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Association of vitamin E and cognitive decline in older adults with and without the *APOE*-ε4 allele: a biracial population-based community study

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Abstract

Introduction—The association of different types of tocopherols (vitamin E) with cognition might vary by the *APOE*-ε4 allele status. We examined the association of dietary tocopherols with cognitive decline among participants with and without the *APOE*-ε4 allele over a median of 12 years.

Methods—2,193 participants from the Chicago Health and Aging Project were included in the analyses. Global cognition was assessed in three year cycles. We used a 144-item FFQ to assess dietary intakes of tocopherols and hME Sequenom mass-array platform to assess APOE genotype. We used linear mixed effects models to examine the relationship between tocopherol from food sources and global cognitive decline.

Results—The mean baseline age was 74.1 (SD=5.9) years. Among *APOE*-ε4 carriers, participants in the highest quintile of intakes of dietary vitamin E had a slower cognitive decline of 0.022 SDU (95% CI: 0.000, 0.043) compared to those in the lowest quintile. A higher intake of dietary α-tocopherol from food sources only was associated with slower cognitive decline in *APOE*-ε4 carriers (P for trend 0.002) but not among the non-carriers (P for trend 0.937). Among *APOE*-ε4 carriers, those in the highest quintile of intake of α-tocopherol had a 16.4% slower rate

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The authors report no conflicts of interest.

Consent Statement

The study was approved by the institutional review board of Rush University Medical Center. Written informed consent was obtained from all study participants.

of decline of global cognition compared to those in the lowest quintile (β = 0.034, 95% CI: 0.013, 0.054).

Conclusion: Individuals consuming high α-tocopherol from food sources had slower cognitive decline among *APOE*-ε4 carriers. In older adults, different forms of vitamin E might moderate the relationship of *APOE*-ε4 with global cognition.

Keywords

Alzheimer's disease; antioxidant; nutrients; vitamin E; alpha-tocopherol; dietary; non-supplement; global cognition; cognitive decline; ApoE; *APOE*-ε4; *APOE* polymorphism; bi-racial; longitudinal cohort

Introduction

Cognitive decline and Alzheimer's disease and related dementia (ADRD) are degenerative neurological conditions that significantly impact the quality of life and have adverse health outcomes in older adults [1]. Due to high metabolic activity, the brain is particularly vulnerable to oxidative damage. Given the growing evidence implicating oxidative process in the etiology of neurodegenerative diseases, nutrients with antioxidant capacities have been suggested to have protective effects on brain function [2, 3].

Vitamin E is a fat-soluble vitamin with antioxidant capacities [4]. Strong evidence from animal studies and epidemiological studies suggests that high intakes of vitamin E were correlated with a lower risk of dementia [3], AD [5], and cognitive decline [6, 7]. Long-term vitamin E sufficiency early in life was associated with a significantly lower chance of developing AD neuropathologic changes, thereby suggesting a beneficial effect of long-term vitamin E intake among adults aged 90 years and older [8]. However, findings from randomized controlled trials on vitamin E supplementation in delaying cognitive decline or lowering the risk of AD cognition remain inconclusive [4, 9–12].

The heterogeneity among previous findings might be partially contributed to 1) the different sources and the forms of vitamin E (dietary vs. supplements, alpha-tocopherols vs. other forms), 2) the duration of supplementation, and 3) apolipoprotein E polymorphisms (*APOE*-ε4 allele carrier versus none) [5]. For instance, *APOE*-ε4 allele is a known risk factor for AD. Moreover, ApoE also has a vital function in transportation and the homeostasis of fat-soluble vitamins, such as vitamin E [13].

Individuals with the *APOE*-ε4 allele might respond differently to vitamin E. Nevertheless, the association of different forms of vitamin E on cognition among *APOE*-ε4 carriers and non-carriers remains largely unknown. Our previous investigation suggested that not only alpha-tocopherol but higher intakes of other tocopherol forms like gamma- and delta-tocopherols were associated with a lower risk of incident AD [14]. The present study aims to further examine the association of vitamin E from food sources, varying tocopherol forms, and the influence of the *APOE*-ε4 risk allele on cognitive decline among older persons in a longitudinal bi-racial cohort.

Materials and Methods

Study Population

The Chicago Health and Aging Project (CHAP), initiated in 1993, is a longitudinal, biracial, population-based study with a census of individuals aged 65 years or older located on the south side of Chicago [15]. Of those identified, 6,158 individuals (79%) received an in-home interview. Data on participants' demographic information, health outcomes, and current functioning were collected during the in-home interview. We also conducted tests examing physical and cognitive performance. The initial interview was conducted from 1993 to 1997, and subsequent interviews were repeated at three-year intervals, with up to six data collection cycles. The CHAP study enrolled 62% Black participants, and had 89% follow-up of all surviving participants over the study period. In this analysis, we included participants with APOE genotype assessment, responded to a food frequency questionnaire (FFQ), and had a minimum of two cognitive assessments with up to 10 years of follow-up. The exclusion criteria were individuals with body mass index (BMI) <14 or >55, implausible caloric intakes (<500 kcal or > 3800 kcal for women, < 800 kcal or > 4200 kcal for men), or with FFQs with entire pages or > 50% of pages left blank. The quality of FFQs was screened by a trained research assistant [14]. FFQs were also considered invalid among individuals with Mini-Mental State Examination score <10 at the baseline interview. We included 2,195 participants in the final analyses over a median of 12 years. This study was approved by Rush University Medical Center Institutional Review Board.

Dietary Assessment

We used a self-administered semi-quantitative 144-item FFQ modified from the Harvard FFQ to assess dietary intakes [16]. The FFQ was collected at each cycle. We used vitamin E intakes from the first available FFQ in the present study. Information regarding the computation of nutrient and food intakes based on FFQs has been published previously elsewhere [17]. Vitamin E isoform intake was calculated using the USDA and Harvard University food composition databases. We used FFQs collected prior to 2002 cycle when intakes of individual types of tocopherol were processed and reported from USDA and Harvard database. Because our previous investigation showed no association with vitamin E supplements [5, 18], in the present study, we investigated the association of intakes of total vitamin E isoforms (from both diet and supplements) and vitamin E from dietary sources only. Alpha-, β-, δ- and γ-tocopherol from food sources (i.e., vegetable oils, vegetables, nuts, and seeds) were analyzed. We used the residual regression method[19] to perform gender-specific energy adjustments for these vitamins. In a validation study among a subset of randomly selected CHAP participants (n=232), intakes of individual forms of vitamin E from FFQs (α-, β-, δ- and γ-tocopherols) have a moderate correlation with intakes from multiple 24-h dietary recalls over 12 months [14].

Cognitive Function Assessment

During an in-home interview at each cycle, we conducted four cognitive performance tests consisting of two measures of episodic memory [20, 21], one measure of perceptual speed [22], and the Mini-Mental State Examination [23]. Details on each test were reported in previous publication [17]. We used baseline population mean and standard deviation for

each test to standardize the raw scores to z scores. We then created a composite z score by averaging the z scores from all four tests as the global cognitive score. In this case, the cognitive score was scaled in standard units and a higher score indicates better performance. Compared to analysizing the individual tests, the global measure had the advantages of reducing problems associated with measurement error, including floor and ceiling effects and having an approximately normal distribution.

APOE-ε4 allele

We used two single nucleotide polymorphisms (SNPs), rs7412 and rs429358 to determine *APOE*-ε4 genotypes. These SNPs were measured by the hME Sequenom MassARRAY platform (Sequenom, Inc., San Diego, CA) at the Broad Institute at Harvard University (Cambridge, Massachusetts) [24]. For SNP rs7412 and SNP rs429358, genotyping call rates were 100% and 99.8%, respectively. We created an indicator variable based on the two SNPs for participants with one or more copies of the *APOE*-ε4 risk allele.

Assessment of Demographic variables

We used the 1990 US Census questionnaire during an in-home interview to collect data on social and demographic characteristics [25]. History of medical conditions and medication use was self-reported. Weight (kg) and height (meters) were measured and used to compute BMI (kg/meter^2).

Statistical Analysis

The primary outcome was annual changes in the rate of cognitive decline. For continuous variables, data were presented as mean and standard deviations (SDs); for categorical variables, data were presented as frequency (%). We used Welch Two Sample t-test and Pearson's Chi-square Test to compare baseline characteristics among *APOE*-ε4 carriers versus non-carriers.

Linear mixed effects models were used to examine the association between intakes of vitamin E (total, and the individual tocopherols - alpha, gamma, beta, and delta) and the annual change in cognitive function. The random-effect model includes subject-specific intercept and slope. The random-effect model allows for individual variation in initial cognitive function and the change in annual cognitive function. We used multivariate model accounted for age (years), sex (F/M), education (years), calorie (kcal), smoking status (current, former), race (Blacks, whites), *APOE*-ε4 allele (any ε4 allele or none), and their respective interactions with time, and interaction term between vitamin E (total, and the individual tocopherols - alpha, gamma, beta and delta), time, and *APOE*-ε4 genotype. Based on *a priori* hypothesis, we performed stratification analyses of each model stratified by *APOE*-ε4 allele carriership. Intakes were modeled as both continuous variables and categorical variables in quintiles. We used the lowest quintile as the referent category. We used median values of each quintile to calculate the p-value for the trend. When intakes were modeled as continuous variables, we used 5mg as unit of exposure for total vitamin E (diet and supplements), alpha-, gamma-tocopherol and 1 mg for beta- and delta-tocopherols. SAS version 9.4 was used for data analysis with a type 1 error rate for significance at 0.05, and all tests were 2-sided.

Results

The mean age of study participants was 74.0 (SD 5.9) years, with 62% female and 56% Black participants. Overall, the *APOE*-ε4 allele frequency was higher among Black participants than White participants. Participants without the *APOE*-ε4 allele were older and had a higher global cognition score at baseline assessment than those with the *APOE*-ε4 allele (Table 1). Intakes of tocopherol from food sources were similar between participants with or without the *APOE*-ε4 allele.

We first examined the association between total Vitamin E intake and cognitive decline. We observed that vitamin E from food sources was only associated with a slower cognitive decline in those with the high-risk carrying *APOE*-ε4 allele. Among *APOE*-ε4 carriers, higher intakes of vitamin E from food sources were significantly associated with a slower cognitive decline (P for trend 0.020). Among *APOE*-ε4 carriers, those in the highest quintile of intakes of vitamin E from food sources had a slower cognitive decline of 0.022 SDU (95%CI: 0.000 to 0.043) compared to those in the lowest quintile (Table 2). The differences were equivalent to a 22% slower annual rate of cognitive decline comparing the highest intake to the lowest intake of vitamin E among those with the *APOE*-ε4 allele (Figure 1). Vitamin E from food sources was not associated with the annual rate of cognitive decline in individuals *without APOE*-ε4 allele.

Subsequently, we examined the association of different forms of tocopherols from foods and their association with the annual rate of cognitive decline. Higher intakes of α-tocopherol were associated with slower cognitive decline (P for trend 0.012). The association of α-tocopherol and cognition was dependent on *APOE*-ε4 allele carriership (P for interaction 0.046). Among individuals with *APOE*-ε4 allele, intakes of α-tocopherol were associated with a slower annual change in cognitive function (P for trend 0.002). Per 5 mg increase in the intakes of α-tocopherol was associated with a slower annual change in global cognitive score by 0.008 SDU (SD 0.0048, P = 0.099). Participants with the *APOE*-ε4 allele in the highest quintile of α-tocopherol intakes had a slower annual change in cognitive function by 0.033 SDU (95%CI: 0.013 to 0.054) (Table 3). The differences in cognitive function were equivalent to having a 31.6% slower annual cognitive decline between the highest versus the lowest quintile in those with *APOE*-ε4 allele (Figure 2). In contrast, among individuals *without APOE*-ε4 allele, higher intakes of δ-tocopherol was associated with slower cognitive decline (P for trend = 0.03) (Table 3). There was a tendency of slower cognitive decline associated with higher intake of γ-tocopherol among *APOE*-ε4 allele non-carrier (P=0.07). Intakes of β-tocopherol was not associated with annual change of global cognition. We conducted a sensitivity analysis using alpha-tocopherol equivalents (ateq). Similar results were reported. *APOE*-ε4 carriers, for global cognition, those in the highest quintile of ateq compared to those in the lowest quintile had a slower cognitive decline by $\beta = 0.024 \pm 0.0107$ (p=0.03, data not shown).

We further investigated the association of dietary α-tocopherol with annual change in cognition among participants with different *APOE*-ε4 risk alleles. We found that higher intakes of α-tocopherol were associated with slower annual rates of cognitive decline among participants with *APOE*-ε34, and *APOE*-ε44 risk alleles (Table 4). In individuals carrying

APOE-ε34 allele, those in the highest quintile, and the second highest intakes of dietary α-tocopherol was associated with a slower annual change in global cognition by 0.040 SDU (SD 0.012, P=0.001) and 0.029 (SD 0.012, P=0.012) compared to those in the lowest quintile, respectively. In individuals carrying *APOE*-ε44 allele, individuals with highest α-tocopherol intakes had a slower annual change in global cognition by 0.084 (SD 0.032, P=0.009).

Discussion

In our study, we found that the vitamin E from food sources was associated with a slower cognitive decline. Of the different tocopherol forms, dietary sources of α-tocopherol were associated with slower cognitive decline, specifically among individuals *with APOE*-ε4 allele. Higher intakes of δ-tocopherol were associated with slower cognitive decline among individuals *without APOE*-ε4 allele. These findings suggest that the protective association of vitamin E and brain health might depend on 1) the sources of vitamin E and 2) the APOE risk alleles.

Previous studies suggest that vitamin E intake was protective of risk of dementia [26] and AD [14]. Recent evidence suggests that the sources of vitamin E can be a contributing factor to brain function. Higher intakes of vitamin E were associated with a lower risk of dementia and AD, with vitamin E from dietary sources demonstrating a more robust association with lower risk [27]. Previous findings from our group showed that higher food intakes of α-tocopherol and γ-tocopherols were associated with slower cognitive decline [14]. The antioxidant capacities of vitamin E have been proposed to reduce oxidative stress, preserve neuronal integrity, and normal cell function, therefore, delaying cognitive decline and lowering risk of AD [28].

The recommended dietary allowance (RDA) for vitamin E for adults is 15 mg/day [29]. Although overt vitamin E deficiency is rare, previous evidence suggested that more than 60% of adults in the US have intakes below the recommended level [30]. It is worth noting that the average total vitamin E intake in the present study was 8.5 mg/day. The dietary intake of α-tocopherol from food was 7.2 mg/day, which aligns with previous findings among 18,063 American adults in the NHANES 2003–2006 [30], well below the RDA levels. The threshold effect cannot be sufficiently assessed, given that most participants had intakes below the RDA. Further investigation is warranted to examine the threshold effect and its association with cognition.

We observed that vitamin E and α-tocopherol from food sources *only* were associated with slower cognitive decline among participants with the *APOE*-ε4 risk allele. Nutrients are not consumed in isolation but in the matrix of foods. Therefore, the synergistic effects of vitamin E with other nutrients from the diet may further benefit brain health. Common food sources of dietary tocopherols, i.e., nuts, fruit and vegetables, and vegetable oils [31, 32]. Alpha-tocopherol is the most biologically active form of vitamin E in most human and animal tissues and with the most potent antioxidant capacity [33]. Kinetic studies demonstrated that α-tocopherol has a longer retention rate in plasma and tissues, underscoring the concept that α-tocopherol can be maintained and accumulated in the

tissue, whereas other forms of tocopherols are metabolized quickly [13]. In addition to its antioxidant properties, α-tocopherol enhances the activity of phosphoprotein phosphatase 2A, an enzyme implicated in AD pathophysiology [34].

The associations we observed herein were genotype specific. *APOE* polymorphism plays a critical role in lipoprotein transport and lipid metabolism[35], and *APOE*-ε4 genotype is one of the strongest risk factors for AD. *In vitro,* ApoE protein shows antioxidant activity. Polymorphisms in *APOE*, such as *APOE*-ε4, *APOE*-ε3, or *APOE*-ε2 have been reported to have decreased antioxidant capacity (increased oxidative stress), with *APOE*-ε4 having the least antioxidant capacity, and *APOE*-ε2 with the most potent antioxidant capacity [36–38]. In human studies, those with *APOE*-ε4 versus non-*APOE*-ε4 carriers showed decreased antioxidant status, and increased oxidized LDL[39], and increased oxidative stress [40]. ApoE determines the transportation of vitamin E into peripheral tissues through HDL binding to scavenger receptor class B type I (SR-BI) [41]. In ApoE-deficient mice, lower concentrations of α-tocopherol were observed in different brain regions, indicating the importance of ApoE in transporting α-tocopherol to the brain [13]. Indeed, findings from animal studies suggested differences in the processing of vitamin E regarding *APOE* genotype with an impaired delivery of vitamin E to peripheral tissues observed in the *APOE*4 genotype [35]. These evidence indicate that *APOE*-ε4 carriers have a significantly decreased antioxidant capacity either 1) because of the polymorphism of *APOE*4 and/or 2) the reduced capacity of *APOE*-ε4 in transporting antioxidant nutrients like vitamin E. In the present study, we observed that tocopherols from food sources were associated with slower cognitive decline, particularly in participants with *APOE*-ε4 allele, and δ-tocopherol was associated with slower cognitive decline in participants without *APOE*-ε4 allele. We hypothesize that higher intakes of food α-tocopherol among participants with *APOE*4 genotype might associate with an increase in the uptake of α-tocopherol to the peripheral tissue, including the central nervous system, which may compensate for the reduced antioxidant capacity of e4 allele that could therefore attenuate the cognitive decline.

Our study has limitations. Firstly, intakes of vitamin E were assessed using self-reported FFQ, which could be prone to recall error, and misclassification of dietary intake. However, our previous investigation demonstrated the validity of FFQ using objective biochemical markers in older adults from the CHAP study [42, 43]. We used FFQ data collected prior to 2002 when individual types of tocopherol were reported which decreased the sample size. We excluded participants with MMSE less than 10 to address the potential recall error related to cognitive decline. Second, we used vitamin E intakes from the first available FFQ, which might limit us to assessing the causal association of changes in intakes over time and the changes in cognitive function. There is a potential limitation in generalizing our findings to populations with different socio-economic statuses, given the study demographic represents older adults from the south side of Chicago. Although we have accounted for multiple potential confounders, we cannot completely rule out other residual confounding. We must be cautious against a causal interpretation of the results due to the study's observational nature and lack of objective measurement of vitamin E. Given the relative smaller samples size of each risk allele among participants with *APOE*-ε4 genotype, future studies of different racial groups with larger sample sizes are warranted to validate our findings, and to further investigate the causal role of vitamin E from dietary sources on

cognition. The present study adds to the evidence base by examining intakes of vitamin E and cognitive function in a biracial population-based community study with a long-term follow-up among participants with *APOE* determinations.

Conclusion

Vitamin E from food sources was associated with slower cognitive decline in a high-risk population. Specific forms of vitamin E, i.e. α-tocopherol from food sources, was protective of cognitive decline among those *with APOE*-ε4 allele. Our findings suggest that different forms of dietary vitamin E might have different associations with cognitive decline in older adults depending on their *APOE*-ε4 allele status.

Acknowledgements

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Data Availability

The data are not publicly available due to privacy or ethical restrictions. The data supporting the findings of this study can be requested at [https://www.riha.rush.edu/dataportal.html] pending approval of study proposal and DUA.

Glossary

ApoE	Apolipoprotein E
AD	Alzheimer's dementia
SDU	standardized unit

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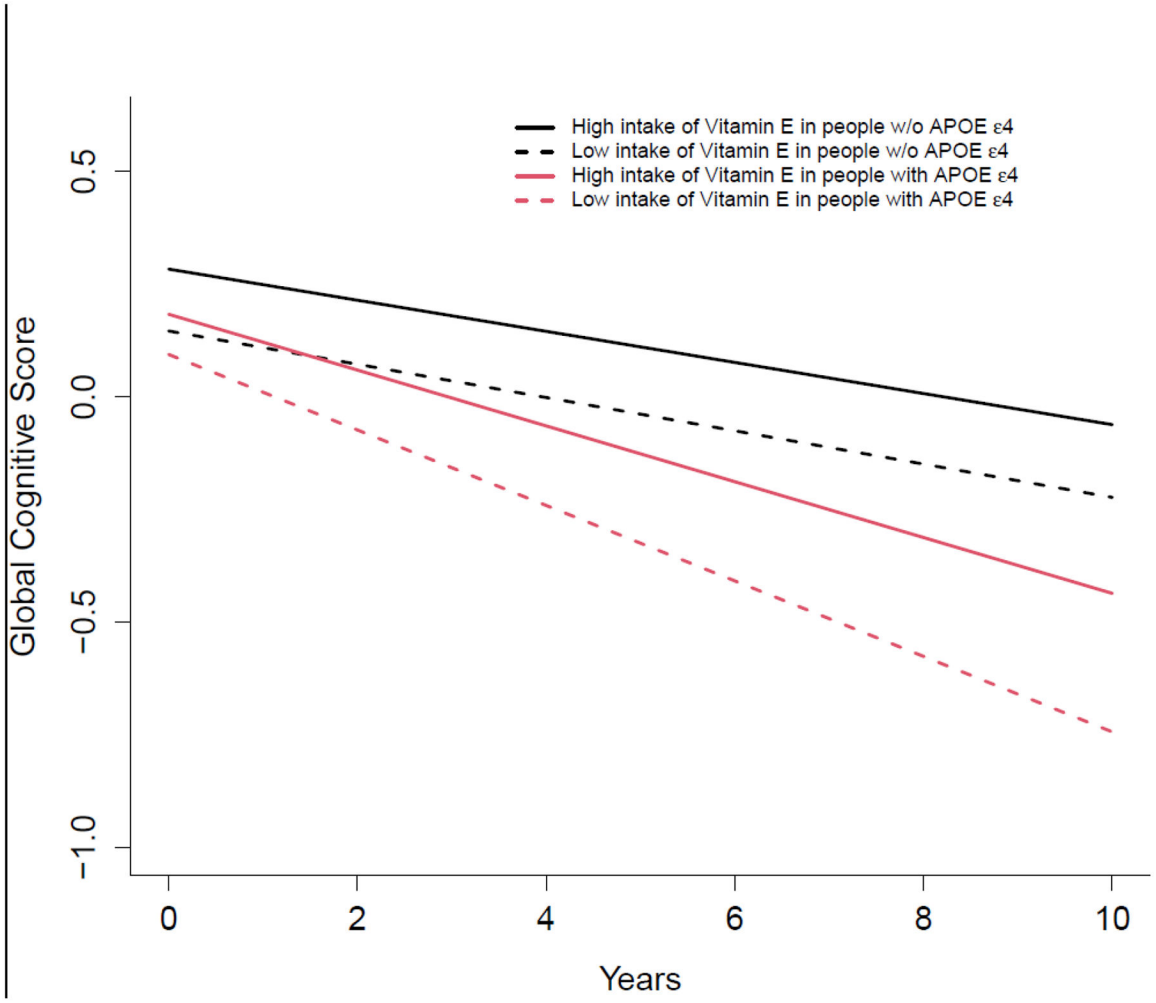

Figure 1.

Intakes of total vitamin E from food sources *only* and annual change of cognitive function among participants with or without *APOE*-ε4 allele (n=2193).

The intakes of total vitamin E from food sources were categorized into quintiles, with the lowest quintile as the referent group.

Red dash line and the solid line represent the lowest and highest quintile of total vitamin E intake among participants with *APOE*-ε4 allele

Black dash line and the solid line represent the lowest and highest quintile of total vitamin E intake among participants without *APOE*-ε4 allele

Model was adjusted for age (years), sex (F/M), education (years), calorie (kcal), smoking status (current, former), race, and their respective interactions with time.

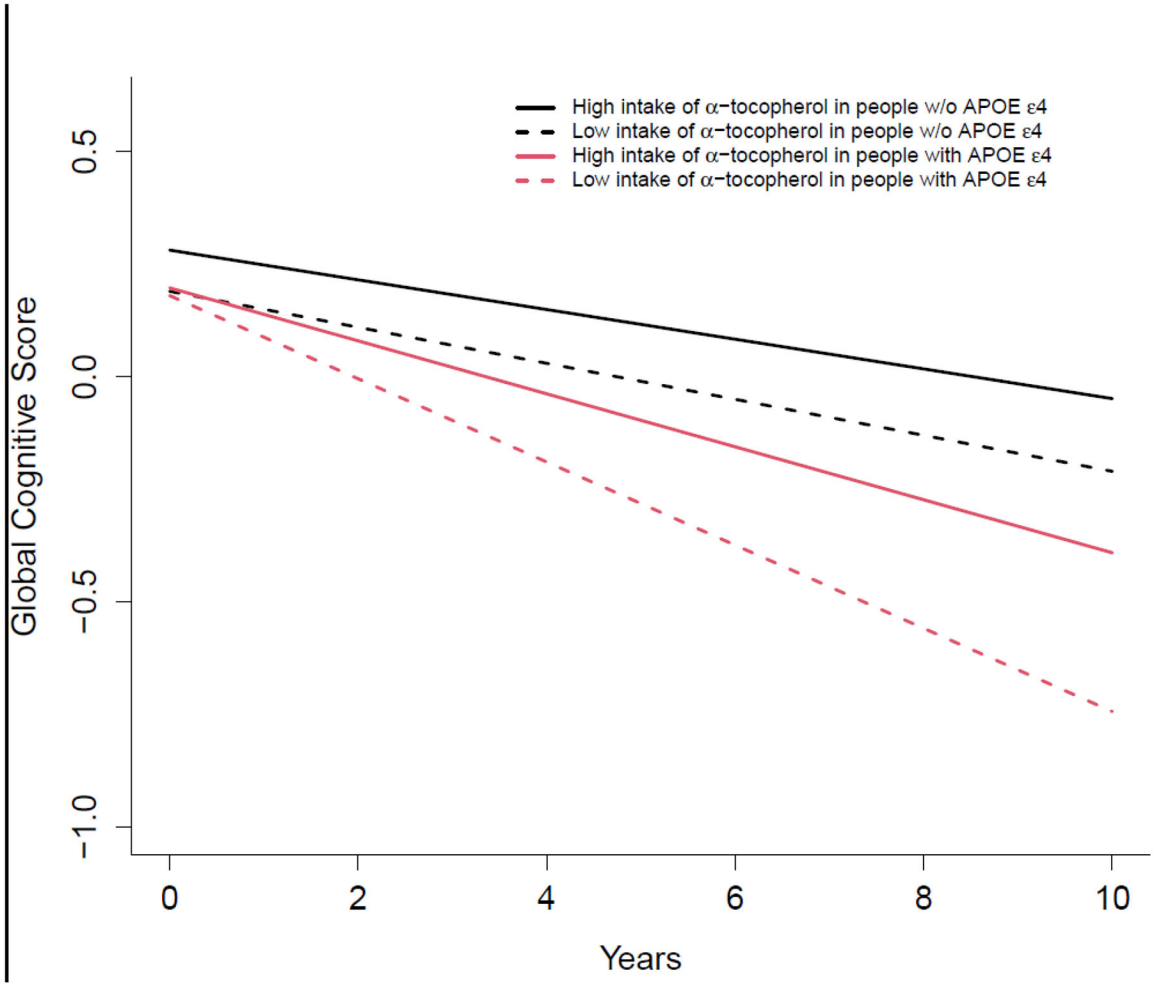

Figure 2.

Intakes of α-tocopherol from food sources *only* and the rate of change in global cognitive score among participants with or without *APOE*-ε4 allele (n=2193)

The intakes of α-tocopherol from food sources were categorized into quintiles, with the lowest quintile as the referent group.

Red dash line and the solid line represent the lowest and highest quintile of α-tocopherol intake among participants with *APOE*-ε4 allele

Black dash line and the solid line represent the lowest and highest quintile of α-tocopherol intake among participants without *APOE*-ε4 allele

Model was adjusted for age (years), sex (F/M), education (years), calorie (kcal), smoking status (current, former), race, and their respective interactions with time.

Table 1.

Participants' baseline characteristics

	Overall N = 2,193	No APOE E4 N=1501	Any APOE E4 N=692	p-value*
Age	74.0 (5.9)	74.2 (6.0)	73.5 (5.7)	0.006
Education	12.6 (3.6)	12.6 (3.6)	12.5 (3.6)	0.65
Daily Calories	1,738 (607)	1,738 (598)	1,738 (627)	>0.99
Global cognition	0.31 (0.67)	0.34 (0.66)	0.26 (0.67)	0.009
Total vitamin E* (mg)	8.5 (5.2, 37.4)	8.8 (5.2, 38.3)	8.3 (5.1, 36.1)	0.34
Tocopherols from food sources (mg)				
α-tocopherol	7.2 (5.5, 9.3)	7.2 (5.6, 9.3)	7.2 (5.5, 9.4)	0.96
β-tocopherol	0.76 (0.54, 1.02)	0.75 (0.54, 1.02)	0.76 (0.54, 1.03)	0.65
δ- tocopherol	3.5 (2.5, 5.0)	3.6 (2.5, 5.0)	3.4 (2.5, 4.9)	0.63
γ- tocopherol	12.2 (8.8, 16.8)	12.2 (8.8, 16.9)	12.0 (8.8, 16.4)	0.46
Male (%)	827 (38)	544 (36)	283 (41)	0.041
Black (%)	1,236 (56)	789 (53)	447 (65)	<0.001
Current smoker (%)	264 (12)	184 (12)	80 (12)	0.69
Former smoker (%)	862 (39)	577 (38)	285 (41)	0.24

*sum of vitamin E from supplements and food sources

Data are mean (SD); Median (IQR); n (%)

P-values were calculated using * Welch Two Sample t-test; Wilcoxon rank sum test; Pearson's Chi-squared test

Table 2.

Association of total vitamin E intakes and intakes of vitamin E from non-supplementary sources with global cognition in participants with or without *APOE*-ε4 allele

Total Vitamin E *							
	Q1[a]	**Q2**	**Q3**	**Q4**	**Q5**	**P for trend**	**Per unit increase** †
Median intakes, mg/d (min, max)	4.43 (1.36,5.04)	5.56 (5.05,6.19)	6.90 (6.20, 8.59)	24.20 (8.68,42.10)	359.40 (42.20,1674.60)		
All	−0.043	0.000 (−0.010, 0.010)	0.005 (−0.005, 0.015)	0.001 (−0.009, 0.011)	0.006 (−0.003, 0.015)	0.23	0.00 (0.00)
with *APOE*-ε4 allele	−0.088	−0.000 (−0.022, 0.021)	0.01 (−0.011, −0.027)	0.003 (−0.018, 0.024)	0.016 (−0.005, 0.037)	0.13	0.00 (0.00)
without *APOE*-ε4 allele	−0.039	0.000 (−0.010, 0.010)	0.003 (−0.008, 0.014)	0.002 (−0.009, 0.012)	0.002 (−0.008, 0.012)	0.72	0.00 (0.00)
Vitamin E from food sources							
	Q1[a]	**Q2**	**Q3**	**Q4**	**Q5**	**P for trend**	
Median intakes, mg/d (min, max)	4.15 (1.51,4.63)	5.01 (4.64,5.33)	5.67 (5.34, 6.01)	6.39 (6.02,6.89)	7.78 (6.9, 43.45)		
All	−0.048	0.01 (0.000, 0.019)	0.0102 (0.000, 0.020)	0.013 (0.004, 0.023)	0.008 (−0.002, 0.017)	0.18	−0.002 (0.002)
with *APOE*-ε4	−0.099	0.012 (−0.009, 0.033)	0.017 (−0.005, 0.038)	0.03 (0.009, 0.051)	0.022 (0.000, 0.043)	0.02	0.005 (0.005)
without *APOE*-ε4	−0.043	0.008 (−0.002, 0.019)	0.007 (−0.003, 0.017)	0.005 (−0.005, 0.016)	0.002 (−0.008, 0.013)	0.94	−0.002 (0.002)

*: Total intakes of vitamin E from foods and supplements

†: Data are expressed as β (SD). β represents per 5mg increased intakes of vitamin E

a: cognitive score (in standard units) of participants in the first quintile. Data in Q2 to Q5 are differences in global cognitive scores compared to Q1. A higher score represents a slower rate of decline in global cognition.

Abbreviation: APOE, Apolipoprotein E

Model 2 was adjusted for age (years), sex (F/M), education (years), calorie (kcal), smoking status (current, former), race, and their respective interactions with time.

The P value for the linear trend was tested by treating the median value of each quintile as a continuous variable.

Table 3.

Association of food sources alpha-, beta-, delta-, and gamma-tocopherol with global cognition in participants with or without *APOE*-ε4 allele

	Q1[a]	Q2	Q3	Q4	Q5	P for trend	
α-tocopherol							
Median intakes, mg/d (min, max)	5.52 (2.08,6.00)	6.43 (6.01,6.75)	7.09 (6.76, 7.44)	7.82 (7.45,8.32)	9.12 (8.33,45.2)		Per unit increase[†]
All	−0.053	0.021 (0.011, 0.030)	0.012 (0.003, 0.022)	0.021 (0.012, 0.031)	0.015 (0.006, 0.025)	0.012	−0.002 (0.002)
with *APOE*-ε4 allele	−0.11	0.028 (0.007, 0.049)	0.03 (0.010, −0.027)	0.0423 (0.021, 0.064)	0.034 (0.013, 0.054)	0.002	0.008 (0.005) [*]
without *APOE*-ε4 allele	−0.05	0.016 (0.006, 0.026)	0.003 (−0.007, 0.014)	0.012 (0.002, 0.022)	0.007 (−0.003, 0.017)	0.51	−0.002 (0.002)
β-tocopherol							
Median intakes, mg/d (min, max)	0.5 (0.12,0.58)	0.65 (0.59,0.70)	0.76 (0.71, 0.81)	0.88 (0.82,0.97)	1.10 (0.98,2.91)		
All	−0.048	0.000 (−0.009, 0.009)	−0.002 (−0.011, 0.007)	0.001 (−0.008, 0.01)	0.00 (−0.010, 0.010)	0.91	0.007 (0.008)
with *APOE*-ε4 allele	−0.099	−0.013 (−0.033, 0.007)	−0.015 (−0.036, −0.027)	−0.0127 (−0.034, 0.009)	−0.015 (−0.037, 0.007)	0.23	−0.019 (0.013)
without *APOE*-ε4 allele	−0.043	0.005 (−0.005, 0.015)	0.003 (−0.007, 0.013)	0.006 (−0.004, 0.016)	0.007 (−0.004, 0.018)	0.19	0.008 (0.007)
δ - tocopherol							
Median intakes, mg/d (min, max)	2.28 (0.33,2.66)	2.98 (2.67,3.25)	3.53 (3.26,3.83)	4.17 (3.84,4.66)	5.38 (4.67,9.76)		
All	−0.048	0.015 (0.006, 0.024)	0.006 (−0.003, 0.015)	0.008 (−0.001, 0.017)	0.010 (0.001, 0.02)	0.17	0.002 (0.002)
with *APOE*-ε4 allele	−0.087	0.026 (0.006, 0.047)	0.003 (−0.016, −0.027)	−0.005 (−0.025, 0.015)	0.008 (−0.013, 0.029)	0.70	−0.000 (0.003)
without *APOE*-ε4 allele	−0.045	0.010 (0.000, 0.020)	0.007 (−0.003, 0.017)	0.013 (0.003, 0.023)	0.011 (0.001, 0.021)	0.03	0.002 (0.001)
γ - tocopherol							
Median intakes, mg/d (min, max)	8.17 (1.41,9.38)	10.4 (9.39,11.25)	12.1 (11.3, 13.0)	14.1 (13.0,15.5)	17.7 (15.5,30.2)		
All	−0.045	0.006 (−0.004, 0.015)	0.007 (−0.003, 0.016)	0.006 (−0.004, 0.015)	0.007 (−0.002, 0.017)	0.21	0.003 (0.002)
with *APOE*-ε4 allele	−0.085	0.009 (−0.011 , 0.030)	0.008 (−0.012 , −0.027)	−0.0108 (−0.031, 0.010)	0.008 (−0.014, 0.030)	0.88	0.003 (0.005)

without *APOE*-ε4 allele	−0.043	0.003 (−0.007 , 0.013)	0.006 (−0.005 , 0.016)	0.012 (0.002 , 0.023)	0.007 (−0.003, 0.018)	0.07	0.003 (0.002)

*p<0.1

†:Data are expressed as β (SD). β represents per 5mg increased intakes of α-tocopherol, γ – tocopherol, and per 1mg increased intakes of β-tocopherol, δ - tocopherol, respectively

a:cognitive score (in standard units) of participants in the first quintile. Data in Q2 to Q5 are differences in global cognitive scores compared to Q1. A higher score represents a slower rate of decline in global cognition.

Abbreviation: APOE, Apolipoprotein E

Model was adjusted for age (years), sex (F/M), education (years), calorie (kcal), smoking status (current, former), race, and their respective interactions with time.

The P value for the linear trend was tested by treating the median value of each quintile as a continuous variable.

Table 4.

Association of food source alpha-tocopherol with global cognition among participants with different *APOE* genotype

	α-tocopherol				
	Q1	**Q2**	**Q3**	**Q4**	**Q5**
APOE-ε24 (n=77)	Ref	0.054 (0.037)	0.051 (0.034)	0.043 (0.039)	−0.006 (0.039)
APOE-ε34 (n=552)	Ref	0.016 (0.012)	0.026 (0.012)	0.040 (0.012) **	0.029 (0.012) *
APOE-ε44 (n=63)	Ref	0.092 (0.033) **	0.045 (0.033)	0.041 (0.038)	0.084 (0.032) **
APOE-ε22 (n=22)	Ref	−0.184 (0.199)	−0.052 (0.127)	0.045 (0.111)	−0.092 (0.132)
APOE-ε23 (n=297)	Ref	0.025 (0.011)	0.004 (0.011)	0.014 (0.011)	0.014 (0.011)
APOE-ε33 (n=1178)	Ref	0.014 (0.006) *	0.001 (0.006)	0.008 (0.006)	0.004 (0.006)

Model was adjusted for age (years), sex (F/M), education (years), calorie (kcal), smoking status (current, former), race, and their respective interactions with time.

Data are expressed as β (SD)

* $p < 0.05$

** $p < 0.01$