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Joint and independent associations of dietary antioxidant intakes with all-cause and cardiovascular mortality among patients with hypertension: a population-based cohort study

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Abstract

Background The evidence regarding dietary antioxidant intake and all-cause and cardiovascular disease (CVD) mortality among patients with hypertension is scarce.

Methods and results This study included 16,190 adults with hypertension from the National Health and Nutrition Examination Survey (NHANES) 1999–2018. Death outcomes were ascertained by linkage to National Death Index records through December 31, 2019. Overall dietary intake was estimated with composite dietary antioxidant index (CDAI). Cox proportional hazards models were used to estimate the risk for all-cause and CVD mortality. Kaplan–Meier curve was used to illustrate the survival probabilities among CDAI quartiles. Weighted quantile sum (WQS) regression was conducted to evaluate the joint and independent associations of antioxidants with all-cause and CVD mortality. The median (interquartile range) age of participants was 59.00 (47.00, 69.00) years. During a median of 94 months of follow-up, 3,858 deaths were documented. Compared to participants with the lowest quartile of CDAI, the multivariable adjusted HR and 95% CI for participants with the highest quartile was 0.76 (0.64, 0.91) for all-cause mortality. The highest quartile (Q4) of vitamin E (HR = 0.69; 95% CI, 0.59–0.80), selenium (HR = 0.84; 95% CI, 0.70–1.00) and total carotenoids (HR = 0.86; 95% CI, 0.75–0.98) intakes were negatively associated with all-cause mortality. Vitamin E and selenium intakes might be the major contributors to this negative relationship. The highest quartile (Q4) of vitamin E (HR = 0.72; 95% CI, 0.56–0.93) intake was negatively associated with CVD mortality.

Conclusion Higher overall dietary antioxidant intake was significantly associated with decreased all-cause and CVD mortality among patients with hypertension. Further randomized controlled trials are required to confirm our findings.

Keywords composite dietary antioxidant index, hypertension, all-cause mortality, CVD mortality, National Health and Nutrition Examination Survey (NHANES), antioxidants

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Introduction

Hypertension, or high blood pressure, is a prevalent medical ailment characterized by persistently elevated arterial blood pressure. It affects approximately one-third of the global adult population [1]. Patients with hypertension have an increased risk of developing severe complications, including cardiovascular disease, stroke, and renal dysfunction, as well as increased mortality [2, 3].

Oxidative stress has been considered a contributor to endothelial dysfunction and vascular stiffness in the pathophysiology of hypertension [4, 5]. Therefore, antioxidant therapy has been introduced to the management of hypertension [6]. Among all antioxidative approaches, diet intervention has drawn increasing attention as a nonpharmacological strategy in clinical practice guidelines [7]. Dietary antioxidant intakes could reduce oxidative stress and thus protect against poor prognosis among patients with hypertension.

Previous studies have reported the inverse relationship between overall dietary antioxidant capacity and all-cause mortality among the general population [8, 9]. This negative association was also demonstrated among patients with chronic diseases like diabetes [10]. However, whether dietary antioxidant intake could improve the prognosis of patients with hypertension is merely discussed. Besides, although some individual antioxidant levels were reported to be associated with a lower risk of all-cause mortality, few studies have estimated the major antioxidant that contributed to the potential negative association between antioxidants and reduced risk of mortality [11, 12]. Moreover, the effect of some antioxidants like vitamin E is still under discussion [13, 14].

To fill this gap, we aim to explore the joint associations of dietary antioxidant intakes (indicated by CDAI) with all-cause and CVD mortality among U.S. participants with hypertension, as well as identifying the individual micronutrients that are predominant in this association.

Materials and methods

Study population

We obtained data from the NHANES, a population-based survey to assess the nutritional and health status of the non-institutionalized United States civilization. The survey was conducted in two-year cycles using a complex stratified, multistage probability design. Using sampling weights, we obtained a nationally representative sample across the U.S.. Methodological details of the NHANES are available at www.cdc.gov/nchs/nhanes/. The Ethics Review Board of the National Center for Health Statistics (NCHS) granted approval for the survey protocol. Written informed consent form was obtained from all participants.

The present study utilized data from ten consecutive NHANES survey cycles (1999–2018). The exclusion criteria were as follows: (1) age < 18 years, (2) pregnant individuals, (3) participants without survival status (4) participants without dietary information, and (5) participants without hypertension. After exclusion, a total of 16,190 participants with hypertension remained for the final analysis (Fig. S1).

Definition of hypertension

Hypertension was defined as self-reported diagnosis by a physician, taking prescribed antihypertensive medications, or presenting with mean SBP ≥ 140 mmHg, or mean DBP ≥ 90 mmHg. In sensitivity analyses, the cut-off value of BP was set as mean SBP ≥ 130 mmHg, or mean DBP ≥ 80 mmHg according to the guidelines of American College of Cardiology/American Heart Association [7].

Collection of dietary information

Total nutrient intakes were obtained from two separate 24-hour dietary recalls, which included the types and amounts of foods and beverages consumed during the 24-hour period prior to the interview. The first recall was collected by an in-person interview in the mobile examination center (MEC), and the second recall was scheduled 3–10 days later by telephone. The mean intake of two dietary recalls was used in our analysis. Six antioxidants were concerned in our study, including vitamin A, vitamin C, vitamin E, zinc, selenium, and total carotenoids. The assessment of dietary antioxidants did not encompass antioxidants derived from dietary supplements, medication, or drinking water. The joint effect of dietary intake was evaluated with CDAI developed by Wright et al. [15, 16]. Briefly, the CDAI was calculated as the sum of the normalized intakes of the six antioxidants. Normalization was performed by subtracting the mean of the intake of each antioxidant and divided by the standard deviation.

Assessment of the outcome

Death outcomes were ascertained by linkage to National Death Index records through December 31, 2019. Follow-up time was defined as the period from the date of interview on MEC to the date of death or to the end of follow-up. CVD death was defined as ICD-10 codes I00-I09, I11, I13, and I20-I51.

Covariates

Covariates include age, sex (male or female), race (non-Hispanic white, non-Hispanic black, or others), educational level (less than high school or high school and above high school), body mass index (BMI), smoking history (current, former, or never), total energy intake (kcal), type 2 diabetes (T2D, yes or no), cardiovascular disease (CVD, yes or no), and chronic kidney disease (CKD, yes or no).

BMI was calculated as the ratio of body weight (kg) to the square of height (m) and expressed as kg/m^2. T2D was diagnosed with the following criteria: fasting glucose ≥ 7 mmol/L, random glucose ≥ 11.1 mmol/L, glycated hemoglobin A1c ≥ 6.5%, the usage of hypoglycemic drugs, or a history of diabetes. CVD was recognized by a self-reported physician's diagnosis of congestive heart failure, coronary heart disease, angina, heart attack, or stroke. The estimated glomerular filtration rate (eGFR) was calculated based on the Chronic Kidney Disease Epidemiology Collaboration creatinine equation [17]. CKD was determined by eGFR < 90 ml/min/1.73m^2 or albuminuria > 30 mg/g [18].

Statistical analysis

All analyses incorporated proper sample weights, and the weighted statistical analyses were conducted with R package "survey" conforming to NHANES analytic guidelines to produce national-representative estimates. Continuous variables were analyzed with Mann-Whitney U test and presented as medians (interquartile ranges). Categorical variables were analyzed with χ^2 test and presented as frequencies. Correlation between pairwise antioxidants was assessed using Spearman correlation coefficients. Missing rates for all covariates were < 5%, and missing data were imputed using the random forest algorithm with the R package "missForest".

We conducted weighted multivariable cox proportional hazards regressions to estimate the risk of antioxidants for all-cause and CVD mortality. Model 1 was unadjusted, whereas Model 2 was adjusted for age, sex, and race. Model 3 was further adjusted for educational level, BMI, smoking status, total energy intake, T2D, CVD, and CKD. The results were expressed as hazards ratios (HRs) with 95% confidence intervals (95% CIs). To explore the potential non-linear relationship, we plotted 4-knots (5th, 35th, 65th, and 95th percentiles) weighted restricted cubic spline (RCS) based on the fully adjusted model. The nonlinearity was tested using the likelihood ratio test. The Kaplan–Meier method was used to construct the survival curves among patients with different CDAI quartiles, and the differences of survival probability were evaluated with log-rank test.

Subgroup analyses were stratified by age (< 60 or ≥ 60 years), sex (male or female), BMI (< 25, 25–30, or ≥ 30 kg/m^2), T2D (yes or no), CVD (yes or no), and CKD (yes or no). The interaction effects between CDAI and those variables were evaluated.

Several sensitivity analyses were also performed to test the robustness of our study. First, patients who died within the first two years of follow-up were excluded to reduce inverse casualty. Second, we further enrolled participants with mean SBP ≥ 130mmHg or mean DBP ≥ 80mmHg [19]. Third, we further adjusted for the supplementary consumption of antioxidants. Fourth, we further adjusted for the medication use. Lastly, we repeated the main analyses after excluding patients with missing covariates.

Additionally, we conducted WQS regression with R package "gWQS". WQS is a novel method used in estimating the joint and independent effects of mixed exposure [20]. The data were randomly split into training sets (40%) and validation sets (60%), and the training set was bootstrapped 400 times. The overall effect of six antioxidants and weight of each component (represents the contribution of certain exposure to all-cause mortality) were calculated. Weights of all antioxidants constrained to sum to 1 and the exposure with weight over 0.17 was considered to be the major contributor of the association between antioxidants and all-cause mortality. The covariates adjusted in WQS were the same as the fully adjusted cox regression model. A two-sided $p < 0.05$ was considered as statistically significant. All analyses were performed with R (version 4.1.0).

Results

Among 16,190 participants with hypertension, the median (interquartile range) age was 59.00 (47.00, 69.00), and 48.51% were male. Table 1 presents the baseline characteristics of study participants stratified by survival status. The participants who survived were more likely to be younger, non-smokers, with higher educational level, higher BMI, higher energy intake and lower prevalence of comorbidities including T2D, CVD, and CKD ($p < 0.001$). Besides, survivors had higher intake of vitamin A, vitamin C, and lower intake of zinc, selenium, and total carotenoids.

The correlation coefficients between either two antioxidants ranged from 0.17 to 0.65 (Fig. 1). The correlation between Se and Zn was strongest ($r = 0.65$), followed by correlation coefficients of vitamin E and Se ($r = 0.52$), vitamin E and Zn ($r = 0.50$), and vitamin A and total carotenoids ($r = 0.50$).

During a median follow-up of 94 months, 3,858 deaths were documented. The crude and adjusted HRs with 95% CIs for joint and independent dietary antioxidant intake are shown in Table 2. We used the CDAI to assess the joint effect of six antioxidants. After multivariable adjustment, the highest quartile (Q4) of CDAI was significantly associated with decreased all-cause mortality among patients with hypertension. The multivariable adjusted HRs and 95% CIs across CDAI quartiles were 1.00 (ref.), 0.90 (0.79, 1.03), 0.81 (0.69, 0.95), and 0.76 (0.64, 0.91) (P_{trend} = 0.002). No significant association was found between CDAI and CVD mortality in the fully adjusted model (Table 3). The RCS curve indicated a L-shaped association of CDAI with all-cause mortality ($P_{non-linear}$<0.001) and a linear association of CDAI with

Table 1 Weighted baseline characteristics of participants according to quartile of the CDAI

Characteristics	Q1	Q2	Q3	Q4	*P* value
Age (year)	59.00 (47.00, 69.00)	60.00 (48.00, 71.00)	59.00 (48.00, 69.00)	56.00 (46.00, 67.00)	< 0.0001
Male sex (%)	34.09 (0.97)	42.92 (1.05)	49.92 (1.18)	62.71 (1.06)	0.75
Race (%)					< 0.0001
Hispanic	11.59 (0.98)	9.42 (0.89)	8.29 (0.67)	8.60 (0.75)	
Non-Hispanic white	63.79 (1.77)	72.08 (1.53)	75.43 (1.29)	75.50 (1.21)	
Non-Hispanic black	18.90 (1.29)	12.92 (0.91)	10.76 (0.77)	10.51 (0.70)	
Others	5.72 (0.58)	5.58 (0.50)	5.52 (0.50)	5.39 (0.42)	
Educational level ≥ High school	73.25 (1.01)	81.25 (0.87)	85.03 (0.85)	87.72 (0.72)	< 0.0001
BMI (kg/m^2)	30.00 (26.10, 34.70)	30.00 (26.30, 34.70)	29.70 (26.00, 34.14)	30.00 (26.40, 34.61)	< 0.0001
Smoking status (%)					< 0.0001
Current	24.02 (0.95)	17.94 (0.84)	15.98 (0.83)	14.76 (0.70)	
Former	29.13 (1.15)	30.89 (1.06)	33.46 (1.20)	34.78 (0.96)	
Never	46.85 (1.25)	51.16 (1.13)	50.56 (1.22)	50.46 (1.00)	
Total energy intake (kcal)	1145.00 (858.00, 1448.00)	1599.00 (1316.00, 1966.00)	1977.00 (1621.00, 2402.00)	2573.00 (1983.00, 3268.00)	< 0.0001
T2D (%)	27.39 (1.00)	25.28 (0.90)	25.85 (0.86)	23.42 (0.90)	< 0.0001
CVD (%)	19.85 (0.87)	19.42 (0.77)	16.86 (0.81)	15.60 (0.78)	< 0.0001
CKD (%)	30.09 (1.05)	29.45 (0.97)	24.75 (0.99)	21.91 (0.92)	< 0.0001
CDAI	-3.11 (-3.83, -2.61)	-1.23 (-1.68, -0.83)	0.65 (0.14, 1.24)	4.16 (2.83, 6.30)	< 0.0001
Vitamin A (mcg)	208.00 (108.00, 337.00)	422.00 (282.00, 599.00)	603.00 (403.00, 847.00)	947.00 (628.00, 1379.00)	0.05
Vitamin C (mg)	17.70 (7.10, 38.10)	42.10 (20.40, 81.30)	70.40 (33.50, 122.50)	118.80 (64.10, 198.90)	0.04
Vitamin E (mg)	3.05 (1.98, 4.28)	5.15 (3.86, 6.73)	7.31 (5.47, 9.48)	11.54 (8.36, 16.47)	< 0.0001
Zinc (mg)	5.20 (3.60, 6.87)	8.29 (6.35, 10.61)	10.80 (8.41, 13.78)	15.58 (11.30, 20.93)	< 0.0001
Selenium (mcg)	56.30 (40.20, 74.00)	86.60 (66.80, 107.00)	110.10 (85.50, 138.50)	147.10 (108.90, 194.20)	< 0.0001
Total carotenoids (mg)	1425.00 (473.00, 3234.00)	4063.00 (1729.00, 7740.00)	7304.00 (3361.00, 13046.00)	14563.00 (6299.00, 27645.00)	< 0.0001

BMI: body mass index; T2D: type 2 diabetes; CVD: cardiovascular disease; CKD: chronic kidney disease; CDAI: composite dietary antioxidant index

CVD mortality (Fig. 2). Kaplan–Meier survival curves according to quartiles of CDAI are displayed in Fig. 3. Significant differences were found in the risk of all-cause and CVD mortality across the quartiles of CDAI.

Additionally, the highest quartile (Q4) of vitamin E (HR = 0.69; 95% CI, 0.59–0.80), selenium (HR = 0.84; 95% CI, 0.70–1.00) and total carotenoids (HR = 0.86; 95% CI, 0.75–0.98) intakes were negatively associated with all-cause mortality. Similarly, a non-linear association of vitamin C, vitamin E, zinc, and total carotenoids intakes with all-cause mortality was observed ($P_{non-linear}$ <0.05; Fig. S2). We also found a negative association between vitamin E intake and CVD mortality after full adjustment (Q4 vs. Q1, HR = 0.72; 95% CI, 0.56–0.93; Table 3). However, a nonlinear relationship was only observed between vitamin C and CVD mortality ($P_{non-linear}$ = 0.016; Fig. S3).

In subgroup analysis, the relationship between dietary antioxidant intakes and all-cause mortality was only significant in participants with age ≥ 60 years, BMI = 25–30 kg/m^2, CVD, CKD, and without T2D. No interaction was found between subgroup variables and the link between CDAI and all-cause mortality ($P_{interaction}$ >0.05, Table 4). No interaction effect was found for CVD mortality (Table S1).

In sensitivity analyses, the negative association of joint antioxidant intake with all-cause mortality was not materially changed after exclusion of patients who died within the first two-years of follow-up (Table S2), diagnosed with other criteria (Table S3), further adjusted for supplementary consumption of antioxidants, medication use and exclusion of patients with missing covariates (Table S4).

WQS analysis showed a significant association between dietary antioxidant mixture intake and decreased all-cause mortality with HR = 0.73 (0.69, 0.77). Besides, vitamin E (weight = 0.490) and selenium (weight = 0.391) intakes were the major factors contributed to the decrease of all-cause mortality (Fig. S4).

Discussion

In this large-scale cohort study of nationally representative U.S. individuals with hypertension, we found that higher intake of specific antioxidants, particularly Vitamin E and selenium, was significantly associated with

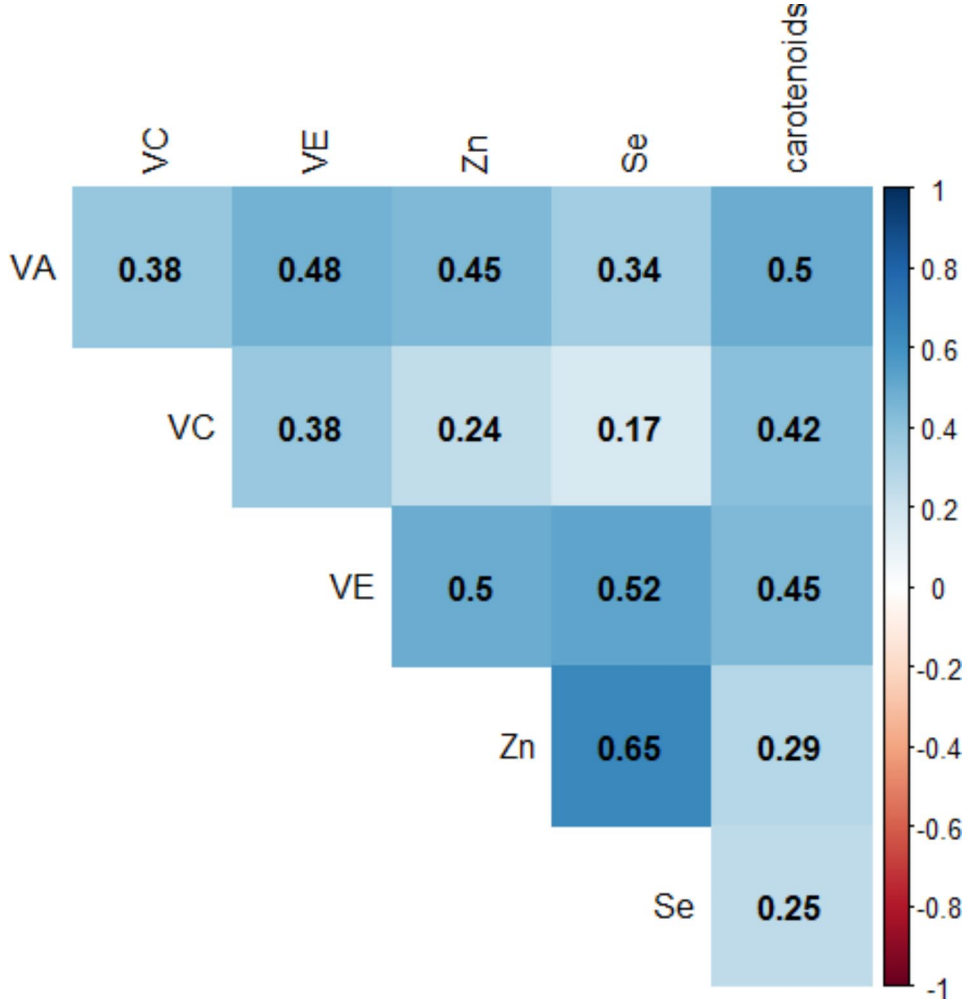

Fig. 1 Correlation between pairwise antioxidants

decreased all-cause mortality. Besides, higher intake of vitamin E was associated with decreased CVD mortality. These associations remained robust across several sensitivity analyses.

Previous studies have reported a link between overall dietary antioxidant intake and mortality among general and specific populations. Wang et al. found an inverse association between CDAI and all-cause mortality [9]. An observational study enrolled participants from the NHANES 2005–2014 suggested increased intake of dietary antioxidants could reduce the risk of all-cause mortality in stroke patients [21]. A similar relationship was also found among patients with diabetes [10]. In line with these studies, our study demonstrated a negative association between CDAI and all-cause mortality among hypertensive patients.

Our study identified vitamin E and selenium as the major contributors to reduced all-cause mortality among patients with hypertension. Vitamin E is a fat-soluble vitamin which modulate enzymes involved in various signal transduction pathways. In our research, vitamin E intake was negatively associated with all-cause mortality among patients with hypertension. Similarly, a systematic review and dose-response meta-analysis of prospective studies demonstrated that higher dietary intake or blood concentrations of α-tocopherol were linked with reduced all-cause mortality [22]. Moreover, dietary vitamin E intake was associated with new-onset hypertension with a reverse J-shaped curve, which was also found in our study (Fig. S3) [23].

Selenium is an essential trace element participating in endogenous antioxidant process. A meta-analysis of randomized controlled trials (RCTs) suggested that selenium should be added to antioxidant mixtures for reduction of all-cause mortality [24]. Another research including 18,932 adults from NHANES database also indicated an inverse association between selenium intake and all-cause mortality among general population [12]. Additionally, an animal experiment on spontaneously hypertensive rats demonstrated higher selenium intake

Table 2 Association of dietary antioxidant intakes with all-cause mortality

	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
CDAI			
Q1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Q2	0.99 (0.87, 1.12)	**0.87 (0.77, 0.99)**	0.90 (0.79, 1.03)
Q3	**0.81 (0.70, 0.93)**	**0.73 (0.64, 0.84)**	**0.81 (0.69, 0.95)**
Q4	**0.66 (0.57, 0.76)**	**0.69 (0.61, 0.78)**	**0.76 (0.64, 0.91)**
P for trend	**< 0.001**	**< 0.001**	**0.002**
Vitamin A			
Q1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Q2	1.13 (0.98, 1.29)	0.93 (0.81, 1.06)	1.00 (0.87, 1.14)
Q3	**1.19 (1.04, 1.37)**	**0.86 (0.75, 0.98)**	0.95 (0.83, 1.09)
Q4	1.14 (0.99, 1.30)	**0.82 (0.71, 0.94)**	0.93 (0.79, 1.09)
P for trend	0.165	**0.004**	0.306
Vitamin C			
Q1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Q2	1.07 (0.93, 1.23)	0.89 (0.79, 1.00)	0.94 (0.84, 1.06)
Q3	1.10 (0.97, 1.25)	**0.73 (0.64, 0.83)**	**0.82 (0.72, 0.93)**
Q4	1.00 (0.87, 1.14)	**0.73 (0.65, 0.82)**	0.89 (0.78, 1.01)
P for trend	0.665	**< 0.001**	0.093
Vitamin E			
Q1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Q2	0.98 (0.88, 1.10)	**0.88 (0.79, 0.98)**	0.93 (0.83, 1.03)
Q3	**0.75 (0.66, 0.85)**	**0.75 (0.66, 0.84)**	**0.76 (0.67, 0.87)**
Q4	**0.62 (0.55, 0.71)**	**0.65 (0.54, 0.74)**	**0.69 (0.59, 0.80)**
P for trend	**< 0.001**	**< 0.001**	**< 0.001**
Zinc			
Q1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Q2	**0.79 (0.71, 0.89)**	**0.79 (0.70, 0.89)**	**0.84 (0.74, 0.96)**
Q3	**0.75 (0.66, 0.85)**	**0.78 (0.69, 0.88)**	**0.86 (0.75, 0.99)**
Q4	**0.64 (0.56, 0.74)**	**0.79 (0.69, 0.90)**	0.89 (0.74, 1.07)
P for trend	**< 0.001**	**0.012**	0.512
Selenium			
Q1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Q2	**0.89 (0.79, 1.00)**	0.92 (0.83, 1.03)	0.94 (0.83, 1.05)
Q3	**0.76 (0.67, 0.87)**	**0.85 (0.75, 0.96)**	**0.91 (0.80, 1.04)**
Q4	**0.55 (0.49, 0.63)**	**0.80 (0.70, 0.92)**	**0.84 (0.70, 1.00)**
P for trend	**< 0.001**	**< 0.001**	**0.049**
Total carotenoids			
Q1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Q2	0.95 (0.84, 1.08)	**0.87 (0.77, 0.98)**	0.92 (0.82, 1.02)
Q3	**0.78 (0.67, 0.91)**	**0.73 (0.63, 0.84)**	**0.81 (0.70, 0.93)**
Q4	**0.76 (0.66, 0.89)**	**0.75 (0.66, 0.85)**	**0.86 (0.75, 0.98)**
P for trend	**< 0.001**	**< 0.001**	0.056

Model 1: unadjusted. Model 2: age, sex, race Model 3: further adjusted for educational level, BMI, smoking status, total energy intake, history of T2D, CVD, and CKD. The bold values indicated statistically significant

was associated with better prognosis [25]. Interestingly, Tan et al. found a U-shaped association between serum selenium and all-cause mortality, while the Denmark PRECISE study reported a 300ug/d dose of selenium taken for 5 years could significantly increase all-cause mortality [26, 27]. These findings suggested that both deficiency and overdose of selenium could cast potential adverse consequences.

Oxidative stress plays a key role in hypertension pathogenesis, which may explain the favorable effect of dietary antioxidant intake on the prognosis of hypertension patients. Cumulative evidence has revealed the underling mechanisms. Reactive oxygen species (ROS)

Table 3 Association of dietary antioxidant intakes with CVD mortality

	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
CDAI			
Q1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Q2	1.18 (0.99, 1.40)	1.04 (0.88, 1.24)	1.13 (0.93, 1.36)
Q3	0.88 (0.70, 1.11)	0.80 (0.64, 1.01)	1.01 (0.77, 1.32)
Q4	**0.66 (0.53, 0.82)**	**0.71 (0.57, 0.87)**	0.93 (0.72, 1.22)
P for trend	**< 0.001**	**< 0.001**	0.330
Vitamin A			
Q1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Q2	1.13 (0.88, 1.44)	0.91 (0.72, 1.14)	0.99 (0.79, 1.24)
Q3	**1.22 (0.96, 1.56)**	0.85 (0.66, 1.09)	1.00 (0.78, 1.29)
Q4	1.15 (0.93, 1.44)	0.80 (0.64, 1.01)	0.99 (0.77, 1.28)
P for trend	0.259	0.060	0.960
Vitamin C			
Q1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Q2	1.12 (0.87, 1.45)	0.91 (0.72, 1.15)	0.99 (0.78, 1.26)
Q3	1.17 (0.94, 1.46)	**0.74 (0.60, 0.92)**	0.87 (0.70, 1.08)
Q4	1.06 (0.84, 1.33)	**0.74 (0.60, 0.92)**	0.96 (0.77, 1.20)
P for trend	0.859	0.004	0.675
Vitamin E			
Q1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Q2	1.06 (0.91, 1.25)	0.95 (0.81, 1.12)	1.05 (0.89, 1.24)
Q3	**0.71 (0.58, 0.87)**	**0.71 (0.58, 0.88)**	**0.78 (0.63, 0.97)**
Q4	**0.56 (0.44, 0.72)**	**0.60 (0.47, 0.77)**	**0.72 (0.56, 0.93)**
P for trend	**< 0.001**	**< 0.001**	**0.003**
Zinc			
Q1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Q2	0.86 (0.72, 1.02)	0.87 (0.72, 1.05)	1.00 (0.80, 1.25)
Q3	**0.79 (0.64, 0.97)**	0.84 (0.69, 1.02)	1.06 (0.83, 1.35)
Q4	**0.61 (0.47, 0.79)**	0.79 (0.61, 1.02)	1.05 (0.75, 1.47)
P for trend	**< 0.001**	0.114	0.743
Selenium			
Q1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Q2	1.00 (0.84, 1.18)	1.05 (0.90, 1.22)	1.11 (0.93, 1.32)
Q3	**0.71 (0.56, 0.90)**	0.81 (0.65, 1.02)	0.95 (0.74, 1.20)
Q4	**0.51 (0.40, 0.64)**	**0.78 (0.61, 1.00)**	0.95 (0.68, 1.32)
P for trend	**< 0.001**	**0.049**	0.528
Total carotenoids			
Q1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Q2	0.97 (0.77, 1.22)	0.88 (0.71, 1.09)	0.94 (0.76, 1.17)
Q3	**0.86 (0.67, 1.11)**	0.80 (0.63, 1.02)	0.93 (0.74, 1.17)
Q4	**0.85 (0.66, 1.09)**	0.84 (0.64, 1.06)	1.00 (0.79, 1.28)
P for trend	0.146	0.250	0.725

Model 1: unadjusted. Model 2: age, sex, race Model 3: further adjusted for educational level, BMI, smoking status, total energy intake, history of T2D, CVD, and CKD
The bold values indicated statistically significant

are generated excessively during the progression of hypertension, leading to endothelial damage and vascular stiffness, which are essential mechanisms involving hypertension [28]. Antioxidants are known to eliminate ROS via different pathways. An animal experiment demonstrated that vitamins C and vitamin E reduced oxidative stress by activating vascular NADPH oxidase and superoxide dismutase, which might contribute to enhanced vascular function and better prognosis [29]. The dietary selenium may also provide protection against oxidative stress through selenoproteins and thioredoxin reductases, which are involved in various cellular functions [30]. It has been reported that selenium deficiency

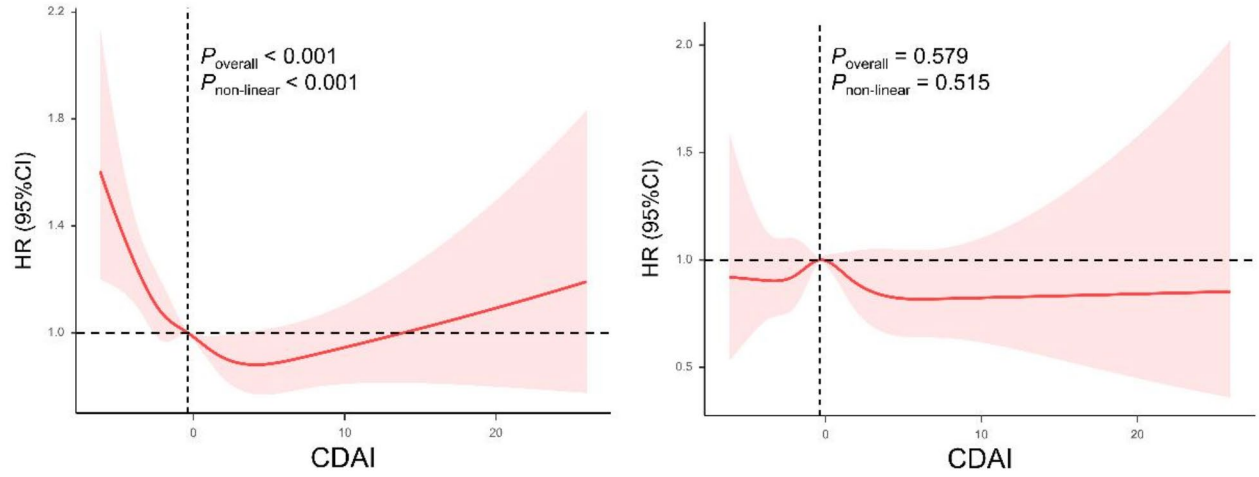

Fig. 2 Restricted cubic spline for the relationship between CDAI and risk of all-cause and CVD mortality

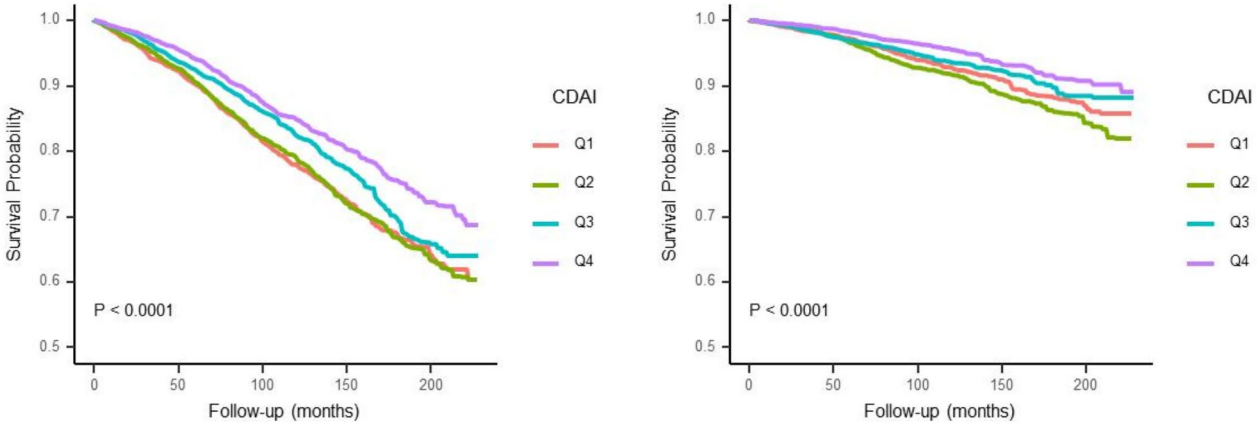

Fig. 3 Kaplan–Meier curves for the all-cause and CVD mortality across quartiles of CDAI

increased renal AT(1) receptor expression via GPx1/H(2)O(2)/NF-κB pathway, leading to hypertension [31].

Given that hypertension is a chronic disease with a high risk of complications and mortality, effective long-term dietary management is crucial. Our findings suggest that maintaining an antioxidant diet may lower mortality risk among individuals with hypertension. Therefore, the present study may provide some potential implications for developing nonpharmacological strategies to improve the prognosis of patients with hypertension. Notably, we observed an L-shaped relationship between total antioxidant intake and all-cause mortality, indicating that insufficient antioxidant intake may lead to poor prognosis, while excessive consumption may not provide additional benefits for mortality. One hypothesis is that excessive antioxidants may paradoxically cause a pro-oxidative effect [32]. For this reason, hypertensive patients should be cautious of excessive antioxidants. Further large-scale clinical trials are necessary to determine appropriate ranges for exogenous antioxidant supplementation in patients with hypertension.

The major strength of our research is its large-scale cohort design and the use of a nationally representative sample. Additionally, we evaluated both the joint and independent effects of six dietary antioxidants, providing more specific evidence for understanding the role of dietary antioxidants in the prognosis of patients with hypertension. Furthermore, the sensitivity analyses have confirmed the robustness of our results.

However, this study has some limitations. First, due to its observational nature, we were unable to draw any causal inferences. Second, although we used the mean intake of two 24-hour dietary recalls in our analysis, recall bias was unavoidable. Third, we only collected baseline dietary information, while dietary habits might have changed during the follow-up period. Finally, despite adjusting for several related variables, residual confounding factors could not be eliminated.

Table 4 Association of CDAI with all-cause mortality among patients with hypertension, stratified by selected patients' characteristics

	composite dietary antioxidant index (CDAI)				P interaction
	Q1 HR (95% CI)	Q2 HR (95% CI)	Q3 HR (95% CI)	Q4 HR (95% CI)	
Age					
< 60	1.00 (ref.)	0.99 (0.68, 1.45)	1.13 (0.75, 1.70)	1.05 (0.66, 1.68)	0.2340
≥ 60	1.00 (ref.)	0.99 (0.86, 1.13)	**0.82 (0.70, 0.97)**	**0.80 (0.67, 0.97)**	
Sex					0.7067
Male	1.00 (ref.)	0.95 (0.77, 1.19)	0.81 (0.65, 1.01)	**0.77 (0.60, 0.99)**	
Female	1.00 (ref.)	0.86 (0.73, 1.02)	0.85 (0.69, 1.05)	**0.78 (0.60, 0.99)**	
BMI, kg/m^2					0.5970
< 25	1.00 (ref.)	0.92 (0.72, 1.19)	0.82 (0.62, 1.09)	0.77 (0.59, 1.02)	
25–30	1.00 (ref.)	0.82 (0.62, 1.09)	**0.67 (0.51, 0.87)**	**0.68 (0.50, 0.92)**	
≥ 30	1.00 (ref.)	0.95 (0.78, 1.07)	0.94 (0.75, 1.17)	0.81 (0.62, 1.06)	
T2D					0.9862
Yes	1.00 (ref.)	0.90 (0.72, 1.11)	0.79 (0.62, 1.00)	0.76 (0.57, 1.02)	
No	1.00 (ref.)	0.90 (0.75, 1.08)	**0.82 (0.67, 0.99)**	**0.77 (0.63, 0.93)**	
CVD					0.3574
Yes	1.00 (ref.)	**0.82 (0.69, 0.98)**	**0.81 (0.65, 0.99)**	**0.70 (0.56, 0.88)**	
No	1.00 (ref.)	0.96 (0.79, 1.16)	0.83 (0.68, 1.01)	0.83 (0.66, 1.04)	
CKD					0.7320
Yes	1.00 (ref.)	0.88 (0.74, 1.04)	**0.80 (0.66, 0.98)**	**0.70 (0.56, 0.87)**	
No	1.00 (ref.)	0.94 (0.76, 1.15)	0.82 (0.65, 1.04)	0.86 (0.69, 1.07)	

Model was adjusted for age, sex, race, educational level, BMI, smoking status, total energy intake, history of T2D, CVD, and CKD

BMI: body mass index; T2D: type 2 diabetes; CVD: cardiovascular disease; CKD: chronic kidney disease

The bold values indicated statistically significant

Conclusion

Higher overall dietary antioxidant intake was significantly associated with decreased all-cause mortality. Vitamin E and selenium intakes might be major contributors to this protective effect. Further randomized controlled trials are required to confirm our findings.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12937-024-01062-9.

Supplementary Material 1

Author contributions

SZ, YC, HL, and AL: project conception, development of overall research plan; SZ: statistical analyses; SZ: writing of the manuscript; SZ, YC: interpretation of the data and critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Data availability

All data are available at www.cdc.gov/nchs/nhanes/.

Declarations

Ethics approval and consent to participate

The Ethics Review Board of the National Center for Health Statistics (NCHS) granted approval for the survey protocol. Written informed consent form was obtained from all participants.

Competing interests

The authors declare no competing interests.

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