The primary outcomes included all-cause mortality and cardiovascular disease (CVD) mortality. Mortality information was obtained from the NHANES Public Use Linked Mortality File, with follow-up available through December 31, 2019. Causes of death were categorized using the ICD-10 system[12].

Follow-up time was calculated from baseline to death or study closure, whichever came first. Deaths resulting from heart or cerebrovascular disorders were classified as cardiovascular mortality, whereas all-cause mortality covered deaths from any cause[13–14].

Definition and staging of CKM syndrome

To further characterize disease severity within the study population, CKM syndrome was categorized according to established staging criteria that integrate metabolic abnormalities, kidney function, and cardiovascular status. This framework reflects the progressive nature of CKM syndrome, in which metabolic disturbances, renal impairment, and cardiovascular involvement tend to coexist and evolve over time.

Metabolic components considered in the classification included obesity, diabetes, hypertension, dyslipidemia, and metabolic syndrome, as detailed in Supplementary Table S1. Kidney function was evaluated based on established clinical guidelines, with eGFR and UACR used to assess CKD risk[15]. The eGFR values were calculated using the CKD-EPI equation[16].

Cardiovascular involvement was defined from both clinical and subclinical perspectives. Clinical CVD was identified based on a self-reported history of major cardiovascular events, including heart failure, coronary heart disease, myocardial infarction, or stroke. For individuals without overt CVD, subclinical status was determined using predicted cardiovascular risk. Specifically, participants were classified as having subclinical CVD if they had a 10-year predicted cardiovascular risk of ≥ 20% or evidence of elevated CKD risk. The detailed algorithm of the simplified 10-year CVD risk models is provided in Additional file 2, and the PREVENT model was used to estimate cardiovascular risk[17].

Based on the combination of these metabolic, renal, and cardiovascular components, participants were assigned to corresponding CKM stages to reflect overall disease burden. The detailed algorithm for evaluating each CKM stage is provided in Supplementary Table S3.

Covariates

Potential confounders assessed in this study included demographic, socioeconomic, lifestyle, and clinical characteristics. These comprised age, sex, race, education, marital status, PIR, smoking status, as well as relevant clinical and laboratory measurements. The PIR was categorized into three groups: low income (< 1.3), middle income (1.3–3.5), and high income (> 3.5)[18]. Smoking status was classified as never smoked (fewer than 100 cigarettes smoked in a lifetime), former smoker (more than 100 cigarettes smoked in a lifetime but not currently smoking), or current smoker (more than 100 cigarettes smoked in a lifetime and smoking every day or sometimes)[19].

However, clinical variables closely related to cardiometabolic status were not included in the fully adjusted model. First, several variables (e.g., TG, FPG and HDL-C) are components of the MCMI, and adjusting for them may lead to over-adjustment and attenuation of the true association. Second, other clinical variables, such as blood pressure and renal function, are closely intertwined with the cardiovascular-kidney-metabolic (CKM) syndrome framework and may reflect disease severity or lie along the pathway linking cardiometabolic dysfunction to mortality. As the study population was restricted to individuals with CKM syndrome, further adjustment for these variables could introduce over-adjustment bias[20].

Therefore, the fully adjusted model included age, sex, race, education, marital status, PIR, and smoking status. Mets was identified according to commonly accepted diagnostic criteria[21].

Handling of missing data

The proportion of missing data for each variable is presented in Supplementary Table S4. PIR had the highest proportion of missing values (8.97%), followed by blood pressure measurements, with missing rates of 7.16% for SBP1, DBP1 and 3.90% for SBP2,

SBP3, DBP2, DBP3. The 10-year cardiovascular risk variable (CVD risk 10y) had a missing rate of 2.38%, whereas the remaining variables (e.g., BMI, UACR, and CKD risk indicators) exhibited minimal

missingness (< 1%).

Given the overall low to moderate levels of missingness, a complete-case approach was adopted. Participants with missing values in PIR, blood pressure measurements, or CVD risk 10y were excluded to maintain consistency across analyses. Considering the relatively modest proportion of missing data, this approach was unlikely to introduce substantial bias. For variables with very low levels of missingness (< 1%), no imputation was performed, as their potential impact on the results was considered negligible.

Bias

Several potential sources of bias, such as selection bias and residual confounding, were addressed during the study design and analysis. This was achieved through the use of standardized NHANES protocols, application of sampling weights, and adjustment for multiple covariates in the regression models.

Statistical analysis

All analyses accounted for the complex, multistage sampling design of NHANES by incorporating appropriate sampling weights, strata, and clustering variables. Appropriate 8-year sampling weights were constructed according to NHANES analytical guidelines[22]. Participants were grouped into tertiles based on their MCMI values (T1–T3).

Baseline characteristics were summarized using appropriate descriptive statistics. Continuous variables were presented as mean ± standard SD or median(IQR), as appropriate, while categorical variables were expressed as counts and percentages. Differences across groups were assessed using one-way (ANOVA) or the Kruskal-Wallis test for continuous variables, and the chi-square test for categorical variables. A two-sided P value < 0.05 was considered statistically significant.

Time-to-event outcomes were analyzed using Kaplan-Meier estimation, and differences in survival between groups were assessed using the log-rank test. The association between MCMI and mortality outcomes was further examined using weighted Cox proportional hazards models, with results reported as hazard ratios and corresponding 95% confidence intervals.

To explore the impact of covariate adjustment, three models with increasing levels of adjustment were constructed. The first model included no covariates. The second model accounted for age and sex. The fully adjusted model further incorporated race, education, marital status, smoking status, and PIR.

To further examine the stability of the results, we conducted additional analyses in several ways. The study population was stratified according to key characteristics, including age, sex, income level, and smoking status, to explore potential variations across different groups. Furthermore, to minimize the influence of early events, sensitivity analyses were performed after excluding participants who died within the first two years of follow-up.

All statistical procedures were carried out using R (version 4.5.2), Feng Rui software (version 2.4.0), and SPSS (version 27).

Results

Baseline characteristics of the participants

The characteristics of the study population are presented in Table 1. The analysis included 7,554 participants, with a mean age of 49.6 ± 17.3 years, of whom 49.5% were men.

Table 1
Baseline characteristics of individuals according to tertiles of MCMI.

Characteristics	Total (n = 7554)	T1 (n = 2498)	T2 (n = 2538)	T3 (n = 2518)	p
Gender, n (%)					< 0.001
Male	3739 (49.5)	1124 (45)	1351 (53.2)	1264 (50.2)	
Female	3815 (50.5)	1374 (55)	1187 (46.8)	1254 (49.8)	
Age	49.6 ± 17.3	44.0 ± 17.7	51.7 ± 16.8	53.0 ± 15.9	< 0.001
Race, n (%)					< 0.001
Mexican American	1027 (13.6)	203 (8.1)	363 (14.3)	461 (18.3)	
Other Hispanic	801 (10.6)	204 (8.2)	270 (10.6)	327 (13)	
Non-Hispanic White	2969 (39.3)	936 (37.5)	943 (37.2)	1090 (43.3)	
Non-Hispanic Black	1546 (20.5)	620 (24.8)	553 (21.8)	373 (14.8)	
Non-Hispanic Asian	945 (12.5)	447 (17.9)	326 (12.8)	172 (6.8)	
Other races	266 (3.5)	88 (3.5)	83 (3.3)	95 (3.8)	
Education, n (%)					< 0.001
<High school	1573 (20.8)	378 (15.1)	532 (21)	663 (26.3)	
High school	1666 (22.1)	502 (20.1)	571 (22.5)	593 (23.6)	
>High school	4313 (57.1)	1618 (64.8)	1434 (56.5)	1261 (50.1)	
Marital status, n (%)					< 0.001
Married/living with a partner	4566 (60.4)	1391 (55.7)	1623 (63.9)	1552 (61.6)	
widowed/divorced/separated	1597 (21.1)	422 (16.9)	560 (22.1)	615 (24.4)	
Single	1391 (18.4)	685 (27.4)	355 (14)	351 (13.9)	
Smoking status, n (%)					< 0.001
Never	4267 (56.5)	1558 (62.4)	1417 (55.8)	1292 (51.4)	
Current	1449 (19.2)	466 (18.7)	487 (19.2)	496 (19.7)	
Former	1833 (24.3)	471 (18.9)	634 (25)	728 (28.9)	

Characteristics	Total (n = 7554)	T1 (n = 2498)	T2 (n = 2538)	T3 (n = 2518)	p
PIR, n (%)					< 0.001
< 1.3	2385 (31.6)	686 (27.5)	772 (30.4)	927 (36.8)	
1.3–3.5	2870 (38.0)	922 (36.9)	953 (37.5)	995 (39.5)	
≥ 3.5	2299 (30.4)	890 (35.6)	813 (32)	596 (23.7)	
BMI	28.2 (24.5, 32.9)	23.6 (21.4, 26.2)	28.2 (25.8, 31.2)	33.7 (30.1, 38.7)	< 0.001
SCR,	0.8 (0.7, 1.0)	0.8 (0.7, 1.0)	0.8 (0.7, 1.0)	0.8 (0.7, 1.0)	< 0.001

Table 1
(continue)

Characteristics	Total (n = 7554)	T1 (n = 2498)	T2 (n = 2538)	T3 (n = 2518)	p
UACR	7.2 (4.7, 14.0)	6.6 (4.4, 11.6)	6.8 (4.5, 12.5)	9.1 (5.4, 20.2)	< 0.001
FPG	101.0 (94.0, 112.0)	96.0 (90.0, 102.0)	101.0 (95.0, 110.0)	111.0 (101.0, 132.0)	< 0.001
HbA1c	5.5 (5.3, 5.9)	5.4 (5.1, 5.6)	5.6 (5.3, 5.9)	5.8 (5.5, 6.6)	< 0.001
HDL-C	51.0 (43.0, 62.0)	63.0 (54.0, 75.0)	51.0 (44.0, 59.0)	43.0 (37.0, 50.0)	< 0.001
TG	96.0 (66.0, 143.0)	62.0 (46.0, 81.0)	98.0 (76.0, 127.0)	151.0 (111.0, 213.0)	< 0.001
TC	187.0 (161.0, 214.0)	180.0 (157.0, 206.0)	190.0 (163.0, 217.0)	191.0 (164.0, 220.0)	< 0.001
eGFR	94.6 (78.2, 108.8)	98.7 (84.2, 113.0)	91.8 (76.2, 105.9)	92.3 (74.4, 106.7)	< 0.001
SBP	121.3 (111.3, 134.0)	116.0 (106.7, 127.3)	122.0 (112.7, 134.7)	126.0 (116.0, 137.3)	< 0.001
DBP	70.7 (63.3, 77.3)	68.7 (62.0, 74.9)	71.3 (64.0, 78.0)	72.0 (64.7, 79.3)	< 0.001
Prediabetes, n (%)					< 0.001
No	4148 (54.9)	1535 (61.4)	1243 (49)	1370 (54.4)	
Yes	3406 (45.1)	963 (38.6)	1295 (51)	1148 (45.6)	
Diabetes, n (%)					< 0.001
No	6000 (79.4)	2371 (94.9)	2110 (83.1)	1519 (60.3)	
Yes	1554 (20.6)	127 (5.1)	428 (16.9)	999 (39.7)	
Hypertension, n (%)					< 0.001
No	3465 (45.9)	1612 (64.5)	1097 (43.2)	756 (30)	
Yes	4089 (54.1)	886 (35.5)	1441 (56.8)	1762 (70)	
Hypertriglyceridemia, n (%)					< 0.001

Characteristics	Total (n = 7554)	T1 (n = 2498)	T2 (n = 2538)	T3 (n = 2518)	p
No	5415 (71.7)	2423 (97)	2004 (79)	988 (39.2)	
Yes	2139 (28.3)	75 (3)	534 (21)	1530 (60.8)	
CKD, n (%)					< 0.001
No	6888 (91.2)	2362 (94.6)	2296 (90.5)	2230 (88.6)	
Yes	666 (8.8)	136 (5.4)	242 (9.5)	288 (11.4)	
Mets, n (%)					< 0.001

Table 1 (continue)

Characteristics	Total (n = 7554)	T1 (n = 2498)	T2 (n = 2538)	T3 (n = 2518)	p
No	4377 (57.9)	2383 (95.4)	1610 (63.4)	384 (15.3)	
Yes	3177 (42.1)	115 (4.6)	928 (36.6)	2134 (84.7)	
CKM stage, n (%)					< 0.001
0	624 (8.3)	607 (24.3)	17 (0.7)	0 (0)	
1	1578 (20.9)	817 (32.7)	640 (25.2)	121 (4.8)	
2	3920 (51.9)	814 (32.6)	1394 (54.9)	1712 (68)	
3	673 (8.9)	126 (5)	228 (9)	319 (12.7)	
4	759 (10.0)	134 (5.4)	259 (10.2)	366 (14.5)	

Continuous variables are presented as mean (standard deviation, SD) or median (interquartile range, IQR), and categorical variables are presented as n (%).

Abbreviations: n, number of subjects; T, tertiles; MCMI, modified cardiometabolic index; PIR, poverty–income ratio; SCR, serum creatinine; UACR, urine albumin-to-creatinine ratio; FPG, fasting plasma glucose; HbA1c, Glycated hemoglobin type A1c; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; TC, total cholesterol; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; CKD, chronic kidney disease; Mets, metabolic syndrome; CKM stage, cardiovascular–kidney–metabolic stage.

When stratified by MCMI tertiles, clear differences in baseline profiles were observed across groups. Individuals in the highest tertile (T3) tended to be older and were more likely to have a history of

smoking, diabetes, hypertension, hypertriglyceridemia, and metabolic syndrome compared with those in the lower tertiles.

Consistent with these patterns, participants in T3 also showed less favorable metabolic and clinical profiles, including higher BMI, blood pressure, triglyceride levels, fasting plasma glucose, HbA1c, and UACR, as well as lower HDL-C concentrations. In addition, variations were noted in renal function indicators and CKM stage distribution across the tertiles. Overall, most baseline variables differed significantly among the three groups ($P < 0.001$). The participant selection process is illustrated in Fig. 1.

Association between MCMI and mortality

During follow-up, 446 participants died, including 134 from cardiovascular causes. Kaplan–Meier curves (Fig. 2) revealed significant differences in survival between MCMI tertiles. Participants in the highest MCMI tertile exhibited lower survival probabilities over time, particularly for cardiovascular mortality. These findings highlight the potential of MCMI as an integrative measure of cardiometabolic burden, suggesting its role in identifying individuals at higher risk of cardiovascular death.

Pairwise comparisons between groups, adjusted for multiple testing using Holm correction, revealed that the survival differences between MCMI tertiles remained statistically significant. This supports a consistent separation of risk across MCMI levels (Supplementary Table S5).

Cox hazards model

The associations between MCMI and mortality outcomes are summarized in Table 2. For all-cause mortality, an apparent association was observed in the unadjusted model; however, this relationship diminished after accounting for potential confounding factors. In the fully adjusted model (Model 3), no significant association was detected across MCMI tertiles. Specifically, using T1 as the reference, the hazard ratios were 1.017 (95% CI: 0.730–1.417, $P = 0.922$) for T2 and 1.126 (95% CI: 0.793–1.598, $P = 0.506$) for T3. These findings suggest that MCMI may not independently predict overall mortality risk after adjustment for conventional risk factors.

Table 2
Cox regression model of the relationship between MCMI and mortality in adults with CKM syndrome

Group(vsT1)	Model1 [HR (95% CI) P]		Model2 [HR (95% CI) P]		Model3 [HR (95% CI) P]	
All-cause mortality						
Tertiles of MCMI						
T1	Reference		Reference		Reference	
T2	1.643 (1.165, 2.318)	0.004	1.041 (0.734, 1.477)	0.82	1.017 (0.730, 1.417)	0.922
T3	2.035 (1.370, 3.025)	< 0.01	1.230 (0.848, 1.785)	0.275	1.126 (0.793, 1.598)	0.506
CVD mortality						
Tertiles of MCMI						
T1	Reference		Reference		Reference	
T2	2.637 (1.445, 4.813)	< 0.001	1.490 (0.837, 2.654)	0.175	1.567 (0.872, 2.814)	0.133
T3	4.389 (2.170, 8.876)	< 0.001	2.450 (1.194, 5.024)	0.0145	2.591 (1.261, 5.320)	0.009
Model 1: no covariates were adjusted for						
Model 2: Adjusted for age and sex						
Model 3: Further adjusted for race, education, marital status, smoking status, and PIR.						
Abbreviations: CI, confidence interval; HR, hazard ratio; T, tertiles; CVD, cardiovascular disease; Covariates include: age, gender, race, education, marital status, smoking status, and PIR.						

In contrast, a different pattern was observed for cardiovascular mortality. After full adjustment, individuals in the highest MCMI tertile exhibited a markedly increased risk compared with those in the lowest tertile, with a hazard ratio of 2.591 (95% CI: 1.261–5.320, P = 0.009). The association for the middle tertile was not statistically significant (HR: 1.567, 95% CI: 0.872–2.814, P = 0.133), indicating that the elevated risk was primarily concentrated at higher levels of MCMI.

Restricted cubic spline analysis did not reveal a statistically significant overall or nonlinear relationship between MCMI and mortality outcomes. However, the spline curve indicated a trend toward higher cardiovascular mortality at elevated MCMI levels, consistent with the pattern observed in the categorical analysis (Supplementary Figure S1).

Subgroup analyses

To assess the consistency of the observed associations, stratified analyses were performed across subgroups defined by age, sex, income level, and smoking status (Fig. 3).

For all-cause mortality, no significant association between MCMI and risk was identified in any subgroup. Additionally, no significant interactions were observed across these stratification factors (all P for interaction > 0.05), indicating that the null association remained consistent across various population characteristics. In contrast, for cardiovascular mortality, a significant interaction was observed between MCMI and age (P for interaction < 0.001). Among participants younger than 60 years, higher MCMI levels were associated with a significantly increased risk of cardiovascular mortality (HR = 2.71, 95% CI: 1.82–4.05, P < 0.001), whereas no significant association was found in those aged 60 years or older, suggesting that the impact of MCMI on cardiovascular mortality may be more pronounced in younger individuals.

No significant interactions were found for sex, income level, or smoking status (all P for interaction > 0.05). While an increased risk of cardiovascular mortality was observed among male participants with higher MCMI levels, this interaction was not statistically significant, indicating that the relationship did not differ substantially by sex.

Sensitivity analyses

To verify the reliability of our key findings, we performed sensitivity analyses by excluding participants who passed away within the first two years of follow-up.

The overall pattern of results remained largely unchanged. No meaningful association between MCMI and all-cause mortality was observed after this exclusion. In contrast, the elevated risk of cardiovascular mortality persisted in the highest MCMI tertile, indicating that the main findings were not driven by early deaths (Table 3).

Table 3
Sensitivity analysis excluding participants who died within the first 2 years of follow-up.

Group (vs T1)	Model1 [HR (95%CI) P]		Model2 [HR (95%CI) P]		Model3 [HR (95%CI) P]	
All-cause mortality						
Tertiles of MCMI						
T1	Reference		Reference		Reference	
T2	1.63 (1.07, 2.47)	0.023	0.99 (0.66, 1.49)	0.963	0.93 (0.62, 1.40)	0.723
T3	2.15 (1.36, 3.41)	0.001	1.294 (0.819, 2.045)	0.27	1.26 (0.80, 1.97)	0.313
CVD mortality						
Tertiles of MCMI						
T1	Reference		Reference		Reference	
T2	3.12 (1.50, 6.50)	0.002	1.75 (0.86, 3.53)	0.12	1.73 (0.86, 3.47)	0.122
T3	4.45 (2.08, 9.51)	< 0.001	2.47 (1.13, 5.42)	0.024	2.35 (1.10, 5.06)	0.028
Abbreviations:						
MCMI, modified cardiometabolic index; HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease.						
T1, lowest tertile; T2, middle tertile; T3, highest tertile.						
Model 1: Unadjusted model.						
Model 2: Adjusted for age and sex.						
Model 3: Adjusted for age, sex, and additional covariates.						

Discussion

This study investigated the association between MCMI and mortality outcomes in individuals with CKM syndrome using a nationally representative dataset. Our findings indicate that higher MCMI levels are associated with an increased risk of cardiovascular mortality, whereas no independent association was observed with all-cause mortality after adjustment for confounding factors. Notably, the elevated risk was primarily concentrated in the highest tertile of MCMI, suggesting that the adverse effects of cardiometabolic burden may become more pronounced at higher levels. These findings are broadly consistent with previous population-based studies showing that greater cardiometabolic burden is associated with higher cardiovascular mortality[23].

Several biological mechanisms may explain the observed relationship between MCMI and cardiovascular mortality. MCMI integrates key features of metabolic dysfunction, including hypertriglyceridemia, hyperglycemia, reduced HDL-C, and central adiposity, all of which are closely linked to insulin resistance[24]. Insulin resistance contributes to endothelial dysfunction, oxidative stress, and chronic low-grade inflammation, thereby accelerating atherosclerosis and vascular damage[25]. In addition, central adiposity reflects visceral fat accumulation, which further exacerbates inflammatory and metabolic disturbances[26]. By integrating these interrelated metabolic abnormalities, MCMI may better capture the cumulative cardiometabolic burden that contributes to cardiovascular death in individuals with CKM syndrome. By capturing these interrelated processes, MCMI may provide a more comprehensive reflection of cardiometabolic burden compared with individual indicators.

In contrast, the absence of a significant association between MCMI and all-cause mortality after full adjustment suggests that cardiometabolic dysfunction may exert a more specific influence on cardiovascular outcomes rather than overall mortality. This discrepancy may be partly explained by competing risks from non-cardiovascular causes, particularly in populations with complex comorbidities such as CKM syndrome[27]. The lack of association with all-cause mortality may also reflect the multifactorial nature of overall mortality, which is influenced by a wide range of non-cardiovascular causes that may dilute the impact of cardiometabolic dysfunction[28].

In subgroup analyses, a significant interaction between MCMI and age was observed for cardiovascular mortality, with a stronger association among individuals younger than 60 years. This finding suggests that metabolic abnormalities may play a more prominent role in premature cardiovascular mortality, potentially because metabolic dysregulation represents an earlier and more dominant pathogenic pathway in younger populations[29].In contrast, the lack of association in older individuals may be attributable to competing risks and a higher burden of comorbidities[30]. No significant interactions were identified for sex, income level, or smoking status, indicating that the observed relationship was generally consistent across these subgroups.

The consistency of the findings across sensitivity analyses further supports the robustness of the observed associations, suggesting that the results were unlikely to be driven by early events or short-term mortality risk.

Compared with traditional single indicators of metabolic dysfunction, such as the triglyceride–glucose (Ty-G) index or individual measures like BMI, MCMI incorporates multiple dimensions of cardiometabolic status, including lipid metabolism, glycemic control, and body fat distribution. This multidimensional structure may provide incremental prognostic value by better reflecting the complex and interconnected pathophysiology underlying CKM syndrome. While indices such as Ty-G have demonstrated predictive value for cardiovascular outcomes[31], MCMI may offer additional advantages by integrating several key components of metabolic dysfunction into a single composite measure. This multidimensional nature may partly explain its stronger association with cardiovascular mortality observed in the present study.

The observed associations may be further supported by the combined effects of insulin resistance, dyslipidemia, and central adiposity on vascular dysfunction and atherosclerotic progression[32–33].

From a clinical perspective, MCMI has several important implications. As it is derived from routinely available clinical parameters, it is easily applicable in both clinical practice and population-based screening. Its association with cardiovascular mortality—particularly among younger individuals—suggests that it may be a useful tool for early risk stratification and identification of high-risk populations. Furthermore, MCMI may complement existing risk assessment models by providing additional information on integrated cardiometabolic burden.

Several issues should be taken into account when interpreting the findings. The study design was observational, which restricts conclusions regarding causality. MCMI was obtained from a single measurement, and thus its variability over time was not evaluated. Although multiple factors were considered in the models, the influence of unmeasured variables cannot be ruled out. Moreover, the reliance on NHANES data may reduce the applicability of the results beyond the U.S. population. Additional studies involving diverse populations and repeated measurements are needed to further assess these associations.

In conclusion, elevated MCMI is independently associated with an increased risk of cardiovascular mortality, but not all-cause mortality, in individuals with CKM syndrome. As a simple and integrative marker of cardiometabolic dysfunction, MCMI may be useful for cardiovascular risk stratification, particularly in younger populations, and may contribute to improved early identification and prevention strategies within the CKM framework.

Conclusions

Higher MCMI was independently associated with cardiovascular mortality, but not with all-cause mortality, in individuals with CKM syndrome. MCMI may serve as a practical tool for cardiovascular risk stratification, particularly in younger adults. Further research in diverse cohorts is needed to confirm its clinical applicability.

Abbreviations

MCMI Modified cardiometabolic index

CKM Cardiovascular-kidney-metabolic syndrome

NHANES National Health and Nutrition Examination Survey

CVD Cardiovascular disease

eGFR Estimated Glomerular Filtration Rate

UACR Urinary albumin-to-creatinine ratio

CKD Chronic kidney disease

PIR Poverty-income ratio

TG Triglycerides

FPG Fasting plasma glucose,

HDL-C High-Density Lipoprotein Cholesterol

Mets Metabolic syndrome

BMI Body mass index

SD Standard deviation

IQR interquartile range

ANOVA One-way analysis of variance

K-M Kaplan-Meier

TC Total cholesterol

HbA1c Glycated hemoglobin type A1c

CI Confidence interval

HR Hazard ratio

T Tertiles

Ty-G Triglyceride–glucose

HR Hazard ratio

NHANES National Health and Nutrition Examination Survey

RCS Restricted cubic spline

Declarations

Acknowledgement

We appreciate all NHANES participants for offering data for our research.

Author contributions

M.W. and F.X. conducted the visualization and investigation of the data.

Y.G. and M.W. were responsible for data curation and the original draft preparation.

Yihong Z. contributed to the conceptualization and methodology of the study, and performed software implementation.

Yishan Z. performed software implementation and validation.

Y.P. and L.C. carried out the writing – review & editing of the manuscript.

Y.P. and X.T. provided supervision for the research.

All authors reviewed the manuscript and approved the final version for submission.

Author relationship statement

Ying Pi serves as the academic supervisor of this study. Mengliu Wu, Yang Gao, Fan Xing, Yishan Zhou and Yihong Zou are graduate students under the supervision of Ying Pi and participated in this research as peer team members. Lili Chen and Xiaona Tang are senior academic collaborators within our institution, who provided professional guidance and overall research coordination for this study.

Ethics approval and consent to participate

The NHANES dataset is publicly available and de-identified; therefore, this study was exempt from additional ethical approval.

Conflict of interest

None

Funding

This work was supported by the Sanming Project of Medicine in Shenzhen (Grant No. SZZYSM202206014), the Shenzhen Clinical Research Center for Traditional Chinese Medicine (Grant No. LCYSSQ20220823091203008), the High-Quality Development Research Project of Public Hospitals in Bao'an District (Grant No. YNXM2024055), and the Bao'an District Medical and Health Research Project (Grant No. 2025JD074), all from the Seventh Clinical Medical College, Guangzhou University of Chinese Medicine, Shenzhen, China.

Data Availability Statement

The datasets presented in this study can be found in online repositories. The names of the repositories and accession numbers are available at: https://www.cdc.gov/nchs/nhanes/index.htm. The datasets

generated and analysed in this study are not publicly accessible owing to privacy constraints. Relevant data can be obtained from the corresponding author upon legitimate academic request. The research team reserves the right of final interpretation of all data.

References

1. Hacker, K. The burden of chronic disease. *Mayo Clin. Proc. Innov. Qual. Outcomes*. **8**, 112–119 (2024).
2. World Health Organization. Noncommunicable diseases: key facts. World Health Organization. (2023). https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases. Accessed 1 Apr 2026.
3. American Heart Association. A synopsis of the evidence for the science and clinical management of cardiovascular-kidney-metabolic (CKM) syndrome: a scientific statement from the American Heart Association. *Circulation* **148**, e524–e548 (2023).
4. Zheng, C. et al. Prevalence and mortality of cardiovascular-kidney-metabolic syndrome in China: a nationwide population-based study. *JACC Asia*. **5**, e100743 (2025).
5. Guo, Y., Su, W., Tao, L., Zhang, G. & Wang, K. The association between modified cardiometabolic index with non-alcoholic fatty liver disease and liver fibrosis: a cross-sectional study. *BMC Gastroenterol.* **25**, 198 (2025).
6. Shabtai, R. et al. Impact of cardiovascular-kidney-metabolic syndrome staging on myocardial infarction outcomes: a retrospective analysis of 2.7 million patients. *Diseases* **13**, 97 (2025).
7. Guo, Y. et al. Modified cardiometabolic index and the risk of new-onset chronic diseases: a nationwide prospective cohort study. *J. Diabetes Complications*. **40**, 108675 (2026).
8. Zhang, C. et al. The modified cardiometabolic index as a simple screening tool for cardiovascular disease risk: a cohort study. *Eur. J. Prev. Cardiol.* **33**, 412–420 (2026).
9. National Health and Nutrition Examination Survey (NHANES) Laboratory Data 1999–2020. Centers for Disease Control and Prevention, Hyattsville. (2020). https://wwwn.cdc.gov/nchs/nhanes/Default.aspx. Accessed 1 Apr 2026.
10. NHANES linked mortality files, 2019 public use data documentation. National Center for Health Statistics, Hyattsville. (2019). https://www.cdc.gov/nchs/data-linkage/mortality.htm. Accessed 1 Apr 2026.
11. Fang, Y. et al. Association between the modified cardiometabolic index and asthma among participants in the United States: a cross-sectional NHANES analysis. *Med. (Baltim).* **105**, e47444 (2026).
12. World Health Organization. *International statistical classification of diseases and related health problems, 10th revision (ICD-10)* (World Health Organization, 1992).
13. Ding, L. et al. The impact of triglyceride-glucose body mass index on all-cause and cardiovascular mortality in elderly patients with diabetes mellitus: evidence from NHANES 2007–2016. *BMC Geriatr.*

24, 356 (2024).

14. Zheng, Q. et al. Association between atherogenic index of plasma with all-cause and cardiovascular mortality in individuals with cardiovascular-kidney-metabolic syndrome. *Cardiovasc. Diabetol.* **24**, 183 (2025).
15. Stevens, P. E. & Levin, A. Evaluation and management of chronic kidney disease: synopsis of the Kidney Disease: Improving Global Outcomes 2012 clinical practice guideline. *Ann. Intern. Med.* **158**, 825–830 (2013).
16. Inker, L. A. et al. New creatinine- and cystatin C-based equations to estimate GFR without race. *N Engl. J. Med.* **385**, 1737–1749 (2021).
17. Sussman, J. B. et al. Clinical characteristics and current management of U.S. adults at elevated risk for heart failure using the PREVENT equations: a cross-sectional analysis. *Ann. Intern. Med.* **178**, 144–147 (2025).
18. Yang, L., Li, J., Xie, Y. & Qian, G. The non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio as a predictor of all-cause and cardiovascular mortality in United States adults with NAFLD: a prospective cohort study. *BMC Gastroenterol.* **25**, 288 (2025).
19. Wu, L. & Huang, Z. Elevated triglyceride-glucose index is associated with advanced cardiovascular-kidney-metabolic syndrome. *Sci. Rep.* **14**, 31352 (2024).
20. Schisterman, E. F., Cole, S. R. & Platt, R. W. Overadjustment bias and unnecessary adjustment in epidemiologic studies. *Epidemiology* **20**, 488–495 (2009).
21. Alberti, K. G. M. M., Zimmet, P. & Shaw, J. The IDF consensus worldwide definition of the metabolic syndrome. *Diabetes Res. Clin. Pract.* **73**, 1–10 (2006).
22. National Health and Nutrition Examination Survey (NHANES). Tutorials – Analytic Guidelines. Centers for Disease Control and Prevention, Hyattsville. Apr (2026). https://wwwn.cdc.gov/nchs/nhanes/tutorials/module4.aspx. Accessed 1.
23. Kim, Y., Kwon, H., Kim, J. & Park, J. Prevalence and mortality association of different stages of cardiovascular-kidney-metabolic syndrome. *PLoS One*. **20**, e0293412 (2025).
24. Bornfeldt, K. E. & Rask-Madsen, C. Insulin resistance and cardiovascular disease in the CKM syndrome era. *Circ. Res.* **134**, 812–832 (2024).
25. Rask-Madsen, C. & King, G. L. Vascular complications of diabetes: from mechanisms to therapeutics. *Nat. Rev. Endocrinol.* **9**, 668–684 (2013).
26. Hotamisligil, G. S. Inflammation and metabolic disorders. *Nature* **444**, 860–867 (2006).
27. Lau, B., Kim, Y. & Ioannidis, J. P. Competing risks in cardiovascular and all-cause mortality among adults with multimorbidity. *Am. J. Epidemiol.* **193**, 328–338 (2024).
28. Ning, Y., Wang, Y. & Liu, J. Cardiometabolic risk factors and cause-specific mortality in a national US cohort. *J. Am. Heart Assoc.* **13**, e032683 (2024).
29. Zhao, Q., Zhang, Y. & Li, N. Age-specific effects of metabolic markers on premature cardiovascular death. *J. Am. Coll. Cardiol.* **85**, 1988–2000 (2025).

30. Murphy, T. E. et al. The competing risk of death in longitudinal geriatric outcomes. *J. Am. Geriatr. Soc.* **67**, 357–362 (2019).
31. Yu, Z., Liu, W., Li, B., Chen, Y. & Li, J. Triglyceride-glucose index and the prognosis of patients with heart failure: a meta-analysis. *Biomol. Biomed.* **25**, 278–290 (2025).
32. Dhondge, R. H. D., Agrawal, S., Patil, R., Kadu, A. & Kothari, M. Metabolic syndrome and its role in cardiovascular disease: mechanisms, risk factors, and management. *Int. J. Mol. Sci.* **26**, 6472 (2025).
33. Horton, W. B., Love, K. M., Gregory, J. M., Liu, Z. & Barrett, E. J. Metabolic and vascular insulin resistance: partners in the pathogenesis of cardiovascular disease in diabetes. *Am. J. Physiol. Heart Circ. Physiol.* **328**, H1218–H1236 (2025).

Figures

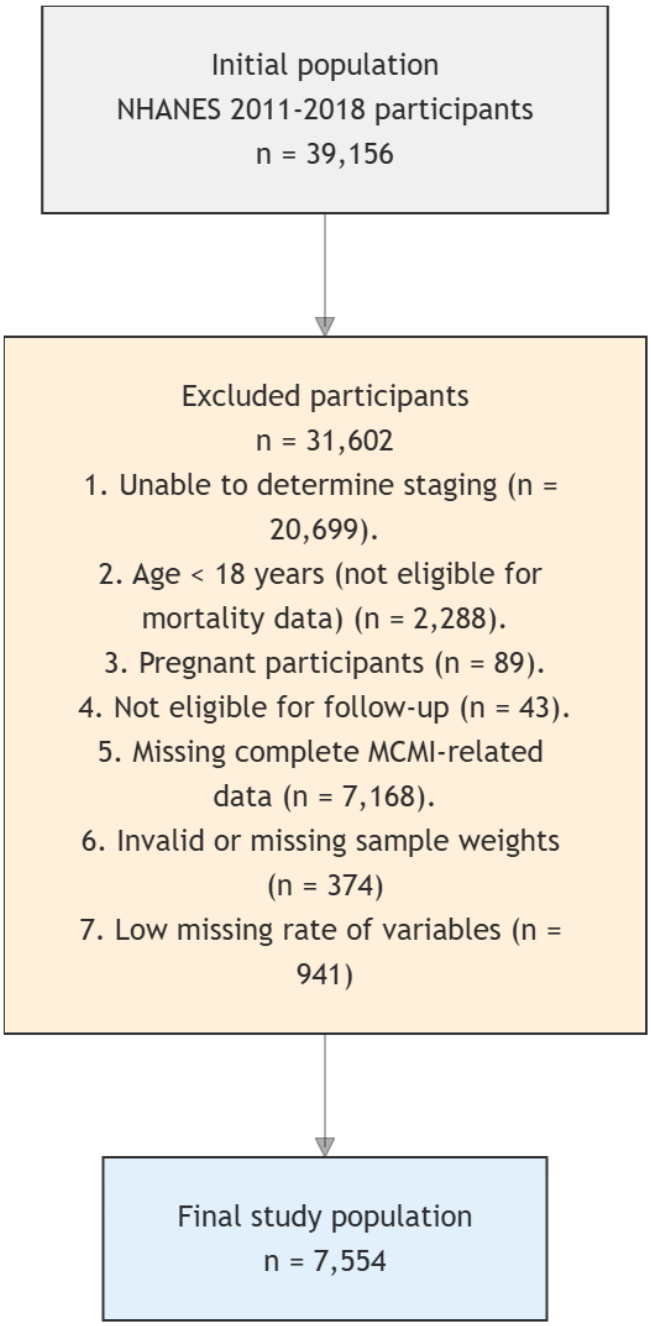


Figure 1

Flowchart of participant selection.

Abbreviation: NHANES, the National Health and Nutrition Examination Survey; MCMI, modified cardiometabolic index;

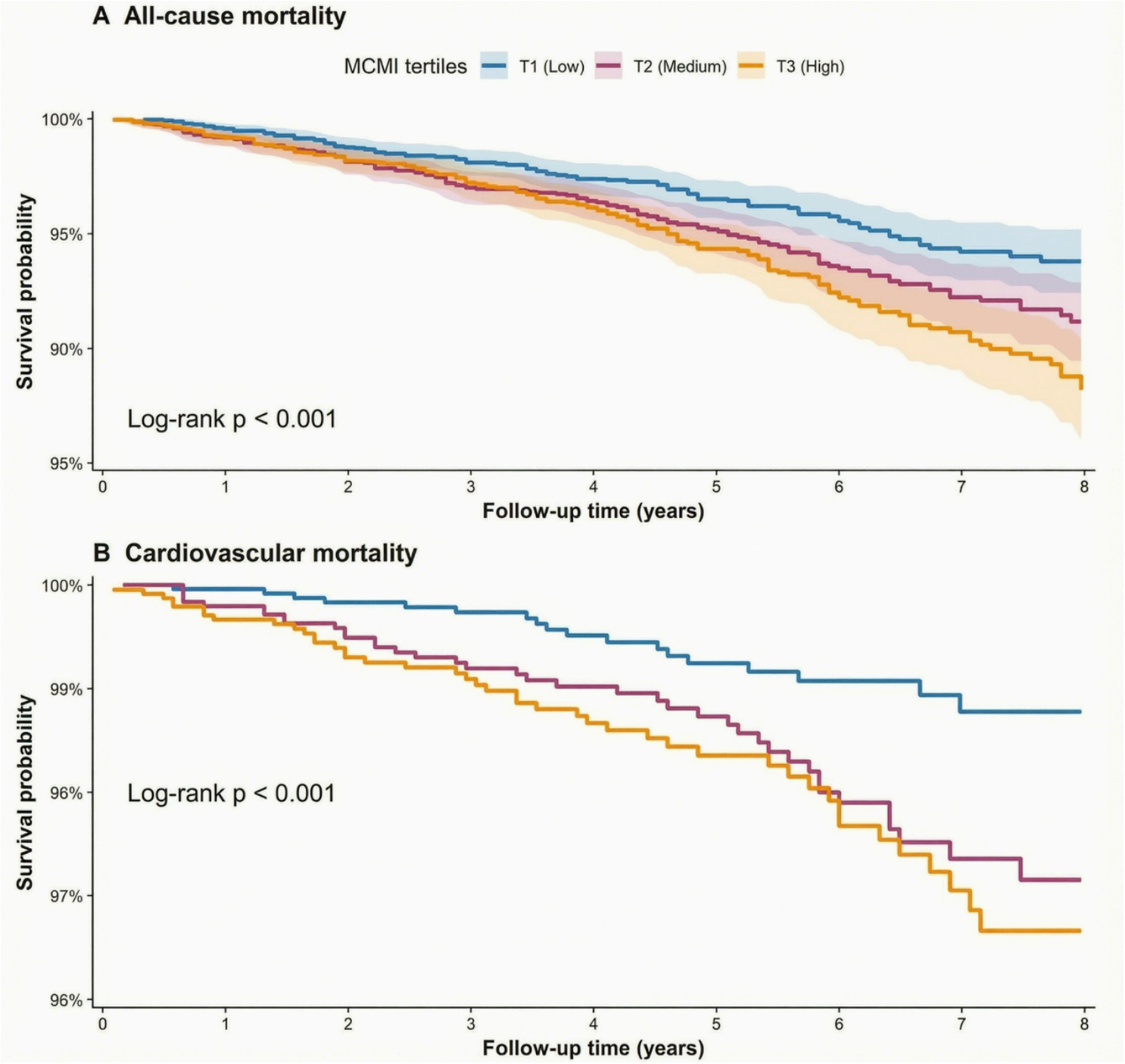


Figure 2

Kaplan–Meier curves showing cumulative incidence of all-cause and cardiovascular mortality across MCMI tertiles.

A All-cause mortality; B Cardiovascular mortality. T, tertiles;

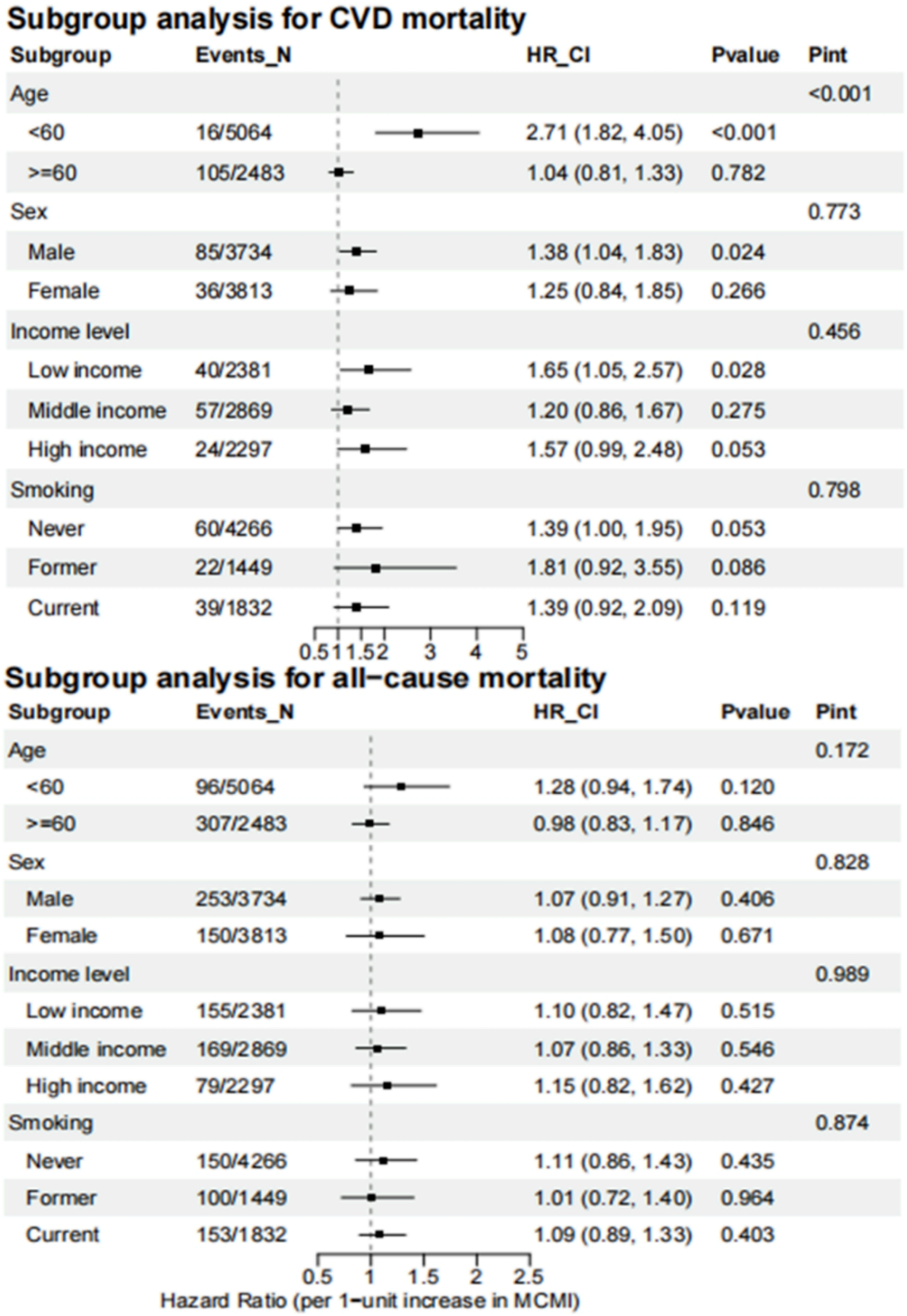


Figure 3

Forest plot of subgroup analyses examining the association between MCMI and cardiovascular disease (CVD) mortality.

Adjusted HRs and 95% CIs were estimated using Cox models. Events N refers to the number of CVD deaths and total participants in each subgroup.

Abbreviations: MCMI, modified cardiometabolic index; HR, hazard ratio; CI, confidence interval; Pint, P for interaction.

Supplementary Files

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

- SupplementaryFigureS1.jpg
- SupplementaryTableS1.xlsx
- SupplementaryTableS3.xlsx
- SupplementaryTableS4.xlsx
- SupplementaryTableS5.xlsx