

## Nutrition and Aging

# Association Between Serum Beta-Carotene Levels and Decline of Cognitive Function in High-Functioning Older Persons With or Without Apolipoprotein E 4 Alleles: MacArthur Studies of Successful Aging

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**Background.** Growing evidence from animal studies suggests an interaction between antioxidants and apolipoprotein E (APOE) alleles on cognitive functioning. We used data from a 7-year cohort study of high-functioning older persons to explore whether the associations between serum beta-carotene level and subsequent decline of cognitive function differed by APOE 4 genotype.

**Methods.** Baseline information on sociodemographic characteristics, serum beta-carotene level, inflammation markers, APOE genotype, and cognitive functioning measured by a 9-item Short Portable Mental Status Questionnaire (SPMSQ) was obtained in 455 survivors. Multivariable logistic regression analyses were used to examine the relation between high serum beta-carotene level and risk of SPMSQ score decline in participants with or without APOE 4 alleles, while adjusting for age, sex, race, baseline SPMSQ score, and other covariates.

**Results.** Nine (2%) study participants had homozygous and 97 (21%) had heterozygous APOE 4 alleles. Two hundred forty-nine (55%) had decline of SPMSQ scores during the follow-up. The presence of an APOE 4 allele was associated with higher risk and larger magnitude of SPMSQ score decline. The adjusted odds ratio of high beta-carotene level for cognitive decline was 0.11 (95% confidence interval, 0.02–0.57) in participants with at least one APOE 4 allele and 0.89 (95% confidence interval, 0.54–1.47) among those who were APOE 4 negative.

**Conclusion.** Among high-functioning older persons, antioxidants and beta-carotene in particular may offer protection from cognitive decline in persons with greater genetic susceptibility as evidenced by the presence of the APOE 4 allele.

ALZHEIMER'S disease (AD) results from the complex interactions of genetic risks and other biological processes, such as degenerative or ischemic changes, environmental trauma, and oxidation (1–3). Accumulated damage to lipid membranes and DNA by free radicals may disrupt normal cell functioning and lead to neuronal death (4). Therefore, there has been great interest in investigating the role of antioxidants in the development of cognitive dysfunction. If low levels of antioxidants contribute to cognitive decline, increased dietary intake of antioxidants or supplementation may potentially modify the disease process.

Beta-carotene is an antioxidant and has other well-established biological effects, such as control of cell differentiation (5). The results from the epidemiological studies on the relationship between beta-carotene and cognitive functioning have been inconsistent. Both dietary intake and serum levels of beta-carotene have been associated with cognitive measures in some (6,7), but not all studies (8,9). Research has also shown that patients with mild cognitive impairment had decreased plasma levels of antioxidants,

including carotenoids (10). It has been suggested that these conflicting results may reflect differences in the sensitivity of cognitive measures, measurement errors, or the presence of unmeasured confounding factors (11).

One possible modifier for the effect of beta-carotene may be apolipoprotein E (APOE) genotype, one of the strongest biological predictors for AD (12). Previous studies have suggested the presence of a gene–disease interaction, such that those persons with any APOE 4 allele in combination with atherosclerosis, peripheral vascular disease, or diabetes mellitus were at substantially higher risk of cognitive decline than those persons without APOE 4 allele (13). Animal research has indicated that APOE genotype is linked to the level of oxidation as well as antioxidant status (14,15). Moreover, in vitro studies have shown that APOE and antioxidants have different mechanisms of inhibiting Alzheimer's beta-amyloid fibril formation (16). In humans, small studies using brain tissues have shown that antioxidant activity is lowest in persons with APOE 4 alleles, compared to those with other APOE genotypes (17).

However, few population-based epidemiologic studies have examined the potential interaction between genetic factors and carotenoids. In previous research, we have demonstrated an association between APOE 4 alleles and cognitive decline among high-functioning older persons (18). Here we seek to extend earlier findings and to explore the effects of the interaction between serum beta-carotene levels and APOE genotype on subsequent decline of cognitive function. We hypothesized that the relationship between serum level of beta-carotene and cognitive functioning might differ by APOE genotype.

## METHODS

### *Study Participants*

The individuals in this study were participants in the MacArthur Research Network Study of Successful Aging, a subset of the Established Populations for Epidemiologic Studies of the Elderly (EPESE). The details of this 7-year cohort study have been described elsewhere (19). Briefly, the EPESE was a community-based cohort study of persons aged 65 years or older residing in Durham, North Carolina, East Boston, Massachusetts, and New Haven, Connecticut. The participants were eligible for the MacArthur study if they were 70–79 years old at its inception in 1988 and met the criteria designed to identify persons functioning in the top third of the age group.

Selection criteria for cognitive performance included: (i) a score of 6 or more correct on the 9-item Short Portable Mental Status Questionnaire (SPMSQ) (20), and (ii) the ability to remember 3 or more of 6 elements on a delayed recall of a short story. Selection criteria for physical function included no reported disability on a 7-item scale of activities of daily living, no more than one disability on 8 items tapping gross mobility and range of motion, ability to hold a semi-tandem balance for at least 10 seconds, and ability to stand from a seated position 5 times within 20 seconds without using the arms (19).

Of 1313 EPESE participants who met the criteria, 1189 (91%) agreed to participate at inception. Nine hundred seventy participants agreed to provide blood samples. Forty-seven (4.8%) refused follow-up visits. Three hundred forty-seven participants were excluded from analyses due to incomplete information on blood chemistry, serum antioxidant concentrations, or APOE genotype. Compared to the 576 older persons who had complete information on biomarkers, the persons excluded were not different in their distributions of common risk factors for cognitive decline or cardiovascular disease. Of the participants with complete baseline information, 121 died during the follow-up. Therefore, the analyses were limited to 455 survivors who had measurements of cognitive status at baseline and 7-year follow-up. Compared to those participants who died during the follow-up, the survivors were more likely to be younger and female, but were not statistically different in baseline beta-carotene levels, APOE allele distribution, and SPMSQ scores.

### *Measures*

Serum beta-carotene concentration was determined by isocratic liquid chromatography method at the Lipids

Laboratory, University of Southern California, Los Angeles (21). APOE genotyping was performed using genetic material isolated from peripheral lymphocytes (22). On the basis of the six standard APOE genotypes (2/2, 2/3, 2/4, 3/3, 3/4, 4/4), the participants were defined as APOE 4 positive if they carried at least one APOE 4 allele. An enzyme-linked immunosorbent assay test was used to measure serum CRP (C-reactive protein ELISA kit; University of Vermont, Burlington) and interleukin-6 (IL-6) levels (High Sensitivity Quantikine kit; R & D Systems, Minneapolis, MN). Serum levels of total and high density lipoprotein (HDL) cholesterol were measured at Nichols Laboratories (San Juan Capistrano, CA) on an automated sequential multiple analyzer.

Decline of cognitive function was defined as having a lower SPMSQ score at 7-year follow-up than at baseline. Sensitivity analysis was conducted to assess the effect of using different cutoff points in SPMSQ decline on the relationship between beta-carotene level and cognitive function. At baseline, study participants completed a standardized self-report assessment of the following: sociodemographic characteristics, such as age, sex, race, education, and income; and health behaviors, including smoking status and alcohol consumption. Body mass index (BMI; weight in kilograms divided by height in meters squared) was calculated on the basis of self-reported height and weight.

### *Data Analysis*

The crude 7-year prevalence of cognitive decline for tertiles of serum concentrations of beta-carotene, from highest to lowest, was 52%, 54%, and 58%, respectively. For this analysis, high or low concentrations of beta-carotene were dichotomized based on the median of the distribution in the cohort (0.19  $\mu\text{mol/L}$ ). The associations between serum beta-carotene level and other variables were first examined in bivariate analyses, stratified on APOE 4 status. For continuous variables, the means and standard deviations (SD) were calculated for participants with high or low beta-carotene concentrations. Because the distributions of some of the variables (such as CRP and IL-6) were right-skewed, the Wilcoxon rank sum test was used to test the significance of the differences. For categorical variables, such as sex, the percentage of participants with certain characteristic (e.g., being male) was calculated for each category of beta-carotene level. Statistical significance was determined by chi-square test.

The risk of SPMSQ score decline was calculated for participants with or without APOE 4 alleles. The significance for the difference in the magnitude of SPMSQ score changes between the two groups was determined using a two-sample *t* test. Because of previous findings that the effect of antioxidants on cognitive decline may be influenced by APOE 4 genotype (23), we performed stratified logistic regression analysis to examine the relationship between beta-carotene and change in cognitive functioning among individuals with or without APOE 4 alleles. Adjusted odds ratios were used to estimate the protective effect of high beta-carotene level, while controlling for age, sex, race, baseline SPMSQ score, education, income, serum CRP and IL-6 levels, total and HDL cholesterol levels,

Table 1. Distributions of Sociodemographic Characteristics, Health Behaviors, and Biomarkers by Serum Levels of Beta-Carotene Among 455 Participants, Stratified by Apolipoprotein E (APOE) Genotype

Characteristics	APOE 4 Positive			APOE 4 Negative		
	Low Serum Beta-Carotene <0.19 $\mu\text{mol/L}$ N = 49	High Serum Beta-Carotene $\geq 0.19 \mu\text{mol/L}$ N = 57	p Value*	Low Serum Beta-Carotene <0.19 $\mu\text{mol/L}$ N = 166	High Serum Beta-Carotene $\geq 0.19 \mu\text{mol/L}$ N = 183	p Value
Age, y	73.9 (2.8)	74.3 (2.6)	.410	74.0 (2.6)	74.3 (2.8)	.516
% Male	55%	40%	.129	42%	36%	.203
% White	86%	67%	.023	91%	79%	.002
% Completing high school education	43%	49%	.519	41%	53%	.024
% With income >\$10K/y	63%	56%	.456	48%	61%	.011
% Current alcohol user	55%	28%	.005	45%	42%	.566
Smoking (pack-years)	24.9 (35.4)	14.3 (22.4)	.154	24.5 (36.0)	14.6 (26.3)	.005
C-reactive protein, mg/L	2.06 (2.04)	1.89 (2.24)	.159	3.25 (4.89)	2.75 (3.63)	.052
Interleukin-6, pg/mL	4.52 (5.58)	3.17 (2.22)	.218	4.61 (5.68)	3.97 (5.06)	.008
Total cholesterol, mg/dL	227 (41)	231 (37)	.638	216 (40)	220 (39)	.455
HDL cholesterol, mg/dL	42 (12)	48 (17)	.215	48 (15)	50 (15)	.026
Body mass index, kg/m <sup>2</sup>	27.0 (4.8)	25.5 (4.1)	.092	26.7 (4.2)	25.3 (3.9)	.001
Baseline SPMSQ score	8.2 (0.7)	8.2 (0.8)	.708	8.2 (0.9)	8.2 (0.8)	.865

Notes: Data are presented as mean (standard deviation) for continuous variables and percentage for categorical variables.

\*Two-sample Wilcoxon rank sum test for continuous variables and chi-square test for categorical variables.

SPMSQ = Short Portable Mental Status Questionnaire; HDL = high-density lipoprotein.

BMI, smoking status, and alcohol consumption. The values of CRP and IL-6 were log transformed. To further assess the modulating effect of APOE 4 genotype on serum beta-carotene level, we also used a multivariate logistic regression model to test the statistical significance of the interaction term between APOE 4 genotype and beta-carotene levels in the entire cohort. All analyses were performed using the SAS system, Windows version 8.1 (SAS Institute, Cary, NC).

## RESULTS

The average age for the entire cohort was 74.1 years. One hundred six participants had at least one APOE 4 allele, and nine participants were homozygous. The mean serum beta-carotene level was 0.27  $\mu\text{mol/L}$  (*SD* 0.31  $\mu\text{mol/L}$ ). There was no significant difference in serum beta-carotene concentrations between participants who were APOE 4 positive and those who were APOE 4 negative ( $p = .71$ ). Table 1 shows comparison of baseline characteristics of the study population by high versus low serum concentrations of beta-carotene in participants with or without APOE 4 alleles. Participants with high serum beta-carotene concentration were more likely to be non-white, regardless of APOE 4 status. Among participants who were APOE 4 negative, those with high serum beta-carotene had significantly lower levels of CRP and IL-6, lower BMI, and fewer pack-years of smoking, but higher serum HDL cholesterol, than did those with lower beta-carotene level. Similar differences were observed among the participants who had at least one APOE 4 allele, although the  $p$  values for these associations ranged from .09 to .22. High concentration of beta-carotene was also associated with completing high school and having income more than \$10,000 per year in the APOE 4-negative group.

Sixty-seven participants with APOE 4 alleles (63%) and 182 participants without APOE 4 alleles (52%) had a decline in SPMSQ score during the 7-year follow-up period ( $p =$

.04). The magnitude of SPMSQ score decline in these two groups was 1.5 (*SD* 2.3) and 0.8 (*SD* 1.8), respectively ( $p = .02$ ). Bivariate analysis showed no significant associations between high serum beta-carotene level and risk of cognitive decline in the cohort (Table 2). Among participants who were APOE 4 negative, there was minimal change in the relationship between serum beta-carotene level and cognitive decline after adjustment for covariates. However, for participants with at least one APOE 4 allele, the odds ratio of high beta-carotene for SPMSQ score decline changed from 0.99 (95% confidence interval [CI], 0.45–2.17) to 0.63 (95% CI, 0.25–1.54) after controlling for age, sex, and race. The adjusted odds ratio was 0.11 (95% CI, 0.02–0.57) after additional adjustment for baseline SPMSQ score, education, income, smoking status, alcohol consumption, serum levels of CRP, IL-6, and total and HDL cholesterol, and BMI (model 3 in Table 2). Using 2-point decline in SPMSQ to define cognitive decline, the adjusted odds ratio of low beta-carotene was 0.25 (95% CI, 0.06–0.99).

Table 2. Bivariate and Multivariate Logistic Regression Analyses of Association Between High Beta-Carotene Level and Subsequent Decline of SPMSQ Scores Among 455 Survivors, Stratified by APOE Genotype

Models	Relative Risks for SPMSQ Score Decline (95% CI)	
	APOE 4 Positive N = 106	APOE 4 Negative N = 349
Unadjusted	0.99 (0.45–2.17)	0.74 (0.49–1.14)
Adjusted (model 1)*	0.63 (0.25–1.54)	0.69 (0.45–1.08)
Adjusted (model 2) <sup>†</sup>	0.20 (0.06–0.72)	0.79 (0.51–1.25)
Adjusted (model 3) <sup>‡</sup>	0.11 (0.02–0.57)	0.89 (0.54–1.47)

Notes: \*Model 1 adjusted for age, sex, and race.

<sup>†</sup>Model 2 adjusted for age, sex, race, education, and body mass index.

<sup>‡</sup>Model 3 adjusted for age, sex, race, baseline SPMSQ score, education, income, smoking status, alcohol consumption, serum levels of C-reactive protein, interleukin-6, and total and HDL cholesterol, and body mass index.

SPMSQ = Short Portable Mental Status Questionnaire; APOE = apolipoprotein E; CI = confidence interval.

The other independent risk factors for cognitive decline in the model included older age, being non-white, lower education, and lower BMI. Among the participants who were APOE 4 positive, the odds ratio of higher beta-carotene for SPMSQ score decline was 0.20 (95% CI, 0.06–0.72) after adjusting for only these 4 covariates and sex (model 2 in Table 2). In logistic regression models using information from the entire sample including participants with or without APOE 4 alleles, the *p* value for the interaction term between low beta-carotene level and presence of APOE 4 alleles was .04. The Hosmer–Lemeshow test did not suggest lack of fit for any of the multivariate models.

## DISCUSSION

The findings from this population of high-functioning community-dwelling older persons suggest that APOE 4 genotype is not only an independent predictor for cognitive decline as previously shown, but also modifies the relation between serum beta-carotene concentrations and subsequent cognitive change. Higher serum beta-carotene level is associated with lower risk of cognitive decline only among participants who have at least one APOE 4 allele.

As reported by Bretsky and colleagues (18), APOE 4 genotype was associated with the decline of cognitive functioning in this cohort. This is consistent with previous research, which has shown that individuals with heterozygous E4 allele had odds ratios between 2.2 and 4.4 for developing AD, and those with homozygous E4 allele had odds ratios ranging from 5.1 to 34.3 (24,25), compared to participants with E3/E3 genotype. The APOE genotype is also associated with the age at onset of AD such that the more E4 alleles there are, the younger the age at disease onset tends to be (26,27). Among older African American and Caucasian community residents, APOE 4 was significantly related to more rapid decline in scores of the SPMSQ, the same measure of cognition used in this study (28).

This study is unique in that it has not only shown the APOE 4 alleles to be a risk factor, but also to be a potential modifier for the association between serum beta-carotene level and cognitive decline. It suggests that high serum beta-carotene is protective against cognitive decline in persons who are APOE 4 positive, but not among those who do not have APOE 4 alleles. Similar effects of APOE 4 on other risk factors for cognitive decline have been reported in older persons. Data from the Cardiovascular Health Study showed that those with any APOE 4 allele in combination with atherosclerosis, peripheral vascular disease, or diabetes mellitus were at substantially higher risk of cognitive decline than were those without an APOE 4 allele (13). In a large cohort of Japanese American men, hypertension and diabetes were also found to have a stronger adverse effect on cognitive function or dementia in persons with higher genetic susceptibility (29,30). The findings from our study further support the importance of the relationship between genetic predisposition and antioxidants. It is possible that, in persons with APOE 4 alleles, beta-carotene level may be more crucial in countering oxidative stress involved in the pathogenesis of AD. This potential modulation of APOE 4

on the effects of serum beta-carotene level could have contributed to the previous inconsistent findings in the literature on the relation between beta-carotene and cognitive decline. Although the results of antioxidant supplementation has generally been disappointing in trials (31), this analysis raises the possibility of a more beneficial role of increased dietary intake of antioxidants or supplementation in high risk groups of cognitive impairment defined by APOE 4 genotype.

The mean serum beta-carotene concentration in the study population was 0.27  $\mu\text{mol/L}$ . The distribution of beta-carotene level was similar to those distributions reported in other older populations (32). No previous studies have examined serum beta-carotene levels across APOE 4 genotype in older people, and no significant association was observed in our population. Older age, being black, lower education, and lower BMI were independent risk factors for cognitive decline and important confounders in the relationship between serum beta-carotene level and cognitive function in this cohort. As a result of these confounding effects, in the crude analysis there was no significant association between beta-carotene and decline of SPMSQ score among participants who were APOE 4 positive. These findings are consistent with previous studies. Advanced age, black race, and lower education are well-known risk factors for dementia (33,34). A similar association between BMI and cognitive changes has been reported in a cohort of healthy French community dwellers who were 68 years old or older (35).

Several possible limitations must be noted. The sample size for participants with APOE 4 alleles was relatively small. Consequently, the CI for the estimated effect size of the relationship between high beta-carotene and cognitive decline was wide in this group. The study was also not powered to examine the associations between beta-carotene and clinical outcomes, such as dementia. No dietary intake of beta-carotene was measured. However, previous research has shown that serum level of beta-carotene is correlated with both dietary intake measured by food frequency questionnaires and supplementation of beta-carotene (36–39). Only 576 participants (48.4% of the baseline cohort) had complete information on antioxidants, APOE 4 genotype, and outcome measurements. The true magnitude of the possible selection bias can not be assessed directly with our data. However, comparing the participants who had complete information with those who were excluded, we found that the two groups were not significantly different in the distributions of common risk factors for cognitive decline.

Despite these limitations, our data suggest that antioxidants and beta-carotene in particular may offer protection from cognitive decline in persons with greater genetic susceptibility as evidenced by the presence of an APOE 4 allele. Further research with larger cohorts is needed to explore the effects of interaction between antioxidants and APOE genotype on cognitive functions and risk of AD in older persons. If our findings are confirmed, new clinical interventions (e.g., dietary intervention or antioxidant supplementation) to improve the cognitive functional status of older persons at high risk of dementia must be evaluated in formal clinical trials.

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