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Short Report

Better cognitive performance in elderly taking antioxidant vitamins E and C supplements in combination with nonsteroidal anti-inflammatory drugs: The Cache County Study

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Abstract Studies have shown less cognitive decline and lower risk of Alzheimer's disease in elderly individuals consuming either antioxidant vitamins or nonsteroidal anti-inflammatory drugs (NSAIDs). The potential of added benefit from their combined use has not been studied. We therefore analyzed data from 3,376 elderly participants of the Cache County Study who were given the Modified Mini-Mental State examination up to three times during a period of 8 years. Those who used a combination of vitamins E and C supplements and NSAIDs at baseline declined by an average 0.96 fewer points every 3 years than nonusers ($P < .05$). This apparent effect was attributable entirely to participants with the *APOE* ε4 allele, whose users declined by 2.25 fewer points than nonusers every 3 years ($P < .05$). These results suggest that among elderly individuals with an *APOE ε4* allele, there is an association between using antioxidant supplements in combination with NSAIDs and less cognitive decline over time.

Keywords: Antioxidant vitamins; NSAIDs; Cognitive performance; Random effect model; Dementia prevention

1. Introduction

Previous analyses of data from the Cache County Study have shown reduced risk of Alzheimer's disease (AD) in elderly taking antioxidant vitamin supplements [1] or nonsteroidal anti-inflammatory drugs (NSAIDs) [2] and less cognitive decline in individuals consuming higher amounts of antioxidants from food sources [3] or NSAIDs [4]. Because antioxidants and anti-inflammatory drugs might target different aspects of AD pathogenesis, we sought to examine the effects of their combined use on cognitive decline as measured by the Modified Mini-Mental State Exam (3MS) [5] at three time points during an 8-year period.

2. Methods

The Cache County Study is a prospective study of the elderly residents of Cache County, Utah [6,7]. Briefly, in

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1995–1996 all residents 65 years or older were invited to participate in an examination of cognitive function (Wave I). Surviving participants were then asked to participate in follow-up examinations in 1998–1999 (Wave II) and again in 2003–2004 (Wave III). At each examination, participants were administered the 3MS and evaluated for dementia with a multistage assessment. Buccal DNA samples were obtained at the baseline, and *APOE* genotypes were determined by restriction enzyme analysis [6]. The institutional review boards of Utah State University, Duke University, and Johns Hopkins University approved all protocols. Informed consent was obtained from all participants at each of the assessments; spouses or next of kin gave consent when participants were unable to provide it.

At the baseline examination, participants were asked to identify all supplements, prescription drugs, and over-the-counter medications they used during the previous 2 weeks. This information was corroborated by a visual examination of the medication containers. Participants were then asked to provide detailed information about when the medications or supplements were started and the frequency and duration of use. Participants were considered users of vitamin E supplements, vitamin C supplements, or non-aspirin NSAIDs if they reported taking one of these agents four times or more a week for a month or longer. Participants were also considered users of vitamin E or vitamin C supplements if they reported similar use of a multivitamin preparation that contained at least 400 IU of vitamin E or 500 mg of vitamin C.

A total of 5,092 elderly individuals from Cache County (90% of those eligible) participated in the baseline examination. We set aside 356 prevalent cases of dementia at baseline, 1,324 other participants who had only one 3MS evaluation, and another 36 who lacked complete data on medication use. Thus, 3,376 were included in the current analyses. Those not included were older (mean years of age, 78.4 [standard deviation (SD), 7.6] vs 74.1 [SD, 6.5]; $P < .001$), less educated (mean years of education, 12.7 [SD, 2.9] vs 13.4 [SD, 2.9]; $P < .001$), and more likely to be male (proportion, 46.9% vs 41.4%; $P < .001$).

We compared changes on 3MS scores over time among five mutually exclusive groups of participants: (1) nonusers of vitamin E, vitamin C, and NSAIDs (nonusers); (2) users of NSAIDs but not vitamin E or C (NSAIDs alone); (3) users of vitamin E and C but not NSAIDs (Vit E and C alone); (4) users of vitamin E or C (but not both) with or without NSAIDs (Vit E or C ± NSAIDs); and (5) users of vitamin E and C and NSAIDs (combined users; Vit E and C + NSAIDs). First, we calculated change scores between Wave I and Wave III and tested for differences in the means for each group compared with the reference group of nonusers by using *t* tests. Then we used random effects models to examine the complete data on change over time while controlling for important potential confounders. Such models accommodate fixed and random effects that capture individual differences in 3MS performance over time and account for the correlation in repeated measures [4]. In these analyses, the mutually exclusive user groups were captured as dummy-coded variables (with nonusers as the reference), and time was operationalized as a nominal variable (0, 3, and 8 years for the mean observation points at the three waves) in linear and quadratic forms to account for curvilinear trajectories. Interaction terms between time and the user groups were constructed, and models with and without these terms were compared by using likelihood ratio tests. Because the interaction terms between the user groups and quadratic time were not significant in the models tested, only the interactions with linear time were retained. Parameterized in this way, the main effect terms for the user groups provide estimates of mean differences in 3MS scores at baseline between each and the reference group of nonusers, whereas the interaction terms provide estimates of the differences in mean rate of change on the 3MS over time.

To assess whether these relationships differed by *APOE* genotype, we stratified the sample by the presence or absence of one or more ε4 alleles and estimated the models in the substrata. All models controlled for other factors found to be significantly associated with baseline 3MS including age, sex, education, *APOE* status, and history of diabetes and stroke.

3. Results

Table 1 presents the demographic characteristics of the participants by use of vitamin E, vitamin C, and/or NSAIDs. Users of vitamin E, vitamin C, or NSAIDs were more likely to be female than nonusers of these compounds (all $P < .05$), whereas users of vitamins E and C alone were more likely to be carriers of an *APOE* ε4 allele ($P < .05$). However, among the ε4-carriers, there were no differences in the specific ε4 genotypes (ie, ε2/ε4, ε3/ε4, and ε4/ε4) across the user groups (data not shown). Table 2 presents the unadjusted mean 3MS scores at the Wave I baseline and change scores between Waves I and III for the five specific user groups. During the 8 years of follow-up, combined users (Vit E and C + NSAIDs) showed less decline on the 3MS than nonusers, but this favorable difference was significant only among ε4-carriers ($t = -2.73$, $P < .01$). Among the ε4-carriers, combined users actually maintained their level of performance (0.65 points, 95% confidence interval [CI], −0.58 to 1.89), whereas nonusers declined by −3.77 points (95% CI, −4.53 to −3.01). Other groups declined at rates similar to nonusers regardless of *APOE* ε4 status.

We next used random effects models to estimate changes in 3MS scores over time while controlling for potential confounders such as age, sex, years of education, and history of diabetes or stroke. Users of vitamin E and C alone performed an average 1.09 points (95% CI, 0.28 to 1.91) better on the 3MS at baseline, whereas users of NSAIDs

Table 1
Demographic characteristics of 3,376 participants at the baseline visit

Characteristic	Nonusers (n = 2,007)	NSAIDs alone (n = 794)	Vit E and C alone (n = 153)	Vit E or C ± NSAIDs (n = 337)	Vit E and C + NSAIDs (n = 85)
Age, mean (SD) (y)	74.3 (6.6)	73.9 (6.3)	73.6 (5.5)	73.4 (6.1)	72.9 (6.1)
Female (%)	1,068 (53.2)	542 (68.3)†	79 (51.6)‡	229 (68.0)†	56 (65.9)‡
Education, mean (SD) (y)	13.4 (2.9)	13.2 (2.7)	13.8 (2.9)	13.5 (2.8)	13.8 (2.6)
No. of *APOE* ε4 alleles*					
0	1,390 (69.8)	554 (70.1)	93 (60.8)	228 (68.1)	56 (65.9)
1 or more	601 (30.2)	236 (29.9)	60 (39.2)‡	107 (31.9)	29 (34.1)

Abbreviation: CABG, coronary artery bypass graft surgery.
* Numbers might not add up to totals in the columns because of missing *APOE* genotype data.
† $P < .001$; comparisons made to reference group of nonusers.
‡ $P < .05$; comparisons made to reference group of nonusers.

alone performed an average 0.49 points (95% CI, 0.08 to 0.90) better, compared with nonusers of these compounds. None of the other user groups showed better performance at baseline. Over time, however, only the combined users appeared to perform better than the nonusers. The combined users declined less than nonusers by 0.32 (95% CI, 0.04 to 0.59) points per year, or 0.96 point every 3 years.

When we stratified the analysis by *APOE* status, the favorable performance over time among combined users was only evident in ε4-carriers (Fig. 1.). Among *APOE* ε4-noncarriers, users of vitamin E and C alone performed better than nonusers at baseline by 1.61 points (95% CI, 0.59 to 2.64), but none of the user groups performed better than the nonusers over time. However, among *APOE* ε4-carriers, combined users declined less than nonusers by 0.75 (95% CI, 0.31 to 1.19) points per year, or 2.25 points less every 3 years. All of the other user groups appeared to decline at approximately the same rate as nonusers. When we formally tested this in a separate model, we observed evidence for a multiplicative interaction between NSAIDs and vitamins E and C ($P < .05$) in association with less decline of 3MS over time among *APOE* ε4 carriers.

Table 2
Mean baseline 3MS and change scores over three waves of observation for the full sample and stratified by *APOE* ε4 status*

Group	n	Baseline 3MS	Change in 3MS†
		Mean (95% CI)	Mean (95% CI)
Full sample			
Nonusers	2,006	90.93 (90.68–91.17)	−2.95 (−3.40 to −2.49)
NSAIDs alone	794	91.68 (91.33–92.03)	−3.13 (−3.83 to −2.43)
Vit E and C alone	153	92.16 (91.41–92.90)	−3.52 (−5.00 to −2.04)
Vit E or C ± NSAIDs	337	91.80 (91.22–92.37)	−3.54 (−4.58 to −2.50)
Vit E and C + NSAIDs	85	90.93 (89.80–92.06)	−1.37 (−2.66 to −0.08)
0 *APOE* ε4 alleles			
Nonusers	1,389	91.05 (90.76–91.34)	−2.58 (−3.14 to −2.03)
NSAIDs alone	554	91.63 (91.20–92.07)	−3.07 (−3.92 to −2.23)
Vit E and C alone	93	92.90 (92.02–93.79)	−2.76 (−4.13 to −1.39)
Vit E or C ± NSAIDs	228	91.72 (90.99–92.45)	−3.19 (−4.41 to −1.98)
Vit E and C + NSAIDs	56	90.48 (88.98–91.98)	−2.67 (−4.56 to −0.78)
1+ *APOE* ε4 alleles			
Nonusers	601	90.63 (90.16–91.10)	−3.77 (−4.53 to −3.01)
NSAIDs alone	236	91.82 (91.20–92.43)	−3.00 (−4.17 to −1.83)
Vit E and C alone	60	91.00 (89.70–92.30)	−4.85 (−8.21 to −1.49)
Vit E or C ± NSAIDs	107	92.02 (91.11–92.93)	−4.12 (−6.12 to −2.12)
Vit E and C + NSAIDs	29	91.79 (90.08–93.50)	0.65 (−0.58 to 1.89)‡

* Of the 3,376 participants included in the analysis, 3,375 provided 3MS scores at baseline, 2,140 provided 3MS scores at all three waves, and 1,236 provided 3MS scores at two of the three waves.
† Mean change was calculated by taking the mean of changes in 3MS scores from Wave III minus Wave I for those participants who had scores at both waves.
‡ Mean baseline 3MS scores and mean change scores for each user group were compared against the reference group of nonusers with *t* tests in the full sample and in the subgroups formed by the presence or absence of the *APOE* ε4 allele; comparison of Vit E and C + NSAID group with nonusers was significant at $P < .01$.

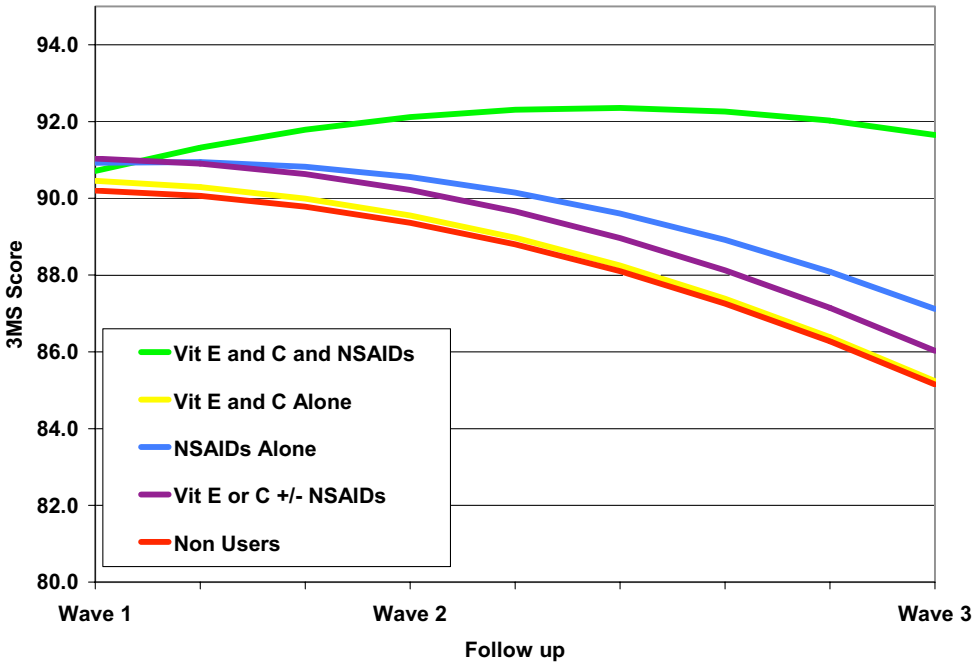

Fig. 1. Estimated trajectories of 3MS scores over three waves of observation, spanning 8 years of follow-up, among those with one or more *APOE* ε4 alleles. Estimates are from mixed models that are adjusted for baseline age, sex, education, history of diabetes and stroke; curves reflect trajectories of the "average" participant.

4. Discussion

In summary, we found an association between using a combination of antioxidant vitamins E and C supplements plus NSAIDs and less cognitive decline among elderly *APOE* ε4-carriers. In previous analyses from the Cache County Study, we reported that high dietary sources of vitamins E and C [3] or NSAIDs initiated earlier in mid-life among *APOE* ε4-carriers [4] were separately associated with less cognitive decline on the 3MS, a global measure of cognitive function that is influenced by a variety of forces including neurodegenerative disease. In the current study, we observed that taking antioxidant supplements and NSAIDs together was especially beneficial and had observable effects on 3MS trajectories even without consideration of the timing of their use, as was done in the previous analyses.

There are biologically plausible reasons why taking NSAIDs and antioxidants in combination might be especially effective, because they act on different pathways involved in neurodegeneration, namely oxidative stress and inflammation [8–10], and targeting both might have added benefits over targeting each separately. These pathways might be particularly salient for *APOE* ε4-carriers who are at high risk for developing AD. However, because the results of the current study were based on a relatively small number of participants who were combined users, it is possible they were due to chance. In addition, although we did not find any evidence of differential attrition among the different user groups (data not shown), it is possible that loss to follow-up might have biased the results. Thus, additional research with larger studies and, eventually, clinical trials are needed to confirm our current findings. Any possible benefits of a combined regimen will have to be weighed against the potential risks of increased cardiovascular complications and/or mortality that recent studies suggest might be associated with using these compounds [11,12].

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