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Associations of composite dietary antioxidant index with premature death and all-cause mortality: a cohort study

Huiqin Zhong[1,4†], Ya Shao[2,4†], Xin Chen[3], Na Wang[3], Yan Zhan[3], Boxiong Gong[1], Rong Zhang[1] and Longti Li[1*]

Abstract

Although previous evidence indicates that the composite dietary antioxidant index (CDAI) is negatively associated with health outcomes, no studies have explored the association between CDAI and premature death. This research utilized a cohort study design with 37,301 participants from the National Health and Nutrition Examination Survey (NHANES) from 2003 to 2018. Cox proportional hazard regression was employed to analyze the association between CDAI and premature death and all-cause mortality. Restricted cubic spline (RCS) analysis was performed to examine the nonlinear relationship between variables, and Kaplan-Meier analysis was used to evaluate survival outcomes over time. Sensitivity and subgroup analyses were conducted to assess the reliability of the findings. During a median follow-up period of 8.25 years, 4487 deaths were recorded, with 1671 classified as premature. The study revealed a negative correlation between CDAI and premature death (Per-SD hazard ratio [HR] 0.91, 95% CI 0.85–0.97; quartiles [Q4:Q1] HR 0.83, 95% CI: 0.70, 0.98) as well as all-cause mortality (Per-SD HR 0.96, 95% CI 0.92-1.00; quartiles [Q4:Q1] HR 0.91, 95%CI: 0.82, 1.01). The RCS analyses indicated a 'U' shaped relationship between CDAI and premature death and all-cause mortality. The threshold effect analysis pinpointed the inflection points for CDAI relative to premature death and all-cause mortality at 1.42 and 1.48, respectively. Kaplan-Meier curves illustrated that the likelihood of individual survival increases with higher CDAI quartiles. The results highlight the significance of dietary antioxidant intake in enhancing extending lifespan. Further research is needed to investigate the underlying mechanisms and determine optimal intake levels for improving health outcomes.

Keywords Composite dietary antioxidant index, Premature death, Mortality, Cohort study, NHANES

Introduction

With the increasing global ageing population and the rising burden of chronic diseases, prolonging healthy lifespan has become a significant goal in public health. Population ageing not only has far-reaching socioeconomic impacts but also presents new challenges for public health policies and healthcare resource allocation [1]. Ageing is associated with a rise in chronic non-communicable diseases (NCDs), such as cardiovascular diseases (CVD), diabetes, and cancer, which have emerged as the leading causes of death worldwide [2]. Consequently, exploring effective interventions to extend healthy

†Huiqin Zhong and Ya Shao contributed equally to this work.

*Correspondence:
Longti Li
longtili@163.com
[1]Innovation Centre of Nursing Research, TaiHe Hospital, Hubei University of Medicine, Shiyan, Hubei, PR China
[2]Health Management Center, Wudangshan Branch, TaiHe Hospital, Hubei University of Medicine, Shiyan, Hubei, PR China
[3]Nursing Department, TaiHe Hospital, Hubei University of Medicine, Shiyan, Hubei, PR China
[4]No. 32, South People's Road, Shiyan, China

lifespan and mitigate the burden of chronic diseases has become an urgent priority in public health [1].

There is growing interest in the impact of diet on individual health and disease prevention, particularly regarding the role of antioxidants in regulating oxidative stress. Oxidative stress, a condition characterized by an excess of reactive oxygen species (ROS), is recognized as a key factor in the development of several chronic diseases [3]. The body's inability to neutralize ROS effectively due to either overproduction or insufficient antioxidant defense leads to cellular damage [4], which accelerates the ageing process and contributes to age-related diseases such as CVD, cancer, and neurodegenerative diseases [5–7]. Furthermore, oxidative stress plays a central role in promoting inflammation and inducing cellular senescence, both of which have been linked to the development of chronic conditions and premature mortality [8].

Studies have demonstrated that dietary antioxidant components can protect cells by neutralizing free radicals and reducing inflammatory responses, thereby contributing to improved aging [9] and lowering the risk of cardiovascular disease [10], cancer [11], and other diseases. The antioxidant defense system in the body includes both enzymatic and non-enzymatic components, with antioxidants such as vitamins A, C, and E, selenium, and zinc serving as critical elements in mitigating oxidative damage. The balance between the oxidative stress production and the antioxidant defense system is essential for maintaining cellular health, and disruptions in this balance are often associated with premature death [12]. While numerous studies focused on the health effects of individual antioxidants (e.g., vitamin C, vitamin E, and carotenoids) [13–15], it remains challenging for single-component studies to fully elucidate the combined effects of dietary antioxidants on health outcomes. This is particularly true when considering the complexity of interactions between various antioxidants and their cumulative effect on the body's antioxidant capacity. Therefore, it is particularly important to quantify and synthesize the total intake of multiple antioxidants.

The Composite Dietary Antioxidant Index (CDAI) serves as a novel evaluation tool designed to quantify the overall intake of various antioxidant components in the diet [16]. It assesses the diet's total antioxidant capacity by considering a range of essential nutrients, including vitamins A, C, and E, as well as selenium and zinc, all of which are recognized for their antioxidant properties [10, 17]. Existing studies have demonstrated a negative association between CDAI and several adverse health outcomes, such as stroke [18], sarcopenia [19], and chronic kidney disease [20]. However, systematic exploration of the relationship between CDAI and both premature and all-cause mortality remains limited. Moreover, premature death is a significant health indicator, reflecting individuals' quality of life and directly impacting the allocation of medical resources and public health strategies. Therefore, investigating the relationship between CDAI and premature death, along with all-cause mortality, is of substantial public health significance.

This study utilized data from the U.S. National Health and Nutrition Examination Survey (NHANES) and employed a large-scale cohort design to systematically analyze the relationship between CDAI, premature death, and all-cause mortality. The aim of this research was to enhance the current understanding of CDAI and provide evidence regarding the potential role of dietary antioxidants in improving health outcomes.

Methods

Study population

The research utilized information from the ongoing NHANES conducted by the National Center for Health Statistics (NCHS) using a sophisticated multistage probability sample design [21]. In the present study, the CDAI values were estimated by averaging two 24-hour dietary recall datasets from participants. However, data prior to 2003 were only collected for one day of the participants' dietary recall data. Consequently, data from 2003 onwards were included in this analysis. Information from eight survey cycles spanning 2003–2004 to 2017–2018 was gathered and connected with the National Death Index (NDI) records updated through Dec 31, 2019. The study selection process is illustrated in Fig. 1. Among the initial 80,312 participants, individuals under 18 years old, those with missing dietary data for any day of the two-day dietary interview, and those with missing mortality data were excluded. Ultimately, 37,301 individuals with comprehensive data were incorporated into the analyses. The research was conducted in accordance with the Declaration of Helsinki and was approved by the ethical review committee of the National Center for Health Statistics, and all participants gave written consent to participate in the survey and allowed their data to be employed for public usage. This study follows the STROBE statement (Supplementary File S1).

Assessment of exposure variable

The dietary antioxidant capacity of an individual was estimated using the CDAI as the exposure variable in this study. CDAI values were calculated using 24-hour dietary recall data from the NHANES database. The 24-hour dietary recall is an effective tool widely employed in epidemiological studies to assess dietary intake and nutritional status. NHANES utilized this method to collect data on the types and amounts of food and beverages consumed by participants over a 24-hour period, estimating the intake of energy, nutrients, and other components in these foods and beverages. To enhance the

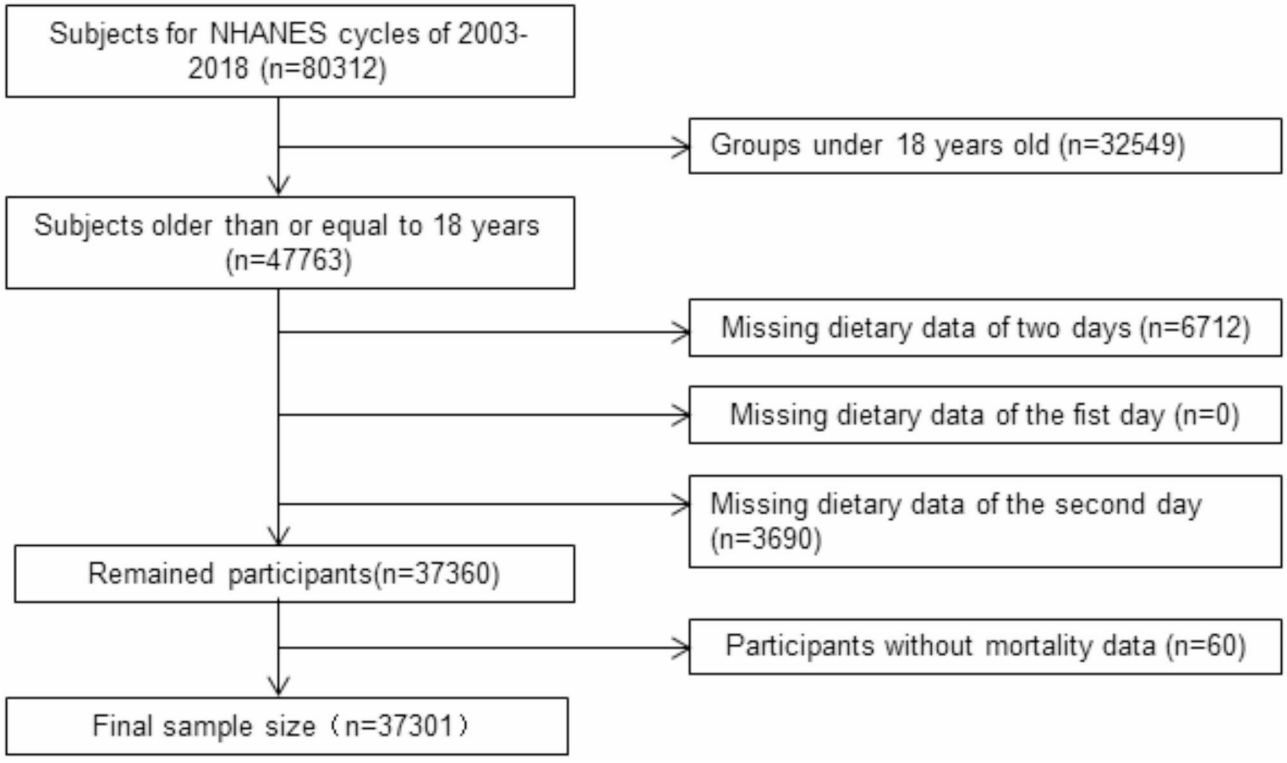

Fig. 1 Flowchart of the selection of the populations

representativeness of dietary intake, two 24-hour dietary recall interviews were used to estimate CDAI in current study. The initial face-to-face interview occurred at the Mobile Examination Center, with a follow-up telephone interview occurring 3 to 10 days later. Average dietary intake over these two days was calculated to determine daily intake. Six different nutritional antioxidants - vitamins A, C, E, zinc, selenium, and β-carotenoids were utilized in calculating the CDAI, following the methodology proposed by Wright et al. [16]. These six components were standardized by subtracting the mean and dividing by the standard deviation, with their sum representing the final CDAI value. The Eq. (1) used for this calculation is as follows: $\mathrm{CDAI} = \sum_{i=1}^{n=6} \left(\frac{individual\ intake - mean}{SD} \right)$

Outcome variables

The study focused on all-cause mortality and premature death as the main outcomes. Participants' mortality status was determined using the NHANES Public Use Linked Mortality File [21, 22], which was matched to the NDI using a unique identifier. Premature death was described as occurring before the age of 75 [23], whereas all-cause mortality included fatalities at any point in time. Follow-up years were computed from the evaluation date until the moment of death or the end of the study period (December 31, 2019), whichever occurred first.

Assessment of covariates

The selection of covariates was guided by existing literature and clinical expertise. Demographic variables such as gender, age, race, education, marital status, and poverty income ratio (PIR) were evaluated by NHANES-trained interviewers. Body mass index (BMI) was assessed in the mobile examination center and categorized into three groups: normal weight (BMI < 25 kg/m^2), overweight (BMI 25-29.9 kg/m^2), and obese (BMI ≥ 30 kg/m^2). Alcohol consumption (yes/no) was determined based on whether individuals had consumed 12 or more drinks in the past 12 months [24]. The smoking status included now, former, never. 'Now' indicated lifetime cigarette use ≥ 100 and current daily or occasional smoking, 'Former' referred to lifetime cigarette use ≥ 100 but currently not smoking, and 'Never' indicated lifetime cigarette use <100 [25]. We also included physical activity as an important confounding factor. Considering the diverse measurements of physical activity in different cycles of NHANES, we categorized physical activity into three categories (low, medium, and high) concerning the previous studies. From 2003 to 2006, physical activity levels were assessed using the question 'Compare activity with others of the same age' (participants were classified as low if they responded 'less active'; as moderate if 'about the same'; and as high if 'more active') [26]. From 2007 to 2018, physical activity was divided according to the metabolic equivalents task (MET) score, as low if MET-min/

week < 600, as moderate if MET-min/week ≥ 600, and MET-min/week < 3000, as high if MET-min/week ≥ 3000 [27]. The energy intake was derived from the average total energy intake of the two-day 24-hour dietary recall.

The medical history relating to chronic illnesses included diseases such as CVD, cancer, diabetes, and hypertension. CVD covered self-reported cases of congestive heart failure, coronary heart disease, angina, heart attack, or stroke. Diabetes was diagnosed based on specific criteria: self-reported diagnosis, use of diabetic medication, glycosylated hemoglobin level ≥ 6.5%, or fasting plasma glucose ≥ 7.0mmol/L. Participants were diagnosed with hypertension if they self-reported the condition, were prescribed medication, or had systolic blood pressure levels ≥ 140 mmHg or diastolic blood pressure levels ≥ 90 mmHg on three or more occasions.

Statistical analyses

Statistical analyses were conducted using R software (http://www.Rproject.org, version 3.4.3) and Empower statistical software (http://www.empowerstats.com, version 2.1). The exposure distribution was described based on CDAI quartiles. Mean ± SD or median with interquartile ranges (IQR) were used to display continuous variables, while categorical variables were presented as frequencies and percentages. Cox proportional hazard regression models were employed to explore the relationship between CDAI and mortality, with hazard ratios (HR) and 95% confidence intervals (CI) estimated using person-years of follow-up as the timescale. Due to the skewed distribution of the independent variables, a Box-Cox transformation was applied to CDAI, a method commonly used to handle skewed data [28]. The transform Eq. (2) was: ((CDAI + 13.158) ^ (-0.534)-1) / (-0.534). Multicollinearity detection was conducted through covariate examination among the independent variables, where a variance inflation factor value lower than ten was deemed satisfactory [29]. Missing data in the covariates were addressed through multiple imputations with five datasets.

We considered four regression models: Model 1 was unadjusted; Model 2 included adjustments for gender, age, race; Model 3 further incorporated adjustments for marital status, education level, PIR, BMI, smoking, alcohol consumption, and activity; and Model 4 further adjusted for energy intakes and major chronic diseases, including hypertension, diabetes, CVD, and cancer based on Model 3. The regression models incorporated the CDAI score as a continuous and categorical variable in quartiles. Furthermore, a linear trend was assessed by including the median value of each CDAI score category in the models as a continuous variable. Additionally, the study employed restricted cubic spline (RCS) analysis to investigate the non-linear connections between CADI and premature death and all-cause mortality. If a non-linear association was found, threshold effects analysis would be used to verify the segmented effects and the turning point. And the two-piecewise Cox regression model on either side of the turning point was tested by the log-likelihood ratio test. Survival distributions were depicted using the Kaplan-Meier survival graph, and distinctions between groups were assessed using the log-rank examination.

Several sensitivity analyses were conducted to ensure the reliability of the findings. Initially, participants were stratified based on gender, age, PIR, BMI, activity, smoking, drinking, and baseline history of hypertension, diabetes, CVD and cancer. Moreover, interactions between independent variables in the final model were examined, and the significance of interaction terms was evaluated using a likelihood ratio test. Subsequently, individuals with less than two years of follow-up (including those who passed away during this period) were excluded from the regression analysis. Furthermore, a regression analysis was performed without any statistical imputation for missing data. Finally, we conducted Cox regression analyses of each of the six components of the CDAI in relation to both premature death and all-cause mortality.

Results

Baseline characteristics of participants

Table 1 illustrates the baseline characteristics of the 37,301 participants, showing an average age of 48.05 ± 18.98 years, with 47.57% being male, categorized by CDAI score quartiles. Significant differences were observed across the CDAI quartiles concerning age, gender, race, education level, marital status, PIR, BMI, smoking habits, physical activity, energy intakes and the presence of CVD, diabetes, and hypertension at baseline. Individuals with higher CDAI scores tended to be younger, male, with higher education and PIR levels, lower BMI, married or cohabitating, non-smokers, more physically active and energy intakes. Moreover, they exhibited lower rates of CVD, diabetes, and hypertension at baseline. Notably, there were no significant differences in baseline cancer incidence or alcohol consumption.

Association of CDAI with premature death and all-cause mortality

Over a median follow-up period of 8.25 years (IQR: 4.58–12.17 years), a total of 4487 deaths were documented, including 1671 deaths occurring before the age of 75. After adjusting for all covariates, the analysis illustrated in Table 2 demonstrated an inverse relationship between CDAI and premature death (HR 0.91, 95% CI: 0.85–0.97) as well as all-cause mortality (HR 0.96, 95% CI 0.92-1.00). In the fully adjusted models, every SD increase in CDAI score was linked to a 9% decline in premature death and

Table 1 Characteristics of participants stratified by CDAI quartiles

Characteristic	Overall (*n* = 37301)	Quartiles of composite dietary antioxidant index (CDAI)				*P*-value
		Q1(*n* = 9325)	Q2(*n* = 9325)	Q3(*n* = 9325)	Q4(*n* = 9326)	
Age (mean ± SD, year)	48.05 ± 18.98	48.53 ± 19.56	48.46 ± 19.14	48.26 ± 18.81	46.97 ± 18.35	< 0.001
PIR (median (IQR)) *	2.12 (1.11, 4.04)	1.65 (0.93, 3.18)	2.06 (1.09, 3.86)	2.38 (1.21, 4.37)	2.55 (1.26, 4.77)	< 0.001
BMI (mean ± SD, kg/m^2) *	29.06 ± 6.96	29.42 ± 7.21	29.33 ± 6.95	29.04 ± 6.84	28.47 ± 6.77	< 0.001
CDAI (median (IQR))	-1.55 (-3.29, 0.66)	-4.32 (-5.05, -3.78)	-2.43 (-2.85, -2.00)	-0.56 (-1.08, 0.01)	2.71 (1.51, 4.73)	< 0.001
CDAI Box-Cox transform (mean ± SD)	1.37 ± 0.07	1.28 ± 0.04	1.35 ± 0.01	1.39 ± 0.01	1.45 ± 0.04	< 0.001
Energy intakes (mean ± SD, kcal)	2039.49 ± 831.99	1391.76 ± 487.39	1845.91 ± 526.74	2188.83 ± 629.40	2731.39 ± 948.53	< 0.001
Gender, n (%)						< 0.001
Male	17,743 (47.57)	3128 (33.54)	3968 (42.55)	4807 (51.55)	5840 (62.62)	
Female	19,558 (52.43)	6197 (66.46)	5357 (57.45)	4518 (48.45)	3486 (37.38)	
Race, n (%)						< 0.001
Non-Hispanic Black	8140 (21.82)	2461 (26.39)	2044 (21.92)	1774 (19.02)	1861 (19.95)	
Hispanic	9240 (24.77)	2382 (25.54)	2381 (25.53)	2324 (24.92)	2153 (23.09)	
Non-Hispanic White	16,485 (44.19)	3779 (40.53)	4126 (44.25)	4292 (46.03)	4288 (45.98)	
Other Race	3436 (9.21)	703 (7.54)	774 (8.30)	935 (10.03)	1024 (10.98)	
Education, n (%) *						< 0.001
Under high school	8353 (23.90)	2737 (31.75)	2184 (25.09)	1867 (21.15)	1565 (17.80)	
High school or equivalent	8130 (23.27)	2268 (26.31)	2055 (23.61)	2000 (22.66)	1807 (20.55)	
Above high school	18,460 (52.83)	3615 (41.94)	4464 (51.29)	4960 (56.19)	5421 (61.65)	
Marital status, n (%) *						< 0.001
Married or living with a partner	21,255 (59.19)	4712 (53.02)	5197 (58.03)	5702 (63.01)	5644 (62.58)	
Widowed/Divorced/Separated	7766 (21.63)	2335 (26.27)	2121 (23.69)	1688 (18.65)	1622 (17.98)	
Never married	6890 (19.19)	1841 (20.71)	1637 (18.28)	1659 (18.33)	1753 (19.44)	
Alcohol, n (%) *						0.213
Yes	467 (2.08)	114 (2.28)	105 (1.87)	110 (1.89)	138 (2.29)	
No	22,020 (97.92)	4892 (97.72)	5515 (98.13)	5713 (98.11)	5900 (97.71)	
Smoking, n (%) *						< 0.001
Now	7014 (19.69)	2297 (25.88)	1726 (19.46)	1507 (16.82)	1484 (16.63)	
Former	8850 (24.84)	1921 (21.64)	2187 (24.66)	2389 (26.67)	2353 (26.37)	
Never	19,762 (55.47)	4658 (52.48)	4955 (55.88)	5062 (56.51)	5087 (57.00)	
Activity, n (%) *						< 0.001
low	7666 (25.72)	1965 (28.29)	1989 (27.21)	1928 (25.36)	1784 (22.46)	
moderate	10,325 (34.65)	2433 (35.03)	2568 (35.13)	2650 (34.86)	2674 (33.66)	
high	11,810 (39.63)	2548 (36.68)	2753 (37.66)	3024 (39.78)	3485 (43.88)	
CVD, n (%) *						< 0.001
Yes	4001 (11.44)	1210 (14.03)	1061 (12.18)	939 (10.63)	791 (8.99)	
No	30,969 (88.56)	7417 (85.97)	7651 (87.82)	7897 (89.37)	8004 (91.01)	
Cancer, n (%) *						0.784
Yes	3485 (9.97)	847 (9.83)	864 (9.93)	905 (10.25)	869 (9.88)	
No	31,457 (90.03)	7772 (90.17)	7840 (90.07)	7922 (89.75)	7923 (90.12)	
Diabetes, n (%) *						< 0.001
Yes	5513 (15.06)	1542 (16.92)	1464 (15.98)	1334 (14.55)	1173 (12.80)	
No	31,094 (84.94)	7572 (83.08)	7695 (84.02)	7836 (85.45)	7991 (87.20)	
Hypertension, n (%)						< 0.001
Yes	14,559 (39.03)	3960 (42.47)	3753 (40.25)	3499 (37.52)	3347 (35.89)	
No	22,742 (60.97)	5365 (57.53)	5572 (59.75)	5826 (62.48)	5979 (64.11)	

Abbreviations: SD = standard deviation; IQR = interquartile range; BMI = body mass index; PIR = poverty income ratio; CDAI = composite dietary antioxidant index; CVD = cardiovascular disease

CDAI has done the Box-Cox transformation that Box-Cox transform equation is (CDAI + 13.158) ^ (-0.534)-1)/ (-0.534)

* The following variables had missing information: PIR (7.68%), education level (6.32%), marital status (3.73%), alcohol (39.71%), smoking (4.49%), activity (20.11%), CVD (6.25%), cancer (6.32%), diabetes (1.86%)

Table 2 Cox proportional hazard regression analysis of association between CDAI and risk of all-cause mortality and premature death

Outcomes	Model 1		Model 2		Model 3		Model 4	
	HR (95%CI)	*P*-value	HR(95%CI)	*P*-value	HR(95%CI)	*P*-value	HR (95%CI)	*P*-value
Premature death								
CDAI (Per-SD)	0.85 (0.81, 0.90)	< 0.001	0.82 (0.78, 0.86)	< 0.001	0.93 (0.88, 0.97)	< 0.001	0.91 (0.85, 0.97)	0.004
Q1(lowest)	Ref.		Ref.		Ref.		Ref.	
Q2	0.78 (0.68, 0.88)	0.001	0.75 (0.66, 0.86)	< 0.001	0.87 (0.76, 0.99)	0.032	0.85 (0.74, 0.97)	0.017
Q3	0.66 (0.58, 0.76)	< 0.001	0.62 (0.54, 0.71)	< 0.001	0.78 (0.68, 0.89)	< 0.001	0.77 (0.66, 0.89)	0.001
Q4(highest)	0.68 (0.60, 0.78)	< 0.001	0.63 (0.55, 0.72)	< 0.001	0.84 (0.73, 0.97)	0.014	0.83 (0.70, 0.98)	0.029
P for trend	< 0.001		< 0.001		0.004		0.011	
All-cause mortality								
CDAI (Per-SD)	0.88 (0.85, 0.91)	< 0.001	0.88 (0.85, 0.91)	< 0.001	0.95 (0.92, 0.98)	0.002	0.96 (0.92, 1.00)	0.031
Q1(lowest)	Ref.		Ref.		Ref.		Ref.	
Q2	0.90 (0.83, 0.98)	0.011	0.88 (0.81, 0.96)	0.002	0.96 (0.89, 1.04)	0.319	0.95 (0.87, 1.03)	0.200
Q3	0.79 (0.72, 0.85)	< 0.001	0.75 (0.69, 0.82)	< 0.001	0.88 (0.81, 0.95)	0.002	0.89 (0.82, 0.98)	0.018
Q4(highest)	0.72 (0.66, 0.78)	< 0.001	0.74 (0.68, 0.80)	< 0.001	0.89 (0.82, 0.97)	0.011	0.91 (0.82, 1.01)	0.063
P for trend	< 0.001		< 0.001		0.002		0.035	

Abbreviations: HR = Hazard Ratio; SD = standard deviation; CI = confidence interval; CDAI = composite dietary antioxidant index

Model 1 was unadjusted; Model 2 was adjusted for gender, age, race; Model 3 was adjusted for gender, age, race, marital status, education level, PIR, BMI, activity, alcohol, smoke; Model 4 was adjusted for gender, age, race, education level, marital status, PIR, BMI, alcohol, smoking, activity, energy intakes, CVD, diabetes, hypertension, cancer

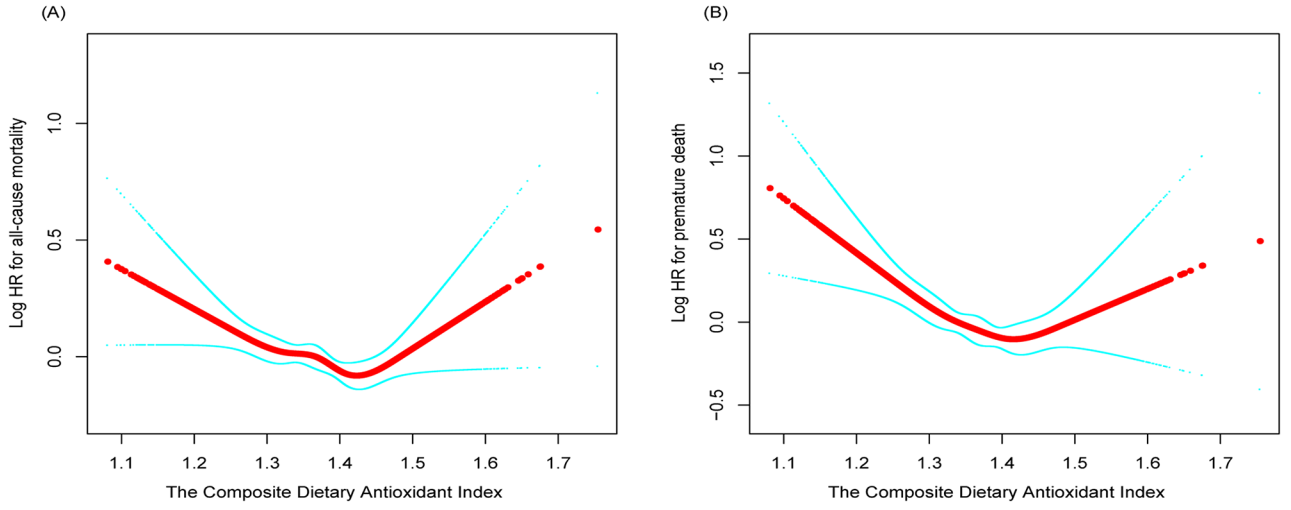

Fig. 2 Restricted cubic spline analyses of the association between CDAI and all-cause mortality (A) and premature death (B). Models were adjusted for gender, age, race, education level, marital status, PIR, BMI, alcohol, smoking, activity, energy intakes, CVD, diabetes, hypertension, cancer

a 4% decrease in all-cause mortality. Examination of the outcomes by quartiles unveiled that individuals in the top quartile (Q4) exhibited an HR of 0.83 (95% CI 0.70–0.98) for premature death and 0.91 (95% CI: 0.82–1.01) for all-cause mortality when compared to those in the lowest quartile (Q1). The trend tests yielded statistically significant results ($P < 0.01$).

The RCS analysis in Fig. 2 demonstrated a non-linear association between CDAI and premature as well as all-cause mortality (both P for nonlinearity < 0.001), showing 'U' shaped patterns. Threshold effect analyses demonstrated that the relationship between the CDAI and premature and all-cause mortality was reversed when the CDAI was 1.42 and 1.48, respectively, and the participants exhibited the lowest rates of premature and all-cause mortality (see Table 3).

The Kaplan-Meier curves indicated that individuals in Q3 and Q4 of CDAI had higher cumulative survival probability, whereas those in quartile 1 of CDAI had a lower cumulative survival probability (Fig. 3).

Stratified and sensitivity analyses

In the subgroup analysis stratified by gender, age, BMI, physical activity, and hypertension, diabetes, CVD, cancer at baseline, negative correlations between CDAI and premature death (Fig. 4), as well as all-cause mortality (Fig. 5), were consistently observed across all categories. Except for the presence or absence of baseline

Table 3 Threshold effect analysis of CDAI with all-cause mortality and premature death using piece-wise linear regression

Outcomes	All-cause mortality		Premature death	
	HR (95%CI)	*P*- value	HR (95%CI)	*P*-value
Model I				
One-line effect	0.91 (0.85, 0.97)	0.004	0.96 (0.92, 1.00)	0.031
Model II				
Inflexion point	1.48		1.42	
< inflexion point	0.88 (0.82, 0.94)	< 0.001	0.93 (0.89, 0.97)	0.001
≥inflexion point	1.34 (1.02, 1.75)	0.034	1.32 (1.10, 1.58)	0.002
Log-likelihood ratio test		0.007		< 0.001

Abbreviations: HR = Hazard Ratio; CI = confidence interval; CDAI = composite dietary antioxidant index

The model was adjusted for gender, age, race, education level, marital status, PIR, BMI, alcohol, smoking, activity, energy intakes, CVD, diabetes, hypertension, cancer

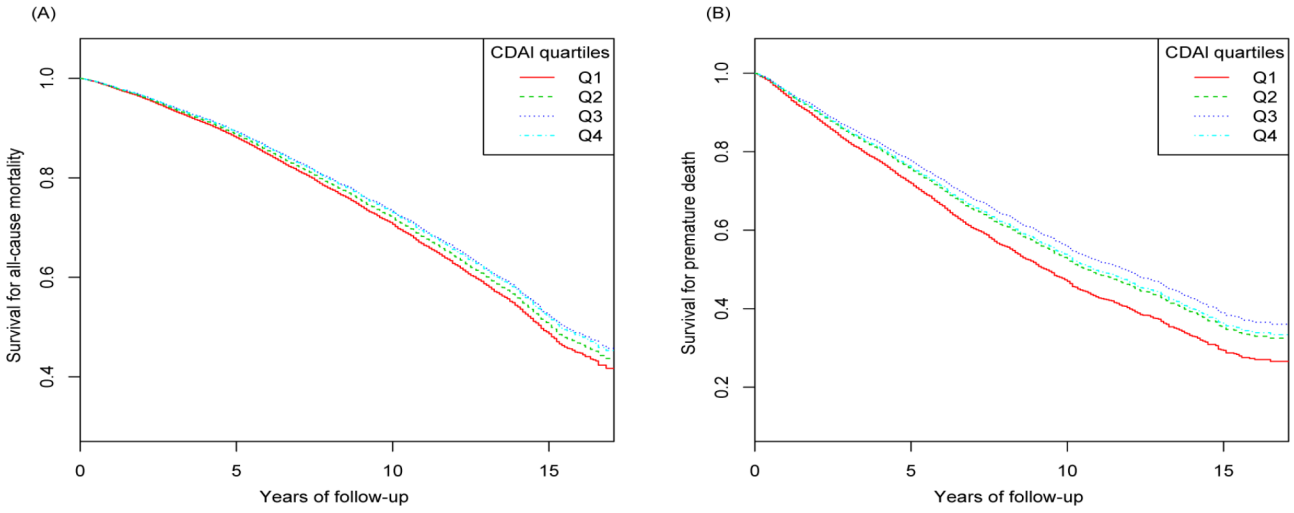

Fig. 3 Kaplan-Meier analysis of CDAI with all-cause mortality (**A**) and premature death by quartiles (**B**) after adjustment for gender, age, race, education level, marital status, PIR, BMI, alcohol, smoking, activity, energy intakes, CVD, diabetes, hypertension, cancer

cardiovascular disease, which affected the magnitude of the association between CDAI and premature death ($P = 0.007$ for the interaction), there was no statistically significant difference in its interaction with the stratification of the variables, which suggests that the associations between CDAI and premature death and all-cause mortality have a considerable degree of robustness.

After the removal of subjects with fewer than two years of follow-up from baseline, the findings of the fully adjusted regression models remained consistent with the primary analysis (Supplementary File S2). Meanwhile, similar results were observed when using a dataset that did not involve imputation of missing data for covariates (Supplementary File S3). Furthermore, all six components of the CDAI exhibited similar negative correlations with both premature death and all-cause mortality (Supplementary file S4).

Discussion

This cohort study included 37,301 participants from NHANES and found a non-linear association between CDAI and premature death and all-cause mortality, demonstrating a 'U' shaped pattern. Regression analyses were adjusted to minimize bias for potential confounders such as general demographic information, physical activity, and common chronic diseases. In addition, subgroup and sensitivity analyses were also carried out. The results showed that variations in these clinical factors did not significantly affect the relationships between the variables, confirming the robustness and reliability of the findings.

The findings of this study indicated a decreased risk of premature death and all-cause mortality with an increasing CDAI score. These negative associations remained consistent and significant across various subgroups and covariates. Our findings align with previous studies that emphasize the protective effects of dietary antioxidants against oxidative stress and inflammation, which are closely related to the development of various chronic diseases and mortality risk [9, 30, 31]. Oxidative stress is associated with medical issues such as atherosclerosis, hypertension, diabetes, neurodegenerative diseases, and cancer, playing both primary and secondary roles in disease progression [32–34]. Dietary antioxidants

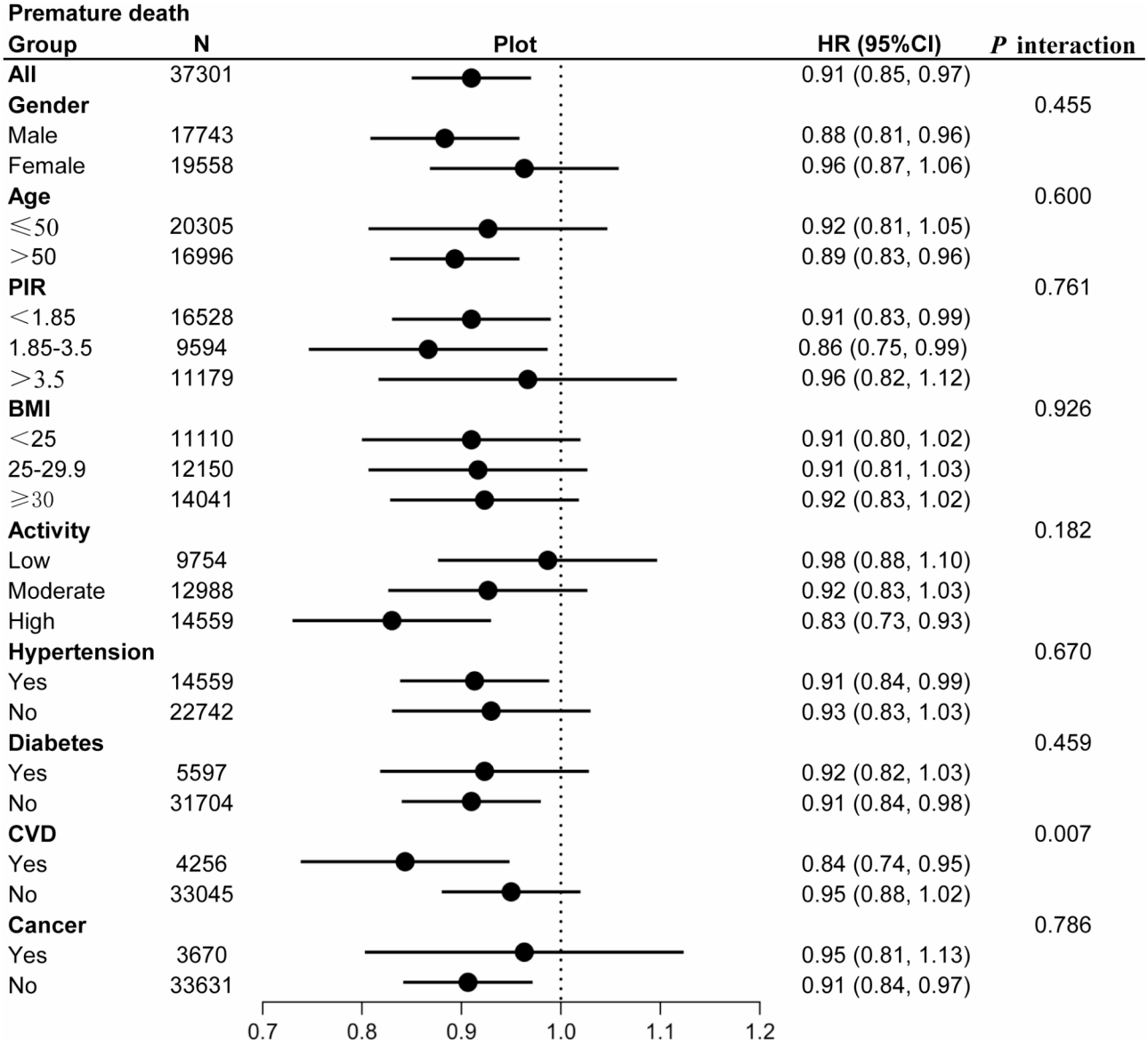

Fig. 4 Forest plot of the HRs of CDAI associated with premature death in different subgroups

play a crucial role in counteracting free radicals, reducing oxidative stress and inflammation, thereby aiding in the prevention of many chronic diseases and premature death [10]. The CDAI serves as a tool designed to assess the overall impact of nutritional antioxidants on human health [35].

The relationship between CDAI and human health has been extensively studied. Most researchers observed that CDAI offers protection against various chronic illnesses. Wu et al. [17] noted a negative linear relationship between CDAI and hypertension among adults. Similarly, Chen et al. [36] showed that increased levels of CDAI were linked to a lower incidence of diabetes, independent of CVD. Furthermore, consuming foods high in CDAI compounds could lower the risk of developing CVD, like heart failure [37], atherosclerotic cardiovascular disease [33], coronary heart disease [10], stroke [18] and cancer [11], which were the primary causes of premature death from NCDs. Moreover, CDAI has also been associated with age-related diseases. He et al. [38] reported a significant link between elevated CDAI scores and delayed biological aging in American adults. Wu et al. [39] discovered a negative correlation between CDAI scores and frailty symptoms in a study with 11,277 participants aged ≥ 60. Liu et al. [40] proposed that a diet rich in dietary antioxidants might lower the risk of osteoporosis.

Furthermore, researchers also explored the connection between CDAI and mortality. A cohort study demonstrated that a higher CDAI score was linked to a lower risk of all-cause mortality [41], consistent with our study.

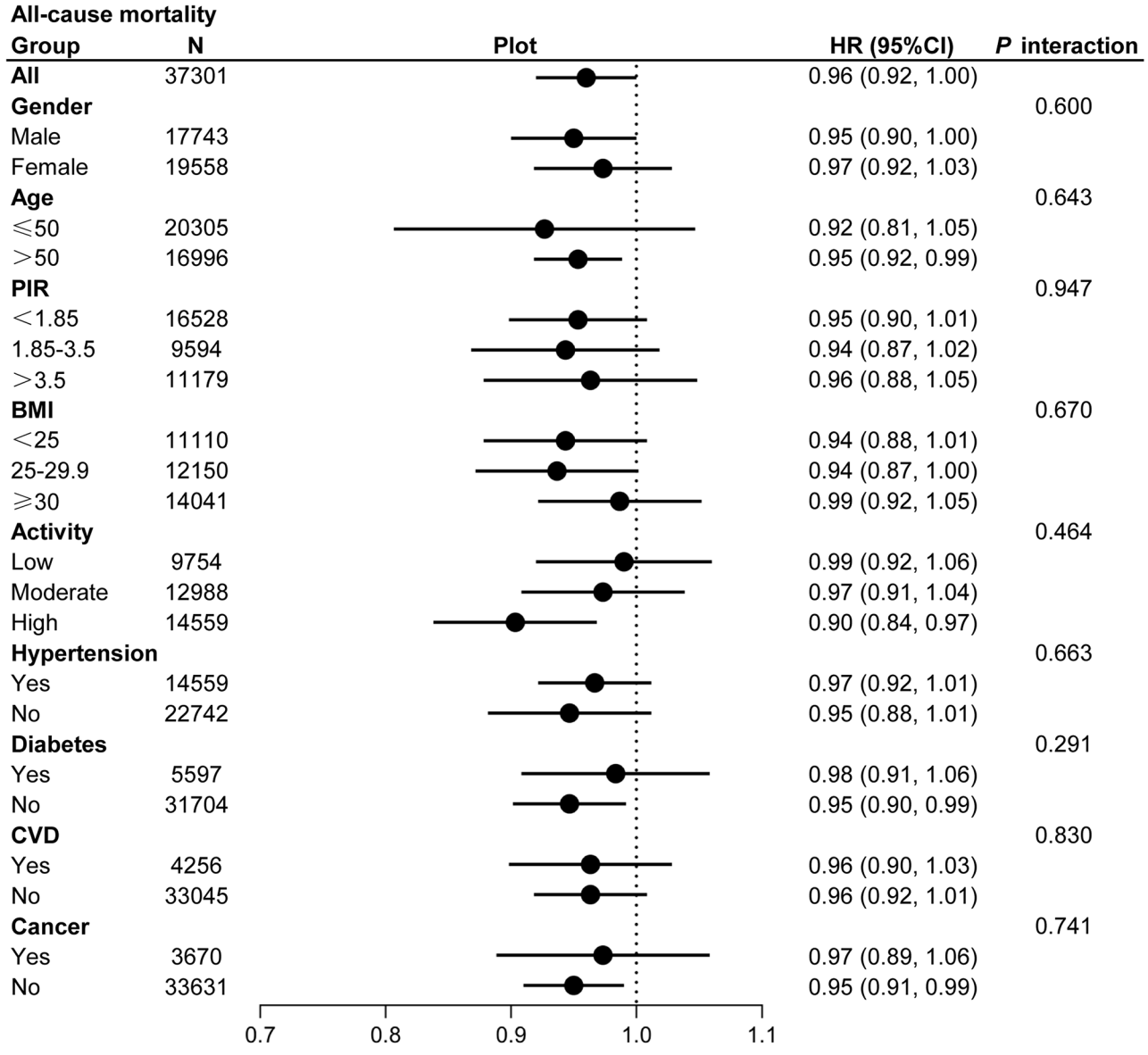

Fig. 5 Forest plot of the HRs of CDAI associated with all-cause mortality in different subgroups

This trend was similar to that seen in type 2 diabetes [31]. Another two studies [42, 43] highlighted the role of CDAI in reducing all-cause mortality in US patients with stage 1–2 chronic kidney disease and osteoarthritis. In a study involving 2077 tumor survivors aged 40 and above, Tan et al. [30] discovered a correlation between higher CDAI levels and a lower probability of all-cause mortality. The mechanism by which CDAI influences mortality can be summarized as follows.

Antioxidants play a crucial role in mitigating oxidative stress, inhibiting inflammatory responses, enhancing metabolic health, and regulating gut microbiota. These biological mechanisms may clarify the correlation between CDAI and reduced mortality. Firstly, antioxidants diminish oxidative stress and the associated cellular damage by neutralizing free radicals, which is vital for preventing various chronic diseases, including CVD, diabetes, and cancer [44]. Concurrently, they enhance cellular antioxidant capacity through the activation of the Nrf2 pathway, further alleviating the effects of oxidative stress [45]. A study by Rup and Pérez et al. demonstrated that plasma levels of antioxidants were associated with various pro-inflammatory and endothelial damage biomarkers, indicating a potential protective role for antioxidants [46]. Additionally, antioxidant-rich dietary patterns, such as the DASH diet and the Mediterranean diet, have been shown to reduce biomarkers of lipid peroxidation [47].

In the context of inflammation regulation, chronic low-grade inflammation is a significant contributor

to metabolic disorders. Antioxidants mitigate chronic inflammation and the associated tissue damage and fibrosis by inhibiting the expression of pro-inflammatory factors, such as TNF-α and IL-6 [48–50]. Additionally, studies have demonstrated that egg white protein peptides derived from simulated gastrointestinal digestion effectively modulate inflammatory diseases, including ulcerative colitis [51]. Furthermore, research by Radkhah et al. indicated a close relationship between antioxidant-rich diets and levels of inflammatory markers, such as IL-1β and PAI-1 [52].

Antioxidants also play a significant role in metabolic health, particularly by enhancing energy metabolism through improved mitochondrial function, increased insulin sensitivity, and the regulation of lipid and carbohydrate metabolism [53]. Furthermore, antioxidants are crucial in regulating the intestinal microbiota, promoting the growth of beneficial bacteria and modulating intestinal metabolic functions, which in turn influence the host's immune system and metabolic processes. Experimental studies in animals demonstrated that antioxidant compounds, such as berry polyphenols and fiber, positively regulate the intestinal microbiota in obese mice [54].

Although most evidence suggests the beneficial effects of dietary antioxidants on health maintenance, several challenges and knowledge gaps persist. Some studies suggest that consuming antioxidants in food can slow down or hinder the advancement of tumors by counteracting free radicals and repairing oxidative damage to minimize the impact of oxidative stress [30, 55]. However, other research has indicated that antioxidant supplements do not enhance survival rates in cancer patients and may even facilitate tumor metastasis [56]. For instance, a study by Zujko et al. found that exogenous supplementation of antioxidant vitamins and minerals in people without nutritional deficiencies has no beneficial effects on the prevention of cardiovascular diseases, suggesting a nuanced understanding of antioxidant sources is necessary [57].

Interestingly, the regression analyses revealed an inverse relationship between CDAI and premature death as well as all-cause mortality. While in the RCS analysis, 'U' - shaped relationships were observed. The result suggests that as one increases their intake of dietary antioxidants, the likelihood of premature death and all-cause mortality decreases initially but may reverse when CDAI value was more than 1.42 or 1.48, highlighting the importance of optimizing dietary recommendations to avoid excessive and insufficient intake. The U-shaped association between CDAI and mortality suggests that more dietary antioxidant intake may not be better. Personalized dietary advice considering individual lifestyle, disease risk, and health status is crucial. This study provides valuable insights for future research, such as validating whether surpassing a certain threshold could potentially result in adverse effects and exploring the mechanisms behind the 'U' shaped association, including dose effects of antioxidants, interactions, and individual variations. Long-term intervention studies could assess the impact of modifying dietary antioxidant intake on the risk of premature and all-cause mortality, supporting clinical practice.

This study had several strengths. First, to our knowledge, this was the first attempt to explore the relationship between CDAI levels and premature death. Second, this study was a large-sample, prospectively designed study with extensive follow-up, controlling for potential confounders and enhancing the reliability of the findings. However, there were limitations, such as reliance on retrospective dietary data prone to recall bias, and the sample's demographic characteristics may restrict generalizability. Moreover, other potential factors like genetics, environment, and lifestyle could influence the association between CDAI and various health outcomes. Future studies should focus on improving study design and considering additional influencing factors for a more comprehensive understanding of this association. Furthermore, seasonal variability may influence the consumption of foodstuffs (especially fruits) intake and antioxidant levels. Nevertheless, seasonal data were not incorporated into the NHANES data collection process, and therefore seasonal confounding could not be included in the analyses. This limitation may introduce confounding bias into our results.

Conclusion

In conclusion, the present study revealed a negative non-linear correlation between CDAI and premature death as well as all-cause mortality, with a 'U' shaped pattern observed. These results underscore the significance of dietary antioxidant intake in promoting overall health and longevity. The non-linear association highlights the need for personalized dietary recommendations. While our findings contribute valuable insights, additional investigation is necessary to explore the fundamental mechanisms and optimize dietary interventions for improving health outcomes.

Abbreviations

BMI	Body mass index
CVD	Cardiovascular disease
CDAI	Composite dietary antioxidant indices
HR	Hazard ratios
IQR	Interquartile range
NCDs	Non communicable diseases
NHANES	National Health and Nutrition Examination Survey
NDI	National Death Index
PIR	Poverty income ratio
RCS	Restricted cubic spline

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-025-21748-x .

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Author contributions

H.Q.Z. and L.T.L. conceived this paper. H.Q.Z. drafted the manuscript under guidance of L.T.L. Y.S. and X.C. contributed to data acquisition and statistical analysis. N.W., Y.Z., B.X.G. and R.Z. reviewed/edited the manuscript. All authors contributed to the writing of the paper and gave final approval of the submitted manuscript.

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Data availability

Data for this article is available at the following websites: https://wwwn.cdc.gov/nchs/nhanes/.

Declarations

Ethics approval and consent for participation

The study utilized publicly available, de-identified data from the National Health and Nutrition Examination Survey (NHANES), which is managed by the National Center for Health Statistics (NCHS). The NCHS Institutional Review Board (IRB) approved all NHANES data collection protocols, and written informed consent was obtained from all participants by the NCHS at the time of data collection. No additional ethical approval was required for the secondary analysis conducted in this study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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