

# Associations of serum levels of vitamins A, C, and E with the risk of cognitive impairment among elderly Koreans

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**BACKGROUND/OBJECTIVES:** Korea is quickly becoming an aged society. Dementia is also becoming a vital public health problem in Korea. Cognitive impairment as a pre-stage of dementia shares most risk factors for dementia. The aim of the present study was to determine associations of serum levels of vitamins A, C, and E with the risk of cognitive impairment among elderly Koreans.

**SUBJECTS/METHODS:** In this cross-sectional study, a total of 230 participants aged 60-79 years from Yangpyeong cohort were included. Cognitive function was assessed by the Korean version of the Mini-Mental State Examination for Dementia Screening. The logistic multivariable regression model was applied to determine the effect of serum vitamins A, C, and E on the risk of cognitive impairment.

**RESULTS:** There was no significant association between the risk of cognitive impairment and serum levels of vitamin A and vitamin C. There was a significant odd ratio when the second tertile group of beta-gamma tocopherol level was compared to the first tertile group [odds ratio (OR) = 0.37, 95% confidence interval (CI) = 0.14-0.98, *P* for trend = 0.051]. In subgroup analyses, there were significant negative associations between beta-gamma tocopherol level and the risk of cognitive impairment in men (OR = 0.17, 95% CI = 0.03-0.87, *P* for trend = 0.028), non-drinkers or former drinkers (OR = 0.13, 95% CI = 0.02-0.66, *P* for trend = 0.025), and non-smokers or former smokers (OR = 0.27, 95% CI = 0.09-0.82, *P* for trend = 0.017).

**CONCLUSION:** Serum beta-gamma tocopherol levels tended to be inversely associated with the risk of cognitive impairment. Further prospective large-scaled studies are needed to examine this association.

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## INTRODUCTION

Korea is the one of rapidly aging countries. There are 678 million elderly people in Korea, accounting for 13.6% of its total population in 2016 [1]. Dementia causes health and social problems. It decreases quality of life of patients and their family. Cognitive impairment is a pre-stage of dementia. The conversion rate of mild cognitive impairment to dementia is approximately 10% [2]. According to a nationwide study in 2008, patients with dementia and mild cognitive impairment may increase from 13.2 million to 26.6 million by 2050 [3]. Hence, enhancing cognitive function and preventing cognitive impairment might have positive effect in reducing dementia.

Vitamins A, C, and E are involved to prevent aging, and other chronic diseases [4-6]. These vitamins are abundant in fruits and

vegetables which have been reported to have associations with cognitive function or the risk of ischemic stroke [7,8]. Higher intake levels of vitamins A, C, and E have been suggested to play a role in defense against oxidative stress associated with age-related neuronal decline [9-11]. However direct mechanisms how these vitamins affect the cognitive function are not clarified. Associations between levels of vitamins A, C, and E and the risk of cognitive impairment have been investigated by several previous studies [12-16]. It has been suggested that vitamins A, C, and E have beneficial effects on the risk of cognitive impairment or cognitive function [12,14,16]. On the contrary, several studies have found no associations between cognitive impairment or cognitive function and levels of vitamins A, C, and E [13,15]. Therefore, the aim of the present study was to examine associations of serum levels of vitamins A, C, and E

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with the risk of cognitive impairment among elderly Koreans.

## SUBJECTS AND METHODS

### *Study population*

The Yangpyeong cohort was established to investigate risk factors of cardiovascular diseases in 2004. The present study primarily included 430 participants aged 60-79 years who were recruited for Yangpyeong cohort in 2014. A total 230 participants were finally included after excluding participants who did not respond to the Korean version of Mini-Mental State Examination for Dementia Screening (MMSE-DS) or did not provide blood specimens. This study was approved by the Institutional Review Board of Hanyang University (HYI-12-038-revision2). All participants provided written informed consent.

### *Anthropometric measurement and general characteristics*

Height (cm) and weight (kg) of participants were measured using a stadiometer and a digital electronic weighing scale, respectively. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Information on socio-demographic status and lifestyles of participants was collected using interviewer-administered questionnaires.

### *Biochemical examination*

After overnight fasting, participants provided blood specimens. After blood collection, blood samples were placed in vacutainer tubes with anticoagulant. They were wrapped immediately in aluminum foil and were kept in a box to block out light. Serum levels of vitamins A, C, and E were measured by High-Performance Liquid Chromatography (HPLC, 1260 series, Agilent Technologies, USA). Serum vitamin E level was measured as alpha tocopherol, beta tocopherol, and gamma tocopherol. Beta-gamma tocopherol was calculated by adding beta tocopherol to gamma tocopherol.

For serum vitamin A levels, participants with less than 0.35 mg/L, 0.35-0.70 mg/L, and more than 0.70 mg/L were classified as severely deficient, deficient, and normal, respectively [17]. For serum vitamin C levels, participants with less than 2 µg/mL, 2-4 µg/mL, and more than 4 µg/mL were classified as deficient, insufficient, and normal, respectively [18]. For serum alpha tocopherol levels, participants with less than 5.7 mg/L and 5.7-20 mg/L were classified as deficient and normal, respectively. For serum beta-gamma tocopherol levels, participants with less than 4.3 mg/L were classified as normal range [19].

### *Cognitive functional examination*

In the current study, cognitive function of participants was assessed by MMSE-DS. The highest score of this screening tool was 30 points, with lower score indicating decreased cognitive function. Cognitive impairment was considered when participant's score of MMSE-DS was less than mean minus 1.5 times of standard deviation (SD). Value of SD was calculated from the mean of MMSE-DS score among 1,008 healthy volunteers aged more than 60 years who had no dementia, cognitive impairment, physical diseases, or psychoneurotic disease [20].

### *Statistical analysis*

Participants were categorized into tertiles according to serum levels of vitamins A, C, and E. Their general characteristics were analyzed according to these tertile groups. Analysis of variance (ANOVA) was used for continuous variables, and Tukey's multiple comparison test was applied as post-hoc test. Chi-square test was used for categorical variables. Fisher's exact test was used only for smoking status because current smokers were less than five according to vitamins. Odds ratios (ORs) and two-sided 95% confidence intervals (CIs) were calculated. Multivariable logistic regression analysis was performed to investigate the association between serum levels of vitamins and the risk of cognitive impairment. Statistical significance was considered when *p*-value was less than 0.05. All statistical analyses were performed using SAS 9.4 statistical package (SAS Institute, Inc., Cary, NC, USA).

## RESULTS

### *Nutritional assessment of serum vitamins A, C, and E*

Table 1 shows the proportion of nutritional assessment status of serum vitamins A, C, and E. For serum vitamin A levels, 31.3% (*n* = 72) of participants were assessed to be deficient while 0.4% (*n* = 1) of participants were assessed to be severely deficient. For serum vitamin C levels, 13.1% (*n* = 30) of participants were deficient while 1.3% (*n* = 3) of participants were severe deficient. All participants were classified into normal group regarding their serum alpha tocopherol and serum beta-gamma tocopherol levels.

### *General characteristics according to serum vitamins A, C, and E*

General characteristics of these study participants according to levels of serum vitamins are shown in Table 2. The 3<sup>rd</sup> tertile group of serum vitamin A levels had higher proportions of men and current drinkers compared to the 1<sup>st</sup> tertile group. The 3<sup>rd</sup> tertile group of serum vitamin C levels had lower proportions of men, current drinkers, and current smokers compared to 1<sup>st</sup> tertile group. The 3<sup>rd</sup> tertile group of serum alpha tocopherol levels was younger than the 1<sup>st</sup> tertile group while the 3<sup>rd</sup> tertile group of serum beta-gamma tocopherol levels had higher BMI levels than the 1<sup>st</sup> tertile group.

### *Associations between the risk of cognitive impairment and serum vitamins A, C, and E*

Results of associations between the risk of cognitive impairment and serum levels of vitamin A, vitamin C, alpha tocopherol, and beta-gamma tocopherol are shown in Table 3. Serum levels of vitamin A, vitamin C, and alpha tocopherol

**Table 1.** Proportion of participants with deficient or normal status of serum vitamins A, C, and E

Vitamins	Assessment status		
	Severe deficient	Deficient	Normal
Vitamin A	1 (0.4) <sup>1)</sup>	72 (31.3)	157 (68.3)
Vitamin C	3 (1.3)	30 (13.1)	196 (85.6)
		Deficient	Normal
Alpha tocopherol		0 (0)	230 (100)
Beta-gamma tocopherol		0 (0)	230 (100)

<sup>1)</sup> N (%)

**Table 2.** General characteristics of participants according to serum levels of vitamins A, C, and E

	Serum levels of vitamins			P-value <sup>1)</sup>
	T1	T2	T3	
Vitamin A (mg/L)	0.6 ± 0.1 <sup>2)</sup> (n = 78)	0.8 ± 0.1 (n = 75)	1.1 ± 0.1 (n = 77)	
MMSE-DS score	25.7 ± 3.9	25.6 ± 3.7	26.1 ± 3.3	0.648
Age (yrs)	70.5 ± 6.4	70.1 ± 6.4	70.0 ± 6.4	0.870
BMI (kg/m <sup>2</sup> )	24.0 ± 3.3	23.8 ± 3.6	24.2 ± 3.0	0.810
Sex, women	58 (74.4) <sup>3)</sup>	41 (54.7)	35 (45.5)	0.001
Current drinker	28 (36.4)	28 (37.8)	44 (57.9)	0.012
Current smoker	3 (3.9)	6 (8.1)	8 (10.5)	0.290
Regular exerciser	44 (57.1)	37 (50.0)	30 (40.0)	0.105
Education status				
Uneducated	15 (19.2)	15 (20.0)	12 (15.8)	0.252
Elementary school	42 (53.8)	30 (40.0)	30 (39.5)	
Middle school	7 (9.0)	13 (17.3)	10 (13.1)	
High school or higher	14 (18.0)	17 (22.7)	24 (31.6)	
Vitamin C (ug/mL)	4.2 ± 1.2 (n = 76)	7.5 ± 1.0 (n = 77)	11.9 ± 2.3 (n = 76)	
MMSE-DS score	26.3 ± 3.2	25.6 ± 3.4	25.6 ± 4.2	0.452
Age (yrs)	71.1 ± 6.13	69.5 ± 6.0	70.0 ± 6.9	0.264
BMI (kg/m <sup>2</sup> )	24.0 ± 3.2	24.3 ± 3.1	23.7 ± 3.6	0.543
Sex, women	33 (43.4)	45 (58.4)	56 (73.7)	0.0008
Current drinker	42 (56.0)	30 (39.0)	28 (37.3)	0.038
Current smoker	12 (16.0)	3 (3.9)	2 (2.7)	0.005
Regular exerciser	43 (57.3)	29 (38.2)	38 (50.7)	0.057
Education status				
Uneducated	11 (14.5)	13 (16.9)	18 (24.0)	0.704
Elementary school	37 (48.7)	32 (41.5)	32 (42.7)	
Middle school	10 (13.1)	12 (15.6)	7 (9.3)	
High school or higher	18 (23.7)	20 (26.0)	18 (24.0)	
Alpha tocopherol (mg/L)	11.9 ± 1.3 (n = 77)	15.5 ± 0.9 (n = 77)	21.2 ± 5.9 (n = 76)	
MMSE-DS score	25.2 ± 3.9	25.8 ± 3.7	26.3 ± 3.3	0.186
Age (yrs)	71.6 ± 6.5 <sup>b,4)</sup>	70.2 ± 6.5 <sup>ab</sup>	68.7 ± 5.8 <sup>a</sup>	0.021
BMI (kg/m <sup>2</sup> )	23.7 ± 3.6	23.9 ± 3.4	24.4 ± 2.9	0.390
Sex, women	41 (53.3)	46 (59.7)	47 (61.8)	0.531
Current drinker	29 (38.2)	36 (47.4)	35 (46.7)	0.445
Current smoker	6 (7.9)	5 (6.6)	6 (8.0)	0.952
Regular exerciser	44 (58.7)	31 (40.8)	36 (48.0)	0.087
Education status				
Uneducated	16 (20.8)	14 (18.2)	12 (16.0)	0.433
Elementary school	40 (51.9)	32 (41.5)	30 (40.0)	
Middle school	9 (11.7)	11 (14.3)	10 (13.3)	
High school or higher	12 (15.6)	20 (26.0)	23 (30.7)	
Beta-gamma tocopherol (mg/L)	0.9 ± 0.2 (n = 70)	1.4 ± 0.1 (n = 78)	2.0 ± 0.4 (n = 82)	
MMSE-DS score	25.2 ± 3.8	26.1 ± 4.0	26.0 ± 3.2	0.321
Age (yrs)	70.9 ± 6.7	70.7 ± 6.0	69.2 ± 6.4	0.200
BMI (kg/m <sup>2</sup> )	22.9 ± 2.9 <sup>a</sup>	23.7 ± 3.2 <sup>a</sup>	25.3 ± 3.3 <sup>b</sup>	< 0.0001
Sex, women	38 (54.3)	45 (57.7)	51 (62.2)	0.610
Current drinker	32 (46.4)	32 (41.0)	36 (45.0)	0.790
Current smoker	7 (10.1)	5 (6.4)	5 (6.3)	0.696
Regular exerciser	33 (48.5)	43 (55.1)	35 (43.8)	0.357
Education status				
Uneducated	12 (17.4)	11 (14.1)	19 (23.2)	0.200
Elementary school	34 (49.3)	39 (50.0)	29 (35.4)	
Middle school	10 (14.5)	12 (15.4)	8 (9.7)	
High school or higher	13 (18.1)	16 (20.5)	26 (31.7)	

T, tertile; MMSE-DS, Mini-Mental State Examination for Dementia Screening; BMI, body mass index.

<sup>1)</sup> P-values were tested by analysis of variance (ANOVA) for continuous variables and Chi-square test or Fisher's exact (only for smoking status) test for categorical variables.<sup>2)</sup> Mean ± SD. <sup>3)</sup> N (%). <sup>4)</sup> Tukey's multiple comparison test was applied at P < 0.05.

**Table 3.** Odds ratio and 95% confidence intervals of the risk of cognitive impairment according to serum levels of vitamins A, C, and E

	Serum levels of vitamins			<i>P</i> for trend <sup>1)</sup>
	T1	T2	T3	
Vitamin A	1.00 (ref.)	2.31 (0.86-6.22) <sup>2)</sup>	1.13 (0.38-3.38)	0.937
Vitamin C	1.00 (ref.)	1.29 (0.48-3.44)	1.15 (0.41-3.19)	0.804
Alpha tocopherol	1.00 (ref.)	0.71 (0.28-1.81)	0.60 (0.22-1.63)	0.304
Beta-gamma tocopherol	1.00 (ref.)	0.37 (0.14-0.98)	0.38 (0.14-1.06)	0.051

T: tertile

All models were adjusted for age and sex.

<sup>1)</sup> *P* for trends were tested by multivariable logistic regression analysis.<sup>2)</sup> Odds ratios (ORs) and 95% confidence intervals (CIs).

were not significantly associated with the risk of cognitive impairment in the crude model or the multivariate model. However, the risk of cognitive impairment in the middle tertile group of beta-gamma tocopherol was 63% lower than that of the first tertile group (OR = 0.37, 95% CI = 0.14-0.98, *P* for trend = 0.051).

#### Associations between the risk of cognitive impairment and serum vitamins A, C, and E by sex, drinking status, and smoking status

Results of associations between serum levels of vitamins and the risk of cognitive impairment by sex, drinking status, and smoking status as subgroup analyses are shown in Table 4. The highest group with serum beta-gamma tocopherol had lower odds ratio for the risk of cognitive impairment compared to the lowest group in men (OR = 0.17, 95% CI = 0.03-0.87, *P* for trend = 0.028), non-drinkers or former drinkers (OR = 0.13, 95%

CI = 0.02-0.66, *P* for trend = 0.025), and non-smokers or former smokers (OR = 0.27, 95% CI = 0.09-0.82, *P* for trend = 0.017)

## DISCUSSION

The current study was performed to investigate associations between serum levels of vitamins (A, C, and E) and the risk of cognitive impairment in elderly Koreans. Serum levels of vitamin A and vitamin C were not associated with cognitive impairment. Serum alpha tocopherol and beta-gamma tocopherol levels were inversely associated with cognitive impairment, although associations between serum alpha tocopherol levels and cognitive impairment were not statistically significant. However, there were inverse associations between beta-gamma tocopherol levels and the risk of cognitive impairment in non-drinkers or former drinkers and non-smokers or former smokers.

The present study revealed no significant association between serum vitamin A or vitamin C level and the risk of cognitive impairment. Hu *et al.* [12] have reported that high levels of plasma carotenoid concentrations are related to high cognitive scores in the Nurses' Health study. However, Kang *et al.* [13] also reported that there is no association between serum vitamin A level and cognitive function. Consistent with our results, Lindeman *et al.* [15] have shown that there is no association between serum concentration of vitamin C and cognitive function. Other studies have indicated that a high score of MMSE is positively associated with serum vitamin C level [14]. Possible mechanisms involved in the association

**Table 4.** Odds ratio and 95% confidence intervals of the risk of cognitive impairment according to serum levels of vitamins by sex, drinking status, smoking status, and regular exercise status

	Men <sup>1)</sup> (n = 134)				<i>P</i> for trend <sup>2)</sup>	Women <sup>1)</sup> (n = 96)				<i>P</i> for trend
	Serum levels of vitamins			<i>P</i> for trend		Serum levels of vitamins			<i>P</i> for trend	
	T1	T2	T3			T1	T2	T3		
Vitamin A	1.00 (ref.)	1.82 (0.51-6.53)	1.33 (0.33-5.40)	0.653	1.00 (ref.)	3.05 (0.57-16.37)	1.04 (0.17-6.33)	0.583		
Vitamin C	1.00 (ref.)	1.61 (0.34-7.56)	1.69 (0.40-7.20)	0.183	1.00 (ref.)	1.17 (0.32-4.27)	0.68 (0.12-3.75)	0.725		
Alpha tocopherol	1.00 (ref.)	0.51 (0.15-1.73)	0.22 (0.04-1.11)	0.055	1.00 (ref.)	1.04 (0.25-4.40)	1.49 (0.37-5.95)	0.542		
Beta-gamma tocopherol	1.00 (ref.)	0.59 (0.18-2.01)	0.17 (0.03-0.87)	0.028	1.00 (ref.)	0.10 (0.01-0.88)	0.67 (0.18-2.55)	0.451		
	Current drinker <sup>3)</sup> (n = 100)				<i>P</i> for trend	Non/former drinker <sup>3)</sup> (n = 127)				<i>P</i> for trend
	Serum levels of vitamins			<i>P</i> for trend		Serum levels of vitamins			<i>P</i> for trend	
	T1	T2	T3			T1	T2	T3		
Vitamin A	1.00 (ref.)	3.71 (0.72-19.07)	0.60 (0.11-3.48)	0.380	1.00 (ref.)	1.98 (0.53-7.37)	1.61 (0.37-7.09)	0.505		
Vitamin C	1.00 (ref.)	0.36 (0.07-1.90)	0.58 (0.13-2.53)	0.389	1.00 (ref.)	7.24 (0.85-61.65)	5.19 (0.58-46.44)	0.253		
Alpha tocopherol	1.00 (ref.)	1.58 (0.38-6.59)	0.84 (0.16-4.36)	0.802	1.00 (ref.)	0.34 (0.08-1.37)	0.36 (0.09-1.45)	0.103		
Beta-gamma tocopherol	1.00 (ref.)	0.35 (0.08-1.65)	0.61 (0.14-2.60)	0.461	1.00 (ref.)	0.27 (0.07-1.01)	0.13 (0.02-0.66)	0.025		
	Current smoker <sup>3)</sup> (n = 17)				<i>P</i> for trend	Non/former smoker <sup>3)</sup> (n = 210)				<i>P</i> for trend
	Serum levels of vitamins			<i>P</i> for trend		Serum levels of vitamins			<i>P</i> for trend	
	T1	T2	T3			T1	T2	T3		
Vitamin A	N.A.	N.A.	N.A.	N.A.	1.00 (ref.)	2.22 (0.81-6.09)	0.91 (0.28-2.94)	0.832		
Vitamin C	N.A.	N.A.	N.A.	N.A.	1.00 (ref.)	1.42 (0.50-4.03)	1.28 (0.43-3.76)	0.700		
Alpha tocopherol	N.A.	N.A.	N.A.	N.A.	1.00 (ref.)	0.60 (0.23-1.57)	0.40 (0.13-1.27)	0.099		
Beta-gamma tocopherol	N.A.	N.A.	N.A.	N.A.	1.00 (ref.)	0.38 (0.14-1.01)	0.27 (0.09-0.82)	0.017		

T, tertile; N.A., not applicable.

<sup>1)</sup> Adjusted for age.<sup>2)</sup> *P* for trends were tested by multivariable logistic regression analysis.<sup>3)</sup> Adjusted for age and sex.

between serum levels of vitamin A or vitamin C and cognitive function are bellows. All-trans retinoic acid in carboxylic form known as vitamin A has been suggested to have antioxidation, anti-inflammatory, anti-cholinesterase, and memory-restorative functions [21]. Retinoic acid is responsible for the neuroimmunological functions and has interactions with other nuclear receptor-mediated signalling pathways. Retinoic acid is related to regeneration and cognition [22]. Furthermore, vitamin A might be able to inhibit formation of beta-amyloid fibrins. It has been found that patients with Alzheimer diseases have lower serum vitamin A levels compared to healthy controls [23]. Vitamin C has antioxidant functions. It is required for the synthesis of noradrenalin from dopamine [24]. It is associated with better memory performance [25]. Thus, further research about the effects of serum vitamins A and C on cognitive function are required.

Compared to the first tertile group of beta-gamma tocopherol level, the middle tertile group showed 63% lower risk of cognitive impairment. In addition, there were inverse associations between serum beta-gamma tocopherol levels with the risk of cognitive impairment among non-drinkers or former drinkers and non-smokers or former smokers in sub-group analyses. Consistent with our results, a previous study has suggested that cognitive function is not associated with plasma levels of tocopherols [13]. On the other hand, the study on cardiovascular risk factors, aging, and dementia has found that participants with higher serum levels of beta-tocotrienol and gamma-tocopherol have lower risk of cognitive impairment, although the highest group of gamma tocopherol level is not related to cognitive impairment [16]. Vitamin E is composed of a group of tocopherols and tocotrienols. It might contribute to the lipid antioxidation and membrane stabilization [26]. Furthermore, it has been found that beta-gamma tocopherol levels in the group with healthy life style might have more preventive effects against the risk of cognitive impairment [27-29]. Thus, in the present study, beta-gamma tocopherol levels were inversely associated with the risk of cognitive impairment among non-drinkers or former drinkers and non-smokers or former smokers.

The present study has several limitations. First, this study design was a cross-sectional study. Therefore, it was difficult to examine the causal effect of vitamins A, C, and E on the risk of cognitive impairment. Second, this study was conducted in a specific rural region. Occupations of participants were mainly housewives for women and farmers for men. Education levels of these participants were different from those of the group aged more than 60 years in Korea. The percent of elementary school graduated participants was higher and the percent of high school or higher graduated participants was lower compared to generalized Korean population among similar aged group [30]. Thus, our results may not represent the entire Korean population. However, biological relevance between this study's participants and the entire Korean population may not differ. Third, variance might be decreased because of its small sample size and few participants who were deficient in serum vitamins A, C, and E.

Nevertheless, our study had the following advantages. First, we conducted the first study investigating associations between

the risk of cognitive impairment and serum levels of vitamin A, C, and E in Korea. Second, the present study used serum levels of vitamins A, C, and E reflecting both food consumption and supplement intake.

In conclusion, the present study revealed that there was no significant association between serum levels of vitamin A or vitamin C and the risk of cognitive impairment. However, compared to the group with low beta-gamma tocopherol levels, the group with middle levels of beta-gamma tocopherol showed 63% lower risk of cognitive impairment. In addition, with increasing beta-gamma tocopherol levels, the risk of cognitive impairment tended to be decreased. Results of sub-group analyses revealed that serum beta-gamma tocopherol levels were inversely associated with the risk of cognitive impairment among non-drinkers or former drinkers and non-smokers or former smokers. Thus, further replication studies are needed to investigate these associations in large-scales, especially the true association between beta-gamma tocopherol level and the risk of cognitive impairment.

## CONFLICT OF INTEREST

The author declares no potential conflicts of interests.

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