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Cardiometabolic index and mortality risks: elevated cancer and reduced cardiovascular mortality risk in a large cohort

Junjie Wang[1,2†], Li Xiao[1†] and Zhou Li[3*]

Abstract

Background With metabolic disorders on the rise globally, the cardiometabolic index (CMI) has emerged as a crucial predictor of mortality risks linked to cancer, cardiovascular disease, and diabetes. This novel index, which combines lipid metabolism and body composition, is the focus of this study, aimed at exploring its association with all-cause and specific mortality in an all-age adult population.

Methods A longitudinal cohort study including 5,728 participants aged over 18 from nine cycles between 2001 and 2018 was enrolled and assessed. CMI served as the exposure variable, while outcomes included all-cause mortality and mortality due to cardiovascular disease, cancer, and diabetes. The Cox frailty model and average marginal effects were employed to evaluate the contribution of CMI to all-cause and specific mortality collectively. Restricted cubic spline analyses and stratified analyses were conducted to investigate potential nonlinear effects and interactions.

Results The decreased participants exhibited considerably higher CMI than the alive's. A positive association was found between CMI and all-cause mortality (HR=1.05, 95% CI=1.01-1.10). Notably, CMI was linked to an increased risk of cancer mortality (HR=1.02) and a reduced risk of cardiovascular disease mortality (HR=0.85). Furthermore, the average marginal effect of CMI on diabetes mortality was the largest (AME=0.499). The RCS curves revealed that participants had the lowest risk of all-cause mortality at a CMI of 0.618. Sensitivity analyses further supported these findings.

Conclusion This study represents the first comprehensive assessment on the contribution of CMI to mortality across an all-age adult population, providing some insights for the comprehensive assessment of health and disease states.

Keywords Cardiometabolic index, All-cause and specific mortality, Longitudinal cohort study, Cox Frailty model, Average marginal effects

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Background

Cardiometabolic index (CMI) is an innovative clinical tool to assess individual risk for cardiometabolic diseases, including cardiovascular disease (CVD), type 2 diabetes, and metabolic syndrome (MetS). These conditions significantly contribute to global morbidity and mortality. The CMI aggregates multiple metabolic and cardiovascular risk factors into a single score, providing a comprehensive assessment of cardiometabolic health. It primarily incorporates measurements such as waist-to-height ratio and triglyceride-to-high-density lipoprotein cholesterol (TG/HDL-C) ratio, both of which are closely associated with central obesity and dyslipidemia, respectively [1, 2].

What sets the CMI apart is its ability to reflect the combined impact of various risk factors, offering a holistic view of an individual's cardiometabolic status. Unlike traditional indices that consider individual parameters in isolation, the CMI integrates easily obtainable anthropometric and biochemical markers, facilitating early detection and prevention of cardiometabolic diseases in high-risk populations [3, 4].

Compared to other indices, such as body mass index (BMI) or waist circumference, the CMI provides a more accurate prediction of cardiometabolic events. As opposed to BMI, which does not account for fat distribution, the CMI utilizes the waist-to-height ratio to better indicate central obesity—a crucial risk factor for cardiovascular issues [5]. Additionally, the TG/HDL-C ratio incorporated in the CMI offers deeper insights into lipid metabolism, enhancing its ability to assess cardiometabolic risk [6]. Thus, the CMI is regarded as a more refined and precise tool for identifying individuals at risk of cardiometabolic diseases [7].

The increasing focus on the CMI aligns with broader research efforts to understand risk factors for both all-cause and specific mortality. All-cause mortality refers to deaths from any cause, whereas specific mortality pertains to deaths from particular conditions, such as CVD or cancer [8, 9]. Recent research underscores the need to investigate how metabolic health influences these mortality outcomes, especially in light of the growing global burden of cardiometabolic diseases [3]. There is a clear push for developing integrated risk assessment tools that capture the complex interactions between metabolic and cardiovascular factors [10].

Current research on the relationship between the CMI and mortality outcomes is still emerging but promises to be fruitful. Several studies have indicated that higher CMI is associated with an increased risk of all-cause and cardiovascular mortality in specific populations [1]. These findings suggest that the CMI could be a valuable predictor not only of cardiometabolic events but also of overall survival. Ongoing research aims to further elucidate these associations in adults of all ages and contribute to the development of strategies to reduce premature deaths associated with cardiometabolic diseases.

Method and participants

Study design and participants

This study was a longitudinal cohort study with a database from the National Health and Nutrition Examination Survey (NHANES), a comprehensive survey designed to collect data on the health status of the U.S. population [11]. The protocols for NHANES were approved by the Research Ethics Review Board of the National Center for Health Statistics (NCHS). The datasets for this study were publicly accessible on the NHANES website (https://www.cdc.gov/nchs/nhanes/index.htm) [12, 13]. Participants aged over 18 years were recruited from nine NHANES cycles between 2001 and 2018. Individuals with incomplete sociodemographic information, missing TG and HDL-C measurements for calculating CMI, and no relevant mortality data were excluded from the analysis. In the end, a total of 5,728 participants were included, consisting of 2,296 females and 3,432 males (as shown in Fig. 1).

Definitions of the exposure and outcome variables

The exposure variable was the CMI, which was calculated using the formula:

$$CMI = \left[\frac{triglyceride\,(TG, mmol/L)}{high-density\,lipoprotein\,cholesterol\ (HDL-C,\ mmol/L)}\right] \times \left[\frac{waist\,circumference\,(WC, cm)}{height\,(cm)}\right]$$

[14].

All variables in the equations above were measured following standard protocols established by the U.S. Centers for Disease Control and Prevention (CDC) and were expressed in international standard units [15]. CMI was considered as a continuous exposure variable. Subsequently, to investigate the specific effects of varying levels of CMI, we stratified our study participants into four groups based on CMI quartiles.

The outcomes were all-cause mortality, cancer mortality, CVD mortality, and diabetes mortality. The National Center for Health Statistics (NCHS) determined mortality status by integrating the NHANES Public Use Link

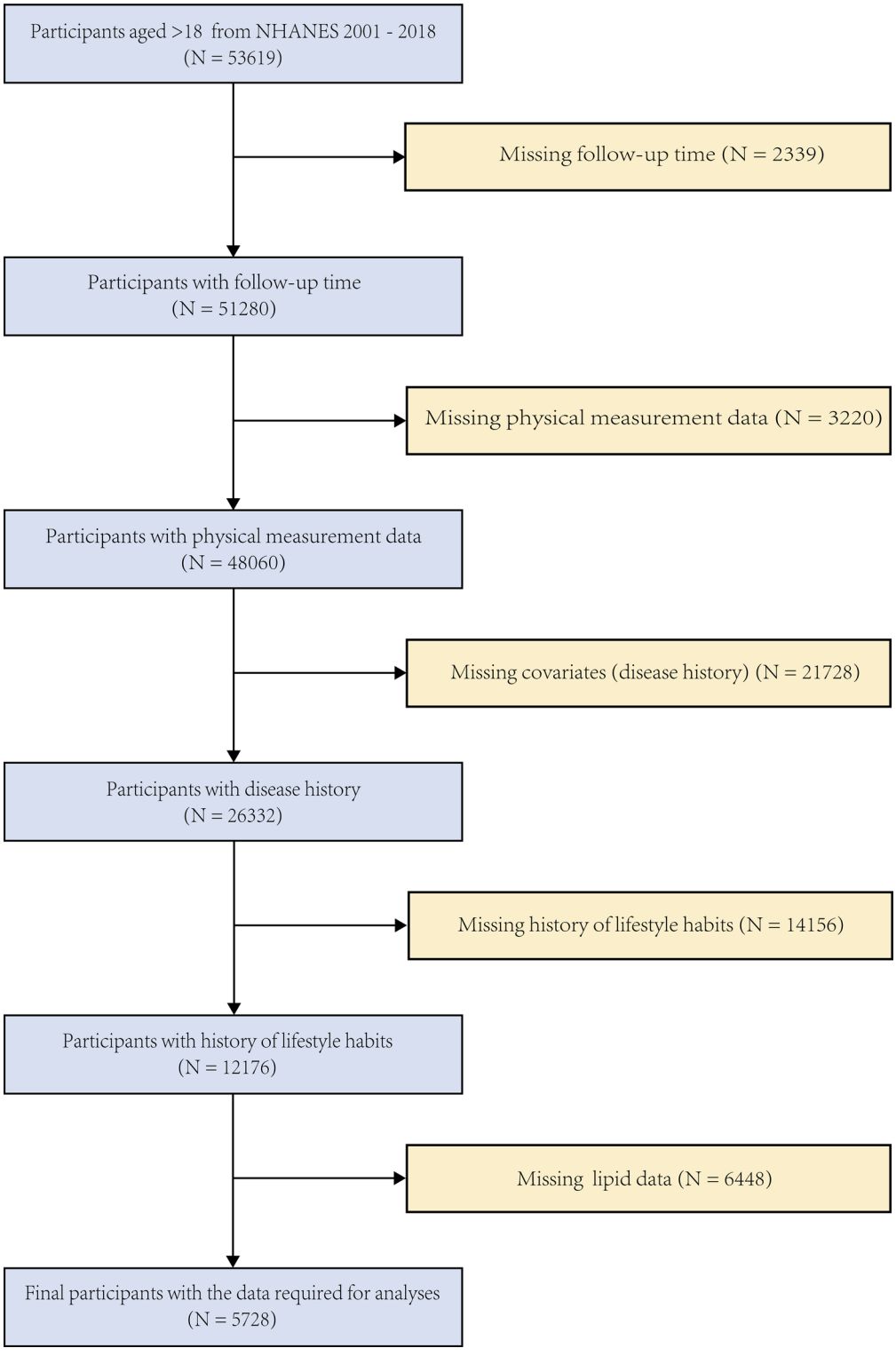

Fig. 1 A flowchart for participant selection

Mortality File with the National Death Index (NDI) through December 31, 2019, using a probability matching algorithm (www.cdc.gov/nchs/data-linkage/mortalitypublic.htm).In a further step, to ascertain the cause of death among participants, we employed the Tenth Revision of the International Statistical Classification of Diseases (ICD-10) as a guideline [16]. According to ICD-10, cancer mortality was defined by codes C00-C97, diabetes

mortality by codes E10-E14 and does not include cardiovascular complications arising from diabetes, deaths from heart disease by codes I00-I09, I11, I13, and I20-I51, and deaths from cerebrovascular disease by codes I60-I69. Cardiovascular mortality was classified as any death related to heart disease, cerebrovascular disease, and/or hypertension, which includes essential (primary) hypertension, hypertensive heart disease, hypertensive renal disease, hypertensive heart and renal disease, secondary hypertension.

Assessment of covariates

Eleven covariates, including age, gender, income-to-poverty ratio (PIR), BMI, race, the disease history of hypertension, hypercholesterolemia, diabetes, and CVD, as well as history of alcohol use and smoking, were enrolled in this study. Data on age, gender, PIR, race, the disease history of hypertension, hypercholesterolemia, diabetes, and CVD, as well as history of alcohol use and smoking, were obtained through a questionnaire, while BMI (kg/m^2), waist circumference (cm), and height (cm) were measured during a physical examination. BMI was the ratio of weight (kg) to height (m) squared. According to the World Health Organization's recommended guidelines [17], a PIR below 1.3 implies poverty, a BMI of less than 25 signifies underweight, a BMI between 25 and 30 denotes overweight, and a BMI over 30 is classified as obesity. Furthermore, a waist circumference of ≥80 suggests obesity. The definitions of hypertension, hypercholesterolemia, and diabetes involved a positive response to the following questions:

(1) Have you ever been told by a doctor or other health professional that you had hypertension, also called high blood pressure?
(2) Have you ever been told by a doctor or other health professional that your blood cholesterol level was high?
(3) Have you ever been told by a doctor or health professional that you have diabetes or other health problems?

Statistical analysis

All statistical analyses were performed with R software (version 4.2.2) and SPSS (9.0). A p-value of <0.05 was deemed statistically significant. Categorical variables were reported as frequencies and percentages, while continuous variables were presented as means with standard deviations. Continuous variables were analyzed using the Wilcoxon rank-sum test, whereas categorical variables were assessed with Pearson's Chi-squared test.

The Cox frailty model was employed to generate hazard ratios (HRs) for the association between CMI and both all-cause and specific cause mortality, incorporating age at the onset of major cardiovascular disease, diabetes, and cancer as random intercepts to account for age-specific mortality. Each model adjusted for different covariates: Model 1 (unadjusted), Model 2 (adjusted for gender), and Model 3 (adjusted for gender, hypertension, diabetes, hypercholesterolemia, cardiovascular disease, alcohol use, smoke now, race, PIR, BMI). The results from the Cox frailty model were expressed as HRs and 95% confidence intervals (CIs). Kaplan-Meier curves were generated to estimate survival over time, and the log-rank test was employed to evaluate differences in survival curves across varying CMI levels. In addition, when analyzing cause-specific mortality, we also considered competing risks between causes, for which we constructed a Fine-Gray sub-distribution hazard model, plotted Nelson-Aalen cumulative risk curves [18].

Several sensitivity analyses were performed to ensure the robustness of our findings. First, to mitigate the potential influence of reverse causation, we excluded participants with self-reported CVD. Second, we reassessed the association between CMI and both all-cause and specific cause mortality by additionally adjusted for self-reported cancer status.

To explore potential dose-response patterns, restricted cubic spline (RCS) curves were employed. Threshold effects analyses were conducted if the relationship was nonlinear, which meant that we used a two-piece Cox proportional risk model on either side of the point of infection to examine the relationship between CMI and the risk of all-cause and specific mortality.

In order to compare the associations between commonly used status indicators regarding CMI (CMI, age, sex, BMI, and PIR) and all-cause and specific mortality, the average marginal effect was calculated. Briefly, the average marginal effect of a variable represents the mean predicted change in the fitted value associated with a change in the independent variable across all observations where the covariate is present [19, 20]. These average marginal effects are compared across models, with larger average marginal effects indicating stronger correlations. Average marginal effects were derived from independent logistic regression models, each incorporating the five status indicators, and included covariates such as hypertension, diabetes, hypercholesterolemia, cardiovascular disease, alcohol use, smoking status, race, PIR, and BMI.

Finally, stratified analyses were performed based on gender, hypertension, diabetes, hypercholesterolemia, cardiovascular disease, alcohol use, smoking status, race, PIR, and BMI. Interaction effects among these variables were assessed using interaction terms.

Results

Participants characteristics

Over nine cycles of follow-up from 2001 to 2018, this study identified a total of 1,337 cases of mortality (1,337 out of 5,728), comprising 344 mortalities due to cancer, 390 from cardiovascular disease (CVD), and 50 from diabetes, after excluding cases with missing variables. As detailed in Table 1, when grouped by sex, female participants were significantly younger, experienced fewer mortality events, had longer survival times, lower PIR, and higher BMI compared to their male counterparts. Furthermore, these females were predominantly Non-Hispanic White and had a higher prevalence of hypertension, hypercholesterolemia, and CVD, while being infrequent consumers of alcohol. When grouped by survival status, the deceased participants were significantly older and had lower PIR and BMI compared to the alive participants, who were more likely to be men with hypertension, hypercholesterolemia, but not diabetes. Notably, male participants had significantly higher CMI than females, and deceased participants exhibited considerably higher CMI values compared to those who were alive at the end of follow-up.

Association between CMI and all-cause mortality and specific mortality

After adjusting for potential covariates, Table 2 outlines the associations between the CMI and both all-cause and specific mortality for each model. In Model 1, CMI was not significantly associated with all-cause or specific mortality, either continuously or stratified (all p-values > 0.05). In Model 2, CMI was positively associated

Table 1 Participants characteristics by gender or statues

Characteristic	Overall *N* = 5,728	Gender			Statues		
		Female *N* = 2,296	Male *N* = 3,432	*p*-value[1]	Alive *N* = 4,391	Decrease *N* = 1,337	*p*-value[1]
Age, Mean (SD)	61.05 (11.86)	60.19 (11.91)	61.62 (11.80)	**< 0.01**	58.40 (10.91)	69.73 (10.66)	**< 0.01**
Statues-decrease, n (%)	1,337 (23%)	454 (20%)	883 (26%)	**< 0.01**			
Gender, n (%)							**< 0.01**
Female	2,296 (40%)				1,842 (42%)	454 (34%)	
Male	3,432 (60%)				2,549 (58%)	883 (66%)	
Time, Mean (SD)	98.75 (59.07)	103.25 (59.36)	95.74 (58.69)	**< 0.01**	103.81 (60.12)	82.13 (52.13)	**< 0.01**
PIR, Mean (SD)	2.60 (1.55)	2.55 (1.56)	2.64 (1.54)	**0.01**	2.69 (1.58)	2.31 (1.38)	**< 0.01**
BMI, Mean (SD)	29.24 (6.40)	29.96 (7.41)	28.75 (5.57)	**< 0.01**	29.52 (6.42)	28.32 (6.26)	**< 0.01**
Race, n (%)				**< 0.01**			**< 0.01**
Mexican American	691 (12%)	250 (11%)	441 (13%)		571 (13%)	120 (9.0%)	
Non-Hispanic Black	1,086 (19%)	443 (19%)	643 (19%)		882 (20%)	204 (15%)	
Non-Hispanic White	3,154 (55%)	1,334 (58%)	1,820 (53%)		2,235 (51%)	919 (69%)	
Other Hispanic	441 (7.7%)	157 (6.8%)	284 (8.3%)		382 (8.7%)	59 (4.4%)	
Other Race	356 (6.2%)	112 (4.9%)	244 (7.1%)		321 (7.3%)	35 (2.6%)	
Hypertension, n (%)	2,929 (51%)	1,213 (53%)	1,716 (50%)	**0.04**	2,100 (48%)	829 (62%)	**< 0.01**
Diabetes, n (%)				**0.02**			**< 0.01**
Borderline	181 (3.2%)	71 (3.1%)	110 (3.2%)		145 (3.3%)	36 (2.7%)	
No	4,470 (78%)	1,833 (80%)	2,637 (77%)		3,495 (80%)	975 (73%)	
Yes	1,077 (19%)	392 (17%)	685 (20%)		751 (17%)	326 (24%)	
Hypercholesterolemia, n (%)	2,906 (51%)	1,177 (51%)	1,729 (50%)	0.5	2,216 (50%)	690 (52%)	0.5
CVD, n (%)	1,869 (33%)	774 (34%)	1,095 (32%)	0.2	1,395 (32%)	474 (35%)	**0.01**
Alcohol use, n (%)	4,837 (84%)	1,750 (76%)	3,087 (90%)	**< 0.01**	3,782 (86%)	1,055 (79%)	**< 0.01**
Smoke now, n (%)				**< 0.01**			**< 0.01**
Everyday	1,709 (30%)	753 (33%)	956 (28%)		1,342 (31%)	367 (27%)	
Not at all	3,713 (65%)	1,419 (62%)	2,294 (67%)		2,788 (63%)	925 (69%)	
Some days	306 (5.3%)	124 (5.4%)	182 (5.3%)		261 (5.9%)	45 (3.4%)	
Height, Mean (SD)	168.79 (9.50)	161.11 (6.65)	173.93 (7.43)	**< 0.01**	168.83 (9.45)	168.67 (9.67)	> 0.9
WC, Mean (SD)	102.64 (15.40)	100.30 (16.35)	104.20 (14.52)	**< 0.01**	102.55 (15.27)	102.92 (15.80)	0.4
WHtR, Mean (SD)	0.61 (0.09)	0.62 (0.10)	0.60 (0.08)	**< 0.01**	0.61 (0.09)	0.61 (0.09)	0.3
HDL-C, Mean (SD)	1.37 (0.44)	1.53 (0.47)	1.26 (0.38)	**< 0.01**	1.37 (0.43)	1.37 (0.47)	0.5
TG, Mean (SD)	1.65 (1.51)	1.56 (1.15)	1.72 (1.71)	0.03	1.64 (1.57)	1.68 (1.31)	**< 0.01**
TG/HDL-C, Mean (SD)	1.48 (1.98)	1.22 (1.39)	1.65 (2.27)	**< 0.01**	1.47 (2.09)	1.49 (1.55)	**< 0.01**
CMI, Mean (SD)	0.92 (1.25)	0.79 (0.92)	1.01 (1.42)	**< 0.01**	0.92 (1.30)	0.94 (1.03)	**< 0.01**

[1]Pearson's Chi-squared test; Wilcoxon rank sum test

Table 2 The associations of CMI with all-cause mortality and specific mortality

		HR (95%CI)		
	N	Model 1	Model 2	Model 3
All-cause mortality				
CMI	5728	0.97(0.93, 1.02)	**1.05(1.01, 1.1)**	1.03(0.98, 1.08)
Q1	1432	Reference	Reference	Reference
Q2	1432	0.94(0.8,1.09)	0.86(0.73, 1)	**0.82(0.7, 0.97)**
Q3	1432	0.99(0.84,1.15)	0.91(0.77, 1.06)	0.87(0.73, 1.02)
Q4	1432	1.03(0.89,1.2)	1.11(0.96, 1.3)	1.01(0.85, 1.21)
p for trend		0.25	**0.01**	0.19
Cancer mortality				
CMI	344	0.99(0.84, 1.17)	1.02(0.86, 1.21)	0.84(0.65, 1.08)
Q1	99	Reference	Reference	Reference
Q2	89	1.64(0.84, 3.2)	1.52(0.77, 2.98)	1.72(0.85, 3.51)
Q3	84	1.74(0.88, 3.42)	1.35(0.68, 2.67)	1.35(0.6, 3.0)
Q4	72	1.80(0.92, 3.55)	1.55(0.78, 3.08)	1.06(0.48, 2.36)
p for trend		0.92	0.85	0.17
Cardiovascular disease mortality				
CMI	390	0.78(0.6, 1.02)	0.85(0.65, 1.13)	0.99(0.75, 1.31)
Q1	92	Reference	Reference	Reference
Q2	95	0.86(0.49, 1.49)	0.7(0.4, 1.24)	0.73(0.4, 1.35)
Q3	99	0.73(0.4, 1.3)	0.56(0.31, 1.03)	0.82(0.41, 1.66)
Q4	104	0.51(0.27, 0.94)	0.56(0.3, 1.06)	0.78(0.38, 1.59)
p for trend		0.07	0.27	0.94
Diabetes mortality				
CMI	50	0.98(0.63, 1.54)	1.15(0.71, 1.85)	1.08(0.6, 1.94)
Q1	7	Reference	Reference	Reference
Q2	16	1.6(0.019, 13.22)	0.8(0.08, 8.06)	0.8(0.4, 17.75)
Q3	14	2(0.022,18.22)	1.53(0.15, 15.26)	1.95(0.03, 128.62)
Q4	13	1.75(0.02, 15.09)	1.46(0.16, 13.05)	1.39(0.02, 84.58)
p for trend		0.95	0.57	0.8

Multivariable Cox frailty model, with age at onset as a random intercept

Model 1 adjust for: none;

Model 2 adjust for: gender;

Model 3 adjust for: gender, hypertension, diabetes, hypercholesterolemia, cardiovascular disease, alcohol use, smoke now, race, PIR, BMI;

Number in bold indicates p less than 0.05

with all-cause mortality (HR=1.05, 95%CI=1.01–1.1), and the HRs for all-cause mortality trendily higher and higher with increasing CMI levels compared with Q1 (p for trend<0.05). In the meantime, we were also concerned that CMI appeared to increase the risk of cancer mortality (HR=1.02; HR for Q2=1.52; HR for Q3=1.35; HR for Q4=1.55) while decreasing the risk of CVD mortality (HR=0.85; HR for Q2=0.70; HR for Q3=0.56; HR for Q4=0.56). Yet, none of these associations reached statistical significance. In Model 3, after accounting for all confounding factors, CMI continued to show a positive association with all-cause mortality. However, upon stratification, Quartile 2 exhibited a significant negative association with all-cause mortality compared to Quartile 1, indicating some fluctuation in the data. The role of CMI on the risk of CVD mortality was consistent with Model 2. In addition, Kaplan-Meier survival curves presented in Fig. 2 revealed no significant differences in all-cause or specific-cause mortality among participants stratified by CMI. The p-values for all-cause mortality (Fig. 2A), cancer mortality (Fig. 2B), diabetes mortality (Fig. 2C), and CVD mortality (Fig. 2D) were 0.30, 0.18, 0.85, and 0.89, respectively. As shown in Figure S1, there was no significant difference in Nelson-Aalen Cumulative Risk across specific causes, indicating that there is no competing risk (Figure S1).

Sensitivity analyses showed no substantial change in results after adjustment for covariates in Model 3 (Tables 1S, 2S). After excluding participants with self-reported diagnosis of CVD, HRs for Q4 participants were much lower than for Q1 participants in all models, with HRs for CVD mortality of 0.48 (0.24, 0.88), 0.51 (0.29, 1.01), and 0.75 (0.42, 1.61) in Models 1, 2, and 3. After excluding participants with a self-reported diagnosis of cancer, CMI was still observed to increase the risk of cancer mortality in all models.

Nonlinear associations between CMI and all-cause mortality and specific mortality

After taking into account the nonlinear relationship between CMI and outcomes, this study implemented RCS curves and analyzed the thresholds for each curve (Fig. 2). As illustrated in Fig. 3, a significant nonlinear dose-response pattern was identified between CMI and all-cause mortality (Fig. 3A; p-overall=0.002, p-nonlinear=0.001). Specifically, the hazard ratio for all-cause mortality initially decreases and then increases with increasing CMI, ultimately reaching a plateau. Conversely, no significant nonlinear dose-response patterns were found between CMI and cancer mortality, cardiovascular disease (CVD) mortality, or diabetes mortality (nonlinear p-values of 0.482, 0.495, and 0.693, respectively). But an L-shaped linear association was observed between CMI and CVD mortality and diabetes mortality (Fig. 3C and D) indicating that the risk for these outcomes decreased with increasing CMI until a stable threshold was achieved. Based on these findings, to further validate these associations, we conducted a threshold effect analysis, revealing thresholds for the curves at 0.618, 0.838, 1.232, and 0.941, respectively. Remarkably, participants possessed the lowest risk of all-cause mortality at a CMI of 0.618.

Stratified analyses

The findings from the stratified analyses, adjusted for all covariates, are presented in Fig. 4. According to the RCS curves, the stratified analyses between CMI and all-cause

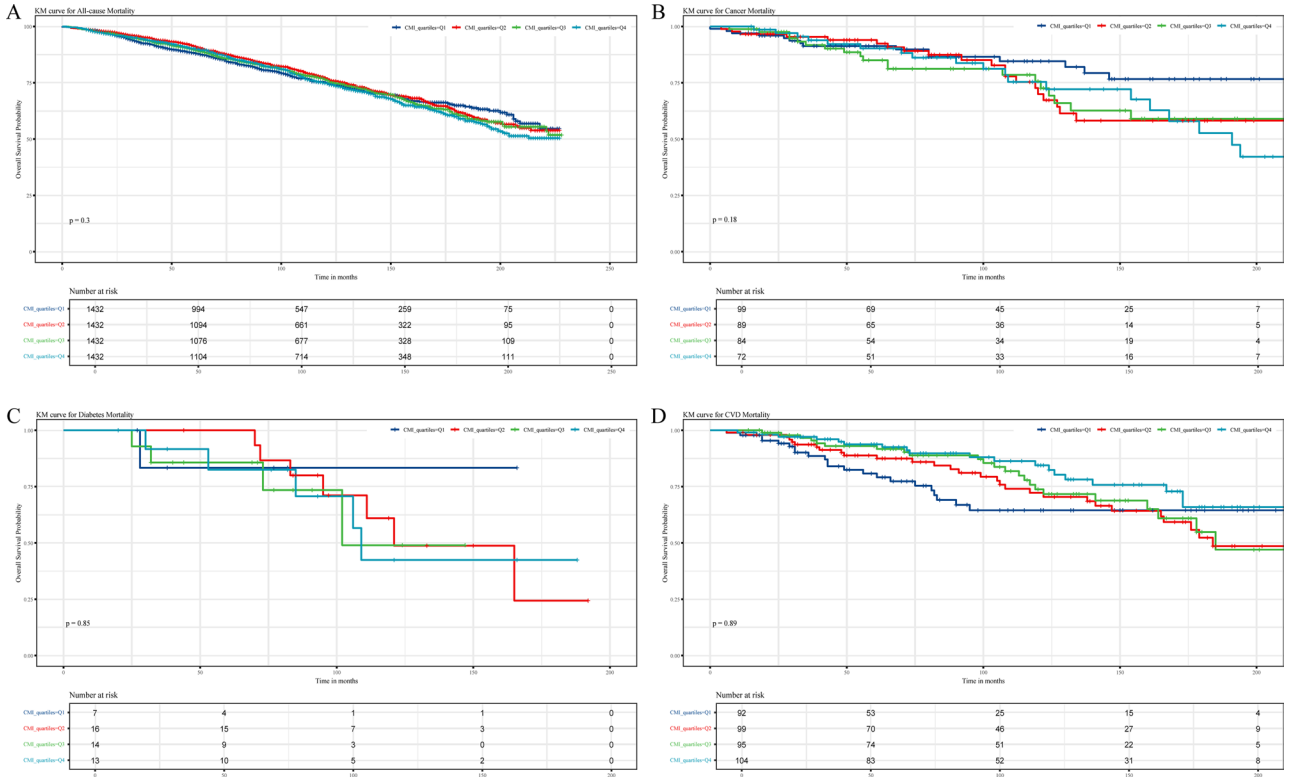

Fig. 2 Kaplan–Meier curves of the survival rate of participants with CMI quartiles. CMI was divided into 4 groups from smallest to largest, and survival probabilities for the 4 causes were calculated by stratification. Kaplan-Meier survival curves indicated that there was no difference between all-cause and specific-cause mortality among stratified participants by CMI. P-values for all-cause mortality (**A**), cancer mortality (**B**), diabetes mortality (**C**), and CVD mortality (**C**), were calculated in a stratified manner. P-value for all-cause mortality (**A**), cancer mortality (**B**), diabetes mortality (**C**), and CVD mortality (**D**) is 0.3, 0.18, 0.85, and 0.89 respectively

Table 3 Average marginal effects of status indicators on all-cause mortality and specific mortality

	All-cause mortality	Cancer mortality	Cardiovascular disease mortality	Diabetes mortality
CMI	**0.081**	-0.050	0.162	0.499
Age	**0.097**	**0.069**	**0.071**	**0.228**
Gender	**0.406**	0.734	0.279	0.634
BMI	**-0.020**	0.020	-0.041	0.013
PIR	**-0.161**	-0.040	**-0.236**	**-1.118**
AIC	4962.6	338.9	382.75	53.722

Data are average marginal effects

Multivariable logistic regression model adjusted for hypertension, diabetes, hypercholesterolemia, cardiovascular disease, alcohol use, smoke now, race

Numbers in bold indicate p-values less than 0.05

AIC: Akaike's Information Criteria

mortality were meaningful. Interestingly, most analyses did not reveal significant differences within groups; however, a stronger positive correlation between CMI and all-cause mortality was observed among participants aged 60 years or younger ($p=0.013$; p for interaction=0.015).

Average marginal effects of status indicators

Of the five status indicators for CMI, gender exhibited the largest average marginal effects, with values of 0.406 for all-cause mortality, 0.734 for cancer mortality, 0.279 for CVD mortality, and 0.634 for diabetes mortality. At the same time, age was the only indicator significantly associated with all four outcomes across all average marginal effect models, with values of 0.097 for all-cause mortality, 0.069 for cancer mortality, 0.071 for CVD mortality, and 0.228 for diabetes mortality. For CMI, the indicator focused on in this study, the average marginal effect on diabetes mortality was the largest at 0.499, while for all-cause mortality, the average marginal effect was 0.081 ($p<0.05$). In contrast, the average marginal effect of CMI on cancer mortality was negative at -0.050.

Discussion

CMI, a novel index related to lipid metabolism, fuses lipid metabolism indices and body physical indicators [1, 21, 22]. It has increasingly been emphasized by researchers of cardiovascular diseases. In fact, CMI has also been robustly associated with various conditions linked to metabolic disorders [23–25], suggesting its potential as a

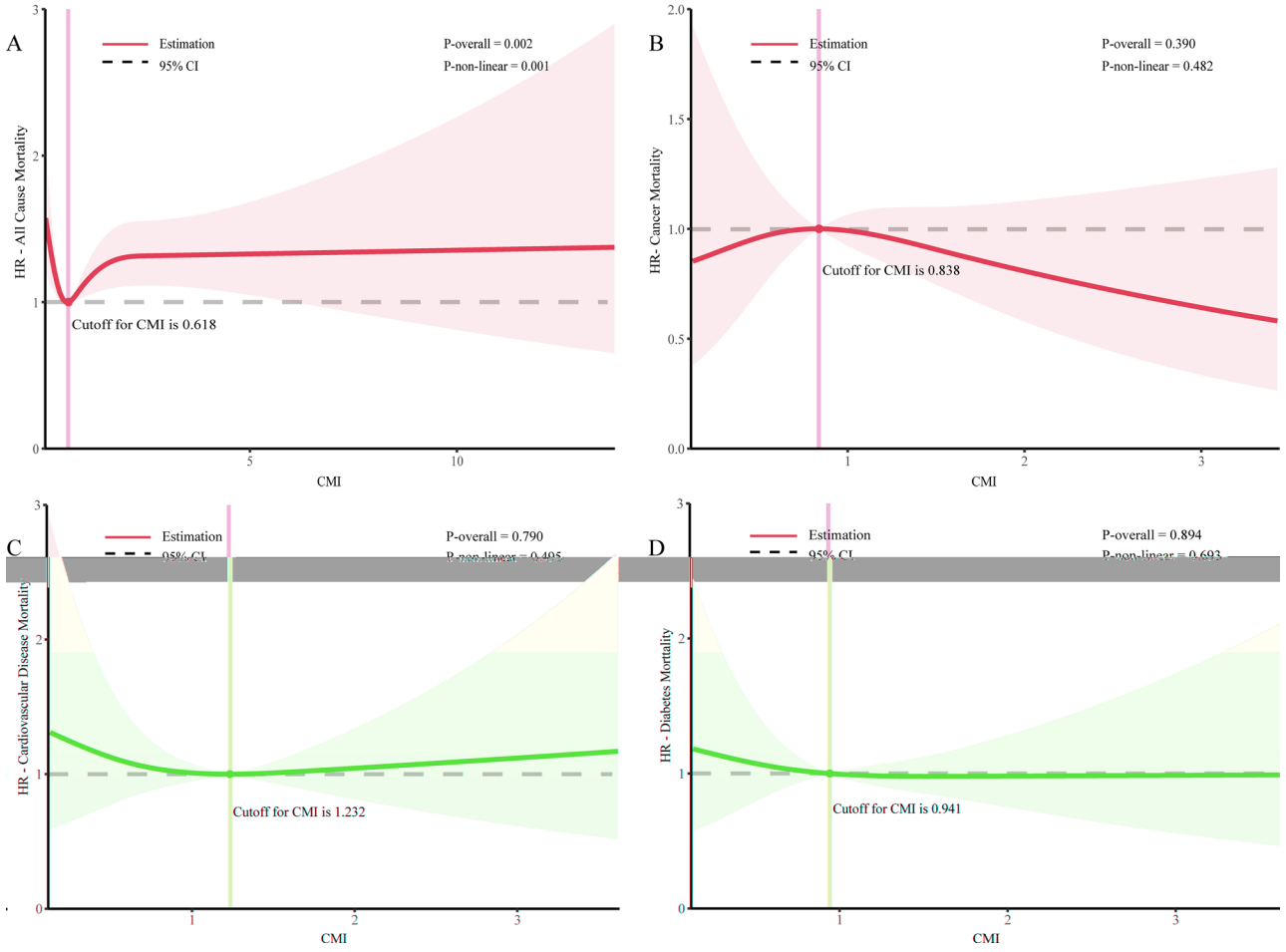

Fig. 3 Dose-response curves of CMI and all-cause mortality and specific-mortality. Restricted cubic spline curves (RCS) were used to explore potential dose-response patterns, and thresholds were calculated for each curve. For all-cause mortality (**A**), the hazard ratio decreases and then increases with increasing CMI until a plateau. For cancer mortality (**B**), the hazard ratio rises and then falls with increasing CMI. For CVD and diabetes mortality (**C** and **D**), the risk ratios declined with increasing CMI to the thresholds and then stabilized

comprehensive indicator for assessing overall health status and mortality risk.

The present study explored the association between CMI and all-cause mortality, as well as the three leading causes of mortality. Our findings revealed a significant positive association between CMI and all-cause mortality, with an approximately 5% increased risk of all-cause mortality for each unit increase in CMI. Interestingly, Xu et al. also reported that CMI was correlated with all-cause mortality risk [1], though their results pertain specifically to older adults, whereas our analysis encompasses all age adults. To further elucidate the association of CMI with all-cause and specific mortality, five status indicators related to CMI were creatively introduced to assess their average marginal effects on mortality as a whole, and CMI was found to have the largest average marginal effect on diabetes mortality. The average marginal effect (AME) quantifies the change in the probability of a specific outcome associated with a one-unit change in an explanatory variable of a given set of categories [18, 26]. This metric offers insight into the extent to which independent variables influence response variables. For instance, Zhu employed AME to examine the relationships among various socioeconomic indicators (including socioeconomic status, education, occupation, and household income) and cardiovascular outcomes [27], highlighting its robustness as an analytical tool in the context of confounding factors. Moreover, while our study considered a range of covariates, it remains uncertain whether additional, unmeasured variables may also significantly impact the outcomes. The Cox frailty model was chosen to account for potential clustering effects within subgroups, such as variations across NHANES waves, which may violate the independence assumption of the standard Cox proportional hazards model. Similar to Zhu, we utilized the Cox frailty model, calculating both hazard ratios and the correlation of CMI with all-cause and specific mortality. This dual approach provides

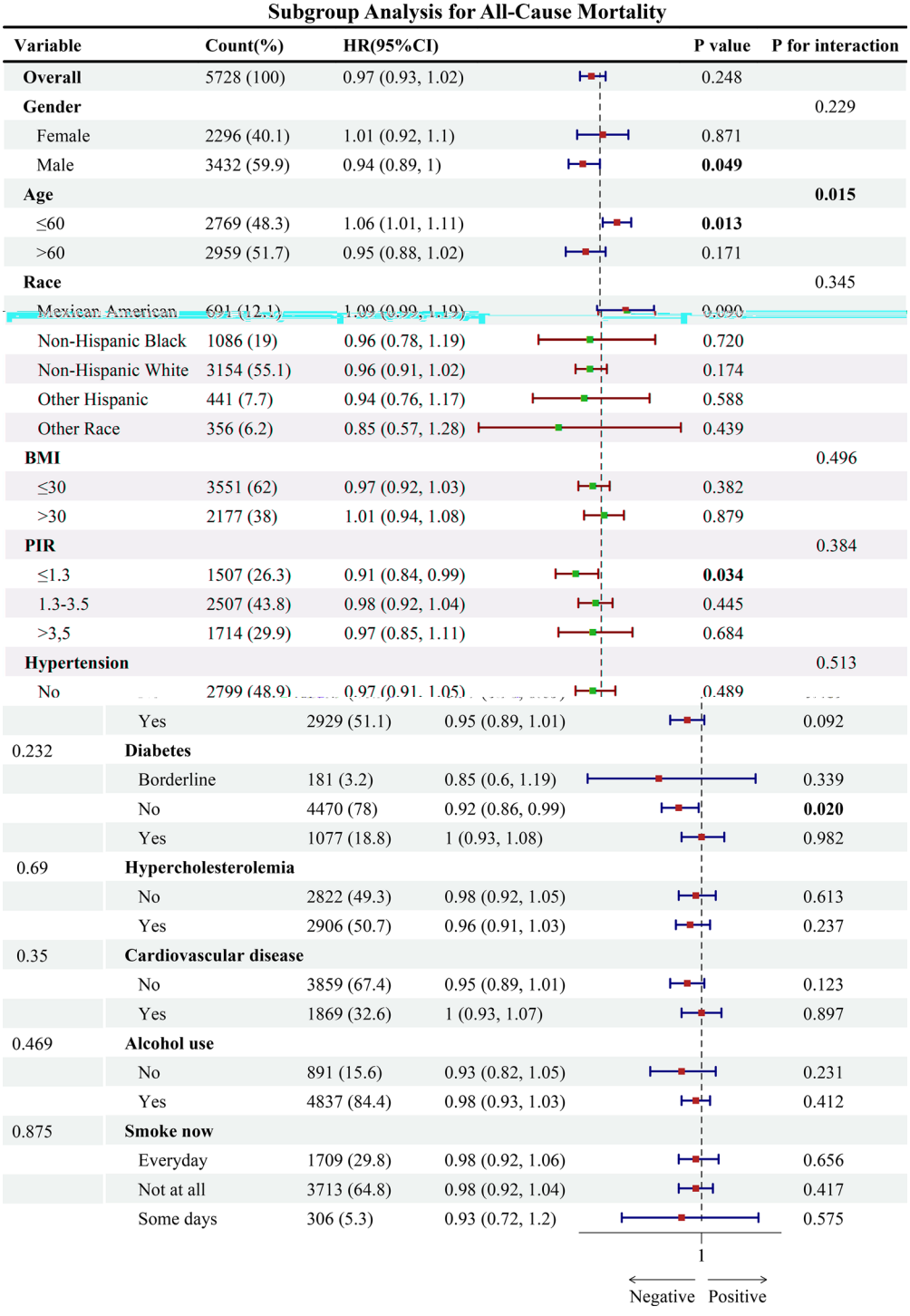

Fig. 4 Subgroup analysis for all-cause mortality. Gender, age, race, BMI, PIR, and history of hypertension, diabetes, hypercholesterolemia, and cardiovascular disease alcohol use, smoke now were all adjusted except for the covariates themselves. Bold values indicate p-value < 0.05, which is statistically significant

a comprehensive evaluation of CMI's contributions to the four types of mortality examined.

CMI was originally introduced by Wakabayashi in 2015 as an influential anthropometric index for identifying diabetes mellitus, demonstrating a notable correlation with hyperglycemia [14]. Subsequent research by Zha and Qiu further established that CMI was increasingly associated with the risk of developing diabetes in older adults [28, 29]. This finding aligns closely with our results, which indicate that CMI has the largest average marginal effect

on diabetes mortality. Further, our study identified an L-shaped association between CMI and the risk of diabetes mortality, suggesting that the risk decreases until CMI reaches a threshold of 0.941. In contrast, a separate cross-sectional study indicated that another lipid metabolism index, the atherogenic index of plasma (AIP), exhibited a J-shaped relationship with diabetes mortality risk, where increased AIP corresponded with higher mortality risk beyond a certain threshold [30]. This discrepancy may arise from the CMI's incorporation of participants' stature metrics, whereas AIP relies solely on lipid-related parameters. Thus, CMI serves as a comprehensive index, integrating both lipid metabolism and anthropometric measures, thereby providing a more holistic view of an individual's overall health status.

A growing body of research has shown the relationship between CMI and diabetes risk, and its implication in cardiovascular and other metabolic diseases. Wang's study showed the use of CMI in screening for obstructive sleep apnea and its combination with MetS [31]. Cai found a positive association between CMI and CVD risk in hypertensive patients with obstructive sleep apnea, which contrasts with our study, which observed CMI reducing cardiovascular disease mortality, possibly due to participant differences [32]. Cancer mortality is a public health concern. Our study is the first to show that CMI increases cancer mortality risk continuously and by stratification. There are no similar studies. You previously have found AIP to increase cancer death risk in those under 65 [30]. These suggest lipid metabolism disorders may be a key cancer risk factor, needing further examination.

To address the biological mechanisms underlying the associations between CMI and mortality from cancer and CVD, it is essential to delve into several key pathways. One significant mechanism involves inflammation, where elevated levels of inflammatory markers—often linked to poor metabolic health—can contribute to the development of both cancer and cardiovascular diseases. Mok and Kaptoge et al. revealed that elevated levels of inflammatory markers, such as C-reactive protein (CRP), are frequently associated with poor metabolic health and have been implicated in the pathogenesis of both cancer and CVD. Chronic inflammation can facilitate tumor progression and atherogenesis, leading to increased mortality risk [33–35]. Additionally, insulin resistance is a critical factor; Wang and Kim also expressed that insulin resistance not only disrupts glucose metabolism but also promotes the development of atherosclerosis and tumorigenesis, and link obesity and metabolic syndrome to heightened cardiovascular and cancer risks [36, 37]. Furthermore, dyslipidemia, characterized by abnormal lipid profiles, plays a role in increasing cardiovascular risk and is associated with cancer progression. O'Keefe and Duncan's study uncovered that abnormal lipid profiles, characterized by elevated triglycerides and low high-density lipoprotein cholesterol (HDL-C), are associated with increased cardiovascular mortality and have been linked to cancer progression as well [38, 39]. Understanding these mechanisms highlights the need for integrating metabolic health assessments into public health strategies aimed at reducing mortality risks associated with these diseases.

In the context of existing public health initiatives aimed at reducing mortality from cancer and CVD, our findings suggest that the CMI could be a valuable addition to current strategies. The CMI's ability to predict mortality related to both cancer and cardiovascular disease highlights its potential to improve existing frameworks for risk assessment and prevention. Public health programs, such as the *Million Hearts* initiative led by the CDC, prioritize reducing cardiovascular events through lifestyle interventions like dietary improvements, increased physical activity, and better management of blood pressure and cholesterol levels [40]. Integrating CMI into these initiatives could enhance early identification of individuals at high risk by providing a more comprehensive evaluation of metabolic health compared to traditional tools like the Framingham Risk Score [41]. The CMI, which combines waist-to-height ratio and triglyceride-to-HDL-C ratio, offers a more complete measure of metabolic disturbances that often underlie both cancer and cardiovascular mortality. Including CMI as part of routine screenings could support public health efforts aimed at reducing the burden of metabolic syndrome, a condition closely associated with these diseases [42]. Additionally, our findings underscore the need to address socioeconomic disparities that contribute to poor metabolic health outcomes. This aligns with global health goals advocated by the World Health Organization to ensure equitable access to preventive care, particularly in high-risk populations [43]. Incorporating CMI into public health initiatives could thus refine prevention strategies and improve health outcomes for vulnerable groups.

Strengths and limitations

This study presents several significant strengths. First, we employed the Cox frailty model to evaluate the impact of CMI on all-cause mortality, effectively addressing potential omissions of critical covariates, resulting in more informative outcomes compared to alternative analytical approaches. Second, we utilized average marginal effects to examine the association between CMI and all-cause mortality, providing a more comprehensive understanding of CMI's role in these outcomes. Third, our study draws from a nationally representative U.S. sample, with various data points measured through rigorous standardized methods, thereby enhancing the robustness of our

analyses, which included physical measurements (waist circumference and height) and serum biomarkers (triglycerides and high-density lipoprotein). The large sample size further contributes to the generalizability of our findings. Finally, we bolstered the validity of our results by carefully adjusting for an array of demographic factors, physical measurements, medical histories, and other potential confounders.

Nonetheless, this study has several limitations. Firstly, the cohort consisted only of Americans, restricting the generalizability to other ethnicities, as genetic, lifestyle, and physiological differences among ethnic groups might affect the CMI-mortality relationship. Secondly, serial CMI changes during follow-up were unrecorded. Longitudinal CMI variations could offer insights into the temporal nature of its association with mortality, and their absence leaves our understanding incomplete. Finally, the self-reported histories of hypertension, diabetes, and coronary heart disease via questionnaires are subject to recall bias. This may lead to inaccurate prevalence and diagnosis data, potentially distorting the analysis of comorbidities' interactions with CMI and mortality, thus affecting result reliability. Future research should address these issues by diversifying the study population, capturing serial variable changes, and using more objective medical history collection methods to strengthen the robustness and generalizability of CMI-mortality related findings.

Conclusion

The current study provides a comprehensive evaluation of the association between CMI and mortality within an all-age adult population. We examined the influence of CMI on all-cause mortality by taking into account both hazard ratios and correlations. The results suggest that CMI is related to an elevated risk of all-cause and cancer mortality, and shows a relatively strong correlation with diabetes mortality. As CMI is a relatively easily measurable metabolism-related factor, these findings might potentially contribute valuable perspectives for the general understanding of health and disease conditions.

Abbreviations

CMI	Cardiometabolic Index
CVD	Cardiovascular disease
MetS	Metabolic syndrome
TG	Triglyceride
HDL-C	High-density lipoprotein cholesterol
BMI	Body mass index
NHANES	National health and nutrition examination survey
NCHS	National center for health statistics
WC	Waist circumference
CDC	Centers for disease control
NDI	National death index
ICD-10	Tenth revision of the international statistical classification of diseases
PIR	Income-to-poverty ratio
HR	Hazard ratio
CI	Confidence intervals
RCS	Restricted cubic spline
AME	Average marginal effect
AIP	Atherogenic index of plasma
CRP	C-reactive protein
WHO	World Health Organization

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions

ZL conceived the study design and are responsible for the overall content. ZL and JJW analyzed and interpreted the data. JJW and LX prepared the manuscript. ZL edited the manuscript. All authors approved the submitted and final versions.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The protocols of NHANES were approved by the institutional review board of the National Center for Health Statistics, CDC (https://www.cdc.gov/nchs/nhanes/irba98.htm). NHANES has obtained written informed consent from all participants.

Consent for publication

Written informed consent for publication was obtained from all participants.

Competing interests

The authors declare no competing interests.

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