Dietary Antioxidant Intake and Its Association With Cognitive Function in an Ethnically Diverse Sample of US Adults

May A. Beydoun, PhD, MPH, Marie T. Fanelli-Kuczmarski, PhD, Melissa H. Kitner-Triolo, PhD, Hind A. Beydoun, PhD, MPH, Jay S. Kaufman, PhD, Marc A. Mason, MS, Michele K. Evans, MD, and Alan B. Zonderman, PhD

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 1274 adults (541 men and 733 women) aged 30 to 64 years at baseline (mean [standard deviation] = 47.5 [9.3]) in the Healthy Aging in Neighborhoods of Diversity Across the Lifespan Study, 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 was used to measure depressive symptoms. Dietary intake was assessed with two 24-hour recalls, estimating daily consumption of total carotenoids and vitamins A, C, and E per 1000 kcal. **Results:** Among key findings, 1 standard deviation (~2.02 mg/1000 kcal) higher vitamin E was associated with a higher score on verbal memory, immediate recall (β = +0.64 [0.19], p = .001), and better language/verbal fluency performance (β = +0.53 [0.16], p = .001), particularly among the younger age group. Women with higher vitamin E intake (β = +0.68 [0.21], p = .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. **Key words:** antioxidants, cognitive function, depressive symptoms, midlife.

AA = African American; **AD** = Alzheimer's disease; **AF** = Animal Fluency; **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 Scale; **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 Backward 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; **MTE** = marginal total effect; **NDE** = natural direct effect; **NIE** = natural indirect effect; **OLS** = ordinary least square; **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; ***X*** = antioxidant exposure.

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 older than 65 years 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 that oxidative stress plays an important role in neurodegenerative processes accompanying cognitive impairment and dementia, especially 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-aged 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

From the National Institute on Aging (M.A.B., M.H.K.-T., M.K.E., A.B.Z.), NIA/NIH/IRP, Baltimore, Maryland; Department of Behavioral Health and Nutrition (M.T.F.-K.), University of Delaware, Newark, Delaware; Graduate Program in Public Health (H.A.B.), Eastern Virginia Medical School, Norfolk, Virginia; Department of Epidemiology, Biostatistics, and Occupational Health, (J.S.K.) McGill University, Montreal, Quebec, Canada; and Statistical Information Systems (M.A.M.), MedStar Research Institute, Baltimore, Maryland.

Address correspondence and reprint requests to May A. Beydoun, PhD, NIH Biomedical Research Center, National Institute on Aging, IRP, 251 Bayview Blvd, Suite 100, Room #04B118, Baltimore, MD 21224.
E-mail: baydounm@mail.nih.gov

M.K.E. and A.B.Z are co-senior authors.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.psychosomaticmedicine.org).

Received for publication February 27, 2014; revision received August 12, 2014.
DOI: 10.1097/PSY.0000000000000129

0033-3174/15/7701–0068

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 role 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), whereas other studies have shown that those associations were restricted to specific sociodemographic groups or genotypes in others (34–36). Moreover, the bioavailability of many nutrients, including antioxidants, is highly dependent on sociodemographic 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, whereas 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 sociodemographic differences in those associations and the mediating role of depressive symptoms.

METHODS

Database and Study Sample

The Healthy Aging in Neighborhoods of Diversity across the Life Span (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, MD, using an area probability sampling design of 13 census segments. The initial phase of HANDLS involved screening, recruitment, and household interviews, whereas Phase 2 included examinations in mobile Medical Research Vehicles (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 3720 participants sampled in Phase 1 (Sample 1), complete Phase 2 examination data at baseline were available for 2802 (Sample 2a). This study included only participants with 2 days of dietary recall and Center for Epidemiologic Studies Depression Scale (CES-D) data (n = 1739; 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 versus 64.8% above poverty, and 47.1% are men in remaining participants in Sample 1), with participants in Sample 2b having higher African American representation (i.e., 67.7% versus 55.9%). Sample size of participants with complete and reliable cognitive tests (main outcome) as well as predictor/covariate variables was 1274 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 seven domains (global, attention, learning/memory, executive function, visuospatial/visuoconstruction ability, psychomotor speed, language/verbal) were outcomes: the Mini-Mental State Examination (MMSE); the California Verbal Learning Test immediate free recall, List A (CVLT-List A) and delayed free recall (CVLT-DFR); Digit Span Forward and Backward tests (DS-B and DS-F); the Benton Visual Retention Test (BVRT); Animal Fluency (AF) test; 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, http://links.lww.com/PSYMED/A171). 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-hour dietary recalls using the US Department of Agriculture's Automated Multiple Pass Method, a standardized five-step process validated for protein, carbohydrate, fat, and energy intakes in obese and nonobese individuals (42–44). A database converted grams of US Department of Agriculture 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 per 1000 kcal per day, milligrams per 1000 kcal per day, and milligrams per 1000 kcal per d, respectively, and the sum of five carotenoids (α-carotene, β-carotene, lutein + zeaxanthin, β-cryptoxanthin, and lycopene) termed "total carotenoids" and expressed as micrograms per 1000 kcal of dietary intake per day.

Depressive Symptom Assessment

The 20-item Center for Epidemiologic Studies Depression Scale (CES-D) 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

Sociodemographic, life-style, and Health-Related Potential Confounders

The sociodemographic and life-style factors age, sex, race/ethnicity (white versus African American), marital status (married versus unmarried), completed years of education (<high school [HS], HS, and >HS), poverty income ratio (<125% for "poor"), measured body mass index (in kilograms per meter squared), lifetime drugs use (opiates, marijuana, or cocaine versus 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 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 (HUFA; % 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 the following: 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-standard-deviation (SD) increase in their value. In all multivariate analyses, adjustment was made on other sociodemographic, life-style, and health-related and selected dietary covariates. Key findings regarding significant covariates predicting each of the cognitive test score outcomes in those models were also presented. Sex, race, and age group (<median versus ≥median) were considered as potential effect modifiers in the associations between antioxidants and cognitive test scores. In a separate model, two-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 (SEMs) were carried out where antioxidants, sociodemographic, life-style, and health-related factors were exogenous to CES-D and each of the three domain scores separately (see Eqs. 1.1–1.4, 2, and 3).

$$X_i = \sum_{j=1}^{k} \alpha_{Z_{j1i}} Z_j + e_{1i} \qquad 1.1 - 1.4$$

$$\text{CES-D} = \alpha_{21i} X_i + \sum_{j=1}^{k} \alpha_{Z_{j2}} Z_j + e_2 \qquad 2$$

$$\text{CS}_l = \alpha_{31i} X_i + \alpha_{32}\text{CES-D} + \sum_{j=1}^{k} \alpha_{Z_{j3}} Z_j + e_3 \qquad 3$$

where X is the main dietary exposure variable (each antioxidant per 1000 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 sociodemographic, life-style, 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: MP = (indirect effect) * 100/(total effect). Based on Eqs. 1.1–1.4, 2, and 3: α_{31} = direct effect; $\alpha_{21}\times\alpha_{32}$ = indirect effect; total effect = $\alpha_{31} + \alpha_{21}\times\alpha_{32}$ (72,73). The significance of the MP 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 additivity between each antioxidant 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 versus 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 predefined 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, an MP can be estimated as MP = (NIE * 100)/MTE (77). In all approaches (i.e., SEM, S-G test, versus relaxing the assumption for additivity), only results with significant total effects of antioxidants versus 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 = 3720) sociodemographic variables such as age, sex, marital status, and smoking status (79).

Type I error was set at 0.05 for main effects, while $p < .10$, was considered significant for interaction terms, before 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, $p < .004$ was deemed significant for cognitive test performance versus antioxidants hypotheses (13 test scores), but a Type I error of 0.05 was used for all other hypotheses. Because of their lower statistical power compared with main effects, interaction terms had critical *p* values reduced to .05.

RESULTS

Study characteristics by sex, race, and two age groups (less than the median age of 48 years versus greater than or equal to the median age of 48 years) are shown in Table 1. Women (versus men), African Americans (versus whites), and younger participants (versus older) were more likely to be below poverty. African Americans and younger participants had, on average, lower educational attainment and literacy compared with 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 participants had a higher prevalence of illicit drug ever use compared with whites, women, and older participants, respectively. Average body mass index (BMI) was higher among women than men. Men, whites, and younger individuals were more likely to be married compared with women, African Americans, and older individuals, respectively.

Women had higher dietary intakes than did men in vitamins C and E per 1000 kcal, whereas whites had higher intakes of total carotenoids, vitamin E, and folate than did 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 with their younger counterparts. Mean CES-D score was higher among women compared with men (11.9 versus 10.3, $p < .001$), although 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-B, DS-F, and 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 DS-B, DS-F and CDT.

When examining the relationship between CES-D score and all other variables (Table S1, Supplemental Digital Content 2, http://links.lww.com/PSYMED/A172), certain patterns emerged. Importantly, a higher level of depressive symptoms was associated

TABLE 1. Selected Study Participant Characteristics by Sex and Race/Ethnicity (n = 1274): HANDLS Study[a]

	All	Men	Women	Whites	African Americans	Age <48 y	Age ≥48 y	p[b] Men Versus Women	p[b] Whites Versus African Americans	p[b] Age <48 y versus ≥48 y
n	1274	541	733	513	761	621	653			
Age, y	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)	.36	1.00	<.001
Men, %	42.5	—	—	40.3	43.9	40.1	44.7	—	.21	.10
African American, %	59.7	61.7	58.2	—	—	60.0	59.6	.21	—	.90
Married, %	53.3	60.6	47.9	60.3	48.6	58.6	48.1	<.001	<.001	<.001
Education, %								.44	<.001	.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)	.71	<.001	.31
PIR <125%, %	48.7	43.6	52.5	36.6	56.9	52.7	45.0	.002	<.001	.006
Current smoking status, %								.001	.31	.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, %								<.001	.034	<.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, $kg \cdot m^{-2}$	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)	<.001	.58	.09
Dietary intake, per 1000 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)	.05	.011	.74
Vitamin A, RAE	344 (541)	312 (508)	367 (564)	330 (253)	353 (669)	326 (586)	360 (496)	.07	.45	.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)	.030	.003	.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)	<.001	<.001	.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)	.77	.12	.033
Vitamin B_{12}, μg	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)	.97	.15	.99
Folate, μg	187 (102)	182 (103)	191 (102)	205 (111)	175 (95)	179 (93)	194 (110)	.09	<.001	.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)	.27	<.001	.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)	.003	<.001	.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)	<.001	<.001	<.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)	<.001	<.001	<.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)	<.001	.019	<.001

(Continued on next page)

TABLE 1. *(Continued)*

	All	Men	Women	Whites	African Americans	Age <48 y	Age ≥48 y	p^b			
								Men Versus Women	Whites Versus African Americans	Age <48 y versus ≥48 y	
Digit Span Backward	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)	.52	<.001	.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)	.10	<.001	.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)	<.001	<.001	<.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)	.017	<.001	.009	
Trailmaking Test, A, s	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)	.40	<.001	<.001	
Trailmaking Test, B, s	147 (157)	153 (163)	142 (152)	108 (123)	173 (171)	128 (143)	165 (169)	.21	<.001	<.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)	<.001	<.001	<.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)	.001	<.001	<.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)	.026	<.001	.99	

HANDLS = Healthy Aging in Neighborhoods of Diversity across the Life Span; HS = high school; WRAT = Wide Range Achievement Test; PIR = poverty income ratio; RAE = Retinol Activity Equivalent; HUFA = highly unsaturated fatty acids; RE = retinol equivalent; CES-D = Center for Epidemiologic Studies Depression Scale; MMSE = Mini-Mental State Examination; CVLT = California Verbal Learning Task; DFR = Delayed Free Recall; BVRT = Benton Visual Retention Task.

[a] Values are mean (standard deviation) or percent.

[b] p Value was based on two-sided independent-samples t test when row variable is continuous and χ^2 when row variable is categorical.

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 with nonsmokers 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 of associations between sociodemographic, life-style, and dietary correlates with the main dietary antioxidant exposures. Among key findings, age and education were positively linked to vitamin E intake per 1000 kcal/d and African Americans had higher intakes of vitamin C compared with whites, whereas men had lower intakes of both vitamins A and E compared with 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 and *n*-3 HUFA (% energy) but inversely related to vitamin B_{12} (per 1000 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 1000 kcal was associated with a 0.64-point higher score on the CVLT-List A (reflecting the verbal memory domain, $p = .001$), independent of other antioxidants, dietary, and sociodemographic, life-style, 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, $\beta = +0.53$, $p = .001$). Table 3 also presents subgroup 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 ($\beta = +0.68$, $p = .001$). Moreover, Table S2 (Supplemental Digital Content 3, http://links.lww.com/PSYMED/A173) shows findings from covariates entered into the model for the total population, presenting only those that were statistically significant at a Type I error of 0.05. Aside from the findings for age, sex, and race, which were consistent with the bivariate results in Table 1, other notable

TABLE 2. Sociodemographic, Life-style, and Dietary Correlates of Each of the Selected Dietary Antioxidants: Multiple OLS Regression Models (n = 1274): HANDLS Study

	Total Carotenoids			Vitamin A			Vitamin C			Vitamin E		
	β	(SEE)	p_{Wald}	β	(SEE)	p	β	(SEE)	p_{Wald}	β	(SEE)	p_{Wald}
Age	−7.5	(13.0)	.56	**+1.83**	**(0.79)**	**.020**	−0.19	(0.11)	.09	+0.01	(0.01)	.18
Men versus women	+322.4	(264.4)	.22	**−35.1**	**(16.0)**	**.029**	+0.20	(2.26)	.93	**−0.42**	**(0.11)**	**<.001**
African American versus white	−512.4	(265.4)	.05	+28.0	(16.1)	.08	**+11.9**	**(2.2)**	**<.001**	−0.16	(0.11)	.14
Married versus unmarried	−44.6	(46.8)	.34	−2.2	(2.8)	.44	+2.1	(2.2)	.33	−0.03	(0.02)	.16
Education												
<HS	Ref			Ref			Ref			Ref		
HS	+298.0	(502.1)	.55	−1.2	(30.5)	.97	+0.35	(4.29)	.94	−0.03	(0.20)	.87
>HS	+132.5	(545.2)	.81	−8.1	(33.2)	.81	−1.34	(4.66)	.77	**+0.45**	**(0.22)**	**.041**
Missing	+1,010.1	(896.2)	.26	−12.8	(54.5)	.82	−6.97	(7.66)	.36	+0.43	(0.37)	.24
Literacy (WRAT score)	+27.6	(17.6)	.12	−0.65	(1.07)	.55	+0.08	(0.15)	.60	+0.01	(0.01)	.06
PIR <125%	−363.5	(255.4)	.16	+2.22	(15.55)	.89	+2.10	(2.18)	.34	+0.03	(0.10)	.75
Current smoking status												
Currently smoking	+10.9	(278.3)	.97	−19.1	(16.9)	.26	**−5.6**	**(2.4)**	**.019**	−0.20	(0.11)	.08
Missing	+564.7	(939.3)	.55	−40.9	(57.1)	.47	+2.0	(8.7)	.81	−0.36	(0.38)	.34
Ever use of illicit drugs												
Never used	Ref			Ref			Ref			Ref		
Used any type	−232.2	(276.8)	.40	−19.1	(16.9)	.26	**−5.4**	**(2.3)**	**.023**	+0.07	(0.11)	.51
Missing	−619.4	(1,018.6)	.54	−40.9	(57.1)	.47	+2.0	(8.7)	.81	+0.59	(0.42)	.16
Body mass index	+2.90	(16.4)	.86	−0.75	(1.00)	.45	−0.12	(0.14)	.38	−0.004	(0.007)	.50
Energy	−0.10	(0.13)	.46	−0.01	(0.01)	.19	**−0.003**	**(0.001)**	**.006**	+0.000	(0.000)	.05
Total carotenoids	—			**+0.02**	**(0.00)**	**<.001**	**+0.001**	**(0.000)**	**<.001**			
Vitamin A	**+5.27**	**(0.44)**	**<.001**	—			+0.007	(0.004)	.06	−0.000	(0.000)	.95
Vitamin C	**+19.07**	**(3.27)**	**<.001**	+0.37	(0.20)	.06	—			**+0.006**	**(0.001)**	**<.001**
Vitamin E	**+508.2**	**(67.8)**	**<.001**	−0.28	(4.22)	.95	**+2.66**	**(0.59)**	**<.001**	—		
Vitamin B_6	+227.0	(347.8)	.51	**−75.8**	**(21.0)**	**<.001**	**+15.7**	**(2.9)**	**<.001**	**+0.92**	**(0.14)**	**<.001**
Vitamin B_{12}	**−490.4**	**(42.1)**	**<.001**	**+82.2**	**(1.4)**	**<.001**	**−1.12**	**(0.38)**	**.003**	−0.02	(0.02)	.34
Folate	+2.45	(1.62)	.13	**+0.55**	**(0.10)**	**<.001**	**+0.04**	**(0.01)**	**.002**	**+0.003**	**(0.001)**	**<.001**
n-3 HUFA	**+2343**	**(476.6)**	**<.001**	**−309.8**	**(27.9)**	**<.001**	−0.12	(4.11)	.98	**+0.62**	**(0.20)**	**.002**

Values in bold indicate the significant main effects and interaction terms prior to correction for multiple testing.
OLS = ordinary least square; HANDLS = Healthy Aging in Neighborhoods of Diversity across the Life Span; HS = high school; WRAT = Wide Range Achievement Test; PIR = poverty income ratio; HUFA = highly unsaturated fatty acids; RE = retinol equivalent; SEE = standard error of the estimate.

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, and IP), lower CES-D score (all tests), higher BMI (CVLT-List A and CVLT-DFR), lower vitamin B_{12} intake (BVRT), drug users versus not (AF, BTA, and Trails B), and higher energy intake (CR and IP).

Table 4 shows findings from subgroup analyses by race and age group (<48 years versus ≥48 years), 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 (<48 years) was linked to better performance on CVLT-List A (β = +1.06, p < .001), CVLT-DFR (β = +0.46, p = .001; p for interaction by age group < .05), and AF (β = +0.77, p = .003). Tests of effect modification only showed a few other instances of heterogeneity between strata (e.g., vitamin E versus MMSE by race and age group; total carotenoids versus BVRT by race). A consistent although marginally significant result was found whereby vitamin E was positively related to IP among the younger group (β = +0.67, p = .016). Similarly, higher vitamin E intake was marginally related to a smaller number of errors among whites in both MMSE and BVRT (.004 < p < .05), with a significant racial difference in the case of MMSE (p = .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, http://links.lww.com/PSYMED/A174). 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

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[a]

	All (n = 1274)			Men (n = 541)			Women (n = 733)			
	β	(SEE)	p_{Wald}	β	(SEE)	p_{Wald}	β	(SEE)	p_{Wald}	p_{sex}[b]
MMSE										
Total carotenoids	−0.02	(0.02)	.38	−0.03	(0.03)	.33	−0.02	(0.03)	.64	.38
Vitamin A	−0.05	(0.04)	.26	−0.09	(0.06)	.15	−0.00	(0.06)	.97	.65
Vitamin C	+0.03	(0.02)	.17	+0.03	(0.03)	.32	+0.03	(0.03)	.35	.74
Vitamin E	−0.03	(0.03)	.26	−0.02	(0.04)	.68	−0.05	(0.03)	.14	.77
CVLT, List A										
Total carotenoids	−0.32	(0.19)	.08	−0.47	(0.27)	.09	−0.20	(0.26)	.44	.42
Vitamin A	+0.18	(0.34)	.59	+0.31	(0.48)	.52	+0.12	(0.51)	.82	.65
Vitamin C	−0.02	(0.18)	.90	−0.05	(0.28)	.85	−0.06	(0.25)	.82	1.00
Vitamin E	**+0.64**	**(0.19)**	**.001**	+0.48	(0.34)	.16	**+0.72**	**(0.24)**	**.002**	.38
CVLT, DFR										
Total carotenoids	−0.09	(0.09)	.29	−0.18	(0.13)	.19	−0.03	(0.13)	.82	.74
Vitamin A	+0.23	(0.17)	.17	**+0.54**	**(0.23)**	**.021**	−0.01	(0.25)	.97	.22
Vitamin C	+0.03	(0.09)	.70	−0.00	(0.13)	.98	+0.04	(0.12)	.73	.75
Vitamin E	**+0.22**	**(0.09)**	**.007**	+0.31	(0.16)	.06	+0.22	(0.12)	.06	.78
BVRT										
Total carotenoids	+0.11	(0.15)	.44	+0.11	(0.22)	.61	−0.00	(0.20)	1.00	.47
Vitamin A	**−0.67**	**(0.27)**	**.013**	−0.52	(0.39)	.18	−0.61	(0.40)	.13	.41
Vitamin C	+0.00	(0.14)	1.00	−0.05	(0.22)	.81	+0.11	(0.19)	.57	.75
Vitamin E	−0.29	(0.15)	.06	+0.12	(0.27)	.66	**−0.48**	**(0.19)**	**.010**	**.09**
Digit Span Backward										
Total carotenoids	+0.07	(0.06)	.24	+0.10	(0.10)	.30	+0.11	(0.08)	.16	.35
Vitamin A	−0.08	(0.11)	.51	−0.20	(0.17)	.23	+0.01	(0.15)	.95	.33
Vitamin C	+0.03	(0.06)	.65	−0.05	(0.10)	.64	+0.06	(0.07)	.44	.33
Vitamin E	+0.05	(0.06)	.41	+0.13	(0.12)	.26	+0.02	(0.07)	.78	.55
Digit Span Forward										
Total carotenoids	+0.03	(0.06)	.61	+0.10	(0.10)	.30	+0.00	(0.09)	.97	0.30
Vitamin A	−0.19	(0.12)	.11	−0.28	(0.17)	.11	−0.15	(0.17)	.39	.17
Vitamin C	−0.08	(0.06)	.18	−0.08	(0.10)	.41	−0.09	(0.08)	.25	.55
Vitamin E	+0.08	(0.07)	.18	+0.12	(0.12)	.34	+0.09	(0.08)	.28	.53
Animal fluency										
Total carotenoids	+0.04	(0.16)	.81	+0.39	(0.25)	.12	−0.15	(0.22)	.50	.21
Vitamin A	+0.48	(0.29)	.11	+0.21	(0.44)	.63	+0.58	(0.43)	.18	.49
Vitamin C	−0.02	(0.16)	.92	−0.27	(0.25)	.29	+0.10	(0.21)	.63	.66
Vitamin E	**+0.53**	**(0.16)**	**.001**	+0.48	(0.30)	.11	**+0.52**	**(0.20)**	**.009**	.93
Brief Test of Attention										
Total carotenoids	−0.00	(0.07)	.99	−0.13	(0.10)	.21	+0.08	(0.09)	.34	**.09**
Vitamin A	+0.18	(0.12)	.14	+0.09	(0.17)	.59	+0.27	(0.18)	.14	.42
Vitamin C	−0.05	(0.06)	.48	+0.03	(0.10)	.77	−0.13	(0.09)	.15	.61
Vitamin E	−0.04	(0.07)	.59	−0.01	(0.12)	.94	−0.05	(0.08)	.57	.81
Trailmaking Test, A, s										
Total carotenoids	+0.69	(1.00)	.49	+1.12	(1.41)	.43	+0.20	(1.46)	.89	.80
Vitamin A	+0.26	(1.85)	.89	−0.83	(2.45)	.73	+1.22	(2.88)	.67	.66
Vitamin C	−1.25	(0.98)	.20	−1.33	(1.41)	.34	−1.09	(1.38)	.43	.76
Vitamin E	+0.88	(1.03)	.39	+0.29	(1.71)	.87	+0.98	(1.34)	.46	.69
Trailmaking Test, B										
Total carotenoids	+8.50	(4.64)	.07	+4.77	(7.26)	.51	+7.93	(6.22)	.20	.77
Vitamin A	−9.86	(8.53)	.25	−11.8	(12.6)	.34	−8.04	(12.24)	.51	.48

(continued on next page)

TABLE 3. *(Continued)*

	All (n = 1274)			Men (n = 541)			Women (n = 733)			
	β	(SEE)	p_{Wald}	β	(SEE)	p_{Wald}	β	(SEE)	p_{Wald}	p_{sex} [b]
Vitamin C	+3.34	(4.53)	.46	+3.10	(7.25)	.67	+3.63	(5.88)	.54	.99
Vitamin E	−2.60	(4.75)	.58	+8.44	(8.81)	.34	−8.92	(5.70)	.12	.60
Card Rotation										
Total carotenoids	**−1.14**	**(0.53)**	**.033**	−0.66	(0.82)	.42	−1.31	(0.72)	.07	.97
Vitamin A	+1.07	(0.98)	.28	−0.54	(1.43)	.70	+2.20	(1.43)	.12	.41
Vitamin C	+0.19	(0.52)	.71	−0.01	(0.82)	.99	+0.05	(0.68)	.94	.88
Vitamin E	+1.05	(0.55)	.05	+0.27	(0.99)	.79	**+1.40**	**(0.66)**	**.035**	.43
Identical Pictures										
Total carotenoids	−0.13	(0.17)	.44	−0.33	(0.26)	.20	+0.02	(0.23)	.94	.20
Vitamin A	+0.25	(0.31)	.42	−0.08	(0.45)	.86	+0.61	(0.45)	.18	.19
Vitamin C	+0.15	(0.17)	.40	+0.34	(0.26)	.19	−0.09	(0.22)	.69	.29
Vitamin E	**+0.38**	**(0.17)**	**.030**	−0.09	(0.32)	.78	**+0.68**	**(0.21)**	**.001**	.13
Clock Drawing Test										
Total carotenoids	+0.03	(0.04)	.48	+0.08	(0.06)	.16	+0.01	(0.05)	.90	.45
Vitamin A	−0.11	(0.07)	.13	−0.18	(0.10)	.07	−0.06	(0.10)	.53	.26
Vitamin C	+0.04	(0.04)	.37	+0.04	(0.06)	.49	+0.01	(0.05)	.90	.51
Vitamin E	+0.05	(0.04)	.17	−0.04	(0.06)	.49	+0.09	(0.05)	.06	.33

Values in bold indicate the significant main effects and interaction terms prior to correction for multiple testing.
SD = standard deviation; OLS = ordinary least square; HANDLS = Healthy Aging in Neighborhoods of Diversity across the Life Span; MMSE = Mini-Mental State Examination; CVLT = California Verbal Learning Task; DFR = Delayed Free Recall; BVRT = Benton Visual Retention Task; SEE = standard error of the estimate; WRAT = Wide Range Achievement Test; HUFA = highly unsaturated fatty acids; CES-D = Center for Epidemiologic Studies Depression Scale.
[a] 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 1000 kcal, namely, vitamin B_6, vitamin B_{12}, folate, n-3 HUFA, and CES-D total score.
[b] p for interaction term exposure × sex in a model with exposure main effect and main effect of sex and other covariates listed above.

inverse relationship between those two cognitive test scores and CES-D. When CES-D was entered into the model with antioxidants versus CVLT-List A and CVLT-DFR, the net effect of vitamin E was markedly altered compared with the total effect, with a significant S-G test (p = .032 and .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 an SEM 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 among associations in which vitamin E was positively associated with CES-D, CES-D inversely related to CVLT-List A, whereas 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 nonsignificant.

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 seemed to be partially mediated through CES-D with a significant NIE and an MP estimated at 13% to 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 [age <48 years]), verbal fluency (total population and the younger group [age <48 years]), 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, whereas the results of this study reflect intake of only one form of vitamin E, α-tocopherol. Because of the increased use of oils in the US diet,

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[ab]

			Whites (n = 513)			African Americans (n = 761)			Age <48 y (n = 621)			Age ≥48 y (n = 653)		
	p_{race}[b]	p_{age}[c]	β	(SEE)	p_{Wald}	β	(SEE)	p_{Wald}	β	(SEE)	p_{Wald}	β	(SEE)	p_{Wald}
MMSE														
Total carotenoids	.11	.49	+0.06	(0.04)	.15	−0.05	(0.03)	.07	−0.01	(0.03)	.67	−0.05	(0.03)	.12
Vitamin A	.30	.92	−0.08	(0.10)	.44	−0.05	(0.05)	.36	+0.10	(0.06)	.08	+0.03	(0.06)	.60
Vitamin C	.59	**.07**	+0.06	(0.04)	.12	+0.02	(0.03)	.54	+0.01	(0.03)	.76	+0.04	(0.03)	.14
Vitamin E	**.033**	**.042**	**−0.13**	**(0.05)**	**.009**	−0.01	(0.03)	.67	−0.07	(0.04)	.07	−0.00	(0.03)	.93
CVLT, List A														
Total carotenoids	.43	.67	−0.17	(0.31)	.58	−0.32	(0.23)	.18	−0.35	(0.26)	.18	+0.26	(0.27)	.35
Vitamin A	.45	.22	−0.88	(0.77)	.25	+0.16	(0.46)	.73	+0.69	(0.48)	.15	−0.45	(0.50)	.37
Vitamin C	.80	.71	−0.28	(0.36)	.43	+0.19	(0.21)	.37	+0.04	(0.26)	.87	−0.09	(0.25)	.82
Vitamin E	.21	**.06**	+0.63	(0.32)	.05	**+0.58**	**(0.24)**	**.014**	**+1.06**	**(0.29)**	**<.001**	+0.27	(0.25)	.29
CVLT, DFR														
Total carotenoids	.61	.63	−0.04	(0.15)	.78	−0.07	(0.12)	.56	−0.14	(0.12)	.26	−0.02	(0.14)	.89
Vitamin A	.42	.32	−0.12	(0.36)	.63	+0.03	(0.23)	.88	**+0.49**	**(0.22)**	**.031**	−0.15	(0.25)	.56
Vitamin C	.99	.51	−0.08	(0.17)	.63	+0.09	(0.10)	.37	+0.06	(0.12)	.59	+0.03	(0.13)	.84
Vitamin E	.51	**.016**	+0.21	(0.15)	.16	+0.22	(0.12)	.06	**+0.46**	**(0.14)**	**.001**	+0.08	(0.13)	.52
BVRT														
Total carotenoids	**.033**	.24	**−0.41**	**(0.20)**	**.039**	**+0.42**	**(0.21)**	**.046**	−0.10	(0.19)	.61	+0.29	(0.23)	.23
Vitamin A	.63	.91	+0.34	(0.49)	.49	**−1.01**	**(0.41)**	**.015**	−0.53	(0.35)	.13	−0.77	(0.43)	.07
Vitamin C	.88	.53	+0.22	(0.23)	.33	−0.04	(0.19)	.82	−0.04	(0.19)	.84	−0.01	(0.22)	.95
Vitamin E	.12	.92	**−0.53**	**(0.20)**	**.009**	−0.13	(0.21)	.55	−0.13	(0.22)	.56	−0.35	(0.22)	.10
Digit Span Backward														
Total carotenoids	.92	.23	+0.07	(0.10)	.49	+0.07	(0.08)	.33	+0.03	(0.08)	.72	+0.17	(0.09)	.05
Vitamin A	.79	.46	−0.25	(0.25)	.31	+0.01	(0.15)	.97	−0.06	(0.16)	.70	+0.12	(0.16)	.48
Vitamin C	.69	.58	−0.05	(0.11)	.69	+0.07	(0.07)	.27	−0.08	(0.09)	.37	−0.03	(0.08)	.72
Vitamin E	.31	.35	+0.08	(0.10)	.45	+0.04	(0.08)	.57	−0.02	(0.10)	.87	+0.12	(0.08)	.15
Digit Span Forward														
Total carotenoids	.94	.93	−0.03	(0.10)	.80	+0.07	(0.08)	.40	−0.00	(0.09)	.97	+0.08	(0.10)	.38
Vitamin A	.69	.23	−0.35	(0.25)	.16	−0.23	(0.17)	.17	−0.30	(0.16)	.06	−0.13	(0.18)	.46
Vitamin C	.64	**.09**	−0.06	(0.11)	.59	−0.06	(0.08)	.42	+0.00	(0.09)	.06	−0.16	(0.09)	.08
Vitamin E	.11	.23	+0.18	(0.10)	.09	+0.04	(0.09)	.66	+0.14	(0.10)	.17	+0.05	(0.09)	.54
Animal fluency														
Total carotenoids	.30	.48	+0.14	(0.27)	.61	−0.04	(0.20)	.85	+0.02	(0.22)	.91	+0.02	(0.24)	.94
Vitamin A	.30	.75	+0.99	(0.65)	0.13	+0.33	(0.40)	.42	+0.81	(0.41)	.05	+0.07	(0.43)	.88
Vitamin C	.93	.87	−0.13	(0.30)	.68	−0.03	(0.18)	.86	−0.03	(0.23)	.89	+0.04	(0.22)	.87
Vitamin E	.29	.15	+0.50	(0.27)	.07	**+0.45**	**(0.20)**	**.027**	**+0.77**	**(0.26)**	**.003**	+0.34	(0.22)	.12
Brief Test of Attention														
Total carotenoids	.59	.27	+0.03	(0.10)	.75	+0.00	(0.09)	.96	+0.10	(0.09)	.26	−0.08	(0.11)	.45
Vitamin A	.66	.11	−0.04	(0.24)	.86	+0.35	(0.18)	.05	+0.17	(0.16)	.28	+0.19	(0.19)	.32
Vitamin C	.15	.96	−0.22	(0.11)	.06	+0.03	(0.08)	.67	−0.07	(0.09)	.40	−0.01	(0.10)	.95
Vitamin E	.38	.96	+0.06	(0.10)	.58	−0.09	(0.09)	.31	+0.06	(0.10)	.57	−0.04	(0.10)	.65
Trailmaking Test, A														
Total carotenoids	.38	.88	−0.36	(0.54)	.51	+0.88	(1.69)	.60	+1.31	(1.17)	.26	−0.64	(1.70)	.71
Vitamin A	.72	.95	+2.58	(1.33)	.05	+0.72	(3.34)	.83	−0.78	(2.14)	.72	+2.56	(3.11)	.41
Vitamin C	.87	.96	+0.21	(0.61)	.69	−1.98	(1.51)	.19	−0.07	(1.18)	.95	−1.82	(1.59)	.25
Vitamin E	**.07**	**.06**	−1.00	(0.55)	.07	+1.99	(1.70)	.24	−1.60	(1.33)	.23	+2.96	(1.57)	.06
Trailmaking Test, B														
Total carotenoids	.41	.60	−0.17	(5.75)	.98	+12.1	(6.9)	.08	+4.92	(5.93)	.41	+10.4	(7.4)	.16
Vitamin A	.92	.46	+6.48	(14.14)	.65	−22.1	(13.6)	.11	−18.4	(10.9)	.09	+0.33	(13.5)	.98

(continued on next page)

TABLE 4. *(Continued)*

			Whites (n = 513)			African Americans (n = 761)			Age <48 y (n = 621)			Age ≥48 y (n = 653)		
	p_{race}[b]	p_{age}[c]	β	(SEE)	p_{Wald}	β	(SEE)	p_{Wald}	β	(SEE)	p_{Wald}	β	(SEE)	p_{Wald}
Vitamin C	.73	.64	+2.75	(6.51)	.67	+4.25	(6.16)	.49	+5.68	(5.98)	.34	+0.14	(6.89)	.98
Vitamin E	.88	.38	+0.44	(5.88)	.94	−5.97	(6.97)	.39	+0.72	(6.76)	.91	−1.20	(6.89)	.86
Card Rotation														
Total carotenoids	.37	.31	−0.46	(0.89)	.61	**−1.55**	**(0.68)**	**.023**	**−1.55**	**(0.76)**	**.041**	−0.61	(0.78)	.43
Vitamin A	.87	.13	−0.26	(2.19)	.91	+2.07	(1.35)	.13	+1.21	(1.40)	.39	+1.14	(1.41)	.42
Vitamin C	.43	.69	−1.03	(1.01)	.31	+0.69	(0.61)	.26	+0.15	(0.77)	.84	+0.18	(0.72)	.80
Vitamin E	.16	.97	+1.72	(0.91)	.06	+0.68	(0.69)	.32	+1.35	(0.86)	.12	+0.66	(0.72)	.36
Identical Pictures														
Total carotenoids	.32	1.00	−0.05	(0.27)	.85	−0.31	(0.22)	.17	−0.24	(0.24)	.32	+0.00	(0.25)	.99
Vitamin A	**.08**	.77	+0.52	(0.67)	.44	+0.79	(0.44)	.10	+0.30	(0.45)	.50	+0.33	(0.45)	.47
Vitamin C	.54	.11	−0.28	(0.31)	.36	+0.33	(0.20)	.10	+0.37	(0.25)	.13	−0.08	(0.23)	.74
Vitamin E	**.05**	.18	**+0.63**	**(0.28)**	**.028**	+0.25	(0.22)	.27	**+0.67**	**(0.28)**	**.016**	+0.25	(0.23)	.28
Clock Drawing Test														
Total carotenoids	.54	.83	+0.07	(0.06)	.22	−0.00	(0.05)	.95	+0.06	(0.05)	.26	−0.00	(0.06)	.95
Vitamin A	.42	**.05**	−0.07	(0.14)	.63	−0.10	(0.10)	.32	−0.13	(0.09)	.17	−0.09	(0.11)	.41
Vitamin C	.74	.10	−0.01	(0.07)	.90	+0.06	(0.05)	.17	+0.02	(0.05)	.72	+0.10	(0.05)	.07
Vitamin E	.79	.84	+0.01	(0.06)	.88	+0.08	(0.05)	.13	+0.07	(0.06)	.21	+0.01	(0.05)	.89

Values in bold indicate the significant main effects and interaction terms prior to correction for multiple testing.

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

[a] 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 1000 kcal, namely, vitamin B_6, vitamin B_{12}, folate, n-3 highly unsaturated fatty acids, and CES-D total score.

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

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

there has been an increase in the γ-tocopherol, the form that has similar antioxidant capacity but greater anti-inflammatory properties compared with α-tocopherol. Morris et al. (82) reported that only α- and γ-tocopherols found in foods were linked to slower rate of cognitive decline over a 6-year period. This observation was corroborated by Wengreen and colleagues (20).

It is worth noting, however, that in the case of vitamin E, our study population had, on average, a level of α-tocopherol consumption that meets roughly 50% of Estimated Average Requirement (EAR; mean [SD] = 6.8 [5.0 mg/d versus 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 with other studies whose selected population consumed higher amounts of vitamin E or included supplemental intake in addition to dietary sources. (e.g., Refs. (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 that examined the association of other dietary antioxidants with various cognitive outcomes. One cross-sectional study found that participants in the lowest 10th 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 was 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), whereas Sato and colleagues (36) only found this association in men.

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, although 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

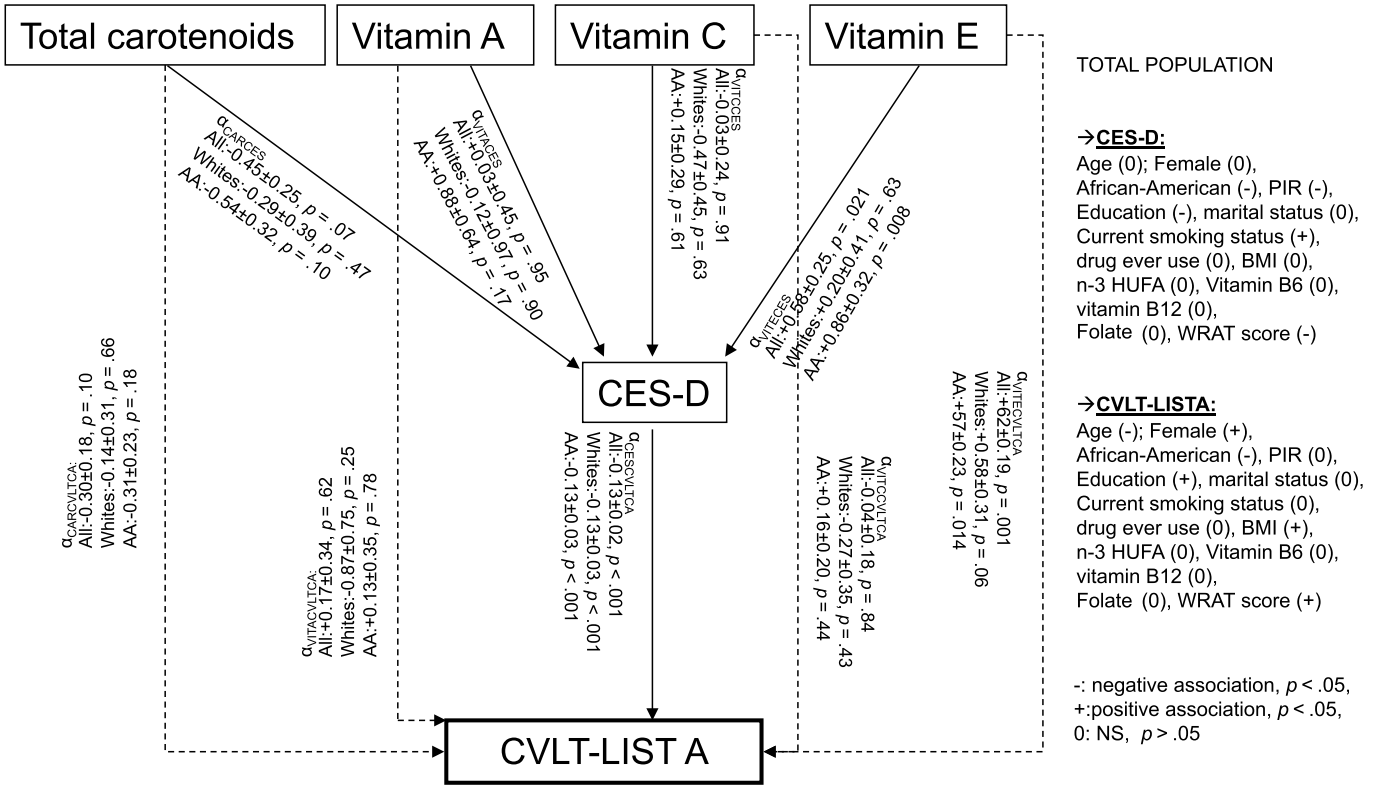

Figure 1. SEM for associations between antioxidants and a test of verbal memory (CVLT-List A): mediating effects of depressive symptoms (CES-D): HANDLS study. Note: path coefficients between antioxidant exposure and CES-D or cognitive scores are denoted by α and labeled by to the predictor and outcome variables of each path. SEM = Structural Equation Model; CVLT-List A = California Verbal Learning Test, immediate free recall, List A; CES-D = Center for Epidemiologic Studies Depression Scale; HANDLS = Healthy Aging in Neighborhoods of Diversity across the Life Span; AA = African American; HS = high school; HUFA = highly unsaturated fatty acids; OLS = ordinary least square; PIR = poverty income ratio; RAE = retinol active equivalent; SEE = standard error of the estimate; WRAT = Wide Range Achievement Test.

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), although 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). However, Grodstein and colleagues (92) found this effect to be specific to vitamin E supplements. 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 and vitamins C and E can improve verbal memory in the long-term (6 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 SEM, mediation analyses, and Heckman selection models, among others. Second, it is one of few to use the average of two 24-hour 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 US community. Moreover, because of a 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 and 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 nonusers. However, they

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 Additivity Assumption and Allowing for Interaction Between CES-D and the Antioxidant Exposure: HANDLS Study[a]

	CDE			NDE			NIE			MTE		
	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)	.10	−0.30	(0.19)	.11	+0.04	(0.03)	.11	−0.26	(0.19)	.17
Vitamin A	+0.23	(0.36)	.51	+0.22	(0.34)	.52	−0.00	(0.07)	.95	+0.22	(0.35)	.53
Vitamin C	−0.03	(0.18)	.86	−0.03	(0.18)	.86	+0.00	(0.03)	.91	−0.03	(0.19)	.87
Vitamin E	**+0.63**	**(0.19)**	**.001**	**+0.62**	**(0.19)**	**.001**	**−0.07**	**(0.04)**	**.040**	**+0.55**	**(0.19)**	**.005**
CVLT, DFR												
Total carotenoids	−0.09	(0.09)	.30	−0.09	(0.09)	.31	+0.02	(0.01)	.12	−0..07	(0.09)	.42
Vitamin A	+0.25	(0.17)	.13	+0.25	(0.17)	.13	−0.00	(0.03)	.95	+0.25	(0.16)	.14
Vitamin C	−0.04	(0.09)	.69	+0.04	(0.09)	.69	+0.00	(0.01)	.91	+0.04	(0.09)	.68
Vitamin E	**+0.23**	**(0.09)**	**.013**	**+0.23**	**(0.09)**	**.012**	**−0.03**	**(0.01)**	**.049**	**+0.20**	**(0.09)**	**.029**
BVRT												
Total carotenoids	+0.10	(0.15)	.48	+0.10	(0.15)	.51	−0.01	(0.01)	.33	+0.08	(0.15)	.56
Vitamin A	**−0.63**	**(0.27)**	**.021**	**−0.63**	**(0.27)**	**.020**	+0.00	(0.02)	.95	**−0.63**	**(0.27)**	**.021**
Vitamin C	+0.02	(0.15)	.84	+0.03	(0.15)	.86	−0.00	(0.01)	.91	+0.03	(0.15)	.86
Vitamin E	−0.30	(0.15)	.05	−0.29	(0.15)	.06	+0.04	(0.02)	.06	−0.25	(0.15)	.10
Animal fluency												
Total carotenoids	+0.04	(0.16)	.78	+0.04	(0.16)	.81	+0.03	(0.02)	.12	+0.07	(0.16)	.65
Vitamin A	+0.44	(0.30)	.13	+0.45	(0.30)	.13	−0.00	(0.02)	.95	+0.45	(0.30)	.13
Vitamin C	−0.00	(0.16)	.99	−0.00	(0.16)	1.00	−0.00	(0.02)	.91	+0.00	(0.16)	1.00
Vitamin E	**+0.57**	**(0.16)**	**.001**	**+0.57**	**(0.16)**	**.001**	−0.05	(0.03)	.05	**+0.52**	**(0.17)**	**.002**
Card Rotation												
Total carotenoids	**−1.15**	**(0.53)**	**.031**	**−1.15**	**(0.53)**	**.031**	+0.06	(0.05)	.21	**−1.09**	**(0.53)**	**.042**
Vitamin A	+0.94	(0.99)	.34	+0.95	(0.99)	.33	−0.00	(0.04)	.95	+0.95	(0.99)	.34
Vitamin C	+0.19	(0.53)	.71	+0.19	(0.53)	.71	+0.00	(0.04)	.91	+0.20	(0.53)	.71
Vitamin E	+1.08	(0.55)	.05	+1.07	(0.55)	.05	−0.11	(0.07)	.10	+0.96	(0.55)	.08

Values in bold indicate the significant main effects and interaction terms prior to correction for multiple testing.

CES-D = Center for Epidemiologic Studies Depression Scale; SD = standard deviation; HANDLS = Healthy Aging in Neighborhoods of Diversity across the Life Span; CVLT = California Verbal Learning Task; DFR = Delayed Free Recall; BVRT = Benton Visual Retention Task; CDE = controlled direct effect; NDE = natural direct effect; NIE = natural indirect effect; MTE = marginal total effect; SEE = standard error of the estimate; OLS = ordinary least square; WRAT = Wide Range Achievement Test.

[a] 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 1000 kcal, namely, vitamin B_6, vitamin B_{12}, folate, n-3 highly unsaturated fatty acids. CES-D score was entered as potential mediator alternatively for each antioxidant exposure, whereas 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, and 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.

also tended to exceed the tolerable upper intake level for vitamins A and C compared with nonusers (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.

Source of Funding and Conflicts of Interest: This study was entirely supported by the National Institute on Aging, Intramural Research Program (NIA/NIH/IRP). The authors declare no conflict of interest.

REFERENCES

1. Lobo A, Launer LJ, Fratiglioni L, Andersen K, Di Carlo A, Breteler MM, Copeland JR, Dartigues JF, Jagger C, Martinez-Lage J, Soininen H, Hofman A. Prevalence of dementia and major subtypes in Europe: a collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology 2000;54:S4–9.
2. Hendrie HC. Epidemiology of dementia and Alzheimer's disease. Am J Geriatr Psychiatry 1998;6:S3–18.
3. 2008 Alzheimer's disease facts and figures. Alzheimers Dement 2008; 4:110–33.
4. 2009 Alzheimer's disease facts and figures. Alzheimers Dement 2009; 5:234–70.
5. Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, Hall K, Hasegawa K, Hendrie H, Huang Y, Jorm A, Mathers C, Menezes PR, Rimmer E, Scazufca M. Global prevalence of dementia: a Delphi consensus study. Lancet 2005;366:2112–7.
6. Carney JM, Starke-Reed PE, Oliver CN, Landum RW, Cheng MS, Wu JF, Floyd RA. Reversal of age-related increase in brain protein oxidation, decrease in enzyme activity, and loss in temporal and spatial memory by chronic administration of the spin-trapping compound *N*-tert-butyl-alpha-phenylnitrone. Proc Natl Acad Sci U S A 1991;88:3633–6.
7. Wang J, Markesbery WR, Lovell MA. Increased oxidative damage in nuclear and mitochondrial DNA in mild cognitive impairment. J Neurochem 2006;96:825–32.
8. Mao G, Pan X, Zhu BB, Zhang Y, Yuan F, Huang J, Lovell MA, Lee MP, Markesbery WR, Li GM, Gu L. Identification and characterization of OGG1 mutations in patients with Alzheimer's disease. Nucleic Acids Res 2007;35:2759–66.
9. Jacob KD, Noren Hooten N, Tadokoro T, Lohani A, Barnes J, Evans MK. Alzheimer's disease-associated polymorphisms in human OGG1 alter catalytic activity and sensitize cells to DNA damage. Free Radic Biol Med 2013;63:115–25.
10. Behl C. Amyloid beta-protein toxicity and oxidative stress in Alzheimer's disease. Cell Tissue Res 1997;290:471–80.
11. Christen Y. Oxidative stress and Alzheimer disease. Am J Clin Nutr 2000;71:621S–9.
12. Grundman M. Vitamin E and Alzheimer disease: the basis for additional clinical trials. Am J Clin Nutr 2000;71:630S–6.
13. Ekinci FJ, Linsley MD, Shea TB. Beta-amyloid–induced calcium influx induces apoptosis in culture by oxidative stress rather than tau phosphorylation. Brain Res Mol Brain Res 2000;76:389–95.
14. Carty JL, Bevan R, Waller H, Mistry N, Cooke M, Lunec J, Griffiths HR. The effects of vitamin C supplementation on protein oxidation in healthy volunteers. Biochem Biophys Res Commun 2000;273:729–35.
15. Brennan LA, Morris GM, Wasson GR, Hannigan BM, Barnett YA. The effect of vitamin C or vitamin E supplementation on basal and H_2O_2-induced DNA damage in human lymphocytes. Br J Nutr 2000;84: 195–202.
16. Jama JW, Launer LJ, Witteman JC, den Breeijen JH, Breteler MM, Grobbee DE, Hofman A. Dietary antioxidants and cognitive function in a population-based sample of older persons. The Rotterdam Study. Am J Epidemiol 1996;144:275–80.
17. Kalmijn S, Feskens EJ, Launer LJ, Kromhout D. Polyunsaturated fatty acids, antioxidants, and cognitive function in very old men. Am J Epidemiol 1997;145:33–41.
18. Ortega RM, Requejo AM, Andres P, Lopez-Sobaler AM, Quintas ME, Redondo MR, Navia B, Rivas T. Dietary intake and cognitive function in a group of elderly people. Am J Clin Nutr 1997;66:803–9.
19. Lee L, Kang SA, Lee HO, Lee BH, Park JS, Kim JH, Jung IK, Park YJ, Lee JE. Relationships between dietary intake and cognitive function level in Korean elderly people. Public Health 2001;115:133–8.
20. Wengreen HJ, Munger RG, Corcoran CD, Zandi P, Hayden KM, Fotuhi M, Skoog I, Norton MC, Tschanz J, Breitner JC, Welsh-Bohmer KA. Antioxidant intake and cognitive function of elderly men and women: the Cache County Study. J Nutr Health Aging 2007;11:230–7.
21. Commenges D, Scotet V, Renaud S, Jacqmin-Gadda H, Barberger-Gateau P, Dartigues JF. Intake of flavonoids and risk of dementia. Eur J Epidemiol 2000;16:357–63.
22. Engelhart MJ, Geerlings MI, Ruitenberg A, van Swieten JC, Hofman A, Witteman JC, Breteler MM. Dietary intake of antioxidants and risk of Alzheimer disease. JAMA 2002;287:3223–9.
23. Laurin D, Masaki KH, Foley DJ, White LR, Launer LJ. Midlife dietary intake of antioxidants and risk of late-life incident dementia: the Honolulu-Asia Aging Study. Am J Epidemiol 2004;159:959–67.
24. Luchsinger JA, Tang MX, Shea S, Mayeux R. Antioxidant vitamin intake and risk of Alzheimer disease. Arch Neurol 2003;60:203–8.
25. Oishi J, Doi H, Kawakami N. Nutrition and depressive symptoms in community-dwelling elderly persons in Japan. Acta Med Okayama 2009; 63:9–17.
26. Owen AJ, Batterham MJ, Probst YC, Grenyer BF, Tapsell LC. Low plasma vitamin E levels in major depression: diet or disease? Eur J Clin Nutr 2005;59:304–6.
27. Niti M, Yap KB, Kua EH, Ng TP. APOE-epsilon4, depressive symptoms, and cognitive decline in Chinese older adults: Singapore Longitudinal Aging Studies. J Gerontol A Biol Sci Med Sci 2009;64:306–11.
28. Murphy M, O'Leary E. Depression, cognitive reserve and memory performance in older adults. Int J Geriatr Psychiatry 2009; 25:665–71.
29. Panza F, D'Introno A, Colacicco AM, Capurso C, Del Parigi A, Caselli RJ, Todarello O, Pellicani V, Santamato A, Scapicchio P, Maggi S, Scafato E, Gandin C, Capurso A, Solfrizzi V. Depressive symptoms, vascular risk factors and mild cognitive impairment. The Italian longitudinal study on aging. Dement Geriatr Cogn Disord 2008;25:336–46.
30. Dotson VM, Beydoun MA, Zonderman AB. Recurrent depressive symptoms and the incidence of dementia and mild cognitive impairment. Neurology 2010;75:27–34.
31. Kesse-Guyot K-GE, Fezeu L, Jeandel C, Ferry M, Andreeva V, Amieva H, Hercberg S, Galan P. French adults' cognitive performance after daily supplementation with antioxidant vitamins and minerals at nutritional doses: a post hoc analysis of the Supplementation in Vitamins and Mineral Antioxidants (SU.VI.MAX) trial. Am J Clin Nutr 2011;94:892–9.
32. La Rue A, Koehler KM, Wayne SJ, Chiulli SJ, Haaland KY, Garry PJ. Nutritional status and cognitive functioning in a normally aging sample: a 6-y reassessment. Am J Clin Nutr 1997;65:20–9.
33. Goodwin JS, Goodwin JM, Garry PJ. Association between nutritional status and cognitive functioning in a healthy elderly population. JAMA 1983;249:2917–21.
34. Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Aggarwal N, Wilson RS, Scherr PA. Dietary intake of antioxidant nutrients and the risk of incident Alzheimer disease in a biracial community study. JAMA 2002;287:3230–7.
35. Morris MC, Evans DA, Bienias JL, Tangney CC, Wilson RS. Vitamin E and cognitive decline in older persons. Arch Neurol 2002;59:1125–32.
36. Sato R, Helzlsouer KJ, Comstock GW, Hoffman SC, Norkus EP, Fried LP. A cross-sectional study of vitamin C and cognitive function in older adults: the differential effects of gender. J Nutr Health Aging 2006; 10:37–44.
37. IOM. Dietary Reference Intakes. The Essential Guide to Nutrient Requirements. Washington, DC: National Academy of Science; 2006.
38. Guenther PM, Reedy J, Krebs-Smith SM. Development of the Healthy Eating Index–2005. J Am Diet Assoc 2008;108:1896–901.
39. U.S. Department of Agriculture (USDA). Healthy Eating Index 2005. Available at: http://www.cnpp.usda.gov/Publications/HEI/healthyeatingindex2005factsheet.pdf. vol. 2007: Center for Nutrition Policy and Promotion2005.
40. McCullough ML, Feskanich D, Rimm EB, Giovannucci EL, Ascherio A, Variyam JN, Spiegelman D, Stampfer MJ, Willett WC. Adherence to the dietary guidelines for Americans and risk of major chronic disease in men. Am J Clin Nutr 2000;72:1223–31.
41. Evans MK, Lepkowski JM, Powe NR, LaVeist T, Kuczmarski MF, Zonderman AB. Healthy aging in neighborhoods of diversity across the life span (HANDLS): overcoming barriers to implementing a longitudinal, epidemiologic, urban study of health, race, and socioeconomic status. Ethn Dis 2010;20:267–75.
42. Conway JM, Ingwersen LA, Moshfegh AJ. Accuracy of dietary recall using the USDA five-step multiple-pass method in men: an observational validation study. J Am Diet Assoc 2004;104:595–603.
43. Conway JM, Ingwersen LA, Vinyard BT, Moshfegh AJ. Effectiveness of the US Department of Agriculture 5-step multiple-pass method in assessing food intake in obese and nonobese women. Am J Clin Nutr 2003;77:1171–8.
44. Moshfegh AJ, Rhodes DG, Baer DJ, Murayi T, Clemens JC, Rumpler WV, Paul DR, Sebastian RS, Kuczynski KJ, Ingwersen LA, Staples RC, Cleveland LE. The US Department of Agriculture Automated Multiple-Pass Method reduces bias in the collection of energy intakes. Am J Clin Nutr 2008;88:324–32.
45. United States Department of Agriculture (USDA), Agriculture Research Service. Database for Analyzing Dietary Sources of Nutrients Using USDA Survey Food Codes version 3.0. Available at: http://www.ars.usda.gov/Services/docs.htm?docid=17031. Accessed February 2008. USDA2008.

46. Radloff L. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1977;1:385–401.
47. Nguyen HT, Kitner-Triolo M, Evans MK, Zonderman AB. Factorial invariance of the CES-D in low socioeconomic status African Americans compared with a nationally representative sample. Psychiatry Res 2004;126:177–87.
48. Wilkinson GS. Wide Range Achievement Test–Revision 3. Wilmington, DE: Jastak Association; 1993.
49. Sanchez-Villegas A, Doreste J, Schlatter J, Pla J, Bes-Rastrollo M, Martinez-Gonzalez MA. Association between folate, vitamin B(6) and vitamin B(12) intake and depression in the SUN cohort study. J Hum Nutr Diet 2009;22:122–33.
50. Morris DW, Trivedi MH, Rush AJ. Folate and unipolar depression. J Altern Complement Med 2008;14:277–85.
51. Scott TM, Tucker KL, Bhadelia A, Benjamin B, Patz S, Bhadelia R, Liebson E, Price LL, Griffith J, Rosenberg I, Folstein MF. Homocysteine and B vitamins relate to brain volume and white-matter changes in geriatric patients with psychiatric disorders. Am J Geriatr Psychiatry 2004;12:631–8.
52. D'Anci KE, Rosenberg IH. Folate and brain function in the elderly. Curr Opin Clin Nutr Metab Care 2004;7:659–64.
53. Tolmunen T, Hintikka J, Ruusunen A, Voutilainen S, Tanskanen A, Valkonen VP, Viinamaki H, Kaplan GA, Salonen JT. Dietary folate and the risk of depression in Finnish middle-aged men. A prospective follow-up study. Psychother Psychosom 2004;73:334–9.
54. Bottiglieri T. Folate, vitamin B_{12}, and neuropsychiatric disorders. Nutr Rev 1996;54:382–90.
55. Kivela SL, Pahkala K, Eronen A. Depression in the aged: relation to folate and vitamins C and B_{12}. Biol Psychiatry 1989;26:210–3.
56. Levitt AJ, Joffe RT. Folate, B_{12}, and life course of depressive illness. Biol Psychiatry 1989;25:867–72.
57. Murakami K, Mizoue T, Sasaki S, Ohta M, Sato M, Matsushita Y, Mishima N. Dietary intake of folate, other B vitamins, and omega-3 polyunsaturated fatty acids in relation to depressive symptoms in Japanese adults. Nutrition 2008;24:140–7.
58. Kamphuis MH, Geerlings MI, Grobbee DE, Kromhout D. Dietary intake of B(6-9-12) vitamins, serum homocysteine levels and their association with depressive symptoms: the Zutphen Elderly Study. Eur J Clin Nutr 2008;62:939–45.
59. Cherubini A, Martin A, Andres-Lacueva C, Di Iorio A, Lamponi M, Mecocci P, Bartali B, Corsi A, Senin U, Ferrucci L. Vitamin E levels, cognitive impairment and dementia in older persons: the InCHIANTI study. Neurobiol Aging 2005;26:987–94.
60. Astorg P, Couthouis A, Bertrais S, Arnault N, Meneton P, Guesnet P, Alessandri JM, Galan P, Hercberg S. Association of fish and long-chain n-3 polyunsaturated fatty acid intakes with the occurrence of depressive episodes in middle-aged French men and women. Prostaglandins Leukot Essent Fatty Acids 2008;78:171–82.
61. Sanchez-Villegas A, Henriquez P, Figueiras A, Ortuno F, Lahortiga F, Martinez-Gonzalez MA. Long chain omega-3 fatty acids intake, fish consumption and mental disorders in the SUN cohort study. Eur J Nutr 2007;46:337–46.
62. Strom M, Mortensen EL, Halldorsson TI, Thorsdottir I, Olsen SF. Fish and long-chain n-3 polyunsaturated fatty acid intakes during pregnancy and risk of postpartum depression: a prospective study based on a large national birth cohort. Am J Clin Nutr 2009;90:149–55.
63. Sublette ME, Hibbeln JR, Galfalvy H, Oquendo MA, Mann JJ. Omega-3 polyunsaturated essential fatty acid status as a predictor of future suicide risk. Am J Psychiatry 2006;163:1100–2.
64. Conquer JA, Tierney MC, Zecevic J, Bettger WJ, Fisher RH. Fatty acid analysis of blood plasma of patients with Alzheimer's disease, other types of dementia, and cognitive impairment. Lipids 2000;35:1305–12.
65. Tully AM, Roche HM, Doyle R, Fallon C, Bruce I, Lawlor B, Coakley D, Gibney MJ. Low serum cholesteryl ester-docosahexaenoic acid levels in Alzheimer's disease: a case-control study. Br J Nutr 2003;89:483–9.
66. Schaefer EJ, Bongard V, Beiser AS, Lamon-Fava S, Robins SJ, Au R, Tucker KL, Kyle DJ, Wilson PW, Wolf PA. Plasma phosphatidylcholine docosahexaenoic acid content and risk of dementia and Alzheimer disease: the Framingham Heart Study. Arch Neurol 2006; 63:1545–50.
67. Beydoun MA, Kaufman JS, Satia JA, Rosamond W, Folsom AR. Plasma n-3 fatty acids and risk of cognitive decline among older adults: The Atherosclerosis Risk in Communities (ARIC) study. Am J Clin Nutr 2007;85:1103–11.
68. Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Wilson RS, Aggarwal N, Schneider J. Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. Arch Neurol 2003; 60:940–6.
69. Kalmijn S, van Boxtel MP, Ocke M, Verschuren WM, Kromhout D, Launer LJ. Dietary intake of fatty acids and fish in relation to cognitive performance at middle age. Neurology 2004;62:275–80.
70. Willet WC. Nutritional Epidemiology. 2nd ed. New York: Oxford University Press; 1998.
71. STATA. Statistics/Data Analysis: Release 13.0. Texas: Stata Corporation; 2013.
72. Ditlevsen S, Christensen U, Lynch J, Damsgaard MT, Keiding N. The mediation proportion: a structural equation approach for estimating the proportion of exposure effect on outcome explained by an intermediate variable. Epidemiology 2005;16:114–20.
73. Beydoun MA, Wang Y. How do socio-economic status, perceived economic barriers and nutritional benefits affect quality of dietary intake among US adults? Eur J Clin Nutr 2008;62:303–13.
74. MacKinnon DP, Dwyer JH. Estimating mediated effects in prevention studies. Eval Rev 1993;17:144–58.
75. Beydoun MA, Fanelli Kuczmarski MT, Beydoun HA, Shroff MR, Mason MA, Evans MK, Zonderman AB. The sex-specific role of plasma folate in mediating the association of dietary quality with depressive symptoms. J Nutr 2010;140:338–47.
76. Valeri L, Vanderweele TJ. Mediation analysis allowing for exposure-mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. Psychol Methods 2013;18:137–50.
77. VanderWeele TJ. Policy-relevant proportions for direct effects. Epidemiology 2013;24:175–6.
78. Heckman JJ. Sample selection bias as a specification error. Econometrica 1979;47:153–61.
79. Beydoun MA, Kuczmarski MT, Mason MA, Ling SM, Evans MK, Zonderman AB. Role of depressive symptoms in explaining socioeconomic status disparities in dietary quality and central adiposity among US adults: a structural equation modeling approach. Am J Clin Nutr 2009; 90:1084–95.
80. Hochberg Y, Tamhane AC. Multiple Comparison Procedures. New York: Wiley; 1987.
81. Cook-Mills JM. Isoforms of vitamin E differentially regulate PKC and inflammation: a review. J Clin Cell Immun 2013;4.
82. Morris MC, Evans DA, Tangney CC, Bienias JL, Wilson RS, Aggarwal NT, Scherr PA. Relation of the tocopherol forms to incident Alzheimer disease and to cognitive change. Am J Clin Nutr 2005;81:508–14.
83. (USDA) USDoA. Dietary Guidance: Dietary Reference Intakes. Food and Nutrition Information Center; 2014.
84. Paleologos M, Cumming RG, Lazarus R. Cohort study of vitamin C intake and cognitive impairment. Am J Epidemiol 1998;148:45–50.
85. Peacock JM, Folsom AR, Knopman DS, Mosley TH, Goff DC Jr., Szklo M. Dietary antioxidant intake and cognitive performance in middle-aged adults. The Atherosclerosis Risk in Communities (ARIC) Study investigators. Public Health Nutr 2000;3:337–43.
86. McNeill G, Jia X, Whalley LJ, Fox HC, Corley J, Gow AJ, Brett CE, Starr JM, Deary IJ. Antioxidant and B vitamin intake in relation to cognitive function in later life in the Lothian Birth Cohort 1936. Eur J Clin Nutr 2011;65:619–26.
87. Devore EE, Kang JH, Stampfer MJ, Grodstein F. Total antioxidant capacity of diet in relation to cognitive function and decline. Am J Clin Nutr 2010;92:1157–64.
88. Morris MC, Beckett LA, Scherr PA, Hebert LE, Bennett DA, Field TS, Evans DA. Vitamin E and vitamin C supplement use and risk of incident Alzheimer disease. Alzheimer Dis Assoc Disord 1998;12:121–6.
89. Zandi PP, Anthony JC, Khachaturian AS, Stone SV, Gustafson D, Tschanz JT, Norton MC, Welsh-Bohmer KA, Breitner JC. Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: the Cache County Study. Arch Neurol 2004;61:82–8.
90. Maxwell CJ, Hicks MS, Hogan DB, Basran J, Ebly EM. Supplemental use of antioxidant vitamins and subsequent risk of cognitive decline and dementia. Dement Geriatr Cogn Disord 2005;20:45–51.
91. Fotuhi M, Zandi PP, Hayden KM, Khachaturian AS, Szekely CA, Wengreen H, Munger RG, Norton MC, Tschanz JT, Lyketsos CG, Breitner JC, Welsh-Bohmer K. Better cognitive performance in elderly taking antioxidant vitamins E and C supplements in combination with nonsteroidal anti-inflammatory drugs: the Cache County Study. Alzheimers Dement 2008;4:223–7.

92. Grodstein F, Chen J, Willett WC. High-dose antioxidant supplements and cognitive function in community-dwelling elderly women. Am J Clin Nutr 2003;77:975–84.
93. Gray SL, Hanlon JT, Landerman LR, Artz M, Schmader KE, Fillenbaum GG. Is antioxidant use protective of cognitive function in the community-dwelling elderly? Am J Geriatr Pharmacother 2003;1:3–10.
94. Masaki KH, Losonczy KG, Izmirlian G, Foley DJ, Ross GW, Petrovitch H, Havlik R, White LR. Association of vitamin E and C supplement use with cognitive function and dementia in elderly men. Neurology 2000;54:1265–72.
95. Mendelsohn AB, Belle SH, Stoehr GP, Ganguli M. Use of antioxidant supplements and its association with cognitive function in a rural elderly cohort: the MoVIES Project. Monongahela Valley Independent Elders Survey. Am J Epidemiol 1998;148:38–44.
96. Fillenbaum GG, Kuchibhatla MN, Hanlon JT, Artz MB, Pieper CF, Schmader KE, Dysken MW, Gray SL. Dementia and Alzheimer's disease in community-dwelling elders taking vitamin C and/or vitamin E. Ann Pharmacother 2005;39:2009–14.
97. Gray SL, Anderson ML, Crane PK, Breitner JC, McCormick W, Bowen JD, Teri L, Larson E. Antioxidant vitamin supplement use and risk of dementia or Alzheimer's disease in older adults. J Am Geriatr Soc 2008;56:291–5.
98. Alzheimer's Disease Cooperative Study G. Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med 2005;352:2379–88.
99. Bailey RL, Gahche JJ, Lentino CV, Dwyer JT, Engel JS, Thomas PR, Betz JM, Sempos CT, Picciano MF. Dietary supplement use in the United States, 2003–2006. J Nutr 2011;141:261–6.
100. Bailey RL, Fulgoni VL 3rd, Keast DR, Dwyer JT. Examination of vitamin intakes among US adults by dietary supplement use. J Acad Nutr Diet 2012;112:657–63 e4.