

Serum nutrient markers and skin prick testing using data from the Third National Health and Nutrition Examination Survey

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Background: Diet nutrients and allergic sensitization both affect the development and severity of asthma, but the interrelationship between oral intake and allergic sensitization is not well characterized, although previous work suggests that a higher vitamin E intake may be protective against allergic sensitization.

Objective: To determine whether serum levels of dietary antioxidants, lipids, and other nutrients are associated with the presence of allergen skin sensitization.

Methods: Cross-sectional logistic regression analysis of 30 serum nutrient levels in relation to 10 skin test allergens in adults and children in the Third National Health and Nutrition Survey.

Results: In adults, allergic skin sensitization was less common in participants with higher serum levels of vitamin E: the adjusted odds ratio (OR) per SD difference in vitamin E level was 0.93 (95% CI, 0.87-0.99). Two of the carotenoids, β -cryptoxanthin and α -carotene, were also inversely associated with allergic skin sensitization (OR, 0.89; 95% CI, 0.83-0.95; and OR, 0.95; 95% CI, 0.91-0.99, respectively). Among adults, serum lycopene had a positive association with allergen sensitization. In youths, however, vitamin A was associated with an increased risk, and high-density lipoprotein cholesterol was associated with a decreased risk of allergic sensitization. The use of vitamin or mineral supplements had little effect on the magnitude of all reported associations.

Conclusion: Overall, there were no strong or consistent associations between serum levels of potentially antiallergic nutrients, and the occurrence of allergic skin sensitization in these data. However limited, findings suggest that increases in vitamin E, carotenoids, and high-density lipoprotein cholesterol

may reduce the risk of allergic skin sensitization. (*J Allergy Clin Immunol* 2004;114:1398-402.)

Key words: Atopy, allergic sensitization, serum nutrients, vitamin E

Current evidence indicates that dietary intake, particularly of the antioxidant vitamins, flavonoids, lipids, and some minerals, may have an important influence on lung function and the prevalence of asthma and other respiratory disease.¹⁻³ However, the effect of these and other nutrients on allergy, one of the major risk factors for asthma, has attracted far less interest. Recent work suggested that a high intake of vitamin E may protect against the development of high IgE levels and allergic sensitization,^{4,5} whereas other studies have implicated a high intake of polyunsaturated fatty acids⁶⁻⁸ as a risk factor for allergic sensitization. A European ecologic study found that enhanced intake of monounsaturated fats was associated with an increased prevalence of allergen skin sensitization, and that a high intake of fruits was associated with a reduced prevalence of allergen skin sensitization.⁹ Further evidence that foods rich in antioxidant flavonoids and vitamins may protect against sensitization was recently reported by Woods et al,¹⁰ who found that allergen skin sensitization was less common among people who reported a high intake of whole milk, berries, and tomatoes.

To date, the evidence linking diet to allergic sensitization has been generally based on estimates of dietary intake derived from food frequency questionnaires, the limitations of which are well recognized.¹¹ Because there is very little evidence based on objective biological measures of nutrient levels, we have examined the relation between diet and allergic skin sensitization by using data on serum nutritional markers from the Third National Health and Nutrition Examination Survey (NHANES III). We took a comprehensive approach to this question, including nutrients of previous interest and nutrients that had not been investigated previously. We investigated the association of 30 serum nutrients, including vitamins, minerals, lipids, and others, with allergen skin sensitization in both adults and in children, in separate analyses.

METHODS

NHANES III is a survey designed to examine the health and nutrition of the noninstitutionalized US population and includes data

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TABLE I. Demographics of the study populations

Descriptive statistics	Adults		Children	
	N (%)	Mean (SD)	N (%)	Mean (SD)
Male subjects	2746 (46.9)		2194 (49.6)	
Female subjects	3112 (53.1)		2234 (50.5)	
Age		33.6 (12.2)		10.7 (3.10)
Ethnicity				
White, non-Hispanic	1858 (31.7)		1142 (25.8)	
Black, non-Hispanic	1833 (31.3)		1507 (34.1)	
Mexican-American	1897 (32.4)		1577 (35.6)	
Other	270 (4.6)		202 (4.6)	
Atopic	3376 (57.6)		2321 (52.6)	

Abbreviations used

BMI: Body mass index
HDL: High-density lipoprotein
LDL: Low-density lipoprotein
NHANES III: Third National Health and Nutrition Survey
TIBC: Total iron binding capacity

for more than 30,000 participants. The cross-sectional survey was conducted between 1988 and 1994, and full details of the design and examination procedure have been published by the National Center for Health Statistics.¹² All participants between the ages of 6 and 16 years and a randomly selected sample of 50% of the adults between 17 and 59 years old underwent allergen skin testing. In addition to random selection, exclusions from allergen skin testing included the following: participants who usually did not have trouble breathing, but who were having trouble breathing at the time of examination, with the difficulty not a result of nasal congestion or a cold; participants who usually had breathing difficulty and had increased difficulties at the time of the examination; participants who previously had a severe response to allergen skin testing; and participants who had severe eczema or infection on both arms.

Data collection

Trained interviewers administered a detailed questionnaire to collect information on socioeconomic status, medical history, use of vitamins or minerals, and smoking history. Participants then attended a session in a mobile examination unit in which blood samples were taken for biochemical assays, anthropometric measures were made, and skin prick testing using the prick-puncture technique was performed with 10 allergens including *Dermatophagoides farinae*, cat, German cockroach, short ragweed, perennial rye, *Alternaria alternata*, Bermuda grass, Russian thistle, white oak, peanut, and both positive (histamine) and negative (glycerinated saline) controls. Mean wheal responses to each test were measured at 15 minutes. Venous blood was collected and sent for laboratory processing as described elsewhere.¹³

Nutrient markers analyzed in blood samples were vitamin A, α -carotene, β -carotene, β -cryptoxanthin, lutein/zeaxanthin, lycopene, retinyl esters, vitamin B12, folate, red blood cell folate, vitamin C, vitamin E, normalized serum calcium, total calcium, iron, total iron binding capacity (TIBC), transferrin saturation, ferritin, potassium, selenium, sodium, chloride, and total protein. Lipid measures were apolipoprotein AI, apolipoprotein B, lipoprotein a, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides.

Statistical analyses

Individuals were defined as having a positive allergen skin test (sensitized) if the mean wheal diameter of any allergen response was at least 3 mm greater than the mean saline response. We conducted an initial exploratory analysis of the relation between several serum nutritional markers and skin sensitization, estimating the effect of an approximate (rounding to the nearest suitable number) SD increase in a univariate association and with adjustment for age and sex. Significant findings were further investigated for the possibility of confounding by smoking by adjusting for smoking status defined as never, former, or current smokers by self-report, and for reported pack-years smoked in adults, or serum cotinine levels in children (not exposed, <2.9 ng/mL; passive exposure, 2.9-20 ng/mL, and active exposure, >20 ng/mL). We also adjusted for body mass index (BMI; in children, BMI was converted to a z score¹⁴), poverty index, and race or ethnicity. Models including fat-soluble vitamins were further adjusted for serum levels of total cholesterol and triglycerides.

On the basis of previous research, there were a priori hypotheses for antioxidants, and particularly for vitamin E and cholesterol levels. Given that the NHANES III included a set of 30 biological markers of nutritional status, we looked comprehensively across all of the serum nutrient levels to generate hypotheses for further work. The interpretation of these results is therefore guided by statistical consideration, with a *P* value of less than or equal to .05 flagging results that are discussed further. Given that the number of participants exceeded 5000 in most analyses of adults, and exceeded 4000 in most analyses of youths, effects sizes of biological interest were easily detected at this type I error level.

Because of the complex, multistage probability sample design of NHANES III, estimates were calculated accounting for the survey design by using the specialized survey command within STATA SE 8.0 (Stata Corp, College Station, Tex). Because apolipoprotein AI and apolipoprotein B were measured only between 1988 and 1991 and vitamin B12 and lipoprotein a between 1991 and 1994, there were considerably fewer participants in analyses including these variables; thus, these analyses could only be performed accounting for the survey design at the strata level.

RESULTS

Demographic details for eligible adults and children with serum nutrient data are presented in Table I. There were slightly more female subjects than male subjects in both groups, and the distribution of individuals by race and ethnicity was similar. Participants undergoing allergic sensitization testing were all youth and a randomly

TABLE II. Levels of serum nutritional markers in adults and children

Nutrient category	Nutrient	Adults			Children		
		N	Mean	SD	N	Mean	SD
Vitamins	Vitamin A ($\mu\text{g/dL}$)	5742	53.8	15.4	4271	39.1	9.1
	α -Carotene ($\mu\text{g/dL}$)	5742	4.0	5.2	4271	3.3	2.7
	β -Carotene ($\mu\text{g/dL}$)	5742	16.2	16.2	4271	15.6	9.0
	β -Cryptoxanthin ($\mu\text{g/dL}$)	5742	10.5	8.0	4271	11.9	6.7
	Lutein/zeaxanthin ($\mu\text{g/dL}$)	5742	21.4	13.5	4271	19.4	8.1
	Lycopene ($\mu\text{g/dL}$)	5742	23.9	11.1	4271	24.1	10.3
	Retinyl esters ($\mu\text{g/dL}$)	5742	5.2	3.4	4271	5.0	2.9
	Vitamin B12 (pg/mL)	2956	573.1	2203.8	2196	669.7	291.6
	Folate (ng/mL)	5794	5.4	4.1	4371	7.7	5.3
	Red blood cell folate (ng/mL)	5779	166.4	79.7	4362	176.3	69.6
	Vitamin C (mg/dL)	5562	0.7	0.4	4058	1.0	0.4
	Vitamin E ($\mu\text{g/dL}$)	5742	1006.8	405.5	4271	768.7	173.1
Minerals	Normalized calcium (mmol/L)	5133	1.2	0.1	1546	1.3	0.04
	Total calcium (mmol/L)	5690	2.3	0.1	1716	2.4	0.1
	Iron ($\mu\text{g/dL}$)	5795	90.2	39.4	4385	82.1	35.0
	TIBC ($\mu\text{g/dL}$)	5788	363.1	60.5	4357	383.1	53.8
	Transferrin saturation (%)	5779	25.6	11.8	4356	21.8	9.8
	Ferritin (ng/mL)	5795	109.0	125.3	4365	38.9	33.3
	Potassium (mmol/l)	5710	4.0	0.3	1701	4.1	0.3
	Selenium (ng/mL)	5666	122.8	16.5	1693	117.2	14.2
	Sodium (mmol/L)	5710	141.2	2.3	1701	141.1	2.0
Lipids	Apolipoprotein AI (mg/dL)	2789	141.8	26.1	2111	138.0	20.1
	Apolipoprotein B (mg/dL)	2805	98.7	26.8	2128	79.7	17.2
	Lipoprotein a (mg/dL)	2951	26.1	28.5	2195	26.8	27.7
	Total cholesterol (mg/dL)	5773	193.6	43.3	4332	166.1	29.6
	HDL cholesterol (mg/dL)	5730	51.0	14.6	4313	52.8	12.7
	LDL cholesterol (mg/dL)	2470	118.3	37.0	647	95.2	26.7
	Triglycerides (mg/dL)	5758	131.0	117.2	4326	94.3	52.3
Other	Chloride (mmol/L)	5710	104.7	3.2	1701	104.4	2.9
	Total protein (g/dL)	5710	7.4	0.5	1701	7.5	0.4

selected 50% sample of adults; thus, no selection bias is likely. Indeed, there were no notable differences between adults with and without allergic sensitization data in terms of demographic characteristics (data not shown). Only 174 participants were excluded from testing for medical reasons.

The prevalence of allergen sensitization in the adult population was 57.6%, and in children, 52.6%. The mean values for the serum nutrients were predominantly similar in adults and children, and are shown in Table II.

In adults, there was no relation between the odds of allergen sensitization and blood levels of the majority of nutrients in the unadjusted models, but for lipid-soluble nutrients, further adjustment for blood lipids was necessary to best describe the associations. In the fully adjusted models, inverse associations were demonstrated for α -carotene, β -cryptoxanthin, and vitamin E (Table III). We detected a direct association between serum lycopene and risk of allergen skin sensitization.

Consistent with the findings in adults, the majority of the nutrients were unrelated to allergen skin sensitization in youth (Table IV). However, higher levels of

HDL cholesterol were inversely associated with allergen skin sensitization, whereas vitamin A levels were positively associated. The protective effects of vitamin E, α -carotene, and β -cryptoxanthin found in adults were not present in children. Adjustment for cotinine made little difference to the results (data not shown). Adjusting for BMI or poverty index did not affect any of the results in either adults or children. These associations were also examined both adjusting for and stratifying for vitamin and mineral supplement usage and smoking status, and there was no notable difference from the results presented, because majority of the estimates were within 5% of the original estimate, and all were within 10%.

DISCUSSION

This study used an existing major data set to determine whether the risk of allergic skin sensitization was associated with blood levels of a range of nutrients. In addition to studying several vitamins and other antioxidants, lipids, and minerals that in previous studies have

TABLE III. Association of serum nutrients (1 SD difference) and the prevalence of atopy in adult participants in NHANES III*

Nutritional category	Nutrient	Adjusted OR*	95% CI
Vitamins	Vitamin A†	1.03	0.97-1.09
	α-Carotene†	0.95	0.91-0.99
	β-Carotene†	0.96	0.91-1.01
	β-Cryptoxanthin†	0.89	0.83-0.95
	Lutein/zeaxanthin†	0.97	0.93-1.01
	Lycopene†	1.08	1.03-1.14
	Retinyl esters†	1.01	0.93-1.09
	Vitamin B12‡	1.02	0.97-1.09
	Folate	0.99	0.92-1.06
	Red blood cell folate	0.95	0.88-1.03
	Vitamin C	0.98	0.92 to 1.04
	Vitamin E†	0.93	0.87-0.99
Minerals	Normalized calcium	1.03	0.96-1.10
	Total calcium	1.00	0.94-1.06
	Iron	1.04	0.98-1.10
	TIBC	1.04	0.98-1.10
	Transferrin saturation	1.02	0.98-1.06
	Ferritin	1.02	0.96-1.08
	Selenium	1.03	0.96-1.11
	Sodium	0.98	0.93-1.03
	Potassium	1.03	0.95-1.12
Lipids	Apolipoprotein AI‡	0.98	0.90-1.08
	Apolipoprotein B‡	1.09	0.98-1.19
	Lipoprotein a‡	1.04	0.95-1.13
	Total cholesterol	0.98	0.94-1.04
	HDL cholesterol	1.01	0.92-1.09
	LDL cholesterol	0.95	0.88-1.03
	Triglycerides	1.05	0.99-1.09
Other	Chloride	1.01	0.91-1.11
	Total protein	0.96	0.91-1.01

*Adjusted for age, sex, race/ethnicity, and smoking; findings in bold, $P < .05$; see Table II for SD.

†Also adjusted for total cholesterol and triglycerides.

‡Because of smaller numbers, analyses able to account only for the strata clustering in the analyses.

been directly linked with the expression of allergic skin sensitization, or indirectly linked through effects on asthma or other allergic disease, we also examined other serum nutrient data available in NHANES III. The analyses of adults and youth were conducted separately because of different confounding factors that might operate at different ages, such as exposure to smoking and BMI.

Overall, our findings for the majority of antioxidant nutrients did not support the hypothesis that levels are strongly related to allergic skin sensitization before and after adjusting for potential confounders. A notable exception was vitamin E, which was associated with a reduced risk of allergen sensitization in the adult members of NHANES III, supporting our own⁴ and others⁵ previous observations. Our previous study sug-

TABLE IV. Association of serum nutrients (1 SD difference) and the prevalence of atopy in youth participants in NHANES III

Nutritional category	Nutrient	Adjusted OR*	95% CI
Vitamin	Vitamin A†	1.11	1.04-1.78
	α-Carotene†	0.96	0.89-1.02
	β-Carotene†	0.95	0.87-1.03
	β-Cryptoxanthin†	0.91	0.81-1.03
	Lutein/zeaxanthin†	0.97	0.89-1.05
	Lycopene†	1.03	0.96-1.11
	Retinyl esters†	1.03	0.97-1.10
	Vitamin B12‡	1.09	0.98-1.20
	Folate	1.04	0.99-1.09
	Red blood cell folate	0.97	0.89-1.05
	Vitamin C	0.95	0.88-1.03
	Vitamin E†	1.01	0.93-1.09
Minerals	Normalized calcium	0.96	0.84-1.10
	Total calcium	1.01	0.93-1.10
	Iron	1.03	0.97-1.09
	TIBC	1.05	0.95-1.15
	Transferrin saturation	1.01	0.94-1.09
	Ferritin	1.01	0.95-1.07
	Selenium	0.99	0.94-1.05
	Sodium	0.93	0.84-1.02
	Potassium	1.01	0.93-1.09
Lipids	Apolipoprotein AI‡	0.96	0.88-1.05
	Apolipoprotein B‡	1.07	0.96-1.18
	Lipoprotein a‡	1.04	0.94-1.15
	Total cholesterol	1.01	0.95-1.07
	HDL cholesterol	0.92	0.87-0.96
	LDL cholesterol‡	1.04	0.95-2.25
	Triglycerides	1.05	0.90-1.12
Other	Chloride	1.01	0.90-1.12
	Total protein	1.04	0.95-1.14

*Adjusted for age, sex, and race/ethnicity; findings in bold, $P < .05$; see Table II for SD.

†Also adjusted for total cholesterol and triglycerides.

‡Because of smaller numbers, analyses able to account only for the strata clustering in analyses.

gested that this protective effect was mediated by a general effect on IgE levels,⁴ as did the results of a supplementation study in patients with atopic dermatitis.⁵ Vitamin E has also been shown to inhibit IgE production in allergic model mice.¹⁵ Unfortunately, IgE, which was to be assayed in NHANES III blood samples, could not be considered because insurmountable laboratory difficulties with the assay methodology meant that the National Center for Health Statistics did not conduct the assays.

We also found that α-carotene and β-cryptoxanthin were associated with a reduced risk of allergic sensitization. These findings support 2 previous studies suggesting that the risk of sensitization is lower in people with a higher intake of fruits,^{9,10} perhaps because such foods are relatively rich sources of carotenoids, which have antioxidant properties. In contrast, we found an increased

risk of atopy associated with increased lycopene levels in adults and increased vitamin A in children. There is evidence from murine models that supplementation with high levels of vitamin A suppresses the T_H1 response,¹⁶ whereas another study found that high levels of vitamin A supplementation in mice reduced IFN- γ , a T_H1 cytokine,¹⁷ thus creating a biological milieu consistent with an increased tendency to allergy. Another possible explanation for this association is that several antioxidant nutrients can act as pro-oxidants at higher doses, through reduction of transition metal ions. In addition, it is possible that our results do not represent a true association, and that a confounder that we were unable to account for causes the apparent association.

There is a mixed evidence for the effect of HDL cholesterol on allergy and allergic disease. Some studies have found increased levels of HDL cholesterol associated with increased positive skin prick test or positive RAST test⁶ or increased levels in children with allergic disease.¹⁸ HDL cholesterol has anti-inflammatory effects,¹⁹ consistent with a protective role in allergy, and we found that increased levels of HDL were associated with a decreased risk of atopy. In a study of lung function, increased HDL cholesterol was associated with better FEV₁,²⁰ although a case-control study of patients with asthma found no significant differences in HDL levels.²¹

We recognize that a large number of statistical tests were performed in these analyses, and that some of our findings may be a result of chance. However, our a priori objective was to test all available nutrients in the NHANES data set in a single model to identify with independent effect. Another limitation of our study is that the data set we analyzed is cross-sectional, and therefore, the associations described are not necessarily causal. One likely influence that the cross-sectional nature of the data prevents us from exploring is that of reverse causation, such that people who have allergies may modify their diets in an attempt to reduce or prevent allergic symptoms. However, if this were the case, an increased use of supplements by individuals with allergy would be expected, and we did not observe this empirically. In addition, there is the possibility that people with allergy may have altered metabolism, which could include alterations to nutrient metabolism.

We found that the majority of nutritional serum markers were unrelated to atopy in NHANES III data. Thus, dietary intake, as reflected by serum nutrient biological markers, does not appear to be associated with allergen sensitization as it is with other markers of respiratory disease health. Similar to the results of previous studies, we found a protective effect of vitamin E, HDL, and the carotenoids on the risk of atopy in adults and an increased risk of atopy in children with higher levels of vitamin A.

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