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Association between cardiometabolic index and all-cause and cause-specific mortality among the general population: NHANES 1999–2018

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Abstract

Background Cardiometabolic index (CMI) is a comprehensive clinical parameter which integrates overweight and abnormal lipid metabolism. However, its relationship with all-cause, cardiovascular disease (CVD), and cancer mortality is still obscure. Thus, a large-scale cohort study was conducted to illustrate the causal relation between CMI and CVD, cancer, and all-cause mortality among the common American population.

Methods Our research was performed on the basis of National Health and Nutrition Examination Survey (NHANES) database, involving 40,275 participants ranging from 1999 to 2018. The formula of CMI is [waist circumference (cm) / height (cm)] × [triglyceride (mg/dL) / high-density lipoprotein cholesterol (mg/dL)]. Outcome variables consisted of CVD, cancer, and all-cause mortality, which were identified by the International Classification of Diseases (ICD)-10. The correlation between CMI and mortality outcomes was analyzed utilizing the Kaplan–Meier survival modeling, univariate/multivariate Cox regression analysis, smooth curve fitting analysis, threshold effect analysis, and subgroup analysis. Stratification factors for subgroups included age, race/ethnicity, sex, smoking behavior, drinking behavior, BMI, hypertension, and diabetes.

Results The baseline characteristics table includes 4,569 all-cause-induced death cases, 1,113 CVD-induced death cases, and 1,066 cancer-induced death cases. Without adjustment for potential covariates, significantly positive causal correlation existed between CMI and all-cause mortality (HR = 1.03, 95% CI 1.02,1.04, *P*-value<0.05), CVD mortality (HR = 1.04, 95% CI 1.03, 1.05, *P*-value<0.05) and cancer mortality(HR = 1.03, 95% CI 1.02, 1.05, *P*-value<0.05); whereas, after confounding factors were completely adjusted, the relationship lost statistical significance in CMI subgroups (*P* for trend>0.05). Subgroup analysis found no specific subgroups. Under a fully adjusted model, a threshold effect analysis was performed combined with smooth curve fitting, and the findings suggested an L-shaped nonlinear association within CMI and all-cause mortality (the Inflection point was 0.98); in particular, when the baseline CMI was below 0.98, there existed a negative correlation with all-cause mortality with significance (HR 0.59, 95% CI 0.43, 0.82,

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P-value<0.05). A nonlinear relation was observed between CMI and CVD mortality. Whereas, the correlation between CMI and cancer mortality was linear.

Conclusions Among the general American population, baseline CMI levels exhibited an L-shaped nonlinear relationship with all-cause mortality, and the threshold value was 0.98. What's more, CMI may become an effective indicator for CVD, cancer, and all-cause mortality prediction. Further investigation is essential to confirm our findings.

Background

Abnormal lipid metabolism has caused various diseases like cardiovascular disease (CVD), cancer, liver illness, kidney disease, diabetes mellitus, obesity, and neurodegeneration disease [1]. In recent years, researches on lipid metabolism mainly focused on CVD and cancer. For example, lipid metabolism biomarkers like peroxisome proliferator-activated receptor-alpha and perilipin 1 were proven to take an important part in the CVD pathological process [2, 3]. In addition, apart from its role on the pathological process, abnormal lipid metabolism did have an important influence on mortality outcomes. For instance, results from a cohort study revealed that the occurrence of hypertriglyceridemia notably heightened the prevalence of CVD and the risk of all-cause mortality among adults [4]. The study by Yu et al. revealed that patients with type 2 diabetes and newly diagnosed diabetic nephropathy who had remnant cholesterol levels of 30 mg/dL or above exhibited a markedly elevated risk of CVD mortality over a two-year follow-up period compared with those with lower levels [5]. What's more, Zheng et al. suggested a connection between lipid metabolism and inflammation in abdominal aortic aneurysms and cardiometabolic traits [6]. Abnormal lipid metabolism is also involved in cancer metastasis and stemness [7, 8]. One authoritative review has demonstrated lipid metabolism as a new therapy target in pancreatic cancer [9]. Therefore, lipid metabolism in CVD, and cancer has been the hot topic.

Traditional clinical obesity measurements like waist circumference (WC) and body mass index (BMI) cannot accurately assess dyslipidemia. For instance, Agarwal et al. reported that BMI tended to overestimate the degree of obesity in chronic kidney patients, especially in the case of swelling, elevated muscle mass, and/or peripheral adiposity distribution [10]. WC had a low efficiency in evaluating systemic lipid metabolism as it only focused on the accumulation of abdominal fat [11]. In the following period, although indicators like Triglyceride/High-Density Lipoprotein Cholesterol (TG/HDL-C) [12], and Visceral Adiposity Index [13] to some extent improved the accuracy of lipid metabolism assessment, they still failed to evaluate metabolism and obesity comprehensively. In recent years, the Cardiometabolic index (CMI), an emerging clinical indicator that incorporates obesity with abnormal lipid metabolism, has been established [14]. The formula for CMI is [WC (cm)/height (cm)] × [TG (mg/dL)/HDL-C (mg/dL)]. As the CMI incorporates the obesity markers WC/height with the lipid metabolism markers TG/HDL-C, it has a better capacity to reflect the lipid metabolism disorders compared with other biomarkers. For instance, a cross-sectional survey that was carried out to evaluate the correlation between CMI and hyperuricemia confirmed the role of CMI as a monitoring indicator for hyperuricemia management [15]. Besides, the CMI was taken to discriminate the type 2 diabetes mellitus under logistic regression modeling [16]. Interestingly, a retrospective cohort study in the Japanese population revealed that the relationship between the CMI and the diabetes risk was non-linear [17].

CVD, a classic metabolic disease, is characterized by lipid metabolism disorder and vascular endothelial injury [18]. As Wakabayashi et al. has found CMI may be a potential vascular endothelial injury biomarker [19]. Thus, CMI was indispensable in the pathophysiological process of CVD. Investigations into the causal relation between CMI and mortality induced by all causes and CVD were insufficient. Only one cohort study suggested a causal relation between CMI and CVD-related and all-cause mortality in age-limited participants [20]. It has been widely accepted that cancer and CVD share common risk factors, especially obesity and lipid metabolism disorder [21]. An authoritative review of the literature on the use of statins in patients with abnormal lipid metabolism in both the United States and Japan has revealed a reduction in cancer-related mortality among those who were taking statins. These finding lends further support to the point that dyslipidemia has a detrimental effect on cancer mortality [22, 23]. However, research on the relationship between CMI and cancer was inadequate. To our knowledge, up to now, only one cohort study reported the value of CMI in predicting the aggressiveness of renal cell cancer [24]. Therefore, we performed a large-scale cohort study to investigate the causal relationship between CMI and all-cause, CVD, and cancer mortality among the general population.

In this research, samples from the National Health and Nutrition Examination Survey (NHANES) database were utilized to investigate the causal relation between CMI and mortality from the all-cause, CVD, and cancer within common population respectively. This study may unveil the potential role of CMI in monitoring all-cause-related and cause-specific related mortality rates.

Methods

Study participants

This study utilized data from the NHANES database that was implemented by the NCHS (National Center for Health Statistics) [25]. The NHANES database selects typical samples from the American population through a comprehensive method involving multiple stages, stratification, and probability sampling subgroups, primarily to evaluate the American children and adults health and nutritional status [26]. All the research plans have been approved by NCHS and each participant has submitted an informed consent document [27]. Therefore, this study did not have to bother with ethical problems.

In this cohort study, 101,316 participants were enrolled during the 10 cycles of NHANES 1999–2018. The participants were excluded due to the following criteria: the individuals who were lack of CMI data (n=40,131), absence of mortality follow-up data (n=11,170), pregnant (n=1,410), using lipid-lowering medication (n=7,662), died within 12 months of follow-up (n=266), and missing key covariates (n=402: BMI, n=47; diabetes, n=16; hypertension, n=204; leukocyte, n=69; neutrophil, n=66). After ruling out the above individuals, this study was conducted based on 40,275 participants eventually. The flow chart is exhibited in Fig. 1.

Definitions of exposure and outcome variables

CMI was chosen as the exposure variable. It is a parameter that corporates both obesity markers and lipid metabolism markers. The formula of CMI is [WC (cm)/height (cm)] × [TG (mg/dL)/HDL-C (mg/dL)] [14]. Then, 40,275 participants were stratified into four groups according to the quartile of CMI, including group Q1 (n=10,069), group Q2 (n=10,068), group Q3 (n=10,069), and group Q4 (n=10,069).

The outcome variables were mortality from all-cause, CVD, and cancer respectively. The mortality information is accessible from the NDI (National Death Index) death certificate (www.cdc.gov/nchs/data-linkage/mortality-records public.htm). Thus, the corresponding mortality information of each participant was ascertained by connecting to the NDI until December 31, 2019. The disease-specific mortality was identified through the International Classification of Diseases (ICD)-10 coding system. CVD mortality was characterized by cardiovascular conditions, stroke, and/or high blood pressure-related deaths. CVD mortality was categorized under the codes I00-I09, I11, I13, and I20-I51. Cancer mortality was identified by codes ranging from C00 to C97.

Potential covariates

In this study, we collected data on sociodemographic characteristics, health condition characteristics, anthropometric measurements, and laboratory test results employing computer-assisted personal interviewing. Sociodemographic features contained age (years), gender (male/female), race/ethnicity (Mexican American, non-Hispanic white, non-Hispanic black, other Hispanic, and other races), education level (less than high school, high school or general educational development (GED), and above high school), marital status (married/living with partner, widowed/divorced/separated, and never married) and the ratio of family income to poverty (PIR). Health conditions characteristics covered drinking status (yes/no), smoking behavior (now, former, and never), diabetes (yes, no, borderline), hypertension (yes/no), CVD history (yes/no), and cancer history (yes/no). Specifically, drinking behavior was divided into two categories: those who drink at least 12 times a year and those who do not less than 12 times a year [28]. Smoking status was categorized into three groups: current smokers (people who consumed cigarettes ≥ 1/day), former smokers (people who consumed over 100 cigarettes previously but quit smoking at present), and never smokers (people who consumed less than 100 cigarettes within their whole lifetime) [29]. Histories of hypertension, diabetes, CVD, and cancer were statistically gathered through self-reports of subjects. For anthropometric measurements, the BMI (kg/m^2) was chosen. The body weight was categorized by BMI: normal weight (18.5 $kg/m^2 \leq$ BMI < 25 kg/m^2), overweight (25 $kg/m^2 \leq$ BMI < 30 kg/m^2), and obese (BMI ≥ 30 kg/m^2) [30]. Laboratory tests included total cholesterol (TC, mg/dL), alanine aminotransferase (ALT, U/L), aspartate aminotransferase (AST, U/L), glycosylated hemoglobin (HbA1C, %), serum glucose (mg/dl), leukocyte count (10^9/L) and neutrophil count (10^9/L).

Statistical analysis

Participants were classified into four categories based on CMI quartile ranges: Q1 for those below or equal to the 25th percentile, Q2 for those greater than the 25th percentile and less than the 50th percentile, Q3 for those greater than the 50th percentile and less than the 75th percentile, and Q4 for those above the 75th percentile. In the baseline characteristics table, variables were described according to their type: means and standard error were used to describe normally distributed continuous variables, median (Q1-Q3) were employed to describe continuous variables exhibiting a skewed distribution, and percentages were adopted to describe categorical variables. In order to explore the differences in mortality respectively from all-cause, CVD, and cancer among four CMI subgroups, the Kaplan-Meier survival analysis was applied under an unadjusted model. This study calculated the HR (hazard ratios) and P values under the Log-Rank Test.

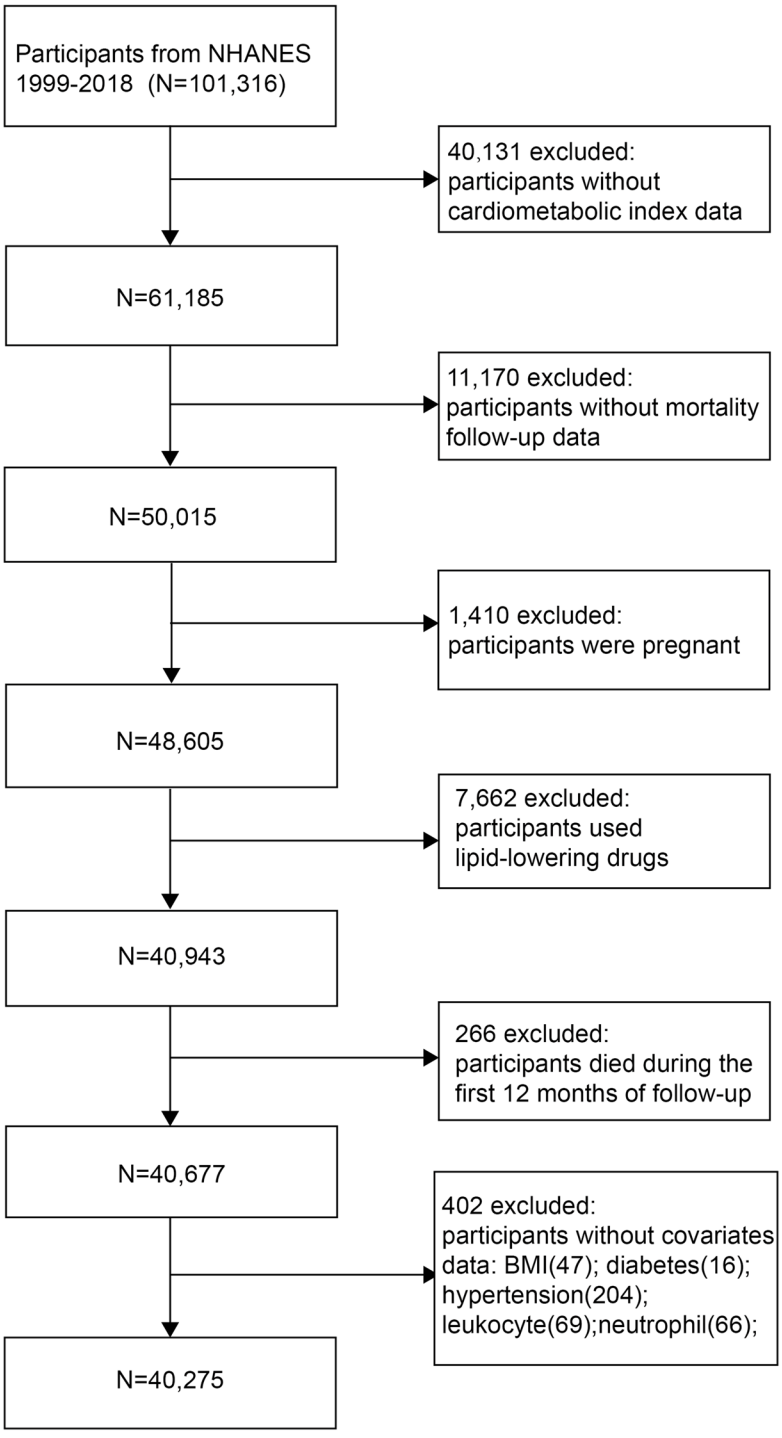

Fig. 1 Flow chart of study sample screening

Following the principle of Strengthening the Reporting of Observational Studies in Epidemiology, three models were built [31]. In model 1 (unadjusted model), no confounding factors were controlled for. In model 2 (minimally adjusted model), adjustments were only made for age, gender, and race/ ethnicity. Finally, in model 3 (fully adjusted model), this study adjusted for age, gender, race/ ethnicity, marital status, PIR, education level, smoking behavior, drinking status, BMI, TC, ALT, AST, HbA1c, serum glucose, leukocyte count, neutrophil count, diabetes, hypertension, and history of CVD and cancer. Subsequently, the Cox regression analysis with single and multiple risk factors was conducted to confirm the causal relation between CMI and mortality outcomes

in three models. The proportionality assumption was evaluated through the application of Schoenfeld residuals, which indicated that this assumption was violated. Consequently, the HRs were regarded as weighted averages of the time-varying HRs throughout the entire duration of follow-up in the study [32]. Besides, the current study investigated the dose-response correlation between CMI and outcome variables through smooth curve fitting analysis under the standard linear model and threshold effect analysis under the two-piecewise linear model [33]. A log-likelihood ratio test was performed to ascertain whether a threshold existed in the two-piecewise linear regression model. A two-step recursive method was used to pinpoint the inflection point further. A linear correlation existed when the *P*-value of the standard linear model was less than 0.05 and a threshold effect existed when the log-likelihood ratio test *P*-value was less than 0.05.

Finally, a subgroup analysis was performed to explore the heterogeneity among subgroups. Subgroups were stratified by socioeconomic and lifestyle characteristics, including age, race/ethnicity, sex, smoking behavior, drinking behavior, BMI, hypertension, and diabetes. The interaction *P*-value was calculated under interaction tests. *P*-value of the interaction was over 0.05, indicating that results of the different strata were significantly reliable. Otherwise, there may exist a special population [34].

All the data analyses were conducted by R software and EmpowerStats (version 4.2). This research integrated ten cycles of NHANES data sets and accounted for stratification and clustering resulting from the complicated sample design, using the MEC sample weights from 1999 to 2018 for analyses. A *P*-value of less than 0.05 from two sides was deemed to indicate statistical significance.

Results

Characteristics of the participants

After a rigorous filtering process, 40,275 participants who met the criteria were retained eventually, representing an estimated total population of 169,329,696 individuals after the application of appropriate weighting. Table 1 was the baseline table and participants were grouped by CMI. In comparison with the Q1 subgroup, the Q4 subgroup contained more relatively aged people, more low PIR people, more male, more Mexican American or Non-Hispanic White, more married/living with partner people or widowed/divorced/separated people, more never drinking people, more people with ≤high school education, more diabetes or at the borderline of diabetes, more hypertension, and had high levels of BMI, TC, ALT, AST, glucose, HbA1c, leukocyte, and neutrophil. All these results had statistical significance (all *P*-values<0.05). In terms of CVD history and cancer history, we did not detect significant difference between subgroups, suggesting that the history of CVD and cancer had much less influence on CMI than previously believed (All *P*-value>0.05). In terms of smoking behavior, although no significant differences were reported among CMI subgroups (*P*-value>0.05), Q4 subgroup showed the tendency to have more current smokers compared to other subgroups. This phenomenon can be attributed to the fact that the impact of smoking behavior on cardiovascular diseases and lipid metabolism varies among different populations and lifestyles [35]. Importantly, the mortality respectively from all-cause, CVD, and cancer all significantly increased in the Q4 subgroup (all *P*-values<0.05). It was worth noting that cancer mortality in Q4 subgroup was slightly lower than that in Q3 subgroup (2.40 vs. 2.42), which may be attributed to the TG paradox [36, 37], suggesting that we should explored the dose-response correlation between CMI and outcome variables. To better demonstrate this phenomenon, the Kaplan–Meier survival analysis was performed under the unadjusted model subsequently (Fig. 2). The results indicated that participants in the Q4 group did have the least follow-up time with statistical significance (all *P*-values <0.05).

Association between CMI and all-cause mortality

As shown in Table 2, the causal relation between CMI and all-cause mortality was complicated under different models. In model 1, an unadjusted Cox regression analysis, the all-cause mortality rose significantly with the increase of continuous CMI (HR=1.03, 95% CI: 1.02, 1.04, *P*-value<0.05) and this causality remained when CMI was categorized into quartiles (*P* for trend<0.05). To be specific, HRs and 95% CIs ranging from Q1 to Q4 were 1.00 (reference), 1.34 (1.20, 1.49), 1.54 (1.40, 1.69), and 1.72 (1.55, 1.92), respectively. In model 2 (minimally adjusted model), the continuous CMI was still statistically significantly positively related to all-cause mortality (HR=1.03, 95% CI: 1.02, 1.04, *P*-value<0.05). And the statistical relevance remained in specific subgroups, namely the Q4 subgroup (HR=1.20, 95% CI: 1.08, 1.34, *P*-value<0.05). In model 3 (fully adjusted model), the association of continuous CMI and CMI subgroups with the all-cause mortality both disappeared as a *P*-value over 0.05 and *P* for trend over 0.05.

To explain above phenomenon, we proposed a dose-response correlation within CMI and all-cause mortality [33]. Therefore, smooth curve fitting was employed. As exhibited in Fig. 3; Table 3, CMI and all-cause mortality were not linearly related under the standard linear model (HR=1.01, 95% CI: 0.98, 1.04, *P* for linear>0.05). Based on this, we then took a threshold effect analysis under a two-piecewise Cox regression model and found an L-type relationship. The Inflection point was 0.98 (*P* for Log-likelihood ratio<0.05). When CMI was less than

Table 1 Baseline characteristics of study participants according to quartile(Q) groups of CMI, weight

Characteristics	Total	Q1	Q2	Q3	Q4	*P*-value
	40,275	**10,069**	**10,068**	**10,069**	**10,069**	
CMI	1.22 (0.68, 2.32)	0.47 (0.36, 0.58)	0.93 (0.80, 1.07)	1.67 (1.43, 1.95)	3.60 (2.82, 5.16)	< 0.0001
Age(years)	43.25 ± 0.17	39.89 ± 0.24	42.81 ± 0.26	44.92 ± 0.21	45.46 ± 0.21	< 0.0001
PIR	2.98 ± 0.03	3.13 ± 0.03	3.01 ± 0.04	2.94 ± 0.03	2.83 ± 0.03	< 0.0001
BMI (kg/m^2)	28.28 ± 0.07	24.01 ± 0.06	27.18 ± 0.08	29.85 ± 0.10	32.16 ± 0.10	< 0.0001
TC (mg/dL)	196.72 ± 0.41	184.24 ± 0.51	192.24 ± 0.63	199.29 ± 0.62	211.39 ± 0.62	< 0.0001
ALT(U/L)	21.00 (16.00, 29.00)	18.00 (14.00, 23.00)	19.00 (15.00, 26.00)	22.00 (17.00, 30.00)	26.00 (19.00, 36.00)	< 0.0001
AST(U/L)	22.00 (19.00, 27.00)	22.00 (19.00, 26.00)	22.00 (19.00, 26.00)	22.00 (19.00, 27.00)	24.00 (20.00, 29.00)	< 0.0001
Glucose (mg/dL)	95.12 ± 0.20	88.73 ± 0.21	91.80 ± 0.22	95.96 ± 0.33	104.16 ± 0.53	< 0.0001
HbA1c (%)	5.46 ± 0.01	5.25 ± 0.01	5.36 ± 0.01	5.51 ± 0.01	5.72 ± 0.02	< 0.0001
Leukocyte, 10^9/L	7.22 ± 0.02	6.46 ± 0.03	7.04 ± 0.03	7.43 ± 0.03	7.98 ± 0.03	< 0.0001
Neutrophil, 10^9/L	4.27 ± 0.02	3.80 ± 0.02	4.16 ± 0.02	4.41 ± 0.02	4.71 ± 0.02	< 0.0001
Gender (%)						< 0.0001
Male	48.75	35.67	45.01	51.84	62.74	
Female	51.25	64.33	54.99	48.16	37.26	
Race/ethnicity (%)						< 0.0001
Mexican American	8.95	5.84	7.92	10.09	12.03	
Other Hispanic	5.96	4.81	5.56	6.82	6.70	
Non-Hispanic White	67.42	66.77	67.92	66.43	68.53	
Non-Hispanic Black	10.85	15.65	12.15	9.69	5.81	
Other Races	6.82	6.93	6.45	6.97	6.93	
Marital status (%)						< 0.0001
Married/Living with Partner	62.73	58.24	60.79	64.23	67.64	
Widowed/Divorced/Separated	16.54	14.94	16.71	17.20	17.28	
Never married	20.73	26.82	22.50	18.57	15.08	
Education level (%)						< 0.0001
Less than high school	5.49	3.10	4.93	6.50	7.39	
High school or GED	34.75	28.59	33.52	36.78	39.93	
Above high school	59.76	68.31	61.55	56.72	52.68	
Drinking status (%)						0.002
Yes	76.13	77.94	75.95	75.87	74.84	
No	23.87	22.06	24.05	24.13	25.16	
Smoking behavior (%)						0.9057
Now	41.39	41.08	41.21	41.60	41.59	
Former	9.00	9.73	9.02	8.68	8.70	
Never	49.61	49.19	49.77	49.72	49.71	
Diabetes (%)						< 0.0001
Yes	8.02	2.68	5.34	8.76	15.42	
No	64.49	78.25	68.77	59.59	51.02	
Borderline	27.49	19.07	25.89	31.65	33.56	
Hypertension (%)						< 0.0001
Yes	22.97	13.33	19.56	26.88	32.34	
No	77.03	86.67	80.44	73.12	67.66	
CVD history (%)						0.9032
Yes	11.73	12.07	11.65	11.72	11.49	
No	88.27	87.93	88.35	88.28	88.51	
Cancer history (%)						0.0845
Yes	7.59	6.87	7.52	8.12	7.85	
No	92.41	93.13	92.48	91.88	92.15	
All-cause mortality (%)	8.32	6.18	8.07	9.16	9.91	< 0.0001
CVD mortality (%)	1.88	1.27	1.85	1.93	2.47	< 0.0001

Table 1 (continued)

Characteristics	Total	Q1	Q2	Q3	Q4	*P*-value
	40,275	**10,069**	**10,068**	**10,069**	**10,069**	
Cancer mortality (%)	2.07	1.57	1.92	2.42	2.40	0.001
Follow-up time(months)	123.11 ± 1.02	126.16 ± 1.53	123.75 ± 1.36	122.69 ± 1.29	119.78 ± 1.48	0.0095

Abbreviations: Q: quartile; CMI: cardiometabolic index; PIR: ratio of family income to poverty; BMI: body mass index; ALT: alanine aminotransferase; AST: aspartate aminotransferase; HbA1c: glycated hemoglobin; TC: total cholesterol; CVD: cardiovascular diseases

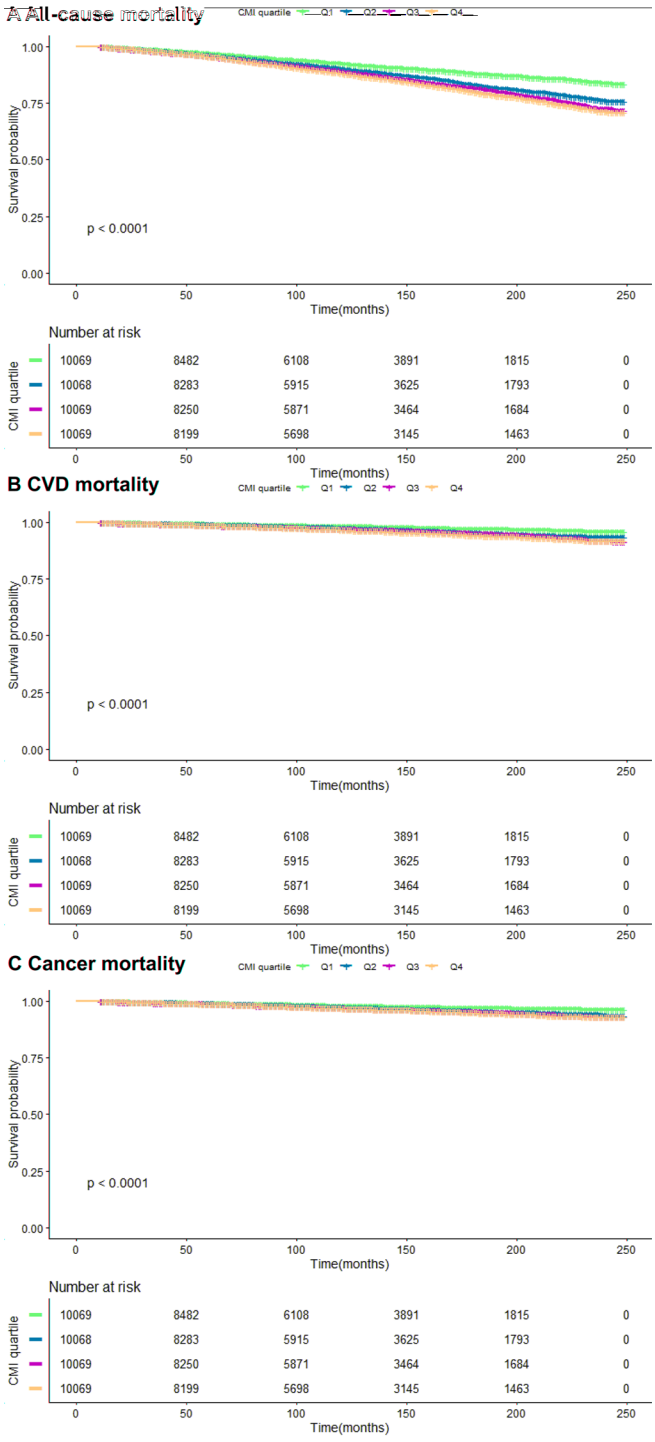

Fig. 2 Kaplan–Meier survival analysis curves for all-cause(**A**), CVD(**B**), and cancer mortality(**C**)

Table 2 HR (95% CI) for outcomes across CMI quartiles under three models, weight

Outcomes	Model 1 [HR (95% CI)] *P*-value	Model 2 [HR (95% CI)] *P*-value	Model 3 [HR (95% CI)] *P*-value
All-cause mortality			
Continuous CMI	1.03(1.02,1.04) < 0.0001	1.03(1.02,1.04) < 0.0001	1.01(0.97,1.05) 0.6510
Q1	1	1	1
Q2	1.34(1.20,1.49) < 0.0001	0.99(0.89,1.10) 0.8580	0.85(0.66,1.09) 0.2054
Q3	1.54(1.40,1.69) < 0.0001	0.99(0.90,1.10) 0.9167	0.82(0.65,1.04) 0.1025
Q4	1.72(1.55,1.92) < 0.0001	1.20(1.08,1.34) 0.0008	0.89(0.67,1.17) 0.4079
P for trend	< 0.0001	0.0007	0.5270
CVD Mortality			
Continuous CMI	1.04(1.03,1.05) < 0.0001	1.05(1.04,1.07) < 0.0001	0.98(0.92,1.04) 0.4450
Q1	1	1	1
Q2	1.49(1.17,1.90) 0.0011	1.05(0.80,1.36) 0.7282	0.94(0.54,1.65) 0.8328
Q3	1.58(1.25,1.99) 0.0001	0.98(0.76,1.23) 0.8538	0.86(0.53,1.42) 0.5644
Q4	2.10(1.69,2.60) < 0.0001	1.48(1.18,1.85) 0.0006	0.97(0.57,1.64) 0.9148
P for trend	< 0.0001	0.0005	0.9514
Cancer Mortality			
Continuous CMI	1.03(1.02,1.05) < 0.0001	1.03(1.00,1.06) 0.0205	1.05(1.01,1.10) 0.0154
Q1	1	1	1
Q2	1.26(0.96,1.64) 0.0994	0.95(0.73,1.24) 0.7139	0.79(0.50,1.26) 0.3233
Q3	1.59(1.23,2.06) 0.0004	1.05(0.82,1.34) 0.7135	0.93(0.57,1.50) 0.7550
Q4	1.63(1.28,2.09) < 0.0001	1.11(0.87,1.42) 0.3990	0.98(0.61,1.57) 0.9223
P for trend	< 0.0001	0.2577	0.7853

Abbreviations: HR, hazard ratio; CI, confidence interval

Model 1: no adjustments

Model 2: adjusted for age, gender, and race/ ethnicity

Model 3: adjusted for age, gender, race/ethnicity, marital status, PIR, education level, smoking behavior, drinking status, BMI, TC, ALT, AST, HbA1c, serum glucose, leukocyte count, neutrophil count, diabetes, hypertension, and history of CVD and cancer

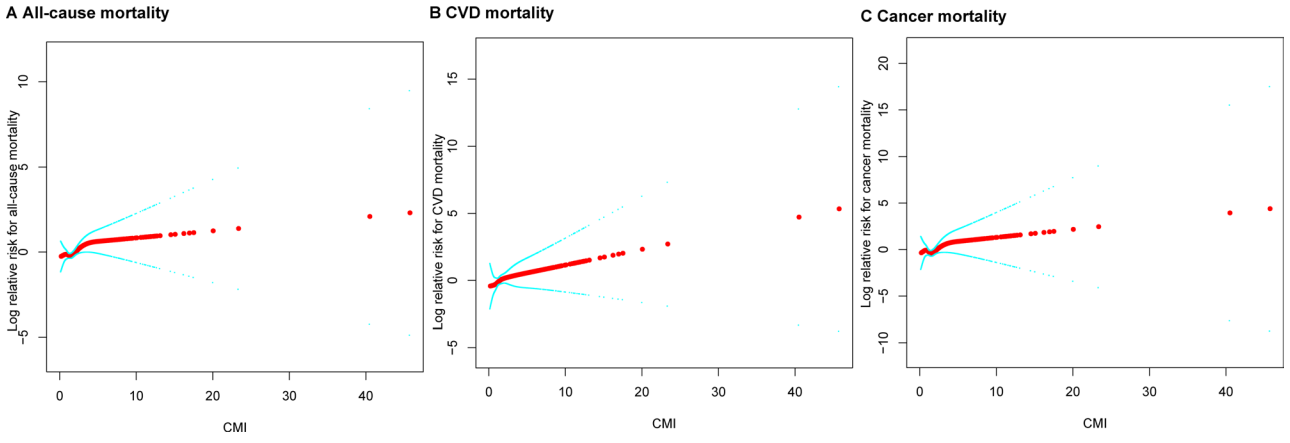

Fig. 3 Association between CMI and mortality outcomes. The red and blue dotted lines represent the estimated values and their corresponding 95% CIs. Adjusted for the variables listed in model 3

0.98, the negative relationship between CMI and all-cause mortality was statistically significant (HR = 0.59, 95% CI: 0.43, 0.82, *P*-value<0.05). However, the relationship lost significance when CMI was over 0.98 (HR = 1.02, 95% CI: 0.99, 1.05, *P*-value>0.05) (Fig. 3; Table 3). This L-type association suggested that appropriate CMI was also essential for good health.

Association between CMI and CVD mortality

In this study, 1113 individuals died from CVD among 40,275 participants. We investigated the correlation between CMI and CVD mortality under three models. The construction criteria for all models were the same as described in the Methods section. Under model 1 (unadjusted model), an increase of one unit CMI contributed to 4% higher hazard of CVD mortality risk (HR = 1.04, 95% CI: 1.03, 1.05, *P*-value<0.05). In model 2 (minimally

Table 3 Threshold effect analysis. Adjusted for the variables listed in model 3

	All-cause mortality	CVD mortality	Cancer mortality
Fitting by the standard linear model	1.01 (0.98, 1.04) 0.6381	1.01 (0.96, 1.07) 0.7228	1.04 (1.00, 1.08) 0.0286
Fitting by the two-piece-wise linear model			
Inflection point	0.98	0.48	1.39
< Inflection point	0.59 (0.43, 0.82) 0.0016	2.38 (0.06, 98.98) 0.6482	0.84 (0.59, 1.19) 0.3248
> Inflection point	1.02 (0.99, 1.05) 0.1957	1.01 (0.95, 1.07) 0.7558	1.05 (1.01, 1.08) 0.0084
P for Log-likelihood ratio	0.002	0.644	0.229

adjusted model), CMI was found in a positive relation with CVD-related mortality (HR = 1.05, 95% CI: 1.04, 1.07, *P*-value < 0.05), and the statistical significance still existed in the Q4 subgroup (HR = 1.48, 95% CI: 1.18, 1.85, *P*-value<0.05). Like the all-cause mortality, under model 3 (fully adjusted model), the significant correlation between CMI and CVD mortality was lost regardless of the continuous CMI (HR = 0.98, 95% CI: 0.92, 1.04, *P*-value>0.05) or CMI subgroups (*P* for trend>0.05) (Table 2).

The smooth curve fitting suggested a significant nonlinear association of CMI and CVD mortality under the standard linear model (HR = 1.01, 95% CI: 0.96, 1.07, *P*-value>0.05). However, the Inflection point 0.48 failed to achieve statistical significance (*P* for Log-likelihood ratio>0.05). (Fig. 3; Table 3).

Association between CMI and cancer mortality

In this study, 1,066 participants died from cancer. In model 1 (unadjusted model), the risk of cancer mortality rose by 3% per 1 unit CMI upregulation (HR = 1.03, 95% CI: 1.02, 1.05, P-value<0.05). After controlling for confounding factors, we observed an interesting phenomenon in model 2 (minimally adjusted model) and model 3 (fully adjusted model) that the statistical significance between CMI and cancer mortality depended on the type of CMI. To be specific, in model 2, the cancer mortality was statistically significant with continuous CMI (HR = 1.03, 95% CI: 1.00, 1.06, *P*-value<0.05) while lost significance with categorized CMI (*P* for trend>0.05). In model 3, positive causal correlation between continuous CMI and cancer mortality with statical significance (HR = 1.05, 95% CI: 1.01, 1.10, *P*-value<0.05) whereas the significance disappeared in categorized CMI (*P* for trend>0.05). Generally speaking, despite the statistical significance of CMI subgroups between cancer mortality gradually faded as confounding factors were adjusted from model 1 to model 3, the statistical significance between continuous CMI still remained. This finding was encouraging, indicating that CMI has the potential to be a highly effective indicator for cancer management in the future.

Aimed at having a deeper insight into the correlation between CMI and cancer mortality, we performed smooth curve fitting analysis and threshold effect analysis. A statistically significant linear association between CMI and cancer mortality was observed under the standard linear model (HR = 1.04, 95% CI: 1.00, 1.08, *P*-value<0.05). Correspondingly, the threshold effect analysis did not report a statistically significant infection point (*P* for Log-likelihood ratio>0.05) (Fig. 3; Table 3).

Sensitivity analysis

To further validate the results, this study explored the nonlinear relationship between CMI and all-cause mortality after removing extreme values on the right side of CMI. The results were found to be consistent with those of the main analyses. For reference, the results of the L-shaped relationship between CMI and all-cause mortality were presented in Supplementary Table 1.

Subgroup analysis

As many studies have already verified that differences in population characteristics played an important role in the mortality risk from all-cause, CVD, and cancer [38–40], this study stratified participants by sex, age, race/ethnicity, BMI, smoking behavior, drinking behavior, hypertension, and diabetes respectively in the subgroup analysis. In different strata, the relation between CMI and all three outcome variables was robust (all *P*-values>0.05). Therefore, the above factors were not interactive factors between the CMI and the mortality from all-cause, CVD, and cancer in our study (Fig. 4).

Discussion

In this large-scale cohort study, CMI, a novel indicator, was applied to investigate its association with all-cause mortality, CVD mortality, and cancer mortality among general population. First, in univariate Cox regression analysis, we found that CMI was significantly positively related to mortality from all-cause, CVD, and cancer. The Kaplan–Meier survival analysis of CMI subgroups showed consistent results. Second, a multivariate Cox regression analysis was performed after adjusting covariates. In model 2, mortality of all-cause and CVD remained a significant association in certain CMI subgroups, while the cancer mortality was not. In Model 3, the statistical significance between the CMI subgroup and outcome variables all disappeared. Third, the smooth curve fitting and threshold effect analysis were employed to study the dose-response correlation. An L-shaped type nonlinear relationship was observed in all-cause mortality and a nonlinear relationship was reported in CVD mortality, whereas the relationship between CMI

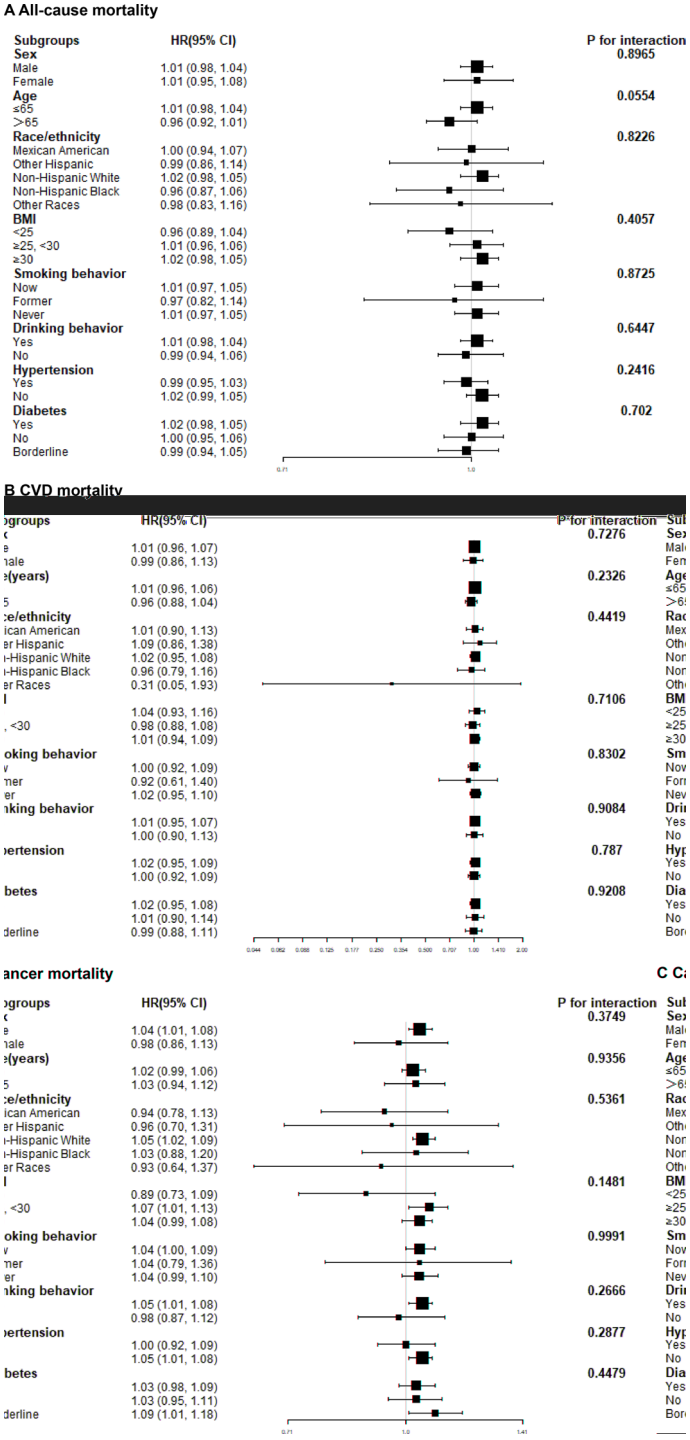

Fig. 4 Forest plots of Subgroup analyses of AIP and mortality outcomes. Adjusted for the variables listed in model 3 except for the variable used for stratification

and cancer mortality was linear. Fourth, no differences were observed in subgroups divided by certain covariates. Together, these findings indicated that CMI has the potential to become an effective indicator for monitoring mortality from all-cause, CVD, and cancer. Besides, certain covariates deserved our attention as well. In a recent study that excluded participants under the age of 20, the individuals who never drank alcohol or received more education had the highest CMI level [41]. However, our findings indicated contrary results. The underlying reason may be ascribed to the inclusion of younger individuals in our study, who may have been in the early stages of

alcohol experimentation and had not yet completed their education. As shown in Table 1, in conventional risk factors, such as BMI, TC, ALT, AST, glucose, HbA1c, diabetes or borderline of diabetes, and hypertension, was more likely to occur in the Q4 subgroup. Our research showed leukocyte and neutrophil levels were elevated in the Q4 subgroup. The underlying mechanism can be attributed to a non-specific inflammatory response. Non-specific inflammation has been deemed as a potential mechanism for CVD caused by obesity nowadays [42].

Subcutaneous adipose tissue (SAT) and visceral AT (VAT) are two distinct types of AT, determined by their anatomical location [43]. Compared to SAT, VAT is more likely to cause inflammatory reactions in obesity [44]. The term "residual cardiovascular risk" denotes the persisting danger faced by individuals diagnosed with CVD who may still experience further cardiac complications despite the implementation of rigorous secondary prevention strategies [45]. And VAT is strongly associated with an elevated residual cardiovascular risk. As previous research has indicated, the pro-inflammatory state created by VAT plays an important role in the development of pathophysiological processes such as hypertension, endothelial dysfunction, and increased vascular stiffness, thereby underscoring the detrimental impact of VAT accumulation on cardiovascular health [46]. Moreover, VAT has a better mortality prediction efficiency than SAT [47]. Concerning the pathological link, prior research has suggested that the accumulation of VAT is a significant contributor to chronic low-grade inflammation, which has notable implications for all-cause mortality and the likelihood of experiencing a myocardial infarction [48]. A growing number of studies indicated dysfunctional adipose tissue can release inflammatory mediators and then recruit inflammatory cells including leukocytes and neutrophils, ultimately leading to vascular endothelial injury in patients with visceral obesity [49]. What's more, the lipid may be toxic to inflammation cells. For example, macrophages phagocytose lipids and transform into foam cells, which can induce vascular inflammation [50]. Apart from inflammation cells, various recent researches focused on the molecular pathways in the relationship between lipid metabolism and inflammation. Liver X receptor and peroxisome proliferator-activated receptor are both important lipid metabolism-related transcriptional regulators and can regulate inflammation as well [51]. Huang et al. reported that Dual Specificity Phosphatase 12 suppressed inflammatory response and fatty degeneration via blocking apoptosis Signal-Regulating Kinase 1 Pathways [52]. Furthermore, Fibrinogen-like protein 2 disordered the lipid metabolism and released inflammation NOD-, LRR- and pyrin domain-containing protein 3 inflammasomes via nuclear factor kappa-B pathway and p38 mitogen-activated protein kinase pathway [53]. Lipid metabolism-related inflammation also affects the occurrence and development of cancer [54]. For example, monoacylglycerol lipase, a key enzyme in lipid metabolism, has become a therapeutic target in inflammatory diseases and cancer [55]. A study conducted by Afonso et al. reported Receptor-interacting serine/threonine-protein kinase 3 functioned as a lipid metabolism regulator promoting inflammatory responses and cancer development [56]. Therefore, inflammation and lipid biomarkers both deserve our attention in CVD and cancer management.

It is well acknowledged that obesity and abnormal lipid metabolism are both key risk factors for mortality from all-cause, CVD, and cancer [21, 57–59]. As previous research demonstrated TG/HDL cholesterol ratio is an independent prognostic factor for the prediction of overall survival among triple-negative breast cancer patients [60]. However, comprehensive indicators like CMI have not been widely utilized up to now. Consequently, we employed CMI as the exposure variable and ruled out potential confounding factors to investigate the correlation between CMI and mortality from all-cause, CVD, and cancer under three models. As we expected, the significance of the relationship gradually diminished as more confounding factors were adjusted. So, these confounding factors may act as mediating variables between CMI and outcome variables [61]. Generally speaking, on one hand, as the pathophysiological procedure of CVD and cancer and their related death are multistage and complicated, these covariates are influence factors. On the other hand, CMI as a comprehensive indicator is impacted by these covariates as well [62]. To be specific, we illustrated the mediation effects of additional covariates (covariates in Model 3 that are not in Model 2). First, Demographic factors including marital status, PIR, and education level, influence the CMI and mortality of CVD, cancer and all-cause. The reasons lie in that people with less education and lower income are more likely to indulge in high-fat diet while have poor health consciousness, which leads to their abnormal CMI level, as well as higher incidence and mortality rates for CVD and cancer. And a cross-sectional study has proved this [63]. Additionally, it has been widely acknowledged that sex hormones affect lipid metabolism, cardiovascular diseases, and cancers [64, 65]. Since marital status is one of the important factors affecting sex hormones, marital status also has a mediating effect on CMI and mortality of CVD, cancer, and all-cause. Second, living habits like smoking behavior and drinking status which are measured with indicators such as BMI, TC, ALT, AST, HbA1c, and serum glucose have a mediate effect between lipid metabolism and mortality of CVD, cancer, and all-cause. For example, a cohort study performed on middle-aged males with low HDL suggested that alcohol consumption was positively related

both to lipid triglycerides and progression and death of hypertension, one typical CVD [66]. Third, numerous studies have indicated that inflammation indicators especially immune cells served as a link between CMI and CVD and cancer [20, 67]. Therefore, we adjusted leukocyte and neutrophil, two typical immune cells, in model3. Fourth, Endocrine and metabolic diseases not only affect lipid metabolism indicators like CMI but also exacerbate the progression and mortality of CVD and cancer, forming a positive feedback loop [68]. Thus, we make adjustment for diabetes and hypertension. Last, a completely adjusted model included history of CVD and cancer. As previously mentioned, in the CVD-cancer-lipid metabolism network [68], previous CVD and cancer profoundly influence current CMI levels. At the same time, patients with a history of CVD or cancer are prone to recurrence [69]. In summary, considering covariates including marital status, PIR, education level, smoking behavior, drinking status, BMI, TC, ALT, AST, HbA1c, serum glucose, leukocyte count, neutrophil count, diabetes, hypertension, and history of CVD and cancer play a mediate role between exposure (CMI) and outcomes (mortality of CVD, cancer, and all-cause), we adjusted them in model3 and found significance faded in the meantime.

In order to study the dose-response relationship, we combined smooth curve fitting analysis with threshold effect analysis. In the L-shaped relationship between CMI and all-cause mortality, the CMI was significantly negatively related to all-cause mortality risk when CMI was<0.98 and the significance disappeared when CMI was>0.98. This puzzling phenomenon could be explained by the "TG paradox" concept that the TG level was negatively correlated with the death risk under certain conditions [36, 37]. The reason may lie in that TG is positively correlated with BMI [70], therefore people with extremely low TG often suffer from malnutrition and are more prone to death [71]. As CMI is calculated by the formula [WC (cm)/height (cm)] × [TG (mg/dL)/HDL-C (mg/dL)], the lower the TG level, the lower the CMI, and at the same time, the all-cause mortality risk increased within a certain range. In the nonlinear relationship between CMI and CVD mortality, we failed to find a precise Inflection point. On the one hand, there may be some inevitable errors in the measurement and calculation of CMI; on the other hand, as CVD is a complex disease involving many risk factors, it is difficult to find a single and clear significant threshold point [72]. Murat et al. reported that the significant increase in CMI may become a novel mechanism for the aggressiveness of renal cell cancer [24]. In the linear relationship between CMI and cancer mortality, we confirmed a significant positive relationship. In order to elucidate the underlying mechanism, we explained the molecular, pathway, and (subcellular) organelle-level processes. In molecular, peroxisome proliferator-activated receptor-gamma was the most representative molecular as it was an important shared molecular in lipid metabolism, inflammation, and cancer [73, 74]. In recent years, Wang et al. demonstrated that Arf1, a key lipid metabolism regulator, can enrich cancer stem cells and thereby suppress anti-tumor immunity as well [75]. From the perspective of signal pathways, the Akt-Sterol Regulatory Element-Binding Protein and transforming growth factor-βpathways participated in the lipid metabolism related to cancer [76, 77]. In (subcellular) organelles, lysosomes and peroxisomes were reported [78, 79]. On top of that, ferroptosis emerged as a novel mechanism between lipid metabolism and cancer [80]. In addition to the aforementioned mechanisms that may be involved, further fundamental research is needed to ascertain the intrinsic linkage between CMI and cancer mortality. In summary, CMI was a potential clinical indicator in predicting mortality of all-cause, CVD, and cancer.

In subgroup analysis, we took sex, age, race/ethnicity, BMI, smoking behavior, drinking behavior, hypertension, and diabetes as stratification factors [81–87]. Our findings indicated that despite the differences among different subgroups, they were not statistically significant. Nevertheless, some research findings differed from ours. For example, a systematic review emphasized that the differences in smoking, hypertension, diabetes, countries, and regions played an important role in CVD mortality [88]. We thought the limited selection of our participants, such as all being Americans, and the exclusion of pregnant women, may explain our results. Studies have confirmed that the physiological environment of pregnancy can trigger or exacerbate CVD, and CVD can in turn make pregnancy more dangerous [89]. A quarter of the link between preterm delivery and subsequent CVD hospitalization was reported by Nathalie et al. in a longitudinal cohort study [90]. Hence, we had better take pregnant and lactating women into account in future clinical CVD trials [91]. On top of the participant selection, outcome variables deserve our consideration as well, especially in cancer mortality. The same stratification factor can have different impacts on different cancers. For instance, prostate cancer can only occur in males while ovarian cancer can only occur in females. Due to the limitation of the database, we could just explore cancer mortality in general terms, so the differences in the stratification factor among specific tumor types would overlap. Thus, a cohort study with comprehensive participants and more detailed outcome variables is indispensable to further confirm our findings.

Strengths and limitations

Our study had several advantages. First, we utilized a nationwide representative sample to investigate the

causal relation between CMI and the mortality risk from all-cause, CVD, and cancer respectively among the general population. By employing a substantial sample of individuals from ten survey cycles spanning 1999 to 2018, the study enhanced statistical power and validated the reliability. Second, the NHANES database itself is a reliable data source because it collects data in a standard and unified manner. Third, covariates adjustment, smooth curve fitting, threshold effect analysis, and subgroup analysis were carried out in our study, making the results more convincing. Our study also had some weaknesses as follows. Firstly, due to the limitations of the study design, we were unable to rule out all confounding factors. Secondly, this study utilized self-reported retrospective data on smoking and drinking behaviors, thus recall bias and social desirability bias were inevitable. Thirdly, the study participants were all Americans, making it difficult to extend the results to other populations. Finally, it should be noted that the HRs presented in this study represented the mean values observed over the entire follow-up period, rather than being limited to specific time frames. In cases where nonproportional hazards are present or where there are notable differences in period-specific HRs (for example, in the absence of an immediate effect), the null HR may not accurately indicate predictive significance [92]. Furthermore, the uncertainty regarding the relationship between covariates and time precluded the application of a method that could address nonproportional hazards in the analysis for estimating period-specific HRs in this study. Regardless of these limitations, our findings still have clinical importance because we shed light on the relationship between CMI and all-cause mortality, CVD mortality, and cancer mortality.

Conclusion

Our study findings indicated that the CMI is a highly valuable clinical tool for the prediction of all-cause mortality, CVD mortality, and cancer mortality. To validate these findings, a multicenter, prospective epidemiological study in diverse populations is necessary.

Abbreviations

CMI	Cardiometabolic index
CVD	Cardiovascular disease
BMI	Body mass index
WC	Waist circumference
TG/HDL-C	Triglyceride/High-Density Lipoprotein Cholesterol
NHANES	National Health and Nutrition Examination Survey
NCHS	National Center for Health Statistics
NDI	National Death Index
ICD	International Classification of Diseases
GED	General educational development
PIR	Ratio of family income to poverty
TC	Total cholesterol
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
HbA1C	Glycosylated hemoglobin
Q	Quartile
HR	Hazard ratios
CI	Confidence interval
SAT	Subcutaneous adipose tissue
VAT	Visceral adipose tissue

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-024-02408-2.

Supplementary Material 1

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Author contributions

M.L., C.W., and R.L. contributed equally to this paper. M.L., C.W., and R.L.: Methodology implementation, software Formal analysis, Writing original draft. Y.W.: Validation, Writing original draft, Writing-review, and editing. B. W.: Methodology guidance, Project administration, Validation, Writing-review, and editing. All authors approved the manuscript and agreed to publish it.

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Data availability

The survey data are publicly available on the website: https://wwwn.cdc.gov/Nchs/Nhanes/.

Declarations

Ethics approval and consent to participate

This study used publicly available summary data and ethics approval was not necessary.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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