DOI: 10.26599/FSHW.2026.9251349

Contents lists available at SciOpen

Food Science and Human Wellness

journal homepage: https://www.sciopen.com/journal/2097-0765

China Food Publishing Co.

Analysis of data from the NHANES 1999-2018 and Mendelian randomization studies reveals the relationship between composite dietary antioxidant index and cardiovascular-kidney-metabolic syndrome

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ABSTRACT: Background and purpose: Cardiovascular-kidney-metabolic (CKM) syndrome emphasized the key role of abnormal metabolism in the pathological processes of the comorbidity of cardiovascular and renal diseases, which was suggested to be influenced by different dietary intake patterns. The composite dietary antioxidant index (CDAI) was often used to assess the level of dietary antioxidant intakes. However, the exact relationship between CDAI and the risk of CKM is still elusive. The purpose of our study was to provide insight into the association between the CDAI and the CKM syndrome, taking into account multiple covariates that may influence this relationship, based on data from the National Health and Nutrition Examination Survey (NHANES). **Methods:** Information was extracted from NHANES data involving 24,578 participants recruited between 1999 and 2018. The relationship between CDAI levels and CKM syndrome was assessed using logistic regression models, restricted cubic spline (RCS) analysis, mediation analysis, interaction analysis, and Kaplan-Meier (KM) curves analysis. Subsequently, two-sample Mendelian randomization (MR) was employed to explore the associations of dietary antioxidant levels with CKM syndrome. **Results:** There were 24,578 participants in the study, 5,964 of whom had advanced CKM syndrome (24.27%). CDAI and advanced CKM syndrome were significantly negatively associated, even after adjusting for a series of potential variables (Tertile 2: OR = 0.81, 95% CI: 0.74–0.89, $P < 0.001$; Tertile 3: OR = 0.74, 95% CI: 0.67–0.82, $P < 0.001$). According to RCS regression analysis, advanced CKM syndrome had a nonlinear relationship with CDAI and its other components (p for nonlinear < 0.05), except for selenium (p for nonlinear = 0.178). No significant interaction between CDAI and CKM syndrome was observed in most subgroups, except for age, where the interaction was significant ($P < 0.05$), indicating that the association may vary with age. Specifically, age modified this association, with the inverse association being weaker in the oldest age group (CDAI × age continuous: OR = 1.13, $P < 0.001$; CDAI × oldest age group: OR = 1.18, P = 0.017). Mediation analysis showed that the atherogenic index of plasma (AIP) statistically accounted for 8.32% of the observed association between CDAI and advanced CKM syndrome, indicating a potential mediating role. Mendelian randomization analysis showed that the suggestive associations of vitamin A with atrial fibrillation and vitamin E with coronary artery disease are

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Received 19 October 2025
Received in revised from 8 April 2026
Accepted 23 June 2026

exploratory nominal signals. **Conclusion:** Our analysis showed that an association did exist between antioxidant diets (based on CDAI) and the risk of CKM syndrome. However, prospective cohort studies or randomized controlled trials are still needed to further validate the antioxidant diet's potential role in CKM prevention.

Keywords: Composite dietary antioxidant index; Cardiovascular-kidney-metabolic syndrome; National Health and Nutrition Examination Survey; Mendelian randomization.

1. Introduction

Cardiovascular-Kidney-Metabolic (CKM) Syndrome is defined as a systemic disease that recognizes obesity, diabetes, cardiovascular disease, and chronic kidney disease as an interacting spectrum of diseases [1]. CKM syndrome is increasingly becoming a major challenge to global public health, and the health and economic burden on individual countries is growing.

Disability-adjusted life years (DALYs) attributable to CKM syndrome–related diseases showed a general upward trend from 1990 to 2021. In addition, age-standardized DALY rates for stroke, peripheral arterial disease, and ischemic heart disease decreased, while DALY rates for diabetes and high BMI trended upward [2-3].

The pathophysiologic mechanism of CKM syndrome involves a multifactorial and complex process. These include: insulin resistance, abnormal activation of the RAAS system, chronic inflammatory response, and endothelial dysfunction. These mechanisms promote each other and form a vicious circle of disease progression. CKD was confirmed to be a pro-inflammatory state, and elevated systemic biomarkers of inflammation were shown to be strongly associated with poor prognosis of these vulnerable patients [4-5]. Consequently, whether dietary antioxidants are associated with CKM syndrome warrants further investigation.

An increasing number of studies have focused on the potential health benefits of antioxidant dietary patterns. Several studies have reported that adopting dietary patterns rich in naturally occurring antioxidants, such as the Mediterranean diet and the DASH (Dietary Approaches to Stop Hypertension) diet, significantly reduces the risk of developing diseases associated with CKM syndrome [6-8]. These dietary patterns are characterized by the inclusion of large amounts of fruits, vegetables, nuts, etc. The Composite Dietary Antioxidant Index (CDAI) covers a wide range of vitamins, minerals, and phytochemicals such as vitamin A, vitamin C, vitamin E, zinc, selenium, and carotenoids [9-10]. CDAI was shown to be negatively associated with hyperlipidemia in the US adult population (OR = 0.98, 95%CI: 0.96–0.99, $P < 0.01$) [11], which suggested that dietary interventions might be beneficial in reducing the incidence of hyperlipidemia. As an emerging lipid metabolism biomarker, AIP is calculated as the logarithmic ratio of triglycerides TG to high-density lipoprotein cholesterol HDL, which has been implicated in playing a significant role in coronary heart disease, hypertension, diabetes, stroke, and metabolic syndrome [12]. Therefore, we further investigated whether AIP mediates the potential relationship between CDAI and CKM syndrome.

The exact nature of the association between CDAI and CKM syndrome has not yet been fully evaluated and confirmed. We assessed the correlation between CDAI and CKM syndrome risk and its various components based on an extensive dataset from the National Health and Nutrition Examination Survey

(NHANES) from 1999 to 2018 to provide more precise targets for future dietary recommendations and lifestyle interventions.

2. Methods

2.1 Study design and population

To explore the nutritional status of individuals and its association with health, researchers conducted a detailed analysis of data from the National Health and Nutrition Examination Survey (NHANES) program (1999-2018). NHANES is a nationally representative survey of adults and children living in the U.S. The study collects a wide range of health- and nutrition-related data to gain insights into Americans' patterns of nutritional intake, health status, and the complex links between them [13-14].

The protocol of the NHANES study strictly adhered to the ethical principles set out in the Declaration of Helsinki, ensuring that all research activities met the highest ethical standards. During the analysis process, the researchers excluded a number of participants based on a number of criteria to ensure the accuracy and reliability of the study results. Exclusion criteria included: (1) 60,049 participants who were younger than 30 or older than 79 years of age (because the American Heart Association (AHA) predicted cardiovascular disease event risk equation, which is used to define CKM staging, is only applicable to individuals aged 30–79 years), (2) 7,254 individuals who lacked sufficient information on CKM syndrome, (3) 9,435 individuals with missing covariate and CDAI data. Using the above exclusion criteria, the final analytical sample included 24,578 participants (Figure 1).

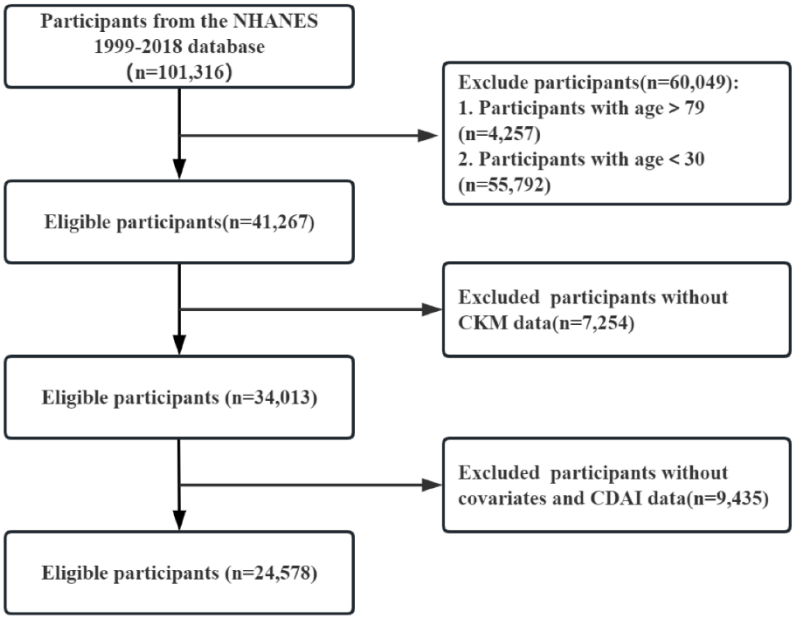


Figure 1. Screening flow of study participants.

2.2 Estimation of composite dietary antioxidant index

The CDAI used 24-hour dietary recall data from the NHANES database to quantify and standardize participants' daily intake of six important antioxidant nutrients. For the calculation of CDAI, if a participant completed two dietary recall interviews, the CDAI_MEAN was used as the CDAI result value; if only one recall was completed, the CDAI value from that single recall was used as the final result. According to the

equal-weight Z-score standardization method used by Vahid, we calculated the standardized Z-score for each antioxidant nutrient (vitamins A, C, E, as well as selenium, zinc, and carotenoids) based on the individual's intake relative to the study population [15]. For participants with repeated measurements, the CDAI was calculated based on their initial measurement data to ensure consistency and avoid potential bias from repeated assessments. The specific formula is as follows:

$$CDAI = \sum_{i=1}^{n=6} \frac{Individual\ \ Intake\ (i) - Mean}{SE}$$

2.3 Definition of cardiovascular-kidney-metabolic syndrome

We followed the standard definitions provided in the American Heart Association (AHA) Scientific Statement for staging CKM syndrome, with appropriate adjustments for type and availability of NHANES data [1]. The stages of CKM syndrome are delineated below: Stage 0: Individuals in this stage do not have any CKM risk factors. Stage 1: Subjects who are overweight/obese, abdominally obese, or prediabetic. Stage 2: Participants in this stage have some metabolic risk factors (elevated fasting serum triglyceride levels, hypertension, diabetes mellitus, etc.) or are at moderate-to-high risk for chronic kidney disease (staged classification of chronic kidney disease based on urinary albumin/creatinine ratio [16]). Stage 3: In this stage, participants have a very high risk of chronic kidney disease or are expected to have a high risk of cardiovascular disease in the next 10 years (10-year cardiovascular disease risk of 20% or more, which is estimated according to the PREVENT program [17]). Stage 4: Participants in this stage self-report that they already have cardiovascular disease. For the purpose of the study, participants were also categorized as having advanced (stage 3 or 4) or non-advanced (stage 0, 1, or 2) CKM. The specific criteria for each stage are detailed in Table S1 in the Supplementary Material. This staging system helps to describe the spectrum of CKM syndrome and may guide future research on prevention and treatment strategies.

2.4 Mendelian randomization analysis

Dietary antioxidant variables associated with CKM syndrome outcomes were extracted from GWAS databases (Table S2). For genetic tool selection, we identified Single Nucleotide Polymorphisms (SNPs) strongly associated with exposure ($P < 5 \times 10^{-6}$). For the MR analysis, SNPs associated with each exposure at $P < 5\times10^{-6}$ were selected as instrumental variables because only a limited number of genome-wide significant variants were available for several vitamin-related exposures. Instrument strength was evaluated using F-statistics. For each SNP, the F-statistic was calculated as β^2/SE^2, and instruments with F-statistics below 10 were considered potentially weak. We eliminated linkage disequilibrium between SNPs ($r^2 < 0.001$) and set the gene region size to 10,000 kb [18]. CDAI comprises dietary antioxidants, including vitamin A, vitamin C, vitamin E, selenium, and zinc. Since carotenoids primarily circulate in the human body as carotenoid forms, we utilized GWAS data for circulating carotenoids as a substitute [19]. CKM, as the outcome variable, represents a systemic disease. Relevant conditions were selected based on their clinical significance and association [20], including atrial fibrillation, coronary artery disease, chronic kidney disease, heart failure, ischemic stroke, myocardial infarction, and type 2 diabetes. To account for multiple testing

across 6 exposures and 7 outcomes, we applied a Bonferroni-corrected significance threshold of 0.05/42 = 1.19×10^{-3}. Associations with $P < 0.05$ but not meeting this corrected threshold were interpreted as nominal or exploratory findings.

2.5 Assessment of Covariates

A range of covariates related to demographic characteristics and lifestyle habits were included in our study, including sex, race, age, educational attainment, household poverty-to-income ratio (PIR, categorized as ≤3.0 and >3.0, which was derived by calculating the ratio of household income to the federal poverty line for the corresponding year) [21], smoking habits (categorized as nonsmokers and smokers), and drinking habits (categorized as nondrinkers, i.e., those who consume fewer than 12 drinks per year, and those who consume alcohol) with the aim of controlling for these potential confounders to increase the study's accuracy and validity of the results.

2.6 Statistical Analysis

Given that NHANES is a multi-stage, probability sampling design survey, the complexity of the survey design was addressed using strata, primary sampling units, and sample weights [22].

Participants were categorized into two different groups based on the presence or absence of advanced CKM syndrome. In the baseline analysis, for continuous variables, mean ± standard deviation (SD) was used to describe the data. For comparisons between the two groups of continuous variables, the weighted t-test was used. For categorical variables, data were expressed as frequencies or percentages, and comparisons were analyzed using the chi-square (Chi-square) test.

Both univariate and multivariate logistic regression analyses were used to assess the association between CDAI and the presence of CKM syndrome. Three different statistical models were constructed for this analysis: model 1: no adjustment for covariates; model 2: adjustment for three basic demographic variables: sex, race, and age; and model 3: model 3 further extends the adjustment for covariates. Kaplan-Meier survival curves were used to illustrate the association between CDAI levels and all-cause mortality in patients with CKM syndrome. Restricted cubic spline curve (RCS) analysis was chosen to explore possible nonlinear relations between advanced CKM syndrome and CDAI and its components. Subgroup analyses were performed stratified by multiple covariates to assess the robustness of the association between CDAI and advanced CKM syndrome. In addition, interaction analysis primarily tested the CDAI × age product term to evaluate whether age modified the CDAI–advanced CKM association. Additionally, mediation analysis was conducted to explore the mediating role of the AIP in the associations of CDAI and its components with advanced CKM syndrome. Random-effects inverse variance weighting (IVW) regression was employed as the primary analytical framework, supplemented by weighted median (WM) and MR-Egger regression for cross-validation. Concurrently, Cochran’s Q statistic (based on IVW) was used to detect heterogeneity, while the MR-Egger intercept test identifies potential horizontal multi-effect bias, ensuring robust and reliable results.

All statistical analyses were performed using R software (version 4.4.2, from Vienna, Austria). In the statistical analysis, a P value of less than 0.05 was considered statistically significant.

3. Results

3.1 Baseline characteristics

Table 1 details the basic demographic characteristics of the 24,578 volunteers who participated in this study. Among these participants, categorized according to whether they had advanced CKM syndrome, it was found that 5,964 (24.27%) were diagnosed as patients with advanced CKM syndrome. Participants with advanced CKM syndrome were more likely to be older, male, obese, low PIR, less educated, smokers, non-drinkers, hypertensive, diabetic, and have a lower CDAI.

Table 1. Baseline characteristics by advanced CKM syndrome.

	Overall	**Advanced CKM syndrome (Stages 3 or 4)**		*P*
Characteristic	(n = 24578)	No (n = 18614)	Yes (n = 5964)	
Age, y	54.19 ± 14.97	49.07 ± 12.27	70.17 ± 10.77	**<.001**
BMI	29.41 ± 6.52	29.33 ± 6.58	29.66 ± 6.31	**<.001**
WC, cm	100.82 ± 15.53	99.54 ± 15.50	104.82 ± 14.92	**<.001**
PIR	2.66 ± 1.63	2.77 ± 1.66	2.34 ± 1.47	**<.001**
TG (mg/dl)	159.66 ± 135.74	157.45 ± 140.18	166.58 ± 120.58	**<.001**
TC (mg/dL)	198.45 ± 42.59	202.25 ± 41.15	186.59 ± 44.78	**<.001**
HDL-C (mg/dl)	53.09 ± 16.35	53.84 ± 16.64	50.72 ± 15.16	**<.001**
HBA1C (%)	5.82 ± 1.10	5.68 ± 1.00	6.25 ± 1.28	**<.001**
Scr (mg/dl)	79.67 ± 23.24	75.15 ± 17.50	93.79 ± 31.75	**<.001**
CDAI	0.55 ± 4.08	0.78 ± 4.20	-0.16 ± 3.59	**<.001**
Sex, n (%)				**<.001**
Female	12349 (50.24)	9898 (53.18)	2451 (41.10)	
Male	12229 (49.76)	8716 (46.82)	3513 (58.90)	
Race, n (%)				**<.001**
Mexican American	3817 (15.53)	3144 (16.89)	673 (11.28)	
Other Hispanic	2048 (8.33)	1682 (9.04)	366 (6.14)	
Non-Hispanic White	11818 (48.08)	8369 (44.96)	3449 (57.83)	
Non-Hispanic Black	4757 (19.35)	3608 (19.38)	1149 (19.27)	
Other	2138 (8.70)	1811 (9.73)	327 (5.48)	
Marital, n (%)				**<.001**
Married/living with a partner	15976 (65.00)	12528 (67.30)	3448 (57.81)	
Other	8602 (35.00)	6086 (32.70)	2516 (42.19)	
Education, n (%)				**<.001**
Less than high school	6041 (24.58)	4122 (22.14)	1919 (32.18)	
High school graduate/higher	18537 (75.42)	14492 (77.86)	4045 (67.82)	
Smoke, n (%)				**<.001**
Yes	11706 (47.63)	7960 (42.76)	3746 (62.81)	
No	12872 (52.37)	10654 (57.24)	2218 (37.19)	
Alcohol, n (%)				**<.001**

Yes	18105 (73.66)	13824 (74.27)	4281 (71.78)	
No	6473 (26.34)	4790 (25.73)	1683 (28.22)	
Hypertension, n (%)				**<.001**
No	14757 (60.04)	13018 (69.94)	1739 (29.16)	
Yes	9821 (39.96)	5596 (30.06)	4225 (70.84)	
Diabetes, n (%)				**<.001**
No	20493 (83.38)	16783 (90.16)	3710 (62.21)	
Yes	4085 (16.62)	1831 (9.84)	2254 (37.79)	
CVD, n (%)				**<.001**
No	21547 (87.67)	18614 (100.00)	2933 (49.18)	
Yes	3031 (12.33)	0 (0.00)	3031 (50.82)	

Data are expressed as n (%) or mean ± SD as appropriate. Each percentage is calculated based on the sub-group total.
BMI: Body Mass Index; WC: Waist circumference; PIR Poverty income ratio; TC: Total Cholesterol; TG: Triglycerides; Scr: Serum Creatinine; HDL-C: High-Density Lipoprotein Cholesterol; CDAI: Composite dietary antioxidant index; CVD: Cardiovascular Disease; CKM syndrome: Cardiovascular-Kidney-Metabolic Syndrome.

Table S3 shows the detailed investigated characteristics of CKM syndrome stages 0–4. Levels of vitamins A, C, E, selenium, zinc, and carotenoids significantly decreased across CKM stages. All six antioxidant nutrients were highest at stage 0 and essentially at their lowest levels at stage 4. This pattern is consistent with the possibility of reverse causality: patients with advanced CKM syndrome often experience reduced dietary intake due to systemic changes (e.g., decreased appetite, impaired digestion and absorption, metabolic disturbances), leading to lower levels of antioxidant nutrients. Table S4 shows that among the various CKM metabolic indicators, BMI, WC, HDL, HbA1c, CKD, hypertension, diabetes, CMS, and CVD showed significant differences between the three tertiles of the CDAI, except for TG.

3.2 Association of CDAI and advanced CKM syndrome

In unadjusted models, we found that for each unit increase in CDAI, there was a lower odds of having advanced CKM syndrome, and this association was statistically significant (OR: 0.94, 95%CI: 0.93–0.94). Further, in Model 3, which adjusted for potential confounders including sex, age, race, education level, and smoking and drinking habits, the negative association of CDAI with advanced CKM syndrome persisted (OR: 0.97, 95%CI: 0.96–0.98). In addition, we stratified participants according to tertiles of CDAI. The results showed that in the unadjusted model, the highest tertile had a significantly lower odds of advanced CKM syndrome compared with the lowest tertile (OR: 0.55, 95%CI: 0.51–0.59, $P < 0.001$). The significant negative association between CDAI and advanced CKM syndrome was also maintained in the adjusted models (Tertile 3: OR: 0.74, 95% CI: 0.67–0.82, $P < 0.001$). These results suggest that higher CDAI values may be associated with lower odds of advanced CKM syndrome, even after accounting for multiple potential confounders (Table 2).

Table 2. Association of CDAI with advanced CKM syndrome.

Variables	Model 1		Model 2		Model 3	
	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
Continuous 1 unit	0.94 (0.93 ~ 0.94)	**<.001**	0.95 (0.94 ~ 0.96)	**<.001**	0.97 (0.96 ~ 0.98)	<.001

CDAI (categories)							
Tertile1	1.00 (Reference)		1.00 (Reference)			1.00 (Reference)	
Tertile2	0.76 (0.71 ~ 0.81)	**<.001**	0.72 (0.66 ~ 0.79)	**<.001**		0.81 (0.74 ~ 0.89)	**<.001**
Tertile3	0.55 (0.51 ~ 0.59)	**<.001**	0.63 (0.57 ~ 0.70)	**<.001**		0.74 (0.67 ~ 0.82)	**<.001**

OR: Odds Ratio; 95% CI: 95% Confidence Interval; CDAI: Composite dietary antioxidant index; CKM syndrome: Cardiovascular-Kidney-Metabolic Syndrome
Model1: Crude
Model2: Adjust: Sex, Race, Age
Model3: Adjust: Sex, Race, Marital, Education, Smoking, Alcohol, Age, PIR

A nonlinear relationship was shown between advanced CKM syndrome and the CDAI and its individual components by means of RCS regression analysis (Figure 2), which revealed a potential linear relationship between advanced CKM syndrome and selenium (p for nonlinear = 0.178), whereas the relationship with the CDAI as a whole, including vitamin A, vitamin C, vitamin E, zinc, and carotenoids, showed a significant nonlinear character (p for nonlinear < 0.05).

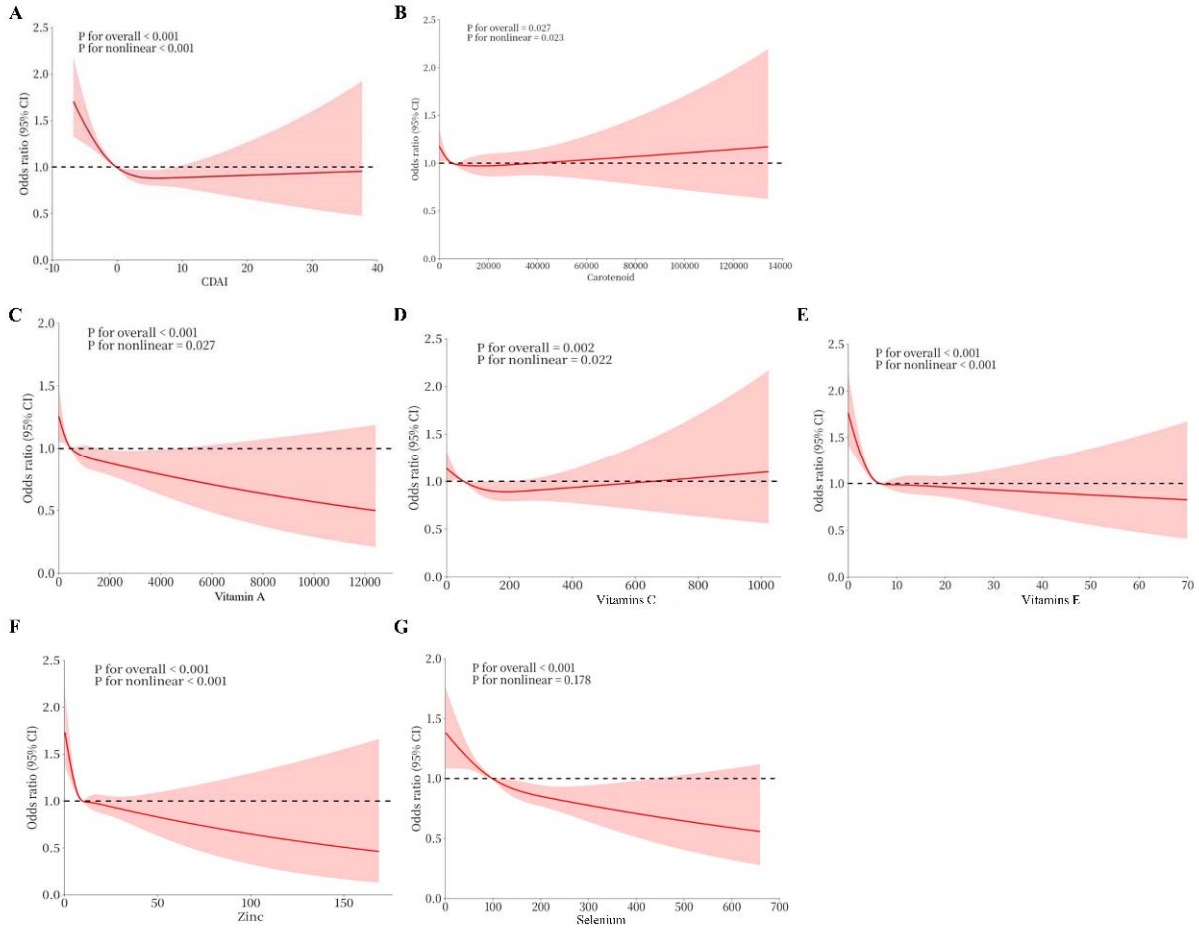


Figure 2. Nonlinear relationship between CDAI and CKM syndrome and its components.

A. nonlinear relationship between CDAI and CKM syndrome; B. nonlinear relationship between carotenoid and CKM syndrome; C. nonlinear relationship between Vitamin A and CKM syndrome; D. nonlinear relationship between Vitamin C and CKM syndrome; E. nonlinear relationship between Vitamin E and CKM syndrome; F. nonlinear relationship between Zinc and CKM syndrome; G. nonlinear relationship between Se and CKM syndrome. CDAI: Composite dietary antioxidant index. CKM syndrome: Cardiovascular-kidney-metabolic syndrome.

The odds of having advanced CKM syndrome varied nonlinearly with the intake levels of antioxidant nutrients. Inflection points (where the direction or slope of the association changed) were observed at

approximately the following values: vitamin A: 478, vitamin C: 54.2, vitamin E: 6.54, zinc: 9.7, selenium: 98.8, and carotenoids: 5218 (units as defined in the dietary assessment).

Assigning the group with lower levels of dietary oxidative indices as the reference, in the crude model, no lower odds of having advanced CKM syndrome were observed for vitamin A or vitamin C ($P >$ 0.05). After adjusting for confounding factors, individuals with elevated vitamin A, vitamin C, vitamin E, zinc, and selenium showed a reduced probability of advanced CKM syndrome, with ORs of 0.86 (0.79–0.93), 0.90 (0.83–0.98), 0.86 (0.79–0.93), 0.85 (0.79–0.93), and 0.82 (0.76–0.89), which are all significant ($P < 0.05$). However, in the fully adjusted model 3, the relationship between carotenoids and advanced CKM syndrome failed to reach statistical significance ($P > 0.05$) (Table 3).

Table 3. Regression analysis of CDAI components with advanced CKM syndrome.

Variables	Model1 Model2				Model3	
	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
Vit A						
＜478	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
≥478	1.02 (0.96 ~ 1.08)	0.484	0.76 (0.71 ~ 0.83)	<.001	0.86 (0.79 ~ 0.93)	<.001
Vit C						
＜54.2	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
≥54.2	1.04 (0.98 ~ 1.10)	0.227	0.78 (0.72 ~ 0.85)	<.001	0.90 (0.83 ~ 0.98)	0.012
Vit E						
＜6.54	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
≥6.54	0.73 (0.69 ~ 0.77)	<.001	0.76 (0.71 ~ 0.83)	<.001	0.86 (0.79 ~ 0.93)	<.001
Zinc						
＜9.7	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
≥9.7	0.70 (0.66 ~ 0.75)	<.001	0.80 (0.74 ~ 0.87)	<.001	0.85 (0.79 ~ 0.93)	<.001
Se						
＜98.8	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
≥98.8	0.61 (0.57 ~ 0.64)	<.001	0.77 (0.71 ~ 0.84)	<.001	0.82 (0.76 ~ 0.89)	<.001
Carotenoid						
＜5218	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
≥5218	0.82 (0.77 ~ 0.87)	<.001	0.83 (0.77 ~ 0.90)	<.001	0.93 (0.86 ~ 1.01)	0.097

OR: Odds Ratio; 95% CI: 95% Confidence Interval; CDAI: Composite dietary antioxidant index; CKM syndrome: Cardiovascular-Kidney-Metabolic Syndrome
Model1: Crude
Model2: Adjust: Sex, Race, Age
Model3: Adjust: Sex, Race, Marital, Education, Smoking, Alcohol, Age, PIR

Mortality data in this study were derived from the linked records of NHANES (1999–2018) participants and the National Death Index (NDI). Follow-up time was calculated from the examination date to the date of death or the study end date. Death events served as the endpoint, with the underlying cause of death coded according to the International Classification of Diseases (ICD-10) [23]. After accounting for all potential confounders, the fully adjusted statistical model showed that higher CDAI values were significantly associated with a lower hazard of all-cause mortality in patients with advanced CKM syndrome (Table S5).

In Tertile 3, each prespecified unit increase in CDAI was associated with a 15% lower hazard of outcome events (HR: 0.85; 95% CI: 0.77–0.93; $P < 0.001$). In addition, the study found a similar negative association between CDAI and the hazard of death among those who died from cardiovascular causes. In Tertile 3, the risk of cardiovascular death was associated with a 14% lower hazard (HR 0.86; 95% CI 0.73 ~ 1.01, p = 0.067). Additionally, we plotted KM survival curves stratified by CDAI quartiles (Supplementary Figure 1). The Kaplan-Meier curves demonstrated higher overall survival probability and higher cardiovascular-related survival probability among participants with higher CDAI levels. These results indicate an association between higher CDAI and better survival outcomes in patients with CKM syndrome.

3.3 Subgroup analysis and interaction analysis

After correcting for potential confounders, including age, sex, race, marital status, education level, PIR, and smoking and drinking habits, we conducted subgroup analyses of the association between CDAI and advanced CKM syndrome (Figure 3). The study results showed that there was no statistically significant interaction between CDAI and the presence of CKM syndrome in subgroups such as marital status, educational level, drinking habits, PIR, gender, and smoking habits (p for interaction > 0.05), suggesting that these factors do not modify the association between CDAI and CKM syndrome. However, in the age subgroup, an interaction was observed between CDAI and CKM syndrome (p for interaction < 0.05), suggesting that the association between CDAI and CKM syndrome may vary with age.

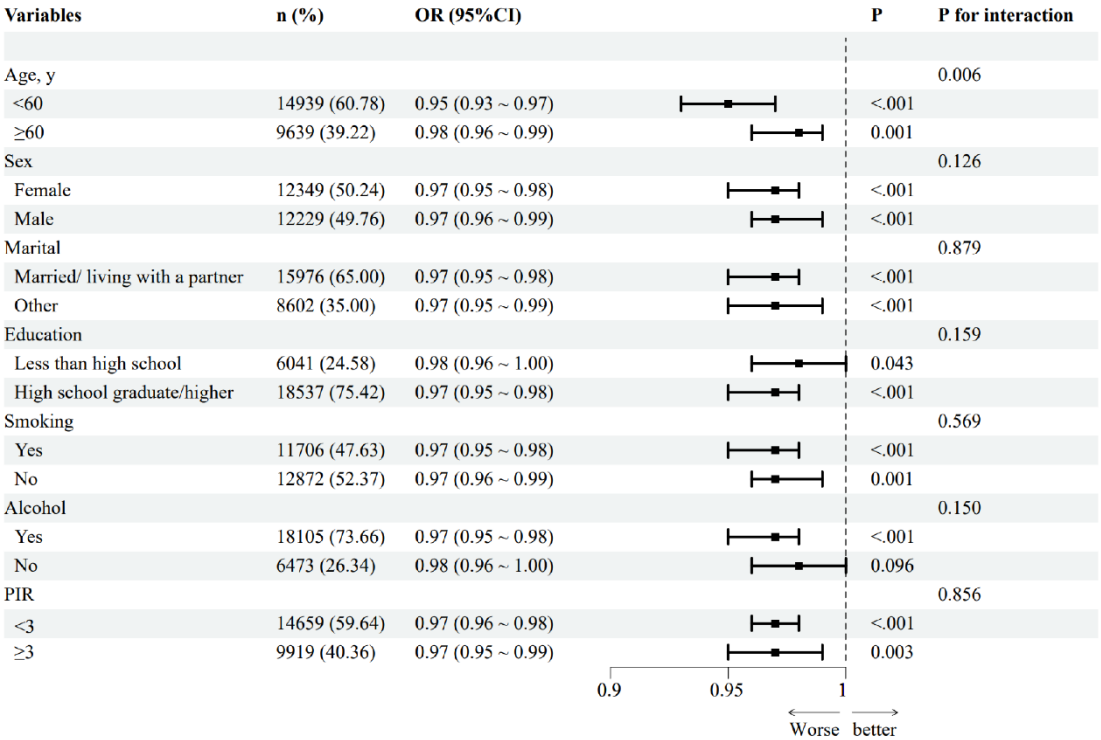


Figure 3. Subgroup analysis for the association between CDAI and advanced CKM syndrome. PIR: Poverty-to-Income Ratio.

To evaluate the effect modification of age on the association between CDAI and advanced CKM syndrome, we first treated age as a continuous variable and included a CDAI × age product term in a logistic regression model. The interaction term was statistically significant (OR = 1.13, 95% CI: 1.06–1.21, $P < 0.001$), indicating that age significantly modified the association between CDAI and advanced CKM

syndrome. After adjustment for other confounders, we further categorized age into three groups (30–49, 50–64, and ≥65 years) for stratified interaction analysis, with the youngest group as the reference. The results showed that the interaction between CDAI and the middle-aged group was not significant (OR = 1.06, 95% CI: 0.92–1.24, p = 0.408), whereas the interaction with the oldest age group was significant (OR = 1.18, 95% CI: 1.03–1.36, p = 0.017) (Table 4). This pattern suggests that the inverse association between CDAI and advanced CKM syndrome was relatively weaker in the oldest age group; that is, the inverse association of CDAI became weaker with increasing age.

Table 4. Interaction analysis of age on the association between CDAI and advanced CKM syndrome.

Variables	*P*	OR (%95CI)
Continuous age interaction		
CDAI	**<.001**	0.75 (0.70 ~ 0.81)
Age	**<.001**	8.79 (8.28 ~ 9.33)
CDAI*Age	**<.001**	1.13 (1.06 ~ 1.21)
Age category interaction		
CDAI × age group(30–49 years)	1.00 (Reference)	1.00 (Reference)
CDAI × age group(50–64 years)	0.408	1.06 (0.92 ~ 1.24)
CDAI × age group (≥65 years)	**0.017**	1.18 (1.03 ~ 1.36)

OR: Odd Ratio, CI: Confidence Interval

3.4 Mediating role of AIP on CDAI and its components and advanced CKM syndrome

A mediation analysis was performed using a Bayesian mediation model. The results demonstrated that AIP played a potential mediating role in the observed associations of CDAI and its components with advanced CKM syndrome (Figure 4). Specifically, 8.32% of the total observed association of CDAI was statistically attributed to AIP (mediation proportion). Moreover, marked heterogeneity was observed in the AIP-mediated effects across individual CDAI components, with vitamin E (28.49%) and vitamin A (17.45%) showing the highest estimated proportions, both statistically significant ($P < 0.05$). These findings suggest AIP as a potential mediator in the cross-sectional relationship between dietary antioxidant status and advanced CKM syndrome, providing a robust basis for future mechanistic investigations.

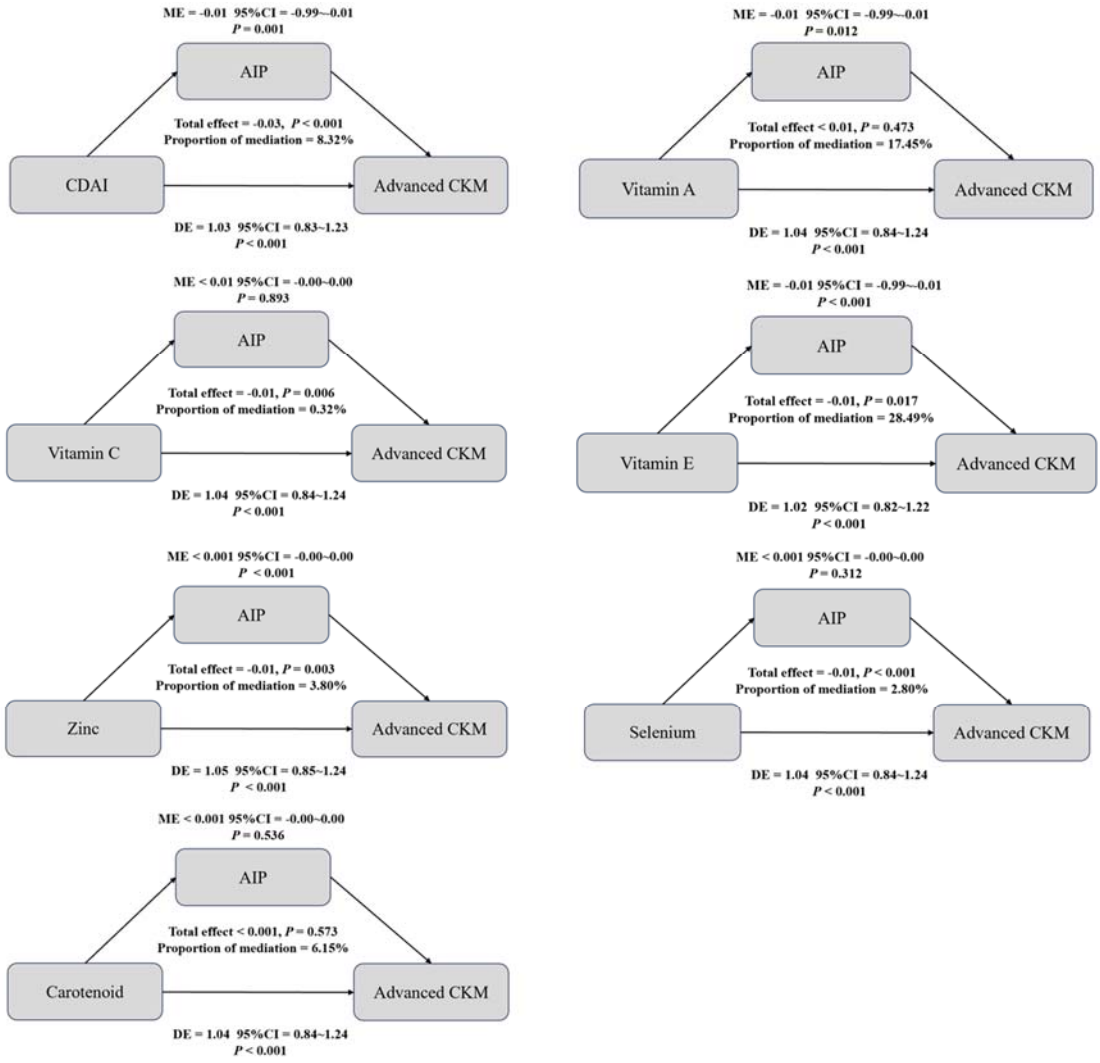


Figure 4. Mediating role of AIP on CDAI and its components and advanced CKM syndrome. AIP: Atherogenic Index of Plasma; DE: Direct Effect; ME: Indirect Effect.

3.5 Mendelian randomization

Detailed information on dietary antioxidant instrumental variables is summarized in Supplementary Table 6. The F-statistics of the selected instrumental variables are now provided in Supplementary Table 7. The mean F-statistics ranged from 23 to 37 across exposures, and all instruments exceeded the conventional threshold of 10, suggesting limited evidence of weak instrument bias. Analysis using the IVW method revealed that vitamin A levels showed a suggestive association with lower odds of atrial fibrillation (OR = 0.974, 95% CI 0.950–0.999, p = 0.041), and vitamin E levels showed a suggestive association with lower odds of coronary artery disease (OR = 0.756, 95% CI 0.618–0.926, p = 0.007) (Figure 5). After Bonferroni correction for 42 tests, no MR association remained statistically significant. Furthermore, after false discovery rate (FDR) correction (Benjamini-Hochberg, $q < 0.05$), all exposure–outcome pairs had q-values > 0.05 (Supplementary Table 8), consistent with the Bonferroni-corrected findings. The associations of genetically predicted vitamin A with atrial fibrillation and vitamin E with coronary artery disease reached only nominal significance and were therefore interpreted as exploratory signals. Furthermore, we constructed a scatter plot (Figure 6). The IVW slope was negative, and the MR-Egger and weighted median

results aligned with IVW findings. Additionally, the forest plot displayed effect sizes for each SNP consistent with the aforementioned results (Supplementary Figure 2). In summary, the MR analyses showed that the suggestive associations of vitamin A with atrial fibrillation and vitamin E with coronary artery disease are exploratory nominal signals.

Variable	nsnp	OR(95%CI)	P value
Vitamin A			
CKD	4	0.951 (0.862~1.050)	0.319
CAD	11	1.017(0.987~1.047)	0.274
AF	12	0.974 (0.950~0.999)	0.041
T2D	7	1.020 (0.987~1.054)	0.235
HF	11	0.996 (0.970~1.022)	0.759
MI	11	1.006 (0.975~1.038)	0.71
IS	12	1.000 (0.999~1.001)	0.791
Vitamin C			
CKD	3	1.035 (0.535~2.002)	0.918
CAD	10	0.886(0.680~1.154)	0.371
AF	11	0.976 (0.804~1.185)	0.807
T2D	5	0.734 (0.531~1.015)	0.061
HF	8	0.867 (0.703~1.070)	0.183
MI	11	0.886 (0.697~1.075)	0.191
IS	11	0.998 (0.992~1.003)	0.43
Vitamin E			
CKD	6	1.049 (0.601~1.829)	0.867
CAD	11	0.756(0.618~0.926)	0.007
AF	12	0.913(0.787~1.058)	0.225
T2D	6	0.838(0.662~1.060)	0.141
HF	11	1.105 (0.928~1.315)	0.264
MI	12	0.830(0.659~1.045)	0.113
IS	11	1.000 (0.995~1.005)	0.882
Zinc			
CKD	4	0.984 (0.795~1.219)	0.885
CAD	9	0.985(0.877~1.107)	0.804
AF	10	1.010(0.926~1.101)	0.825
T2D	5	0.995(0.903~1.097)	0.924
HF	9	0.994 (0.875~1.129)	0.924
MI	10	0.947(0.840~1.067)	0.372
IS	10	1.001 (0.999~1.004)	0.359
Selenium			
CKD	3	0.980 (0.743~1.292)	0.887
CAD	16	0.937(0.847~1.037)	0.207
AF	18	0.963(0.920~1.008)	0.105
T2D	7	1.006(0.912~1.109)	0.905
HF	14	0.961 (0.894~1.034)	0.287
MI	18	1.046 (1.001~1.093)	0.054
IS	17	1.001 (0.999~1.002)	0.435
Carotene			
CKD	2	0.747 (0.313~1.782)	0.511
CAD	15	0.987(0.864~1.128)	0.848
AF	16	0.987(0.864~1.128)	0.848
T2D	2	1.011(0.658~1.554)	0.961
HF	13	1.072 (0.897~1.283)	0.444
MI	17	1.101 (0.848~1.429)	0.47
IS	17	1.002 (0.997~1.007)	0.385

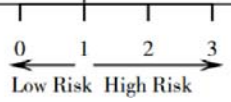


Figure 5. Forest plot analyzing the effects of dietary antioxidants on CKM using inverse variance weighting. CKD, Chronic kidney disease; CAD, Coronary artery disease; AF, Atrial fibrillation; T2D, Type 2 diabetes; HF, Heart failure; MI, Myocardial infarction; IS, Ischemic stroke.

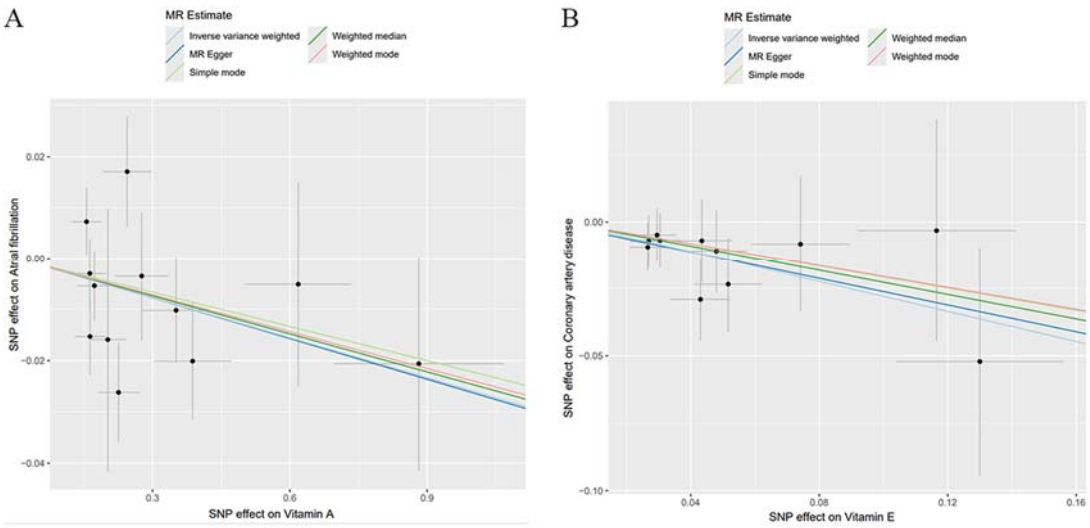


Figure 6. Scatter Plot Evaluation of Mendelian Randomized Trials.

A. Effect of Vitamin A on Atrial Fibrillation. B. Effects of Vitamin E on Coronary Artery Disease.

3.6 Sensitivity analysis

Multiple sensitivity analyses from different perspectives supported the robustness of our findings. First, the results from the CDAI quartile categorical model were consistent with those from the continuous variable model, indicating that the association was not influenced by the modeling approach of the exposure variable (Supplementary Table 9), further supporting the inverse association between CDAI and advanced CKM syndrome. Second, after excluding participants with baseline hypertension or diabetes (11,149 participants were excluded, and then 13,429 participants were included in the following analysis), the association remained stable, suggesting that the association between CDAI and advanced CKM syndrome was independent of common comorbidities (Supplementary Table 10). Finally, the results remained unchanged after excluding extreme CDAI values, confirming that the main findings were not driven by unusual dietary intake or outliers (Supplementary Table 11**)**. Collectively, these analyses effectively reduced the impact of potential bias and enhanced the credibility of the conclusions. In addition, multiple imputation sensitivity analyses were performed on approximately 10,000 participants with missing data on key variables (Supplementary Table 12), and the results further supported the robustness of the main findings.

4. Discussion

This study examined the association between CDAI and CKM syndrome. The findings reveal a negative association between CDAI and the stage of CKM syndrome, which remained even after multivariate adjustment for potential confounders such as age, gender, race, and smoking. Except for selenium, which showed a linear relationship with CKM syndrome ($p = 0.178$), the relationship between CDAI and its other dietary antioxidants, including vitamin A, vitamin C, vitamin E, zinc, and carotenoids, with CKM syndrome exhibited a nonlinear character ($P < 0.05$). Furthermore, higher CDAI scores were associated with lower all-cause mortality hazard in patients with CKM syndrome. These results suggest an inverse association between CDAI and adverse outcomes in patients with CKM syndrome.

Further subgroup analyses revealed no statistically significant interaction between CDAI and the presence of CKM syndrome in subgroups such as marital status, educational level, drinking habits, PIR, gender, and smoking habits (all p for interaction > 0.05). However, in the age subgroup, a significant interaction was observed. When age was treated as a continuous variable, the CDAI × age product term was significant (OR = 1.13, 95% CI: 1.06–1.21, $P < 0.001$), indicating that the association between CDAI and CKM syndrome varied with age. When age was categorized into three groups (30–49, 50–64, and ≥65 years) with the youngest as reference, the interaction between CDAI and the middle age group was not significant (OR = 1.06, 95% CI: 0.92–1.24, p = 0.408), whereas the interaction with the oldest age group was significant (OR = 1.18, 95% CI: 1.03–1.36, p = 0.017). These results suggest that the inverse association between CDAI and CKM syndrome is weaker in older adults. Moreover, our analysis using the IVW method revealed that vitamin A levels showed a suggestive association with lower odds of atrial fibrillation (OR = 0.974, 95% CI: 0.950–0.999, p = 0.041), and vitamin E showed a suggestive association with lower odds of coronary artery disease (OR = 0.756, 95% CI: 0.618–0.926, p = 0.007).

In mediation analysis, 8.32% of the total observed association between CDAI and advanced CKM syndrome was statistically attributable to AIP. AIP is a novel lipid metabolism biomarker that exhibits strong correlations with the risk of CVD and metabolic syndrome. Previous studies have provided evidence of the association between the CDAI and the risk of various components of the CKM syndrome, such as hyperlipidemia, hypertension, diabetes mellitus, and cardiovascular disease [24-28]. These studies have shown that CKM syndrome is usually associated with excess or dysfunctional adipose tissue in the body, sometimes both, a condition that leads to increased secretion of pro-inflammatory and pro-oxidant products, which in turn damages vital tissues such as the arteries, the heart, and the kidneys, and triggers impaired glucose tolerance, insulin resistance, or diabetes mellitus [29-30]. In addition, the systemic inflammatory response and insulin resistance further exacerbate cardiovascular and renal diseases associated with metabolic disorders, which include pathological changes such as atherosclerosis and myocardial injury, glomerulosclerosis, renal tubular inflammation, and renal fibrosis [1]. These findings suggest that an antioxidant-rich diet could be related to a lower prevalence of advanced CKM syndrome by improving lipid profiles, reducing oxidative stress, and ameliorating insulin resistance. However, due to the cross-sectional design, causal inference cannot be drawn, and these mediation results should be interpreted as exploratory.

In addition to the mediating role of AIP, we also observed direct associations between CDAI and other CKM-related outcomes. A higher CDAI was significantly associated with lower odds of stroke (OR = 0.96, 95% CI: 0.94–0.98, $P < 0.001$). Further RCS analysis revealed that the relationship between CDAI and stroke risk was not simply linear, but showed a nonlinear negative correlation [31]. This is supported by data from another study, which, after controlling for all potential confounders, found that individuals in the highest quartile of the CDAI had a 31% lower risk of developing metabolic syndrome (MetS) compared to individuals in the lowest quartile of the CDAI, with an OR of 0.69 and a 95% confidence interval of 0.57 to 0.82 [32]. This finding suggests an association between higher CDAI and lower odds of MetS. In addition to

this, according to a cross-sectional analysis using NHANES data from 2011 to 2018, results showed that CDAI was positively associated with a lower prevalence of chronic kidney disease (CKD) in US adults [33]. These findings indicate that higher dietary antioxidant capacity is associated with lower prevalence of CKD.

MR analysis showed that for the vast majority of antioxidant nutrient–cardiovascular disease combinations, no statistically significant associations were observed. Only vitamin A with atrial fibrillation (OR = 0.974, 95% CI: 0.950–0.999, p = 0.041) and vitamin E with coronary artery disease (OR = 0.756, 95% CI: 0.618–0.926, p = 0.007) reached nominal significance ($P < 0.05$); however, neither remained significant after Bonferroni correction for multiple testing (corrected threshold $P < 0.0012$). Several factors may explain these findings. First, circulating vitamin levels are phenotypes with typically low heritability; the SNP heritability for most vitamins is only 5–15%. Therefore, even with stringent instrument selection criteria, the proportion of phenotypic variation explained by the genetic instruments remains limited. Second, many of the observed associations between vitamins and cardiovascular diseases in observational studies are likely driven by residual confounding. Even after adjusting for known factors in multivariate analyses, numerous unmeasured or inaccurately measured confounders (e.g., overall health awareness, healthcare accessibility, and family environment) may persist. Third, MR captures lifelong genetically predicted exposure levels, whereas the CDAI in the present study reflects short-term dietary changes; thus, genetically predicted exposure cannot capture such dynamic variations. Finally, CDAI is a composite index whose antioxidant effects may depend on synergistic interactions among multiple nutrients. MR typically analyzes single exposures and has difficulty detecting interactions or nonlinear synergistic effects among components within a composite index. This may explain why observational analyses showed an overall inverse association for CDAI, whereas MR results for individual nutrients were largely null.

Although the associations of vitamin A with atrial fibrillation and vitamin E with coronary artery disease did not survive strict multiple testing correction, these findings still warrant attention. Vitamin A (retinol) is an essential fat-soluble vitamin. All-trans retinoic acid (atRA) is the active form of vitamin A. Preclinical studies have demonstrated vitamin A's crucial role in metabolic regulation [34]. Previous studies have reported that vitamin A may influence cardiac development and adult cardiovascular function through MAPK, AMPK, and other kinase pathways, possibly affecting anti-remodeling and anti-arrhythmic processes [34]. Vitamin E compounds encompass various tocopherols and tocotrienols, which could not only exhibit anti-inflammatory and anti-atherothrombotic effects, but also regulate platelet and coagulation systems. High-dose vitamin E supplementation was demonstrated to correlate with significant improvements in plasma lipid profiles, particularly through reduced LDL and increased HDL cholesterol [35]. Supplementation of vitamin E was found not only to positively impact blood lipids but also to benefit postprandial blood glucose and blood pressure in diabetic patients, which was associated with significantly reduced levels of TNF-α, MMP-2, and MMP-9 [35].

Oxidative stress is the result of an imbalance between free radical production and antioxidant defense systems in the body. Regulating oxidative stress levels has been proposed as important for slowing the

progression of CKM syndrome [36-37]. Vitamin C and Vitamin E are two essential antioxidant vitamins that are able to scavenge and neutralize free radicals, thereby reducing the level of oxidative stress [38-39]. Supplementation with Vitamins C and E was found to decrease the expression of oxidative stress markers in endometriosis patients [40]. In addition, minerals such as zinc and selenium are important components of antioxidants and would play key roles in maintaining enzyme activity [41-43].

Our study has several limitations. First and foremost, this study utilizes a cross-sectional design, which only captured data at a single time point and did not allow for tracking longitudinal trends. Second, during the data analysis phase, a certain proportion of missing values in some key variables was excluded, which may introduce potential selection bias and reduce the robustness of our conclusions. Third, the causality of risk factors and their impact on diseases cannot be robustly established owing to the observational research design of NHANES, even after considering the potential confounding factors in our study. Fourth, NHANES represents only the non-institutionalized US civilian population. Thus, our findings may not be generalizable to hospitalized patients, nursing home residents, or other ethnic/geographic populations. Additionally, several limitations of MR analysis should be acknowledged. Owing to the limited number of genome-wide significant instruments for some vitamin exposures, we adopted a relaxed instrument-selection threshold of $p < 5\times10^{-6}$, which may increase susceptibility to weak instrument bias despite F-statistic assessment. Moreover, because we performed 42 exposure–outcome comparisons, the nominally significant associations did not survive Bonferroni correction. Likewise, after FDR correction, all associations had q-values > 0.05. Therefore, these MR findings should be regarded as hypothesis-generating rather than confirmatory causal evidence. Ultimately, more rigorously designed randomized controlled trials are needed to investigate whether interventions targeting higher CDAI are associated with changes in the progression of CKM syndrome.

5. Conclusions

The CDAI is a comprehensive measure of dietary antioxidant capacity, reflecting an individual's overall intake of antioxidants through diet. It has been used in studies exploring the association between antioxidant-rich diets and CKM syndrome. Higher antioxidant diets (i.e., those with higher CDAI scores) are associated with lower levels of oxidative stress and inflammatory responses, both of which are considered key factors in the development of CKM syndrome. Therefore, higher antioxidant diets may be linked to a lower prevalence of CKM syndrome, and prospective studies are needed to investigate whether improving dietary antioxidant intake is associated with a lower risk of CKM progression.

Ethics statement

This study used data from the NHANES database rather than individual-level data. All adult participants provided written informed consent, and because this study did not involve new data collection, it did not require ethical approval.

Acknowledgments and Funding

We sincerely appreciate the essential contributions made by the committed team and all of the participants in the NHANES project. This study was supported by NSFC grants (82474250), Noncommunicable Chronic Diseases-National Science and Technology Major Project (2026ZD0555201,2026ZD0555200), National Clinical Collaboration Program of Traditional Chinese and Western Medicine for Major and Intractable Diseases Ischemia with non-obstructive coronary arteries (ZDYN-2024-A-154), National Key R&D Program of China (2022YFC3501701), Shanghai Pujiang Program (22PJD071), and the Program of EnShi TuJia and Miao Autonomous Prefecture Bureau of Scientific and Technological Affairs.

Conflict of interest

The authors report no conflict of interest.

Data sharing statement

All of the data created and utilized for this investigation are either included in this paper (as well as its Supplementary Information) or can be obtained from the corresponding author on reasonable request.

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