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Composite dietary antioxidant index and abdominal aortic calcification: a national cross-sectional study

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Abstract

Purpose The Composite Dietary Antioxidant Index (CDAI) is a novel, inclusive measure for evaluating the antioxidant potential of diets. We aim to explore the link between the CDAI and abdominal aortic calcification (AAC) in U.S. adults aged ≥ 40 years.

Methods This cross-sectional study collected dietary and AAC data for individuals aged ≥ 40 years from the 2013–2014 National Health and Nutrition Examination Survey (NHANES) database. The CDAI was calculated using six dietary antioxidants. AAC was evaluated using a semi-quantitative scoring system known as AAC-24, with an AAC score greater than 6 as severe AAC (SAAC). To examine the association between CDAI and AAC, including SAAC, liner/logistic regression analyses and smooth curve fitting were applied.

Results A total of 2,640 participants were included in this study, and significant decreases in AAC score and SAAC prevalence were observed with ascending CDAI levels ($P < 0.01$). After adjusting for confounding factors, a clear link was established between the CDAI and both AAC score (β = -0.083, 95% CI -0.144–0.022, $P = 0.008$) and SAAC (OR = 0.883, 95% CI 0.806–0.968, $P = 0.008$), respectively. Further smooth curve fitting indicated a negative correlation between CDAI and both AAC score and SAAC.

Conclusions Dietary antioxidant consumption, as quantified by the CDAI, shows an inverse relationship with AAC risk. Additional longitudinal and intervention studies are essential.

Keywords Oxidative stress, Antioxidant, CDAI, Abdominal aortic calcification, NHANES

Introduction

Vascular calcification, characterized by the abnormal accumulation of calcium phosphate crystals within the arterial intima, is identified as a significant risk factor for cardiovascular disease [1]. It is strongly linked to an increased risk of rupture in atherosclerotic plaques, adverse cardiovascular incidents, and all-cause mortality [2]. Physiologically, vascular smooth muscle cells (VSMCs) maintain the tone and elasticity of blood vessels [3]. However, under pathological stimuli such as oxidative stress, aging, uremia, mechanical stress, and inflammation, VSMCs will accept the characteristics of

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collagen-secreting osteoblasts, leading to vascular calcification [3–5].

Abdominal aortic calcification (AAC) appears before coronary artery calcification and is an independent predictor of subclinical and future cardiovascular events, beyond traditional risk factors [6, 7]. Diet-associated cardiometabolic disorders account for around one-fifth of all premature deaths worldwide, presenting a substantial health challenge [8]. Dietary risk factors are known to exert an impact on various vascular-related health issues, including peripheral arterial disease, atrial fibrillation, chronic kidney disease, heart failure and cognitive decline [9]. Consuming dietary antioxidants has been proven to mitigate the adverse health effects associated with oxidative stress and chronic inflammation [10]. Previous studies also indicated that a diet rich in antioxidants is linked to a lower risk of AAC [11]. The Comprehensive Dietary Antioxidant Index (CDAI) is an effective nutritional tool designed to measure the antioxidant quality of a diet [12, 13]. It evaluates the combined effects of six key dietary antioxidants (vitamins A, C, and E, selenium, zinc, and carotenoids), representing a comprehensive profile of dietary antioxidant intake. The CDAI has been proven to have a positive impact on various chronic diseases, including hypertension, diabetes, visceral obesity, chronic kidney disease, and other related conditions [14–17].

However, it is uncertain whether CDAI could effectively identify those at increased risk of AAC. By analyzing data from the National Health and Nutrition Examination Survey (NHANES) database, this study aims to examine the potential relationship between CDAI and AAC risk through a comprehensive cross-sectional analysis.

Materials and methods

Study population

Data for this study were sourced from the NHANES, a comprehensive survey conducted by the National Center for Health Statistics at the Centers for Disease Control and Prevention. The NHANES employed a rigorously structured, stratified, randomized, multi-stage approach to sampling, ensuring a nationally representative sample. Participants underwent detailed physical exams, completed health and nutrition surveys, and participated in lab tests [18, 19]. The NHANES study protocol received approval from the Ethics Review Board at the National Center for Health Statistics. Written informed consent was obtained from all participants. Detailed methodologies and data are accessible at https://www.cdc.gov/nchs/nhanes/. This analysis compiled NHANES 2013–2014 data, selecting a total of 2,640 qualified participants. Criteria for inclusion were being 40 years or older, not being pregnant, and having complete dietary questionnaire and AAC data.

Exposure and outcome definitions

Dietary and nutrient intakes of participants in the NHANES database were tracked through a 24-hour dietary recall interview, first face-to-face and then via a second recall by telephone within 3 to 10 days. The CDAI was established using food frequency questionnaire (FFQ) data, which identified antioxidant consumption including vitamins A, C, E, zinc, selenium, and carotenoids. Normalization of these antioxidants was achieved by mean subtraction and standard deviation division, with the CDAI representing the total of these normalized values. The calcification severity of abdominal aorta was quantified using the AAC score, derived exclusively from the NHANES 2013–2014 dataset. This score, based on the Kauppila scoring system and measured via dual-energy X-ray absorptiometry (DXA, Densitometer Discovery A, Hologic, Marlborough, MA, USA), varied from 0 to 24, with higher scores indicating greater calcification. An AAC score above 6 was considered as SAAC [20]. Both AAC score and SAAC were analyzed as outcome measures in this study.

Covariate definitions

Our study included some potential covariates including demographic information (age, gender, race), socio-economic status (marital status, annual income, education level), physical activity (vigorous or moderate), smoking status, health conditions (hypertension, diabetes, and cardiovascular disease), body mass index (BMI), glycohemoglobin (HbA1c), triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), serum creatinine (Scr), estimated glomerular filtration rate (eGFR), bone metabolism markers (serum calcium, phosphorus, and total 25-hydroxyvitamin D), and total energy intake. Estimation of eGFR was conducted using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, accounting for age, gender, race, and Scr levels [21]. Diagnosis of diabetes and hypertension was based on individuals' self-reported health records. The determination of cardiovascular diseases required participants to report history of heart attacks, strokes, heart failure, coronary artery disease, or angina.

Statistical analysis

The statistical approach adhered to the protocols set by the Centers for Disease Control and Prevention, utilizing a complex multistage cluster survey methodology and applying weights from a single cycle. Continuous variables were presented as means with standard errors (SE), while categorical variables were shown as percentages. The comparison of continuous and categorical variables across groups was performed using the weighted Student's t-test chi-squared test, respectively.

The association between CDAI (continuous /categorical) and AAC score, SAAC was analyzed using weighted linear and logistic regression models. Further, subgroup analyses were also conducted. Additionally, the potential nonlinear relationship between CDAI and AAC score, SAAC was explored using weighted smooth curve fitting. All statistical analyses were conducted using Empower software (http://www.empowerstats.com) and R software (http://www.R-project.org), with statistical significance set at a two-sided P value < 0.05.

Results

Baseline characteristics of study population

The study included 2,640 eligible participants. The majority were non-Hispanic whites at 72.77%, followed by non-Hispanic blacks at 9.92%, Mexican Americans at 6.47%, other Hispanics at 4.50%, and other races making up 6.34%. The average age of the participants was 57.64 years, with 46.68% being males (Table 1). The average nutritional intake was recorded as 656.27 mcg of vitamin A, 80.87 mg of vitamin C, 10.05 mg of vitamin E, 9817.17 mcg of carotenoids, 114.36 mcg of selenium, and 10.86 mg of zinc. Based on CDAI levels, participants were divided into three groups. The analysis showed that

Table 1 Baseline characteristics of participants grouped by CDAI levels

	Overall (N = 2640)	Low (-8.09, -1.42)	Middle (-1.42, 1.67)	High (1.67, 44.56)	P value
Age (years)	57.64 ± 0.30	58.98 ± 0.56	57.86 ± 0.51	56.15 ± 0.46	0.012
Male gender, %	46.68	32.95	45.86	58.99	< 0.001
Race, %					< 0.001
Mexican American	6.47	6.25	6.41	6.71	
Non-Hispanic Black	9.92	14.14	8.19	8.15	
Non-Hispanic White	72.77	68.91	74.47	74.25	
Other Hispanic	4.50	4.92	4.44	4.21	
Other Races	6.34	5.78	6.48	6.68	
Married, %	66.66	58.97	68.80	70.92	< 0.001
Annual household income (under $20,000), %	12.19	16.92	11.22	9.19	< 0.001
Education level (above high school), %	64.65	53.99	65.57	72.61	< 0.001
Physical activity, %	38.57	37.37	37.05	41.11	0.319
Smokers, %	44.95	48.10	45.06	42.19	0.167
Diabetes, %	12.52	16.08	12.81	9.25	0.001
Hypertension, %	44.31	52.70	43.53	38.08	< 0.001
Cardiovascular diseases, %	11.11	14.41	10.09	9.40	0.019
BMI (kg/m^2)	28.57 ± 0.17	28.89 ± 0.27	28.79 ± 0.27	28.08 ± 0.21	0.042
HbA1c (%)	5.75 ± 0.02	5.82 ± 0.04	5.73 ± 0.03	5.71 ± 0.05	0.134
TG (mmol/L)	1.43 ± 0.05	1.45 ± 0.03	1.48 ± 0.11	1.36 ± 0.05	0.167
TC (mmol/L)	5.05 ± 0.02	5.16 ± 0.04	5.01 ± 0.04	5.01 ± 0.03	0.009
HDL-c (mmol/L)	1.42 ± 0.01	1.41 ± 0.01	1.42 ± 0.02	1.44 ± 0.01	0.182
LDL-c (mmol/L)	2.98 ± 0.02	2.97 ± 0.05	2.96 ± 0.05	3.02 ± 0.05	0.682
Scr (μmol/L)	81.72 ± 0.74	82.58 ± 1.48	80.88 ± 0.86	81.85 ± 0.97	0.483
eGFR (ml/min/1.73 m^2)	84.14 ± 0.48	83.26 ± 0.53	84.11 ± 0.70	84.91 ± 0.64	0.092
Serum calcium (mg/dL)	9.46 ± 0.01	9.47 ± 0.02	9.45 ± 0.02	9.46 ± 0.02	0.616
Serum phosphorus (mg/dL)	3.80 ± 0.02	3.81 ± 0.03	3.82 ± 0.02	3.78 ± 0.02	0.217
Total 25-hydroxyvitamin D (nmol/L)	75.82 ± 1.46	71.69 ± 1.84	75.48 ± 1.31	79.63 ± 2.25	0.014
Total energy (kcal)	2010.91 ± 26.44	1429.11 ± 16.23	1994.47 ± 29.18	2513.57 ± 53.20	< 0.001
Vitamin A (mcg)	656.27 ± 12.08	336.81 ± 10.13	572.38 ± 13.17	1008.37 ± 18.06	< 0.001
Vitamin C (mg)	80.87 ± 1.88	38.11 ± 1.61	69.54 ± 1.70	128.11 ± 4.13	< 0.001
Vitamin E (mg)	10.05 ± 0.25	5.20 ± 0.09	8.92 ± 0.21	15.24 ± 0.28	< 0.001
Selenium (mcg)	114.36 ± 1.26	75.35 ± 0.68	112.33 ± 1.85	149.02 ± 2.82	< 0.001
Zinc (mg)	10.86 ± 0.12	6.88 ± 0.11	10.39 ± 0.13	14.65 ± 0.31	< 0.001
Carotenoids (mcg)	9817.17 ± 227.11	3924.14 ± 115.67	7991.24 ± 203.79	16594.98 ± 606.04	< 0.001
AAC score	1.47 ± 0.12	1.85 ± 0.18	1.45 ± 0.11	1.16 ± 0.15	0.007
SAAC, %	7.73	10.39	7.97	5.26	0.002

Abbreviations BMI, body mass index; HbA1c, glycohemoglobin; TG, triglyceride; TC, total cholesterol; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; Scr, serum creatinine; eGFR, estimated glomerular filtration rate; AAC, abdominal aortic calcification; SAAC, severe abdominal aortic calcification

Table 2 Results from logistic regression analysis on SAAC

	OR (95%CI) *P* value		
SAAC	**Model 1**	**Model 2**	**Model 3**
Continuous			
CDAI	0.937 (0.903, 0.971) < 0.001	0.934 (0.896, 0.974) 0.001	0.883 (0.806, 0.968) 0.008
Categories			
Low (-8.09, -1.42)	reference	reference	reference
Middle (-1.42, 1.67)	0.857 (0.633, 1.160) 0.317	0.829 (0.591, 1.161) 0.275	0.542 (0.304, 0.968) 0.038
High (1.67, 44.56)	0.504 (0.357, 0.712) < 0.001	0.486 (0.332, 0.712) < 0.001	0.352 (0.167, 0.741) 0.006
P for trend	< 0.001	< 0.001	0.005

OR: odds ratio.

95% CI: 95% confidence interval.

Model 1: no covariates adjusted.

Model 2: adjusted for age, gender, and race.

Model 3: adjusted for age, gender, and race, marital status, annual household income, education level, physical activity, smoking status, diabetes, hypertension, cardiovascular diseases, BMI, HbA1c, TG, TC, LDL-c, HDL-c, Scr, eGFR, serum calcium, serum phosphorus, total 25-hydroxyvitamin D, and total energy intake.

Table 3 Results from linear regression analysis on AAC score

	β (95%CI) *P* value		
AAC score	**Model 1**	**Model 2**	**Model 3**
Continuous			
CDAI	-0.056 (-0.088, -0.023) < 0.001	-0.042 (-0.072, -0.012) 0.006	-0.083 (-0.144, -0.022) 0.008
Categories			
Low (-8.09, -1.42)	reference	reference	reference
Middle (-1.42, 1.67)	-0.293 (-0.627, 0.041) 0.085	-0.261 (-0.567, 0.046) 0.096	-0.571 (-1.055, -0.086) 0.021
High (1.67, 44.56)	-0.655 (-0.988, -0.321) < 0.001	-0.544 (-0.856, -0.232) < 0.001	-0.834 (-1.404, -0.264) 0.004
P for trend	< 0.001	< 0.001	0.004

95% CI: 95% confidence interval.

Model 1: no covariates adjusted.

Model 2: adjusted for age, gender, and race.

Model 3: adjusted for age, gender, and race, marital status, annual household income, education level, physical activity, smoking status, diabetes, hypertension, cardiovascular diseases, BMI, HbA1c, TG, TC, LDL-c, HDL-c, Scr, eGFR, serum calcium, serum phosphorus, total 25-hydroxyvitamin D, and total energy intake.

those in the highest CDAI group were typically younger, mostly male and married, with higher annual household incomes ($P<0.001$). They also had a lower prevalence of diabetes, hypertension, and cardiovascular diseases ($P<0.05$). Furthermore, these individuals had lower BMI and TC measurements, but higher levels of total 25-hydroxyvitamin D, vitamins A, C, E, selenium, zinc, carotenoids, and total energy intake ($P<0.05$). There were also notable differences in racial distribution among the groups. Notably, higher CDAI levels were associated with a lower AAC score and a decreased prevalence of SAAC, with percentages decreasing from 10.39 to 7.97%, and then to 5.26% ($P<0.01$).

Associations between CDAI and SAAC, AAC score

Our findings show a strong association between higher CDAI levels and a reduced risk of SAAC, which is consistently significant in unadjusted (OR=0.937, 95% CI 0.903–0.971, $P<0.001$), partially adjusted (OR=0.934, 95% CI 0.896–0.974, $P=0.001$), and fully adjusted models (OR=0.883, 95% CI 0.806–0.968, $P=0.008$) (Table 2). Further analysis by splitting CDAI levels into three groups reveals that individuals in the highest group face a significantly decreased risk of SAAC ($P=0.006$). Compared to the lowest group, their risk in the fully adjusted model is reduced by 64.8%, with an OR of 0.352 and a 95% CI ranging from 0.167 to 0.741. Additionally, linear regression analysis indicates a significant negative relationship between CDAI and AAC score (β = -0.083, 95% CI -0.144–0.022, $P=0.008$) (Table 3). Smooth curve fitting analysis also indicated a negative correlation between CDAI and both AAC score and SAAC (Fig. 1).

Subgroup analyses

Subgroup analyses were conducted to confirm the consistency of the relationships between CDAI and SAAC across various demographic groups, as shown in Fig. 2. The impact of factors such as age, gender, race, marital status, annual household income, education level, smoking status, BMI, diabetes, hypertension cardiovascular diseases, and eGFR on these relationships was found to be statistically insignificant (***P*** for interaction > 0.05).

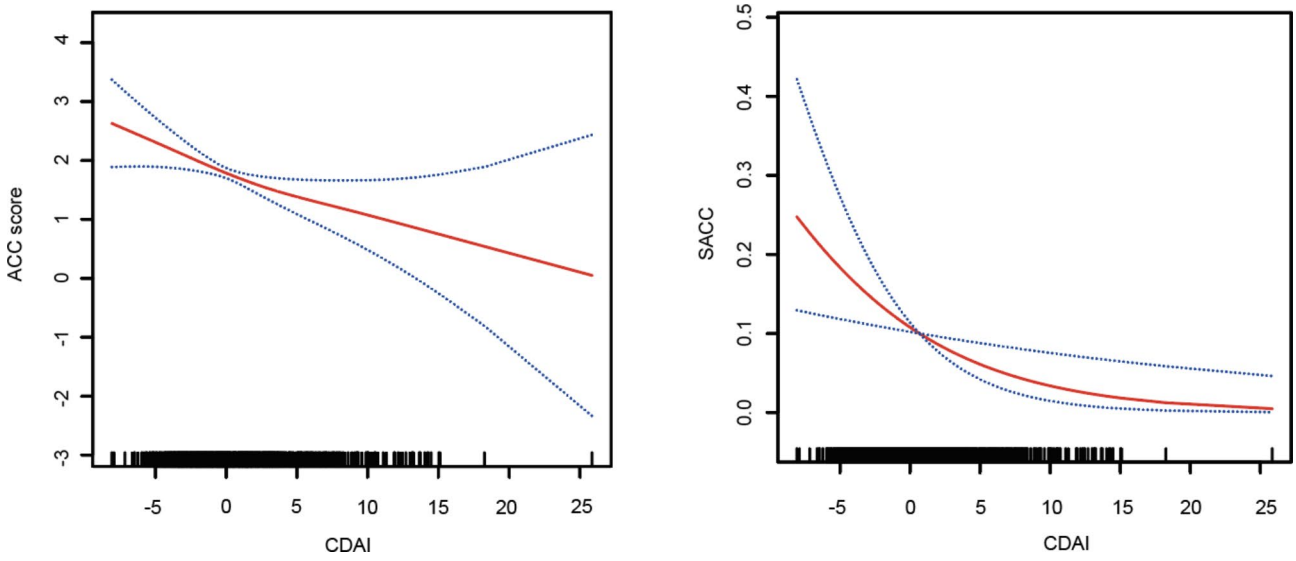

Fig. 1 Results from smooth curve fitting

Discussion

To our understanding, this study is the first in-depth examination of the relationship between CDAI levels and the risk of AAC. Our findings indicate a negative correlation between CDAI levels and both AAC score and SAAC, even when accounting for a range of potential confounding factors. This implies that higher CDAI levels might act as a protective element against AAC risk.

Calcification in arterial layers, specifically the intima and media, is driven by an osteogenic activity in VSMCs, resembling osteoblast-like cell formation [22]. The differentiation of VSMCs is majorly influenced by oxidative stress. The accumulation of reactive oxygen species (ROS) following exposure to hydrogen peroxide or oxidized low-density lipoprotein results in elevated Runx2 expression, potentially steering the VSMCs phenotype towards osteoblastic characteristics and initiating calcification in vessels [23, 24]. Oxidative stress also activates inflammatory cells like macrophages, which release inflammatory mediators in the arterial walls, further facilitating calcification [25]. Additionally, oxidative stress may induce the apoptosis or programmed cell death of VSMCs, turning these cells into potential focal points for calcification [26, 27]. It also leads to the degeneration of vascular wall matrix proteins such as collagen and elastin, laying the groundwork for calcium salt deposition [28]. Studies in uremic rats have shown that antioxidants can reduce oxidative stress both in the aorta and systemically, curbing the osteogenic differentiation of VSMCs and the progression of arterial calcification [29].

Vitamin A, a fat-soluble nutrient, plays a critical role in maintaining visual health, supporting the immune system, ensuring skin health, and facilitating cell growth [30]. In a study identifying dietary components associated with abdominal aortic calcification, information on 35 macro and micronutrients was analyzed [30]. Among these, vitamin A was negatively correlated with AAC [30]. Known as ascorbic acid, vitamin C is a naturally occurring, water-soluble substance in food. It plays roles in antioxidation, collagen support, immune system regulation, and diminishing inflammation [31]. Vitamin C acts to lower the production of reactive oxygen species (ROS) like superoxide radicals and hydrogen peroxide by blocking the Jak2/Stat1/IRF1 signaling in endothelial cells [31, 32]. Similarly, vitamin E, another fat-soluble antioxidant, is crucial for preserving cell membrane integrity and safeguarding the body against oxidative stress [33]. Animal experiments have demonstrated that supplementation with vitamin E in the diet provides protection against vascular calcification in rats with uremia induced by a high-fat diet [34]. Selenium and its derivatives, notably selenoproteins that contain selenium in the form of selenocysteine, have been proven to have antioxidant effects [35]. In conditions where oxidative stress is induced by hydrogen peroxide, selenium has been shown to block the process of calcification and differentiation in osteoblastic VSMCs, which lowers the accumulation of calcium in the extracellular matrix by enhancing antioxidant selenoproteins and suppressing the PI3K/AKT and ERK signaling pathways [36–38]. Voelkl et al. demonstrated through in vitro and animal studies that zinc supplementation mitigates phosphate-induced arterial calcification [39]. In their experiments with human aortic VSMCs, the application of zinc sulfate was shown to inhibit calcification induced by phosphate and reduce the expression of osteogenic marker mRNA [39]. This effect was attributed to the induction of the zinc-finger protein A20 and the inhibition of NF-κB activation [39].

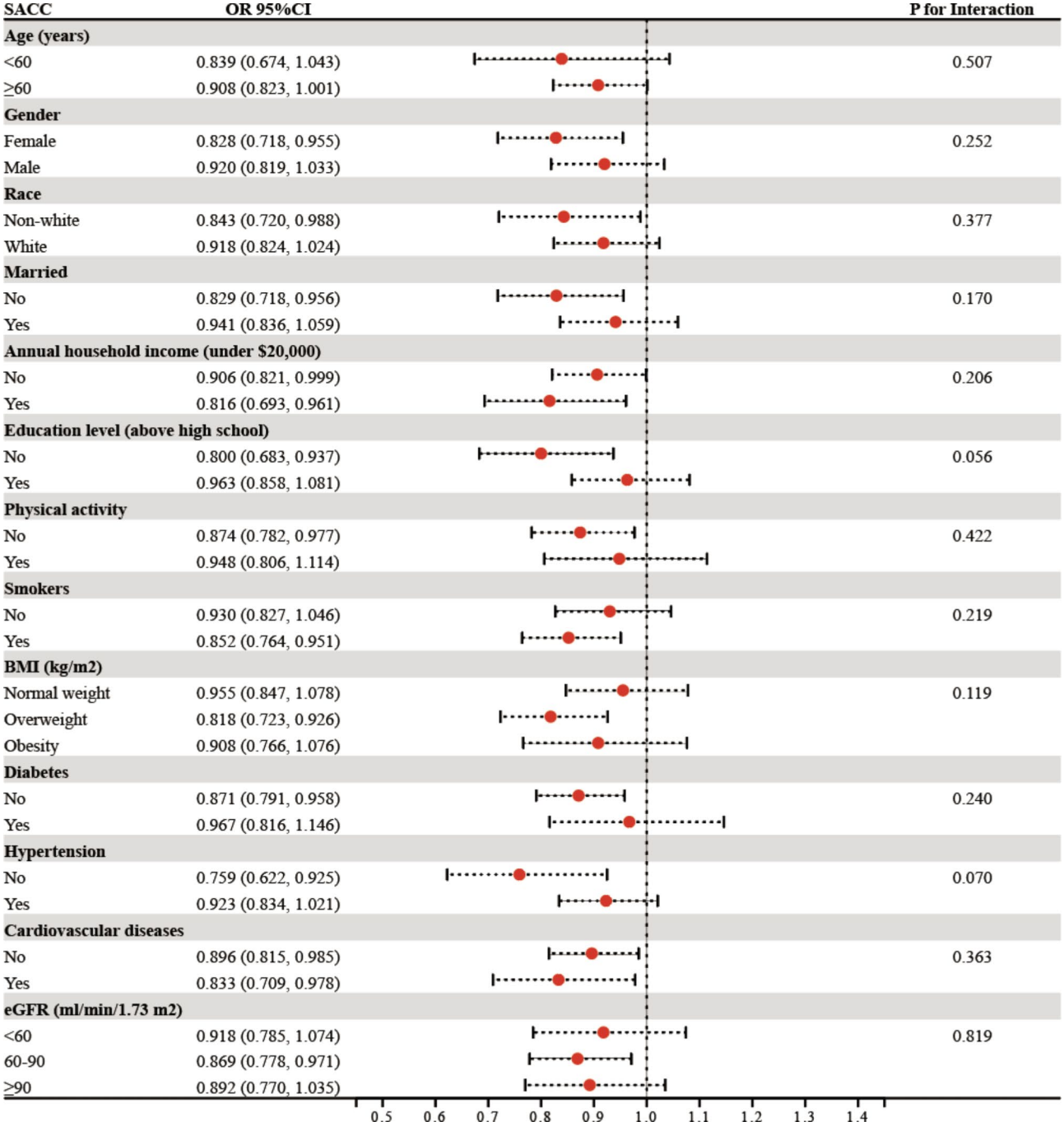

Fig. 2 Results from subgroup analyses

Carotenoids, fat-soluble pigments found in fruits, vegetables, and seaweed, possess antioxidant capabilities. Previous research also indicated a nonlinear negative association between carotenoid consumption and SAAC [40]. However, as the current U.S. Dietary Guidelines for 2020–2025 highlighted, the significance of adopting comprehensive dietary practices instead of concentrating on specific nutrients, foods, or groups in isolation [41, 42]. The research by Senoner and his team suggests diets that could help reduce ROS related to cardiovascular diseases [43]. They also highlighted the complexity of pinpointing the antioxidant-contributing elements within foods, recommending a varied diet encompassing antioxidants from sources like fruits, vegetables, and fish over single-antioxidant supplements [43]. Research on the CDAI also showed its association with inflammatory indicators such as IL-1β and TNFα, which are implicated in atherosclerosis [12, 44]. Research shows that the CDAI is strongly

linked with various adverse health outcomes, highlighting its advantages and usefulness compared to traditional dietary antioxidant indexes in epidemiological research [14, 17, 45, 46].

This study, with its sophisticated sampling weights, depicts the demographic landscape of the United States. Nonetheless, this study also presents certain limitations. First, given the cross-sectional design's inability to establish causality, there is a crucial need for prospective cohort studies and intervention trials in further investigations. Second, the study did not account for potential confounding factors such as non-alcoholic fatty liver disease and metabolic syndrome, which could result in biased outcomes. Third, the dietary information was based on self-reports, potentially impacting accuracy due to recall bias. Lastly, with the sample derived from the single population, confirming the broader applicability of the results requires further examination.

Conclusion

In a nationally representative study conducted among adults aged ≥ 40 years, a higher overall dietary antioxidant intake, measured by CDAI, is associated with a lower risk of AAC. Additional longitudinal and intervention studies are essential.

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Author contributions
Z.W. and Q.Y. wrote the main manuscript text. F.T., B.Z., H.Y., and X.S. prepared figures and tables. All authors reviewed the manuscript.

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Data availability
The datasets generated and/or analyzed during the current study are available in the NHANES database (https://www.cdc.gov/nchs/nhanes/).

Declarations

Ethical approval
This study involving human participants were reviewed and approved by the Ethics Review Board of the National Center for Health Statistics.

Informed consent
The patients/participants provided their written informed consent to participate in this study.

Competing interests
The authors declare no competing interests.

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