

Supplemental Use of Antioxidant Vitamins and Subsequent Risk of Cognitive Decline and Dementia

Colleen J. Maxwell^{a, b} Matthew S. Hicks^a David B. Hogan^{a-c} Jenny Basran^b
Erika M. Ebly^c

Departments of ^aCommunity Health Sciences, ^bMedicine, and ^cClinical Neurosciences, University of Calgary, Calgary, Canada

Key Words

Antioxidant vitamins · Cognitive decline · Dementia · Vascular cognitive impairment · Alzheimer's disease

Abstract

There are conflicting reports about the potential role of vitamin antioxidants in preventing and/or slowing the progression of various forms of cognitive impairment including Alzheimer's disease (AD). We examined longitudinal data from the Canadian Study of Health and Aging, a population-based, prospective 5-year investigation of the epidemiology of dementia among Canadians aged 65+ years. Our primary objective was to examine the association between supplemental use of antioxidant vitamins and subsequent risk of significant cognitive decline (decrease in 3MS score of 10 points or more) among subjects with no evidence of dementia at baseline ($n = 894$). We also explored the relationship between vitamin supplement use and incident vascular cognitive impairment (VCI; including a diagnosis of vascular dementia, possible AD with vascular components and VCI but not dementia), dementia (all cases) and AD. After adjusting for potential confounding factors assessed at baseline, subjects reporting a combined use of vitamin E and C supplements and/or multivitamin consumption

at baseline were significantly less likely (adjusted OR 0.51; 95% CI 0.29–0.90) to experience significant cognitive decline during a 5-year follow-up period. Subjects reporting any antioxidant vitamin use at baseline also showed a significantly lower risk for incident VCI (adjusted OR 0.34, 95% CI 0.13–0.89). A reduced risk for incident dementia or AD was not observed. Our findings suggest a possible protective effect for antioxidant vitamins in relation to cognitive decline but randomized controlled trials are required for confirmation.

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Introduction

Interest in the potential role of vitamin antioxidants in preventing and/or slowing the progression of Alzheimer's disease (AD) [1] has been heightened with the recent publication of several large prospective cohort studies [2–5]. Experimental, clinical, neuropathological and epidemiological investigations have implicated oxidative stress, involving the accumulation of free radicals with resultant oxidative damage, as a possible factor in the pathogenesis of dementia [6, 7]. Select antioxidants, including vitamins E, C and A, may reduce neuronal damage and death from oxidative reactions by inhibiting the

generation of reactive oxygen species, lipid peroxidation, apoptosis, protein oxidation, damage to cell membranes and/or DNA and beta-amyloid toxicity or deposition [7–11].

Early observational studies of antioxidant supplement use and the subsequent risk of AD provided conflicting results [12, 13]. The Honolulu-Asia Aging Study, a longitudinal study of 3,385 older Japanese-American men followed from 1988 to 1993, demonstrated a significant association between the combined use of vitamin E and C supplements and a reduced risk of vascular dementia and mixed/other dementia, but not AD [12]. During a 4-year follow-up of 633 older community-based adults participating in the East Boston Study, Morris et al. [13] observed no incident AD cases among subjects reporting the use of vitamin E or C at baseline; however, the adjusted risk reduction was statistically significant for vitamin C supplement users only.

More recent epidemiologic reports [2–4] extend previous research by examining the relationship between dietary intake of antioxidants and incident AD risk. In the Rotterdam Study [2], high dietary intake, but not supplement use, of vitamin C or E was associated with a significantly lower risk of AD. Morris et al. [3] found that increasing vitamin E intake from foods, but not other antioxidants or supplement use, was associated with reduced AD risk. This apparent protective effect was evident only for subjects who were APOE ϵ 4 negative and did not remain significant after adjusting for baseline memory score. Luchsinger et al. [4], using data from 980 elderly participants in the Washington Heights-Inwood Columbia Aging Project who were followed for a mean of 4 years, failed to show any significant associations between dietary, supplemental or total intake of vitamins A, C and E and risk of developing AD. In the most recent prospective study of supplement use conducted among 3,227 older residents of Cache County, Utah, Zandi et al. [5] reported a significantly reduced risk of AD for subjects using vitamin E and C in combination, but not for those using either supplement alone.

The apparent inconsistencies in the studies reported to date may reflect a number of methodological factors including differences across investigations in the sample size, age and ethnic characteristics, length of follow-up, validity of exposure measures and relative control of potential confounding factors. At present, these findings are not without controversy and raise further questions regarding the relevance of particular antioxidants and exposure measures (e.g., supplement use vs. dietary intake and dose vs. duration of intake) to the development and

progression of neurodegenerative disorders and cognitive impairment.

Recently, Morris et al. [14] showed that subjects with relatively high total vitamin E intake (from foods and supplements), vitamin E supplement use (and low food intake of vitamin E) or vitamin C supplement use had a significantly reduced rate of cognitive decline. The possibility that antioxidant supplement use may reduce the risk of cognitive decline among persons prior to the onset of dementia provides an avenue for further research. At present, there have been few population-based longitudinal studies examining such an association among older persons.

Our primary objective was to examine, in a prospective manner, the association between supplemental use of antioxidant vitamins and subsequent risk of significant cognitive decline in a cohort of elderly persons followed over 5 years. Additional analyses were conducted to explore the relationship between vitamin supplement use and risk of other relevant health outcomes during follow-up, including vascular cognitive impairment (VCI), dementia (all cases) and AD.

Methods

Sample

We used data from the Canadian Study of Health and Aging (CSHA), a population-based prospective investigation of the epidemiology of dementia among a representative sample of Canadians aged 65 years and older. The study involved 18 centers grouped into five geographic regions (British Columbia, the Prairie Provinces, Ontario, Quebec and the Atlantic Provinces). The total sample, initially interviewed between February 1991 and May 1992, included 10,263 persons, 9,008 from the community and 1,255 residing in institutions. The baseline assessment is identified here as CSHA-1.

All community subjects first underwent a standardized screening interview that included the Modified Mini-Mental State (3MS) examination [15]. Possible scores on this examination range from 0 to 100 with higher values representing better cognitive functioning. Subjects scoring <78 on the 3MS examination, a random sample of those with a score of 78+, and subjects unable to be screened were invited to undergo a comprehensive clinical examination. All institutional subjects underwent the 3MS and clinical examinations. The multidisciplinary clinical examination included a medical history, an informant interview, a physical examination, extensive neuropsychologic testing (for those with 3MS scores \geq 50) and selected laboratory tests. Neuroimaging was not performed.

A consensus conference was held to review all available information and to classify each person as cognitively normal, cognitively impaired but not demented, or demented (on the basis of DSM-III-R criteria) [16]. For subjects classified as demented, a specific diagnosis as to the likely cause was made on the basis of NINCDS-ADRDA criteria for probable and possible AD [17],

while ICD-10 criteria were used for vascular dementia [18]. For the second cycle of the study (CSHA-2), the original cohort was re-contacted in 1996–97, approximately 5 years after the baseline examination. The follow-up assessment was equivalent to that performed at baseline (CSHA-1) with a few exceptions (e.g., laboratory tests were not done for CSHA-2 participants). More comprehensive descriptions of the study design and methodology have been published elsewhere [19, 20].

The present analyses were restricted to subjects who at CSHA-1 underwent the clinical examination, were identified at baseline as not having dementia and had available outcome data from CSHA-2. For our primary outcome of significant cognitive decline our sample size was 894 subjects.

Measures

During the baseline clinical examination, subjects were asked to report their current prescription and over-the-counter medication use, including current use of supplements, complementary and alternative products. Where possible, research nurses also recorded medication/product information from the actual containers presented by the subjects during the in-home or clinic assessment. For institutional subjects, drug data were obtained from review of their health record. The drug data were coded according to the American Hospital Formulary System Pharmacologic/Therapeutic Classification Scheme.

We examined health outcome risks for vitamin E or C supplement use alone and for the combined use of vitamin E and C and/or multivitamins. This latter group included subjects using vitamins E and C (with or without multivitamins), vitamin E and multivitamins, vitamin C and multivitamins and those using multivitamins alone. Multivitamins were included in this latter group since they typically include both vitamins, albeit at relatively lower dosages. No subjects used only vitamin A. Dosage and duration of supplement use was not available.

Other covariates examined included: age, sex, education, self-rated health, history of stroke, history of arterial hypertension, diabetes (history of or drug treatment for), intermittent claudication or cardiac symptoms (as determined by the examining physician), sitting systolic/diastolic blood pressure, smoking status, alcohol use, serum creatinine, serum albumin, body mass index and 3MS score. Cardiac symptoms included chest pain, dyspnea, palpitations and/or edema. Specific questions on smoking and drinking behaviors were not asked of subjects. However, a question on subjects' current or past heavy smoking ('has he/she ever been a heavy smoker, say 20 or more cigarettes a day for a year or more?') was asked as part of the informant interview. Similarly, a question regarding history of heavy drinking ('did you ever think he/she was a heavy drinker? and/or 'did drinking ever cause him/her any problems such as losing jobs, or with driving?') was asked in the informant interview. The informant was a relative or friend identified by the subject.

Our primary outcome of significant cognitive decline was defined as a decrease in 3MS score of 10 points or more between CSHA-1 and CSHA-2. This definition was based on previous analyses [21, 22]. Other health outcomes examined during follow-up included an incident diagnosis of dementia (all cases), AD or VCI. Subjects were coded as experiencing VCI if any of the following conditions were documented at follow-up: a diagnosis of vascular dementia, possible AD with vascular components, or VCI without dementia [23]. For the above outcomes incorporating data on the

incidence of dementia at follow-up, it was necessary to restrict our analyses to surviving subjects who underwent a clinical examination at CSHA-2. It was also necessary to exclude subjects residing in Newfoundland because a legal interpretation of the province's advance directives legislation held it to be unacceptable for a proxy to give consent to participate in a research study on behalf of a person unable to give fully informed consent themselves. As a result of these exclusions, the sample sizes vary according to the specific outcome examined.

Analysis

Bivariate associations were examined using cross-tabulations and χ^2 tests of significance for categorical variables and t tests for continuous variables. Multivariate logistic regression techniques [24] were employed to examine the independent effects and relative importance of subjects' baseline characteristics and supplemental use of antioxidant vitamins in relation to risk of significant cognitive decline and dementia during follow-up. Only factors significant at the bivariate level ($p \leq 0.05$) or identified as clinically relevant to the outcomes of interest were entered into the multivariate logistic regression models. CSHA-1 measures of serum albumin, body mass index, history of heavy drinking and self-rated health were excluded from our final models because of the number of missing values (table 1). However, we also conducted separate analyses for the subgroup of subjects with available data for these variables. All analyses were performed using the SAS (version 8.2) software packages [25].

Results

Among participants who underwent the clinical examination and were identified at baseline as not having dementia ($n = 1,782$), 698 were lost to follow-up because of death. A further 190 subjects had missing values for either time 1 or time 2 3MS scores, resulting in a sample size of 894 subjects for our primary outcome. The mean age of subjects was 78.1 (SD 6.8) years, 64% were female and 20.1% were residing in an institution at baseline (table 1). Compared to nonusers, subjects using vitamin supplements (E, C or multivitamin) were significantly more likely to be older, to not have a history of heavy smoking and to have lower serum albumin levels. These two groups did not differ significantly on other demographic, health or nutritional indices.

Approximately 31.2% ($n = 279$) of the sample experienced significant cognitive decline by the time of CSHA-2. After adjusting for relevant covariates (including baseline 3MS and institutional residence), subjects using both vitamin E and C supplements and/or multivitamins were significantly less likely to experience a decline in their 3MS score of 10 points or more during follow-up (table 2). A similar inverse association was observed for any of vitamin E, C or multivitamin supplement use at baseline.

Table 1. Mean values and percentage distribution of baseline demographic and health characteristics according to vitamin (E, C or multivitamin) supplement use among CSHA participants (n = 894)

Characteristic	Total (n = 894)	Vitamin E, C or multivitamin use	
		yes (n = 121)	no (n = 773)
Age, years	78.1 ± 6.8	79.3 ± 7.1	77.9 ± 6.8*
Females	64.0 (572)	68.6 (83)	63.3 (489)
Education ^a , years	9.0 ± 4.1	9.5 ± 3.9	8.9 ± 4.1
Institutional residence	20.1 (180)	21.5 (26)	19.9 (154)
Heavy smoker (ever) ^a	30.3 (262)	19.1 (22)	32.0 (240)**
Heavy drinker (ever) ^a	9.0 (71)	6.3 (7)	9.4 (64)
Poor self-rated health ^a	17.9 (127)	20.2 (19)	17.6 (108)
Diabetes ^a	10.3 (91)	7.6 (9)	10.7 (82)
History of stroke ^a	8.5 (75)	6.7 (8)	8.8 (67)
Cardiac symptoms ^a	23.6 (209)	24.2 (29)	23.5 (180)
History of arterial hypertension ^a	34.4 (306)	29.2 (35)	35.2 (271)
Systolic blood pressure ^a , mm Hg	145.1 ± 22.6	142.3 ± 21.6	145.6 ± 22.7
Diastolic blood pressure ^a , mm Hg	78.2 ± 12.9	76.4 ± 11.6	78.5 ± 13.0
Serum albumin ^a , g/l	40.4 ± 3.7	39.1 ± 3.4	40.7 ± 3.7**
Body mass index ^a	25.0 ± 4.5	24.3 ± 4.4	25.2 ± 4.5 ^b
3MS score ^a	78.1 ± 12.4	78.9 ± 13.1	78.0 ± 12.2

Values are represented as percent (n) or mean ± SD. Difference between vitamin user (any) and nonuser is statistically significant: * p < 0.05; ** p < 0.01.

^a Variables with missing values; variables with relatively large percentage of missing values include serum albumin (n = 619), body mass index (n = 74), heavy drinking (n = 103) and self-rated health (n = 186).

^b p < 0.10.

Table 2. Percentage distribution and estimated ORs of selected neurocognitive outcomes (1991–1996) according to vitamin supplement use

Baseline vitamin supplement use	Neurocognitive outcome			
	cognitive decline ^a		VCI ^b	
	% (n)	OR (95% CI)	% (n)	OR (95% CI)
No use	31.9 (247/773)	1.00	14.3 (77/537)	1.00
Vitamin E use only	12.5 (1/8)	0.64 (0.08–5.41)	0 (0/6)	–
Vitamin C use only	30.0 (6/20)	0.83 (0.29–2.39)	7.7 (1/13)	0.31 (0.04–2.74)
Vitamin E and C and/or multivitamin use	26.9 (25/93)	0.51 (0.29–0.90)*	5.8 (4/69)	0.39 (0.14–1.14)
Any vitamin use	26.5 (32/121)	0.57 (0.34–0.93)*	5.7 (5/88)	0.34 (0.13–0.89)*

ORs were obtained from multivariate logistic regression models and adjusted for the factors stated below. * p < 0.05.

^a Significant cognitive decline (decrease in 3MS score of 10 points or more; based on a sample of 894 subjects and excluding those with dementia at baseline); model adjusted for age, sex, education level, sitting diastolic blood pressure, baseline 3MS score and institutional residence at baseline; other factors examined but not significant in full model included BMI, serum creatinine and albumin, history of heavy smoking and/or drinking, self-rated health, other drug/supplement use (vitamin B₁₂, aspirin, nonaspirin NSAIDs), history of stroke and arterial hypertension, diabetes (history of or drug treatment for), intermittent claudication, cardiac symptoms and systolic blood pressure.

^b VCI (includes diagnosis of vascular dementia, possible AD with vascular components and VCI but not dementia; based on a sample of 625 subjects and excluding those with dementia or VCI but not dementia at baseline); model adjusted for age, sex, baseline 3MS score, history of stroke and arterial hypertension; other factors examined but not significant in full model included other nutritional, comorbid and health factors as described above.

Subjects reporting any vitamin supplement use at baseline were also significantly less likely to be diagnosed with VCI at follow-up after adjusting for potential confounding or effect modifying factors (table 2). None of the covariates we excluded from our final multivariate models (serum albumin, body mass index, history of heavy drinking and self-rated health) due to a large number of missing values were observed to be significant predictors of significant cognitive decline or VCI.

Neither the combined use of vitamin E and C supplements and/or multivitamin use OR any vitamin supplement use was significantly associated with incident dementia (all cases) or probable AD (data not shown in table). During the 5-year follow-up, there were 230 incident cases of dementia (all causes) and 107 incident cases of probable AD. Among those diagnosed with dementia at follow-up, 79.1% were also coded as positive for our primary outcome of significant cognitive decline (i.e., decline in 3MS score of 10 points or more) during follow-up. Further, among those exhibiting significant cognitive decline, approximately 62% were diagnosed with dementia at follow-up. The adjusted (for age and sex) ORs (95% CIs) associated with the combined use of vitamin E and C supplements and/or multivitamin use for incident dementia and probable AD were 0.79 (0.48–1.32) and 1.00 (0.53–1.87), respectively. There were no incident probable AD cases observed among the 14 subjects reporting a combined use of vitamin E and C supplements (with or without multivitamin use) at baseline (data not shown).

Discussion

Our prospective investigation showed that older subjects reporting a combined use of vitamin E and C supplements and/or multivitamin consumption at baseline were significantly less likely to experience significant cognitive decline during the 5-year follow-up period. In addition, older subjects reporting supplemental use of any antioxidant vitamin at baseline (E, C or multivitamin) were significantly less likely to experience significant cognitive decline or to be diagnosed with VCI during follow-up. These associations remained significant even after adjustment for numerous potential confounders, including age, sex, baseline 3MS score, institutional residence, education and various nutritional and clinical/health characteristics. Although dietary intake of antioxidant vitamins was not assessed in the CSHA, our findings regarding a possible protective effect of vitamin supplement use in relation to cognitive decline and vascular dementia

among older persons are consistent with the previous studies conducted by Morris et al. [14] and Masaki et al. [12]. In the present study, very few subjects reported using only vitamin E or C at baseline (1991); thus, our interpretation of the relative importance of selected antioxidant vitamins (alone vs. in combination) to cognitive risk is limited. However, these associations were in the expected direction with our outcomes of interest.

Contrary to the earlier findings reported by Morris et al. [13] and the most recent large population-based investigation by Zandi et al. [5], we failed to observe a statistically significant association between antioxidant vitamin supplement use and subsequent risk of AD. Relative to the East Boston Study [13], our CSHA cohort was larger and arguably more cognitively vulnerable at baseline. We also observed a greater number of incident probable AD cases over a longer follow-up period (e.g., 107 cases over a 5-year period vs. 91 cases over an average follow-up of 4.3 years, respectively). However, our prevalence estimates for any vitamin E or any vitamin C use (not reported in table) were comparable to those reported by Morris et al. [13]. Although the CSHA was more similar in study design to the Cache County Study [5], the latter investigation included a larger sample (3,227 at risk subjects) and shorter follow-up period (3 years), and was conducted during a more recent time period (mid to late 1990s) than the CSHA. This would account for the relatively higher baseline supplement exposure levels observed in the Cache County Study. Also, unlike the current study, Zandi et al. [5] included estimates of antioxidant dose and duration of use (e.g., only subjects using multivitamins with >400 IU of vitamin E were combined with those using vitamin E supplements and over 97% of both vitamin E and C users reported use of these supplements for 2 or more years). Consequently, it is plausible that methodological limitations related to our exposure measure (e.g., small cell sizes, insufficient dose and duration of use) may account for our failure to observe a significantly reduced risk of AD among antioxidant supplement users. In this regard, it is of interest that we found no incident AD cases among CSHA subjects reporting the combined use of vitamins E and C (regardless of multivitamin use) at baseline.

The strengths of the CSHA include the incorporation of a nationally representative sample of high-risk seniors, rigorous diagnostic procedures and the availability of data on a diverse range of potentially confounding variables. However, our study has several limitations. As noted above, the relatively small numbers of CSHA subjects reporting antioxidant supplement use at baseline and the

absence of data on supplement dose, duration of use and dietary sources of antioxidants limit the inferences we can make regarding the protective effect of vitamins E and C (alone or in combination) in relation to the development of dementia and, more specifically, AD. Although dietary sources have been observed to provide much lower levels of antioxidants than individual supplements, including multivitamins [4, 5], the potential (nondifferential) misclassification of antioxidant exposure among CSHA subjects would be expected to bias the magnitude of any observed associations (e.g., with AD) toward the null.

Although the recent prospective study by Luchsinger et al. [4] also failed to observe any significant associations between antioxidant supplement use and AD risk, despite higher supplement exposure levels and a greater number of incident AD cases, their findings may reflect unique sample characteristics and/or methodological limitations. Most notable are concerns regarding measurement error in their assessment of antioxidant exposure (which may have resulted in a bias toward the null) and the generalizability of their findings. Their study sample was comprised of 43% Hispanic and 32% African American older adults from a defined area of Northern Manhattan. The unique ethnic composition of their cohort appears to explain, in part, their unusually high number of incident AD cases during follow-up [26].

Although our analyses of associations between antioxidant supplement use and subsequent significant cognitive decline and VCI included adjustment for a diverse range of potential confounding factors, we cannot completely exclude the possibility that residual confounding may have affected our findings. Older adults using vitamin supplements may be either relatively healthier or in poorer health compared with nonusers, a potential source of bias in this and other epidemiologic studies. However, relative to previous studies, we examined and controlled for a greater number of potential confounders in our analyses. Further, we observed few significant differences in the sociodemographic and health characteristics of vitamin supplement users compared with nonusers.

A further concern is the possibility that the inverse association observed between antioxidant supplement use and cognitive decline and VCI in the present study may be the result of a reduced reporting and/or use of vitamin supplements among subjects with pre-existing cognitive impairment at baseline. To minimize this source of bias, we adjusted our models for baseline 3MS and other proxy indicators of cognitive impairment, including institutional residence.

Conclusions

Although the relationship between supplemental use of antioxidant vitamins and risk of AD remains unclear, our findings and those of others [12, 14] suggest a possible protective effect of vitamin supplement use in relation to cognitive decline among older persons. Whether or not supplemental use of antioxidant vitamins will actually reduce the risk of cognitive impairment and the burden of neurodegenerative disorders awaits data from ongoing large-scale randomized clinical trials.

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