Preventive Medicine Reports 41 (2024) 102704

Contents lists available at ScienceDirect

Preventive Medicine Reports

journal homepage: www.elsevier.com/locate/pmedr

Composite dietary antioxidant index is associated with reduced prevalence of metabolic syndrome but not mortality in metabolic syndrome: Results from NHANES 2001–2018

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ARTICLE INFO

Keywords:
Metabolic syndrome
NHANES
Diet
Antioxidants
Mortality

ABSTRACT

The relationship between the composite dietary antioxidant index (CDAI), a comprehensive measure of individual dietary antioxidants, and the prevalence and mortality of metabolic syndrome (MetS) remains unknown. We aimed to explore these relationships in the National Health and Nutrition Examination Survey (NHANES). We explored these relationships using two independent cohorts. First, we addressed CDAI and the prevalence of MetS in the general population; second, we explored the association between CDAI and mortality in patients with MetS by following NHANES 2001–2018 participants through December 31, 2019. In addition, restricted cubic spline (RCS), stratified analysis, and sensitivity analysis were used for further interpretation. We included 24,514 participants aged 20–85 years, in which the prevalence of MetS was 27.61 %. CDAI was negatively and dose-responsively associated with the prevalence of MetS, however it was not associated with mortality in patients with MetS. In addition, CDAI was associated with a reduced prevalence of certain components of MetS, including dyslipidemia and central obesity. RCS showed a linear correlation between CDAI and MetS and the above components. Stratified analyses indicated that alcohol consumption was a significant influence of CDAI-MetS and that socioeconomic status and lifestyle specificity existed. Sensitivity analysis confirmed the stability of the results. CDAI was protective against the development of MetS in the general population, but not against mortality in patients with MetS. Clinicians need to develop individualized prevention strategies to reduce the development of MetS by modifying CDAI.

1. Introduction

Metabolic syndrome (MetS) is a state in which multiple metabolic abnormalities coexist in an individual, characterized by dyslipidemia (abnormal serum triglycerides [TG] and high-density lipoprotein-cholesterol [HDL-C]), elevated fasting plasma glucose [FPG], insulin resistance, hypertension, and abdominal obesity (Bovolini et al., 2021). The prevalence of MetS usually parallels that of obesity and type 2 diabetes and is one of the most common non-communicable diseases worldwide, resulting in a significant public health burden (Saklayen, 2018). A recent study using a nationally representative survey showed an increase in the prevalence of MetS among U.S. adults from 37.6 % in 2011–2012 to 41.8 % in 2017–2018 (p for trend = 0.028) (Liang et al., 2023). A similar trend of increasing prevalence over time has also been observed in countries in the Asia-Pacific region, including China (Ranasinghe et al., 2017). MetS is associated with an increased burden of multiple medical conditions such as cardiovascular disease (CVD), neuropsychiatric disorders, chronic kidney disease, nonalcoholic fatty liver disease (NAFLD), and increased mortality (Al-Khatib et al., 2022; Dietrich and Hellerbrand, 2014; Kane et al., 2017; Mottillo et al., 2010; Vancampfort et al., 2015; Zhang and Lerman, 2017). To date, management strategies for MetS are still largely based on modifying poor lifestyles such as unhealthy eating habits and physical inactivity (De Sousa and Norman, 2016).

Accumulating evidence suggests that oxidative stress may play an integral part in the pathophysiological mechanisms of MetS. The increase in reactive oxygen species due to the imbalance of pro-oxidants and antioxidants is involved in the development of several aberrant

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https://doi.org/10.1016/j.pmedr.2024.102704
Received 12 October 2023; Received in revised form 24 March 2024; Accepted 25 March 2024
Available online 26 March 2024

biological processes in MetS such as mitochondrial dysfunction, endoplasmic reticulum stress, lipid peroxidation, and insulin resistance (Masenga et al., 2023). Dietary antioxidants have been proposed to have the potential to prevent the onset and development of MetS by reducing oxidative stress and inflammation (Bahadoran et al., 2012; Mancini et al., 2015; Puchau et al., 2010; Wei et al., 2015). Higher dietary total antioxidant capacity (DTAC) is associated with improved anthropometric parameters in patients with MetS (Lopez-Legarrea et al., 2013).

The composite dietary antioxidant index (CDAI) is an emerging indicator for assessing the intake of six antioxidant vitamins/minerals (vitamin A, C, E, selenium, zinc, and carotenoids) in an individual's diet, reflecting the overall diet-dependent antioxidant potential (Wright et al., 2004). CDAI has demonstrated its clinical relevance and predictive/prognostic value in numerous epidemiologic studies. However, the relationship between CDAI and the odds of MetS remains unknown. There are no studies revealing the association between dietary antioxidant capacity and the prognosis of patients with MetS. Addressing these questions will help to clarify the public health implications of dietary antioxidants in MetS.

2. Methods

2.1. Study design and population

The Ethics Review Board of the National Center for Health Statistics reviewed and approved all NHANES surveys. We initially included 50,201 individuals aged 20–85 years from NHANES 2001–2018 and sequentially excluded participants with missing MetS diagnostic information (n = 1280), missing CDAI data (n = 10195), and missing other covariates (n = 14212). A final total of 24,514 eligible participants were enrolled in our analysis (Fig. 1).

2.2. Composition of the CDAI

In NHANES, two 24-hour dietary review interviews were included, and we used the average intake from the two interviews. We obtained the mean intake of vitamin A, vitamin C, vitamin E, zinc, selenium, and carotenoids from the CDAI (excluding intake from dietary supplements, medications, or plain drinking water). The CDAI was derived according to the validated method from previous studies (Wu et al., 2023; Yu et al., 2022), which is to subtract the mean intake of each antioxidant from its intake, normalize by dividing by the standard deviation, and then combine all the figures. The CDAI was calculated as follows (where x represents the intake of individual dietary antioxidants, mean represents the average intake of each component, and SD represents the standard deviation of the mean):

$$CDAI = \sum_{n=1}^{6} \frac{x - mean}{SD}$$

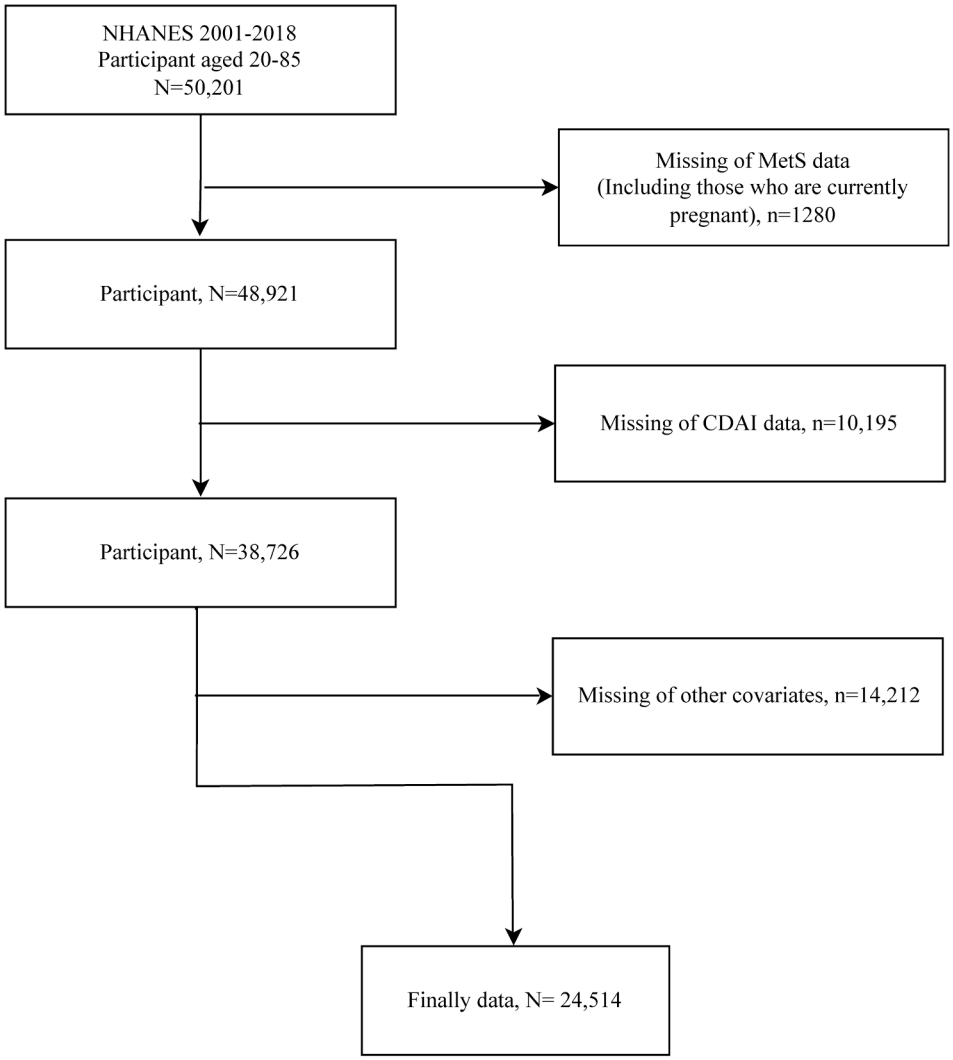

Fig. 1. Flowchart of study population selection, NHANES 2001–2018.

2.3. Definition of MetS

We used the criteria according to the National Cholesterol Education Program-Adult treatment Panel III for the diagnosis of MetS in our study (Alberti et al., 2009). The ATP III criteria are based on five indicators: abdominal obesity, elevated TG, decreased HDL-C, elevated blood pressure, and elevated FPG. MetS was diagnosed when ≥3 of the following five components were met: 1. Waist circumference (WC) ≥ 102 cm in men or ≥88 cm in women; 2. Serum TG ≥ 150 mg/dL; 3. Serum HDL-C < 40 mg/dL in men or <50 mg/dL in women; 4. FPG ≥ 100 mg/dL or use of hypoglycemic drugs; 5. Blood pressure ≥130/85 mmHg or receiving related medications. Information on participants' WC was obtained by self-report in NHANES Demographic Profile. Serum TG, HDL-C, and FPG were obtained based on biochemical test documents, whereas blood pressure was obtained from three consecutive measurements taken by a professional at the Mobile Examination Center.

2.4. Classification criteria for alcohol intake

We categorized alcohol consumption into never, former, and current drinking following the approach of Hicks et al. (2021) (Specific categorization criteria were available in this article). Current drinkers were further divided into light, moderate, and heavy consumers according to their degree of alcohol consumption. Specifically, alcohol intake is categorized as follows: (1) never: had <12 drinks in a lifetime; (2) former: had ≥12 drinks in 1 year and did not drink last year or did not drink last year but drank ≥12 drinks in a lifetime; (3) Heavy drinkers: 3 drinks per day for women, ≥ 4 drinks per day for men, or binge drinking 5 or more days per month; (4) moderate drinkers: ≥ 2 drinks per day for women, ≥3 drinks per day for men, or ≥2 days per month for binge drinking; (5) mild drinkers: <2 drinks per day for women or <2 drinks per day for men.

2.5. Mortality data collection

We employed NHANES 2001–2018 and prospectively linked to National Death Index mortality data with follow-up until December 31, 2019. Our study outcomes included all-cause mortality, CVD mortality, and cancer-related mortality. All-cause mortality includes deaths from any cause. CVD mortality was defined by ICD-10 codes I00-I09, I11, I13, I20-I51, or I60-I69, and cancer-related mortality was determined by ICD-10 codes C00-C97.

2.6. Covariate

We selected several important potential covariates based on previous studies, including age, gender (male or female), ethnicity/race (classified as Mexican American, non-Hispanic black, non-Hispanic white, other Hispanic, or other races), education level (<high school, high school, or >high school), marital status (single or non-single), family income to poverty (PIR), smoking, alcohol consumption, physical activity, and total daily energy intake (kcal/day). Participants' smoking status was obtained by self-report in the questionnaire and categorized as non-smoking (less than 100 lifetime cigarettes), former smoking (>100 lifetime cigarettes but not smoking now), and current smoking (>100 lifetime cigarettes and currently smokes). Physical activity was measured in metabolic equivalents [MET] based on the information in the questionnaire and MET ≥600 min/week was considered physically active.

2.7. Statistical analysis

All analyses were performed using EmpowerStats (X&Y Solutions, Inc., Boston, MA) and R software (R-4.3.2). We did properly complex sampling analysis according to NHANES reporting guidelines for the survey due to the complex design of NHANES (Johnson et al., 2013). In this study, we used the weighting variable WTMEC2YR to consider the sampling design. Continuous variables (mean ± standard error) and categorical variables (percentage) were used to characterize the study population. In baseline analysis, the student's *t*-test for continuous variables or chi-square test for categorical variables was applied. For follow-up duration, we used median and interquartile range to indicate.

The relationship between CDAI and MetS was explored using multivariate-adjusted logistic regression models. We constructed three models. The first model was a crude model that did not adjust for any covariates. The adjusted model 1 was a partially adjusted model that adjusted for age, gender, race, marital status, PIR, and education level, and total energy intake. The adjusted model 2 was a fully adjusted model that further adjusted for smoking, alcohol consumption, and physical activity.

In the association of CDAI with mortality in MetS, we performed multifactorial analyses using multiple multivariate-adjusted proportional hazards Cox regressions to explore whether the predictive value of CDAI for mortality was independent of other prognostic factors. We similarly modeled three multivariate adjustments.

We also performed multiple restricted cubic spline (RCS) analysis to explore potential nonlinear relationships between CDAI and odds of MetS and its components and mortality in MetS. Finally, we conducted stratified and sensitivity analyses to confirm the consistency and stability of the findings across subgroups and in other contexts. In all statistical analyses, a two-sided $p < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics

Of the 24,514 participants included (mean age: 46.03 years), 7,271 had a diagnosis of MetS, corresponding to a prevalence of 27.61 %. We grouped the included participants according to the quartile distribution of the CDAI. In baseline analyses, we found significant trends in participants' age, PIR, total energy intake, gender, race, marital status, education level, smoking, and alcohol consumption as quartiles of the CDAI changed. Significant differences between groups also existed for CDAI and its components (all $p < 0.0001$). Notably, there was a significant trend of decreasing prevalence of MetS with increasing quartiles of CDAI ($p = 0.002$). In addition, there were significant changes in the prevalence of components of MetS including HDL-C, WC, and hypertension (Table S1).

3.2. Multivariate adjusted logistic regression

To explore whether CDAI was independently associated with a reduced prevalence of MetS, we performed multiple multivariable-adjusted logistic regression analyses. In both unadjusted and partially adjusted models, we found that CDAI was associated with reduced odds of MetS when used as both a continuous and categorical variable, with a dose–response relationship. After adjusting for all confounding variables, we still similarly observed a protective effect of CDAI (continuous) against MetS (odds Ratio [OR] (95 % Confidence Interval [CI]) = 0.97 (0.96, 0.99), $p < 0.0001$) and a dose–response relationship (p for trend = 0.0282). CDAI at Q4 compared to the reference value (Q1) was associated with a borderline reduction in the prevalence of MetS of 13 % ($p = 0.0506$) (Table S2).

We also explored the relationship between the components of CDAI and the odds of MetS. After adjusting for all confounders, Vitamin A, Vitamin C, Vitamin E, and carotenoid were all associated with a reduced prevalence of MetS and showed a dose–response relationship (Q4 compared to Q1: Vitamin A: OR and 95 % CI = 0.78 (0.69, 0.87), $p < 0.0001$; Vitamin C: 0.66 (0.59, 0.73), $p < 0.0001$; Vitamin E: 0.72 (0.63,

0.81), p < 0.0001; carotenoid: 0.88 (0.78, 0.98), p = 0.022). However, we found that zinc (OR = 1.15, p = 0.0365) and selenium (OR = 1.55, p < 0.0001) were positively associated with the prevalence of MetS (Table S3) We also explored the association of CDAI with components of the MetS. After adjusting for all confounders, CDAI was dose-responsively associated with a reduced prevalence of abnormal HDL-C, TG, and WC, yet not with the prevalence of dysglycemia and hypertension (Table S4).

3.3. Association of CDAI with mortality in MetS

In a baseline analysis of patients with MetS stratified into quartile groups according to CDAI, we found similar differences between groups as in the overall population (Table S5). After a median follow-up duration of 102 months (interquartile range: 57–149 months) among 7,270 patients with MetS with available mortality data, 1,157 patients with MetS died, including 374 and 276 CVD- and cancer-related deaths, respectively (Table S6). In the crude model, CDAI was significantly and negatively associated with all-cause, CVD, and cancer mortality in MetS and had a dose–response relationship. However, in the partial and fully adjusted models, we did not observe an association between CDAI and mortality in patients with MetS, suggesting that CDAI is not independently associated with reduced mortality (Table S7).

3.4. Nonlinear relationship exploration

We then used RCS curves to explore the potential nonlinear relationship of CDAI with MetS and its components. The RCS model revealed a significant linear relationship between CDAI and the odds of MetS (p nonlinear = 0.1745). Similarly, there was a linear relationship between CDAI and the components of MetS including abnormal TG, HDL-C, and WC (p nonlinear = 0.8125, 0.1745, and 0.5516, respectively). CDAI was not associated with other MetS components including abnormal blood glucose and hypertension (Fig. 2).

3.5. Stratified analysis

In stratified analyses, we found that the relationship between CDAI and MetS remained stable across most subgroups. However, we noted a significant impact of alcohol consumption on this association (p for interaction = 0.0053). In addition, we found this association was only present among those who were >60 years old, female, non-Hispanic white, PIR ≥1, >high school education level, non-current smokers, and physically active (Fig. 3).

3.6. Sensitivity analysis

We performed sensitivity analyses using another composition (vitamins A, C, E, zinc, selenium, and magnesium) of CDAI. Similarly, CDAI was negatively correlated with the odds of MetS and had a dose–response relationship (Table S8). After replacing carotenoids with magnesium, the new CDAI remained non-significantly associated with mortality in patients with MetS (Table S9). We verified the stability of the protective effect against MetS using CDAI in tertiles and quintiles.

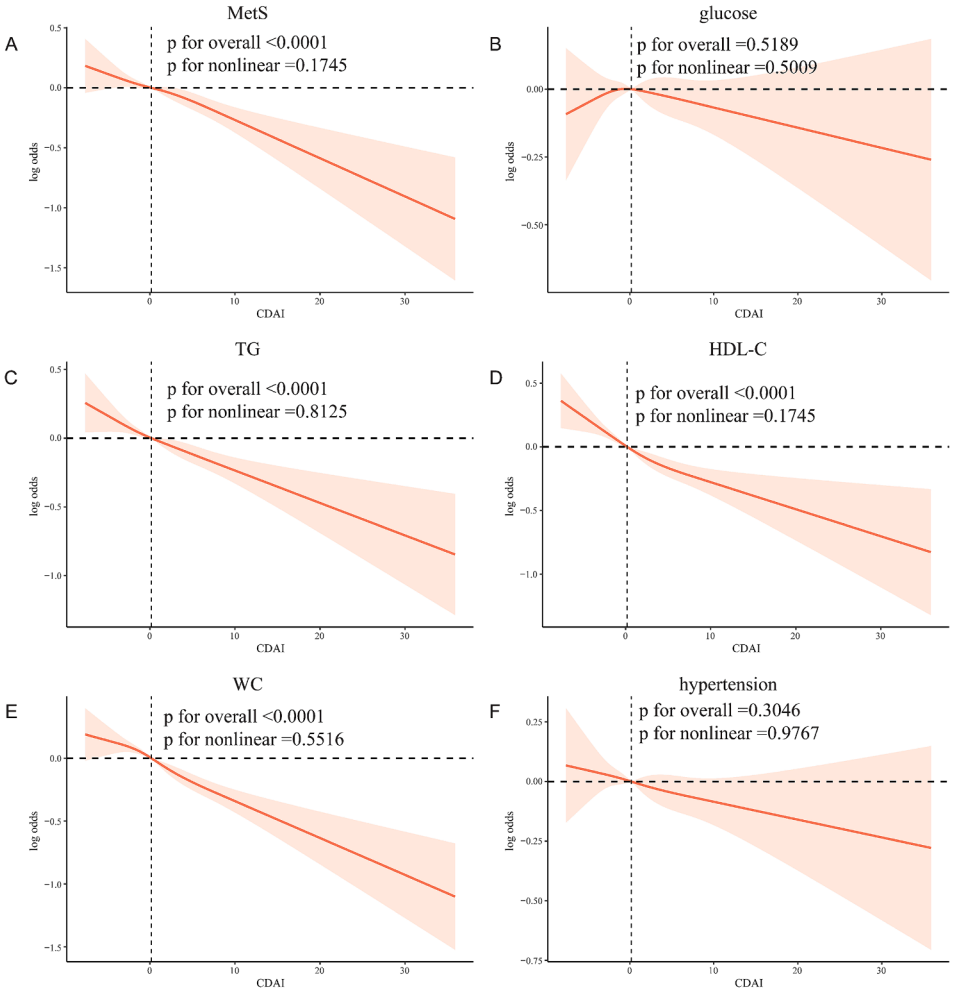

Fig. 2. Exploration of non-linear associations between CDAI and METS and its components in US adults.

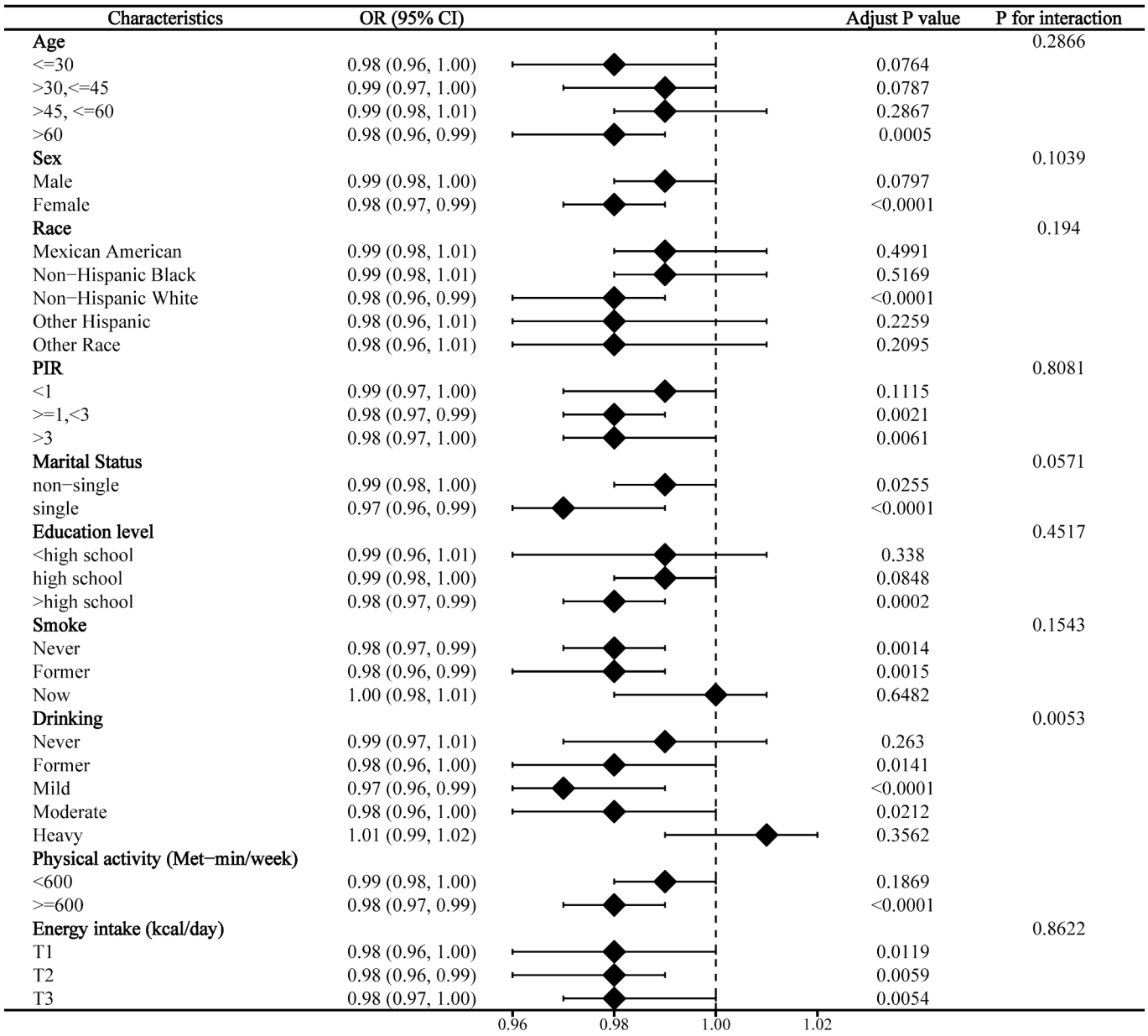

Fig. 3. Stratified analysis of the association between CDAI and MetS in the US adult population.

CDAI (both continuous and categorical) was negatively associated with the prevalence of MetS with a similar dose–response trend. CDAI in tertiles and quintiles at T3 and Q5 was associated with an 18 % reduction in MetS prevalence (p for trend = 0.0034 and 0.0089, respectively) (Table S10).

4. Discussion

Our separate analysis of the components of the CDAI showed that vitamins A, C, E, and carotenoids were all negatively associated with the prevalence of MetS. Our results suggested that selenium and zinc are positively associated with the development of MetS. The association between selenium intake and the development of MetS is still in controversy. A systematic review incorporating several studies with different conclusions suggested that selenium intake seemed to be unrelated to MetS in adults (Retondario et al., 2019). In fact, several studies using NHANES have shown that selenium intake is positively associated with the prevalence of other metabolic disorders including NAFLD (Cardoso et al., 2021; Deng and Tan, 2022; Liu et al., 2022). This may indicate that selenium itself is not deficient among U.S. adults and that excessive selenium intake contributes to selenium toxicity. A recent meta-analysis suggested that dietary zinc intake was negatively associated with the prevalence of MetS, contrary to our findings (Ding et al., 2022). A previous analysis of a cohort from China showed that dietary zinc intake was associated with lower blood pressure and FPG in female subjects, but increased TG levels in all Chinese participants (Wang et al., 2018). Analysis of the Multi-Ethnic Study of Atherosclerosis cohort indicated that dietary zinc from red meat, but not from other sources, was associated with an increased risk of MetS (de Oliveira Otto et al., 2012).

The CDAI, as a comprehensive measure of dietary antioxidant vitamins/minerals, indicates the antioxidant potential of an individual's dietary sources. Dietary antioxidant supplementation has been shown to be associated with reductions in serum markers of oxidative stress and improvements in chronic inflammation (Bacchetti et al., 2019; Luu et al., 2015). Thus, it is not inconceivable that amelioration of oxidative stress and chronic inflammation, which are key components in the pathogenesis of MetS, could be associated with reduced odds of MetS

(Francisqueti et al., 2017; Monteiro and Azevedo, 2010). However, it is important to note that the nature of our cross-sectional study prevents temporal causality from being derived from the CDAI-MetS association. Based on the cross-sectional nature of our CDAI-MetS prevalence cohort, more prospective studies are needed to explore these relationships in the future.

Similarly, the negative association of dietary antioxidant capacity with the prevalence of MetS and its components has been demonstrated from cohorts in other countries/regions, although there are controversial results. A large cross-sectional study from Korea showed that DTAC was negatively correlated with serum TG (Kim et al., 2019). A Spanish cohort including young adults showed that DTAC was associated with lower systolic blood pressure and FPG (Puchau et al., 2010). Similar findings were found in a longitudinal cohort and in a short-term randomized controlled trial (Bahadoran et al., 2012; Lopez-Legarrea et al., 2013). In our study, CDAI was negatively associated with the prevalence of abnormal serum TG, HDL-C, and WC in MetS, but not FPG and hypertension. Previous NHANES-based analyses have shown CDAI to be negatively associated with diabetes and hypertension (Chen et al., 2023; Wu et al., 2023). A major difference is that our subjects were the components of the MetS (FPG $\geq$ 100 mg/dL or hypoglycemic medications; and abnormal blood pressure or use of related medications), which are judged by criteria that are inconsistent with those used for the diagnosis of diabetes and hypertension.

Another important finding was that CDAI was not independently associated with mortality in patients with MetS. A cohort study from UK Biobank showed that antioxidant supplementation was not associated with all-cause, non-cancer, and cancer mortality in the general population (Behrendt et al., 2020). A recent study suggested that CDAI was associated with reduced all-cause and CVD mortality in diabetic patients (Wang et al., 2022).

The results of our stratified analyses indicated that alcohol consumption had a significant impact on the relationship between CDAI and MetS. The protective effect of CDAI was most pronounced in light drinkers, suggesting that light-moderate alcohol consumption may be beneficial for dietary antioxidants to exert their effects. Moderate alcohol consumption may improve serum markers of oxidative stress in postmenopausal women and decrease the risk of colorectal cancer in rats by increasing antioxidant enzymes (Hartman et al., 2005; Klarich et al., 2017). Moderate alcohol consumption has been shown to potentially reduce cardiometabolic risk in men with MetS by increasing HDL-C levels (Gigleux et al., 2006). In addition, there may also be a possible, although still controversial, association between mild-moderate alcohol consumption and a reduction in the development of NAFLD, which is thought to be the hepatic manifestation of MetS (Magherman et al., 2023). Our findings supported the beneficial effect of light-moderate alcohol intake on the prevention of MetS by modifying dietary antioxidants in the general population.

5. Conclusion

In two independent cohorts from a large population-based study, CDAI was negatively and linearly associated with the prevalence of MetS in the general population but not with mortality in patients with MetS. These effects were age-, sex-, and race-specific and may be influenced by alcohol consumption.

6. Funding

None.

7. Ethics statement

The protocol was approved by the Institutional Review Board of National Center for Health Statistics and no new data was added.

CRediT authorship contribution statement

Qing Zhou: Writing – review & editing, Writing – original draft, Investigation, Data curation, Conceptualization. **Lijun Zhou:** Resources, Formal analysis. **Xi Chen:** Resources, Formal analysis. **Qiuyan Chen:** Resources, Formal analysis. **Lu Hao:** Writing – review & editing, Writing – original draft, Supervision, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmedr.2024.102704.

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