

A Prospective Study of Diet and Adult-Onset Asthma

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A role for diet in the pathophysiology of asthma may be mediated by altered immune or antioxidant activity with consequent effects on airway inflammation. We evaluated associations between several dietary factors assessed by a semiquantitative food frequency questionnaire, and incidence of asthma over a 10-yr period in 77,866 women 34 to 68 yr of age. Women in the highest quintile of vitamin E intake from diet, but not from supplements, had a risk of 0.53 (95% confidence interval [CI] = 0.33 to 0.86) compared with women in the lowest quintile. This relationship, however, was attenuated when the contribution from nuts, a major source of vitamin E in these data and a possible allergen, was removed (relative risk = 0.74 [0.50 to 1.10], *p* for trend = 0.007). Positive associations were found for vitamins C and E from supplements, but appeared to be explained by women at high risk of asthma initiating use of vitamin supplements prior to diagnosis. A nonsignificant inverse association with carotene intake was noted, but no clear relations with asthma were demonstrated for intake of linoleic acid or omega-3 fatty acids. These data suggest that antioxidant supplementation and intake of various fats during adulthood are not important determinants of asthma, although vitamin E from diet may have a modest protective effect. Troisi RJ, Willett WC, Weiss ST, Trichopoulos D, Rosner B, Speizer FE. 1995. A prospective study of diet and adult-onset asthma. *Am J Respir Crit Care Med* 1995;151:1401-8.

The etiology of new-onset asthma in adults is not well understood, in part because few longitudinal studies have characterized its development (1, 2). Epidemiologic data from several sources including studies of migrants (3), rural populations relocating to urban areas (4), and families (5) suggest that both genetics and environment play key roles in the expression of asthma. One potential environmental factor may relate to specific components in the diet.

Asthma is characterized by airway hyperresponsiveness and airway inflammation and appears to involve a complex interaction of immune and neural responses. Airway hyperresponsiveness is believed to exist intrinsically or to develop in response to airway inflammation resulting from exposure to allergens, respiratory infections, cigarette smoke, or other irritants. Acting as antioxidants or through influences on immune function, vitamins C and E and beta carotene in the diet may reduce airway inflammation, thereby decreasing the severity of asthma or preventing altogether the expression of asthma in susceptible individuals. Fatty acid composition of the diet—in particular, the relative amounts of n-6 and n-3 polyunsaturated fatty acids—may also be associated with the risk of asthma. Increased production of prostanoids and leukotrienes active in bronchoconstriction and neutrophil chemotaxis occurs when linoleic acid is converted to arachidonic acid. Intake of linoleic acid may therefore increase bronchoconstriction and airway inflammation by enhancing production of the arachi-

donic acid metabolites PGD₂, PGF₂, LTB₄, LTC₄, and LTD₄. In contrast, omega-3 fatty acids compete with arachidonic acid to form less active prostanoids and leukotrienes, thereby potentially acting to reduce airway inflammation and bronchoconstriction.

Whereas several epidemiologic studies have addressed the relation of diet and the development of chronic obstructive pulmonary disease (6-8), fewer studies have investigated the possible role of diet in the pathophysiology of asthma. The majority of data on diet and asthma are from experimental studies conducted in asthmatics, that have focused exclusively on effects of vitamin C (9-13) or fish oil (14, 15). To further investigate these relationships, we assessed prospectively in a large cohort of women the hypothesis that usual dietary intake of vitamins A, C, and E, and fish oil lowers the risk of developing adult-onset asthma.

METHODS

Study Population

The Nurses' Health Study (NHS) is a prospective investigation of major diseases among a cohort of 121,700 female registered nurses 30 to 55 yr of age in 1976 and residing in one of 11 states when the study began. In 1980, a semiquantitative food frequency questionnaire (SFFQ) was added to the study, and additional questionnaires were sent in 1984 and 1986 (an abbreviated form of the questionnaire was sent in 1982 ascertaining information on frequency of intake of certain foods but not total nutrient intake). Every 2 yr a mailed questionnaire eliciting information on other exposures (e.g., cigarette smoking), dietary supplements, and self-reported diseases is completed by participants.

Complete dietary information was available for 93,184 subjects who returned the food frequency questionnaire in 1980. Subjects reporting a doctor's diagnosis of cancer, cardiovascular disease, diabetes, emphysema, chronic bronchitis, or asthma on or before the 1980 questionnaire were excluded from this analysis. After these exclusions, the 1980 baseline study population consisted of 77,866 women.

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Measurement of Diet

Briefly, the SFFQ asks about usual dietary intake over the past year by listing food items with serving sizes and nine options for frequency of intake ranging from never or less than once per month to six or more servings per day. Nutrient scores are computed by multiplying the frequency of intake by the nutrient content of the food item using data from the U.S. Department of Agriculture, food manufacturers, and other published sources (16-18).

The questionnaire has been extensively validated (19, 20). Correlations between energy-adjusted intakes of vitamins A and C as assessed by the 1980 questionnaire and by four 1 wk diet records collected over a 1-yr period were 0.49 and 0.36 for vitamin A (with and without supplements, respectively) and 0.75 and 0.66 for vitamin C. Validation of a later version of the questionnaire allowed evaluation of vitamin E in a similar manner ($r = 0.92$ and $r = 0.42$ with and without supplements, respectively, and corrected for week-to-week variation in the diet records).

The 1984 food frequency questionnaire differentiated dark meat fish, which is higher in eicosapentaenoic acid (EPA), from other types of fish. Fat aspirates were used to compare EPA stored in adipose tissue with EPA as assessed by questionnaire in 118 Boston-area men (21). Mean fat intake from EPA as assessed by two questionnaires administered 6 to 7 mo apart was similar: 0.19 ± 0.18 g/d versus 0.21 ± 0.24 g/d. The Spearman correlation between EPA expressed as percentage of total fat from the fat aspirates, and EPA estimated from the first and second questionnaires was $r = 0.47$ and $r = 0.49$, respectively. A similar correlation between total EPA and docosahexaenoic acid (DHA) content of adipose tissue and total EPA and DHA as a percentage of total fat intake from the food frequency questionnaire ($r = 0.48$) was found in a case-control study of postmenopausal Boston-area women (22).

Validation of Asthma Diagnosis

Cases of asthma for this investigation were based on the nurses' response to the following question on the 1988 and 1990 NHS questionnaires: "Have you had any of the following illnesses or procedures? Asthma, Dr. Diagnosed?" We attempted to contact by mail subjects who reported a diagnosis of asthma since 1980 ($n = 1,446$). Subjects were asked to complete a supplementary questionnaire eliciting information on date of diagnosis and date of first asthma symptoms, medication use, and seasonality, severity, and precipitators of asthma attacks. Almost 97% (1,400) of the nurses responded to the questionnaire. Approximately 86% (1,206) of the original diagnoses of those who responded were reproduced on the supplementary questionnaire; 9% (126) of the nurses contacted denied a diagnosis of asthma, about 4% (61) reported a diagnosis other than asthma (e.g., asthmatic bronchitis), and fewer than 0.5% (seven) did not provide sufficient information to confirm their diagnosis.

Of the 1,206 nurses classified as a confirmed diagnosis of asthma, only 5.5% reported never taking medication specifically for asthma. Fifty percent of all cases reported being diagnosed within 1 yr of the onset of symptoms and 95% within 10 yr.

For this investigation cases were defined as nurses who confirmed their NHS questionnaire report of a doctor's diagnosis of asthma on the supplementary questionnaire and who reported using asthma medication since diagnosis. After censoring for cancer, cardiovascular disease, and diabetes diagnoses made after 1980 and before the date of diagnosis of asthma, 760 cases and 647,551 person-years of follow-up remained for analysis.

Statistical Methods

Values for nutrient intake were adjusted for total energy by regression analysis (23), standardized to 1,600 Kcal (6.7 MJ)/d, and classified into quintiles. Nutrient intake was calculated with and without the contribution from vitamin supplements. Analyses using nutrient intake from diet alone excluded person-time from individuals reporting use of either the individual supplements or multivitamins. For example, to assess the association of vitamin C without supplements and risk of asthma, person-time from users of vitamin C, vitamin E, and multivitamin supplements was excluded from the analysis.

For each participant remaining alive and free of asthma, follow-up time

equal to the number of months between the return of the 1980 questionnaire and the return of the 1982 questionnaire was assigned to each covariate according to covariate status on the 1980 questionnaire. Similarly, for each 2-yr interval additional months of follow-up were assigned to each covariate according to status at the beginning of the closest interval with information until June 1, 1990. Three variations of nutrient analyses were performed: (1) using nutrient values as assessed in 1980 and risk of asthma from 1980 to 1990, (2) using nutrient values as assessed in 1984 and risk of asthma from 1984 to 1990, and (3) using nutrient values as assessed in 1980 and updated in 1984 and 1986, so that follow-up time for the first two intervals was assigned to 1980 quintile values, follow-up time for the third interval was assigned to 1984 quintile values, and follow-up time for the last two intervals was assigned to 1986 quintile values. Only the updated analyses are presented in the tables; it is noted in the text when the results from the three types of analyses disagreed. For participants who reported a diagnosis of asthma, or who died, follow-up time accumulated until the date of diagnosis reported on the supplementary questionnaire or the date of death, respectively. For participants reporting a diagnosis of cardiovascular disease, cancer, or diabetes, follow-up time accumulated until the beginning of the interval during which the disease was diagnosed.

Incidence rates were calculated for each quintile of nutrient intake by dividing the number of cases assigned to the quintile by the person-time at risk for the quintile. Relative risks were calculated by dividing the incidence rates in each of the second through fifth quintiles by the incidence rate in the first (lowest) quintile and were summarized across age in 5-yr categories and smoking status (never/past/1 to 14/15 to 24/> 25 cigarettes per day). A Mantel extension test was performed to test for trends over multiple categories. Relative risks were adjusted simultaneously for multiple covariates with use of proportional hazards models (24). To assess the relationship of intake of individual foods to risk of asthma, analyses adjusted for age and smoking status were performed separately for foods as assessed in 1980, 1982, and 1984 without update. Ninety-five percent confidence intervals (CI) were calculated for each relative risk.

RESULTS

The crude incidence rate for asthma was 1.17/1,000 person-years. Seventy-seven percent (588) of cases reported using asthma medication within the past year. Among asthmatics using medication within the past year, beta agonists (63%) were the most commonly reported class of drugs, followed by theophylline (56%), steroids (inhaled 52%; oral or intravenous, 30%), and cromolyn sodium (19%). Medication use within the past year increased somewhat with age (Table 1).

Dietary Antioxidants

Vitamin E with and without the contribution from supplements as assessed in 1980 was not associated with 10-yr risk of asthma adjusted for age and smoking (the relative risks [RR] for quintiles two through five versus quintile one [lowest] of vitamin E from diet and supplements were: 0.89, 1.03, 1.14, 1.06; p value for trend = 0.08, and the RR of vitamin E from diet only were: 1.07, 0.87, 0.98, 1.23; p value for trend = 0.34). Vitamin E as assessed in 1984 from diet but not from supplements, however, was inversely associated with 6-yr-risk of asthma (RR for quintiles two through five versus quintile one were: 0.86, 0.80, 0.60, 0.73; p value for trend = 0.03). Similarly, in analyses using vitamin E as assessed in 1980 and updated in 1984 and 1986, a significant inverse trend was demonstrated for vitamin E from diet but not from supplements (Table 2); suggesting that recent intake of dietary vitamin E may be more important than past intake in relation to asthma. The association became stronger with simultaneous adjustment for vitamin C and carotene in addition to several potential risk factors for asthma. Women in the highest quintile of daily vitamin E intake (energy-adjusted quintile range in 1984 = 9.0 to 125 mg) from

TABLE 1
INCIDENCE OF ASTHMA AND USE OF ASTHMA MEDICATION BY AGE GROUP, NURSES' HEALTH STUDY I

Age at Diagnosis	N	Person-Time	Incidence Rate (per 1,000)	% Hospitalized	Taking Medication within Past Year	% of Cases Taking Indicated Medication within Past Year				
						Beta Agonist	Theophylline	Inhaled Steroids	Oral or Intravenous Steroids	Cromolyn
30-34	8	6,640	1.20	13	50	63	25	25	0	13
35-39	75	64,433	1.16	17	79	55	37	37	21	15
40-44	152	120,593	1.26	14	75	49	36	36	17	15
45-49	175	136,216	1.28	22	74	50	43	37	23	15
50-54	138	131,376	1.05	23	78	52	51	51	30	18
55-59	137	118,791	1.15	23	82	47	49	44	27	12
60-64	67	60,377	1.11	15	82	40	51	45	25	9
65-69	8	9,124	0.88	13	88	63	50	63	13	13

diet alone had a 47% lower risk of asthma than women in the lowest quintile (range = 0.3 to 6.0 mg) after adjustment for age, smoking status, body mass index, area of residence, number of physician's visits in 1978, quintiles of energy intake, vitamin C without supplements, and carotene.

Vitamin C with supplements as assessed in 1980 and updated in 1984 and 1986 was positively associated with risk of asthma (Table 2). The association became stronger with simultaneous adjustment for vitamin E and carotene in the multivariate model. Without the contribution of vitamin C from supplements, the relative

TABLE 2
RELATIVE RISK OF ASTHMA FROM 1980 TO 1990 BY QUINTILES OF ENERGY-ADJUSTED INTAKE OF VITAMINS E, C, AND CAROTENE*

Nutrient	Quintiles of Intake					p Value for Trend
	1	2	3	4	5	
Vitamin E, mg						
With supplements	3.3	4.4	5.7	17.1	209.8	
No. of cases	156	165	123	156	160	
Adjusted for age and smoking [†]	1.0	1.01	0.74	0.98	1.0	0.94
Multivariate [‡] (95% CI)	1.0	0.97 (0.78-1.22)	0.70 (0.54-0.89)	0.82 (0.64-1.05)	0.83 (0.64-1.08)	0.07
From diet only [§]	3.2	4.0	4.7	5.4	6.9	
No. of cases	59	73	49	39	27	
Adjusted for age and smoking [†]	1.0	1.28	0.88	0.75	0.58	0.001
Multivariate [‡] (95% CI)	1.0	1.22 (0.86-1.73)	0.82 (0.55-1.21)	0.69 (0.45-1.05)	0.53 (0.33-0.86)	0.0005
Vitamin C, mg						
With supplements	70	113	154	229	705	
No. of cases	127	156	144	156	177	
Adjusted for age and smoking [†]	1.0	1.20	1.14	1.25	1.47	0.003
Multivariate [‡] (95% CI)	1.0	1.29 (1.01-1.64)	1.27 (0.99-1.64)	1.43 (1.10-1.86)	1.69 (1.28-2.23)	0.0001
From diet only [§] , mg	61	94	120	152	209	
No. of cases	49	52	54	54	38	
Adjusted for age and smoking [†]	1.0	1.11	1.21	1.28	0.98	0.70
Multivariate [‡] (95% CI)	1.0	1.14 (0.76-1.70)	1.30 (0.86-1.95)	1.42 (0.93-2.16)	1.11 (0.69-1.77)	0.38
Carotene, IU	2,935	4,707	6,610	9,456	14,558	
No. of cases	166	149	151	154	140	
Adjusted for age and smoking [†]	1.0	0.90	0.90	0.92	0.86	0.21
Multivariate [‡] (95% CI)	1.0	0.88 (0.71-1.10)	0.87 (0.70-1.09)	0.90 (0.71-1.12)	0.82 (0.65-1.05)	0.08

* As assessed in 1980 and updated in 1984 and 1986.

† Median values for nutrients as assessed in 1980. Vitamin E is in α -tocopherol equivalents.

‡ Adjusted with use of indicator variables for age (in 5-yr categories) and smoking (never, past, current in three levels of cigarettes smoked per day).

§ Logistic model includes age and smoking as described above, body mass index (< 21, 21-23, 23-25, 25-29, > 29 kg/m²), area of residence (northeast USA, north central USA, Florida, Texas, California), number of physician's visits (0, 1, 2-3, \geq 4), and quintiles of energy intake, vitamin C, E, and carotene.

¶ Nutrient value does not include contribution from supplements. Supplement users are excluded from analysis. Models for nutrients without supplements include vitamins C and E without the contribution from supplements.

risks for the third and fourth quintiles remained the same; however, the relative risks for the second (energy-adjusted quintile range in 1984 = 2 to 85 mg) and fifth quintiles (range = 181 to 822 mg) were attenuated, and the trend was no longer significant.

The age- and smoking-adjusted relative risks for carotene intake as assessed in 1980 and updated in 1984 and 1986 were below 1. Simultaneous adjustment for vitamins E and C strengthened the inverse trend, which became borderline significant (Table 2). No relations of total vitamin A or retinol with or without supplements were found with risk of asthma (results not shown).

The association of vitamin C (with or without supplements) and asthma did not differ by smoking status as assessed in multivariate analyses performed separately in never and current smokers (results not shown). Despite neither test for trend reaching statistical significance, the inverse association noted for carotene intake appeared stronger in current smokers (RR for quintiles two through five versus quintile one were: 0.69, 0.95, 0.69, 0.64; p for trend = 0.17) than in never smokers among whom the trend was positive (RR = 0.78, 0.85, 0.88, 0.91; p for trend = 0.09); the confidence intervals, however, for the corresponding estimates overlapped.

Supplement Use

Duration of use of individual supplements and multivitamins was assessed with adjustment for age and smoking and in multivariate analyses that included use of the other supplements (Table 3). Women using vitamins C, E, or multivitamins prior to diagnosis had a higher risk of asthma than nonusers. The RR associated with use of vitamins C and E approached unity with 10 or more years' duration prior to diagnosis, although use of multivitamins

did not confirm this pattern. No clear trends were noted with dose of vitamin C or E.

Food Intake

To understand the basis for the inverse association with dietary vitamin E in these data, we examined the association with individual foods known to contain relatively high concentrations of vitamin E and whose consumption explained the greatest between-person variation in vitamin E intake in this cohort. These foods included nuts, peanut butter, cold cereals, cabbage, tomato sauce, apples, sweet potatoes, mushrooms, mayonnaise, and oil and vinegar as a salad dressing (the best predictor of plasma α -tocopherol levels [25]). The only foods that appeared to be related to the risk of new-onset asthma after adjustment for smoking and age were an inverse association with nuts, cold breakfast cereal, and cabbage (trend not significant); in each case as reported in 1980 but not in 1982 or 1984 (data not shown). The use of tomato sauce (a high source of lycopene) two or more times per week was associated with a significantly lower risk of asthma.

A total fruit score calculated from 1980 intake of fruits and fruit juices showed little relation to risk of asthma (RR for quintiles of servings per day adjusted for age and smoking were 1.0, 0.98, 0.92, 0.96, and 1.06; p value for trend = 0.60).

Six-year risk of asthma was unrelated to frequency of intake of dark meat fish ($\chi = -0.13$; $p = 0.90$), tuna fish ($\chi = 0.19$; $p = 0.85$), and shrimp ($\chi = -0.21$; $p = 0.83$) as measured in 1984.

Fatty Acids

In general, the results from analyses using fatty acid intake as

TABLE 3
RELATIVE RISK OF ASTHMA BY DURATION OF VITAMIN SUPPLEMENT USE*

Supplement	Duration of Use (yr)						p Value for Trend†
	0	< 2	2-4	5-9	10-14	15+	
Vitamin E†							
No. of cases	624	43	31	41		19	
Person-years	551,426	27,790	22,790	27,254		15,798	
Age and smoking adjusted RR‡	1.0	1.37	1.20	1.34		1.08	0.66
Multivariate RR§ (95% conf. limits)	1.0	1.30 (0.94, 1.79)	1.15 (0.79, 1.68)	1.18 (0.84, 1.65)		0.94 (0.58, 1.52)	0.27
Vitamin C							
No. of cases	518	60	59	83	24	15	
Person-years	482,181	43,113	37,440	47,336	19,811	13,482	
Age and smoking adjusted RR‡	1.0	1.28	1.45	1.61	1.13	1.03	0.75
Multivariate RR§ (95% conf. limits)	1.0	1.28 (0.97, 1.69)	1.43 (1.08, 1.90)	1.45 (1.12, 1.87)	1.02 (0.67, 1.57)	0.96 (0.56, 1.62)	0.49
Vitamin A							
No. of cases	729	12	5		14		
Person-years	618,333	11,816	6,484		9,730		
Age and smoking adjusted RR‡	1.0	0.85	0.64		1.22		0.33
Multivariate RR§ (95% conf. limits)	1.0	0.68 (0.38, 1.22)	0.51 (0.21, 1.23)		0.90 (0.52, 1.57)		0.58
Multivitamins							
No. of cases	446	68	49	85	49	59	
Person-years	407,384	53,957	53,085	64,395	29,448	32,450	
Age and smoking adjusted RR‡	1.0	1.14	0.84	1.19	1.48	1.62	0.0009
Multivariate RR§ (95% conf. limits)	1.0	1.14 (0.88, 1.48)	0.80 (0.60, 1.08)	1.03 (0.81, 1.31)	1.32 (0.97, 1.80)	1.48 (1.12, 1.97)	0.01

* Total number of cases and person-years vary due to missing data.

† p for trend calculated for duration of use among supplement users.

‡ Adjusted for age (in 5-yr categories) and smoking (never/past/current in three levels of cigarettes smoked per day).

§ Logistic model includes age and smoking as described above, body mass index (< 21, 21-23, 23-25, 25-29, > 29 kg/m²), area of residence (northeast USA, north central USA, Florida, Texas, California), number of physician's visits 0, 1, 2-3, > 4, and use of vitamins E, C, A and multivitamins.

assessed in 1980 and updated in 1984 and 1986 (except omega-3 fatty acids, which were assessed in 1984 and updated in 1986) showed a slight inverse association with risk of asthma, although none of the tests for trend was significant (Table 4). A comparison of the highest and the lowest quintile of monounsaturated fat and linoleic acid intake resulted in significant inverse associations, although these results were not found in analyses using fatty acid intake in 1980 and 1980-1990 incidence of asthma, or in analyses using fatty acid intake in 1984 and 1984-1990 incidence of asthma. Polyunsaturated oils are an important source of vitamin E. Because vitamin E was found to be inversely associated with asthma, we repeated the fatty acid analyses, adjusting for intake of vitamin E with and without supplements. RR were essentially unchanged.

Several subjects reported on the supplementary questionnaire that their asthma was exacerbated by certain foods including nuts and peanut butter. Nuts and peanut butter contributed to between-person variance in dietary vitamin E intake in these data, and, if future cases were more likely to avoid nuts than the rest of the cohort, then an inverse association between dietary vitamin E and risk of asthma might result. Therefore, we reassessed the relation of updated dietary vitamin E to risk of asthma, excluding the contribution from nuts and peanut butter. This analysis resulted in an attenuation of RR associated with the fifth quintile, although the test for trend remained significant (RR for quintiles one through five from the multivariate model = 1.0, 1.14, 0.84, 0.62, and 0.74; *p* for trend = 0.007). Thus, the association with nuts and peanut

butter could not entirely explain the relation with vitamin E that we observed.

In summary, recent intake of vitamin E from diet but not from supplements was found to be inversely related to adult-onset asthma in these prospective data. Women in the highest quintile of dietary vitamin E intake had a 47% lower risk than women in the lowest quintile; however, exclusion of the contribution to dietary vitamin E from nuts and peanut butter to address a possible bias due to food allergies attenuated the association, which nevertheless remained significant. Intake of carotene had a weak inverse association with asthma. No relation with risk of asthma was noted for dietary vitamin C or total fruit intake, but short-term users of vitamin C and vitamin E supplements had an increased risk. Risk of asthma was not significantly associated with omega-3 fatty acids, and the data were not consistent with a positive association between linoleic acid and asthma risk.

DISCUSSION

Dietary Vitamin E and Supplements

To our knowledge, no other study has assessed the relation of vitamin E and respiratory disease. Nevertheless, an effect of vitamin E on the inflammatory process seems plausible. Vitamin E is a naturally occurring antioxidant and free-radical-quenching agent. It is lipid soluble, is most effective at high O₂ concentrations, and is found in lipid structures exposed to high partial pressures of O₂ such as erythrocyte membranes and cell membranes

TABLE 4
RELATIVE RISK OF ASTHMA FROM 1980 TO 1990 BY QUINTILES OF ENERGY-ADJUSTED FAT INTAKE*

Type of Fat	RR for Indicated Quintiles of Intake					p Value for Trend
	1	2	3	4	5	
Total Fat, g [†]	51.9	62.7	69.9	77.0	87.4	
No. of cases	157	144	163	147	149	
Adjusted for age and smoking [‡]	1.0	0.87	0.99	0.90	0.91	0.54
Multivariate [§] (95% CI)	1.0	0.84 (0.67-1.06)	0.94 (0.75-1.17)	0.84 (0.67-1.06)	0.87 (0.70-1.09)	0.29
Saturated, g	20.0	24.7	27.9	31.2	36.1	
No. of cases	167	152	154	174	113	
Adjusted for age and smoking [‡]	1.0	0.86	0.88	1.00	0.79	0.35
Multivariate [§] (95% CI)	1.0	0.83 (0.67-1.04)	0.83 (0.67-1.03)	0.95 (0.77-1.18)	0.80 (0.63-1.02)	0.37
Monounsaturated, g	20.1	25.1	28.6	32.1	37.5	
No. of cases	167	153	138	163	139	
Adjusted for age and smoking [‡]	1.0	0.87	0.79	0.94	0.82	0.20
Multivariate [§] (95% CI)	1.0	0.84 (0.68-1.05)	0.74 (0.59-0.93)	0.89 (0.71-1.10)	0.78 (0.62-0.97)	0.12
Linoleic, g	4.49	6.00	7.23	8.63	11.1	
No. of cases	171	131	150	169	139	
Adjusted for age and smoking [‡]	1.0	0.72	0.82	0.90	0.75	0.15
Multivariate [§] (95% CI)	1.0	0.71 (0.57-0.89)	0.80 (0.64-1.00)	0.86 (0.70-1.07)	0.74 (0.59-0.93)	0.14
Omega-3, g	0.05	0.09	0.13	0.21	0.36	
No. of cases	104	101	74	105	84	
Adjusted for age and smoking [‡]	1.0	0.89	0.80	1.03	0.88	0.87
Multivariate [§] (95% CI)	1.0	0.89 (0.68-1.15)	0.78 (0.59-1.04)	0.96 (0.74-1.24)	0.85 (0.65-1.12)	0.37

* As assessed in 1980 and updated in 1984 and 1986 (omega-3 fatty acids assessed in 1984 and updated in 1986).

[†] Median values for fats (except omega-3 fatty acids) as assessed in 1980. Medians presented for omega-3 fatty acids are from 1984.

[‡] Adjusted with use of indicator variables for age (in 5-yr categories) and smoking (never, past, current in three levels of cigarettes smoked per day).

[§] Logistic model includes age and smoking as described above, body mass index (< 21, 21-23, 23-25, 25-29, ≥ 29 kg/m²), area of residence (northeast USA, north central USA, Florida, Texas, California), number of physician's visits (0, 1, 2-3, ≥ 4), and quintiles of energy intake.

of the respiratory tree. Vitamin E may also modify prostaglandin formation, thereby enhancing production of PGI₂, which inhibits the effects of histamine and relaxes vascular smooth muscle.

Vitamin E from diet but not from supplements was inversely related to asthma risk. One possible explanation for this finding is that women experiencing asthma symptoms prior to diagnosis were more likely to take vitamin supplements. If this were the case, then the association of asthma to vitamin E from supplements would be biased upward such that a null or adverse effect would be noted if the relationship were truly protective. The increased risks associated with vitamin E supplement use relative to non-users decreased to unity with 10 or more years' duration of supplement use, thus providing some evidence to support the possibility that women initiated use of vitamin E supplements with onset of symptoms.

A measure of atopy was not available in these data. Atopy, or more specifically food allergies, may have led to a biased RR for dietary vitamin E. Subjects with asthma were asked to list on the supplementary questionnaire foods they believed were responsible for asthma attacks. Ten of the subjects reported that nuts or peanut butter, foods that contribute to dietary vitamin E intake, precipitated attacks. Although diet was measured before diagnosis of asthma in this investigation, if some of the subjects, prior to their diagnosis of asthma, avoided these foods because of symptoms, then an inverse relationship of dietary vitamin E intake and risk of asthma might result. To address this concern, we repeated the analysis using dietary vitamin E without the contribution from nuts and peanut butter. The RR associated with the fifth quintile was attenuated (0.53 to 0.74), although the trend remained significant. This analysis, however, may have led to an overly conservative estimate of effect since excluding vitamin E from nuts and peanut butter (two of the highest sources of vitamin E in this dataset) will increase misclassification in the measurement of total dietary vitamin E intake, causing some attenuation in the RR.

Dietary Vitamin C and Supplements

Contrary to our earlier hypothesis, use of vitamin C supplements was associated with a significant increase in the risk of asthma. A protective effect of vitamin C against respiratory illnesses or symptoms is widely perceived and nurses with recurrent respiratory problems may have been more likely to take vitamin C supplements. To the extent that respiratory illnesses are associated with adult-onset asthma, confounding by indication may have resulted in a spurious positive relationship between use of vitamin C supplements and asthma. Several observations support this hypothesis. When the effect of vitamin C was assessed in women not using supplements, the positive trend disappeared. Furthermore, the positive association of vitamin C with supplements assessed in 1980 with 10-yr risk of asthma was somewhat attenuated when similar analyses were performed replacing date of diagnosis with date of first asthma symptoms (RR = 1.0, 1.06, 1.10, 1.04, and 1.41; *p* for trend = 0.01). Finally, long-term duration of supplement use (10 yr) was not associated with an increased risk of asthma. Analogously, a weak protective effect of dietary vitamin C may have been missed if nurses at high risk of asthma who were not taking supplements added vitamin C-rich foods to their diets. This appears unlikely, however, since orange juice, the greatest source of dietary vitamin C, was not related to an increased risk of asthma. In addition, no relation was found for total fruit intake.

Over 50 yr ago, Hunt (26) treated 25 asthmatics with 50 mg of ascorbic acid twice daily over a 2-week period with no improvement in wheezing or frequency of attacks. In contrast, a more re-

cent study found a significant decrease in frequency and severity of asthma attacks in asthmatics treated with 1 g of ascorbic acid daily for 14 wk, suggesting that higher doses over a longer period are required to affect asthma symptoms. Several studies assessing the acute effect of vitamin C administration in asthmatics have shown an attenuation in bronchial responsiveness (10, 11), although other studies have failed to demonstrate this effect (9, 12).

Few epidemiologic studies have evaluated the relation of vitamin C to asthma. Schwartz and Weiss (8) found an inverse association between serum vitamin C, but not dietary intake of vitamin C as measured by 24-hr recall, and prevalence of wheezing within the past year in data from the National Health and Nutritional Examination Survey II (NHANES II) (odds ratio [OR] and 95% CI were 0.71 [0.58 to 0.88] for a two-standard deviation increase in vitamin C adjusting for age, sex, race, socioeconomic status, cigarette smoking, and total energy intake) (8). An association with serum levels, but not self-reported dietary intake, may indicate that misclassification, in addition to confounding by indication, reduced the likelihood of finding a significant inverse relationship between vitamin C and asthma in the present study. Additionally, because mean dietary vitamin C consumption in the NHS is greater than in the general population (19), a beneficial effect of vitamin C may only be demonstrable at low levels of intake. It may be useful in future epidemiologic studies of diet and asthma to target populations with low intakes of vitamin C.

The epidemiologic data are stronger in support of the role of vitamin C in the etiology of chronic obstructive pulmonary disease. In NHANES I data, dietary vitamin C was positively correlated with FEV₁ (27), and vitamin C-rich foods were inversely associated with prevalence of airway obstruction defined as FEV₁/FVC < 65%, (OR = 2.2 comparing one or fewer servings per week to more than one serving per week) (28). In a prospective study conducted in the Netherlands (6), solid fruit was inversely associated with 25-yr-risk of chronic nonspecific lung disease (CNSLD), defined as asthma, chronic bronchitis, and emphysema. Thus dietary vitamin C intake may be more important in pulmonary diseases when oxidant injury may be playing a major causal role.

β-Carotene and Other Antioxidants

An inverse association of borderline significance was found between carotene and risk of asthma in the present study that was stronger in current smokers than in never smokers, although neither the trend nor the interaction was significant. Because smokers generally have lower antioxidant levels (29), these results suggest that carotene intake is most beneficial when antioxidant levels are low.

In addition to β-carotene, other antioxidants in the diet include α-carotene, lycopene, lutein, zeaxanthin, and β-cryptoxanthin. Specific foods that are major contributors to total antioxidant intake were evaluated separately. Carrots, the richest source of β-carotene, were not related to asthma, although tomato juice ($\chi = -2.30$; *p* = 0.02), tomato sauce ($\chi = -1.64$; *p* = 0.10), and pizza ($\chi = -2.17$; *p* = 0.03) as assessed in 1984 and adjusted for age and smoking were inversely related to 6-yr risk of asthma. The association demonstrated with tomato products raises the possibility that the carotenoid lycopene plays a more important role in the pathophysiology of asthma than β-carotene.

Further assessment of specific foods suffers from the difficulty in assessing diet that precedes disease onset when the disease, like asthma, does not suddenly become manifest and the patient has had time to adjust behaviors, including dietary changes, to cope with symptoms before being diagnosed.

Fish Oils and Fatty Acids

Results of the few experimental studies that have evaluated the relationship of fish oil to pulmonary function show the expected physiologic changes but no effect on asthma severity (14, 30). We also were unable to demonstrate an inverse association between omega-3 fatty acids or dark meat fish consumption and the risk of developing asthma. Several epidemiologic studies, however, have found associations of fish consumption or fish oil with other pulmonary outcomes including bronchial hyperresponsiveness (31), and chronic bronchitis and emphysema (6), although neither study adjusted their results for other dietary factors.

Miedema and colleagues (6) found a positive association of monounsaturated and polyunsaturated fats and risk of CNSLD. The risk of CNSLD for men in the highest quartile of linoleic acid intake was 1.49 (CI = 1.06 to 2.09) relative to men in the lowest quartile of intake assessed 25 yr earlier, and was independent of fruit and alcohol consumption. These limited data suggest that intake of omega-3 fatty acids and linoleic acid during early adulthood influences the development of obstructive disease. Our data, however, do not support important effects of omega-3 fatty acids and several polyunsaturated fats consumed during recent adulthood on asthma risk.

Limitations

Some potential limitations of this investigation should be mentioned. The case definition for asthma required that the nurses reproduce their self-report of a physician's diagnosis and report having taken medication specifically for asthma since diagnosis. The validation study provided data to assess the predictive value positive of the asthma question on the 1988 and 1990 questionnaires, but no information to assess sensitivity and specificity. The incidence of asthma in the NHS ranged from 0.9 to 1.3 per 1,000 person-years compared with 1.4 to 7.0 per 1,000 person-years in women of the same age in a random sample of Tucson, Arizona residents (2), thus underascertainment of cases seems more probable than overascertainment. Misclassification in the assignment of asthma status due to underascertainment, however, should not have biased the estimates of rate ratio presented in these analyses unless the misclassification was nonrandom with respect to dietary intake. Furthermore, the incidence rates from the NHS are consistent with rates estimated by review of inpatient and outpatient medical records of potential cases identified by a record linkage system in a population-based study from Rochester, Minnesota (32) (1.4/1,000 person-years for women 30 to 49 and 1.15/1,000 for women over 50 yr of age). In addition, the subjects in this study are nurses with a demonstrated interest in medical research. The validity of their self-report of several other diseases has been investigated previously and found to be quite accurate (33).

Information on atopic status was unavailable in our study. If dietary antioxidant intake is effective in preventing asthma only in atopic individuals, then our inability to classify asthmatics by atopic status may have caused us to miss an effect.

Another limitation relates to the assessment of diet in any disease in which significant symptoms may precede diagnosis by a considerable period of time. Evidence suggesting that this was the case in the present study relates to the finding of an excess of disease among the women who used vitamin C supplements. Furthermore, this bias may work in the opposite direction: symptomatic subjects may avoid certain foods they believe exacerbate their symptoms. These foods, in turn, may coincidentally be high in antioxidant content, resulting in an apparently protective association with asthma risk. We found such cases among the nurses in assessing those believed to be allergic to nuts, a relatively com-

mon source of vitamin E. However, after addressing this source of confounding we were still able to identify a trend with dietary vitamin E intake.

To gain further insight into the potential role for diet will require the use of biomarkers of exposure that are representative of long-term dietary trends for a given individual. Because the bulk of these antioxidants are fat-soluble and we have stored serum specimens collected in 1989, with several further years of follow-up we may be in a position to assess this relationship prospectively.

In summary, intake of vitamin E from diet, but not from supplements, was inversely related to adult onset of asthma in women. Strong or consistent relationships of decreased risk of asthma with individual food sources of vitamin E, however, were not noted, and analyses addressing a possible bias due to food allergies showed an attenuation of the inverse trend with risk of asthma. Our results suggest that antioxidant supplementation and foods high in antioxidants are not major determinants of adult-onset asthma risk. In addition, we were not able to demonstrate an inverse association with omega-3 fatty acids. Additional prospective studies of dietary intake, along with biochemical markers of these antioxidants, including most particularly vitamin E and the different carotenoid types, and risk of asthma are warranted to further examine these associations.

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