Dietary carotenoids and cognitive function among US adults, NHANES 2011–2014

Krista Christensen, Carey E. Gleason & Julie A. Mares

Published online: 16 Oct 2018.

Submit your article to this journal ⬈

View Crossmark data ⬈

Dietary carotenoids and cognitive function among US adults, NHANES 2011–2014

Krista Christensen [1], **Carey E. Gleason**[2,3,4], **Julie A. Mares**[1]

[1]Department of Ophthalmology and Visual Sciences, University of Wisconsin, 610 N. Walnut Street, 1069 WARF Building, Madison, WI 53726, USA, [2]Division of Geriatrics and Gerontology, Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA, [3]Geriatric Research, Education and Clinical Center (11G), William S. Middleton Memorial Veterans Hospital, Madison, WI, USA, [4]Wisconsin Alzheimer's Disease Research Center, Madison, WI, USA

Objectives: Dietary carotenoids may limit neuronal damage from free radicals, potentially serving as a modifiable risk factor for cognitive decline. We examined intake of lutein and zeaxanthin (L and Z) in relation to cognitive performance among 2011–2014 National Health and Nutrition Examination Survey participants aged ≥60 years.

Methods: L and Z intake from foods and supplements was estimated from two non-consecutive 24-hour diet recalls. Outcomes included the CERAD Word Learning sub-test score, Animal Fluency test score, and Digit Symbol Substitution test score. Regression models were adjusted for survey design variables, year, sex, age, race/ethnicity, body mass index, family income, education, alcohol, and smoking.

Results: Among the 2796 participants, higher dietary intake of L and Z was associated with higher score on each test. For example, the highest quartile of L and Z intake was associated with a 2.52 point increase (SE=0.86 points, P=0.01) on the digit symbol score test, compared with the lowest quartile. There were differences by race/ethnicity, with positive associations generally stronger for Black compared to white participants.

Discussion: Further research from longitudinal studies is needed, but increasing L and Z intake may help to prevent or slow cognitive decline.

Keywords: Lutein, Zeaxanthin, NHANES, Cognition

Introduction

Age-related cognitive decline and dementia are common – but not inevitable – consequences of aging and increasing lifespans. Based on numerous failed treatment trials, current approaches are to intervene early to modify or prevent progressive cognitive impairment through lifestyle and other interventions. The pathophysiology of cognitive decline is complex and involves multiple (potentially overlapping) mechanisms, one of which is oxidative and inflammatory injury.[1–7] Consequently, a modifiable risk factor for cognitive decline may be insufficient intake of dietary antioxidants. Antioxidants may limit damage caused by free radicals, prevalence of which increases with age, and thus prevent or slow cognitive decline due to the damaging effects of free radicals on neurons.[8] Increasing dietary intake of antioxidants may represent a simple and cost-effective way for individuals to protect cognitive health throughout the lifespan, and in the clinical setting, measurement of dietary carotenoid status could serve as a marker for risk of cognitive decline.

Lutein and zeaxanthin (L and Z) are two dietary carotenoids which accumulate in the brain,[9,10] and intake and circulating levels of L and Z have previously been studied in relation to cognitive function (e.g.[11–16]) As summarized in recent reviews,[17–20] results from both observational and intervention studies show that higher levels of L and Z measured in the brain, diet, serum, and eye (as macular pigment) have been positively associated with multiple measures of cognitive function. Perhaps the most direct evaluation of L and Z in the brain and association with cognitive function comes from a 2013 study by Johnson et al. which looked at concentrations of carotenoids, alpha-tocopherol, and retinol in brain tissue of centenarians.[10] In this group, lutein was consistently associated with better performance on both global and domain-specific (executive function, language, learning, and memory) measures; there were fewer associations seen for beta-carotene or alpha-tocopherol and a negative

Correspondence to: Krista Christensen, Department of Ophthalmology and Visual Sciences, University of Wisconsin, 610 N. Walnut Street, 1069 WARF Building, Madison, WI 53726, USA. Email: krista. christensen@wisc.edu

association with retinol. Serum L and Z were also reported to be associated with improved cognition in a larger subset of the same study, along with serum beta-carotene, suggesting the importance of these carotenoids to cognition across multiple domains. This was a cross-section evaluation, but further evidence from the same research team showed in a small randomized trial, that supplementation with 12 mg/day of L led to an improvement in verbal fluency scores.[21] Among women who received a supplement containing both L and 800 mg of docosahexaenoic acid (DHA), memory scores and learning speed were also improved after the four-month trial (these improvements were not seen for women receiving DHA alone). Although these small studies provide compelling evidence for the role of L and Z in cognitive function, there is not an up-to-date population-based study of the association in older adults.

L and Z may impact cognitive function through their general antioxidant and anti-inflammatory action,[22] or may act more specifically in the neural system, for example by increasing neural efficiency[23,24] or neural membrane stability.[25] However, the underlying mechanisms remain unclear, as are potential differences in associations of L and Z from diet versus supplements. Furthermore, associations by race/ethnicity and other individual characteristics are not well-described.

The objective of this analysis is to examine cross-sectional associations between dietary and supplement intake of L and Z in relation to cognitive performance among a nationally representative sample of US older adults.

Material and methods
Design
The National Health and Nutrition Examination Survey (NHANES) is a cross-sectional survey, designed to provide a representative sample of the US non-institutionalized civilian population.[26] For these analyses, the two cycles with information on L and Z intake as well as cognitive performance measures, were used (2011/2012, 2013/2014) to conduct a cross-sectional analysis in the combined set of participants. L and Z were measured in serum in certain NHANES cycles (2003–2006) but unfortunately these do not overlap with the cycles where cognitive performance was evaluated and thus could not be used as additional measures of L and Z status. All NHANES protocols were approved by the CDC's National Center for Health Statistics Ethics Review Board, and all survey participants provided written informed consent.

Lutein and zeaxanthin in diet and supplements
In each NHANES cycle, participants provided detailed dietary intake information for two 24-hour periods, which are then used to estimate intakes of energy, nutrients, and other food components. The first dietary recall was collected in-person during the NHANES visit, while the second was collected by telephone 3 to 10 days later. For these analyses, total estimated dietary L and Z intake (micrograms, μg), was averaged over the two recall periods (if only the first day was available, that value was used instead of an average). Participants were also queried about supplement use for the same two 24-hour periods; L and Z intake from supplements was also averaged over two days if available. Total L and Z intake was calculated as the sum of dietary and supplement intake.

Cognitive outcomes
For 2011–2014, cognitive testing was performed for participants aged 60 years and older.[27,28] Assessments were performed by trained interviewers during the in-person interview at the Mobile Examination Center. There were three tests administered: the CERAD Word Learning sub-test (CERAD W-L) to assess immediate and delayed recall of new verbal information (memory sub-domain); the Animal Fluency test to assess categorical verbal fluency (component of executive function); and the Digit Symbol Substitution Test (DSST) to assess processing speed, sustained attention, and working memory. The CERAD test consists of three consecutive learning trials as well as a delayed recall; consequently, results are presented as three individual trial scores ranging from 0 to 10, a total score across all three trials ranging from 0 to 30, and one delayed recall score ranging from 0 to 10. Although no upper limit exists, practically, the Animal Fluency test score ranges from 3 to 39, and the digit symbol score ranges from 0 to 105.

Statistical analysis
The analyses presented here include a pooled sample of all individuals aged 60 years or older in each of the two survey cycles, with completed cognitive performance test results, dietary L and Z intake information, and information on important confounders (age, sex, race/ethnicity, smoking, educational attainment). Of the 3632 participants aged 60 years and older, 2796 had complete data and comprise the analysis dataset. Participants who were included in the analysis tended to be younger (e.g. 16.5% were aged 80 years or older, compared with 30.3% of those not included), more likely to be non-Hispanic white, to be former rather than current smokers, and to be more highly educated (e.g. 22.8% had a college degree or greater, compared with 15.3% of those not included). There was no difference in average dietary intake of lutein and zeaxanthin, but differences in the included versus not included participants does

mean that results may not be generalizable to all population groups.

All data analysis was performed using SAS/STAT software version 9.4[1]. Regression models were used to identify associations between L and Z intake (in quartiles and over the continuous range of intake levels and cognitive measures, controlling for survey cycle. Covariates considered include several demographic characteristics: sex, age (years), race/ethnicity, body mass index (BMI), family income (poverty income ratio, PIR), educational attainment (less than a high school education, some high school, high school graduate/GED, some college or associate's degree, college graduate or more), alcohol intake (non-drinker, 1 to <5 drinks/month, 5 to <10 drinks/month, or 10+ drinks/month), and smoking status (current, former, or never smoker). We also evaluated food intake of certain other dietary factors as potential covariates – other carotenoids (alpha-carotene, beta-carotene, beta-cryptoxanthin, lycopene), choline, and docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), based upon (1) potential for high correlation with L and Z and (2) previous evidence for associations between these substances and cognition. Dietary, supplement, and total L and Z intake were evaluated as both continuous and categorical (quartiles) variables.

Due to the skewed and truncated distribution of the cognitive scores, ordinal logistic regression models (SURVEYLOGISTIC procedure) were used to evaluate associations with CERAD W-L individual trial and delayed recall scores (range: 0–10) while linear regression models (SURVEYREG procedure) were used to evaluate associations with CERAD W-L total score (range: 0–30), Animal Fluency score (range: 0–39) and DSST score (range: 0–105). All statistical analyses were adjusted for survey design and weighting variables.

We performed additional sensitivity analyses. First, analyses were repeated removing those who reported supplement use to determine relationships with dietary L and Z alone. Second, we also repeated analyses restricting to participants who did not self-report cognitive issues on the medical conditions questionnaire (that is, did not answer yes to 'difficulties in thinking or remembering' or to 'ever told you had a stroke,' and did not report having trouble remembering more than once in the past 7 days. Finally, we evaluated associations among non-Hispanic white and non-Hispanic Black participants separately, to evaluate potential differences by race/ethnicity.

Results

Across the two NHANES cycles, there are 2796 participants who had information on cognitive performance and dietary L and Z intake (some missing supplement intake), and who had information on important covariates (sex, age, race/ethnicity, smoking, education). Characteristics of the study population are shown in Table 1. Participants were relatively evenly split across NHANES cycles and gender; the majority (56%) were 60–69 years old at the time of the NHANES exam. The majority self-reported non-Hispanic white (nearly 80%) race/ethnicity, with the next largest proportion self-reporting non-Hispanic Black (8.4%). About one-quarter were of underweight or normal BMI while about a third were overweight and a third obese. Most were moderate drinkers and never or former smokers. About half of participants had at least a high school education. There were no notable differences between all NHANES participants aged 60 years and older in 2011–2014, and those with the information needed to be included in this analysis; one exception was that those included in the analysis were slightly younger (e.g. 56% were aged 60–69 years, compared to 53% overall) (Table 1). With respect to L and Z, the median total intake was 1046 µg/day (25th, 75th percentiles: 567, 1950 µg/day), similar to previous reports of 1–2 mg/day in the American population.[29] There was no correlation between dietary intakes of L and Z with either DHA or EPA (weighted Pearson correlation coefficients of 0.03 (*P*-value=0.14) and 0.01 (*P*=0.45), respectively). However, dietary intake of L and Z was associated with dietary intake of alpha-carotene and beta-carotene, and choline (correlation coefficients of 0.85, 0.91, and 0.16; *P*<0.0001 for all). Thus, in a sensitivity analyses, we included dietary intake of these two carotenoids and choline in regression modeling.

The median CERAD score across three recall trials (maximum 30) was 19.6, while the median animal fluency test and digit symbol scores were 17.4 and 52.7, respectively. Mean cognitive scores were typical of a cognitively healthy population.[30,31]

Unweighted Spearman correlation coefficients showed significant associations between all cognitive measures, with (1) dietary L and Z intake, (2) supplementary L and Z intake, and (3) total L and Z intake (dietary plus supplementary). Cognitive performance was positively associated with dietary and total L and Z intake using Kruskal–Wallis tests of association, but no difference was seen across quartiles of supplementary L/Z intake (Table 2). Multivariate logistic regression models for individual CERAD W-L scores showed small significant associations for higher score with dietary and total L and Z as

Table 1 Characteristics of NHANES participants, 2011–2014

Characteristic	All NHANES participants aged ≥60 years (*n*=3632)		NHANES participants included in this analysis (*n*=2796)	
	N (SD)	Percent (SE)	*N* (SD)	Percent (SE)
Total	59,659,564 (SD=3,326,722)	100 (--)	51,418,258 (SD=3,112,950)	100 (--)
NHANES cycle				
2011–2012	28,921,337 (SD=2,695,469)	48.48 (SE=2.82)	24,651,382 (SD=2,557,726)	47.94 (SE=3.07)
2013–2014	30,738,226 (SD=1,949,750)	51.52 (SE=2.82)	26,766,876 (SD=1,774,400)	52.06 (SE=3.07)
Age group				
60–69 years	31,835,457 (SD=2,093,055)	53.36 (SE=1.31)	28,811,686 (SD=2,041,591)	56.03 (SE=1.34)
70–79 years	17,543,119 (SD=1,089,446)	29.41 (SE=1.05)	15,187,589 (SD=974,756)	29.54 (SE=1.13)
80+ years	10,280,989 (SD=718,559)	17.23 (SE=0.91)	7,418,982 (SD=578,975)	14.43 (SE=0.84)
Sex				
Male	26,890,724 (SD=1,728,902)	45.07 (SE=0.82)	23,835,553 (SD=1,711,599)	46.36 (SE=1.05)
Female	32,768,839 (SD=1,722,195)	54.93 (SE=0.82)	27,582,704 (SD=1,559,967)	53.64 (SE=1.05)
Race/ethnicity				
Non-Hispanic white	46,147,370 (SD=3,641,818)	77.35 (SE=1.97)	41,063,971 (SD=3,345,615)	79.86 (SE=1.85)
Non-Hispanic Black	5,400,977 (SD=513,354)	9.05 (SE=1.2)	4,317,830 (SD=451,111)	8.4 (SE=1.22)
Mexican American	2,288,482 (SD=441,207)	3.84 (SE=0.81)	1,737,624 (SD=336,941)	3.38 (SE=0.74)
Other Hispanic	2,324,583 (SD=411,194)	3.9 (SE=0.73)	1,870,422 (SD=299,131)	3.64 (SE=0.63)
Other/multiracial	3,498,153 (SD=419,150)	5.86 (SE=0.69)	2,428,410 (SD=350,674)	4.72 (SE=0.63)
BMI				
Underweight (<18.5)	922,549 (SD=162,030)	1.58 (SE=0.29)	669,236 (SD=135,192)	1.32 (SE=0.27)
Normal (18.5 to <25)	14,811,476 (SD=1,104,420)	25.34 (SE=1.15)	12,650,325 (SD=996,598)	24.89 (SE=1.21)
Overweight (25 to <30)	21,083,463 (SD=1,408,924)	36.08 (SE=1.08)	18,158,308 (SD=1,296,239)	35.73 (SE=1.08)
Obese (30 or greater)	21,625,514 (SD=1,345,036)	37.00 (SE=1.3)	19,341,699 (SD=1,281,893)	38.06 (SE=1.31)
Alcohol intake				
Non-drinker	13,713,712 (SD=983,059)	28.3 (SE=1.5)	12,168,050 (SD=912,367)	27.34 (SE=1.59)
1 to <5 drinks/month	33,415,576 (SD=2,226,874)	68.96 (SE=1.59)	31,121,641 (SD=2,219,922)	69.92 (SE=1.71)
5 to <10 drinks/month	1,099,924 (SD=197,101)	2.27 (SE=0.41)	1,026,162 (SD=196,308)	2.31 (SE=0.44)
10+ drinks/month	230,553 (SD=111,533)	0.48 (SE=0.23)	192,806 (SD=102,774)	0.43 (SE=0.22)
Smoking status				
Current smoker	6,710,553 (SD=564,833)	11.25 (SE=0.69)	5,496,350 (SD=508,971)	10.69 (SE=0.71)
Former smoker	23,161,737 (SD=1,656,639)	38.84 (SE=1.35)	20,499,192 (SD=1,543,712)	39.87 (SE=1.41)
Never smoker	29,757,190 (SD=1,684,224)	49.9 (SE=1.37)	25,422,715 (SD=1,603,440)	49.44 (SE=1.59)
Educational attainment				
Less than 9th grade	4,756,957 (SD=386,408)	7.97 (SE=0.82)	3,025,865 (SD=307,241)	5.88 (SE=0.74)
9–11th grade (12th grade with no diploma)	6,465,144 (SD=787,744)	10.84 (SE=1.14)	5,213,098 (SD=648,682)	10.14 (SE=1.07)
High school graduate/GED	13,220,857 (SD=1,185,853)	22.16 (SE=1.37)	11,453,699 (SD=1,103,796)	22.28 (SE=1.45)
Some college or AA	18,005,197 (SD=1,450,788)	30.18 (SE=1.27)	16,190,075 (SD=1,335,684)	31.49 (SE=1.36)
College graduate or above	17,150,944 (SD=1,409,430)	28.75 (SE=1.94)	15,535,521 (SD=1,320,921)	30.21 (SE=2)
	Mean (SE)	Median (25th, 75th percentiles)	Mean (SE)	Median (25th, 75th percentiles)
Age (years)	69.65 (0.2)	68.16 (63.04, 75.38)	69.52 (0.2)	67.62 (62.88, 74.01)
PIR	3.02 (0.07)	2.89 (1.55, 4.97)	2.6 (0.07)	3.09 (1.65, 4.96)
BMI	28.96 (0.2)	27.87 (24.61, 32.08)	29.14 (0.14)	28 (24.69, 32.3)
Waist Circumference (cm)	102.28 (0.5)	101.42 (92.13, 110.89)	102.13 (0.34)	101.95 (92.56, 111.27)
Total calories	1864.62 (17.88)	1780.59 (1403.45, 2239.31)	1809.72 (15.36)	1793.53 (1410.36, 2249.66)
Dietary L and Z intake (mg/day)	1.91 (0.17)	0.93 (0.52, 1.76)	1.81 (0.10)	0.94 (0.53, 1.77)
Supplement L and Z intake (mg/day; *n*=471)	1.32 (0.21)	0.24 (0.22, 0.3)	1.27 (0.19)	0.24 (0.22, 0.30)
Total L and Z intake (mg/day)	2.18 (0.18)	1.04 (0.57, 1.95)	2.02 (0.11)	1.05 (0.57, 1.95)
CERAD: Trial 1 Score	–	–	4.66 (0.05)	4.5 (3.35, 5.62)
CERAD: Trial 2 Score	–	–	6.66 (0.05)	6.58 (5.31, 7.77)
CERAD: Trial 3 Score	–	–	7.48 (0.06)	7.44 (6.26, 8.54)
CERAD: Total Score (3 Recall trials)	–	–	18.8 (0.16)	19.63 (16.44, 22.4)
CERAD: Delayed Recall Score	–	–	5.87 (0.06)	5.93 (4.25, 7.47)
Animal Fluency: Total Score	–	–	16.57 (0.15)	17.4 (13.6, 20.98)
Digit Symbol: Score	–	–	46.1 (0.63)	52.66 (40.94, 63.58)

Table 2 Median (25th, 75th percentiles) score on cognitive tests, by quartile of L and Z intake

Cognitive test	Q1	Q2	Q3	Q4	*P*-value for difference*
		Dietary L and Z intake			
Dietary L and Z intake	0.3 (0.2, 0.4)	0.7 (0.6, 0.8)	1.20 (1.0, 1.4)	2.8 (2.1, 5.1)	N/A
Men only	0.3 (0.2, 0.4)	0.7 (0.6, 0.8)	1.18 (1.0, 1.3)	2.6 (2.0, 4.6)	N/A
Women only	0.3 (0.2, 0.4)	0.7 (0.6, 0.8)	1.20 (1.0, 1.4)	3.0 (2.1, 5.3)	N/A
Animal Fluency: Score Total	16.2 (12.5, 19.5)	17.1 (13.4, 20.68)	17.18 (13.7, 20.9)	18.9 (14.6, 23.2)	<0.0001
CERAD: Score Delayed Recall	5.8 (4.1, 7.3)	6.0 (4.2, 7.4)	5.53 (4.1, 7.2)	6.4 (4.7, 7.9)	<0.0001
CERAD: Score Trial 1 Recall	4.0 (3.1, 5.2)	4.5 (3.3, 5.6)	4.42 (3.3, 5.6)	5.0 (3.9, 5.9)	<0.0001
CERAD: Score Trial 2 Recall	6.4 (4.9, 7.6)	6.5 (5.3, 7.8)	6.4 (5.2, 7.5)	7.1 (5.8, 8.2)	<0.0001
CERAD: Score Trial 3 Recall	7.3 (6.0, 8.4)	7.5 (6.2, 8.5)	7.23 (6.2, 8.3)	7.8 (6.6, 8.9)	<0.0001
CERAD: Total Score	19.0 (15.1, 21.6)	19.6 (16.3, 22.3)	18.88 (16.5, 21.7)	20.9 (17.9, 23.3)	<0.0001
Digit Symbol: Score	48.0 (35.6, 58.8)	51.8 (40.2, 63.1)	52.57 (41.0, 63.7)	56.0 (45.2, 66.4)	<0.0001
		Supplementary L and Z intake (*n*=471)			
Supplementary L and Z intake	0.1 (0.1, 0.2)	0.3 (0.3, 0.3)	0.3 (0.3, 0.3)	2.0 (0.87, 5.25)	N/A
Men only	0.1 (0.1, 1.1)	0.3 (0.3, 0.3)	0.3 (0.3, 0.3)	1.8 (0.5, 5.6)	N/A
Women only	0.1 (0.1, 0.2)	0.3 (0.3, 0.3)	0.3 (0.3, 0.3)	2.0 (1.0, 5.1)	N/A
Animal Fluency: Score Total	18.8 (16.7, 21.4)	18.9 (14.4, 23.2)	17.3 (14.7, 19.4)	18.3 (14.7, 20.8)	0.84
CERAD: Score Delayed Recall	5.8 (5.2, 7.8)	5.8 (4.4, 7.3)	6.5 (4.5, 7.8)	6.3 (4.8, 7.6)	0.63
CERAD: Score Trial 1 Recall	5.1 (3.8, 5.7)	4.6 (3.5, 5.7)	4.6 (3.4, 5.8)	4.8 (3.5, 6.0)	0.99
CERAD: Score Trial 2 Recall	7.2 (6.4, 7.6)	6.7 (5.5, 7.8)	6.8 (5.8, 7.9)	6.9 (5.8, 8.0)	0.53
CERAD: Score Trial 3 Recall	7.7 (6.8, 8.4)	7.4 (6.4, 8.3)	8.0 (6.7, 8.8)	7.6 (6.2, 8.6)	0.26
CERAD: Total Score	20.8 (17.8, 22.3)	19.6 (17.1, 22)	20.7 (17.9, 22.7)	20.4 (17.2, 23.1)	0.62
Digit Symbol: Score	63.2 (52.6, 70.5)	53.6 (43.2, 63.6)	57.6 (45.9, 70.2)	54.5 (48.1, 63.7)	0.28
		Total L and Z intake			
Total L and Z intake	0.4 (0.2, 0.5)	0.7 (0.6, 0.8)	1.3 (1.1, 1.5)	3.3 (2.3, 6.1)	N/A
Men only	0.4 (0.2, 0.5)	0.7 (0.6, 0.8)	1.3 (1.1, 1.5)	3.0 (2.2, 5.7)	N/A
Women only	0.4 (0.2, 0.4)	0.7 (0.6, 0.8)	1.3 (1.1, 1.5)	3.5 (2.4, 6.2)	N/A
Animal Fluency: Score Total	16.1 (12.6, 19.5)	16.5 (13.0, 20.3)	17.7 (13.9, 21.4)	18.8 (14.7, 22.8)	<0.0001
CERAD: Score Delayed Recall	5.8 (4.1, 7.3)	5.7 (4.0, 7.2)	5.7 (4.2, 7.4)	6.4 (4.7, 7.8)	<0.0001
CERAD: Score Trial 1 Recall	4.1 (3.1, 5.3)	4.4 (3.3, 5.5)	4.5 (3.3, 5.7)	4.9 (3.8, 5.8)	<0.0001
CERAD: Score Trial 2 Recall	6.4 (4.9, 7.5)	6.5 (5.16, 7.7)	6.4 (5.3, 7.6)	7.1 (5.9, 8.1)	<0.0001
CERAD: Score Trial 3 Recall	7.3 (6.0, 8.4)	7.3 (6.2, 8.4)	7.4 (6.3, 8.5)	7.8 (6.6, 8.8)	<0.0001
CERAD: Total Score	19.0 (15.3, 21.7)	19.3 (16.1, 22.0)	19.2 (16.5, 22.2)	20.8 (18.0, 23.2)	<0.0001
Digit Symbol: Score	48.2 (36.1, 58.4)	50.3 (37.8, 62.0)	53.4 (41.7, 64.6)	56.2 (45.6, 66.1)	<0.0001

*Kruskal–Wallis test

continuous measures (Table 3). In contrast, there was a small negative association with supplementary L and Z. Analysis by quartile of L and Z showed a positive association (better cognitive performance) with higher L and Z, and this was significant for several associations (Table 3). Results were very similar when removing those who reported use of supplements containing L and Z, or when restricting to those not reporting cognitive issues (Supplementary Table 1).

As shown in Table 4, a similar pattern of results was seen in linear regression models for total CERAD W-L score, Animal Fluency score, and Digit Symbol

Table 3 Adjusted* odds ratios (95% confidence intervals) for score on CERAD Word Learning sub-test, for each mg/day increase in L and Z intake

	CERAD: Score Delayed Recall	CERAD: Trial 1 Score	CERAD: Trial 2 Score	CERAD: Trial 3 Score
Dietary L and Z (mg/day)				
Age-adjusted	1.01 (0.98, 1.05)	**1.04 (1.02, 1.06)**	1.01 (0.99, 1.03)	1.01 (0.98, 1.04)
Fully adjusted	1 (0.97, 1.03)	**1.04 (1.02, 1.06)**	1.01 (0.99, 1.03)	1.01 (0.99, 1.04)
Supplementary L and Z (mg/day)				
Age-adjusted	0.95 (0.91, 0.99)	1.01 (0.95, 1.08)	0.97 (0.92, 1.03)	0.99 (0.94, 1.04)
Fully adjusted	**0.93 (0.89, 0.98)**	1.01 (0.93, 1.09)	0.98 (0.92, 1.06)	0.98 (0.92, 1.04)
Total L and Z (mg/day)				
Age-adjusted	1 (0.98, 1.03)	**1.04 (1.02, 1.05)**	1.01 (0.99, 1.03)	1.01 (0.99, 1.03)
Fully adjusted	1 (0.98, 1.02)	**1.03 (1.02, 1.05)**	**1.01 (1, 1.02)**	**1.01 (1, 1.02)**
Quartile of total L and Z				
Q4 vs. Q1, Age-adjusted	**1.66 (1.36, 2.03)**	**2.22 (1.72, 2.86)**	**2.08 (1.68, 2.57)**	**1.73 (1.4, 2.13)**
Q4 vs. Q1, Fully adjusted	1.28 (0.97, 1.69)	**1.77 (1.31, 2.4)**	**1.62 (1.2, 2.19)**	**1.36 (1.03, 1.81)**
Q3 vs. Q1, Age-adjusted	1.18 (0.9, 1.54)	**1.59 (1.22, 2.08)**	1.22 (0.99, 1.51)	1.23 (0.95, 1.6)
Q3 vs. Q1, Fully adjusted	1.03 (0.75, 1.43)	**1.44 (1.04, 2.01)**	1.02 (0.78, 1.33)	1.09 (0.8, 1.47)
Q2 vs. Q1, Age-adjusted	0.99 (0.79, 1.25)	**1.36 (1.06, 1.74)**	1.25 (0.99, 1.59)	1.05 (0.84, 1.3)
Q2 vs. Q1, Fully adjusted	0.83 (0.6, 1.13)	1.27 (0.97, 1.67)	1.09 (0.78, 1.54)	0.86 (0.65, 1.16)

*Fully adjusted models are adjusted for survey cycle, age, sex, BMI, alcohol intake, smoking, PIR, and education.

Table 4 Adjusted* beta coefficients (standard error (SE), *P*-value) for score on CERAD Word Learning sub-test, Animal Fluency test, and DSST, for each mg/day increase in L and Z intake, stratified by race/ethnicity

	CERAD: Total score	Animal Fluency score	Digit Symbol Score
Dietary L and Z (mg/day)			
Age-adjusted	0.06 (0.03), *P*=0.03	0.05 (0.04), *P*=0.22	0.07 (0.14), *P*=0.61
Fully adjusted	0.06 (0.02), *P*=0.01	0.01 (0.02), *P*=0.74	−0.08 (0.06), *P*=0.23
Supplementary L and Z (mg/day)			
Age-adjusted	−0.03 (0.06), *P*=0.64	−0.04 (0.07), *P*=0.54	−0.02 (0.22), *P*=0.93
Fully adjusted	−0.03 (0.08), *P*=0.74	−0.09 (0.06), *P*=0.18	−0.15 (0.22), *P*=0.5
Total L and Z (mg/day)			
Age-adjusted	0.05 (0.02), *P*=0.02	0.04 (0.03), *P*=0.21	0.08 (0.13), *P*=0.55
Fully adjusted	0.04 (0.01), *P*<0.01	0 (0.02), *P*=0.88	−0.07 (0.06), *P*=0.23
Quartile of total L and Z			
Q4 vs. Q1, Age-adjusted	1.87 (0.23), *P*<0.01	2.67 (0.44), *P*<0.01	8.36 (1.03), *P*<0.01
Q4 vs. Q1, Fully -adjusted	1.15 (0.27), *P*<0.01	1.4 (0.43), *P*<0.01	2.52 (0.86), *P*=0.01
Q3 vs. Q1, Age-adjusted	0.87 (0.3), *P*=0.01	2.06 (0.41), *P*<0.01	6.5 (1.28), *P*<0.01
Q3 vs. Q1, Fully adjusted	0.42 (0.31), *P*=0.18	1.23 (0.42), *P*=0.01	2.67 (0.9), *P*=0.01
Q2 vs. Q1, Age-adjusted	0.51 (0.25), *P*=0.05	0.66 (0.4), *P*=0.11	2.81 (1.07), *P*=0.01
Q2 vs. Q1, Fully adjusted	0.19 (0.3), *P*=0.54	0.27 (0.47), *P*=0.56	1.59 (0.98), *P*=0.12

*Fully adjusted models are adjusted for survey cycle, age, sex, BMI, alcohol intake, smoking, PIR, and education.

score. Greater L and Z intake both on the continuous scale and categorical scale were significantly associated with higher scores on each of the three tests. As above, results for these analyses conducted only among those reporting non-supplement intake and those denying cognitive issues were very similar (Supplementary Table 2). When including alpha-carotene, beta-carotene and choline in the regression models, the effect estimates for associations with L and Z did not change substantially (e.g. odds ratios changed by <5%, data not shown). However, confidence intervals and standard errors were slightly greater, indicating less precision possibly due to high correlation between the three carotenoids (all present in fruits and vegetables) and choline (present, along with L, in eggs).

Finally, we examined these associations separately among non-Hispanic white and non-Hispanic Black participants; note that for these models, the association with supplemental L and Z by itself was not evaluated due to the small number (*n*=77) of non-Hispanic Black participants reporting supplement

use and subsequent model instability. As shown in Table 5, there were significant associations between continuous measures of dietary L and Z only among white participants (CERAD trial 1 score), but associations for both groups when looking at the highest quartile of L and Z intake. The pattern of associations was different by test – for example, the effect estimate for the highest quartile of L and Z intake was strong among white participants for CERAD trial 1 score, but among Black participants for CERAD delayed recall score. Interestingly, the patterns of association by race were more consistent when looking at the continuous test outcomes (Table 6); although not always statistically significant, associations were consistently stronger for Black participants compared with white participants both for dietary and for total L and Z intake, across the three tests.

Discussion

This cross-sectional analysis utilized data from 2 waves of the NHANES (2011–2014) to evaluate the cross-sectional associations between L and Z intake and

Table 5 Adjusted* odds ratios (95% confidence intervals) for score on CERAD Word Learning sub-test, for each mg/day increase in L and Z intake, stratified by race/ethnicity

	CERAD: Score Delayed Recall	CERAD: Trial 1 Score	CERAD: Trial 2 Score	CERAD: Trial 3 Score
Dietary L and Z (mg/day)				
White	1.00 (0.97, 1.03)	1.04 (1.02, 1.06)	1.01 (0.99, 1.03)	1.01 (0.99, 1.04)
Black	1.04 (0.99, 1.09)	1.01 (0.95, 1.06)	1.03 (0.99, 1.08)	1.03 (0.99, 1.08)
Total L and Z (mg/day)				
White	1.00 (0.98, 1.01)	1.03 (1.02, 1.05)	1.01 (1.00, 1.02)	1.01 (1.00, 1.02)
Black	1.03 (0.98, 1.08)	0.99 (0.95, 1.04)	1.02 (0.97, 1.08)	1.03 (0.98, 1.08)
Quartile of total L and Z				
Q4 vs. Q1, White	1.21 (0.87, 1.70)	1.95 (1.35, 2.80)	1.67 (1.14, 2.44)	1.40 (0.97, 2.01)
Q4 vs. Q1, Black	1.84 (1.24, 2.74)	1.21 (0.78, 1.88)	1.83 (1.20, 2.78)	1.82 (1.09, 3.04)
Q3 vs. Q1, White	1.01 (0.70, 1.45)	1.54 (0.99, 2.39)	1.02 (0.72, 1.43)	1.14 (0.78, 1.67)
Q3 vs. Q1, Black	1.48 (0.91, 2.41)	1.32 (0.86, 2.04)	1.59 (0.94, 2.70)	1.48 (0.97, 2.24)
Q2 vs. Q1, White	0.77 (0.50, 1.18)	1.27 (0.9, 1.80)	1.04 (0.68, 1.60)	0.80 (0.54, 1.20)
Q2 vs. Q1, Black	1.13 (0.58, 2.18)	1.59 (1.04, 2.42)	1.48 (0.89, 2.47)	1.80 (0.89, 3.62)

*Fully adjusted models are adjusted for survey cycle, age, sex, BMI, alcohol intake, smoking, PIR, and education.

Table 6 Adjusted* beta coefficients (SE, *P*-value) for score on CERAD Word Learning sub-test, Animal Fluency test, and DSST, for each mg/day increase in L and Z intake, stratified by race/ethnicity

	CERAD: Total score	Animal Fluency score	Digit Symbol Score
Dietary L and Z (mg/day)			
White	**0.06 (0.02), *P*=0.01**	0.003 (0.02), *P*=0.88	−0.09 (0.06), *P*=0.12
Black	0.07 (0.05), *P*=0.15	0.02 (0.08), *P*=0.81	0.22 (0.13), *P*=0.09
Total L and Z (mg/day)			
White	**0.04 (0.01), *P*<0.01**	−0.002 (0.02), *P*=0.89	−0.08 (0.05), *P*=0.10
Black	0.04 (0.05), *P*=0.41	0.04 (0.08), *P*=0.58	0.22 (0.11), *P*=0.05
Quartile of total L and Z			
Q4 vs. Q1, White	**1.28 (0.35), *P*<0.01**	**1.47 (0.52), *P*=0.01**	**2.47 (1.06), *P*=0.03**
Q4 vs. Q1, Black	**1.25 (0.51), *P*=0.02**	1.06 (0.96), *P*=0.28	**4.74 (1.47), *P*<0.01**
Q3 vs. Q1, White	0.50 (0.40), *P*=0.23	**1.25 (0.54), *P*=0.03**	**2.97 (1.12), *P*=0.01**
Q3 vs. Q1, Black	1.08 (0.56), *P*=0.07	0.89 (0.75), *P*=0.25	3.97 (2.61), *P*=0.14
Q2 vs. Q1, White	0.12 (0.40), *P*=0.77	0.07 (0.59), *P*=0.91	1.63 (1.18), *P*=0.18
Q2 vs. Q1, Black	0.92 (0.58), *P*=0.12	1.47 (0.78), *P*=0.07	3.39 (2.17), *P*=0.13

*Fully adjusted models are adjusted for survey cycle, age, sex, BMI, alcohol intake, smoking, PIR, and education.

cognitive function among US older adults. We found that higher L and Z intake was associated with better performance on cognitive measures of memory, language, and executive function domains. These findings align with previous studies of L and Z and association with cognitive function (e.g.[11–14]) Previously demonstrated associations were noted across age groups, even young healthy individuals, and across multiple domains. However, previous observational studies largely characterized L and Z using measures in the retina or in serum, with less evidence for the association between cognition and dietary and supplement intake of L and Z. For example, the most recently published study, an observational analysis of older adults in France, showed that L and Z measured both in the eye (as macular pigment) and in serum, were associated with measures of memory, verbal learning, verbal fluency, and global function.[15] Such observational data are strengthened by findings from intervention studies where increased L and Z intake (via supplementation) improved cognitive function measures in as few as four months.[20]

Interestingly, we did note a small negative association between supplementary L and Z and score on the CERAD test. This could be due to chance (noting that relatively few participants reported taking supplements), or it could be that these individuals were advised to take supplements by their healthcare provider in reaction to a diagnosis (such as for age-related macular degeneration) or because they were at high risk for some disease outcome. We also found that for certain cognitive test outcomes, associations with L and Z intake were stronger for non-Hispanic Black participants compared with non-Hispanic white participants. The highest levels of L and Z intake were associated with CERAD scores among white participants (indicating beneficial association for learning), and associated with CERAD delayed recall score among Black participants (indicating beneficial association for learning and recall). Our findings

suggest that L and Z intake is positively associated with executive function in both race/ethnicity group, but that the association may be more pronounced for Black participants. This could be in part due to differences in intake levels and pattern for L and Z – an earlier report among NHANES III participants reported higher L and Z intake among non-Hispanic Black participants aged 60 years and older.[32] In the current analysis, we found a possibly higher dietary L and Z intake comparing non-Hispanic Black versus white participants (mean (SE) of 2.03 (0.15) mg versus 1.96 (0.22) mg), but the total L and Z intake was equal (mean of 2.2 mg for both groups). However, the NHANES dietary data report on combined L and Z – a 2010 analysis specifically identified higher lutein intake among non-Hispanic Blacks compared to other race/ethnicity groups, while there was little or no difference in zeaxanthin intake.[33] It is possible that these dietary patterns along with other cultural, concomitant diet, genetic and environmental differences, could affect individual ability to absorb and accumulate L and Z in neural tissue.

There are many proposed mechanisms by which increases in L and Z could improve or help maintain cognitive function, including the antioxidant capabilities described above, or general anti-inflammatory action.[22] Another proposed mechanism is through increased neural efficiency (which would manifest as improvements in multiple domains).[23,24] L and Z may also enhance the structure and stability of brain membranes.[25]

Higher L and Z intake may also serve simply as a marker of better overall diet (rich in fruits and vegetables) and related markers of healthy lifestyle, and access to more nutritious foods. However, associations were seen in the NHANES population even when adjusting for other factors associated with general good health, such as income, education, alcohol intake, and smoking. One major limitation of this analysis is the cross-sectional design of the survey;

consequently, it is impossible to determine whether there is a causal association between L and Z intake and cognitive performance, or if the association signifies a true relationship between dietary L and Z and cognition. Another limitation is the use of 24-hour dietary recalls, which may not capture 'usual' patterns of intake, which may be important for L and Z accumulation. Strengths of this analysis include a large and representative sample, ability to control for multiple potential confounders, and information on a variety of cognitive measures evaluating cognitive domains relevant to neurodegenerative diseases like Alzheimer's disease, e.g. memory and executive function. Admittedly, associations are inconsistent in strength, but even modestly effective interventions that may delay the onset of cognitive impairment or dementia can substantially alleviate the growing economic and social burden associated with these conditions.[34, 35] Moreover, dietary interventions are relatively inexpensive and side-effect free.

Conclusions

This analysis found that lutein and zeaxanthin intake were positively associated with multiple measures of cognitive performance in a sample of the U.S. general population of older adults; for specific measures, associations were stronger among non-Hispanic Black participants and suggest benefits in multiple domains. The tests evaluated measure performance across a variety of domains important for continued independence and good health through the lifespan. These findings are in accordance with the larger body of literature showing that higher dietary intakes of foods rich in phytochemicals and fatty acids with anti-inflammatory and antioxidant properties are protective against cognitive decline.[36–39] While broad recommendations for healthier diets and lifestyles can be made to the general public, these recommendations often go unheeded. Targeting at-risk individuals for whom a dietary and lifestyle intervention may be most beneficial could be a more effective approach.

Disclaimer statements

Contributors None

Disclosure of interest The authors declare no conflict of interest.

ORCID

Krista Christensen http://orcid.org/0000-0003-4431-336X

References

1 Engelhart MJ, Geerlings MI, Meijer J, Kiliaan A, Ruitenberg A, van Swieten JC, *et al*. Inflammatory proteins in plasma and the risk of dementia: the rotterdam study. Arch Neurol. 2004;61(5):668–72. PubMed PMID: 15148142. doi:10.1001/archneur.61.5.668.

2 Keller JN, Schmitt FA, Scheff SW, Ding Q, Chen Q, Butterfield DA, *et al*. Evidence of increased oxidative damage in subjects with mild cognitive impairment. Neurology. 2005;64(7):1152–6. PubMed PMID: 15824339. doi:10.1212/01.WNL.0000156156.13641.BA.

3 McGeer PL, McGeer EG, Yasojima K. Alzheimer disease and neuroinflammation. J Neural Trans Suppl. 2000;59:53–7. PubMed PMID: 10961418.

4 Pappolla MA, Smith MA, Bryant-Thomas T, Bazan N, Petanceska S, Perry G, *et al*. Cholesterol, oxidative stress, and Alzheimer's disease: expanding the horizons of pathogenesis. Free Radical Biol Med. 2002;33(2):173–81. PubMed PMID: 12106813.

5 Pratico D, Trojanowski JQ. Inflammatory hypotheses: novel mechanisms of Alzheimer's neurodegeneration and new therapeutic targets? Neurobiol Aging. 2000;21(3):441–5; discussion 51-3. PubMed PMID: 10858591.

6 Tarkowski E, Andreasen N, Tarkowski A, Blennow K. Intrathecal inflammation precedes development of Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2003;74(9):1200–5. PubMed PMID: 12933918; PubMed Central PMCID: PMCPMC1738668.

7 Teunissen CE, van Boxtel MP, Bosma H, Bosmans E, Delanghe J, De Bruijn C, *et al*. Inflammation markers in relation to cognition in a healthy aging population. J Neuroimmunol. 2003;134 (1–2):142–50. PubMed PMID: 12507782.

8 Nooyens AC, Milder IE, van Gelder BM, Bueno-de-Mesquita HB, van Boxtel MP, Verschuren WM. Diet and cognitive decline at middle age: the role of antioxidants. Br J Nutr. 2015;113(9):1410–7. PubMed PMID: 25851267. doi:10.1017/S0007114515000720.

9 Craft NE, Haitema TB, Garnett KM, Fitch KA, Dorey CK. Carotenoid, tocopherol, and retinol concentrations in elderly human brain. J Nutr Health Aging. 2004;8(3):156–62. Epub 2004/05/07. PubMed PMID: 15129301.

10 Johnson EJ, Vishwanathan R, Johnson MA, Hausman DB, Davey A, Scott TM, *et al*. Relationship between serum and brain carotenoids, alpha-tocopherol, and retinol concentrations and cognitive performance in the oldest old from the georgia centenarian study. J Aging Res. 2013;2013:951786. Epub 2013/07/11. PubMed PMID: 23840953; PubMed Central PMCID: PMC3690640. doi:10.1155/2013/951786.

11 Hammond BR, Jr., Miller LS, Bello MO, Lindbergh CA, Mewborn C, Renzi-Hammond LM. Effects of lutein/zeaxanthin supplementation on the cognitive function of community dwelling older adults: a randomized, double-masked, placebo-controlled trial. Front Aging Neurosci. 2017;9:254. PubMed PMID: 28824416; PubMed Central PMCID: PMCPMC5540884. doi:10.3389/fnagi.2017.00254.

12 Lindbergh CA, Mewborn CM, Hammond BR, Renzi-Hammond LM, Curran-Celentano JM, Miller LS. Relationship of lutein and zeaxanthin levels to neurocognitive functioning: an fMRI study of older adults. J Int Neuropsychol Soc. 2017;23(1):11–22. doi:10.1017/S1355617716000850. PubMed PMID: 27776568.

13 Lindbergh CA, Renzi-Hammond LM, Hammond BR, Terry DP, Mewborn CM, Puente AN, *et al*. Lutein and zeaxanthin influence brain function in older adults: a randomized controlled trial. J Int Neuropsychol Soc. 2017:1–14. doi:10.1017/S1355617717000534. PubMed PMID: 28695791.

14 Renzi LM, Dengler MJ, Puente A, Miller LS, Hammond BR, Jr. Relationships between macular pigment optical density and cognitive function in unimpaired and mildly cognitively impaired older adults. Neurobiol Aging. 2014;35(7):1695–9. Epub 2014/02/11. PubMed PMID: 24508218. doi:10.1016/j.neurobiolaging.2013.12.024

15 Ajana S, Weber D, Helmer C, Merle BM, Stuetz W, Dartigues JF, et al. Plasma concentrations of lutein and zeaxanthin, macular pigment optical density, and their associations with cognitive performances among older adults. Invest Ophthalmol Vis Sci. 2018;59(5):1828–35. PubMed PMID: 29610850. doi:10.1167/iovs.17-22656.

16 Akbaraly NT, Faure H, Gourlet V, Favier A, Berr C. Plasma carotenoid levels and cognitive performance in an elderly population: results of the EVA Study. J Gerontol A Biol Sci Med Sci. 2007;62(3):308–16. PubMed PMID: 17389729.

17 Erdman JW, Jr., Smith JW, Kuchan MJ, Mohn ES, Johnson EJ, Rubakhin SS, et al. Lutein and brain function. Foods. 2015;4(4):547–64. doi:10.3390/foods4040547. PubMed PMID: 26566524; PubMed Central PMCID: PMCPMC4638416.

18 Johnson EJ. A possible role for lutein and zeaxanthin in cognitive function in the elderly. Am J Clin Nutr. 2012;96(5):1161S-5S. Epub 2012/10/12. ajcn.112.034611 [pii]. PubMed PMID: 23053547. doi:10.3945/ajcn.112.034611.

19 Johnson EJ. Role of lutein and zeaxanthin in visual and cognitive function throughout the lifespan. Nutr Rev. 2014;72(9):605–12. Epub 2014/08/12. PubMed PMID: 25109868. doi:10.1111/nure.12133.

20 Maci S, Fonseca B, Zhu Y. The role of lutein in brain health and function. Nutrafoods. 2016;15:179–88. doi:10.17470/NF-016-1014-3.

21 Johnson EJ, McDonald K, Caldarella SM, Chung H-Y, Snoddery DM. Cognitive findings of an exploratory trial of docosahexaenoic acid and lutein supplementation in older women. Nutr Neurosci. 2008;11:75–83.

22 Li SY, Fung FK, Fu ZJ, Wong D, Chan HH, Lo AC. Anti-inflammatory effects of lutein in retinal ischemic/hypoxic injury: in vivo and in vitro studies. Invest Ophthal Vis Sci. 2012;53(10):5976–84. doi:10.1167/iovs.12-10007. PubMed PMID: 22871829.

23 Renzi LM, Hammond BR, Jr. The relation between the macular carotenoids, lutein and zeaxanthin, and temporal vision. Ophthal Physiol Opt. 2010;30(4):351–7. PubMed PMID: 20492542. doi:10.1111/j.1475-1313.2010.00720.x.

24 Zimmer JP, Hammond BR, Jr. Possible influences of lutein and zeaxanthin on the developing retina. Clin Ophthalmol. 2007;1(1):25–35. Epub 2007/03/01. PubMed PMID: 19668463; PubMed Central PMCID: PMC2699988.

25 Sujak A, Gabrielska J, Grudzinski W, Borc R, Mazurek P, Gruszecki WI. Lutein and Zeaxanthin as Protectors of Lipid Membranes against Oxidative Damage: The Structural Aspects. Arch Biochem Biophys. 1999;371(2):301–7.

26 CDC. Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National health and nutrition examination survey data. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2007-2014. 2016.

27 CDC. National Health and Nutrition Examination Survey 2011–2012 Data Documentation, codebook and Frequencies. Cognitive Functioning. Available at: https://wwwn.cdc.gov/Nchs/Nhanes/2011-2012/CFQ_G.htm. 2012.

28 CDC. National Health and Nutrition Examination Survey 2013–2014 Data Documentation, codebook and Frequencies. Cogn Funct. Available at: https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/CFQ_H.htm. 2014.

29 Ranard KM, Jeon S, Mohn ES, Griffiths JC, Johnson EJ, Erdman JW, Jr. Dietary guidance for lutein: consideration for intake recommendations is scientifically supported. Eur J Nutr. 2017;56 (Suppl 3):37–42. PubMed PMID: 29149368; PubMed Central PMCID: PMCPMC5715043. doi:10.1007/s00394-017-1580-2.

30 Welsh KA, Butters N, Mohs RC, Beekly D, Edland S, Fillenbaum G, et al. The consortium to establish a registry for Alzheimer's disease (CERAD). Part V. A normative study of the neuropsychological battery. Neurology. 1994;44(4):609–14. PubMed PMID: 8164812.

31 Weschler D. Weschler Memory Scale – Revised Manual. Psychological Corporation. 1997.

32 Mares-Perlman JA, Fisher AI, Klein R, Palta M, Block G, Millen AE, et al. Lutein and zeaxanthin in the diet and serum and their relation to age-related maculopathy in the third national health and nutrition examination survey. Am J Epidemiol. 2001;153(5):424–32. PubMed PMID: 11226974.

33 Johnson EJ, Maras JE, Rasmussen HM, Tucker KL. Intake of lutein and zeaxanthin differ with age, sex, and ethnicity. J Am Diet Assoc. 2010;110(9):1357–62. PubMed PMID: 20800129. doi:10.1016/j.jada.2010.06.009.

34 Ernst RL, Hay JW. The US economic and social costs of Alzheimer's disease revisited. Am J Public Health. 1994;84(8):1261–4. PubMed PMID: 8059882; PubMed Central PMCID: PMCPMC1615456.

35 Ernst RL, Hay JW, Fenn C, Tinklenberg J, Yesavage JA. Cognitive function and the costs of Alzheimer disease. An exploratory study. Arch Neurol. 1997;54(6):687–93. PubMed PMID: 9193203.

36 Kang JH, Ascherio A, Grodstein F. Fruit and vegetable consumption and cognitive decline in aging women. Ann Neurol. 2005;57(5):713–20. PubMed PMID: 15852398. doi:10.1002/ana.20476.

37 Kesse-Guyot E, Ahluwalia N, Lassale C, Hercberg S, Fezeu L, Lairon D. Adherence to Mediterranean diet reduces the risk of metabolic syndrome: a 6-year prospective study. Nutr Metab Cardiovasc Dis. 2013;23(7):677–83. Epub 2012/05/29. S0939-4753(12)00054-3 [pii]. PubMed PMID: 22633793. doi:10.1016/j.numecd.2012.02.005.

38 Morris MC, Evans DA, Tangney CC, Bienias JL, Wilson RS. Associations of vegetable and fruit consumption with age-related cognitive change. Neurology. 2006;67(8):1370–6. PubMed PMID: 17060562; PubMed Central PMCID: PMCPMC3393520. doi:10.1212/01.wnl.0000240224.38978.d8.

39 Parrott MD, Shatenstein B, Ferland G, Payette H, Morais JA, Belleville S, et al. Relationship between diet quality and cognition depends on socioeconomic position in healthy older adults. J Nutr. 2013;143(11):1767–73. PubMed PMID: 23986363. doi:10.3945/jn.113.181115.