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Association of Antioxidants With Allergic Rhinitis in Children From Seoul

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Purpose: The prevalence of allergic diseases has risen over the last few decades. Many factors, including environmental factors such as those related to diet, have been considered. Among dietary factors, intake of antioxidant-related nutrients has been associated with the risk of allergic disease. We investigated the association of antioxidant nutritional status with allergic rhinitis (AR) in Korean schoolchildren aged 6-12 years. **Methods:** Subjects were 4,554 children in Seoul, Korea. The risk of allergic disease was measured using the Korean version of the International Study of Asthma and Allergies in Childhood, and dietary intake was measured by a semi-quantitative food frequency questionnaire. Intake of vitamins A (including retinol and β-carotene), C, and E was used in the analysis. **Results:** Vitamin C intake was negatively associated with an increased risk of current symptoms (adjusted odds ratio, 0.886; 95% confidence interval, 0.806-0.973). There was no association between AR and intake of vitamin A, retinol, β-carotene, or vitamin E. Total serum IgE level and sensitization to allergen did not differ according to nutrient intake. **Conclusions:** The group of children with increased vitamin C consumption had fewer AR symptoms, despite the lack of a difference in total serum IgE level or allergen sensitization. These findings suggest that nutrient intake, especially that of vitamin C, influences AR symptoms.

Key Words: Allergic rhinitis; antioxidant; vitamin C

INTRODUCTION

The prevalence of allergic diseases, including allergic rhinitis (AR), has risen markedly in recent years,[1,2] including in Korea.[3] This increasing prevalence is thought to be due to lifestyle and environmental changes rather than genetic factors. Coincident with the increased prevalence of allergic disease, there has been a significant change in diet in many countries, such as decreased consumption of fresh fruit, vegetables, and fish and increased intake of high-fat foods. This has led to the hypothesis that changes in the prevalence of allergic disease are associated with re-

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duced intake of the antioxidant vitamins C, E, and β-carotene, which is the result of lower dietary intake of fresh green vegetables.[4]

A number of studies have investigated the relationship between dietary antioxidants and allergic disease in adults. Total plasma carotenoids were negatively associated with prevalence of AR in one study,[5] and vitamin E supplementation did not decrease the percentage of days with serious symptoms or on which medications were used to control allergic symptoms.[6] However, there is considerably less data relating to children.[4] Some studies have reported that fruit and vegetable intake provides a protective effect against wheezing, current asthma symptoms, and rhinoconjuctivitis in children.[7-9] Similarly, intake of vegetables and vitamin E protected against the development of atopy and wheezing in young children, although fruit intake and vitamin C had no effect on current wheezing.[10]

The above studies focused on wheezing, asthma, and atopic dermatitis in children, and there have been few studies on AR and antioxidant intake. A negative association between AR and intake of dietary antioxidants and milk has been reported in 6 to 7-year-old children, and a positive association with consumption of nuts and butter has been reported.[11] However, it is difficult to draw conclusions about the importance of specific antioxidants from this latter study, since it focused on foods and not nutrients. In the vitamin E (400 IU/day) supplement study of 63 AR patients aged 12-19 years, there was no effect of vitamin E on the severity of nasal symptoms or on the concentration of allergen-specific serum IgE.[12]

No epidemiologic data of an association between AR and antioxidant nutrients in children are currently available. In the present study, we addressed this deficiency by focusing on the association between dietary antioxidant nutrients and AR and allergic sensitization in Korean schoolchildren.

MATERIALS AND METHODS

Study population

This study included 5,036 students (enrolled in first through sixth grade) from five elementary schools that were randomly selected from five areas of Seoul City (downtown, northeastern, northwestern, southeastern, and southwestern) in Korea.

A total of 4,731 children responded to the questionnaire (response rate, 93.9%). Of the responders, 4,554 (2,317 [50.9%] boys and 2,237 [49.1%] girls) were included in this study. The remaining 177 children, who did not answer the age or sex questions, were excluded because of insufficient responses to the questionnaire. The mean age of the enrolled children was 9.50±1.73 years (Table 1). The parents or guardians of all participants signed a written informed consent form. This study was approved by the International Review Board of Asan Medical Center, University of Ulsan, Seoul, Korea.

Table 1. General characteristics of the study participants

Variable	N (%) or Mean (±SD)
Sex (M)	2,317/4,554 (50.9%)
Age (yr)	9.50 (±1.73)
Height (cm)	137.81 (±12.13)
Weight (kg)	34.36 (±10.40)
Body mass index (kg/m^2)	17.91 (±3.14)
Family history of allergic disease	
Parental history of asthma	125/4,025 (3.1%)
Parental history of AR	1,279/4,025 (31.8%)
Parental history of allergic disease*	1,458/4,025 (36.2%)
Family income (Korean Won/month)	
Low (< 2 million)	554/4,382 (12.6%)
Middle (2-5 million)	3,209/4,382 (73.2%)
High (≥ 5 million)	619/4,382 (14.1%)
AR	
Symptom ever	1,604/4,076 (39.4%)
Current symptoms	1,526/4,264 (35.8%)
Current AR	980/4,408 (22.2%)
Diagnosis ever	1,440/4,225 (34.1%)
Treatment	1,097/4,198 (26.1%)

*Allergic diseases: asthma, allergic rhinitis, or atopic dermatitis.
AR, allergic rhinitis.

Methods

Questionnaire survey

A modified International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire was used in this study.[13] The questionnaire consisted of three main sections: (1) general characteristics, including name, sex, date of birth, height, and weight, (2) histories of symptoms related to asthma, AR, atopic dermatitis, allergic conjunctivitis, and food allergy, and (3) exposure to environmental factors associated with allergic diseases. Our ISAAC questionnaire was the same as the original ISAAC questionnaire[14] except that the core question about disease was modified with regard to environmental risk factors. The questions regarding AR were as follows:

- Have you ever had a problem with sneezing or a runny or blocked nose when you did not have a cold or the flu?
- In the past 12 months, have you had a problem with sneezing or a runny or blocked nose when you did not have a cold or the flu?
- Have you ever been diagnosed with AR by a doctor?
- In the past 12 months, have you been treated for AR?

We defined current AR when the child was diagnosed with AR by doctors and had AR symptoms during the last 12 months. The questionnaire was explained to the parents or guardians of the students, and written consent was obtained. The parents or guardians completed the questionnaires.

Dietary intake was assessed by the semi-quantitative food frequency questionnaire (FFQ), which assesses the portion size and frequency of consumption of 86 different food items during the previous year. The FFQ was answered by the parents or guardians. Using the Computer Aided Nutritional Analysis Program III (CAN PRO III) developed by the Korean Nutrition Society the amount of each food item included in the FFQ was converted into grams, from which daily nutrient intake was calculated.

Skin prick and blood tests

Skin prick and blood tests were conducted on 1,376 students from one of the five elementary schools in the study. The skin prick test measured the responses to 18 allergens (*Dermatophagoides pteronyssinus, Dermatophagoides farinae*, cockroach, dog dander, cat dander, tree 1, tree 2, grasses, alder, oak, mugwort, ragweed, *Alternaria, Aspergillus*, peanut, milk, egg white, and soyabean), together with a positive and a negative control. A positive result for each allergen was defined as a wheal diameter for the allergen, plus the positive control, of greater than 3 mm. Total serum IgE was measured using the uniform capitalization method.

Statistical analysis

Statistical analyses were conducted with the PASW software, version 18 (SPSS Inc., Chicago, IL, USA). The children were divided evenly into four groups based on the levels of nutrient residuals, which were obtained by adjusting for total calories using a linear regression model. Multiple logistic regression analysis was performed by adjusting key covariates such as age, sex, body mass index, parental history of allergic disease, and monthly household income. The odds ratios (ORs) and 95% confidence intervals (CIs) were obtained, and a P value of <0.05 was considered to indicate statistical significance.

RESULTS

Baseline characteristics

A parental history of AR was noted in 31.8% of the subjects. The prevalence of AR diagnosis ever was 33.9%, and 21.1% of children had current AR (AR symptoms during the last 12 months together with previous diagnosis of AR) (Table 1). Daily nutrient intake is described in Table 2. The average vitamin C intake was within the dietary reference intake (DRI) for Koreans. The average intakes of total calories and vitamins A and E were slightly above the DRI for Koreans.

Relationship between nutrient intake and AR

Vitamin C intake was negatively associated with current AR symptoms (P for trend=0.003, OR=0.904, 95% CI=0.847-0.966) and current AR (P for trend=0.007, OR=0.901, 95% CI=0.835-0.972) by univariate analysis. No association between intake of vitamin A or E and AR was found (data not shown).

Table 2. Daily nutrient intake distribution

Nutrient	Mean (±SD)	DRIs for Koreans (6-14 year-old children)
Total calories (kJ)	1,958.675 (±1,271.203)	1,500-1,900
Carbohydrate (g)	275.911 (±165.953)	-
Vegetable protein (g)	32.874 (±21.180)	-
Animal protein (g)	41.006 (±38.643)	-
Vegetable fat (g)	27.947 (±24.101)	-
Animal fat (g)	36.798 (±32.190)	-
Vitamin A (μg)	824.803 (±702.189)	400-700
Retinol (μg)	228.625 (±172.424)	-
β-carotene (μg)	3,351.850 (±3,484.160)	-
Vitamin C (mg)	88.218 (±86.980)	60-100
Vitamin E (mg)	15.520 (±14.837)	7-10

DRIs, dietary reference intakes.

In multiple logistic regression analysis, after adjusting for age, sex, body mass index, parental history of allergic disease, and monthly household income, there was an inverse relationship between vitamin C intake and the risk of current AR symptoms (P for trend=0.011, adjusted OR=0.886, 95% CI=0.806-0.973) (Table 3).

Relationship between nutrient intake and serum total IgE or allergic sensitization

Children from one of the five schools also underwent skin prick testing and blood sampling. Intake of vitamins A and C and β-carotene protected from sensitization as measured by skin prick testing in univariate analysis. However, there was no association between sensitization and intake of any of the measured nutrients after adjusting for age, sex, body mass index, parental history of allergic disease, and monthly household income (Table 4). We also analyzed AR according to allergic sensitization, but there was no significant association. Similarly, there was no association between total serum IgE level and intake of antioxidant-related nutrients by univariate analysis (Table 5).

DISCUSSION

We investigated the association between antioxidant-related nutrient intake and AR in Korean schoolchildren aged 6-12 years. A higher vitamin C intake was negatively associated with AR symptoms. However, there was no association between dietary antioxidants and sensitization measured by skin prick test or serum total IgE after adjusting for confounding factors. These results suggested that nutritional factors, such as vitamin C, influenced the symptoms of AR, but had no effect on atopy.

Inflammatory disorders, such as asthma and AR, may be mediated by oxidative stress and the failure of antioxidant defenses.[15] Antioxidants may prevent the free radical-induced chain

Table 3. Association between antioxidant nutrient intake and AR in school children aged 6-12 years by multiple logistic regression analysis

	AR symptom ever* 970/2,379	Current AR symptom† 926/2,480	Current AR‡ 622/2,539	AR diagnosis§ 910/2,432	AR treatment‖ 678/2,417
Variable	aOR¶ (95% CI)	aOR¶ (95% CI)	aOR¶ (95% CI)	aOR¶ (95% CI)	aOR¶ (95% CI)
Vitamin A					
Q1	1.000	1.000	1.000	1.000	1.000
Q2	0.924 (0.728-1.173)	0.823 (0.649-1.043)	0.883 (0.676-1.153)	0.939 (0.735-1.199)	0.914 (0.704-1.187)
Q3	0.742 (0.582-0.945)	0.666 (0.523-0.847)	0.726 (0.553-0.954)	0.958 (0.749-1.224)	0.824 (0.632-1.074)
Q4	0.970 (0.749-1.256)	0.910 (0.704-1.176)	1.168 (0.879-1.151)	1.219 (0.937-1.587)	1.273 (0.964-1.680)
P for trend	0.935	0.512	0.701	0.265	0.186
Total OR** (95% CI)	1.004 (0.920-1.095)	0.971 (0.889-1.061)	1.019 (0.924-1.125)	1.051 (0.963-1.146)	1.064 (0.970-1.168)
Retinol					
Q1	1.000	1.000	1.000	1.000	1.000
Q2	1.024 (0.807-1.300)	0.895 (0.706-1.135)	0.896 (0.686-1.170)	1.149 (0.902-1.464)	0.983 (0.759-1.273)
Q3	1.010 (0.793-1.286)	0.946 (0.745-1.202)	0.945 (0.723-1.234)	1.098 (0.859-1.404)	0.952 (0.732-1.238)
Q4	0.900 (0.705-1.148)	0.894 (0.703-1.138)	0.877 (0.668-1.150)	0.991 (0.771-1.272)	0.909 (0.697-1.187)
P for trend	0.915	0.336	0.550	0.894	0.431
Total OR** (95% CI)	0.995 (0.912-1.086)	0.957 (0.876-1.046)	0.969 (0.876-1.073)	0.994 (0.907-1.089)	0.961 (0.870-1.061)
β-carotene					
Q1	1.000	1.000	1.000	1.000	1.000
Q2	1.136 (0.896-1.440)	1.002 (0.791-1.269)	0.958 (0.734-1.250)	1.027 (0.806-1.309)	0.949 (0.731-1.231)
Q3	0.923 (0.723-1.177)	0.885 (0.695-1.127)	0.864 (0.658-1.135)	0.979 (0.764-1.253)	0.944 (0.724-1.229)
Q4	1.016 (0.802-1.287)	0.972 (0.769-1.230)	1.085 (0.834-1.410)	1.141 (0.897-1.451)	1.163 (0.900-1.501)
P for trend	0.773	0.735	0.528	0.223	0.113
Total OR** (95% CI)	1.013 (0.929-1.104)	0.985 (0.903-1.075)	1.032 (0.937-1.136)	1.055 (0.968-1.150)	1.076 (0.983-1.179)
Vitamin C					
Q1	1.000	1.000	1.000	1.000	1.000
Q2	1.079 (0.854-1.364)	0.973 (0.771-1.229)	0.937 (0.721-1.216)	0.871 (0.684-1.109)	0.864 (0.668-1.118)
Q3	0.981 (0.769-1.252)	0.923 (0.725-1.175)	0.961 (0.735-1.256)	0.943 (0.738-1.207)	0.902 (0.694-1.173)
Q4	0.861 (0.676-1.097)	0.797 (0.626-1.015)	0.788 (0.599-1.036)	0.845 (0.661-1.080)	0.858 (0.660-1.116)
P for trend	0.086	0.011	0.103	0.581	0.103
Total OR** (95% CI)	0.923 (0.842-1.011)	0.886 (0.806-0.973)	0.915 (0.823-1.018)	0.975 (0.890-1.067)	0.915 (0.823-1.018)
Vitamin E					
Q1	1.000	1.000	1.000	1.000	1.000
Q2	0.981 (0.773-1.245)	1.071 (0.845-1.357)	1.076 (0.825-1.403)	0.888 (0.697-1.132)	0.829 (0.638-1.076)
Q3	1.085 (0.852-1.383)	1.039 (0.816-1.323)	1.076 (0.821-1.411)	0.985 (0.770-1.261)	0.956 (0.735-1.243)
Q4	1.095 (0.858-1.397)	1.087 (0.853-1.386)	1.051 (0.798-1.383)	1.046 (0.818-1.338)	1.063 (0.818-1.380)
P for trend	0.238	0.662	0.303	0.098	0.303
Total OR** (95% CI)	1.056 (0.965-1.156)	1.019 (0.937-1.109)	1.050 (0.956-1.154)	1.073 (0.987-1.167)	1.050 (0.956-1.154)

*AR symptoms ever: sneezing or rhinorrhea or nasal obstruction without respiratory infection; †Current AR symptoms: allergic rhinitis symptoms without cold during last 12 months; ‡Current AR: allergic rhinitis symptoms during last 12 months plus previous diagnosis by a doctor; §AR diagnosis: diagnosed by a doctor ever in their lifetime; ‖AR treatment: treated during the previous 12 months; ¶Adjusted for age, sex, BMI, family income, parental allergic disease, and total calories; **Total OR: the odds ratio between mean data of each nutrient intake and allergic rhinitis.
AR, allergic rhinitis; OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio; BMI, body mass index.

reactions that lead to lipid peroxidation and damage to cell membranes or DNA, both of which may be involved in the pathogenesis of allergic disease.[16]

Associations between antioxidants and allergic disease have been reported in numerous epidemiological and immunological studies. Most observational studies report potentially beneficial associations between dietary antioxidants and allergic disease. For example, low consumption of fruit and vegetables, which are rich sources of antioxidants, and low intake of dietary antioxidants such as vitamin C, vitamin E, and selenium are as-

Table 4. Association between antioxidant nutrient intake and sensitization by skin prick test

	Univariate analysis	Multiple logistic regression analysis
Variable	Crude OR (95% CI)	Adjusted OR* (95% CI)
Vitamin A		
Q1	1.000	1.000
Q2	0.904 (0.646-1.266)	0.864 (0.553-1.350)
Q3	0.649 (0.464-0.906)	0.564 (0.356-0.895)
Q4	0.677 (0.485-0.946)	0.891 (0.559-1.421)
P for trend	0.005	0.271
Total OR (95% CI)	0.861 (0.774-0. 987)	0.921 (0.795-1.066)
Retinol		
Q1	1.000	1.000
Q2	1.062 (0.761-1.483)	1.513 (0.962-2.380)
Q3	1.002 (0.719-1.395)	1.353 (0.857-2.136)
Q4	1.246 (0.889-1.747)	1.371 (0.859-2.187)
P for trend	0.275	0.241
Total OR (95% CI)	1.061 (0.954-1.180)	1.093 (0.942-1.268)
β-carotene		
Q1	1.000	1.000
Q2	0.901 (0.644-1.259)	0.836 (0.534-1.310)
Q3	0.709 (0.507-0.991)	0.693 (0.434-1.105)
Q4	0.684 (0.488-0.957)	0.843 (0.530-1.342)
P for trend	0.011	0.348
Total OR (95% CI)	0.871 (0.783-0.968)	0.932 (0.805-1.079)
Vitamin C		
Q1	1.000	1.000
Q2	0.966 (0.693-1.346)	0.981 (0.620-1.551)
Q3	0.919 (0.659-1.281)	0.954 (0.598-1.524)
Q4	0.693 (0.496-0.969)	0.911 (0.576-1.441)
P for trend	0.034	0.679
Total OR (95% CI)	0.892 (0.802-0.992)	0.970 (0.838-1.122)
Vitamin E		
Q1	1.000	1.000
Q2	1.084 (0.776-1.515)	1.323 (0.835-2.095)
Q3	0.845 (0.606-1.178)	1.123 (0.707-1.782)
Q4	0.962 (0.688-1.346)	1.123 (0.707-1.782)
P for trend	0.493	0.850
Total OR (95% CI)	0.964 (0.867-1.071)	1.014 (0.876-1.174)

*Adjusted for age, sex, BMI, family income, parental allergic disease, and total calories.
OR, odds ratio; CI, confidence interval; BMI, body mass index.

Table 5. Association between antioxidant nutrient intake and total serum IgE by univariate analysis

	Total serum IgE (kU/L)				
Nutrient	Vitamin A	Retinol	β-carotene	Vitamin C	Vitamin E
Q1	139.59	142.16	130.30	143.10	137.78
Q2	149.67	158.48	148.62	150.19	171.63
Q3	152.62	127.53	164.37	145.67	138.87
Q4	151.15	165.22	149.60	154.35	144.40
P for trend	0.956	0.444	0.614	0.974	0.502

sociated with respiratory symptoms and reduced lung function.[8,9,17-20] However, the precise nature of these associations and the potential for therapeutic intervention remain unclear.[17]

The role of oxidative stress in AR has not been well-studied, but may be similar to that in asthma.[21] Few epidemiologic studies have focused on the relationship between antioxidant intake and AR, particularly in children. The Mediterranean diet, which has a high antioxidant content due to its high content of fruit, vegetables, legumes, nuts, and wholegrain cereals, is associated with a decreased incidence of AR.[7,22,23] However, it is difficult to draw firm conclusions about the role of antioxidants from these studies because they did not focus on specific nutrients within the Mediterranean diet.

Vitamin C has intracellular and extracellular aqueous-phase antioxidant capacity primarily by scavenging oxygen free radicals and suppressing macrophage secretion of superoxide anions.[24] Most studies of dietary vitamin C and asthma have reported that consumption of the former is associated with improved ventilator function. In contrast, no association was reported between serum vitamin C and diagnosis of AR.[5] There was also no association in our study between dietary vitamin C and diagnosis of AR and atopic sensitization or total serum IgE. This result was consistent with others of sensitization and vitamin C.[5,25,26] In our study, vitamin C consumption was associated with reduced symptoms of AR. This result was consistent with an animal study, which showed that administered vitamin C exerted a moderate anti-inflammatory effect, although it did not show any Th1/Th2 shifting effect.[27] The anti-inflammatory effect of vitamin C was ascribed to its antioxidant property, and some investigators insist that vitamin C directly inhibited IkB kinase phosphorylation leading to eventual inhibition of NF-kB activation, which plays a critical role in inflammation.[27,28] We conclude that higher consumption of vitamin C may improve the symptoms of AR despite having little effect on allergic sensitization.

Vitamin A comprises retinol and more than 600 carotenoids, many of which (β-carotene, β-cryptoxanthin, lutein-zeaxanthin, and lycopene) have strong antioxidant activity.[24] The role of vitamin A in asthma is not clear. Two analyses of children aged 4-17 years from National Health and Nutrition Examination Survey III demonstrated negative associations between asthma and serum levels of α-carotene and β-carotene,[29,30] while the Dutch MORGEN cross-sectional intervention study of 5,744 adults aged 20-59 reported that dietary β-carotene intake was positively associated with the 12-month prevalence of wheezing in the absence of respiratory infection.[31] Our results are consistent with a previous study showing no association between

AR and α-carotene or β-carotene.[5]

Vitamin E is the principal defense against oxidant-induced membrane injury and has additional effects on immune function that might account for differences reported in epidemiologic studies of its associations with allergic disease and asthma.[24] There are several reports of an effect of vitamin E in AR. In a randomized, double-blind, placebo-controlled study, vitamin E supplementation in 112 patients with seasonal AR who received conventional treatment to control symptoms led to an improvement in the symptoms reported by the patient but not by the investigators.[6] In contrast, another double blind, placebo-controlled study, which evaluated the effect of vitamin E supplementation in 63 patients with perennial AR, showed no significant effect on nasal symptoms or on the serum concentration of specific IgE.[12] These two studies did not investigate dietary consumption of vitamin E in addition to the supplement, making it difficult to assess total vitamin E intake. Our study did not distinguish between seasonal or perennial AR, and we conclude only that vitamin E was not associated with symptoms of AR.

There were several drawbacks to this study, including the diagnosis of AR by way of questionnaire and not by a medical examination. In addition, recall bias could have affected the FFQ, as it recorded dietary habits from the past year, and parents may have underreported bad and overreported good foods. In addition, we did not record the use of other supplements, such as multivitamins, and we could not confirm the correlation of dietary nutrient intake to serum levels because we did not measure serum antioxidant level.

The strengths of the present study include the large number of participants, the detailed assessment of AR, and the comprehensive assessment of dietary intake of antioxidants using a semi-quantitative FFQ focusing on 86 different foods especially in schoolchildren. The ISAAC questionnaire has been validated in a number of Korean studies.[13,32] Sensitization was evaluated by skin prick test, and total IgE was measured, although these were not correlated with nutrient intake.

In conclusion, our data suggest that a higher vitamin C intake may be beneficial in AR, although it is not associated with allergen sensitization.

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