

# Association of Serum Antioxidant Vitamins and Carotenoids With Incident Alzheimer Disease and All-Cause Dementia Among US Adults

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## Study Question

Do serum vitamins A, C, and E and total and individual serum carotenoids associate individually or interactively with incident Alzheimer disease (AD) and all-cause dementia?

## What Is Known and What This Paper Adds

Serum antioxidant vitamins and carotenoids may protect against neurodegeneration with age. No nationally representative study to date has investigated whether serum levels of carotenoids in general may interact with each other and with vitamins A, C, or E in relation to incidence rates of AD or all-cause dementia. This study provides Class II evidence that incident all-cause dementia was inversely associated with serum lutein+zeaxanthin and  $\beta$ -cryptoxanthin levels.

## Methods

Using data from the third National Health and Nutrition Examination Surveys (1988–1994), linked with Centers for Medicare & Medicaid Services follow-up data, we tested associations and interactions of serum vitamins A, C, and E and total and individual serum carotenoids and interactions with incident AD and all-cause dementia. Cox proportional hazards regression models were conducted.

## Results and Study Limitations

After  $\leq 26$  years follow-up (mean 16–17 years,  $n = 7,283$  participants age 45–90 years at baseline), serum lutein + zeaxanthin was associated with reduced risk of all-cause dementia (65 + age group), even in the lifestyle-adjusted model (per SD, hazard ratio [HR] 0.93, 95% CI 0.87–0.99;  $p = 0.037$ ), although attenuated in comparison with a socioeconomic status (SES)-adjusted model (HR 0.92, 95% CI 0.86–0.93;  $p = 0.013$ ) (Table). An inverse relationship was detected between serum  $\beta$ -cryptoxanthin (per SD increase) and all-cause dementia (45+ and 65+) for age- and sex-adjusted models (HR 0.86, 95% CI 0.80–0.93;  $p < 0.001$  for 45+; HR 0.86, 95% CI 0.80–0.93;  $p = 0.001$  for 65+), a relationship remaining strong in SES-adjusted

**Table** Serum Lutein + Zeaxanthin and  $\beta$ -Cryptoxanthin (z Scores) vs Dementia Incidence<sup>a,b</sup>

	Age 45+ y (n = 7,257)	Age 65+ y (n = 3,593)
<b>Lutein + zeaxanthin</b>		
<b>Model 1</b>	-0.084 $\pm$ 0.033; $p = 0.016$	-0.088 $\pm$ 0.034; $p = 0.013$
<b>Model 2</b>	-0.061 $\pm$ 0.032; $p = 0.063$	-0.071 $\pm$ 0.033; $p = 0.037$
<b>Model 3</b>	-0.061 $\pm$ 0.041; $p = 0.14$	-0.083 $\pm$ 0.044; $p = 0.062$
<b><math>\beta</math>-cryptoxanthin</b>		
<b>Model 1</b>	-0.115 $\pm$ 0.040; $p = 0.006$	-0.126 $\pm$ 0.045; $p = 0.007$
<b>Model 2</b>	-0.070 $\pm$ 0.041; $p = 0.092$	-0.076 $\pm$ 0.047; $p = 0.11$
<b>Model 3</b>	-0.072 $\pm$ 0.047; $p = 0.13$	-0.074 $\pm$ 0.054; $p = 0.18$

<sup>a</sup>  $\beta = \text{Log}_e$  (HR), SE.

<sup>b</sup> Model 1: demographics/socioeconomic factors; model 2: model 1+ lifestyle-related factors; model 3: model 2+health-related factors.

models (HR 0.89, 95% CI 0.82–0.96;  $p = 0.006$  for 45+; HR 0.88, 95% CI 0.81–0.96;  $p = 0.007$  for 65+), but attenuated in subsequent models (Table). Some antagonistic interactions were detected among carotenoids and between carotenoids and antioxidant vitamins in relation to both outcomes. Our study has several limitations, including worse overall health and access to health care among those diagnosed earlier, baseline exclusion of dementia or cognitive impairment cases based on a household screener, and the possible confounding effects of medications and other nutrients on the main findings.

## Study Funding and Competing Interests

This work was supported partly by the Intramural Research Program of the NIH, National Institute on Aging, NIH project number AG000513. The authors report no competing interests. Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures.

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