ONLINE SUPPORTING MATERIALS

Association of serum antioxidant vitamins and carotenoids with incident Alzheimer's Disease and all-cause dementia among US adults By May A. Beydoun et. al.

eMETHODS 1: CMS-Medicare and NDI linkage

Administered by CMS, Medicare is the primary health insurance program for people ≥65 y, people <65y with specific disabilities, and all individuals with End-Stage Renal Disease (ESRD).[1] Medicare enrollment and fee-for-service (FFS) claims data were linked to NHANES III participants by matching on Social Security Number (SSN), date of birth (month, day, year), and sex. CMS performed linkage on NHANES participants matching them with corresponding Medicare FFS annual claims data, and with Medicare Part D prescriptions since 2006.[1] Annual files are available for Part A (inpatient, outpatient, Skilled Nursing Facility [SNF], hospice, or Home Health Agency [HHA]) and Part B (Carrier, Durable Medical Equipment).[1] These files were used to identify the first report of dementia and AD diagnoses for NHANES participants. Methods published elsewhere were used to estimate earliest occurrence of the two incident outcomes of interest 1991 through 1998.[1] Restricted mortality data linked to NHANES III through the National Death Index was used to examine AD mortality risk through 2013 in all analyses. [2] While AD was diagnosed using ICD-9 code 331.0 (any DX on the claim) from inpatient, SNF, HHA, Health Options Program [HOP] or Carrier claims during a 3-year period, all-cause dementia was defined with or more of the following diagnostic codes : 331.0, 331.1, 331.11, 331.19, 331.2, 331.7, 290.0, 290.10, 290.11, 290.12, 290.13, 290.20, 290.21, 290.3, 290.40, 290.41, 290.42, 290.43, 294.0, 294.1, 294.10, 294.11, 294.8 and 797.

eMETHODS 2: COVARIATES

Socio-demographic factors and socio-economic status (SES)

Key socio-demographic covariates included age (y), sex, race (Non-Hispanic white (NHW), Non-Hispanic black (NHB), Mexican-American (MA), other ethnicity (OTHER)); marital status (Never married, Married, Divorced, Widowed, Other), household size and urban-rural residence (Urban, Rural). Among SES factors, educational level (years completed); poverty income ratio (PIR) were selected.

Lifestyle and social support factors

Lifestyle factors include "substance abuse" operationalized as "alcohol consumption (g/d)" and drug use (Ever, Never); "nutritional factors" as 1995-Healthy Eating Index (1995-HEI) ranging from 0-100,[3] and mean adequacy ratio score (MAR), [4-6] (**Tables II.1** and **II.2**); "Physical activity" measured with 3 items: (1) "Compare activity for past month to past year (less, same, more), (2): "Active compared with men/women your age" (less, same, more), and (3): "Active now compared with self, 10 years ago" (less, same, more); "Smoking" with two items: (1): "number of cigarettes smoked per day" (0 among non-smokers); (2): "years smoked cigarettes" (0 among non-smokers), drug and alcohol use. Five items were used for social support: "In a typical week, how many times do you" … (1) talk on the telephone with family, friends, or neighbors?", (2) "get together with friends or relatives? (# per year)", (3) "visit with any of your other neighbors, either in their homes or in your own? (# per year)", (4) "attend church or religious services? (# per year)", (5) "attend meetings of the clubs or organizations (# per year)".

Nutritional biomarkers and health-related factors

Several nutritional biomarkers were included among potential confounders, namely serum 25-hydroxyvitamin D [25(OH)] and folate.

The "Health" construct was operationalized with self-rated health, co-morbidity index and an allostatic load (AL) score. Self-rated their health as: "Excellent" (referent), "Very good", "Good", "Fair" or "Poor." The co-morbidity index is an unweighted sum of 14 binary self-reported conditions, including "arthritis", "congestive heart failure", "stroke", "asthma", "chronic bronchitis", "emphysema", "hay fever", "cataracts", "goiter", "thyroid disease", "lupus", "gout", "skin cancer", and "other cancer". The allostatic load (AL) total score (0-9) consists of 9 items which are described in details elsewhere.[7] AL total score sums up cardiovascular (systolic and diastolic blood pressure, pulse rate), metabolic (total cholesterol, HDL-cholesterol, glycosylated Hb, sex-specific waist-to-hip ratio) and inflammatory (albumin and C-reactive protein (CRP)) risk indicators. Clinical criteria are summarized in **Table II.3**. Weight status was measured using body mass index (weight/squared-height, $kg.m^{-2}$) categorized as: <18.5 (underweight), 18.5-24.9 (normal weight), 25-29.9 (overweight), ≥30 as obese.

Total cholesterol (mg/dl), HDL-cholesterol (mg/dl), CRP (mg/dl), albumin (g/dl) and glycosylated hemoglobin (%) were measured by laboratories using reference analytical methods (See Laboratory Procedures for NHANES III).[8] Using standard protocols, waist-to-hip ratio, radial pulse (beats/min), and systolic and diastolic blood pressure (mmHg) were measured by trained examiners. Blood pressure was determined using a mercury sphygmomanometer.[8] The arithmetic mean of three systolic and diastolic pressures was used in the analysis.

Table II. 1. 1995-HEI

	Criteria[1]		
Components	<50y	≥50y	Score
Grains	9.1 servings/d	7.4 servings/d	10; 1 point less for each 10% less than intake required for full score Range: 0-10
Vegetables	4.2 servings/d	3.5 servings/d	Same as above
Fruit	3.2 servings/d	2.5 servings/d	Same as above
Milk	2.0 servings/d	2.0 servings/d	Same as above
Meat	2.4 servings/d	2.2 servings/d	Same as above
Total fat	≤30% energy	≤30% energy	10

	31-44% of energy	31-44% of energy	5
	≥45% of energy	≥45% of energy	0
Saturated fat	≤10% of energy	≤10% of energy	10
	11-14% of energy	11-14% of energy	5
	≥15% of energy	≥15% of energy	0
Cholesterol	<300 mg	<300 mg	10
	301-449 mg	301-449 mg	5
	≥450 mg	≥450 mg	0
Sodium	≤2,400 mg	≤2,400 mg	10; 1 point less for each 10% less intake required for full score
Variety	Top 10% intake of sum of unique foods	Top 10% intake of sum of unique foods	Same as above

[1] Based on 2,200 kcal for the <50 y category and 1,900 kcal for the ≥51 y category.

Source: [3, 9]

MAR scores

RDAs of 16 vitamins and minerals were used to determine the nutrient adequacy ratio (NAR), using the following formula: NAR = [Subject's daily intake of nutrient] / [RDA of nutrient]. An adjustment of an additional 35 mg Vitamin C must be applied to the RDA for participants who were current smokers.

The NAR of each nutrient is converted to a percent, and percentages greater than 100 are truncated to 100. The total quality of the diet is then calculated from the NARs to form a mean adequacy ratio (MAR) using the following formula: MAR = [Sum of all 16 nutrient NARs]/16. The NAR and MAR for each day were calculated and then averaged over the two days.

Table II. 2. Recommended Dietary Allowance (RDA) Values for Nutrients accessed from USDA DRI Tables to MAR Score

Nutrient	**Men 19-30yrs**	**Men 31-50yrs**	**Men 51-70 yrs**	**Women 19-30yrs**	**Women 31-50yrs**	**Women 51-70 yrs**
Vitamin A	900 ug/day	900 ug/day	900 ug/day	700 ug/day	700 ug/day	700 ug/day
Vitamin C	90 mg/day	90 mg/day	90 mg/day	75 mg/day	75 mg/day	75 mg/day
Vitamin C for smokers	125 mg/day	125 mg/day	125 mg/day	110 mg/day	110 mg/day	110 mg/day
Vitamin D	15 ug/day	15 ug/day	15 ug/day	15 ug/day	15 ug/day	15 ug/day
Vitamin E	15 mg/day	15 mg/day	15 mg/day	15 mg/day	15 mg/day	15 mg/day
Vitamin B6	1.3 mg/day	1.3 mg/day	1.7 mg/day	1.3 mg/day	1.3 mg/day	1.5 mg/day
Vitamin B12	2.4 ug/day	2.4 ug/day	2.4 ug/day	2.4 ug/day	2.4 ug/day	2.4 ug/day
Thiamin	1.2 mg/day	1.2 mg/day	1.2 mg/day	1.1 mg/day	1.1 mg/day	1.1 mg/day
Riboflavin	1.3 mg/ day	1.3 mg/ day	1.3 mg/day	1.1 mg/day	1.1 mg/day	1.1 mg/day
Niacin	16 mg day	16 mg day	16 mg/day	14 mg/day	14 mg/day	14 mg/day

Folate	400 ug/day	400 ug/day	400 ug/day	400 ug/day	400 ug/day	400 ug/day
Iron	8 mg/day	8 mg/day	8 mg/day	18 mg/day	18 mg/day	8 mg/day
Copper	900 ug/day	900 ug/day	900 ug/day	900 ug/day	900 ug/day	900 ug/day
Zinc	11 mg/day	11 mg/day	11 mg/day	8 mg/day	8 mg/day	8 mg/day
Calcium	1,000 mg/day	1,000 mg/day	1,000 mg/day	1,000 mg/day	1,000 mg/day	1,200 mg/day
Magnesium	400 mg/day	420 mg/day	420 mg/day	310 mg/day	320 mg/day	320 mg/day
Phosphorous	700 mg/day	700 mg/day	700 mg/day	700 mg/day	700 mg/day	700 mg/day

ug= micrograms; mg= milligrams; g=grams

http://www.nal.usda.gov/fnic/DRI/DRI_Tables/RDA_AI_vitamins_elements.pdf

http://ods.od.nih.gov/factsheets/VitaminC-HealthProfessional/

Allostatic Load (AL)

A total AL score was computed using a method described in a previous study.[7] AL total score sums up cardiovascular (systolic and diastolic blood pressure, pulse rate), metabolic (total cholesterol, HDLcholesterol, glycosylated Hb, sex-specific waist-to-hip ratio) and inflammatory (albumin and C-reactive protein (CRP)) risk indicators. Clinical criteria summarized in Table I.2 were used to obtain risk indicators which were summed with equal weighting to compute total AL score (range: 0-9).

Total cholesterol (mg/dl), HDL-cholesterol (mg/dl), CRP (mg/dl), albumin (g/dl) and glycosylated hemoglobin (%) were measured by contract laboratories using reference analytical methods (See Laboratory Procedures for NHANES III).[8] Using standard protocols, waist-to-hip ratio, radial pulse (beats/min), and systolic and diastolic blood pressure (mmHg) were measured by trained examiners. Specifically, blood pressure was measured using a mercury

sphygmomanometer [8] The arithmetic mean of three systolic and diastolic pressures was used in analysis.

Table II.3 Allostatic load indicator criteria[7]

	High-risk clinical
Albumin (g/dL)	< 3.8 [10]
C-reactive protein (mg/dL)	≥ 0.3 [11]
Waist:Hip Ratio	>0.9 for men; > 0.85 for women [12]
Total cholesterol (mg/dL)	≥240[13]
HDL (mg/dL)	<40[13]
Glycated hemoglobin (%)	≥6.4[14, 15]
Resting heart rate (beat/min)	≥90[16]
Systolic BP	≥140[17]
Diastolic BP	≥90[17]

eRESULTS 1

The selected sample consisted of 7,283 NHANES III participants aged ≥45y at baseline with complete nutritional biomarker data after accounting for CMS-Medicare exclusion. Among this sample, and after ≤26 y of follow-up, 1,913 had incident dementia, of whom 982 were AD. Among the final eligible sample, 3,618 were aged ≥65y at baseline. Of those, 1,383 had incident dementia over the same follow-up period, of whom 702 were AD. Total carotenoid first, second and third tertiles in the final eligible sample (baseline age ≥45y) had mean±SD (μg/dL) and

ranges as follows: T_1:45.0±11.7 (0-61); T_2:76.2±8.7 (62-92); T_3:130±41.8 (93-655). Incidence rates of all-cause dementia within each tertile was as follows for the 45+y baseline age group: T_1: 13.57 per 1,000 Person-Years (P-Y) (95%CI: 12.11-15.25); T_2: 13.05 per 1,000 P-Y (95% CI: 11.67-14.63); T_3: 12.95 per 1,000 P-Y (95%CI: 11.62-14.46). AD incidence rates within that age group and for each tertile of total carotenoids were as follows: T_1: 6.79 per 1,000 P-Y (95%CI: 5.86-7.90); T_2: 6.28 per 1,000 P-Y (95% CI: 5.39-7.35); T_3: 6.35 per 1,000 P-Y (95% CI: 5.51-7.35). This translated into a median survival time difference between T_3 and T_1 free from both AD and all-cause dementia of ~1.8 y. For the 65+ baseline age group, differences in incidence rates between T_3 and T_1 translated into a difference of survival time free from AD of 1.53y; and 1.14y in the case of all-cause dementia.

All-cause dementia and AD and independently associated lifestyle, health-related factors and nutritional biomarkers

In fully adjusted models with only main effects (**Tables 2**, Model 4), a few lifestyle and health-related factors were also shown to be independently associated with dementia risk of all causes and with AD risk, specifically. These associations were in some cases baseline age group-specific. For instance, HEI was generally marginally associated with reduced dementia risk ($p<0.10$) in most models with carotenoids, total and individual, and was significantly associated with reduced AD risk in the older group (65+, Model 4 with total carotenoids, per unit: β±SE: -0.013±0.005, p= 0.018). More notably, one of 3 physical activity covariates ("Compare activity for past month to past year": 0=Less, 1=Same, 2=more; per unit:β±SE: -0.22±0.07, p=0.003; Model 4, with total carotenoids) was inversely associated with dementia risk in the 45+ group. This association was comparable in the 65+ group (per unit:β±SE:-0.22±0.08, p=0.011; Model 4, with total carotenoids). Among health-related factors, the allostatic load was directly but

marginally associated with dementia risk (45+ group) in some models with individual carotenoids, while self-rated poor/fair health was significantly associated with increased dementia risk in most models (poor/fair health vs. Excellent/very good health: β±SE: +0.39±0.10, p<0.001 ; Model 4, with total carotenoids) . More notably, BMI was inversely related to dementia risk in the 65+ group (per unit: β±SE: -0.036±0.010, p=0.001; Model 4, with total carotenoids), with a similar pattern observed between BMI and AD risk in the older group. Furthermore, the total number of cigarettes smoked was associated with increased AD risk (45+, Model 4, total carotenoids, per unit: β±SE: 0.019±0.006, p=0.006), a relationship not detected between smoking and all-cause dementia risk. In contrast, serum folate and 25(OH)D were not associated with all-cause or AD risk in both age groups.

eDISCUSSION 1. BIOLOGICAL MECHANISMS

There are multiple biological pathways through which mitochondrial dysfunction and oxidative stress may influence neurodengeerative processes, including AD. The brains of AD patients have been found to contain lesions that are typically associated with free radical attacks (e.g., damage to DNA, protein oxidation, lipid peroxidation, and advanced glycosylation end products), and metals (e.g., iron, copper, zinc, and aluminum). A number of studies suggest that plant based exogenous antioxidants (e.g., carotenoids, vitamins E and C, Ginkgo biloba extract EGb 761, melatonin, anthocyanins, tretaterpenoids and flavonoids) may reduce the toxicity of Aβ amyloids in the brains of AD patients and animal studies [18-22]. In vitro studies suggest that higher levels of lutein and zeaxanthin in the brain may provide benefit by inhibiting amyloid

plaque and neurofibrillary tangle formation through induction of NF-kb nuclear expression and up-regulation of Nerf-2 expression.[23] Clinical studies suggest a role for lutein and zeaxanthin function broadly in a number of brain regions that are associated with visual perception,cognition, decision-making, and motor coordination.[24] Carotenoids and their retinoid coversion products may possibly exhibit a range of anti-inflammatory, neuroprotective, and cognitive benefits mechanistically linked to mitoprotective properties and be suitable therapeutic targets for AD prevention and treatment.[25] Carotenoids activate the NRF2 pathway and, hence, cellular antioxidant defences to suppress plaque formation, cholinergic transmission, ApoE and ABCA1 expressions, cholesterol content in the gut microbiota and the pro-inflammatory environment of the brain, that contribute to AD pathology [26]. As evidence of this, Subash and colleagues tested a mouse model which featured dietary supplementation derived from date palm fruits and was found to reduce cognitive and behavioral deficits in a transgenic mouse model for AD (amyloid precursor protein [APPsw]/Tg2576) offering neuroprotective effects [27]. In addition to its role as an antioxidant, vitamin E independently functions as an inhibitor of brain protein kinase C activity [28] among other roles which may be attributable to the multiple isoforms of Vitamin E [29] including α-tocopherol which was used to assess vitamin E in the current study. Therefore, plant-based dietary antioxidants may help reduce the risk of AD.

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eTable 1. Study sample characteristics by tertile of serum total carotenoids for sub-sample with complete and valid plasma nutritional biomarker data, NHANES III 1988-1994 [a]

	Overall (45+y at baseline)	**By plasma total carotenoids tertiles (µg/dL) [a]**			
		T_1	**T_2**	**T_3**	***p*** [b]
	(X ± SEM), %	(X ± SEM), %	(X ± SEM), %	(X ± SEM), %	
	(N=7,283)	**(N = 2,469)**	**(N =2,404)**	**(N =2,410)**	
1995-HEI total score	66.67±0.31	62.79±0.41	66.22±0.49	70.76±0.51	<0.001[d]
MAR total score	73.47±0.32	70.60±0.50	74.29±0.47	75.33±0.47	<0.001[d]
Serum folate, ng/mL	8.34±0.21	7.00±0.22	8.15±0.29	9.78±0.32	<0.001[d]
Serum 25-hydroxyvitamin D, ng/mL	28.04±0.26	26.94±0.36	28.07±0.40	29.03±0.34	0.0002[d]
Physical activity *0=Less, 1=Same, 2=more*					
Compare activity for past mo to past yr					0.8488
Less	24.89	24.35	24.99	25.29	
Same	63.30	64.11	61.96	63.89	
More	11.81	11.54	13.06	10.82	
Active compared with men/women your age					<0.001[d]
Less	18.72	25.03	17.78	13.74	
Same	42.07	41.65	44.03	40.49	
More	39.22	33.33	38.19	45.76	
Active now compared with self 10 yrs ago					0.0086[d]
Less	59.89	64.88	58.79	56.31	
Same	30.03	26.94	30.70	32.27	
More	10.08	8.19	10.50	11.42	

Smoking					
# cigarettes/day	7.87±0.24	11.02±0.49	7.85±0.36	4.95±0.30	<0.001[d]
Years smoked cigarettes	8.25±0.28	10.79±0.47	8.14±0.43	5.98±0.35	<0.001[d]
Alcohol consumption (g/d)	6.88±0.48	9.16±0.97	6.27±0.52	5.37±0.82	0.0028[d]
Social support					
(1) In a typical week, how many times do you talk on the telephone with family, friends, or neighbors?	10.19±0.25	9.62±0.36	10.22±0.34	10.71±0.57	0.1322
(2) How often do you get together with friends or relatives; I mean things like going out together or visiting in each other's homes? (per year)	114.89±3.71	119.03±7.16	112.98±3.69	112.93±4.28	0.4148
(3) About how often do you visit with any of your other neighbors, either in their homes or in your own? (per year)	71.87±3.8	72.55±6.69	69.69±4.11	73.42±5.34	0.9076
(4) How often do you attend church or religious services? (per year)	37.48±1.51	30.42±1.91	38.42±2.15	43.14±1.84	<0.001[d]
(5) Altogether, how often do you attend meetings of the clubs or organizations (per year)	14.47±0.75	12.61±1.05	14.56±1.27	16.13±1.27	0.0389[d]
Health-related factors					
Self-rated health					<0.001[d]
Excellent/Very Good	43.05	35.9	41.26	51.53	
Good	33.66	34.43	36.94	29.66	
Fair/Poor	23.29	29.67	21.80	18.81	
Co-morbidity index[c]	1.22±0.03	1.28±0.04	1.22±0.05	1.18±0.04	0.0447[d]
Allostatic load, AL score[c]	2.47±0.05	2.71±0.05	2.41±0.06	2.32±0.06	<0.001[d]
BMI	27.32±0.10	28.42±0.20	27.47±0.14	26.15±0.14	<0.001[d]

Abbreviations: 1995-HEI=Healthy Eating Index 1995; AD=Alzheimer's Disease; AL=Allostatic Load; BMI=Body Mass Index;. NHANES III=Third National Health and Nutrition Examination Survey.

[a]Values are means (X) ±SD for continuous variables and % for categorical variables. The sample selected has complete data on nutritional biomarkers, including carotenoids and vitamins A, C and E. The same visit and approach were applied to other dietary factors, including other antioxidants. Tertiles of total carotenoids were determined using the final analytic sample.

[b] *p*-value from OLS linear regression models with carotenoid tertile as the only covariate for continuous variables, and multinomial logit model with carotenoid tertile as the only covariate for categorical variables, with carotenoid tertile as an ordinal variable.

[c] See Methods section for definitions for AL and the co-morbidity index.

[d] $p<0.05$ upon further adjustment for age, sex, race, and poverty income ratio in multiple linear, logistic and multinomial logit models with carotenoid tertile entered as an ordinal variable.

*$p < 0.05$** $p < 0.01$; *** $p < 0.001$, *t*-test for null hypothesis of no between-tertile differences, taking T_1 as the referent.

eTable 2. Association of serum vitamins A, C and E with incident all-cause and AD dementia (45+ and 65+): Cox proportional hazards models , NHANES III, 1988-1994[a]

	Exposure=Serum antioxidant					
	Vitamin A, z-scores		Vitamin C, z-scores		Vitamin E, z-scores	
	45+	65+	45+	65+	45+	65+
	β±SE[b]	β±SE	β±SE	β±SE	β±SE	β±SE
Overall						
All-cause dementia	(N=7,257)	(N=3,593)	(N=7,257)	(N=3,593)	(N=7,257)	(N=3,593)
Model 1	-0.0035±0.046	-0.002±0.041	-0.122±0.038**	-0.098±0.038*	-0.011±0.035	-0.0014±0.033
Model 2	+0.014±0.045	+0.008±0.041	-0.070±0.035*	-0.074±0.036*	+0.027±0.033	+0.021±0.033
Model 3	+0.025±0.043	+0.011±0.042	-0.035±0.038	-0.049±0.041	+0.039±0.032	+0.027±0.035
Model 4	+0.009±0.043	+0.005±0.043	-0.046±0.044	-0.077±0.051	+0.025±0.037	+0.040±0.041
AD	(N=7,283)	(N=3,618)	(N=7,283)	(N=3,618)	(N=7,283)	(N=3,618)
Model 1	-0.095±0.056	-0.042±0.051	-0.125±0.062*	-0.091±0.063	+0.014±0.053	-0.009±0.051
Model 2	-0.080±0.054	-0.038±0.053	-0.084±0.058	-0.071±0.064	+0.051±0.050	+0.014±0.054
Model 3	-0.053±0.052	-0.028±0.050	-0.029±0.060	-0.038±0.065	+0.074±0.047	+0.028±0.057
Model 4	-0.085±0.053	-0.039±0.047	-0.052±0.068	-0.082±0.075	+0.093±0.049	+0.040±0.057
Bottom tertile of total carotenoids						
All-cause dementia	(N=2,462)	(N=1,204)	(N=2,462)	(N=1,204)	(N=2,462)	(N=1,204)
Model 1	-0.040±0.067	-0.092 ±0.073	-0.099±0.069	-0.071±0.069	-0.081±0.057	-0.013±0.071

Model 2	-0.029± 0.068	-0.101±0.072	-0.056±0.068	-0.071±0.068	-0.041±0.053	-0.016±0.072
Model 3	-0.029±0.067	-0.138±0.084	-0.026±0.067	-0.064±0.076	-0.029±0.051	-0.021±0.073
Model 4	-0.022±0.074	-0.157±0.087	-0.014±0.075	-0.076±0.082	-0.030±.070	+0.016±0.083
AD	(N=2,469)	(N=1,210)	(N=2,469)	(N=1,210)	(N=2,469)	(N=1,210)
Model 1	-0.094±0.087	-0.049±0.089	-0.118±0.137	-0.063±0.119	-0.080±0.088	+0.042±0.109
Model 2	-0.083±0.085	-0.063±0.088	-0.103±0.140	-0.096±0.117	-0.048±0.088	+0.031±0.118
Model 3	-0.119±0.092	-0.142±0.092	-0.051±0.137	-0.099±0.128	-0.039±0.091	+0.020±0.131
Model 4	-0.134±0.086	-0.181±0.092	-0.020±0.156	-0.092±0.132	+0.024±0.097	+0.081±0.128
Middle tertile of total carotenoids						
All-cause dementia	(N=2,397)	(N=1,160)	(N=2,397)	(N=1,160)	(N=2,397)	(N=1,160)
Model 1	-0.029±0.070	+0.010±0.080	-0.127±0.052*	-0.100±0.068	+0.055±0.062	+0.024±0.066
Model 2	-0.003±0.064	+0.039±0.069	-0.093±0.054	-0.089±0.057	+0.081±0.058	+0.041±0.060
Model 3	0.010±0.062	+0.045±0.066	-0.077±0.054	-0.076±0.065	+0.090±0.055	+0.032±0.063
Model 4	-0.046±0.069	+0.031±0.066	-0.065±0.060	-0.054±0.069	+0.084±0.064	+0.065±0.075
AD	(N= 2,404)	(N=1,167)	(N= 2,404)	(N=1,167)	(N= 2,404)	(N=1,167)
Model 1	-0.156±0.141	-0.070±0.117	-0.161±0.074*	-0.100±0.090	+0.115±0.100	+0.027±0.082
Model 2	-0.121±0.122	-0.046±0.107	-0.113±0.074	-0.065±0.088	+0.151±0.100	+0.056±0.081
Model 3	-0.096±0.121	-0.055±0.114	-0.063±0.066	-0.031±0.089	+0.172±0.097	+0.069±0.094
Model 4	-0.209±0.141	-0.096±0.128	-0.063±0.079	-0.027±0.102	+0.190±0.100	+0.102±0.104
Top tertile of total carotenoids	(N=2,398)	(N=1,229)	(N=2,398)	(N=1,229)	(N=2,398)	(N=1,229)

All-cause dementia						
Model 1	+0.097±0.072	+0.083±0.059	-0.073±0.063	-0.093±0.063	+0.037±0.057	+0.023±0.056
Model 2	+0.097±0.070	+0.087±0.060	-0.005±0.057	-0.044±0.059	+0.067±0.055	+0.057±0.057
Model 3	+0.104±0.073	+0.101±0.060 [c]	+0.023±0.053	-0.002±0.061	+0.070±0.052	+0.073±0.057
Model 4	+0.094±0.069	+0.097±0.068	-0.032±0.070	-0.078±0.079	+0.027±0.057	+0.065±0.071
AD	(N=2,410)	(N=1,241)	(N=2,410)	(N=1,241)	(N=2,410)	(N=1,241)
Model 1	+0.023±0.069	+0.037±0.071	+0.022±0.108	-0.039±0.120	+0.084±0.080	-0.026±0.106
Model 2	+0.021±0.068	+0.042±0.070	+0.076±0.101	+0.016±0.124	+0.121±0.076	+0.025±0.103
Model 3	+0.053±0.071	+0.072±0.075	+0.092±0.090	+0.067±0.115	+0.119±0.069	+0.049±0.103
Model 4	+0.045±0.069	+0.103±0.076	+0.002±0.108	-0.015±0.137	+0.069±0.086	-0.008±0.129

Abbreviations: AD=Alzheimer's Disease; NHANES III=Third National Health and Nutrition Examination Survey.

[a] Model 1: age- and sex-adjusted; Model 2: Model 2 + other demographic factors, education and income; Model 3: Model 2+ lifestyle-related factors, including diet quality indices; Model 4: Model 3+health-related factors and other nutritional biomarkers (serum folate and 25-hydroxyvitamin D, total carotenoids and the remaining two antioxidant vitamins).

[b] Values are $\beta=\text{Log}_e(\text{HR})$ with their associated Standard Errors (SE) for main effect of each antioxidant on the two main outcomes: all-cause and AD dementia, overall and across carotenoid tertiles. Analyses are conducted on the total eligible sample (45+) and a sub-analysis is conducted among older adults (65+). [b] Standard deviation values for each antioxidant vitamin were as follows: Vitamin A, 18.0, vitamin C: 0.49; vitamin E: 578. See units in Table 1.

[c] $P<0.05$ for 2-way interaction between total carotenoid tertile and z-score of reach antioxidant vitamin in unstratified model.

*$P<0.05$ **$P<0.01$ ***$P<0.001$ for null hypothesis of $\text{Log}_e(\text{HR})=0$.