

SHORT REPORT

Plasma antioxidants and risk of dementia in older adults

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Abstract

Introduction: Plant-based diets rich in fruits and vegetables have been associated with lower risk of dementia, but the specific role of antioxidants, a key class of bioactive phytochemicals, has not been well ascertained.

Methods: We measured antioxidants in a case-cohort study nested within the Ginkgo Evaluation of Memory Study. We included 996 randomly selected participants and 521 participants who developed dementia, of which 351 were diagnosed with Alzheimer's disease (AD) during a median of 5.9 years of follow-up. We measured baseline plasma levels of retinol, α -, and γ -tocopherol; zeaxanthin and lutein (combined); beta-cryptoxanthin; cis-lycopene; trans-lycopene; α -carotene; and trans- β -carotene by organic phase extraction followed by chromatographic analysis and related these to neurologist-adjudicated risks of all-cause dementia and AD.

Results: Plasma retinol, α -, and γ -tocopherol, and carotenoids were not significantly related to risk of dementia or AD. Associations were not significant upon Bonferroni correction for multiple testing and were consistent within strata of sex, age, apolipoprotein E ϵ 4 genotype, mild cognitive impairment at baseline, and intake of multivitamin, vitamin A or β -carotene, or vitamin E supplements. Higher trans- β -carotene tended to be related to a higher risk of dementia (adjusted hazard ratio [HR] per 1 standard deviation [SD] higher trans- β -carotene: 1.10; 95% confidence interval [CI]: 1.00, 1.20) and α -carotene tended to be associated with higher risk of AD only (adjusted HR per 1 SD higher α -carotene: 1.15; 95% CI: 1.02, 1.29).

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Discussion: Plasma antioxidants were not significantly associated with risk of dementia or AD among older adults. Similar studies in younger populations are required to better understand the association between plasma antioxidants and dementia risk.

KEYWORDS

Alzheimer's disease, antioxidants, carotenoids, dementia, epidemiology, prospective study, retinol, tocopherol

1 | INTRODUCTION

The importance of diet in the etiology of dementia is well recognized. For example, adherence to the Mediterranean diet has been related to a decreased dementia risk and cognitive impairment in both observational studies and randomized controlled trials.¹⁻³ However, the exact nature of how diet plays a role in the prevention of cognitive decline and which nutrients might be particularly beneficial for brain health is not clearly understood.

The implication of oxidative stress in the pathophysiology of dementia⁴ generated the hypothesis that higher intake of antioxidants might be beneficial to cognitive function. Several studies observed that single components of the Mediterranean diet, higher adherence to plant-based diets, and diets rich in fruits and vegetables are associated with reduced dementia risk and slower cognitive decline.^{3,5} The latter studies relied mainly on self-reported dietary intake, which is prone to measurement error and confounding. Studies with plasma measures of antioxidants have related higher levels of lutein, zeaxanthin, and β -carotene to better cognitive function and dementia risk,^{6,7} but few prospective studies exist. Thus, we assessed the association of objectively measured plasma antioxidants with dementia risk in a large population of older adults.

2 | METHODS

2.1 | Study population and design

We used a case-cohort design nested in the Ginkgo Evaluation of Memory (GEM) Study. GEM enrolled 3069 participants aged 72 years and older with normal cognition or mild cognitive impairment (MCI) from 2000 to 2002.⁸ For the present study, we included a random sample of 1000 participants and 523 participants diagnosed with dementia during follow-up, of whom 166 overlapped, as expected in this design. We excluded two participants without plasma samples and four participants without cholesterol measurement, leaving a total of 1351 participants in the analysis. Institutional review boards approved the study, and participants and their proxies provided written informed consent.

2.2 | Biochemical measurements

Plasma retinol, α -, δ -, and γ -tocopherol; lutein and zeaxanthin; β -cryptoxanthin; trans-lycopene; cis-lycopene; total lycopene; α -

carotene; cis- β -carotene; and trans- β -carotene at baseline (2000 to 2002) were measured by organic phase extraction and high-performance liquid chromatography analysis at the Harvard School of Public Health.⁹ Quality control was monitored with duplicate high-level plasma and low-level plasma samples in each batch of samples. Batch correction factors were calculated for each of the analytes from the regression of the obtained versus the expected values. Except for cis- β -carotene and δ -tocopherol, which were excluded, within-run coefficients of variation (CV) were below 7% and between-run CVs were below 17%. The accuracy of measurement was verified through the National Institute of Standards and Technology Micronutrients Measurement Quality Assurance Program.

2.3 | Dementia diagnosis

At baseline, each participant underwent a neuropsychological test battery measuring language, mood, executive and visuospatial function, memory, psychomotor speed, and global cognitive function.⁸ Participants completed the Modified Mini-Mental State Examination (3MS), Clinical Dementia Rating scale, and the Alzheimer's Disease Assessment Scale (ADAS) semi-annually. Starting in 2004 the ADAS was completed annually. Participants completed cognitive testing through the end of follow-up, dementia diagnosis, or death, whichever occurred first. Participants suspected of having cognitive impairment repeated the baseline neuropsychological tests and were referred for neurological and medical evaluation and brain magnetic resonance imaging. After this evaluation, dementia diagnosis and classification (Alzheimer's disease [AD], vascular, mixed, or other dementia) was made by an expert panel using a validated protocol.¹⁰⁻¹²

2.4 | Covariates

Trained technicians collected demographic and health characteristics in interviews and questionnaires, and measured blood pressure, height, and weight at baseline. Participants brought prescription drugs and over-the-counter medications to the study visit for entry into the medication database.

2.5 | Statistical analysis

We assessed the correlation of plasma levels of carotenoids with vitamin E, α -tocopherol, and γ -tocopherol in random subcohort members, controlling for sex and age at study entry.

RESEARCH IN CONTEXT

- 1. Systematic Review:** Plant-based diets rich in fruits and vegetables have been associated with lower risk of dementia, but the specific role of antioxidants, a key class of bioactive phytochemicals, has not been well ascertained.
- 2. Interpretation:** Plasma antioxidants were not significantly associated with risk of dementia or Alzheimer's disease during follow-up after correction for multiple testing.
- 3. Future directions:** Similar studies in younger populations are required to better understand the association between plasma antioxidants and dementia risk.

Inverse sampling probability-weighted Cox proportional hazards models with a robust estimate of variance were used to evaluate the multivariable-adjusted association of antioxidants with dementia risk, with study time as the underlying time axis censoring at the time of death, drop-out, or dementia diagnosis, whichever occurred first. We assigned a weight inversely proportional to the sampling probability (3069/1000) to dementia-free participants to account for the oversampling of participants with dementia. We tested the proportional-hazards assumption based on Schoenfeld residuals. We tested the potential interactions of sex, age, apolipoprotein E (APOE) genotype (APOE $\epsilon 4$ carrier [including APOE $\epsilon 2/\epsilon 4$, APOE $\epsilon 3/\epsilon 4$, and APOE $\epsilon 4/\epsilon 4$], APOE $\epsilon 4$ non-carrier, or missing), MCI at baseline, education, and dietary supplement use with antioxidants on dementia risk by including separate interaction terms. A Bonferroni adjusted critical P -value of .001 was used to account for multiple testing (36 tests calculated as 3 antioxidant classes \times 2 models \times 6 interactions). To account for synergistic effects of antioxidants, we used an antioxidant pattern score created by principal components analysis (PCA) of antioxidants and related the first principal component to dementia and AD risk.

In sensitivity analyses, we assessed the association of antioxidants with cognitive decline as measured by 3MS. Previous research in GEM has indicated practice effects in the repeated administration of the 3MS.¹³ To account for practice effects on the assessment of cognitive function over time, we excluded the first administration of the 3MS and used the 6-month 3MS scores as baseline. We assessed the mean differences in 3MS scores at all follow-up visits compared to baseline according to antioxidant levels using linear mixed models with a random slope and random intercept for each participant adjusting for age, sex, race/ethnicity (White, non-White), clinic site, fasting status (<4 hours, ≥ 4 hours), total cholesterol, and date of blood draw. Analyses were performed using STATA 12.1 (Stata Corp).

3 | RESULTS

Among the 1351 participants, 521 participants were diagnosed with dementia during a median (interquartile range) follow-up time of 5.9

years (3.7 to 6.5). Participants who developed dementia during follow-up were more likely to carry an APOE $\epsilon 4$ allele (Table 1). A total of 962 participants (71%) used either multivitamin, vitamin A or β -carotene, or vitamin E supplements. Six participants had vitamin A deficiency, as defined by plasma retinol concentrations of 196 $\mu\text{g/L}$ or below. Plasma levels of carotenoids correlated directly with vitamin E ($r = 0.35$) and α -tocopherol ($r = 0.35$), and inversely with γ -tocopherol ($r = -0.13$).

Plasma levels of retinol and vitamin E were not statistically significantly associated with risk of dementia, or AD (Table 2). Carotenoids were not significantly related to risk of dementia or AD, except for plasma trans- β -carotene, which showed a trend to be related to a higher risk of dementia (hazard ratio [HR] per standard deviation [SD]: 1.09; 95% confidence interval [CI]: 1.00, 1.20; $P = .06$) and α -carotene, which also trended toward a higher AD risk alone (HR per SD: 1.15; 95% CI: 1.02, 1.29; $P = .02$). Associations were not statistically significant when multiple testing was taken into account using the Bonferroni correction ($P > .001$). All antioxidants except for γ -tocopherol loaded positively onto the antioxidant pattern score created by PCA, with highest loadings for cis- and trans-lycopene and β -cryptoxanthin. The antioxidant pattern score explained 35.6% of variation in antioxidants, but was unrelated to dementia risk (HR per unit: 1.05; 95% CI: 0.98, 1.12) and AD (HR per unit: 1.05; 95% CI: 0.97, 1.13). Associations were consistent within the strata of sex, age, APOE genotype, MCI at baseline, education, and intake of supplements (all interaction P -values $> .001$). 3MS scores did not differ statistically significantly at follow-up compared to baseline by antioxidant levels (all $P > .05$).

4 | DISCUSSION

In this observational study, plasma antioxidants were not significantly related to future risk of dementia, AD, or cognitive decline before dementia diagnosis. Noted were trends toward significance for plasma trans- β -carotene and α -carotene, both with a higher risk of AD. The lack of association was consistent across strata of sex, age, APOE genotype, MCI at baseline, education, or intake of vitamin or multivitamin supplements.

Consistent with our findings, plasma retinol and vitamin E were unrelated to the prevalence of AD in the Rotterdam study.¹⁴ Similarly, plasma carotenoids and tocopherols were unrelated to cognitive decline in the Nurses' Health Study.¹⁵ While results of our study did not differ by APOE genotype, higher serum β -carotene was associated with a lower risk of cognitive decline only among APOE $\epsilon 4$ carriers in participants of the McArthur Study.¹⁶ In the Three-City Bordeaux cohort study, higher plasma lutein was related to a lower risk of dementia.⁶ Further, higher total carotenoids, when expressed as a function of plasma lipids, were related to a reduced risk of dementia. In contrast, we found a tendency for total carotenoids, and specifically trends toward α - and trans- β -carotene being associated with higher risk of dementia and AD.

While α -tocopherol intervention resulted in slower cognitive decline among patients with mild to moderate AD,¹⁷ intervention studies on antioxidants have generally failed to prove cognitive benefit

TABLE 1 Baseline characteristics of the random subcohort of the Ginkgo Evaluation of Memory study and dementia cases that developed during follow-up (n = 1351)

| Characteristics | Median (Q25; Q75) | |
|---|----------------------------|---|
| | Random subcohort (n = 996) | Dementia cases during follow-up (n = 521) |
| Sex, male, n (%) ^a | 536 (53.8) | 266 (51.1) |
| Age, y | 78 (76, 81) | 79 (77, 82) |
| APOE ε4 allele carrier, n (%) ^b | 183 (18.4) | 145 (27.8) |
| Race, White, n (%) | 952 (95.6) | 489 (93.9) |
| Education, y | 14 (12, 16) | 14 (12, 16) |
| Number of alcoholic drinks/wk ^c | 0.1 (0, 2.5) | 0.02 (0, 2) |
| Current smoking, n (%) ^d | 40 (4.0) | 20 (3.8) |
| Body mass index, e kg/m ² | 26.6 (24.4, 29.4) | 26.0 (23.9, 28.4) |
| Dietary supplement use, n (%) | | |
| Multivitamin ^f | 575 (57.7) | 280 (53.7) |
| Vitamin A or β-carotene ^g | 66 (6.6) | 35 (6.7) |
| Vitamin E ^h | 406 (40.8) | 222 (42.6) |
| Lipid-lowering medication use, n (%) | 266 (26.7) | 160 (30.7) |
| Total cholesterol, mg/dL | 189 (162, 213) | 183 (158, 212) |
| History of cardiovascular disease, n (%) | 333 (33.4) | 197 (37.8) |
| History of diabetes, n (%) | 86 (8.6) | 49 (9.4) |
| Mild cognitive impairment at baseline, n (%) ⁱ | 156 (15.7) | 198 (38.0) |
| 3MS at screening visit | 94 (90, 97) | 91 (87, 95) |
| Cognitive subscale of the Alzheimer's Disease Assessment | 6 (5, 8) | 8 (6, 10) |
| Center for Epidemiologic Studies–Depression Scale | 3 (1, 5) | 4 (1, 7) |
| Ginkgo biloba assignment, n (%) | 496 (49.8) | 276 (53.0) |
| Dementia, n (%) ^j | 166 (16.7) | 521 (100) |
| Alzheimer's disease dementia | 112 (11.2) | 351 (67.4) |
| Vascular dementia | 9 (0.9) | 24 (4.6) |
| Mixed dementia | 40 (4.0) | 124 (23.8) |
| Other dementia | 5 (0.5) | 22 (4.2) |
| Antioxidants, median (Q5; Q95) | | |
| Retinol, μg/L | 552 (373, 799) | 537 (368, 794) |
| Vitamin E, mg/L | 26 (14, 52) | 27 (14, 52) |
| α-tocopherol | 24 (12, 51) | 24 (12, 50) |
| γ-tocopherol | 1.5 (0.5, 4.2) | 1.5 (0.4, 4.4) |
| Carotenoids, μg/L | 1514 (594, 3394) | 1547 (595, 3433) |
| Lutein + zeaxanthin ^k | 146 (66, 307) | 148 (72, 299) |
| β-cryptoxanthin | 177 (56, 520) | 178 (58, 497) |
| Lycopene | 560 (189, 1305) | 561 (177, 1266) |
| Trans-lycopene | 268 (86, 627) | 272 (85, 630) |
| Cis-lycopene | 293 (101, 676) | 290 (88, 658) |

(Continues)

TABLE 1 (Continued)

| Characteristics | Median (Q25; Q75) | |
|------------------|----------------------------|---|
| | Random subcohort (n = 996) | Dementia cases during follow-up (n = 521) |
| α-carotene | 102 (27, 311) | 102 (33, 305) |
| Trans-β-carotene | 406 (114, 1375) | 434 (121, 1484) |

Abbreviation: 3MS, Modified Mini-Mental State Examination score; APOE, apolipoprotein E; MCI, mild cognitive impairment.

^aPercentages are calculated with missing data.

^bN = 286 missing.

^cN = 21 missing.

^dN = 24 missing.

^eN = 7 missing.

^fN = 366 missing.

^gN = 490 missing.

^hN = 405 missing.

ⁱMCI was diagnosed if participants scored ≤10th percentile for age and education on at least two tests of the neuropsychological battery using the Cardiovascular Health Study population as a reference population, while also having a Clinical Dementia Rating global score of 0.5.

^jN = Per the case-cohort study design, the 166 cases that occurred within the random subcohort were included in both the case count and the subcohort count.

^kLutein and zeaxanthin were combined because they co-elute.

TABLE 2 Hazard ratios and 95% confidence intervals for risk of dementia and Alzheimer’s disease, according to plasma antioxidants in the Ginkgo Evaluation of Memory case-cohort, n = 1351

| | SD | HR for dementia (95% CI) per SD | | HR for AD (95% CI) per SD | |
|----------------------------------|-----|---------------------------------|--------------------------|---------------------------|--------------------------|
| | | Model 1 ^a | Model 2 ^b | Model 1 ^a | Model 2 ^a |
| Retinol, μg/L | 131 | 0.95 (0.85, 1.07) | 0.97 (0.86, 1.09) | 0.89 (0.78, 1.02) | 0.91 (0.79, 1.04) |
| Vitamin E, mg/L | 12 | 1.03 (0.92, 1.15) | 1.07 (0.96, 1.20) | 1.01 (0.88, 1.15) | 1.06 (0.93, 1.21) |
| α-tocopherol | 12 | 1.03 (0.92, 1.15) | 1.06 (0.95, 1.19) | 1.01 (0.89, 1.15) | 1.05 (0.92, 1.20) |
| γ-tocopherol | 1.2 | 1.01 (0.90, 1.13) | 1.04 (0.93, 1.17) | 0.99 (0.87, 1.13) | 1.04 (0.90, 1.20) |
| Carotenoids, μg/L | 907 | 1.10 (0.99, 1.22) | 1.11 (0.99, 1.24) | 1.11 (0.98, 1.25) | 1.10 (0.97, 1.25) |
| Lutein + zeaxanthin ^c | 101 | 0.98 (0.88, 1.10) | 0.96 (0.84, 1.09) | 1.00 (0.88, 1.13) | 0.96 (0.83, 1.11) |
| β-cryptoxanthin | 161 | 1.00 (0.90, 1.12) | 1.00 (0.89, 1.12) | 1.02 (0.90, 1.15) | 1.00 (0.87, 1.14) |
| Lycopene | 360 | 1.06 (0.95, 1.19) | 1.10 (0.98, 1.24) | 1.05 (0.93, 1.20) | 1.09 (0.95, .25) |
| Trans-lycopene | 182 | 1.07 (0.96, 1.19) | 1.11 (0.99, 1.24) | 1.06 (0.93, 1.20) | 1.09 (0.95, 1.25) |
| Cis-lycopene | 184 | 1.05 (0.94, 1.18) | 1.09 (0.97, 1.22) | 1.05 (0.92, 1.19) | 1.08 (0.94, 1.24) |
| α-carotene | 99 | 1.06 (0.95, 1.17) | 1.08 (0.97, 1.21) | 1.12 (1.00, 1.26) | 1.15 (1.02, 1.29) |
| Trans-β-carotene | 479 | 1.10 (1.00, 1.20) | 1.09 (1.00, 1.20) | 1.10 (0.99, 1.21) | 1.08 (0.97, 1.20) |

Abbreviations: AD, Alzheimer’s disease; APOE, apolipoprotein E; CI, confidence interval; HR, hazard ratio; SD, standard deviation.

^aHRs were obtained from weighted Cox proportional hazard regression models adjusted for age, sex, race/ethnicity (White, non-White), clinic site, fasting status (<4 hours, ≥4 hours), total cholesterol, and date of blood draw.

^bModel 2 was additionally adjusted for education, weekly number of alcoholic drinks (none, 0.1–0.9, 1.0–7.0, 7.1–14.0, >14, missing), smoking status (never, former, current, missing), body mass index (<20, 20–24.9, 25–29.9, ≥30 kg/m², missing), lipid-lowering medication use, history of cardiovascular disease, history of diabetes, Center for Epidemiologic Studies-Depression Scale, treatment assignment, and APOE ε4 carrier status (carrier, non-carrier, missing).

^cLutein and zeaxanthin were combined because they co-elute.

with treatment.^{18–20} Shorter-term trials, and particularly those in the elderly or among participants with established AD or MCI, may not capture the most relevant window of exposure. The correlation of carotenoids and α-tocopherol in plasma and cerebral tissue supports the hypothesis that these peripheral antioxidants enter the brain. Both

antioxidants are lipophilic, allowing them to cross the blood–brain barrier.⁷ In contrast, no correlation of retinol, which is hydrophobic, in plasma and cerebral tissue has been observed.⁷ A previous trial supported the notion that an intervention of vitamin E, C, and α-lipoic acid can improve oxidative stress in the brain. However, the latter

intervention was also associated with faster 16-week cognitive decline compared to placebo.²¹ Given the widespread use of antioxidant supplements in the general population, further studies are needed, especially at earlier stages like midlife, in the pathogenesis of cognitive decline, to clarify the role and safety of antioxidants and antioxidant supplements in the prevention of dementia.

To our knowledge, this study is the largest evaluation of objectively measured plasma antioxidants in relation to dementia risk. Compared to estimated intake, plasma antioxidants may more directly reflect antioxidant exposure within the body, by taking into account variation in absorption, usage, and storage of foods.

Limitations include the lack of information on food sources of different antioxidants. Retinol is found in foods of animal origin including eggs, milk and milk products, and liver. Although some carotenoid compounds found in green leafy vegetables and yellow fruits and vegetables can be metabolized to retinol, plasma retinol concentrations do not correlate with fruit and vegetable intake.^{22,23} The main sources of vitamin E are plant-based oils, nuts, and seeds with only low contributions from fruits and vegetables. Carotenoids are predominantly obtained from fruits and vegetables and although bioavailability depends on the type of fruits and vegetables, processing, and other foods eaten, the correlation between dietary intake of fruits and vegetables and plasma concentrations of carotenoids ranges from 0.53 to 0.59 in US populations.^{24,25}

Our study population was limited to elderly participants aged 75 years or older. Based on the long preclinical phase of dementia, the underlying biological processes leading to dementia may have already been underway when antioxidants were measured. Per trial protocol, cognitive tests were discontinued after the diagnosis of dementia, limiting the analysis to cognitive decline before the diagnosis of dementia. Dietary supplement use in this elderly population was frequent at baseline and there might have been insufficient variation in antioxidant levels to observe significant associations. Thus, findings might not be generalizable to younger populations and populations with lower antioxidant levels. Prospective studies on antioxidant levels in midlife in populations with a wide range of antioxidant levels and early pathophysiological changes would be particularly valuable.

5 | CONCLUSION

In this elderly population, plasma antioxidants were not associated with dementia risk during follow-up. Potential benefits of reducing plasma carotenes for dementia reduction may warrant follow-up in further studies, particularly in younger populations.

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CONFLICTS OF INTEREST

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