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Dietary antioxidant intake and its association with cognitive function in an ethnically diverse sample of US adults

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Abstract

Background—Dietary antioxidants can inhibit reactions accompanying neurodegeneration, and thus prevent cognitive impairment. We describe associations of dietary antioxidants with cognitive function in a large biracial population, while testing moderation by sex, race and age and mediation by depressive symptoms.

Methods—This was a cross-sectional analysis of 1,274 adults (541 men and 733 women) aged 30–64y at baseline (Mean±SD: 47.5±9.3) in the Healthy Aging in Neighborhoods of Diversity Across the Lifespan Study (HANDLS), Baltimore city, MD. Cognitive performance in the domains of memory, language/verbal, attention, spatial, psychomotor speed, executive function, and global mental status were assessed. The 20-item Center for Epidemiologic Studies Depression Scale (CES-D) scale was used to measure depressive symptoms. Dietary intake was assessed with two 24-hr recalls, estimating daily consumption of total carotenoids, vitamins A, C and E, per 1,000 kcal.

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Results—Among key findings, one standard deviation (SD~2.02 mg/1,000kcal) higher vitamin E was associated with a higher score on verbal memory, immediate recall, (β=+0.64±0.19, p=0.001) and better language/verbal fluency performance (β=+0.53±0.16, p=0.001), particularly among the younger age group. Women with higher vitamin E intake (β=+0.68±0.21, p=0.001) had better performance on a psychomotor speed test. The vitamin E-verbal memory association was partially mediated by depressive symptoms (proportion mediated=13–16%).

Conclusions—In sum, future cohort studies and dietary interventions should focus on associations of dietary vitamin E with cognitive decline, specifically for domains of verbal memory, verbal fluency and psychomotor speed.

Keywords

Antioxidants; cognitive function; depressive symptoms; midlife

INTRODUCTION

Impaired cognitive function, a major cause for functional disability in old age, leads to loss of independence ascribed mostly to age-related dementing illnesses, most commonly, Alzheimer's Disease (AD). With the rise in the proportion of people over 65 years of age in the United States and elsewhere, it is expected that AD will quadruple in prevalence by 2050 to more than 100 million people worldwide, when 1 in 85 will be living with AD (1–5). However, efforts are currently under way to uncover modifiable risk factors, including dietary patterns, nutrient and antioxidant intakes, that might reduce the prevalence of cognitive impairment, dementing illnesses and AD.

Several findings suggest oxidative stress plays an important role in neurodegenerative processes accompanying cognitive impairment and dementia, particularly AD. The brain is particularly vulnerable to reactive oxygen species (ROS) as its metabolism accounts for approximately 20% of all oxygen consumption within the body. (6). The exposure of ROS has been shown to result in oxidative modification of DNA in brain tissue that in some cases has been shown to accumulate due to reductions of DNA repair. (7–9) Oxidative stress among AD patients is marked by increased antioxidant brain levels, acting as free radical scavengers. (10) In vitro studies suggest that exogenous antioxidants may reduce β-amyloids toxicity in AD patients' brains (10–12). Dietary antioxidants, mainly β-carotene (as well as other carotenoids), vitamin C and vitamin E, were shown to inhibit lipid peroxidation (6), the production of ROS (13), apoptosis (13), and oxidative damage to protein (14) and DNA (15). It is hypothesized that dietary antioxidants can potentially improve middle-aged adults' cognitive performance and ultimately delay onset of AD in older age.

However, many previous studies used global cognition tests (16–20) or assessed dementia/AD diagnosis in older adults (21–24), and did not examine the association of antioxidants with various cognitive function domains in middle-age adults. It is important to test whether dietary intakes of carotenoids, vitamins A, C and E are differentially associated with areas of cognition among middle-aged US adults and to examine whether associations differ by sex and race. In addition, although many recent studies have found a protective effect of antioxidants against depressive symptoms (25, 26), and depressive symptoms have

been directly related to poor cognitive functioning in middle-age (27–30), no study has assessed the mediating or moderating roles of depressive symptoms in association with antioxidants and middle-aged adults' cognitive functioning. Indeed, dietary antioxidants may affect cognition directly through reducing oxidative stress at the neuronal level in areas of the brain that relate to memory and other cognitive domains or indirectly by affecting oxidative stress in areas that were linked to depressive symptoms which in turn can affect cognitive performance. Associations between antioxidants and cognition were shown to be significant only for specific cognitive domains in some studies (31–33) while other studies have shown that those associations were restricted to specific socio-demographic groups or genotypes in others (34–36). Moreover, the bioavailability of many nutrients, including antioxidants, is highly dependent socio-demographic variables and thus the variable recommendations for different age and sex groups. (37–40). Therefore, it is hypothesized that sex, race and age may moderate the association between antioxidants and cognition while depressive symptoms may act as a mediating factor.

In this report we describe the adjusted associations between dietary antioxidants and cognitive function in various cognitive domains in a large biracial population, while examining socio-demographic differences in those associations and the mediating role of depressive symptoms.

METHODS

Database and study sample

The HANDLS study, an ongoing prospective cohort study, recruited a representative sample of African Americans and whites (30–64 years old) at baseline, living in Baltimore, Maryland, using an area probability sampling design of 13 census segments. The initial phase of HANDLS involved screening, recruitment and household interviews, while phase 2 included examinations in mobile Medical Research Vehicles (MRV). (41) Initiated in 2004, HANDLS completed baseline data in 2009 and recently completed the first follow-up wave data. The protocol of this study was approved by the Institutional Review Board of the National Institute of Environmental Health Sciences. The present study uses baseline HANDLS cohort cross-sectional data (i.e. phases 1 and 2).

Of 3,720 participants sampled in phase 1 (**Sample 1**), complete phase 2 examination data at baseline was available for 2,802 (**Sample 2a**). This study included only participants with two days of dietary recall and CES-D data (n=1,739; **Sample 2b**). Notable income level and sex differences between **Sample 2b** and **Sample 1** were found (51.9% above poverty, 43.2% are men in **Sample 2b** vs. 64.8% above poverty and 47.1% are men in remaining subjects in **Sample 1**), with participants in **Sample 2b** having higher African-American representation (i.e. 67.7% vs. 55.9%). Sample size of participants with complete and reliable cognitive tests (main outcome) as well as predictor/covariate variables was 1,274 participants (**Sample 3**). **Sample 3** did not differ from the remaining group of **Sample 1** participants on sex, age, race or poverty/income ratio distribution.

Cognitive assessment

Nine cognitive tests resulting in 13 test scores that cover 7 domains (Global, attention, learning/memory, executive function, visuo-spatial/visuo-construction ability, psychomotor speed, language/verbal) were outcomes: the Mini-Mental State Examination (MMSE), the California Verbal Learning Test immediate free recall, List A (CLVT-List A) and Delayed Free Recall (CVLT-DFR), Digit Span Forward and Backwards tests (DS-F and DS-B), the Benton Visual Retention Test (BVRT), Animal Fluency test (AF), Brief Test of Attention (BTA), Trailmaking test, parts A and B (Trails A and B), Clock Drawing Test (CDT), Card Rotations (CR) and Identical Pictures (IP) (See Supplemental Digital Content 1 for full tests and score descriptions). Participants ability to undergo informed consent was evaluated through probing for protocol comprehension. Although formal dementia diagnoses were not performed, participants were administered mental status tests, which they completed at adequate levels indicative of normal cognition. Low mental status performance was consistently due to poor literacy skills with no signs of dementia.

For those participants unable to understand a test for cognitive reasons, scores were set to the total sample maximum or minimum, corresponding to the poorest cognitive performance. Scores were considered unreliable and set to missing if participants had sensory problems that precluded them from reliably completing the test.

Dietary assessment

Trained interviewers administered two 24-hr dietary recalls using the U.S. Department of Agriculture's (USDA) Automated Multiple Pass Method (AMPM), a standardized 5-step process validated for protein, carbohydrate, fat and energy intakes in obese and non-obese individuals (42–44). A database converted grams of USDA food codes into nutrients consumed per day (45). The average of the two recalls was considered after nutrient intakes were summed for each individual per recall day.

Four exposures of interest were investigated: Vitamins A, C and E, divided by energy intake and expressed as retinol equivalent, RE/1,000 kcal/d, mg/1,000 kcal/d, and mg/1,000 kcal/d, respectively, and the sum of five carotenoids (α-carotene, β-carotene, lutein+zeaxanthin, β-cryptoxanthin and lycopene) termed "total carotenoids" and expressed as μg per 1,000 kcal of dietary intake per day.

Depressive symptom assessment

The 20-item Center for Epidemiologic Studies Depression Scale (CES-D) scale was used to measure baseline depressive symptoms emphasizing affective and depressed mood (46). CES-D total score was used in all analyses. CES-D was previously shown to have an invariant factor structure between The National Health and Nutrition Examination Survey I and HANDLS data, with four distinct components emerging in both surveys (47).

Covariates

Socio-demographic, lifestyle and health-related potential confounders—The socio-demographic and lifestyle factors age, sex, race/ethnicity (White *vs*. African American), marital status (married *vs*. unmarried), completed years of education (<High

School (HS); HS and >HS), poverty income ratio (PIR<125% for "poor"), measured body mass index (kg/m^2), lifetime drugs use (opiates, marijuana or cocaine" *vs*. not), and smoking status (0: "never or former smoker" and 1 "current smoker" were included in our analyses as potential confounders.. The Wide Range Achievement Test Letter and Word Reading (WRAT) total score (48) was added to multivariate models as a literacy measure.

Dietary potential confounders—Potential confounding by nutrients formerly linked to cognitive performance among other health outcomes was also adjusted for in multivariate models. These nutrients, expressed as per 1000 kcal of energy intake and entered into models as standardized *z*-scores, included specific B-vitamins (B-6, B-12 and folate) (49–59) and *n*-3 highly unsaturated fatty acids (% of energy) (17, 60–69). To emulate a multivariate nutrient density model (70), total energy intake was included as a potentially confounding variable.

Statistical Analyses

Stata release 13.0 was used. (71) First, two-sided independent-samples *t*-tests compared means across binary variables, whereas χ^2 test was conducted to examine relationships between categorical variables. Second, multiple ordinary least square (OLS) models were conducted to evaluate independent predictors of each dietary antioxidant exposure. Four exposures of interest included: total dietary intakes of total carotenoids, vitamin A, vitamin C and vitamin E (α-tocopherol), divided by total energy intake and multiplied by a factor of 1000 (i.e. per 1000 kcal). Third, multiple OLS (most outcomes) and Poisson (MMSE total error count) regression models were conducted to determine the association between dietary antioxidants and individual cognitive scores. In this main part of the analyses, dietary antioxidant exposures were expressed as standardized *z*-score and interpreted as a 1 SD increase in their value. In all multivariate analyses, adjustment was made on other socio-demographic, lifestyle and health-related, and selected dietary covariates. Key findings regarding significant covariates predicting each of the cognitive test score outcomes in those model were also presented. Sex, race and age group (<median vs. ≥median) were considered as potential effect modifiers in the associations between antioxidants and cognitive test scores. In a separate model, 2-way interaction terms between each antioxidant and each of the putative effect modifiers were added and tested for significance, while retaining the main effects.

Each of the 13 cognitive variables was considered as an endogenous variable that was potentially associated with both CES-D total score and dietary antioxidants. To test mediation, two methods were used. First, structural equations models (SEM) were carried out where antioxidants, socio-demographic, lifestyle and health-related factors were exogenous to CES-D and each of the three domain scores separately (See equations 1.1–1.4, 2 and 3).

$$X_i=\sum_{j=1}^{k}\alpha_{Z_{j_{1i}}}Z_j+e_{1i} \quad \text{Eq. 1.1–1.4}$$

$$CESD=\alpha_{21i}X_i+\sum_{j=1}^{k}\alpha_{Z_{j_2}}Z_j+e_2 \quad \text{Eq. 2.}$$

$$CS_l=\alpha_{31i}X_i+\alpha_{32}CESD+\sum_{j=1}^{k}\alpha_{Z_{j_3}}Z_j+e_3 \quad \text{Eq. 3.}$$

Where X is the main dietary exposure variable (each antioxidant per 1,000 kcal, z-score), *i* ranges from 1 to 4, *j* is the number of covariate terms included, CS stands for cognitive score with *l* ranging from 1 to 13 and Z_j is a vector of socio-demographic, lifestyle, health-related and dietary exogenous variables. Assuming additivity between each antioxidant exposure and the CES-D score, a mediation proportion (MP) was computed as the percent of total effect of each antioxidant on each cognitive test that is indirectly explained through CES-D: Mediation Proportion (MP)=(indirect effect)*100/(total effect). Based on Eq. 1.1–1.4, 2 and 3: α_{31}=direct effect; $\alpha_{21}\times\alpha_{32}$=indirect effect; total effect= α_{31} + $\alpha_{21}\times\alpha_{32}$. (72, 73) The significance of the mediation proportion was ascertained using the Sobel-Goodman (S-G) test, with a type I error 0.05. (74) Details about this method are discussed elsewhere. (75)

Second, when relaxing the assumption of addivitiy (RAA) between each antoxidant exposure and the CES-D score by including an interaction term, we further computed four estimates with their SEE and p-values, namely the controlled direct effect (CDE), the natural direct effect (NDE), the natural indirect effect (NIE) and the marginal total effect (MTE). Details about this latter approach are provided elsewhere. (76) The CDE is the effect of setting X to 1 versus 0 (i.e. 1 SD higher than the mean vs. the mean) while controlling M to some defined reference value *m*. In this case, M is the continuous CES-D score which is set at a value close to the mean, namely 11.0. The NDE is the same setting of the exposure X, but this time M (CES-D score) is set not to a single pre-defined value m, but instead a value that is potentially distinct for every person in the data set. It is the value that m would have taken at the referent value of the exposure (in this case, the exposure level that is at the mean). The NIE is the outcome contrast observed when holding exposure constant at the mean, and contrasting two different M values: the value of the CES-D score that would be observed for that person under the X value of the mean and the value of CES-D that would be observed for that person under the 1 SD higher X value. The total effect is the sum of the NIE and the NDE. It is the total effect of varying X by 1 SD, irrespective of M (or the CES-D score). (76) Using NIE and MTE, a mediation proportion can be estimated as MP = (NIE*100)/MTE. (77) In all three approaches (i.e. SEM, S-G test and RAA), only results with significant total effects of antioxidants vs. cognitive tests, controlling for the other covariates, were assessed for mediation.

Potential selection bias in OLS, logistic and Poisson regression models was accounted for using a two-stage Heckman selection model (78), in which an inverse mills ratio was added to all equations and models after predicting the probability of being selected conditional on baseline pseudo-complete (N~3, 720) socio-demographic variables such as age, sex, marital status and smoking status (79).

In all analyses, a type I error of 0.05, while $p<0.10$ was considered significant for interaction terms, prior to correction for multiple testing. Using a familywise Bonferroni procedure, we corrected for multiple testing taking into account only cognitive tests, assuming that hormonal exposures are linked to separate substantive hypotheses. (80) Therefore, for main effects, $p<0.004$ was deemed significant for cognitive test performance vs. antioxidants hypotheses (13 test scores) but a type I error of 0.05 was used for all other hypotheses. Due to their lower statistical power compared to main effects, interaction terms had critical p-values reduced to 0.05.

RESULTS

Study characteristics by sex, race and age group (<median=48y vs. ≥median) are shown in Table 1. Women (vs. men), African-Americans (vs. Whites) and younger participants (vs. older) were more likely to be below poverty. African-Americans and younger participants had on average lower educational attainment and literacy compared to Whites and older participants, respectively. Men and younger participants were more likely to be current smokers than women and older participants, respectively. Similarly, African-Americans, men and younger participatns had a higher prevalence of illicit drug ever use compared to Whites, women and older participants, respectively. Average BMI was higher among women than men. Men, Whites and younger individuals were more likely to be married compared to women, African-Americans and older inidividuals, respectively.

Women had higher dietary intakes than men in vitamins C and E per 1,000 kcal, whereas Whites had higher intakes of total carotenoids, vitamin E, folate than African-Americans but lower intakes of n-3 HUFA (%energy) and vitamin C. Older participants had higher intakes of vitamin B-6 and folate compared to their younger counterparts. Mean CES-D score was higher among women compared to men (11.9 vs. 10.3, $p<0.001$), though no significant differences were noted by race or age. Women outperformed men on the MMSE, CVLT-List A and CVLT-DFR, the BTA and IP. Men performed better on BVRT, AF, CR and CDT. No sex differences were detected for DS-F, DS-B, Trails A or B. Whites outperformed African-Americans on all cognitive tests, and older participants had a poorer performance than younger participants, on all tests except Digits span backwards and forward as well as the clock drawing test.

When examining the relationship between CES-D score and all other variables (Table S1, Supplemental Digital Content 2), certain patterns emerged. Importantly, a higher level of depressive symptoms was associated with poorer cognitive performance on all tests, with the exception of Trailmaking Test, A. Moreover, depressive symptoms were inversely but weakly related to age, they were significantly higher among women, and among individuals with lower educational attainment, income and literacy. Current smokers and unmarried individuals also had higher levels of depressive symptoms compared to non-smokers and married participants, respectively. Among dietary intake covariates, only total carotenoids were found to be significantly and inversely related to CES-D.

Table 2 presents findings from a series of OLS regression models independent associations between socio-demographic, lifestyle and dietary correlates with the main dietary

antioxidant exposures. Among key findings, age and education were positively linked to vitamin E intake per 1,000 kcal/d, African-Americans had higher intakes of vitamin C compared to Whites, whereas men had lower intakes of both vitamins A and E compared to women. Current smokers had lower intake of vitamin C which was also inversely related to BMI and ever use of drugs but positively associated with total energy intake.

Among dietary correlates of four antioxidant exposures, total carotenoids were positively associated with intakes of vitamin A, C and E, *n*-3 HUFA (% energy) but inversely related to vitamin B-12 (per 1,000 kcal/d). Vitamin A was positively related to vitamin B-12 and folate intakes (and total carotenoids), but inversely related to vitamin B-6 and *n*-3 HUFA (%energy) intakes. We additionally detected a positive relationship between vitamin C intake and vitamins E, B-6 and folate intakes, and an inverse relationship with vitamin B-12 intake. Finally, vitamins B-6, folate and *n*-3 HUFA (in addition to vitamin C) were positively and independently related to vitamin E intake.

Table 3 displays associations between the four dietary antioxidant exposures and cognitive performance in separate models, based on multiple regression analyses. Among those exposures, vitamin C was not associated with cognitive performance in the total population. After Bonferroni correction, 1 SD (~2.02 mg) higher intake of vitamin E per 1,000 kcal was associated with a 0.64-point higher score on the CVLT-List A (reflecting the verbal memory domain, p=0.001), independently of other antioxidants, dietary and socio-demographic, lifestyle and health-related factors included in the model. Moreover, higher intake of vitamin E in the diet was linked to better performance on AF (reflecting language/verbal test performance, β=+0.53, p=0.001). Table 3 also presents sub-group analyses by sex. Although the associations between vitamin E and verbal memory and fluency were restricted to women, there was no statistically significant effect modification by sex. Furthermore, vitamin E was positively associated with performance on IP (reflecting psychomotor speed) among women after familywise Bonferroni correction (β=+0.68, p=0.001). Moreover, Table S2 (Supplemental Digital Content 3) shows findings from covariates entered into the model for the total population, presenting only those that were statistically significant at a type I error 0.05. Aside from the findings for age, sex and race which were consistent with the bivariate results in Table 1, other notable findings included the following: Cognitive performance was better with higher literacy (all tests), higher educational attainment (MMSE, CVLT-List A, BVRT, AF, Trails B and IP), above poverty income (MMSE, BVRT, AF, BTA, Trails A and B, IP), lower CES-D score (all tests), higher BMI (CVLT-List A and CVLT-DFR), lower vitamin B-12 intake (BVRT), drug users vs. not (AF, BTA, Trails B) and higher energy intake (CR and IP).

Table 4 shows findings from sub-group analyses by race and age group (<48y vs. ≥48y), while separately evaluating two-way interactions between dietary antioxidant exposures and these potential effect modifiers in relation to cognitive performance. Among stratum-specific associations that survived multiple testing, higher intake of vitamin E in the younger group (<48y) was linked to better performance on CVLT-List A (β=+1.06, p<0.001), CVLT-DFR (β=+0.46, p=0.001; p for interaction by age group<0.05) and AF (β=+0.77, p=0.003). Tests of effect modification only showed a few other instances of heterogeneity between strata (e.g. vitamin E vs. MMSE by race and age group; total carotenoids vs. BVRT

by race). A consistent, though mariginally significant result was found whereby vitamin E was positively related to IP among the younger group (β=+0.67, p=0.016). Similarly, higher vitamin E intake was marginally related to smaller number of errors among among Whites in both MMSE and BVRT (0.004<p<0.05, with a signficant racial difference in the case of MMSE (p=0.033).

Multiple linear regression models were conducted to test mediation of the antioxidant-cognition association through CES-D scores (Table S3, Supplemental Digital Content 4). In the overall population, the total effects of vitamin E on CVLT-List A and CVLT-DFR indicated a putative protective effect, whereas there were positive association between vitamin E and CES-D scores and an inverse relationship between those two cognitive test scores and CES-D. When CES-D was entered into the model with antioxidants vs. CVLT-List A and CVLT-DFR, the net effect of vitamin E was markedly altered compared to the total effect, with a significant S-G test (p=0.032 and 0.035, respectively). In addition, the respective MPs were −13% and −16%. In all other total effects under study, CES-D did not show an appreciable mediating effect, especially when examining the S-G test.

Figure 1 displays the findings from a structural equations model where CVLT-List A is shown as an example for cognitive test score outcomes and predicted by the four antioxidants whose total effect is allowed to be partially mediated by CES-D score, by including a direct effect from each antioxidant into the cognitive test score. Our findings are in line with the S-G test and the MP estimate (~−13%). In addition, when stratifying the SEM by race, we found that associations in which vitamin E was positively associated with CES-D, CES-D inversely related to CVLT-List A while vitamin E had a positive and significant direct effect on CVLT-List A mainly among African-Americans. Among whites, the path coefficient (α) from vitamin E into CES-D was non-significant.

When relaxing the assumption of additivity between the CES-D score (mediator) and each of the antioxidant exposures by allowing for interaction, we computed four distinctive estimates to assess mediation of antioxidant-CS relationship through CES-D (Table 5). Our findings were in line with the previous mediation analysis (Table S1), whereby vitamin E's total effect on CVLT-List A and CVLT-DFR appeared to be partially mediated through CES-D with a significant NIE and a MP estimated at 13–16%.

DISCUSSION

This is one of very few studies that examined the association between antioxidants and cognitive functioning in various domains among young and middle-aged US adults, and is the first to examine potential moderation by sex, race and age and mediation by depressive symptoms. Among key findings, dietary vitamin E intake was positively associated with performance in domains of verbal memory (total population and the younger group (<48y)), verbal fluency (total population and the younger group (Age<48y)) and psychomotor speed (women). Vitamin E was positively linked to CES-D among African-Americans, yet its positive association with verbal memory was only partially mediated by depressive symptoms (total population).

Vitamin E has not only antioxidant activity but also functions in other independent roles such as inhibiting brain protein kinase C activity. This ability is most likely attributed to the multiple isoforms of Vitamin E. (37, 81) It is recognized that the diet contains several Vitamin E isoforms while the results of this study reflect intake of only one form of Vitamin E, alpha tocopherol. Due to the increased use of oils in the US diet, there has been an increase in the gamma tocopherol, the form that has similar antioxidant capacity but greater anti-inflammatory properties compared alpha tocopherol, Morris reported that only α and γ-tocopherols found in foods were linked to slower rate of cognitive decline over a 6y period (82). This observation was corroborated by Commenges and colleagues (20).

It is worth noting, however, that in the case of vitamin E, our study population had on average a level of alpha tocopherol consumption that meets roughly 50% of Estimated Average Requirement (EAR) (Mean±SD: 6.8±5.0 mg/d vs. EAR=12 mg./d), with only 10.1% of the distribution being adequate. This is in contrast with vitamin A (38.8% meeting the EAR) and vitamin C (41.4% meeting the EAR). (83) Thus, our findings should be interpreted in light of this difference in distributions of intakes compared to other studies whose selected population consumed higher amounts of vitamin E or included supplemental intake in addition to dietary sources. (e.g. (32–35)) It is unclear from other publications when the Vitamin E intake included all isoforms due to a lack of description in the diet methodology. Morris and colleagues (34) reported that dietary intake of vitamin E, but not other antioxidants, was associated with a reduced risk of incident AD, although this association was restricted to individuals without the Apolipoprotein E ε4 genotype. Similar findings were reported with cognitive decline as an outcome. (35)

Vitamin C, which is essential for the reduction of vitamin E, was not associated with cognitive performance in the HANDLS study population. This finding differs from the results of a few recent prospective cohort studies which examined the association of other dietary antioxidants with various cognitive outcomes. One cross-sectional study found that participants in the lowest 10^{th} percentile of vitamin C intakes had poorer performance on abstract thinking and problem-solving task. (33) Another study reported that high dietary intake of vitamins C and E may reduce the risk of AD (22). This relationship most pronounced among smokers. The inverse association between vitamin C intake and cognitive impairment as assessed by the MMSE was corroborated by Paleologos and colleagues, (84) while Sato and colleagues only found this association in men (36).

When evaluating the association between antioxidants and cognitive domains, one study found that past intakes of vitamins A and E were associated with better performance on visuospatial recall and/or abstraction performance. (32) These results were similar to ours, though some of our related findings did not survive multiple testing correction. Another study, suggested that dietary antioxidants were not able to reduce AD risk. (24) Similarly, Laurin and colleagues (23) found no association between midlife dietary intake of vitamins E and C and dementia incidence. At least four other cohort studies came to a similar conclusion, especially after adjustment for potentially confounding factors. (16, 85–87) In addition to examining associations of cognition with vitamins A, C and E, other studies found that carotenoids, particularly β-carotene intake, may have beneficial effects of various

cognitive outcomes (16) though others were not able to detect such an association (35, 86, 87).

Epidemiologic studies examining relationships between *supplemental antioxidants* and various cognitive outcomes found mixed results. In fact, vitamin C supplement use was related to lower AD risk in one cohort study, (88) whereas vitamin E and vitamin C supplements in combination were associated with reduced prevalence and incidence of AD and cognitive decline in three other cohort studies (89–91). Yet Grodstein and colleagues, found this effect to be specific to Vitamin E supplements. (92) The putative protective effect of supplemental antioxidant use against adverse cognitive health outcomes was replicated in a large cohort study (93). In addition, a post-hoc analysis of a large trial found that a combination of supplements including but not limited to β-carotene, vitamin C and E can improve verbal memory in the long-term (six years after the trial). (31) However, there was little evidence of a cognitive benefit from use of antioxidant supplements, particularly vitamins C and E, according to at least five independent cohort studies. (24, 94–97) Finally, a recent randomized controlled trial examining transition from mild cognitive impairment to AD, found no significant association between treatment with supplemental vitamin E and the outcome of interest. (98)

Our study has notable strengths. First, it is one of the largest studies examining the primary question of interest, it made use of extensive cognitive function tests, a valid measure of depressive symptoms (the CES-D) and advanced multivariate techniques such as structural equations modeling, mediation analyses, and Heckman selection models among others. Second, it is one of few to use the average of two 24-hr recalls while estimating usual dietary intakes of antioxidants.

Our study also has limitations. First, its cross-sectional design precluded temporality ascertainment, highlighting the importance of conducting further longitudinal studies in a U.S. community. Moreover, due to lack of factorial invariance between race and sex groups as well as poverty income ratio groups, the use of cognitive domains --obtained from confirmatory factor analysis-- that were comparable between those groups was not feasible in this study. Data on supplemental intakes of antioxidants were not available for the baseline wave and thus were not accounted for in estimating total intakes. Generally speaking, it was estimated that between 2003–2006, more than half of adults used dietary supplements. (99) In addition, supplement users also had higher intakes of vitamins A, C and E from foods and in total than non-users. However, they also tended to exceed the tolerable upper intake level for vitamins A and C compared to non-users. (100) Whether antioxidants are obtained from diet or supplements, *plasma concentration* would be a more sensitive indicator of antioxidant and oxidative stress status, while reducing reporting bias. (45, 88–92) Although, the baseline HANDLS study did not incorporate these measures, future waves may support this analysis, thereby enhancing our understanding of these associations in an urban, low-income population.

In conclusion, our study indicated that dietary intakes of selected antioxidant nutrients and cognition are closely related, although these relationships may vary according to sex, race and depressive status and are specific to certain domains of cognition as well as the nutrient.

In particular, and among key findings, we found that vitamin E was positively associated with performance in domains of verbal memory and fluency in the total population and psychomotor speed among women. The association between vitamin E and verbal memory was only partially mediated by depressive symptoms. Future cohort studies and dietary antioxidant interventions should focus on association of dietary vitamin E with age-related cognitive decline, particularly in the domains of verbal memory, verbal fluency, and psychomotor speed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AA	African-American
AD	Alzheimer's Disease
AF	Animal Fluency
AMPM	Automated Multiple Pass Method
BTA	Brief Test of Attention
BVRT	Benton Visual Retention Task
CDE	Controlled Direct Effect
CDT	Clock Drawing Test
CES-D	Center for Epidemiologic Studies-Depression
CR	Card Rotation
CS	Cognitive Score
CVLT-List A	California Verbal Learning Test, immediate free recall, List A
CVLT-DFR	California Verbal Learning Test, delayed free recall, List A
DS-B	Digit Span Backwards test
DS-F	Digit Span Forward test
EAR	Estimated Average Requirement
HANDLS	Healthy Aging in Neighborhoods of Diversity across the Life Span
HS	High School
HUFA	Highly Unsaturated Fatty Acids
IP	Identical Pictures

M	Mediator
MMSE	Mini-Mental State Examination
MP	Mediation Proportion
MRV	Medical Research Vehicles
MTE	Marginal Total Effect
NDE	Natural Direct Effect
NIE	Natural Indirect Effect
OLS	Ordinary Least Square
PIR	Poverty Income Ratio
RAA	Relaxing the Assumption for Additivity
RE	Retinol Equivalent
ROS	Reactive Oxygen Species
SD	Standard Deviation
SEE	Standard error of the estimate
SEM	Structural Equations Modeling
S-G	Sobel-Goodman Test
Trails A	Trailmaking Test, Part A
Trails B	Trailmaking Test Part B
USDA	U.S. Department of Agriculture
WRAT	Wide Range Achievement Test
X	Antioxidant Exposure

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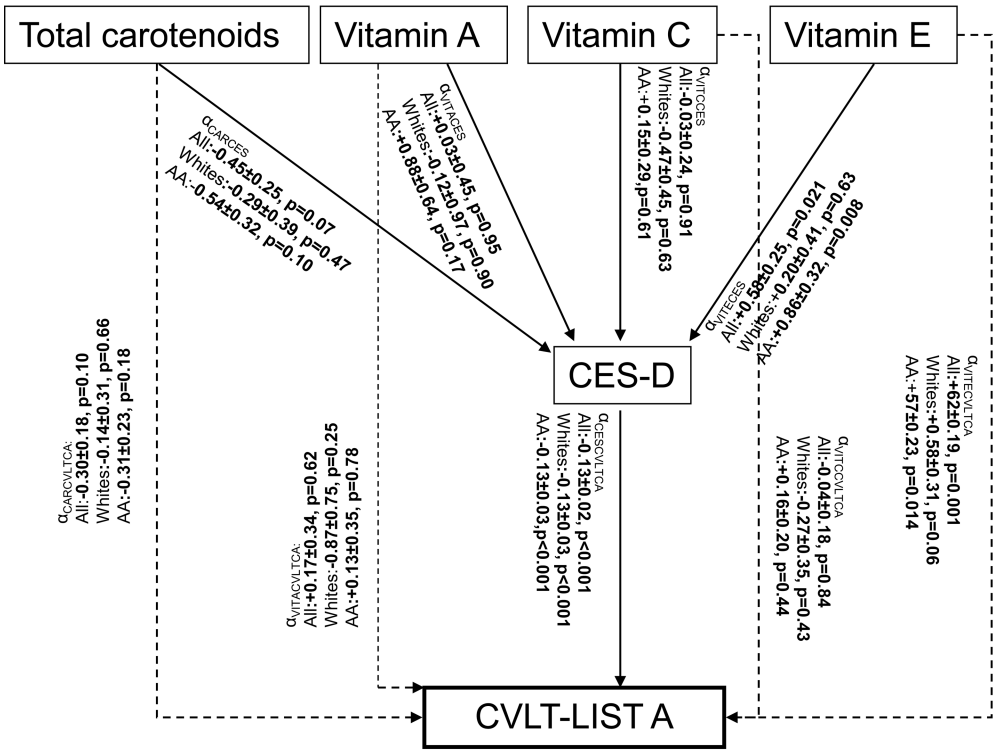

TOTAL POPULATION

→CES-D:
Age (0); Female (0), African-American (-), PIR (-), Education (-), marital status (0), Current smoking status (+), drug ever use (0), BMI (0), n-3 HUFA (0), Vitamin B6 (0), vitamin B12 (0, Folate (0), WRAT score (-).

→CVLT-LISTA:
Age (-); Female (+), African-American (-), PIR (0), Education (+), marital status (0), Current smoking status (0), drug ever use (0), BMI (+), n-3 HUFA (0), Vitamin B6 (0), vitamin B12 (0), Folate (0), WRAT score (+).

-: negative association, p<0.05, +:positive association, p<0.05 , 0: NS, p>0.05; AA=African-American

FIGURE 1.

Structural Equation Model (SEM) for associations between antioxidants and a test of verbal memory (CVLT-List A): mediating effects of depressive symptoms (CES-D): HANDLS study

Key: AA=African-American; HANDLS=Healthy Aging in Neighborhoods of Diversity across the Life Span; HS=High School; HUFA=Highly Unsaturated Fatty Acids; OLS=Ordinary Least Square; PIR=Poverty Income Ratio; RE=Retinol Equivalent; SEE=Standard error of the estimate; WRAT=Wide Range Achievement Test.

Note: Path coefficients between antioxidant exoosure and CES-D or cognitive scores are denoted by α and labelled by to the predictor and otucome variables of each path.

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Table 1

Selected study participant characteristics by sex and race/ethnicity (*n*=1,274); HANDLS study[1]

	All	Men	Women	Whites	African-Americans	Age<48y	Age≥48	*p*[2]		
								Men *vs.* women	Whites *vs.* African-Americans	Age<48 vs.≥48
N	1,274	541	733	513	761	621	653			
Age	47.5±9.3	47.8±9.3	47.3±9.5	47.5±9.5	47.5±9.1	39.5±5.2	55.1±4.8	0.36	1.00	<0.001
Men, %	42.5	—	—	40.3	43.9	40.1	44.7	—	0.21	0.10
African-American, %	59.7	61.7	58.2	—	—	60.0	59.6	0.21	—	0.90
Married, %	53.3	60.6	47.9	60.3	48.6	58.6	48.1	<0.001	<0.001	<0.001
Education, %								0.44	<0.001	0.005
<HS	6.4	7.4	5.7	8.9	4.7	5.0	7.8			
HS	58.8	57.5	59.8	49.1	65.3	63.1	54.7			
>HS	34.8	35.1	34.5	41.9	30.0	31.9	37.5			
Literacy (WRAT score)	42.5±7.8	42.4±8.5	42.6±7.2	45.5±7.3	40.5±7.4	42.7±7.8	42.3±7.8	0.71	<0.001	0.31
PIR <125%, %	48.7	43.6	52.5	36.6	56.9	52.7	45.0	0.002	<0.001	0.006
Current smoking status, %								0.001	0.31	0.002
Currently smoking	43.5	49.3	39.2	40.9	45.1	44.6	41.3			
Missing	9.3	8.7	9.7	9.9	8.8	5.6	4.3			
Ever use of illicit drugs, %								<0.001	0.034	<0.001
Used any type	58.9	67.8	52.4	54.6	61.9	63.3	54.8			
Missing	7.6	7.2	7.9	8.4	7.1	9.2	6.1			
Body mass index, $kg.m^{-2}$	29.7±7.7	27.9±6.0	31.1±8.5	29.9±7.7	29.6±7.7	29.4±7.7	30.1±7.3	<0.001	0.58	0.09
Dietary intake, per 1,000 kcal/d										
Total carotenoids, *mg*	4.09±4.83	3.78±4.61	4.31±4.98	4.51±5.12	3.81±4.61	4.04±4.99	4.13±4.68	0.05	0.011	0.74
Vitamin A, *RE*	344±541	312±508	367±564	330±253	353±669	326±586	360±496	0.07	0.45	0.26
Vitamin C, *mg*	39.3±40.4	36.5±37.5	41.4±42.3	35.3±35.6	42.1±43.2	39.9±39.2	39.36±41.51	0.030	0.003	0.77
Vitamin E, *mg*	3.34±2.02	3.08±1.62	3.54±2.25	3.59±2.07	3.17±1.97	3.24±1.81	3.44±2.19	<0.001	<0.001	0.07
Vitamin B-6, *mg*	0.92±0.47	0.93±0.45	0.92±0.48	0.95±0.53	0.91±0.42	0.89±0.43	0.95±0.50	0.77	0.12	0.033
Vitamin B-12, *mg*	3.19±5.64	3.18±5.74	3.20±5.57	2.91±3.25	3.38±6.79	3.19±6.3	3.19±4.95	0.97	0.15	0.99

	All	Men	Women	Whites	African-Americans	Age<48y	Age≥48	*p*[2]		
								Men *vs.* women	Whites *vs.* African-Americans	Age<48 vs.≥48
Folate, *mg*	187±102	182±103	191±102	205±111	175±95	179±93	194±110	0.09	<0.001	0.011
n-3 HUFA, % *energy*	0.10±0.27	0.09±0.32	0.11±0.21	0.07±0.13	0.13±0.32	0.10±0.31	0.10±0.21	0.27	<0.001	0.99
Depressive symptoms										
CES-D score	11.2±8.0	10.3±7.2	11.9±8.9	11.2±8.4	11.2±7.7	11.5±7.8	10.9±8.2	<0.001	0.95	0.13
Cognitive function test scores										
MMSE, error count	2.16±2.06	2.36±2.23	2.02±1.92	1.72±2.01	2.45±2.05	2.01±1.90	2.29±2.19	0.003	<0.001	0.018
CVLT, List A	25.1±6.7	23.7±6.4	26.2±6.8	27.2±7.2	23.7±6.0	26.1±6.9	24.2±6.5	<0.001	<0.001	<0.001
CVLT, DFR	7.39±3.21	6.81±3.07	7.82±3.25	8.55±3.27	6.61±2.93	7.91±3.23	6.90±3.12	<0.001	<0.001	<0.001
BVRT, error count	6.12±4.93	5.49±4.84	6.58±4.95	5.72±4.65	6.38±5.10	5.32±4.58	6.88±5.13	<0.001	0.019	<0.001
Digit span backwards	5.68±2.15	5.72±2.26	5.65±2.06	6.31±2.27	5.25±1.95	5.77±2.19	5.59±2.10	0.52	<0.001	0.14
Digit span forward	7.30±2.16	7.42±2.21	7.21±2.12	7.70±2.22	7.03±2.08	7.41±2.19	7.19±2.13	0.10	<0.001	0.07
Animal fluency	18.9±5.5	19.6±5.5	18.4±5.4	20.2±6.0	18.0±4.9	19.6±5.7	18.2±5.2	<0.001	<0.001	<0.001
Brief test of Attention	6.63±2.21	6.46±2.17	6.76±2.24	7.18±2.06	6.26±2.24	6.80±2.09	6.47±2.33	0.017	<0.001	0.009
Trailmaking test, A, sec.	36.1±31.5	36.9±28.6	35.4±33.5	30.9±11.5	39.5±39.3	31.9±26.1	40.0±35.4	0.40	<0.001	<0.001
Trailmaking test, B, sec.	147±157	153±163	142±152	108±123	173±171	128±143	165±169	0.21	<0.001	<0.001
Card rotation	34.1±18.7	37.9±18.3	31.3±18.6	40.4±19.0	29.8±17.3	37.3±19.4	31.0±17.6	<0.001	<0.001	<0.001
Identical pictures	23.6±6.6	22.9±6.6	24.1±6.6	25.7±6.8	22.1±6.1	26.0±6.6	21.3±5.8	0.001	<0.001	<0.001
Clock drawing test	8.84±1.20	8.92±1.18	8.77±1.22	9.05±1.17	8.70±1.20	8.84±1.20	8.84±1.20	0.026	<0.001	0.99

Key BVRT=Benton Visual Retention Task; CES-D=Center for Epidemiologic Studies-Depression; CVLT=California Verbal Learning Task; DFR=Delayed Free Recall; HANDLS=Healthy Aging in Neighborhoods of Diversity across the Life Span; HS=High School; HUFA=highly unsaturated fatty acids; MMSE=Mini-Mental State Examination; PIR=Poverty Income Ratio; WRAT=Wide Range Achievement Test.

[1]Values are mean±SD or percent.

[2]P-value was based on 2-sided independent samples t-test when row variable is continuous and χ^2 when row variable is categorical.

Table 2

Socio-demographic, lifestyle and dietary correlates of each of the selected dietary antioxidants: multiple OLS regression models (N=1,274); HANDLS study

	Total carotenoids, *μg per 1,000 kcal/d*			**Vitamin A, *RE per 1,000 kcal/d***			**Vitamin C, *mg per 1,000 kcal/d***			**Vitamin E, *mg per 1,000 kcal/d***		
	β	**(SEE)**	**P_{wald}**	**β**	**(SEE)**	***P***	**β**	**(SEE)**	**P_{wald}**	**β**	**(SEE)**	**P_{wald}**
Age	−7.5	(13.0)	0.56	**+1.83**	**(0.79)**	**0.020**	−0.19	(0.11)	0.09	+0.01	(0.01)	0.18
Men vs. Women	+322.4	(264.4)	0.22	**−35.1**	**(16.0)**	**0.029**	+0.20	(2.26)	0.93	**−0.42**	**(0.11)**	**<0.001**
African-American vs. White	−512.4	(265.4)	0.05	+28.0	(16.1)	0.08	**+11.9**	**(2.2)**	**<0.001**	−0.16	(0.11)	0.14
Married vs. Unmarried	−44.6	(46.8)	0.34	−2.2	(2.8)	0.44	+2.1	(2.2)	0.33	−0.03	(0.02)	0.16
Education												
<HS	Ref			Ref			Ref			Ref		
HS	+298.0	(502.1)	0.55	−1.2	(30.5)	0.97	+0.35	(4.29)	0.94	−0.03	(0.20)	0.87
>HS	+132.5	(545.2)	0.81	−8.1	(33.2)	0.81	−1.34	(4.66)	0.77	**+0.45**	**(0.22)**	**0.041**
Missing	+1,010.1	(896.2)	0.26	−12.8	(54.5)	0.82	−6.97	(7.66)	0.36	+0.43	(0.37)	0.24
Literacy (WRAT score)	+27.6	(17.6)	0.12	−0.65	(1.07)	0.55	+0.08	(0.15)	0.60	+0.01	(0.01)	0.06
PIR <125%	−363.5	(255.4)	0.16	+2.22	(15.55)	0.89	+2.10	(2.18)	0.34	+0.03	(0.10)	0.75
Current smoking status												
Currently smoking	+10.9	(278.3)	0.97	−19.1	(16.9)	0.26	**−5.6**	**(2.4)**	**0.019**	−0.20	(0.11)	0.08
Missing	+564.7	(939.3)	0.55	−40.9	(57.1)	0.47	+2.0	(8.7)	0.81	−0.36	(0.38)	0.34
Ever use of illicit drugs												
Never used	Ref			Ref			Ref			Ref		
Used any type	−232.2	(276.8)	0.40	−19.1	(16.9)	0.26	**−5.4**	**(2.3)**	**0.023**	+0.07	(0.11)	0.51
Missing	−619.4	(1,018.6)	0.54	−40.9	(57.1)	0.47	+2.0	(8.7)	0.81	+0.59	(0.42)	0.16
Body mass index, $kg.m^{-2}$	+2.90	(16.4)	0.86	−0.75	(1.00)	0.45	−0.12	(0.14)	0.38	−0.004	(0.007)	0.50
Energy, kcal/d	−0.10	(0.13)	0.46	−0.01	(0.01)	0.19	**−0.003**	**(0.001)**	**0.006**	+0.000	(0.000)	0.05
Total carotenoids, *μg per 1,000 kcal/d*	—			**+0.02**	**(0.00)**	**<0.001**	**+0.001**	**(0.000)**	**<0.001**			
Vitamin A, RE *per 1,000kcal/d*	**+5.27**	**(0.44)**	**<0.001**	—			+0.007	(0.004)	0.06	−0.000	(0.000)	0.95
Vitamin C, mg *per 1,000kcal/d*	**+19.07**	**(3.27)**	**<0.001**	+0.37	(0.20)	0.06	—			**+0.006**	**(0.001)**	**<0.001**
Vitamin E, mg *per 1,000kcal/d*	**+508.2**	**(67.8)**	**<0.001**	−0.28	(4.22)	0.95	**+2.66**	**(0.59)**	**<0.001**	—		
Vitamin B-6, *mg per 1,000kcal/d*	+227.0	(347.8)	0.51	**−75.8**	**(21.0)**	**<0.001**	**+15.7**	**(2.9)**	**<0.001**	**+0.92**	**(0.14)**	**<0.001**

	Total carotenoids, μg *per 1,000 kcal/d*			**Vitamin A, *RE per 1,000 kcal/d***			**Vitamin C, *mg per 1,000 kcal/d***			**Vitamin E, *mg per 1,000 kcal/d***		
	β	**(SEE)**	***P*$_{wald}$**	**β**	**(SEE)**	***P***	**β**	**(SEE)**	***P*$_{wald}$**	**β**	**(SEE)**	***P*$_{wald}$**
Vitamin B-12, *mg per 1,000kcal/d*	**−490.4**	**(42.1)**	**<0.001**	**+82.2**	**(1.4)**	**<0.001**	**−1.12**	**(0.38)**	**0.003**	−0.02	(0.02)	0.34
Folate, *mg per 1,000kcal/d*	+2.45	(1.62)	0.13	**+0.55**	**(0.10)**	**<0.001**	**+0.04**	**(0.01)**	**0.002**	**+0.003**	**(0.001)**	**<0.001**
n-3 HUFA, *% energy/d*	**+2,343**	**(476.6)**	**<0.001**	**−309.8**	**(27.9)**	**<0.001**	−0.12	(4.11)	0.98	**+0.62**	**(0.20)**	**0.002**

Key HANDLS=Healthy Aging in Neighborhoods of Diversity across the Life Span; HS=High School; HUFA=Highly Unsaturated Fatty Acids; OLS=Ordinary Least Square; PIR=Poverty Income Ratio; RE=Retinol Equivalent; SEE=Standard error of the estimate; WRAT=Wide Range Achievement Test.

Table 3

Cognitive function test scores by SD increase in dietary antioxidant intake: OLS and poisson regression models (all and stratified by sex): HANDLS study[1]

	All (N=1,274)			Men (N=541)			Women (N=733)			P_{sex}[2]
	β	(SEE)	P_{wald}	β	(SEE)	P_{wald}	β	(SEE)	P_{wald}	
MMSE, error count										
Total carotenoids, per 4.83 *mg/1,000 kcal/d*	−0.02	(0.02)	0.38	−0.03	(0.03)	0.33	−0.02	(0.03)	0.64	0.38
Vitamin A, per 541 *RE/1,000 kcal/d*	−0.05	(0.04)	0.26	−0.09	(0.06)	0.15	−0.00	(0.06)	0.97	0.65
Vitamin C, per 40.4 *mg/1,000 kcal/d*	+0.03	(0.02)	0.17	+0.03	(0.03)	0.32	+0.03	(0.03)	0.35	0.74
Vitamin E, per 2.02 *mg/1,000 kcal/d*	−0.03	(0.03)	0.26	−0.02	(0.04)	0.68	−0.05	(0.03)	0.14	0.77
CVLT, List A										
Total carotenoids, per 4.83 *mg/1,000 kcal/d*	−0.32	(0.19)	0.08	−0.47	(0.27)	0.09	−0.20	(0.26)	0.44	0.42
Vitamin A, per 541 *RE/1,000 kcal/d*	+0.18	(0.34)	0.59	+0.31	(0.48)	0.52	+0.12	(0.51)	0.82	0.65
Vitamin C, per 40.4 *mg/1,000 kcal/d*	−0.02	(0.18)	0.90	−0.05	(0.28)	0.85	−0.06	(0.25)	0.82	1.00
Vitamin E, per 2.02 *mg/1,000 kcal/d*	**+0.64**	**(0.19)**	**0.001**	+0.48	(0.34)	0.16	**+0.72**	**(0.24)**	**0.002**	0.38
CVLT, DFR										
Total carotenoids, per 4.83 *mg/1,000 kcal/d*	−0.09	(0.09)	0.29	−0.18	(0.13)	0.19	−0.03	(0.13)	0.82	0.74
Vitamin A, per 541 *RE/1,000 kcal/d*	+0.23	(0.17)	0.17	**+0.54**	**(0.23)**	**0.021**	−0.01	(0.25)	0.97	0.22
Vitamin C, per 40.4 *mg/1,000 kcal/d*	+0.03	(0.09)	0.70	−0.00	(0.13)	0.98	+0.04	(0.12)	0.73	0.75
Vitamin E, per 2.02 *mg/1,000 kcal/d*	**+0.22**	**(0.09)**	**0.007**	+0.31	(0.16)	0.06	+0.22	(0.12)	0.06	0.78
BVRT, error count										
Total carotenoids, per 4.83 *mg/1,000 kcal/d*	+0.11	(0.15)	0.44	+0.11	(0.22)	0.61	−0.00	(0.20)	1.00	0.47
Vitamin A, per 541 *RE/1,000 kcal/d*	**−0.67**	**(0.27)**	**0.013**	−0.52	(0.39)	0.18	−0.61	(0.40)	0.13	0.41
Vitamin C, per 40.4 *mg/1,000 kcal/d*	+0.00	(0.14)	1.00	−0.05	(0.22)	0.81	+0.11	(0.19)	0.57	0.75
Vitamin E, per 2.02 *mg/1,000 kcal/d*	−0.29	(0.15)	0.06	+0.12	(0.27)	0.66	**−0.48**	**(0.19)**	**0.010**	**0.09**
Digit span backwards										
Total carotenoids, per 4.83 *mg/1,000 kcal/d*	+0.07	(0.06)	0.24	+0.10	(0.10)	0.30	+0.11	(0.08)	0.16	0.35
Vitamin A, per 541 *RE/1,000 kcal/d*	−0.08	(0.11)	0.51	−0.20	(0.17)	0.23	+0.01	(0.15)	0.95	0.33
Vitamin C, per 40.4 *mg/1,000 kcal/d*	+0.03	(0.06)	0.65	−0.05	(0.10)	0.64	+0.06	(0.07)	0.44	0.33
Vitamin E, per 2.02 *mg/1,000 kcal/d*	+0.05	(0.06)	0.41	+0.13	(0.12)	0.26	+0.02	(0.07)	0.78	0.55

	All (N=1,274)			Men (N=541)			Women (N=733)			P_{sex} 2
	β	(SEE)	P_{wald}	β	(SEE)	P_{wald}	β	(SEE)	P_{wald}	
Digit span forward										
Total carotenoids, per 4.83 *mg/1,000 kcal/d*	+0.03	(0.06)	0.61	+0.10	(0.10)	0.30	+0.00	(0.09)	0.97	0.30
Vitamin A, per 541 *RE/1,000 kcal/d*	−0.19	(0.12)	0.11	−0.28	(0.17)	0.11	−0.15	(0.17)	0.39	0.17
Vitamin C, per 40.4 *mg/1,000 kcal/d*	−0.08	(0.06)	0.18	−0.08	(0.10)	0.41	−0.09	(0.08)	0.25	0.55
Vitamin E, per 2.02 *mg/1,000 kcal/d*	+0.08	(0.07)	0.18	+0.12	(0.12)	0.34	+0.09	(0.08)	0.28	0.53
Animal fluency										
Total carotenoids, per 4.83 *mg/1,000 kcal/d*	+0.04	(0.16)	0.81	+0.39	(0.25)	0.12	−0.15	(0.22)	0.50	0.21
Vitamin A, per 541 *RE/1,000 kcal/d*	+0.48	(0.29)	0.11	+0.21	(0.44)	0.63	+0.58	(0.43)	0.18	0.49
Vitamin C, per 40.4 *mg/1,000 kcal/d*	−0.02	(0.16)	0.92	−0.27	(0.25)	0.29	+0.10	(0.21)	0.63	0.66
Vitamin E, per 2.02 *mg/1,000 kcal/d*	**+0.53**	**(0.16)**	**0.001**	+0.48	(0.30)	0.11	**+0.52**	**(0.20)**	**0.009**	0.93
Brief test of Attention										
Total carotenoids, per 4.83 *mg/1,000 kcal/d*	−0.00	(0.07)	0.99	−0.13	(0.10)	0.21	+0.08	(0.09)	0.34	**0.09**
Vitamin A, per 541 *RE/1,000 kcal/d*	+0.18	(0.12)	0.14	+0.09	(0.17)	0.59	+0.27	(0.18)	0.14	0.42
Vitamin C, per 40.4 *mg/1,000 kcal/d*	−0.05	(0.06)	0.48	+0.03	(0.10)	0.77	−0.13	(0.09)	0.15	0.61
Vitamin E, per 2.02 *mg/1,000 kcal/d*	−0.04	(0.07)	0.59	−0.01	(0.12)	0.94	−0.05	(0.08)	0.57	0.81
Trailmaking test, A, sec.										
Total carotenoids, per 4.83 *mg/1,000 kcal/d*	+0.69	(1.00)	0.49	+1.12	(1.41)	0.43	+0.20	(1.46)	0.89	0.80
Vitamin A, per 541 *RE/1,000 kcal/d*	+0.26	(1.85)	0.89	−0.83	(2.45)	0.73	+1.22	(2.88)	0.67	0.66
Vitamin C, per 40.4 *mg/1,000 kcal/d*	−1.25	(0.98)	0.20	−1.33	(1.41)	0.34	−1.09	(1.38)	0.43	0.76
Vitamin E, per 2.02 *mg/1,000 kcal/d*	+0.88	(1.03)	0.39	+0.29	(1.71)	0.87	+0.98	(1.34)	0.46	0.69
Trailmaking test, B, sec.										
Total carotenoids, per 4.83 *mg/1,000 kcal/d*	+8.50	(4.64)	0.07	+4.77	(7.26)	0.51	+7.93	(6.22)	0.20	0.77
Vitamin A, per 541 *RE/1,000 kcal/d*	−9.86	(8.53)	0.25	−11.8	(12.6)	0.34	−8.04	(12.24)	0.51	0.48
Vitamin C, per 40.4 *mg/1,000 kcal/d*	+3.34	(4.53)	0.46	+3.10	(7.25)	0.67	+3.63	(5.88)	0.54	0.99
Vitamin E, per 2.02 *mg/1,000 kcal/d*	−2.60	(4.75)	0.58	+8.44	(8.81)	0.34	−8.92	(5.70)	0.12	0.60
Card rotation										
Total carotenoids, per 4.83 *mg/1,000 kcal/d*	**−1.14**	**(0.53)**	**0.033**	−0.66	(0.82)	0.42	−1.31	(0.72)	0.07	0.97
Vitamin A, per 541 *RE/1,000 kcal/d*	+1.07	(0.98)	0.28	−0.54	(1.43)	0.70	+2.20	(1.43)	0.12	0.41
Vitamin C, per 40.4 *mg/1,000 kcal/d*	+0.19	(0.52)	0.71	−0.01	(0.82)	0.99	+0.05	(0.68)	0.94	0.88

	All (N=1,274)			Men (N=541)			Women (N=733)			P_{sex} [2]
	β	(SEE)	P_{wald}	β	(SEE)	P_{wald}	β	(SEE)	P_{wald}	
Vitamin E, per 2.02 *mg/1,000 kcal/d*	+1.05	(0.55)	0.05	+0.27	(0.99)	0.79	+1.40	(0.66)	0.035	0.43
Identical pictures										
Total carotenoids, per 4.83 *mg/1,000 kcal/d*	−0.13	(0.17)	0.44	−0.33	(0.26)	0.20	+0.02	(0.23)	0.94	0.20
Vitamin A, per 541 *RE/1,000 kcal/d*	+0.25	(0.31)	0.42	−0.08	(0.45)	0.86	+0.61	(0.45)	0.18	0.19
Vitamin C, per 40.4 *mg/1,000 kcal/d*	+0.15	(0.17)	0.40	+0.34	(0.26)	0.19	−0.09	(0.22)	0.69	0.29
Vitamin E, per 2.02 *mg/1,000 kcal/d*	**+0.38**	**(0.17)**	**0.030**	−0.09	(0.32)	0.78	**+0.68**	**(0.21)**	**0.001**	0.13
Clock drawing test										
Total carotenoids, per 4.83 *mg/1,000 kcal/d*	+0.03	(0.04)	0.48	+0.08	(0.06)	0.16	+0.01	(0.05)	0.90	0.45
Vitamin A, per 541 *RE/1,000 kcal/d*	−0.11	(0.07)	0.13	−0.18	(0.10)	0.07	−0.06	(0.10)	0.53	0.26
Vitamin C, per 40.4 *mg/1,000 kcal/d*	+0.04	(0.04)	0.37	+0.04	(0.06)	0.49	+0.01	(0.05)	0.90	0.51
Vitamin E, per 2.02 *mg/1,000 kcal/d*	+0.05	(0.04)	0.17	−0.04	(0.06)	0.49	+0.09	(0.05)	0.06	0.33

Key BVRT=Benton Visual Retention Task; CES-D=Center for Epidemiologic Studies-Depression; CVLT=California Verbal Learning Task; DFR=Delayed Free Recal; HANDLS=Healthy Aging in Neighborhoods of Diversity across the Life Span; MMSE=Mini-Mental State Examination; OLS=Ordinary Least Square; SD=Standard Deviation; SEE=Standard error of the estimate; WRAT=Wide Range Achievement Test.

[1] Multivariate OLS or poisson (MMSE error count) models adjusted for age, sex, race/ethnicity, marital status, education, WRAT total score, poverty income ratio, current smoking status, every use of illicit drugs, body mass index, and selected nutrients expressed per 1,000 kcal, namely vitamin B-6, B-12, folate, n-3 HUFA and CES-D total score.

[2] *P* for interaction term exposure×sex in model with exposure main effect and main effect of sex and other covariates listed above.

Table 4

Cognitive function test scores by SD increase in dietary antioxidant intake: OLS and poisson regression models (stratified by race and age): HANDLS study[1,2]

	P_{race}[2]	P_{age}[3]	Whites (N= 513)			African-Americans (N=761)			Age<48y (N=621)			Age≥48y (N=653)		
			β	(SEE)	P_{wald}	β	(SEE)	P_{wald}	β	(SEE)	P_{wald}	β	(SEE)	P_{wald}
MMSE, error count														
Total carotenoids, per 4.83 *mg/1,000 kcal/d*	0.11	0.49	+0.06	(0.04)	0.15	−0.05	(0.03)	0.07	−0.01	(0.03)	0.67	−0.05	(0.03)	0.12
Vitamin A, per 541 *RE/1,000 kcal/d*	0.30	0.92	−0.08	(0.10)	0.44	−0.05	(0.05)	0.36	+0.10	(0.06)	0.08	+0.03	(0.06)	0.60
Vitamin C, per 40.4 *mg/1,000 kcal/d*	0.59	**0.07**	+0.06	(0.04)	0.12	+0.02	(0.03)	0.54	+0.01	(0.03)	0.76	+0.04	(0.03)	0.14
Vitamin E, per 2.02 *mg/1,000 kcal/d*	**0.033**	**0.042**	**−0.13**	**(0.05)**	**0.009**	−0.01	(0.03)	0.67	−0.07	(0.04)	0.07	−0.00	(0.03)	0.93
CVLT, List A														
Total carotenoids, per 4.83 *mg/1,000 kcal/d*	0.43	0.67	−0.17	(0.31)	0.58	−0.32	(0.23)	0.18	−0.35	(0.26)	0.18	+0.26	(0.27)	0.35
Vitamin A, per 541 *RE/1,000 kcal/d*	0.45	0.22	−0.88	(0.77)	0.25	+0.16	(0.46)	0.73	+0.69	(0.48)	0.15	−0.45	(0.50)	0.37
Vitamin C, per 40.4 *mg/1,000 kcal/d*	0.80	0.71	−0.28	(0.36)	0.43	+0.19	(0.21)	0.37	+0.04	(0.26)	0.87	−0.09	(0.25)	0.82
Vitamin E, per 2.02 *mg/1,000 kcal/d*	0.21	**0.06**	+0.63	(0.32)	0.05	**+0.58**	**(0.24)**	**0.014**	**+1.06**	**(0.29)**	**<0.001**	+0.27	(0.25)	0.29
CVLT, DFR														
Total carotenoids, per 4.83 *mg/1,000 kcal/d*	0.61	0.63	−0.04	(0.15)	0.78	−0.07	(0.12)	0.56	−0.14	(0.12)	0.26	−0.02	(0.14)	0.89
Vitamin A, per 541 *RE/1,000 kcal/d*	0.42	0.32	−0.12	(0.36)	0.63	+0.03	(0.23)	0.88	**+0.49**	**(0.22)**	**0.031**	−0.15	(0.25)	0.56
Vitamin C, per 40.4 *mg/1,000 kcal/d*	0.99	0.51	−0.08	(0.17)	0.63	+0.09	(0.10)	0.37	+0.06	(0.12)	0.59	+0.03	(0.13)	0.84
Vitamin E, per 2.02 *mg/1,000 kcal/d*	0.51	**0.016**	+0.21	(0.15)	0.16	+0.22	(0.12)	0.06	**+0.46**	**(0.14)**	**0.001**	+0.08	(0.13)	0.52
BVRT, error count														
Total carotenoids, per 4.83 *mg/1,000 kcal/d*	**0.033**	0.24	**−0.41**	**(0.20)**	**0.039**	**+0.42**	**(0.21)**	**0.046**	−0.10	(0.19)	0.61	+0.29	(0.23)	0.23
Vitamin A, per 541 *RE/1,000 kcal/d*	0.63	0.91	+0.34	(0.49)	0.49	**−1.01**	**(0.41)**	**0.015**	−0.53	(0.35)	0.13	−0.77	(0.43)	0.07
Vitamin C, per 40.4 *mg/1,000 kcal/d*	0.88	0.53	+0.22	(0.23)	0.33	−0.04	(0.19)	0.82	−0.04	(0.19)	0.84	−0.01	(0.22)	0.95
Vitamin E, per 2.02 *mg/1,000 kcal/d*	0.12	0.92	**−0.53**	**(0.20)**	**0.009**	−0.13	(0.21)	0.55	−0.13	(0.22)	0.56	−0.35	(0.22)	0.10
Digit span backwards														
Total carotenoids, per 4.83 *mg/1,000 kcal/d*	0.92	0.23	+0.07	(0.10)	0.49	+0.07	(0.08)	0.33	+0.03	(0.08)	0.72	+0.17	(0.09)	0.05
Vitamin A, per 541 *RE/1,000 kcal/d*	0.79	0.46	−0.25	(0.25)	0.31	+0.01	(0.15)	0.97	−0.06	(0.16)	0.70	+0.12	(0.16)	0.48
Vitamin C, per 40.4 *mg/1,000 kcal/d*	0.69	0.58	−0.05	(0.11)	0.69	+0.07	(0.07)	0.27	−0.08	(0.09)	0.37	−0.03	(0.08)	0.72

	P_{race}[2]	P_{age}[3]	Whites (N= 513)			African-Americans (N=761)			Age<48y (N=621)			Age≥48y (N=653)		
			β	(SEE)	P_{wald}	β	(SEE)	P_{wald}	β	(SEE)	P_{wald}	β	(SEE)	P_{wald}
Vitamin E, per 2.02 *mg/1,000 kcal/d*	0.31	0.35	+0.08	(0.10)	0.45	+0.04	(0.08)	0.57	−0.02	(0.10)	0.87	+0.12	(0.08)	0.15
Digit span forward														
Total carotenoids, per 4.83 *mg/1,000 kcal/d*	0.94	0.93	−0.03	(0.10)	0.80	+0.07	(0.08)	0.40	−0.00	(0.09)	0.97	+0.08	(0.10)	0.38
Vitamin A, per 541 *RE/1,000 kcal/d*	0.69	0.23	−0.35	(0.25)	0.16	−0.23	(0.17)	0.17	−0.30	(0.16)	0.06	−0.13	(0.18)	0.46
Vitamin C, per 40.4 *mg/1,000 kcal/d*	0.64	**0.09**	−0.06	(0.11)	0.59	−0.06	(0.08)	0.42	+0.00	(0.09)	0.06	−0.16	(0.09)	0.08
Vitamin E, per 2.02 *mg/1,000 kcal/d*	0.11	0.23	+0.18	(0.10)	0.09	+0.04	(0.09)	0.66	+0.14	(0.10)	0.17	+0.05	(0.09)	0.54
Animal fluency														
Total carotenoids, per 4.83 *mg/1,000 kcal/d*	0.30	0.48	+0.14	(0.27)	0.61	−0.04	(0.20)	0.85	+0.02	(0.22)	0.91	+0.02	(0.24)	0.94
Vitamin A, per 541 *RE/1,000 kcal/d*	0.30	0.75	+0.99	(0.65)	0.13	+0.33	(0.40)	0.42	+0.81	(0.41)	0.05	+0.07	(0.43)	0.88
Vitamin C, per 40.4 *mg/1,000 kcal/d*	0.93	0.87	−0.13	(0.30)	0.68	−0.03	(0.18)	0.86	−0.03	(0.23)	0.89	+0.04	(0.22)	0.87
Vitamin E, per 2.02 *mg/1,000 kcal/d*	0.29	0.15	+0.50	(0.27)	0.07	**+0.45**	**(0.20)**	**0.027**	**+0.77**	**(0.26)**	**0.003**	+0.34	(0.22)	0.12
Brief test of Attention														
Total carotenoids, per 4.83 *mg/1,000 kcal/d*	0.59	0.27	+0.03	(0.10)	0.75	+0.00	(0.09)	0.96	+0.10	(0.09)	0.26	−0.08	(0.11)	0.45
Vitamin A, per 541 *RE/1,000 kcal/d*	0.66	0.11	−0.04	(0.24)	0.86	+0.35	(0.18)	0.05	+0.17	(0.16)	0.28	+0.19	(0.19)	0.32
Vitamin C, per 40.4 *mg/1,000 kcal/d*	0.15	0.96	−0.22	(0.11)	0.06	+0.03	(0.08)	0.67	−0.07	(0.09)	0.40	−0.01	(0.10)	0.95
Vitamin E, per 2.02 *mg/1,000 kcal/d*	0.38	0.96	+0.06	(0.10)	0.58	−0.09	(0.09)	0.31	+0.06	(0.10)	0.57	−0.04	(0.10)	0.65
Trailmaking test, A, sec.														
Total carotenoids, per 4.83 *mg/1,000 kcal/d*	0.38	0.88	−0.36	(0.54)	0.51	+0.88	(1.69)	0.60	+1.31	(1.17)	0.26	−0.64	(1.70)	0.71
Vitamin A, per 541 *RE/1,000 kcal/d*	0.72	0.95	+2.58	(1.33)	0.05	+0.72	(3.34)	0.83	−0.78	(2.14)	0.72	+2.56	(3.11)	0.41
Vitamin C, per 40.4 *mg/1,000 kcal/d*	0.87	0.96	+0.21	(0.61)	0.69	−1.98	(1.51)	0.19	−0.07	(1.18)	0.95	−1.82	(1.59)	0.25
Vitamin E, per 2.02 *mg/1,000 kcal/d*	**0.07**	**0.06**	−1.00	(0.55)	0.07	+1.99	(1.70)	0.24	−1.60	(1.33)	0.23	+2.96	(1.57)	0.06
Trailmaking test, B, sec.														
Total carotenoids, per 4.83 *mg/1,000 kcal/d*	0.41	0.60	−0.17	(5.75)	0.98	+12.1	(6.9)	0.08	+4.92	(5.93)	0.41	+10.4	(7.4)	0.16
Vitamin A, per 541 *RE/1,000 kcal/d*	0.92	0.46	+6.48	(14.14)	0.65	−22.1	(13.6)	0.11	−18.4	(10.9)	0.09	+0.33	(13.5)	0.98
Vitamin C, per 40.4 *mg/1,000 kcal/d*	0.73	0.64	+2.75	(6.51)	0.67	+4.25	(6.16)	0.49	+5.68	(5.98)	0.34	+0.14	(6.89)	0.98
Vitamin E, per 2.02 *mg/1,000 kcal/d*	0.88	0.38	+0.44	(5.88)	0.94	−5.97	(6.97)	0.39	+0.72	(6.76)	0.91	−1.20	(6.89)	0.86
Card rotation														
Total carotenoids, per 4.83 *mg/1,000 kcal/d*	0.37	0.31	−0.46	(0.89)	0.61	**−1.55**	**(0.68)**	**0.023**	**−1.55**	**(0.76)**	**0.041**	−0.61	(0.78)	0.43
Vitamin A, per 541 *RE/1,000 kcal/d*	0.87	0.13	−0.26	(2.19)	0.91	+2.07	(1.35)	0.13	+1.21	(1.40)	0.39	+1.14	(1.41)	0.42

	P_{race}[2]	P_{age}[3]	Whites (N= 513)			African-Americans (N=761)			Age<48y (N=621)			Age≥48y (N=653)		
			β	(SEE)	P_{wald}	β	(SEE)	P_{wald}	β	(SEE)	P_{wald}	β	(SEE)	P_{wald}
Vitamin C, per 40.4 *mg/1,000 kcal/d*	0.43	0.69	−1.03	(1.01)	0.31	+0.69	(0.61)	0.26	+0.15	(0.77)	0.84	+0.18	(0.72)	0.80
Vitamin E, per 2.02 *mg/1,000 kcal/d*	0.16	0.97	+1.72	(0.91)	0.06	+0.68	(0.69)	0.32	+1.35	(0.86)	0.12	+0.66	(0.72)	0.36
Identical pictures														
Total carotenoids, per 4.83 *mg/1,000 kcal/d*	0.32	1.00	−0.05	(0.27)	0.85	−0.31	(0.22)	0.17	−0.24	(0.24)	0.32	+0.00	(0.25)	0.99
Vitamin A, per 541 *RE/1,000 kcal/d*	**0.08**	0.77	+0.52	(0.67)	0.44	+0.79	(0.44)	0.10	+0.30	(0.45)	0.50	+0.33	(0.45)	0.47
Vitamin C, per 40.4 *mg/1,000 kcal/d*	0.54	0.11	−0.28	(0.31)	0.36	+0.33	(0.20)	0.10	+0.37	(0.25)	0.13	−0.08	(0.23)	0.74
Vitamin E, per 2.02 *mg/1,000 kcal/d*	**0.05**	0.18	**+0.63**	**(0.28)**	**0.028**	+0.25	(0.22)	0.27	**+0.67**	**(0.28)**	**0.016**	+0.25	(0.23)	0.28
Clock drawing test														
Total carotenoids, per 4.83 *mg/1,000 kcal/d*	0.54	0.83	+0.07	(0.06)	0.22	−0.00	(0.05)	0.95	+0.06	(0.05)	0.26	−0.00	(0.06)	0.95
Vitamin A, per 541 *RE/1,000 kcal/d*	0.42	**0.05**	−0.07	(0.14)	0.63	−0.10	(0.10)	0.32	−0.13	(0.09)	0.17	−0.09	(0.11)	0.41
Vitamin C, per 40.4 *mg/1,000 kcal/d*	0.74	0.10	−0.01	(0.07)	0.90	+0.06	(0.05)	0.17	+0.02	(0.05)	0.72	+0.10	(0.05)	0.07
Vitamin E, per 2.02 *mg/1,000 kcal/d*	0.79	0.84	+0.01	(0.06)	0.88	+0.08	(0.05)	0.13	+0.07	(0.06)	0.21	+0.01	(0.05)	0.89

Key BVRT=Benton Visual Retention Task; CES-D=Center for Epidemiologic Studies-Depression; CVLT=California Verbal Learning Task; DFR=Delayed Free Recall; HANDLS=Healthy Aging in Neighborhoods of Diversity across the Life Span; MMSE=Mini-Mental State Examination; OLS=Ordinary Least Square; SD=Standard Deviation; SEE=Standard error of the estimate; WRAT=Wide Range Achievement Test.

[1] Multivariate OLS or poisson (MMSE error count) models adjusted for age, sex, race/ethnicity, marital status, education, WRAT total score, poverty income ratio, current smoking status, every use of illicit drugs, body mass index, and selected nutrients expressed per 1,000 kcal, namely vitamin B-6, B-12, folate, n-3 highly unsaturated fatty acids and CES-D total score.

[2] P for interaction term exposure × race in model with exposure main effect and main effect of race and other covariates listed above.

[3] P for interaction term exposure × age in model with exposure main effect and main effect of age group and other covariates listed above.

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Table 5

Mediating effect of CES-D score on the total effect of dietary antioxidants (per 1 SD) on cognitive function test scores: mediation analysis relaxing the addititivity assumption and allowing for interaction between CES-D and the antioxidant exposure: HANDLS study[1]

	Controlled direct effect			**Natural direct effect**			**Natural indirect effect**			**Marginal total effect**		
	β	**(SEE)**	P_{wald}	**β**	**(SEE)**	P_{wald}	**β**	**(SEE)**	P_{wald}	**β**	**(SEE)**	P_{wald}
CVLT, List A												
Total carotenoids	−0.31	(0.19)	0.10	−0.30	(0.19)	0.11	+0.04	(0.03)	0.11	−0.26	(0.19)	0.17
Vitamin A	+0.23	(0.36)	0.51	+0.22	(0.34)	0.52	−0.00	(0.07)	0.95	+0.22	(0.35)	0.53
Vitamin C	−0.03	(0.18)	0.86	−0.03	(0.18)	0.86	+0.00	(0.03)	0.91	−0.03	(0.19)	0.87
Vitamin E	**+0.63**	**(0.19)**	**0.001**	**+0.62**	**(0.19)**	**0.001**	**−0.07**	**(0.04)**	**0.040**	**+0.55**	**(0.19)**	**0.005**
CVLT, DFR												
Total carotenoids	−0.09	(0.09)	0.30	−0.09	(0.09)	0.31	+0.02	(0.01)	0.12	−0..07	(0.09)	0.42
Vitamin A	+0.25	(0.17)	0.13	+0.25	(0.17)	0.13	−0.00	(0.03)	0.95	+0.25	(0.16)	0.14
Vitamin C	−0.04	(0.09)	0.69	+0.04	(0.09)	0.69	+0.00	(0.01)	0.91	+0.04	(0.09)	0.68
Vitamin E	**+0.23**	**(0.09)**	**0.013**	**+0.23**	**(0.09)**	**0.012**	**−0.03**	**(0.01)**	**0.049**	**+0.20**	**(0.09)**	**0.029**
BVRT, error count												
Total carotenoids	+0.10	(0.15)	0.48	+0.10	(0.15)	0.51	−0.01	(0.01)	0.33	+0.08	(0.15)	0.56
Vitamin A	**−0.63**	**(0.27)**	**0.021**	**−0.63**	**(0.27)**	**0.020**	+0.00	(0.02)	0.95	**−0.63**	**(0.27)**	**0.021**
Vitamin C	+0.02	(0.15)	0.84	+0.03	(0.15)	0.86	−0.00	(0.01)	0.91	+0.03	(0.15)	0.86
Vitamin E	−0.30	(0.15)	0.05	−0.29	(0.15)	0.06	+0.04	(0.02)	0.06	−0.25	(0.15)	0.10
Animal fluency												
Total carotenoids	+0.04	(0.16)	0.78	+0.04	(0.16)	0.81	+0.03	(0.02)	0.12	+0.07	(0.16)	0.65
Vitamin A	+0.44	(0.30)	0.13	+0.45	(0.30)	0.13	−0.00	(0.02)	0.95	+0.45	(0.30)	0.13
Vitamin C	−0.00	(0.16)	0.99	−0.00	(0.16)	1.00	−0.00	(0.02)	0.91	+0.00	(0.16)	1.00
Vitamin E	**+0.57**	**(0.16)**	**0.001**	**+0.57**	**(0.16)**	**0.001**	−0.05	(0.03)	0.05	**+0.52**	**(0.17)**	**0.002**
Card rotation												
Total carotenoids	**−1.15**	**(0.53)**	**0.031**	**−1.15**	**(0.53)**	**0.031**	+0.06	(0.05)	0.21	**−1.09**	**(0.53)**	**0.042**
Vitamin A	+0.94	(0.99)	0.34	+0.95	(0.99)	0.33	−0.00	(0.04)	0.95	+0.95	(0.99)	0.34
Vitamin C	+0.19	(0.53)	0.71	+0.19	(0.53)	0.71	+0.00	(0.04)	0.91	+0.20	(0.53)	0.71
Vitamin E	+1.08	(0.55)	0.05	+1.07	(0.55)	0.05	−0.11	(0.07)	0.10	+0.96	(0.55)	0.08

Key BVRT=Benton Visual Retention Task; CDE=Controlled Direct Effect; CES-D=Center for Epidemiologic Studies-Depression; CVLT=California Verbal Learning Task; DFR=Delayed Free Recall; HANDLS=Healthy Aging in Neighborhoods of Diversity across the Life Span; MMSE=Mini-Mental State Examination; MTE=Marginal Total Effect; NDE=Natural Direct Effect; NIE=Natural Indirect Effect; OLS=Ordinary Least Square; SD=Standard Deviation; SEE=Standard Error of the Estimate; WRAT=Wide Range Achievement Test.

[1]Multivariate OLS models adjusted for age, sex, race/ethnicity, marital status, education, WRAT total score, poverty income ratio, current smoking status, every use of illicit drugs, body mass index, and selected nutrients expressed per 1,000 kcal, namely vitamin B-6, B-12, folate, n-3 highly unsaturated fatty acids. CES-D score was entered as potential mediator alternatively for each antioxidant exposure, while others are kept in the model as covariates. Interaction between CES-D and each of the antioxidant exposure was allowed. Four parameters were estimated with SEE and p-values: CDE, NDE NIE, MTE. Those are described in more detail in statistical analysis section. For CDE, CES-D was set at a value of 11.0 (an approximation of the sample mean). Only results with significant total effects at type I error of 0.05 for at least one antioxidant are presented.