ORIGINAL RESEARCH

Negative Correlation Between Vitamin A and Positive Correlation Between Vitamin E and Inflammation Among Healthy Adults in Korea: Based on the Korea National Health and Nutrition Examination Survey (KNHANES) 2016–2018 7th Edition

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Purpose: Vitamins exert its effect through different isoforms. The isoform conversion phases involved are affected outside factors. Here, we investigated the correlation between serum retinol, α-tocopherol, and serum inflammatory markers using stratified data acquired from 2016 to 2018 Korea National Health and Nutrition Examination Survey (KNHANES).

Materials and Methods: This study was based on data acquired from the 7th edition (2016–2018) of the Korea National Health and Nutrition Examination Survey, consisting of survey data on smoking and alcohol drinking, serum retinol level, serum α-tocopherol level, high-sensitivity C-reactive protein (hs-CRP), and baseline characteristics.

Results: There was a negative correlation between serum retinol and hs-CRP in alcohol drinking men. There was a negative correlation between serum retinol and hs-CRP in the alcohol-nonsmoking female group. There was a positive correlation between α-tocopherol and hs-CRP in the nonsmoking and alcohol-drinking group. There was a positive correlation between α-tocopherol and hs-CRP in the nonsmoking and alcohol-drinking female group. There was positive correlation between vitamin A and E and metabolic syndrome. The lowest vitamin A level was observed in subjects with all five metabolic syndrome criteria matched.

Conclusion: There was a negative correlation between serum retinol and hs-CRP and positive correlation between α-tocopherol and hs-CRP. Absorption and secretion of serum retinol are affected by inflammation status through retinol-binding protein. Alcohol acts as a competitive inhibitor of vitamin A oxidation through alcohol dehydrogenase and ALDH activity. Smoking causes inflammation and induces reactive oxygen species scavenging system and increases cytochrome p450 levels. These factors may have contributed to the observed findings. Metabolic syndrome subjects increased as the levels of vitamin A and vitamin E increased. Since obesity is inversely related to ALDH activity, we postulate that patients with metabolic syndrome may also have low ALDH activity, especially in the Asian population. Future studies are warranted to study the efficacy of ALDH or ALDH inducers in patients with vitamin A deficiency or metabolic syndrome.

Keywords: metabolic syndrome, retinol, α-tocopherol, smoking, drinking

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Plain Language Summary

Alcohol flush is a condition that results from accumulation of acetaldehyde. It is more common in Asians. The enzyme involved in the process is ALDH (Acetaldehyde

dehydrogenase). But action of this enzyme is just not confined to digesting alcohol, it is involved in numerous physiologic functions. ALDH is known to function as detoxifier in our system and is sometimes involved in processing of various nutrients essential for life. One such vitamin is vitamin A. Processing of vitamin A requires ALDH for retinol conversion to retinoic acid which is the active form in our body. Lower action of ALDH leads to lower retinoic acid level, leading to under active vitamin A. ALDH gets affected by outside factors. Sips of alcohol may induce ALDH, whereas chronic binge drinking may diminish ALDH action. Studies of alcohol show that there is a benefit from drinking alcohol, but only in small amount. We postulate that ALDH function may be the key factor in ethnic differences in disease prevalence.

Introduction

Inflammation induces numerous reactions in the human body; prolonged inflammation sometimes results in devastating conditions such as brain infarction, dementia, asthma, and myocardial infarction.[1] An array of inflammatory reactions, also known as chronic inflammation, are newly recognized as risk factors for many diseases, especially those that concern vascular integrity, such as coronary artery disease.[2] Several studies have suggested a correlation between serum vitamin levels and serum inflammatory markers.[3] In this study, we investigated the correlation between serum retinol, α-tocopherol, and hs-CRP levels among Koreans stratified by their smoking and drinking status using data from the Korea National Health and Nutrition Examination Survey (KNHANES), 2016–2018.

Materials and Methods

This study was based on data acquired from the 7th edition (2016–2018) KNHANES. The collected data consisted of survey data on smoking and alcohol drinking, serum retinol level, serum α-tocopherol level, hs-CRP, and baseline characteristics. The data were further stratified by smoking and alcohol consumption. The study protocol was approved by the Institutional Review Board of Veterans Hospital Seoul (IRB Number 2020–06-015) and was in compliance with ethical standards.[4]

Study Population

Subjects aged 20 years and older were included in the KNHANES study from 2016 to 2018. Subjects who had a previous diagnosis of hypertension, dyslipidemia, cerebral infarction, osteoarthritis, rheumatoid arthritis, pulmonary tuberculosis, asthma, and diabetes were excluded from the study. Subjects who had been diagnosed with cancer of any kinds were excluded from the study. Subjects who had not answered the smoking and alcohol surveys were excluded. Subjects who had not been tested for serum retinol, serum α-tocopherol, or serum hs-CRP were excluded from the study. Figure 1 depicts the study subject selection. The final number of eligible study subjects was 3540.

Subjects Grouped by Smoking and Alcohol Drinking

Subjects were grouped into two categories based on whether they smoked or drank alcohol. Surveys on smoking and alcohol consisted of standard questionnaires regarding the amount or frequency of usage. Smoking questionnaire included non-smoking, intermittent smoking, daily smoking, and past smoking. Those who answered yes to non-smoking were considered non-smoking individuals and those who answered yes to the other three questions were categorized as smoking individuals. Alcohol drinking questionnaire included the frequency of alcohol consumption during the past one year, never in the past one year, less than one time a month, about one time a month, two to four times a month, two to three times a week, and more than four times a week. Those who answered yes on never in the past one year were considered non-alcohol drinkers and those who answered yes on the other questions were considered alcohol drinkers. Variables were adjusted for age, sex, current smoking, frequency of drinking, mean monthly family income, BMI, hemoglobin A1c, total cholesterol, high-density lipoprotein (HDL), triglyceride, and mean systolic blood pressure.

Laboratory Measurements

Serum retinol level (mg/L) and serum α-Tocopherol level (mg/L) were measured with Agilent1200 (Agilent1200; Agilent, USA) using Chromsystems (Chromsystems; Chromsystems Instruments & Chemicals, Germany) reagents. The reference normal range for serum retinol level in adults is 0.30 mg/L–0.70 mg/L; reference normal range for α-tocopherol in adults is 5.00 mg/L–20.00 mg/L. Serum hs-CRP was measured with Cobas (Cobas; Roche, Germany) using the Cardiac C-reactive Protein Highly Sensitive kit (Cardiac C-reactive Protein Highly

KNHANES: Korea National Health and Nutrition
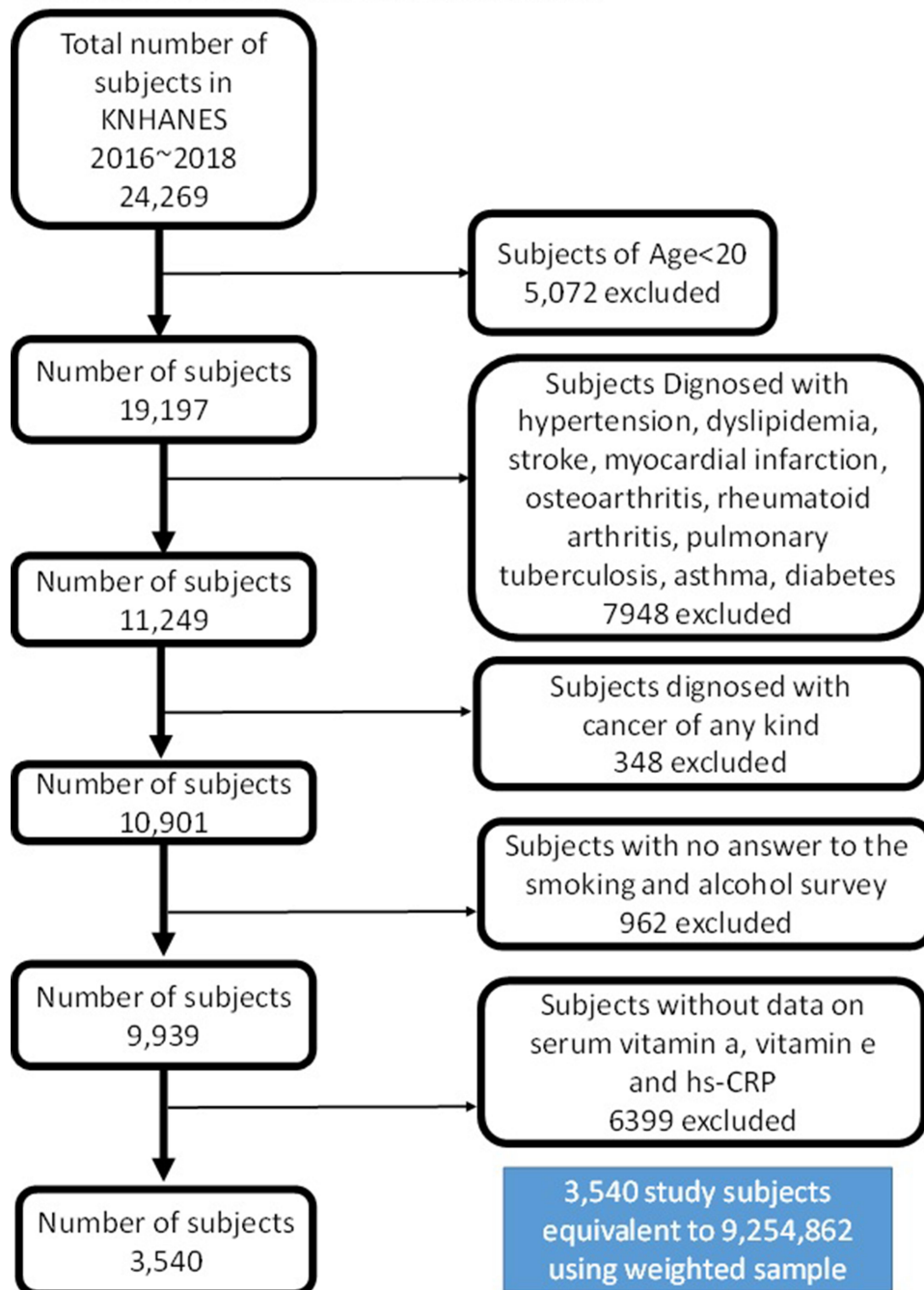Examination Survey Study Subject Selection

Figure 1 KNHANES: Korea National Health and Nutrition Examination Survey study subject selection.

Sensitive; Roche, Germany). The reference normal range for hs-CRP is 0 mg/L–3 mg/L.

Statistical Analysis

Statistical analysis was performed using R software version 3.6.3 (R Foundation, Vienna, Austria). All analyses were performed with the sample weights from the KNHANES data in Phase VII (2016–2018). Data are presented as mean with SE (standard error) for continuous variables and as percentages with SE for categorical variables. Continuous variables were analyzed by independent t-test, while categorical variables were analyzed

using the Rao-Scott chi-square test. Multiple linear regression was performed to evaluate the association between vitamin levels and CRP. All statistical tests were two-sided, and *P*-values <0.05 were considered statistically significant.

Results

General Characteristics of Study Subjects

The total percentage of smokers within the study subjects was 25.1%, smokers in the male study subjects were 40.9%, and smokers in female study subjects were 7.4%. Total percentage of alcohol drinkers were 83.6%, alcohol drinkers in male study subjects were 88.5%, and alcohol drinkers in female study subjects were 78.1%.

Table 1 shows the characteristics of the study subjects stratified by smoking status. The percentage of males and females in the non-smoker group was 41.8% and 58.2%, respectively. The percentage of males and females in the smoker group was 86.1% and 13.9%, respectively. The mean age of the non-smoker and smoker groups was 40.2 years and 39.0 years, respectively. The percentage of alcohol drinkers in the non-smoker and smoker groups was 80.0% and 94.4%, respectively, and this percentage did not differ much between genders. Total cholesterol did not differ significantly between non-smokers and smokers. BMI, hemoglobin A1c did not differ significantly between non-smokers and smokers in male and female groups

separately but showed difference in the whole group. High-density lipoprotein cholesterol and triglyceride levels differed between non-smokers and smokers, 53.47 mg/dL and 47.92 mg/dL for high-density lipoprotein cholesterol levels and 118.53 mg/dL and 179.29 mg/dL for triglyceride levels, respectively. There was a mild difference in vitamin A levels between non-smokers and smokers, 0.48 mg/L and 0.58 mg/L, respectively. Significant difference was not found with vitamin E levels. The hs-CRP levels did not differ much between non-smokers and smokers in clinical levels. Since the values had skewed distribution to be compared raw, we used a logarithmic scale for hs-CRP. The logarithmic scale for hs-CRP between non-smokers and smokers was −0.51 and −0.40, respectively.

Table 2 shows the characteristics of the study subjects stratified by alcohol status. The percentages of males and females in the non-alcohol drinking group were 37.0% and 63.0%, respectively. The percentage of males and females in the alcohol drinking group was 56.0% and 44.0%, respectively. The mean age of the non-alcohol drinking and alcohol drinking groups was 44.4 years and 39.0 years, respectively. The percentage of smokers in the non-alcohol drinking and alcohol drinking groups was 8.7% and 28.4%, respectively. Male and female differences were noted in the percentage of smokers in the non-alcohol drinking and alcohol drinking groups: 20.3% and 43.6% for males, and 1.9% and 9.0% for females. BMI did not differ significantly.

Table 1 Characteristics of Study Subjects Stratified by Smoking Status

		Total	Non-Smoker	Smoker	P-value
Male	Total	52.9 (0.79)	41.8 (0.95)	86.1 (1.24)	
Female	Total	47.1 (0.79)	58.2 (0.95)	13.9 (1.24)	
Age	Total	39.9±0.23	40.2±0.27	39.0±0.45	0.028
Alcohol (%)	Total	83.6 (0.72)	80.0 (0.90)	94.4 (0.84)	<0.001
Alcohol (%)	male	88.5 (0.88)	84.5 (1.33)	94.3 (0.94)	<0.001
Alcohol (%)	female	78.1 (1.07)	76.8 (1.14)	94.5 (2.08)	<0.001
Body Mass Index	Total	23.677±0.0717	23.461±0.0790	24.320±0.1520	<0.001
Waist Circumference(cm)	Total	81.036±0.2078	79.872±0.2268	84.509±0.4206	<0.001
Hemoglobin A1c(%)	Total	5.452±0.0121	5.437±0.0138	5.499±0.0231	0.019
Total Cholesterol(mg/dL)	Total	194.752±0.6914	194.015±0.7711	196.947±1.5034	0.082
High Density Lipoprotein(mg/dL)	Total	52.072±0.2657	53.468±0.2849	47.915±0.5396	<0.001
Triglyceride(mg/dL)	Total	133.800±3.0998	118.525±3.0862	179.294±7.3934	<0.001
Systolic Blood Pressure(mmHg)	Total	113.978±0.2804	113.086±0.3061	116.646±0.5638	<0.001
Diastolic Blood Pressure(mmHg)	Total	75.776±0.2072	75.023±0.2273	78.027±0.3931	<0.001
Log High Sensitivity C-Reactive Protein	Total	-0.479±0.0183	-0.506±0.0202	-0.398±0.0376	<0.001
Vitamin E(mg/L)	Total	13.061±0.1341	13.116±0.1482	12.895±0.2050	0.314
Vitamin A(mg/L)	Total	0.505±0.0043	0.479±0.0043	0.580±0.0085	<0.001

Table 2 Characteristics of Study Subjects Stratified by Alcohol Status

		Total	Non-Alcohol	Alcohol	P-value
Male		52.9 (0.79)	37.0 (2.15)	56.0 (0.88)	
Female		47.1 (0.79)	63.0 (2.15)	44.0 (0.88)	
Age	Total	39.9±0.23	44.4±0.63	39.0±0.24	<0.001
Smoking(%)	Total	25.1 (0.92)	8.7 (1.29)	28.4 (1.03)	<0.001
Smoking(%)	male	40.9 (1.48)	20.3 (3.18)	43.6 (1.59)	<0.001
Smoking(%)	female	7.4 (0.68)	1.9 (0.71)	9.0 (0.84)	<0.001
Body Mass Index	Total	23.677±0.0717	23.573±0.1655	23.698±0.0803	0.501
Waist Circumference(cm)	Total	81.036±0.2078	80.459±0.4395	81.148±0.2288	0.156
Hemoglobin A1c(%)	Total	5.452±0.0121	5.532±0.0369	5.437±0.0123	0.014
Total Cholesterol(mg/dL)	Total	194.752±0.6914	194.883±1.5320	194.726±0.7905	0.929
High Density Lipoprotein(mg/dL)	Total	52.072±0.2657	50.943±0.5546	52.293±0.2870	0.024
Triglyceride(mg/dL)	Total	133.800±3.0998	119.001±3.7198	136.699±3.5979	0.001
Systolic Blood Pressure(mmHg)	Total	113.978±0.2804	113.448±0.6481	114.082±0.3000	0.359
Diastolic Blood Pressure(mmHg)	Total	75.776±0.2072	74.455±0.4155	76.035±0.2302	0.001
Log High Sensitivity C-Reactive Protein	Total	-0.479±0.0183	-0.401±0.0437	-0.494±0.0199	<0.001
Vitamin E(mg/L)	Total	13.061±0.1341	13.294±0.2575	13.015±0.1399	0.284
Vitamin A(mg/L)	Total	0.505±0.0043	0.443±0.0064	0.517±0.0047	<0.001

Hemoglobin A1c levels were slightly different between the non-alcohol drinking and alcohol drinking groups (5.53 and 5.43, respectively). Total cholesterol did not differ significantly between non-alcohol drinkers and alcohol drinkers. High density lipoproteins and triglycerides differed between non-alcohol drinkers and alcohol drinkers: 50.94 mg/dL and 52.29 mg/dL for high-density lipoproteins and 119.0 mg/dL and 136.7 mg/dL for triglycerides, respectively. There was a mild difference in serum retinol levels between non-alcohol drinkers and alcohol drinkers, 0.44 mg/L and 0.52 mg/L, respectively. No significant difference was found in α-tocopherol levels. hs-CRP levels did not differ much between non-alcohol drinkers and alcohol drinkers in clinical levels, which were compared using a logarithmic scale. The logarithmic scale for hs-CRP between non-alcohol drinkers and alcohol drinkers was −0.40 and −0.49, respectively.

Correlation Between Vitamins and Inflammation in Groups Stratified by Smoking, Alcohol Consumption, and Gender

There was a negative correlation between serum retinol and hs-CRP in alcohol-smoking and alcohol-non-smoking men, both adjusted and unadjusted groups with beta constant −0.51, standard error 0.20, confidence interval −0.90~-0.12, P-value 0.01, and beta constant −0.55, standard error 0.23, confidence interval −1.00~-0.10, P-value 0.02, respectively. There was a negative correlation between serum retinol and hs-CRP in alcohol-non-smoking females adjusted group with beta constant −0.49, standard error 0.18, confidence interval −0.85~-0.13, and P-value <0.01. Figure 2 depicts the correlation between log CRP and vitamin A.

There was a positive correlation between α-tocopherol and hs-CRP in non-smoking and alcohol-drinking male and female unadjusted groups, beta constant 0.02, standard error 0.01, confidence interval 0.004 ~ 0.03, P-value<0.01, and beta constant 0.03, standard error 0.01, confidence interval 0.01 ~ 0.04, P-value<0.01, respectively. There was a positive correlation between α-tocopherol and hs-CRP in the non-smoking and alcohol-drinking female adjusted group with beta constant 0.02, standard error 0.01, confidence interval 0.01 ~ 0.03, P-value<0.01. Figure 3 depicts the correlation between log CRP and vitamin E. Table 3 shows the correlation between each metabolic profile criteria and vitamin A and vitamin E.

The percentages of male and female vitamin E deficient subjects who matched metabolic profile criteria were 0.00% and 0.00%, respectively. The percentage of male and female vitamin A deficient subjects who matched metabolic profile criteria were 10.03% and 3.12%, respectively. The percentage of male and female vitamin E sufficient subjects who matched the metabolic profile criteria were 15.65% and
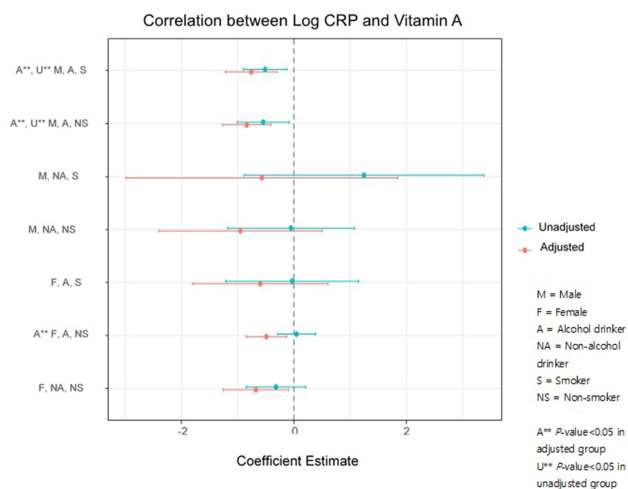
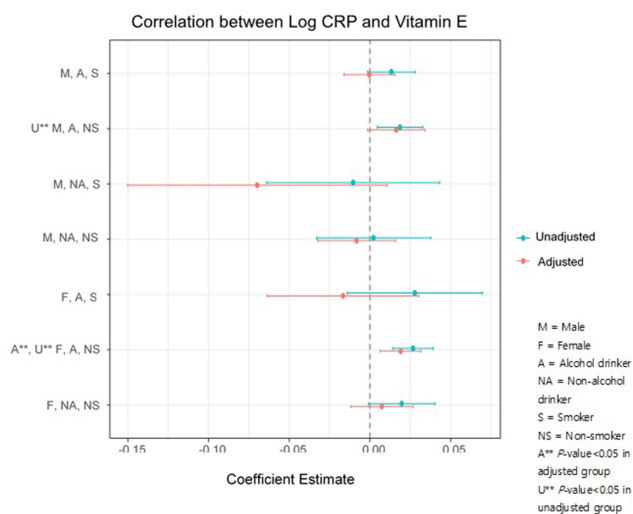**Figure 2** Correlation between Log CRP and Vitamin A.

Figure 3 Correlation between Log CRP and Vitamin E.

7.58%, respectively. The percentage of male and female vitamin A sufficient subjects who matched metabolic profile criteria were 15.46% and 9.18%, respectively. The percentage of male and female vitamin E over-sufficient subjects who matched metabolic profile criteria were 41.91% and 24.06%, respectively. The percentage of male and female vitamin A over-sufficient subjects who matched metabolic profile criteria were 27.45% and 16.73%, respectively. These results are summarized in Table 4–7. The highest percentage of metabolic syndrome criteria matched/whole group in both males and females were observed in the vitamin A and E over-sufficient group. The numbers of matched metabolic criteria increased as vitamin A and E levels increased. However, there was an exception when all five metabolic

syndrome criteria were matched in the vitamin A analysis: female serum vitamin A level was the lowest among all six groups of metabolic syndrome profiles matched from 0 to 5.

Discussion

Vitamin A Signaling is Mediated by Inflammation

Previous studies have shown an inverse correlation between vitamin A and inflammation; many factors are known to influence the level of vitamin A through many phases from transport to metabolism. Inflammation and infection are known to negatively affect vitamin A through decreased absorption, increased urinary excretion, and increased sequestration in the liver. Studies suggest that liver retinol-binding protein (RBP) synthesis is reduced by TNF-α (tumor necrosis factor alpha), IL-1 (Interleukin 1), IL-6 (Interleukin 6), and type 1 interferons through reduced transcription of retinol binding protein 4 *(RBP4) mRNA* signaling.[5] Other studies suggest that enteric infections can decrease vitamin A absorption through damaged intestinal epithelium and leakiness of intestines.[5,6] Septic conditions are also known to decrease vitamin A levels in the kidney. One study done in Birmingham reported that adults with severe infection excreted more vitamin A than healthy controls,[7] while another study suggested that children with severe infection are at risk of increased urinary retinol loss.[8]

Acute inflammation not only decreases serum vitamin A levels but also diminishes retinol availability in peripheral tissues due to decreased mobilization from the liver.[9] One study suggested that a decrease in light sensitivity during infection occurred through decreased availability of retinal for rhodopsin formation.[10]

Vitamin A and Its Anti-Inflammatory Properties

The anti-inflammatory effects of vitamin A are known to occur through macrophage lineage regulation at the monocyte differentiation level. All-trans retinoic acid (ATRA) inhibits the release of macrophage inflammatory cytokines and induces M1 macrophages, which secrete pro-inflammatory cytokines to transform into M2 macrophages, which secrete anti-inflammatory cytokines.[11]

Some studies have reported low serum levels of vitamin A and carotene in elderly patients with chronic leg ulcers.[12] Other studies have shown that vitamin A can reverse the anti-inflammatory steroid effect on wound

Table 3 Correlation Between Metabolic Syndrome Profiles and Serum α-Tocopherol Levels and Serum Retinol Levels

Male			Female		
	he_vita	he_vite		he_vita	he_vite
he_glu	0.074*	0.130*	he_glu	0.079*	0.145*
he_bmi	0.099*	0.147*	he_bmi	0.101*	0.141*
he_wc	0.138*	0.186*	he_wc	0.121*	0.176*
he_hba1c	0.074*	0.161*	he_hba1c	0.045	0.195*
he_chol	0.261*	0.519*	he_chol	0.201*	0.528*
he_hdl_st2	0.079*	-0.021	he_hdl_st2	0.043	0.070*
he_tg	0.262*	0.506*	he_tg	0.298*	0.362*
log_tg	0.349*	0.484*	log_tg	0.327*	0.346*
he_ldl_drct	0.036	-0.025	he_ldl_drct	0.065	0.312*
he_sbp	0.134*	0.147*	he_sbp	0.189*	0.169*
he_dbp	0.183*	0.201*	he_dbp	0.201*	0.153*

Notes: * mark stands for P-value<0.05 shown as blue box.

healing, enhance the production of extracellular matrix components, and increase the proliferation of keratinocytes and fibroblasts in organs. The mechanism underlying the enhancement of the early inflammatory phase is believed to be the stimulation of the local immune response through an increased number of monocytes and macrophages at the wound site.[13] This implies that while vitamin A can work as an anti-inflammatory agent, it may also be pro-inflammatory. Studies have suggested that vitamin A is an immune response regulator; it is crucial in maintaining homeostasis and proper immune regulation. These are known to occur according to the degree of pathogen-induced inflammation. These decrease the

production of retinoic acid, leading to a more pro-inflammatory environment to help fight pathogens.[14]

Vitamin A, Alcohol, and Smoking Interactions

Studies suggest that alcohol consumption affects retinoid storage in two phases. The first is the mobilization phase and the second is the catabolism phase. The mobilization phase occurs through hepatic retinoid redistribution to

Table 4 Male Group Vitamin A and E and Metabolic Syndrome

vita_g	MET_g0	MET_g1	se.MET_g0	se.MET_g1
1	0.899696	0.100304	0.061336	0.061336
2	0.84538	0.15462	0.011175	0.011175
3	0.725527	0.274473	0.027606	0.027606
vita_g	**MET_g0**	**MET_g1**	**se.MET_g0**	**se.MET_g1**
1	1	0	0	0
2	0.84349	0.15651	0.010449	0.010449
3	0.580856	0.419144	0.047746	0.047746

Notes: vita_g = Serum retinol = 1_deficient (<0.30 mg/L), 2_sufficient (0.30 mg/L ~ 0.70 mg/L), 3_over-sufficient (>0.70 mg/L). vite_g = Serum α-tocopherol = 1_deficienct (<5.00 mg/L), 2_sufficient (5.00 mg/L ~ 20.00 mg/L), 3_over-sufficient (>20.00 mg/L). Whole group = Subjects who tested for 3 or more of the male or female metabolic syndrome criteria. MET_g0 = fraction of 2 or less metabolic syndrome criteria matched/whole group. MET_g1 = fraction of 3 or more metabolic syndrome criteria matched/whole group. Male metabolic syndrome criteria = 3 or more of the 1~5 criteria. 1. Waist circumference = 102 cm or higher. 2. Triglyceride = 150mg/dL or higher. 3. High density lipoprotein = 40mg/dL or lower. 4. Systolic blood pressure =135mmHg or higher/or/diastolic blood pressure = 85mmHg or higher. 5. Fasting glucose = 100mg/dL or higher.

Table 5 Male Group Vitamin A and E Matched and Metabolic Syndrome

vita_g	vite_g	MET_g0	MET_g1	se. MET_g0	se. MET_g1
1	1	1	0	0	0
2	1	1	0	0	0
3	1	1	0	0	0
1	2	0.908305	0.091695	0.065096	0.065096
2	2	0.858864	0.141136	0.01122	0.01122
3	2	0.756207	0.243793	0.029359	0.029359
1	3	0.676835	0.323165	0.30933	0.30933
2	3	0.580063	0.419937	0.065058	0.065058
3	3	0.576631	0.423369	0.073735	0.073735

Notes: vita_g = Serum retinol = 1_deficient (<0.30 mg/L), 2_sufficient (0.30 mg/L ~ 0.70 mg/L), 3_over-sufficient (>0.70 mg/L). vite_g = Serum α-tocopherol = 1_deficienct (<5.00 mg/L), 2_sufficient (5.00 mg/L ~ 20.00 mg/L), 3_over-sufficient (>20.00 mg/L). Whole group = Subjects who tested for 3 or more of the male or female metabolic syndrome criteria. MET_g0 = fraction of 2 or less metabolic syndrome criteria matched/whole group. MET_g1 = fraction of 3 or more metabolic syndrome criteria matched/whole group. Male metabolic syndrome criteria = 3 or more of the 1~5 criteria. 1. Waist circumference = 102 cm or higher. 2. Triglyceride = 150mg/dL or higher. 3. High density lipoprotein = 40mg/dL or lower. 4. Systolic blood pressure =135mmHg or higher/or/diastolic blood pressure = 85mmHg or higher. 5. Fasting glucose = 100mg/dL or higher.

Table 6 Female Group Vitamin A and E and Metabolic Syndrome

vita_g	MET_g0	MET_g1	se.MET_g0	se.MET_g1
1	0.968796	0.031204	0.009992	0.009992
2	0.908186	0.091814	0.008234	0.008234
3	0.832676	0.167324	0.040316	0.040316

vita_g	MET_g0	MET_g1	se.MET_g0	se.MET_g1
1	1	0	0	0
2	0.924171	0.075829	0.006888	0.006888
3	0.759387	0.240613	0.041779	0.041779

Notes: vita_g = Serum retinol = 1_deficient (<0.30 mg/L), 2_sufficient (0.30 mg/L ~ 0.70 mg/L), 3_over-sufficient (>0.70 mg/L). vite_g = Serum α-tocopherol = 1_deficient (<5.00 mg/L), 2_sufficient (5.00 mg/L ~ 20.00 mg/L), 3_over-sufficient (>20.00 mg/L). Whole group = Subjects who tested for 3 or more of the male or female metabolic syndrome criteria. MET_g0 = fraction of 2 or less metabolic syndrome criteria matched/whole group. MET_g1 = fraction of 3 or more metabolic syndrome criteria matched/whole group. Female Metabolic syndrome Criteria = 3 or more of the 1~5 criteria. 1. Waist circumference = 89 cm or higher. 2. Triglyceride = 150mg/dL or higher. 3. High density lipoprotein = 50md/dL or lower. 4. Systolic blood pressure =135mmHg or higher/or/diastolic blood pressure = 85mmHg or higher. 5. Fasting glucose = 100mg/dL or higher.

extrahepatic tissues, mediated by an increase in RBP and hepatic RBP expression. The catabolism phase is believed to be mediated by cytochrome (CYP) leading to a decline in hepatic retinoid with no further increase in extrahepatic tissue retinoid levels.[15,16]

Alcohol dehydrogenase (ADH) and acetaldehyde dehydrogenase (ALDH) are also known to affect vitamin A. Retinol is the commonly ingested form of vitamin A. Retinol is converted to retinaldehyde via ADH, and

Table 7 Female Group Vitamin A and E Matched and Metabolic Syndrome

vita_g	vite_g	MET_g0	MET_g1	se. MET_g0	se. MET_g1
1	1	1	0	0	0
1	2	0.968126	0.031874	0.010192	0.010192
2	2	0.920546	0.079454	0.00805	0.00805
3	2	0.838501	0.161499	0.044204	0.044204
1	3	1	0	0	0
2	3	0.74802	0.25198	0.046614	0.046614
3	3	0.804719	0.195281	0.083476	0.083476

Notes: vita_g = Serum retinol = 1_deficient (<0.30 mg/L), 2_sufficient (0.30 mg/L ~ 0.70 mg/L), 3_over-sufficient (>0.70 mg/L). vite_g = Serum α-tocopherol = 1_deficienct (<5.00 mg/L), 2_sufficient (5.00 mg/L ~ 20.00 mg/L), 3_over-sufficient (>20.00 mg/L). Whole group = Subjects who tested for 3 or more of the male or female metabolic syndrome criteria. MET_g0 = fraction of 2 or less metabolic syndrome criteria matched/whole group. MET_g1 = fraction of 3 or more metabolic syndrome criteria matched/whole group. Female Metabolic syndrome Criteria = 3 or more of the 1~5 criteria. 1. Waist circumference = 89 cm or higher. 2. Triglyceride = 150mg/dL or higher. 3. High density lipoprotein = 50md/dL or lower. 4. Systolic blood pressure =135mmHg or higher/or/diastolic blood pressure = 85mmHg or higher. 5. Fasting glucose = 100mg/dL or higher.

retinaldehyde is converted to retinoic acid via ALDH. Retinoic acid is the active form since it can bind to retinoic acid receptors (RARs) and initiate intracellular signaling.[17] With chronic alcohol ingestion, alcohol acts as a competitive inhibitor of vitamin A oxidation via ADH and ALDH, and the conversion process of both retinaldehyde and retinoic acid is altered. This results in inadequate signaling leading to altered proliferation and differentiation of cells.[18,19] Alcohol also induces CYP (particularly CYP2E1) and degrades retinol and retinoid acid. Furthermore, it increases intrahepatic retinol and retinoic acid mobilization.

Numerous studies have investigated the effect of smoking on CYP 450 (cytochrome 450); smoking enhances the expression of CYP, CYP1A1, and CYP1A2 in particular. One study conducted on animals suggested that ferrets exposed to cigarette smoke had increased 4-oxo-RA and 18-hydroxy-RA, the metabolites of retinoic acid. Furthermore, administration of CYP inhibitors such as liarozole or disulfiram, substantially inhibited 4-oxo-RA and 18-hydroxy-RA production.[20] This suggests the role of cigarette smoke in retinoic acid degradation.

Our study results showed that there was a negative correlation between CRP and serum retinol levels in the alcohol drinking smoking/non-smoking male group and the alcohol drinking non-smoking female group. The lack of significant results in alcohol drinking females who were smokers may be attributable to differences in ADH and CYP1A2 activity among genders. Studies suggest that ADH activity is higher in males, CYP1A2 activity is lower in females, and ALDH activity does not show much difference between genders.[21,22]

Vitamin E and Its Anti-Inflammatory Properties

Vitamin E exists in different isoforms in nature. These include α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, and tocotrienol forms. Among the four tocopherols, α-tocopherol and γ-tocopherol are found in the serum and red blood cells (RBCs).[23] The most common form in the human body is α-tocopherol due to the preferential affinity of α-tocopherol transfer protein (100% for α-tocopherol and 9% for γ-tocopherol), and from the faster metabolism of the other forms.[24] There are only scarce concentrations of β-tocopherol and δ-tocopherol found in the serum.[25]

Different isoforms exhibit different ROS-scavenging properties. Studies suggest that ROS scavenging activities in vivo are α> β> Y> δ, and these differences come from the

methylation patterns of each tocopherols.[26] α-Tocopherol and γ-tocopherol both exhibit anti-oxidant activity, but studies suggest that there is a difference in anti-inflammatory properties.[27]

Previous studies have suggested that α-tocopherol therapy has anti-inflammatory effects in vitro and in vivo. Pro-inflammatory cytokines IL-6, IL-1β, TNF-α, chemokine IL-8, and PAI-1 (Plasminogen activator inhibitor 1) were decreased in the α-tocopherol treated group.[28] Studies on γ-tocopherol suggested a difference in the mechanism as compared to that of α-tocopherol. One study suggested that γ-tocopherol inhibits prostaglandin E2 (PGE2) and leukotriene B4 (LTB4) and decreases TNF- α.[29] Another study reported that γ-tocopherol metabolites also inhibited PGE2 through COX-2 (cyclooxygenase 2) inhibition and therefore attenuated inflammation-mediated damage. The unique role of γ-tocopherol comes from its ability to pre-ferentially react with nitrogen oxidant species, thus limiting cellular damage from the enzymatic generation of NO (nitric oxide) more significantly than α-tocopherol.[30]

Studies also imply that γ-tocopherol acts as a trap for membrane-soluble electrophilic nitrogen oxides and other electrophilic mutagens, an action that is not present with α-tocopherol. This suggests the importance of γ-tocopherol and its metabolites in chronic inflammation. Some studies indicate that γ-tocopherol and its metabolites, but not α-tocopherol, possess anti-inflammatory activity.[31]

Vitamin E Interaction with Smoking and Alcohol Consumption

Our results showed a positive correlation between α-tocopherol and hs-CRP in non-smoking and alcohol-drinking male and female unadjusted groups and a positive correlation between α-tocopherol and hs-CRP in the non-smoking and alcohol-drinking female adjusted groups. Studies suggest that smoking increases inflammation and changes levels of γ-tocopherol and α-tocopherol, elevates plasma γ-tocopherol and decreases α-tocopherol levels.[32] Other studies suggest that smoking is inversely associated with both the serum α-tocopherol and γ-tocopherol levels.[33] Studies on alcohol consumption and α-tocopherol suggest that there was a decrease in α-tocopherol with 30 g/day alcohol consumption compared to no alcohol consumption.[34] Other studies have suggested that the frequency of alcohol consumption was positively associated with α-tocopherol.[35]

From previous studies and implications from our study, we believe that non-smokers had increased levels of α-tocopherol through a decrease in γ-tocopherol (as there is an inverse relationship between α and γ-tocopherol) compared to smokers, which might have participated in the observed effect. We believe that lack of significant result in the non-smoking and alcohol drinking male adjusted group may have come from BMI (beta 0.07, standard error 0.01, confidence interval 0.05 ~ 0.09, P-value<0.01). There are studies suggesting a positive correlation between BMI and α-tocopherol levels,[36] whereas other studies suggest a negative correlation.[37] Studies on BMI and α-tocopherol levels have shown conflicting results, and further analysis is warranted. Table 9 shows correlation between α-tocopherol levels and alcohol. It showed that there was an increase in mean serum α-tocopherol level with increase in frequency of drinking (never in the past one year, less than one time a month, about one time a month, two to four times a month, two to three times a week and more than four times a week) and by amount (1–2 g, 3–4 g, 5–6 g, 7–9 g, and 10 g or more of ethanol). The result of this was not purely linear and had an inverse U-shaped graph in the low frequency groups. This result was not applicable to our current study on vitamin A and vitamin E due to very specific subject stratification (over 100 subparts).

Association of Metabolic Syndrome Profiles of α-Tocopherol and Serum Retinol Levels

Vitamin A and vitamin E have been previously reported to benefit patients with metabolic syndrome. Studies on vitamin E reported that participants who were supplemented with α - or γ-tocopherol, or both, showed that the combination of α - and γ-tocopherol supplementation showed superiority in reducing lipid peroxides.[38] Other studies reported that γ-tocopherol supplementation decreased obesity and insulin resistance,[39] reduced triglyceride synthesis and transport,[40] and anti-hypertensive.[41]

Studies on vitamin A reported that patients with metabolic syndrome had lower vitamin A levels;[42] individuals with vitamin A deficiency had a higher risk of hypertri-glyceridemia and hyperglycemia,[43] and RBP4 was posi-tively associated with hip circumference, TG (triglyceride), and diastolic blood pressure.[44] Contrary to previous studies, our results showed different results. Our results showed that the percentage of male and female vitamin E deficient subjects who matched metabolic

Table 8. Number of Metabolic Syndrome Criteria Matched with Vitamin A and E Status

Number of Metabolic Syndrome Criteria Matched	he_vita		he_vite		Ratio of Vitmain A Insufficiency		Ratio of Vitmain E Insufficiency		se.he_vita		se.he_vite		se.ratio of Vitmain A Insufficiency		se.ratio of Vitmain E Insufficiency	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
0	0.512	0.416	11.466	12.446	0.0489	0.1528	0.0084	0.0000	0.0083	0.0054	0.231	0.158	0.0113	0.0135	0.0050	0.0000
1	0.560	0.436	12.574	12.655	0.0386	0.1634	0.0056	0.0053	0.0093	0.0074	0.231	0.272	0.0112	0.0181	0.0036	0.0038
2	0.606	0.461	13.912	14.112	0.0212	0.0780	0.0016	0.0000	0.0119	0.0096	0.302	0.407	0.0077	0.0179	0.0016	0.0000
3	0.636	0.496	15.801	15.254	0.0062	0.0478	0.0000	0.0000	0.0170	0.0135	0.570	0.493	0.0062	0.0213	0.0000	0.0000
4	0.589	0.534	16.247	16.678	0.0556	0.0406	0.0000	0.0000	0.0234	0.0202	0.868	0.878	0.0434	0.0242	0.0000	0.0000
5	0.567	0.404	13.725	17.106	0.0000	0.3033	0.0000	0.0000	0.0510	0.0516	2.413	1.235	0.0000	0.2572	0.0000	0.0000

Notes: He_vita = serum α-tocopherol. He_vite = serum retinol level. Se.he_vita = standard error of serum α-tocopherol. Se.he_vite = standard error of serum retinol.

Table 9 Mean α-Tocopherol Levels of Groups Stratified with Frequency of Drinking and Shots per Drinking

Frequency_ Shotsperdrink	Mean.he_vite
2_1	13.37044423
2_2	11.88878602
2_3	11.20896242
2_4	10.93630585
2_5	13.18545473
3_1	12.68831158
3_2	11.72273785
3_3	11.97179343
3_4	13.42454859
3_5	12.23450029
4_1	12.61745382
4_2	13.55257106
4_3	12.58156809
4_4	12.50382843
4_5	12.04979953
5_1	12.05421547
5_2	13.94244436
5_3	13.92499597
5_4	13.97548002
5_5	13.91085364
6_1	12.32033933
6_2	12.48544278
6_3	14.5170546
6_4	15.52420204
6_5	14.42945303

Notes: about 1 time a month=2, 2–4 times a month=3, 2–3 times a week=4 and more than 4 times a week=5 _ 1–2g of ethanol=1, 3–4g of ethanol=2, 5–6g of ethanol=3, 7–9g of ethanol=4, 10g or more of ethanol=5.

profile criteria were 0.00% and 0.00%, respectively. The percentage of male and female vitamin A deficient subjects who matched metabolic profile criteria were 10.03% and 3.12%, respectively. The percentage of male and female vitamin E sufficient subjects who matched metabolic profile criteria were 15.65% and 7.58%, respectively. The percentage of male and female vitamin A sufficient subjects who matched metabolic profile criteria were 15.46% and 9.18%, respectively. The percentage of male and female vitamin E over-sufficient subjects who matched metabolic profile criteria were 41.91% and 24.06%, respectively. The percentage of male and female vitamin A over-sufficient subjects who matched metabolic profile criteria were 27.45% and 16.73%, respectively. These results were summarized in Table 4 through 7. The highest percentage of metabolic syndrome criteria matched/whole group in both males and females were observed in the vitamin A

& E over-sufficient group.

Table 8 shows the analysis of the number of metabolic criteria matched with levels of vitamin A and E, and the ratio of vitamin A and E deficiency. In male group vitamin A level increased from zero matched to 3 matched and decreased from 4 matched to 5 matched. In female group vitamin A level increased from zero matched to 4 matched and declined at 5 matched. In male group vitamin E level steadily increased from zero matched to 4 matched and declined at 5 matched. In female group vitamin E level steadily increased from zero matched to 5 matched, with no decline. U-shaped correlation between the number of metabolic criterias matched and vitamin A were found. The results resembled those of the previous study. As the numbers of matched metabolic criteria increased, so did vitamin A and E levels, except when all five metabolic syndrome criteria were matched in the vitamin A analysis. Female serum vitamin A level was the lowest when all five metabolic syndrome criteria were matched. Studies have shown that obesity and ALDH function are inversely related, and with bariatric surgery, ALDH shows decreased activity.[45]

Our cross-sectional study used serum retinol and serum α-tocopherol for the analysis of vitamin A and vitamin E status. The circulating vitamins and metabolic syndrome causality could not have been confirmed. However, since the active form of anti-inflammatory vitamin A is retinoic acid, which is excreted from the liver with inflammation, the serum retinol level may be a reflection of retinoic acid during transport. For vitamin E and metabolic syndrome, we postulate that α-tocopherol is inversely related to γ-tocopherol, and the elevation of α-tocopherol may reflect a decrease in γ-tocopherol levels.

Weaknesses and Limitations of Our Study

Our study data consisted of weighted samples of the Korean population and the power comes from the large scale. However, since our study is purely cross-sectional, no causal relationship could be made. Although some sections needed explanation that could have been done with more detailed stratification, this was not feasible due to the relatively small sample size when divided as such. Most studies on vitamin A focus on serum retinol levels, which is a serum sample and relatively easy to obtain; however, since the main active form in the human body is retinoic acid, which is not readily available as a serum sample, gross analysis of retinol had to be made.

ALDH is involved in the conversion of retinol to retinoic acid. Because of the specified measurement of ALDH in different parts of the body, such as biopsy, the data on ALDH are difficult to reach. However, when considering the effect of vitamin A, a more precise interpretation of vitamin A could be possible with the conjunction of serum retinol levels, retinoic acid level, and ALDH levels.

Vast studies on vitamin E consist of two isoforms of vitamin E, α, and γ-tocopherol. Since more emphasis is being placed on γ-tocopherol due to its distinct anti-inflammatory properties compared to α-tocopherol, future studies on vitamin E should consider γ-tocopherol as well as α-tocopherol for vitamin E analysis.

Conclusion

There was a negative correlation between vitamin A and hs-CRP and a positive correlation between vitamin E and hs-CRP. A negative correlation between vitamin A and hs-CRP was found in non-smoking and non-alcohol drinking, non-smoking, and smoking and alcohol drinking groups. A positive correlation between vitamin E and hs-CRP was found in the non-smoking and alcohol drinking groups. Subjects with metabolic syndrome had a positive correlation with serum retinol and α-tocopherol levels; an exception was observed when all five metabolic profiles were met in the study of serum retinol, which was observed to be the lowest. Since obesity is inversely related to ALDH activity, we postulate that patients with metabolic syndrome may also have low ALDH activity, especially in the Asian population. Future studies are warranted to further investigate the efficacy of ALDH or ALDH inducers in patients with vitamin A deficiency or metabolic syndrome.

Disclaimer

The analyses, conclusions, opinions, and statements expressed herein are solely those of the authors and do not reflect those of the data sources; no endorsement is intended or should be inferred.

Abbreviations

SE, standard error; KNHANES, Korea National Health and Nutrition Examination Survey; hs-CRP, high sensitivity C-reactive protein; RBP, retinol binding protein; ADH, alcohol dehydrogenase; ALDH, acetaldehyde dehydrogenase; CYP450, cytochrome p450; ROS, reactive oxygen species; TNF- α, tumor necrosis factor alpha; IL-1, interleukin 1; IL-6, interleukin 6; IL-8, interleukin 8; PAI-1, plasminogen activator inhibitor 1; PGE2, prostaglandin E2; LTB4, leukotriene B4; RBP4 mRNA, retinol binding protein 4 mediator ribonucleic acid; ATRA, all-trans retinoic acid; CYP2E1, cytochrome

P450 2E1; CYP1A1, cytochrome P450 1A1; CYP1A2, cyto-
chrome P450 1A2; 4-oxo-RA, 4-oxoretinoic acid; 18-hydroxy
-RA, 18-hydroxyretinoic acid.

Data Sharing Statement

Korea National Health and Nutrition Examination Survey
(KNHANES) 2016–2018 7th edition can be accessed
through https://knhanes.cdc.go.kr/knhanes/main.do.

Ethic Statement

The study protocol was approved by the Institutional
Review Board of Veterans Hospital Seoul (IRB Number
2020-06-015). In compliance with ethical principles for
medical research involving human subjects (World
Medical Association Declaration of Helsinki, 2013).

Author Contributions

M.D. Hong and M.S. Lee had full access to all of the data in
the study and take responsibility for the integrity of the data
and the accuracy of the data analysis. All authors contributed
to data analysis, drafting or revising the article, have agreed
on the journal to which the article will be submitted, gave
final approval of the version to be published, and agree to be
accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to be declared.

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