Lipids in Health and Disease

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Single and mixed associations of composite antioxidant diet on triglyceride-glucose index

Yaying Xu[1], Yan Zhuang[2] and Huifeng Zhang[3*]

Abstract

Background Although the relationship between oxidative stress and insulin resistance (IR) has been established, the associations of the composite dietary antioxidant index (CDAI) and its components with the surrogate index of insulin resistance (IR), triglyceride-glucose index (TyG), is still not clear.

Methods This study analyzed the cross-sectional data of the National Health and Nutrition Examination Survey (NHANES) from 2003 to 2018. Multivariate linear regression, weighted quantile sum (WQS) regression, and Bayesian kernel machine regression (BKMR) were used to analyze the associations of the CDAI and its components with the TyG. In addition, subgroup analysis and several sensitivity analyses were conducted.

Results A total of 14,673 participants with complete data were included, with a median age of 50 years and 7,257 women (49%). Multivariate linear regression showed that after full adjustment, the CDAI was significantly negatively associated with the TyG [β: -0.005, 95% CI: (-0.008, -0.002), $p = 0.002$]. The model in which six nutrients were mutually corrected showed that vitamin E (per-SD increase) was most strongly associated with the TyG [β: -0.062, 95% CI: (-0.074, -0.050), $p < 0.0001$]. In the WQS model, the WQS index of the antioxidant diet was negatively associated with the TyG (β: -0.060; $P < 0.0001$). Similar effects were observed in the BKMR analysis. Notably, in the WQS and BKMR models, vitamin E became the most influential component. In addition, in the subgroup analysis, the association between the CDAI and the TyG in overweight or obese and diabetic populations was significantly weaker.

Conclusion Antioxidant diets, especially vitamin E, are significantly negatively correlated with TyG. This study emphasizes the important value of supplementing vitamin E to improve IR. However, patients with poor weight management and diabetes seem to benefit less from antioxidant diets.

Keywords CDAI, Antioxidant die, Triglyceride-glucose index, Insulin resistance, Weighted quantile sum regression, Bayesian kernel machine regression, NHANES.

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Introduction

Diabetes mellitus (DM) is a chronic disease with high morbidity and mortality. From 2000 to 2019, deaths from diabetes increased by 3% [1]. Type II diabetes mellitus (T2DM) affects more than 90% of diabetic patients. In this type of patients, the pancreas produces sufficient insulin, but the body is unable to utilize it, that is, insulin resistance (IR) [2]. T2DM is a lifelong metabolic disease that remains incurable under the current medical conditions. However, studies have shown that for overweight and obese patients with T2DM, lifestyle intervention, drug therapy (such as intensive insulin therapy and oral hypoglycemic agents) and metabolic surgery can alleviate T2DM to a certain extent [3].

The beneficial effects of antioxidant diets have been confirmed. For instance, isoflavones and flavones and their antioxidant capacity are negatively correlated with the risk of bladder cancer [4]. Sarcopenia can be improved by using natural products and a large amount of antioxidant substances [5]. Studies have shown that sustained high blood sugar levels increase mitochondrial oxygen consumption, disrupt mitochondrial function, or activate NADPH oxidase, leading to excessive production of reactive oxygen species (ROS) [6]. Increased ROS production or decreased endogenous antioxidant activity leads to oxidative stress, which in turn contributes to poor β-cell function and IR [6]. Over the past five years, several studies have evaluated the value of antioxidant diets in diabetes management. Schaft et al. [7] found in a prospective cohort study that dietary antioxidant capacity, as assessed by plasma reducing capacity, was negatively correlated with T2DM risk and homeostasis model assessment of insulin resistance (HOMA-IR) in the general population or participants with pre-diabetes. Li et al. [8] analyzed 12,467 participants from a natural population cohort in Northwest China, the results of which also indicated a negative association between total dietary antioxidant capacity and T2DM. However, Lampousi et al. [9] combined a case-control study with Mendelian randomization method and found that dietary vitamins C and E were not associated with T2DM, but vitamin E was associated with a higher homeostatic model assessment of β-cell function (HOMA-β) and a lower HOMA-IR. Circulating antioxidants also seemed to be unrelated to T2DM. In addition, a recent meta-analysis found that supplementation of vitamin E or β-carotene had no protective effect against T2DM; however, dietary supplementation with greater amounts of vitamin C and vitamin E effectively reduced IR [10]. In general, these studies have a common limitation of not considering the role of antioxidant dietary factors as a whole.

Fortunately, with the joint efforts of scientists, biologists, and medical scientists, the "family members" of antioxidants are also constantly expanding. The composite dietary antioxidant index (CDAI) is a comprehensive score that assesses the overall antioxidant properties of a diet, which consists of six main dietary antioxidants (including vitamin A, vitamin C, vitamin E, zinc, selenium, and carotenoids) [11, 12]. Existing studies have shown that CDAI is negatively correlated with the incidence of multiple diseases, including hypertension [13], chronic kidney disease [14], and colorectal cancer [11]. Furthermore, there are also studies indicating that among adults with metabolic associated fatty liver disease (MAFLD), it was found that higher levels of CDAI are associated with a reduced risk of sarcopenia [15]. The triglyceride-glucose (TyG) index is an easily measurable biochemical marker, which was first introduced in 2008 to assess insulin sensitivity in humans by combining triglycerides and fasting blood glucose biomarkers [16]. Studies have shown that among elderly people in China, without adjusting for BMI, TyG is negatively correlated with the incidence of sarcopenia [17]. Additionally, TyG was successfully used to assess the presence of non-alcoholic fatty liver disease (NAFLD) and one of its main co-morbidities, through the mediation effect of insulin resistance, that is bladder cancer [18]. Subsequent studies have further demonstrated the superiority of TyG in assessing IR compared with indicators such as HOMA-IR [19, 20]. However, the relationship between CDAI and its components and TyG is still unclear.

Based on the above background, it is speculated that CDAI may effectively reduce TyG, but the contributions of several antioxidant nutrients may not be equivalent. In this study, the cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) were analyzed to systematically explore the relationship of CDAI and its components with TyG.

Methods

Study population

This study adopted a cross-sectional design, and this cross-sectional study investigated the NHANES participants from 2003 to 2018. A total of 80,312 participants were included over 8 cycles, of which 10,777 participants were excluded due to lack of 24-hour dietary recall, 46,538 due to missing TyG data, and 8,324 due to missing covariates. Finally, a total of 14,673 eligible participants with complete data were included (Supplementary Fig. 1).

Composite dietary antioxidant index (CDAI)

CDAI consists of six antioxidants: vitamin A, vitamin C, vitamin E, zinc, selenium, and carotenoids [11, 12]. Since there were unit differences between antioxidants, each antioxidant was first standardized. The standardized values were then summed to obtain the CDAI. The formula is as follows:

$CDAI = \sum_{i=1}^{n=6} (Individual\ intake - Mean)/SD)$. It should be noted that individual dietary nutrient intake represents the average intake from two 24-hour dietary recalls, and the individuals with only one-day reported values were excluded.

Triglyceride-glucose (TyG) index

The TyG index, an alternative indicator of insulin resistance (IR), is calculated as the logarithm of the product of fasting plasma triglycerides and fasting plasma glucose levels, reflecting the interaction between lipid and glucose metabolism. The formula is as follows: $\mathbf{TyG} = \mathbf{Ln}^{[\text{fasting triglyceride (mg/dL)} \times \text{fasting glucose (mg/dL)}/2]}$ [16, 21].

Covariates

Demographic characteristics included age, sex, race, education level, marital status, and poverty income ratio (PIR). Lifestyle and physical indicators included alcohol consumption and smoking status, total dietary energy intake, and body mass index (BMI). The following comorbidities were considered: tumors, liver disease, cardiovascular disease (CVD), chronic kidney disease (CKD), diabetes, arthritis, and thyroid disease. In addition, statin use was also considered.

Statistical analysis

The characteristics of the participants were analyzed. Continuous variables were analyzed using one-way ANOVA or Kruskal-Wallis test, and the results were expressed as means (standard error) or medians (Q1, Q3). Categorical variables were analyzed using chi-square tests, and the results were expressed as the number of cases (n) and percentage (%). The correlation of several antioxidant nutrients was estimated using Pearson's test. Multiple linear regression models were constructed to evaluate the association between CDAI and TyG: (1) unadjusted model (Model 0); (2) Model 1 adjusted for demographic factors (sex, age, race, educational attainment, PIR, and marital status); (3) Model 2 further adjusted for smoking, alcohol consumption, total dietary energy intake, and BMI; (4) Model 3 further adjusted for comorbidities (CVD, CKD, cancer, liver disease, diabetes, arthritis, thyroid disease) and statin use. CDAI was included in the regression models either as a continuous variable or as a three-category variable based on tertiles, and the associated effect size β and confidence interval (CI) with TyG were estimated. Trend effects in gradually increasing exposure groups were calculated using integer values (1, 2, and 3). Collinearity of the linear regression models was assessed using the variance inflation factor (VIF), and all VIFs in this study were less than 2. Additionally, a restricted cubic spline (RCS) regression model with three nodes (10th, 50th, and 90th percentiles) was constructed based on the minimization principle of Akaike information criterion (AIC) to determine the dose-response relationship of CDAI and its components with TyG. In the RCS model, the median of the exposure variable served as the reference point, and nonlinearity was assessed using the Wald test (*P* for nonlinearity). Subgroup analyses were performed to identify potential effect modifiers. Specifically, interaction terms between CDAI and stratification variables were included in the model, and the difference between this model and the original model was compared using the likelihood ratio test (*P* for interaction). Notably, if there was a significant interaction between the categorical covariate and the exposure variable, further analysis was conducted to evaluate the significance of the interaction term in each stratum. In addition, weighted quantile sum (WQS) regression and Bayesian kernel machine regression (BKMR) were carried out to investigate the joint effects and dominant components of the six dietary factors. In the WQS model, a WQS index was created using the quartiles of dietary antioxidant intake, in which the estimated weight of each component was included. Assuming a negative direction, the data were randomly split into training and validation datasets in a 40:60 ratio, and robust estimates were generated through 1000 times of bootstrapping. In the BKMR model, 20,000 Markov Chain Monte Carlo (MCMC) iterations were performed.

Several sensitivity analyses were conducted to assess the robustness of the results. (1) In the first sensitivity analysis, additional adjustments were made for physical activity (PA) due to a high proportion of missing values (>20%). (2) Multiple linear regression was performed considering the sample weights of NHANES (WTDR2D/8). 3–4) Unweighted and weighted (WTDRD1/8) multivariable linear regressions were conducted using the first 24-hour dietary recall to construct CDAI. 5) Additional adjustments were made for depression and serum vitamin D levels. 6) Multiple interpolation for missing covariates. 7) Additionally analyzed the association between CDAI and three TyG surrogate indicators (BMI-adjusted TyG, waist circumference-adjusted TyG, and waist-to-height ratio-adjusted TyG). The TyG surrogates was calculated as described in Fu et al. [22].

The statistical analyses required for this study were completed using R software version 4.3.3 (http://www.r-project.org). The following R packages were mainly used: "BKMR", "gWQS", "car", "rms", and "lmtest". Furthermore, a bilateral P-value of less than 0.05 was considered statistically significant.

Results

Population characteristics

After excluding ineligible participants, a total of 14,673 individuals with complete data were included in the

Table 1 Baseline characteristics of the participants classified by CDAI tertiles

	Total (*n* = 14673)	Tertile 1 (*n* = 4895)	Tertile 2 (*n* = 4887)	Tertile 3 (*n* = 4891)	*P*
Sex, *n* (%)					< 0.001
Female	7257 (49)	2543 (52)	2343 (48)	2371 (48)	
Male	7416 (51)	2352 (48)	2544 (52)	2520 (52)	
Age, Median (Q1,Q3)	50 (35, 64)	51 (36, 66)	50 (35, 65)	47 (34, 62)	< 0.001
Race, *n* (%)					< 0.001
Mexican American	2336 (16)	796 (16)	775 (16)	765 (16)	
Non-Hispanic Black	2899 (20)	1124 (23)	912 (19)	863 (18)	
Non-Hispanic White	6875 (47)	2137 (44)	2341 (48)	2397 (49)	
Other Hispanic	1236 (8)	446 (9)	408 (8)	382 (8)	
Other Race - Including Multi-Racial	1327 (9)	392 (8)	451 (9)	484 (10)	
Education attainment, *n* (%)					< 0.001
Less than college	6925 (47)	2773 (57)	2238 (46)	1914 (39)	
College or higher	7748 (53)	2122 (43)	2649 (54)	2977 (61)	
Marital status, *n* (%)					< 0.001
Never married	2541 (17)	856 (17)	805 (16)	880 (18)	
Divorced/separated/widowed	3252 (22)	1287 (26)	1019 (21)	946 (19)	
Married/living with a partner	8880 (61)	2752 (56)	3063 (63)	3065 (63)	
Poverty Income Ratio, *n* (%)					< 0.001
<1.3	4358 (30)	1752 (36)	1352 (28)	1254 (26)	
1.3–3.5	5686 (39)	2007 (41)	1920 (39)	1759 (36)	
>3.5	4629 (32)	1136 (23)	1615 (33)	1878 (38)	
Alcohol status, *n* (%)					< 0.001
Never	1936 (13)	745 (15)	632 (13)	559 (11)	
Former	2536 (17)	1000 (20)	818 (17)	718 (15)	
Now	10,201 (70)	3150 (64)	3437 (70)	3614 (74)	
Smoke, *n* (%)					< 0.001
Never	7882 (54)	2458 (50)	2647 (54)	2777 (57)	
Former	3751 (26)	1225 (25)	1289 (26)	1237 (25)	
Now	3040 (21)	1212 (25)	951 (19)	877 (18)	
Energy intake, Median (Q1, Q3)	1952 (1444, 2595)	1397 (1060, 1785)	2021 (1609, 2493.5)	2620 (2045, 3348.5)	< 0.001
BMI, Median (Q1, Q3)	27.98 (24.36, 32.48)	28.07 (24.46, 32.72)	28.26 (24.68, 32.55)	27.59 (23.99, 32.24)	< 0.001
Cancer, *n* (%)	1374 (9)	459 (9)	461 (9)	454 (9)	0.967
Thyroid problem, *n* (%)	1524 (10)	516 (11)	520 (11)	488 (10)	0.511
Liver problem, *n* (%)	572 (4)	181 (4)	187 (4)	204 (4)	0.458
Arthritis, *n* (%)	4122 (28)	1536 (31)	1324 (27)	1262 (26)	< 0.001
DM, *n* (%)					< 0.001
DM	2979 (20)	1127 (23)	987 (20)	865 (18)	
IFG	1399 (10)	469 (10)	463 (9)	467 (10)	
IGT	1097 (7)	394 (8)	367 (8)	336 (7)	
No	9198 (63)	2905 (59)	3070 (63)	3223 (66)	
CVD, *n* (%)	1654 (11)	697 (14)	527 (11)	430 (9)	< 0.001
CKD, *n* (%)	2656 (18)	1073 (22)	847 (17)	736 (15)	< 0.001
Statins use, *n* (%)	2779 (19)	1000 (20)	948 (19)	831 (17)	< 0.001
CDAI (Mean (SD))	0.00 (3.91)	-3.42 (1.13)	-0.61 (1.00)	4.03 (3.91)	< 0.001
Z Score-Vitamin A (mean (SD))	0.00 (1.00)	-0.54 (0.32)	-0.12 (0.48)	0.66 (1.39)	< 0.001
Z Score-Vitamin C (mean (SD))	0.00 (1.00)	-0.49 (0.43)	-0.09 (0.70)	0.58 (1.32)	< 0.001
Z Score-Vitamin E (mean (SD))	0.00 (1.00)	-0.65 (0.36)	-0.13 (0.53)	0.78 (1.24)	< 0.001
Z Score-Zinc (mean (SD))	0.00 (1.00)	-0.57 (0.38)	-0.05 (0.54)	0.62 (1.36)	< 0.001
Z Score-Selenium (mean (SD))	0.00 (1.00)	-0.66 (0.47)	-0.04 (0.62)	0.70 (1.21)	< 0.001
Z Score-Carotenoid (mean (SD))	0.00 (1.00)	-0.51 (0.27)	-0.18 (0.50)	0.68 (1.39)	< 0.001
TyG, Median (Q1, Q3)	8.6 (8.18, 9.04)	8.63 (8.23, 9.07)	8.59 (8.19, 9.03)	8.56 (8.12, 9.02)	< 0.001

Notes: TyG, triglyceride-glucose index; DM, diabetes mellitus; CVD, cardiovascular disease; CKD, chronic kidney disease; IFG, impaired fasting glycaemia; IGT, impaired glucose tolerance; SD, standard deviation

analysis (Supplementary Fig. 1). As shown in Table 1, the median age of all participants was 50 years, and 7,257 (49%) were female. Compared to participants in the first tertile of CDAI, those in the third tertile were younger, better educated, and more likely to be married with a higher proportion of males and a higher socioeconomic status. They were more likely to have never smoked but more likely to have consumed alcohol, had approximately twice the dietary energy intake, and had better weight management. Moreover, these participants had a lower prevalence of thyroid disease, diabetes, CVD, and CKD, and less statin use.

The associations of CDAI and its components with TyG

The association between CDAI and TyG is presented in Table 2. In the model using continuous CDAI, a negative association between CDAI and TyG was observed after full adjustment [β: -0.005, 95%CI: (-0.008, -0.002), $P=0.002$]. In the model using categorical CDAI, the third tertile group had a decrease in TyG compared to the first tertile group [β: -0.041, 95%CI: (-0.070, -0.012), $P=0.005$]; although the second tertile group did not show a significant decrease in TyG, there was a significant trend effect across the three groups (P for trend = 0.005).

The Pearson correlation coefficients between CDAI and the six dietary factors are displayed in Fig. 1, ranging from 0.55 to 0.72. The independent associations between six individual dietary antioxidants and TyG are presented in Table 3. After mutual adjustment and consideration of confounding factors, the strongest inverse association was observed between continuous Vitamin E and TyG [β: -0.062, 95%CI: (-0.074,-0.050), $P<0.0001$]; this association was also observed in the categorical Vitamin E model, where participants in the second tertile [β: -0.098, 95%CI: (-0.123,-0.073), $P<0.0001$] and third tertile [β: -0.163, 95%CI: (-0.193,-0.134), $P<0.0001$] had a significant decrease in TyG compared to the first tertile group. The dose-response relationship of CDAI and its components with TyG is shown in Fig. 2. It was observed that CDAI, Vitamin A, and Vitamin E were significantly inversely linearly associated with TyG (all nonlinear $P>0.05$).

WQS regression analysis of single and overall effects of six antioxidant nutrients with TyG

In the WQS model, the WQS index of a mixed antioxidant diet was negatively associated with TyG [β: -0.060, 95%CI: (-0.076, -0.045), $P<0.0001$] (Supplementary Table 1). Besides, the weights of Vitamin E (84.36%) and selenium (10.71%) in the WQS model exceeded the threshold (Fig. 3).

Analysis of the relationship between single and mixed antioxidant nutrients and TyG using BKMR model

In the BKMR model, the effects of single and mixed antioxidant nutrients on TyG were further investigated. The posterior inclusion probability (PIP) values for the six dietary antioxidants and their associations with TyG are displayed in Supplementary Table 2, with Vitamin E contributing the most. Figure 4A shows a significant negative association between dietary antioxidant mixture intake and TyG levels when all nutrient intakes exceeded the 55th percentile. Additionally, when the remaining five nutrients were fixed at the 25th, 50th, and 75th percentiles, respectively, Vitamin E was found to be significantly negatively associated with TyG (Fig. 4B).

Subgroup analysis and effect modification tests

The association between CDAI and TyG in different subgroups is presented in Supplementary Fig. 2. The likelihood ratio test showed significant interactions between race (P for interaction = 0.012), BMI (P for interaction = 0.004), and DM (P for interaction = 0.001) with CDAI. Specifically, the inverse association between CDAI and TyG was stronger in non-Hispanic whites

Table 2 Multivariate linear regression analysis of CDAI with TyG

	Model 0		Model 1		Model 2		Model 3	
	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
CDAI (continuous)	-0.008(-0.011, -0.006)	< 0.0001	-0.005(-0.008, -0.002)	< 0.001	-0.005(-0.008, -0.001)	0.005	-0.005(-0.008, -0.002)	0.002
CDAI (per SD)	-0.033(-0.044, -0.022)	< 0.0001	-0.019(-0.030, -0.009)	< 0.001	-0.019(-0.032, -0.006)	0.005	-0.02(-0.032, -0.008)	0.002
Tertile 1	ref		ref		ref		ref	
Tertile 2	-0.026(-0.053, 0.001)	0.059	-0.02(-0.046, 0.006)	0.124	-0.024(-0.050, 0.002)	0.066	-0.019(-0.043, 0.006)	0.133
Tertile 3	-0.072(-0.099, -0.045)	< 0.0001	-0.042(-0.067, -0.016)	0.002	-0.039(-0.070, -0.008)	0.012	-0.041(-0.070, -0.012)	0.005
p for trend		< 0.0001		0.002		0.012		0.005

Notes:

Model 0: No covariate was adjusted

Model 1: Adjusted for age, sex, race, education attainment, marital status, and poverty-income ratio

Model 2: Further adjusted for smoking, drinking status, BMI, and energy intake based on Model 1

Model 3: Further adjusted for arthritis, thyroid problems, cancer, diabetes, liver diseases, CVD, CKD, and statins use based on Model 2

Abbreviations: CDAI, composite dietary antioxidant index; TyG, triglyceride-glucose index; BMI, body mass index; CVD, cardiovascular disease; CKD, chronic kidney disease; CI, confidence interval; ref, reference

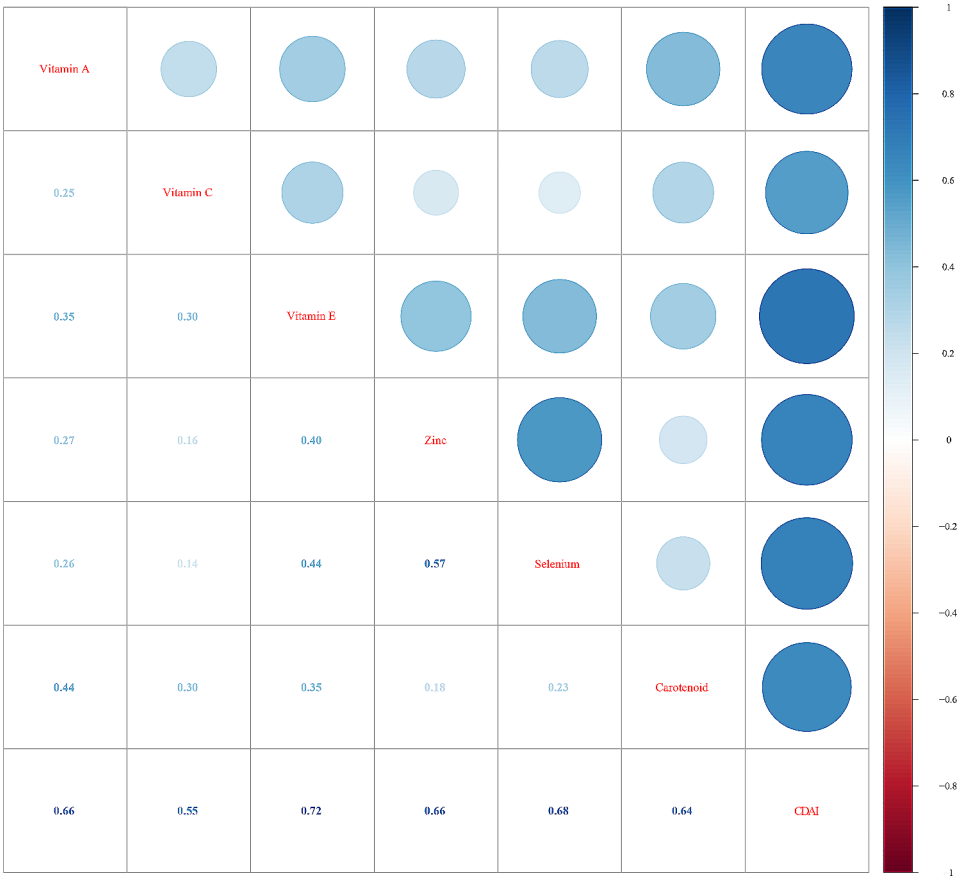

Fig. 1 Pearson correlation coefficients of six antioxidant nutrients and CDAI. **Abbreviations:** CDAI, composite dietary antioxidant index

Table 3 Multivariate linear regression analysis of individual dietary antioxidants with TyG

	Per SD		Tertile 1	Tertile 2		Tertile 3		
	β (95% CI)	*P*		β (95% CI)	*P*	β (95% CI)	*P*	*P* for trend
Vitamin A	-0.014(-0.025, -0.003)	0.012	ref	0.002(-0.023, 0.026)	0.879	-0.02(-0.048, 0.008)	0.156	0.151
Vitamin C	0.013(0.003, 0.023)	0.012	ref	0.026(0.002, 0.050)	0.037	0.041(0.016, 0.066)	0.001	0.002
Vitamin E	-0.062(-0.074, -0.050)	< 0.0001	ref	-0.098(-0.123, -0.073)	< 0.0001	-0.163(-0.193, -0.134)	< 0.0001	< 0.0001
Zinc	0.023(0.011, 0.035)	< 0.001	ref	0.014(-0.011, 0.040)	0.272	0.03(-0.001, 0.061)	0.057	0.057
Selenium	-0.004(-0.018, 0.010)	0.540	ref	0.001(-0.024, 0.027)	0.923	0.006(-0.026, 0.037)	0.721	0.723
Carotenoid	0.015(0.004, 0.026)	0.007	ref	0.004(-0.020, 0.028)	0.734	0.03(0.004, 0.057)	0.023	0.023

Notes:

Models were adjusted for the other five dietary antioxidants and all covariates

Abbreviations: TyG, triglyceride-glucose index

but weakened in overweight or obese individuals (BMI ≥ 25 kg/m^2) and DM patients.

Sensitivity analysis

The results of sensitivity analyses are shown in Supplementary Tables 3 and Supplementary Table 4. Overall, several sensitivity analyses supported a robust inverse association between CDAI and TyG.

Discussion

Linear regression, WQS, and BKMR were integrated in this cross-sectional study to explore the relationship of CDAI and its components with TyG. The results suggested a negative association between CDAI, especially Vitamin E, and TyG, while RCS analysis showed a linear relationship. Further interaction tests indicated that the inverse association between CDAI and TyG was stronger in non-Hispanic whites but weakened in overweight or obese individuals and DM patients. Additionally, sensitivity analyses further confirmed these findings.

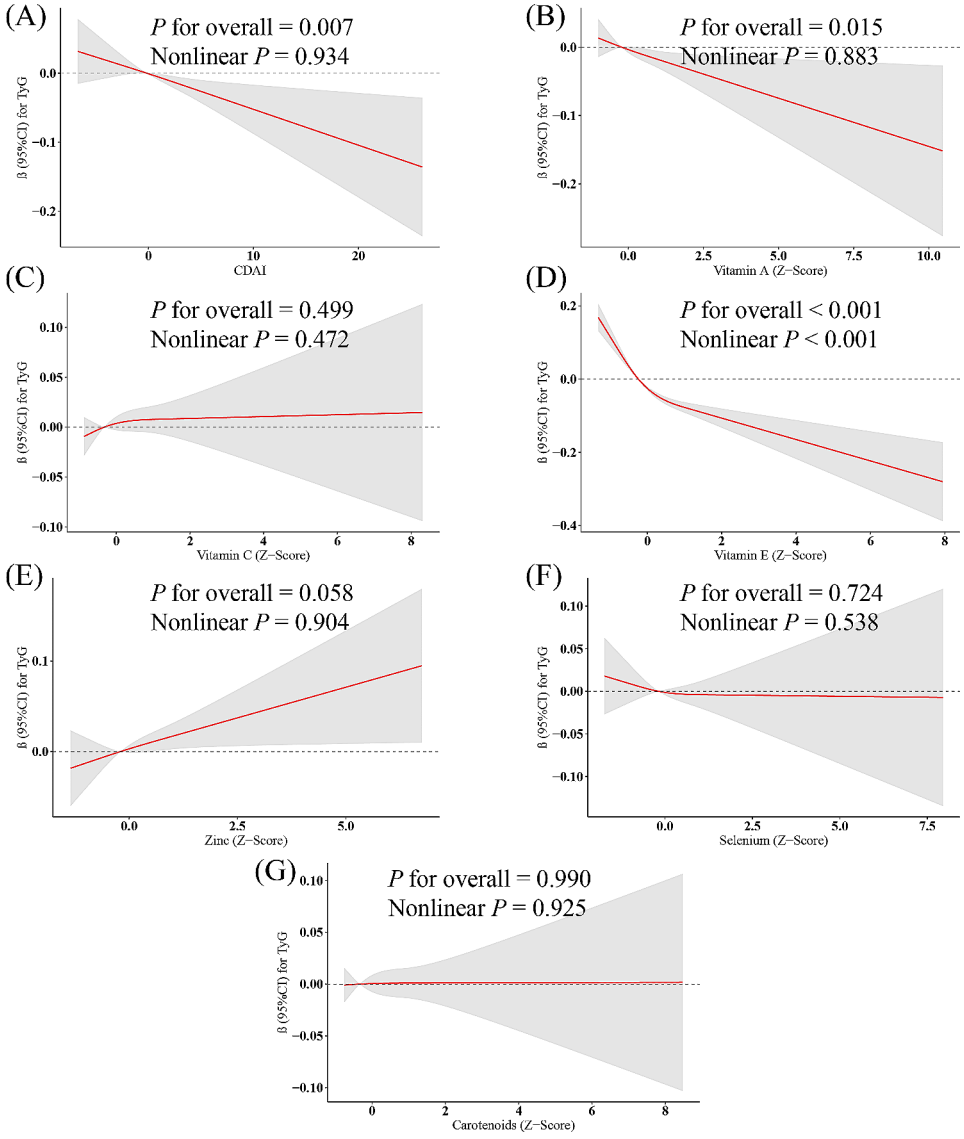

Fig. 2 Dose-response relationship of antioxidant nutrients and CDAI with TyG. **Figure legend**: The red line in the center represents the effect value, and the black shaded area indicates the 95% CI. All models were adjusted for age, sex, race, education attainment, marital status, poverty-income ratio, smoking, drinking status, BMI, energy intake, arthritis, thyroid problems, cancer, diabetes, liver diseases, CVD, CKD, and statin use. When fitting the RCS regression model, the respective median values were used as reference points and the three inflection points were selected at (10th, 50th, and 90th percentile) based on the AIC minimum principle. The Wald Test was used to determine nonlinear *P*-values. **Abbreviations:** CDAI, composite dietary antioxidant index; TyG, triglyceride-glucose index; BMI, body mass index; CVD, cardiovascular disease; CKD, chronic kidney disease; RCS, restricted cubic spline; AIC, Akaike information criterion; CI, confidence interval

This study represents the first systematic exploration of the relationship between various dietary antioxidants and TyG. Previous studies have shown a negative association between several dietary antioxidants and IR. Schaft et al. [7] found in a prospective cohort study that dietary antioxidant capacity, as assessed by plasma reducing capacity, was negatively correlated with the risk of T2DM and HOMA-IR in the general population or individuals with pre-diabetes. Li et al. [8] analyzed 12,467 participants from natural populations in Northwest China and also found that total dietary antioxidant capacity was negatively correlated with T2DM. However, by combining case-control studies and Mendelian randomization, Lampousi et al. [9] found that dietary vitamins C and E were not associated with T2DM, but vitamin E was positively correlated with higher HOMA-β and lower HOMA-IR; circulating antioxidants appeared to be unrelated to T2DM. In addition, a recent meta-analysis found that supplementation of vitamin E or β-carotene had no protective effect against T2DM; however, dietary supplementation with greater amounts of vitamin C and vitamin E effectively reduced IR [10]. Similarly, a

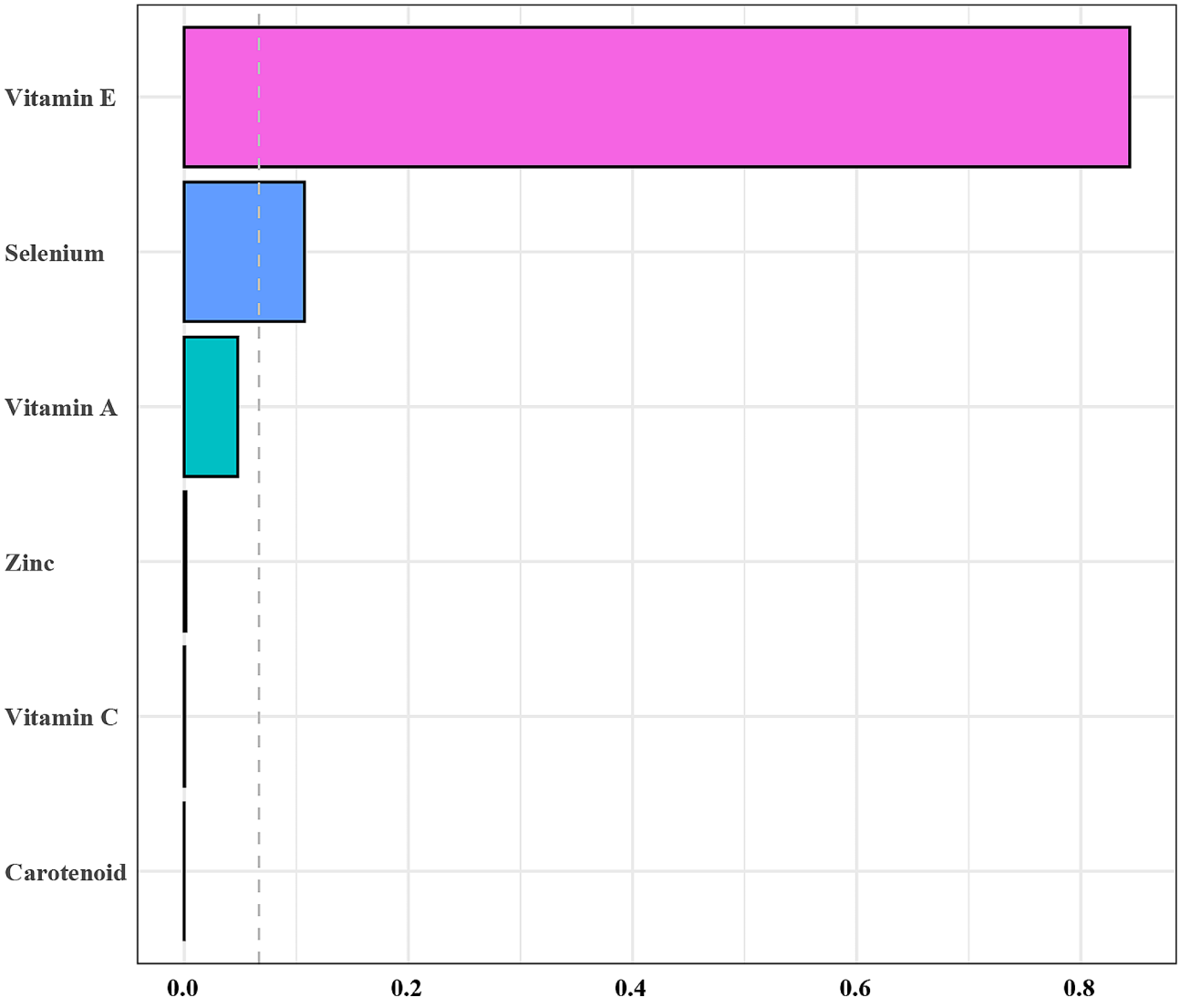

Fig. 3 Weights of WQS index of six dietary antioxidants in TyG. **Figure legend**: The dashed black lines represent the cutoff to discriminate which element has a significant weight. The model was adjusted for age, sex, race, education attainment, marital status, poverty-income ratio, smoking, drinking status, BMI, energy intake, arthritis, thyroid problems, cancer, diabetes, liver diseases, CVD, CKD, and statins use. **Abbreviations:** TyG, triglyceride-glucose index; BMI, body mass index; CVD, cardiovascular disease; CKD, chronic kidney disease

meta-analysis in 2023 showed that vitamin E significantly reduced glycosylated hemoglobin (HbA1c), fasting insulin and HOMA-IR, but this association was not significant in diabetic patients [23]. This study extends the knowledge in this field by revealing a strong negative linear association between CDAI and TyG. Furthermore, in the WQS and BKMR models as well as the linear regression models, vitamin E was an important influencing factor, emphasizing the importance of vitamin E in improving IR.

However, the efficacy of vitamin E in improving IR remains unclear according to current evidence. In Western and some Asian countries, it has been reported that vitamin E improves glycemic indexes and IR in patients with T2DM [24–27]; however, some studies in these regions have shown that this association is not statistically significant in patients with diabetic nephropathy [28–30] and patients with T2DM [31–33]. Interestingly, some studies have shown that blood glucose levels in patients with T2DM increase rather than decrease after vitamin E supplementation [34, 35]. A meta-analysis conducted 10 years ago showed no significant improvement in HbA1c and fasting insulin levels in patients with T2DM after vitamin E supplementation [36]. These studies suggest that the actual intervention effects of antioxidants may vary at different stages of non-DM and DM. Similar conclusions were drawn from the present study; antioxidant-rich diets did not improve IR in diabetic patients and overweight or obese individuals, while the general population and participants with pre-diabetes

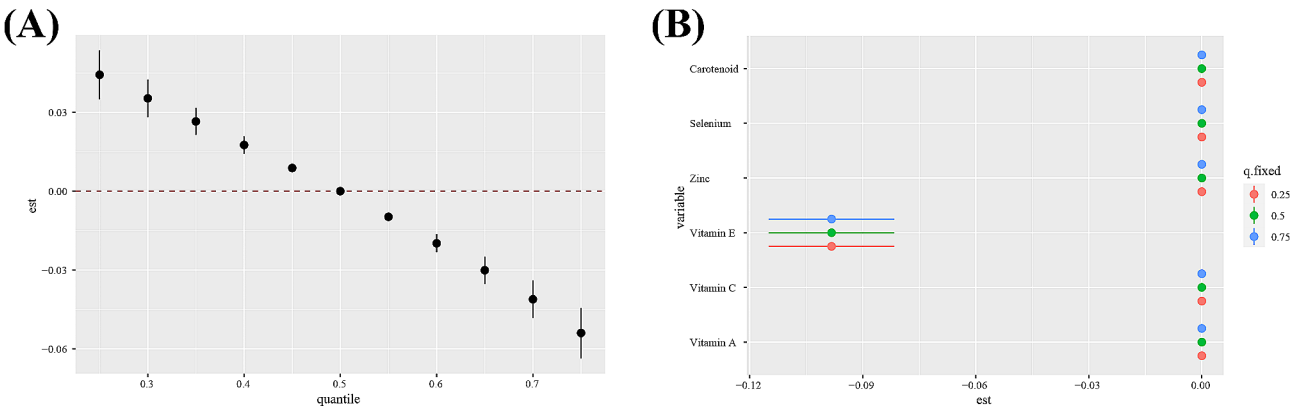

Fig. 4 Single and overall relationship of CDAI and components with TyG in BKMR. **Figure legend**: **(A)**: Overall relationship between CDAI and TyG. **(B)**: Single-exposure effects of individual dietary antioxidants on TyG. **Abbreviations:** CDAI, composite dietary antioxidant index; TyG, triglyceride-glucose index; BKMR, Bayesian kernel machine regression

benefited from antioxidant diets and alleviated IR. The reason for this may be that these populations generally have severe IR, which is more difficult to improve through dietary interventions. Studies have found that a combination of weight management (at least 10% weight loss), exercise, and a healthy diet helps stabilize insulin and blood glucose levels and reduce inflammation in DM patients, thereby preventing or even reversing IR [6, 37].

In this study, several models suggested that vitamin E was the most important dietary antioxidant component. Vitamin E is a family of eight distinct compounds, consisting of four tocopherols and four tocotrienols, i.e., α-, β-, γ- and δ-tocopherols and α-, β-, γ- and δ-tocotrienols. α- and γ-tocopherols upregulate an endogenous ligand and activate PPARγ, which in turn upregulates adiponectin; adiponectin is an endogenous bioactive protein secreted by adipocytes with an insulin-sensitizing effect [38]. Abnormalities in insulin structure are important contributors to IR. Far- and near-UV CD studies have shown that α-tocopherol induces conformational changes in the chemical structure of human insulin and stabilizes the insulin structure by increasing the number of α-helices [39]. Furthermore, vitamin E can regulate the activity of the oxidase responsible for reduced glutathione (GSH), thereby increasing GSH levels. Studies have shown that GSH can increase glucose uptake in peripheral tissues, improve peripheral tissue sensitivity to insulin, and enhance insulin secretion by pancreatic β-cells [40]. Additionally, individuals with IR have elevated levels of oxidative stress. Vitamin E, located between the phospholipid bilayers of the biological membranes, is the first line of defense for membrane antioxidants, and can also maintain the structural integrity of the endoplasmic reticulum in pancreatic endocrine cells, thus exerting a protective effect on pancreatic cells [41].

Advantages and limitations

In this study, the association between CDAI and its components and TyG was systematically explored using a variety of statistical methods, and it was found that CDAI, especially vitamin E, significantly improved IR, which provides some valuable insights into clinical diabetes management. Multiple confounding factors were considered comprehensively, and several sensitivity analyses were conducted in this study, resulting in relatively robust conclusions.

However, some limitations need to be considered. Firstly, due to the limitations of cross-sectional studies, there was a potential causal temporal relationship that could not be revealed in this study. Secondly, although the data on dietary patterns came from two reliable and validated self-reported 24-hour dietary recalls, recall bias definitely exists. Reassuringly, the results were consistent in sensitivity analyses when reconstructing a 24-hour dietary recall with or without considering the sampling weight. In addition, this study relied on a single baseline blood sample to collect information about TyG, so there may be biases. Moreover, since this is a cross-sectional study, there is a lack of access to the dynamic change data of TyG. Therefore, the relationship between CDAI and TyG needs to be explored more meticulously in a prospective cohort study. Further, potential confounding factors were inevitably overlooked. Finally, the conclusions of this study are limited to the adult population in the United States, and caution should be exercised regarding external validity.

Conclusion

In conclusion, this study reveals a negative association between CDAI and TyG. Among the six antioxidant components, vitamin E is probably the most important nutrient for improving IR. However, those with poor

weight management and diabetic patients seem to have more difficulty benefiting from antioxidant diets.

Abbreviations

AIC	Akaike information criterion
ANOVA	One-way analysis of variance
BKMR	Bayesian kernel machine regression
BMI	Body Mass Index
CDAI	Composite dietary antioxidant index
CKD	Chronic kidney disease
CVD	Cardiovascular disease
DM	Diabetes mellitus
FRAP	Plasma reducing ability
GSH	Reduced glutathione
HOMA-IR	Homeostasis model assessment of insulin resistance
HOMA-β	Homeostatic model assessment of β-cell function
IR	Insulin resistance
MAFLD	Metabolic associated fatty liver disease
MCMC	Markov Chain Monte Carlo
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
NAFLD	Non-alcoholic fatty liver disease
NHANES	National Health and Nutrition Examination Survey
PPARγ	Peroxisome Proliferator-Activated Receptor Gamma
RCS	Restricted cubic spline
SD	Standard deviation
T2DM	Type II diabetes
TyG	Triglyceride-glucose index
VIF	Variance inflation factor
WQS	Weighted quantile sum

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-024-02233-7.

Supplementary Material 1

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Data availability
Data used for this study are available on the NHANES website: https://wwwn.cdc.gov/nchs/nhanes/.

Declarations

Ethics approval and consent to participate
The National Health and Nutrition Examination Survey (NHANES) is a publicly available database and approved by the National Center for Health Statistics institutional review board. All participants provided written informed consent when they did the national survey in the United States. Ethical review and approval were waived for this study since secondary analysis did not require additional institutional review board approval.

Consent for publication
Not applicable.

Conflict of interest
The authors declare that there are no commercial or economic relationships that could be construed as potential conflicts of interest in the conduct of this study.

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