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Original Contribution

Antioxidant Intake and Risks of Rheumatoid Arthritis and Systemic Lupus Erythematosus in Women

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Antioxidants may protect against development of rheumatoid arthritis or systemic lupus erythematosus by combating oxidative stress. The authors identified and confirmed incident cases of rheumatoid arthritis and systemic lupus erythematosus among 184,643 US women followed in the Nurses' Health Study and Nurses' Health Study II cohorts in 1980–2004. Semiquantitative food frequency questionnaires assessed intakes of vitamins A, C, and E and α-carotene, β-carotene, β-cryptoxanthin, lycopene, lutein, and zeaxanthin from foods and supplements. The authors examined total antioxidant intake by calculating a ''ferric-reducing ability of plasma'' score, a new method for quantifying the total antioxidant effect of a food based on the reduction of ferric to ferrous iron by antioxidants. Cumulative updated total energy-adjusted dietary intakes were used. Associations between intake of each nutrient and incident rheumatoid arthritis and systemic lupus erythematosus were examined in age-adjusted and Cox proportional hazards models, adjusted for confounders. Results from the cohorts were pooled meta-analytically by using random-effects models. The authors identified 787 incident rheumatoid arthritis cases and 192 systemic lupus erythematosus cases for whom prospective dietary information was available. In these large, prospective cohorts of women, antioxidant intake was not associated with the risk of developing either rheumatoid arthritis or systemic lupus erythematosus.

antioxidants; arthritis, rheumatoid; diet; food; lupus erythematosus, systemic; risk factors; vitamins

Abbreviations: FFQ, food frequency questionnaire; FRAP, ferric-reducing ability of plasma; NHS(II), Nurses' Health Study (II); RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

Rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are related autoimmune diseases of unknown etiology that predominantly affect women. Both of these diseases are marked by persistent systemic inflammation and tissue damage. Antioxidants are known to protect against tissue damage from reactive oxygen species generated by activated macrophages, monocytes, and granulocytes (1–3) and to suppress the activity of cytokines, such as tumor necrosis factor-α (4), an important inflammatory mediator in these diseases. In murine models of SLE, supplementation with antioxidants, including β-carotene, α-tocopherol, ascorbic acid, and selenium, reduced autoantibody production and prolonged survival (5–7). Dietary supplementation with vitamin E modulated levels of inflammatory cytokines and delayed onset of autoimmunity in the MRL/lpr mouse model (8). More recently, it has been shown that retinoic acid, a vitamin A derivative, inhibits formation of the proinflammatory T-helper 17 cells and promotes production of the antiinflammatory T-regulatory cells in autoimmune disease murine models (9).

Relatively little is known about the influence of antioxidant intake on initiation of these diseases in humans (10–14). In subjects with RA and SLE, lower blood levels of antioxidants and decreased antioxidant intake have been reported (15, 16). In a case-control study nested within a Finnish cohort, 14 subjects who developed RA a median of 20 years later had lower total levels of blood antioxidants than did healthy matched controls (17). In a similar study in Maryland, 21 individuals who later developed RA and 6 who later developed SLE had contributed samples to a

Table 1. Age-adjusted Characteristics of NHS Participants in 1990 (at Ages 44–69 Years) and NHSII Participants in 1991 (at Ages 27–44 Years) in the Highest and Lowest Fifths of Energy-adjusted Vitamin A, Vitamin C, and Vitamin E Intake, United States

	Fifth of Vitamin A Intake		Fifth of Vitamin C Intake		Fifth of Vitamin E Intake	
	Lowest	Highest	Lowest	Highest	Lowest	Highest
Age in years, mean (SD)						
NHS	55.0 (7.0)	58.2 (7.0)	55.0 (7.1)	57.8 (7.0)	55.7 (7.2)	57.9 (7.0)
NHSII	36.7 (4.7)	36.5 (4.7)	36.5 (4.6)	37.1 (4.6)	36.3 (4.7)	36.8 (4.7)
Current smoker, %						
NHS	21	16	24	15	22	15
NHSII	17	11	17	12	16	11
Mean no. of pack-years of smoking (smokers)						
NHS	26	23	28	23	27	23
NHSII	13	11	13	11	13	11
Age at menarche $\leq$10 years, %						
NHS	5	6	5	6	5	6
NHSII	8	8	8	8	7	8
Body mass index, kg/m^2						
NHS	26	25	26	25	26	25
NHSII	25	24	25	24	24	24
Oral contraceptive ever use, %						
NHS	49	49	48	50	48	50
NHSII	86	84	86	83	85	85
Parous, %						
NHS	93	92	92	91	93	92
NHSII	73	67	74	64	73	65
Lifetime breastfeeding for $\geq$12 months (parous women), %						
NHS	15	18	15	19	16	18
NHSII	8	10	8	12	8	11

Table continues

serum bank 2–15 years prior to disease onset. Their premorbid blood samples showed lower levels of α-tocopherol, β-carotene, and retinol than those of their age-, sex-, and race-matched controls (18). In the prospective Iowa Women's Health Study of postmenopausal women, higher intakes of supplemental zinc and β-cryptoxanthin at baseline were associated with lower risks of developing RA (19). Using the population-based Norfolk Arthritis Registry and the European Prospective Investigation into Cancer and Nutrition (EPIC) incidence studies, Pattison et al. (20) studied 7-day diet histories of 88 recent-onset inflammatory polyarthritis subjects compared with 176 age- and sex-matched controls. They found that β-cryptoxanthin intake was 40% lower and zeaxanthin intake was 20% lower among those with recent-onset inflammatory polyarthritis. They also reported that, compared with controls, subjects with new inflammatory polyarthritis consumed significantly less fruit and vitamin C at baseline (21).

Our aim in the present study was to investigate cumulative updated intakes of antioxidant vitamins A, C, and E and carotenoids, including α-carotene and β-carotene, β-cryptoxanthin, lutein, and zeaxanthin, and incident RA and SLE. We used 2 large prospective cohorts of women: the Nurses' Health Study (NHS) and the Nurses' Health Study II (NHSII).

MATERIALS AND METHODS

Study population

NHS is a prospective cohort of 121,700 female nurses aged 30–55 years at study inception in 1976. NHSII is a prospective cohort study that began in 1989, enrolling 116,608 female nurses aged 25–42 years. Information about lifestyle and medical history is collected from participants in both cohorts via biennial questionnaires. More than 95% of women in both cohorts are Caucasian, reflecting the ethnicity of women entering the nursing profession during the recruitment years. Participants in both cohorts

Table 1. Continued

	Fifth of Vitamin A Intake		Fifth of Vitamin C Intake		Fifth of Vitamin E Intake	
	Lowest	Highest	Lowest	Highest	Lowest	Highest
Postmenopausal, %						
NHS	71	71	70	70	70	71
NHSII	3	4	3	4	3	4
Current use of postmenopausal hormones (postmenopausal women), %						
NHS	21	26	21	28	16	28
NHSII	84	81	84	81	82	84
Physical exercise, hours/week						
NHS	2.7	3.4	2.5	3.4	2.7	3.4
NHSII	2.7	3.9	2.5	4.0	2.7	3.9
Husband >college education, %						
NHS	18	19	16	20	16	20
NHSII	21	26	20	25	20	25
Daily multivitamin use, %						
NHS	5	81	8	70	4	73
NHSII	6	89	10	78	5	89
Mean daily alcohol intake, g						
NHS	6.3	4.4	5.8	5.1	6.0	4.9
NHSII	3.5	2.7	3.3	3.3	3.2	3.0
Mean daily caffeine intake, mg						
NHS	285	234	309	237	280	233
NHSII	263	208	274	220	246	215
Mean daily protein intake, g						
NHS	72	79	75	76	72	77
NHSII	82	89	85	86	81	88
Mean daily calcium intake, mg						
NHS	744	1,245	806	1,231	873	1,255
NHSII	736	1,283	857	1,205	934	1,256

Abbreviations: NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; SD, standard deviation.

complete semiquantitative food frequency questionnaires (FFQs) (22) approximately every 4 years. Ninety-four percent of NHS participants from 1976 to 2004 and 95% of NHSII participants from 1989 to 2003 remain in active follow-up. The Brigham and Women's Hospital Institutional Review Board (Boston, Massachusetts) approved this study.

Identification of SLE and RA

As previously described (23–26), we used a 2-stage procedure in which nurses who reported RA, SLE, or another connective tissue disease received a connective tissue disease screening questionnaire (27) and, if positive, medical record review. Two rheumatologists trained in chart abstraction independently conducted medical record reviews, examining the charts for the American College of Rheumatology diagnostic criteria for RA (28) and for SLE (29, 30). Incident cases of disease were confirmed if they met American College of Rheumatology criteria.

Population for analysis

We included all participants in the NHS and NHSII cohorts who had completed the FFQ at baseline—1980 in NHS and 1991 in NHSII. From this group, we excluded prevalent cases of RA and SLE (diagnosed before baseline) and all women who reported a connective tissue disease at any time that was not subsequently confirmed as RA or SLE. Women were censored at their last response to questionnaires because incident cases could not be identified. The final group included 90,721 women followed from 1980 to 2004 in NHS and 93,922 women followed from 1991 to 2003 in NHSII. In a sensitivity analysis, we excluded women who reported any cancer (except nonmelanoma skin cancer) at any time because cancer and its treatment may affect vitamin intake and health behaviors.

Nutritional factors

Semiquantitative FFQs, on which participants reported frequency of consumption of specified foods over the prior year, were used to assess nutritional factors. NHS participants completed the FFQ in 1980, 1984, 1986, 1990, 1994, 1998, and 2002; NHSII participants returned FFQs in 1991, 1995, and 1999. In 1980 in NHS and 1991 in NHSII, participants were first asked about their use of multivitamins, including name brand and number of tablets taken per week, and supplements of vitamins A, C, and E as well as zinc (first asked about specifically in 1984), including dose and duration of use. This information has been assessed on each of the biennial questionnaires since then. The sensitivity and specificity of the FFQ regarding supplement use in NHS and NHSII were 78% and 93%, respectively (31).

We calculated nutrient intakes by adding the contributions from multivitamins, specific supplements, and foods. Food intakes were calculated by multiplying the frequency of consumption by the nutrient content of the specified portions. All dietary nutrients, alcohol, and caffeine were calculated according to the nutrient content of foods, derived from the US Department of Agriculture, food manufacturers, and other published sources (32). For carotenoid contents, the US Department of Agriculture–National Cancer Institute carotenoid food composition databases were used (33, 34). Intake data for lutein and zeaxanthin were combined in our databases.

The accuracy and reproducibility of the FFQ for foods and nutrients have been documented in past validation studies comparing the FFQ with both dietary records and plasma nutrient values (22, 35–37). Pearson's correlations between the 1980 NHS FFQ and 4 one-week dietary records were 0.84 for orange and grapefruit juice, 0.80 for apples, 0.69 for broccoli, 0.73 for tomatoes, and 0.40 for raw carrots (35). For vitamins A and C from foods, the correlations were 0.36 and 0.66, respectively (22). The correlation between vitamin E values from FFQ and plasma was 0.52 (38). The correlations between dietary carotenoids and plasma levels among women nonsmokers were 0.21 for lycopene, 0.27 for β-carotene and lutein, 0.32 for β-cryptoxanthin, and 0.48 for α-carotene (37).

Covariate information

Age was updated each cycle. On the basis of past findings, risk factors for RA and SLE in these cohorts (23, 25, 39), including pack-years of cigarette smoking, age at menarche, oral contraceptive use, and menopausal status, were included as potential confounders. Postmenopausal hormone use was included as a covariate in NHS cohort analyses but not in NHSII cohort analyses because few women were postmenopausal during these years. Updated body mass index, computed for each 2-year time interval by using most recent weight in kilograms divided by height in meters squared, and updated hours per week of physical activity were included as potential covariates, as were participants' husbands' educational level and racial and ethnic ancestry (African, Asian, Hispanic, Caucasian, or other).

Statistical analysis

All analyses were conducted separately in the 2 cohorts. Person-years of follow-up accrued from return of the baseline questionnaire until diagnosis of RA and SLE, report of connective tissue disease not confirmed as RA and SLE, death, or loss to follow-up. Age-adjusted relative risks were calculated by stratifying participants into 5-year age categories. Cox proportional hazards regression models were used to study the association of antioxidant vitamin intake with RA and SLE, adjusting for covariates. We used time-varying information for covariates from each 2-year questionnaire to analyze risk of RA and SLE in the next 2-year cycle. The final multivariable models for SLE included age at menarche, oral contraceptive use, menopausal status, postmenopausal hormone use, cigarette smoking, physical activity in metabolic equivalent hours per week, body mass index (kg/m^2), and race. Final multivariable models for RA included the same covariates plus parity and total duration of breastfeeding because we found them to be related to risk of RA in prior analyses (25). Tests for linear trend used the midpoints of the ranges of quintile-divided categories (fifths) in both age-adjusted and multivariable Cox models.

Nutrient intakes correlated with total energy intake (all except caffeine and alcohol) were adjusted for total energy intake with linear regression analyses (40). To compute energy-adjusted nutrient intakes, regression models were run in which the natural log of total energy intake is the independent variable and the natural log of nutrient intake is the dependent variable. The antilog of the residuals represented the energy-adjusted nutrient intakes. Nutrient intake at the median energy intake for the cohort was added to these residual values to create meaningful nutrient values (residuals have a mean of zero and can have negative values). A validation study by Willett et al. (22) found that, with the exception of sucrose and total carbohydrate, nutrient intakes, including all antioxidant vitamin intakes, from weekly diet records correlated more strongly with those computed from FFQ after adjustment for total caloric intake. Thus, in subsequent studies investigating associations between nutrient intake and outcomes using FFQ data from NHS, energy-adjusted nutrient intake values calculated from the FFQ have been used.

For vitamins A, C, and E and β-carotene, we separately analyzed the contributions from foods and supplements alone as well as from foods and supplements combined. Models of vitamin intakes from foods only were adjusted for intakes from supplements, and models of vitamin intakes from supplements only were adjusted for intakes from foods. Intakes of each nutrient were examined as continuous values and in fifths. In primary analyses, all nutrient intake values were cumulatively updated, that is, at each 2-year follow-up cycle, averaging the most recent measures with previous-average measures. Tests for linear trend used the midpoints of the category ranges. To increase precision of risk estimates and to obtain a single summary from the NHS and NHSII cohorts, relative risk results from the 2 cohorts were meta-analytically pooled by using a random-effects model (41).

Table 2. Characteristics of the NHS and NHSII Rheumatoid Arthritis and Systemic Lupus Erythematosus Cases at Diagnosis, United States

	NHS			NHSII		
	Mean (SD)	No.	%	Mean (SD)	No.	%
Rheumatoid Arthritis						
No. of cases		619			168	
Age at diagnosis, years	59.2 (8.9)			44.3 (5.4)		
Rheumatoid-factor positive		353	57		96	57
Rheumatoid nodules		76	12		19	11
Radiographic changes		171	28		42	25
Mean no. of ACR criteria[a]	4.6 (0.8)			4.5 (0.7)		
Diagnosed by an ACR member		511	85		159	95
Systemic Lupus Erythematosus						
No. of cases		118			74	
Age at diagnosis, years	53.7 (8.4)			42.2 (5.2)		
Anti-nuclear-antibody positive[b]		113	97		74	100
Anti-double-stranded DNA-antibody positive[c]		19	16		40	54
Arthritis		19	16		50	68
Hematologic involvement		27	23		41	55
Renal involvement		3	3		4	5
Mean no. of ACR criteria[d]	4.7 (0.9)			4.6 (1.0)		
Diagnosed by an ACR member		84	72		67	91

Abbreviations: ACR, American College of Rheumatology; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; SD, standard deviation.

[a] 4/7 criteria required for diagnosis by ACR criteria (28).

[b] Antinuclear antibody $\geq$1:40 according to medical record review.

[c] According to medical record review.

[d] 4/11 criteria required for diagnosis by ACR criteria (29, 30).

Because antioxidants may act synergistically, we calculated a total antioxidant intake composite score by calculating the ''ferric-reducing ability of plasma'' (FRAP) score. This is a method for quantifying the total antioxidant effect of a food that relies upon direct assessment of the reduction of ferric iron (Fe 3+) to ferrous iron (Fe 2+) in the presence of antioxidants. This is the only method that directly measures antioxidants (or reductants) in a sample (42, 43). A NHS and NHSII ''total antioxidant capacity'' database was developed based on the published total antioxidant capacity of dietary plants, foods, and grains (a total of 290 foods plus multivitamins and supplements). To determine the FRAP value of the foods in our FFQ, we used tables published by the Institute of Nutrition Research, University of Oslo (Norway), which included FRAP measurements on more than 1,000 foods obtained from the US Department of Agriculture National Food and Nutrient Analysis Program (44). When a food item used in our FFQ was not listed in these tables, we worked with nutrition experts to impute reasonable values. For each participant, we multiplied frequency of consumption of each food by the corresponding FRAP value and summed the resulting values across all dietary sources to obtain ''FRAP scores.'' Because FRAP is highly correlated with total energy intake, we calculated energy-adjusted FRAP scores by using the residual method (45). We used cumulative averages of these FRAP scores in each 2-year follow-up cycle.

We performed several sensitivity analyses. First, we evaluated baseline nutrient intakes carried forward and then simple updated nutrient intakes without cumulatively averaging as exposures, calculating follow-up time in the same way. We also examined risks for nonusers compared with users of both vitamin C and vitamin E supplements because these specific supplements typically contain mega-doses of the vitamins. In separate analyses, we excluded from both cohorts all women who reported any cancer at baseline or during follow-up because cancer may affect vitamin intake. In stratified analyses, we investigated antioxidant intakes and the risk of these diseases among women who had smoked more than 10 pack-years of cigarettes in their lifetime because the risk of RA is significantly increased at that threshold of smoking in this cohort (23). We also examined the risk of rheumatoid-factor-positive RA separately because it may be a more homogeneous and severe RA phenotype. SAS version 9 software (1990) was used for all analyses (SAS Institute, Inc., Cary, North Carolina), and all tests of significance were 2-sided.

Table 3. Cohort-specific and Pooled Analyses of Antioxidants in Relation to Risk of Rheumatoid Arthritis in US Women in NHS (1980–2004) and NHSII (1991–2003)

	NHS					NHSII					Pooled RR[a]	95% CI	*P* het[b]
	Median Value	No. of Cases	No. of Person-Years	Multivariable RR[a]	95% CI	Median Value	No. of Cases	No. of Person-Years	Multivariable RR[a]	95% CI			
Vitamin A intake, IU/day[c]													
Fifth 1	670	119	378,193	1.0 (referent)		606	37	210,324	1.0 (referent)		1.0 (referent)		
Fifth 2	1,020	140	389,309	1.1	0.9, 1.4	924	39	214,097	1.1	0.7, 1.7	1.1	0.9, 1.4	1.0
Fifth 3	1,420	119	388,016	0.9	0.7, 1.2	1,318	27	216,813	0.8	0.5, 1.3	0.9	0.7, 1.1	0.5
Fifth 4	2,019	111	383,564	0.9	0.7, 1.1	1,923	34	215,210	1.0	0.6, 1.6	0.9	0.7, 1.1	0.6
Fifth 5	3,236	130	374,253	1.1	0.8, 1.4	3,016	31	211,956	0.9	0.6, 1.5	1.0	0.8, 1.3	0.6
P trend[d]				0.8					0.7		0.7		0.8
Vitamin C intake, mg/day[c]													
Fifth 1	90	119	377,743	1.0 (referent)		83	36	210,969	1.0 (referent)		1.0 (referent)		
Fifth 2	141	127	387,714	1.0	0.8, 1.3	127	40	213,497	1.2	0.7, 1.8	1.1	0.9, 1.3	0.6
Fifth 3	195	135	383,801	1.1	0.9, 1.4	172	30	215,918	0.9	0.5, 1.5	1.1	0.9, 1.3	0.4
Fifth 4	308	111	386,922	0.9	0.7, 1.2	251	26	213,880	0.8	0.5, 1.3	0.9	0.7, 1.1	0.7
Fifth 5	720	127	377,155	1.1	0.8, 1.3	611	36	214,136	1.1	0.7, 1.7	1.0	0.8, 1.3	0.8
P trend[d]				0.6					0.8		0.7		0.7
Vitamin E intake, mg/day[c]													
Fifth 1	6	126	366,299	1.0 (referent)		7	39	210,372	1.0 (referent)		1.0 (referent)		
Fifth 2	8	103	384,125	0.8	0.6, 1.0	8	32	211,746	0.8	0.5, 1.3	0.8	0.6, 1.0	0.7
Fifth 3	11	134	387,157	1.0	0.8, 1.2	11	26	214,391	0.7	0.4, 1.2	0.9	0.7, 1.2	0.3
Fifth 4	19	142	392,385	1.0	0.8, 1.3	17	32	215,616	0.9	0.5, 1.4	1.0	0.8, 1.2	0.6
Fifth 5	128	114	383,369	0.8	0.6, 1.0	99	39	216,274	1.0	0.6, 1.6	0.9	0.7, 1.1	0.4
P trend[d]				0.2					0.4		0.8		0.2
α-Carotenoid intake, mg/day[c]													
Fifth 1	282	97	375,380	1.0 (referent)		195	43	210,992	1.0 (referent)		1.0 (referent)		
Fifth 2	458	122	380,572	1.2	0.9, 1.6	424	21	214,016	0.5	0.3, 0.8	0.8	0.3, 2.0	<0.01
Fifth 3	623	157	387,569	1.5	1.2, 2.0	615	38	215,483	0.9	0.6, 1.4	1.2	0.7, 2.1	0.03
Fifth 4	913	128	390,644	1.2	0.9, 1.6	869	36	215,019	0.8	0.5, 1.3	1.1	0.8, 1.5	0.2
Fifth 5	1,506	115	379,170	1.2	0.9, 1.6	1,455	30	212,890	0.7	0.4, 1.2	1.0	0.6, 1.6	0.1
P trend[d]				0.9					0.6		0.9		0.6
β-Carotenoid intake, mg/day[c]													
Fifth 1	1,923	95	372,689	1.0 (referent)		1,671	38	211,014	1.0 (referent)		1.0 (referent)		
Fifth 2	2,948	155	385,582	1.5	1.2, 1.9	2,712	41	214,202	1.1	0.7, 1.7	1.4	1.0, 1.8	0.2
Fifth 3	3,956	115	387,188	1.1	0.8, 1.5	3,654	24	214,913	0.6	0.4, 1.1	0.9	0.5, 1.5	0.1
Fifth 4	5,267	125	386,770	1.2	0.9, 1.6	4,867	37	214,738	1.0	0.6, 1.5	1.1	0.9, 1.4	0.4
Fifth 5	7,806	129	381,107	1.3	1.0, 1.7	7,445	28	213,533	0.8	0.5, 1.3	1.0	0.6, 1.7	0.1
P trend[d]				0.8					0.3		0.7		0.3

β-Cryptoxanthin intake, mg/day													
Fifth 1	88	114	383,910	1.0 (referent)		51	39	211,784	1.0 (referent)		1.0 (referent)		
Fifth 2	149	141	389,745	1.2	1.0, 1.6	86	35	214,454	0.9	0.6, 1.5	1.2	0.9, 1.5	0.3
Fifth 3	201	124	389,321	1.1	0.9, 1.5	121	36	214,810	1.0	0.6, 1.5	1.1	0.9, 1.4	0.6
Fifth 4	255	125	384,113	1.2	0.9, 1.5	167	28	214,355	0.8	0.5, 1.3	1.0	0.7, 1.4	0.2
Fifth 5	359	115	366,246	1.1	0.9, 1.5	254	30	212,998	0.9	0.5, 1.4	1.1	0.9, 1.4	0.4
P trend[d]				0.7					0.5		0.9		0.5
Lycopene intake, mg/day[c]													
Fifth 1	1,496	97	343,265	1.0 (referent)		3,659	32	209,313	1.0 (referent)		1.0 (referent)		
Fifth 2	3,235	129	386,673	1.1	0.8, 1.4	5,197	30	214,164	0.9	0.6, 1.6	1.0	0.8, 1.3	0.7
Fifth 3	4,268	139	392,841	1.1	0.8, 1.4	6,621	33	215,435	1.0	0.6, 1.6	1.1	0.9, 1.4	0.7
Fifth 4	5,421	124	395,601	1.0	0.7, 1.3	8,609	34	215,433	1.0	0.6, 1.6	1.0	0.8, 1.2	0.8
Fifth 5	7,390	130	394,956	1.0	0.7, 1.3	12,387	39	214,056	1.2	0.7, 1.9	1.0	0.8, 1.3	0.5
P trend[d]				0.6					0.3		0.8		0.3
Lutein/zeaxanthin intake, mg/day[c]													
Fifth 1	1,499	117	381,089	1.0 (referent)		1,039	36	212,021	1.0 (referent)		1.0 (referent)		
Fifth 2	2,301	130	385,182	1.1	0.8, 1.4	1,711	35	214,597	1.0	0.6, 1.6	1.0	0.8, 1.3	0.7
Fifth 3	3,047	122	386,767	1.0	0.8, 1.3	2,361	41	214,730	1.1	0.7, 1.8	1.0	0.8, 1.3	0.6
Fifth 4	4,319	128	388,637	1.0	0.8, 1.3	3,167	31	214,209	0.9	0.5, 1.4	1.0	0.8, 1.2	0.5
Fifth 5	6,970	122	371,660	1.1	0.8, 1.4	4,886	25	212,843	0.7	0.4, 1.2	0.9	0.6, 1.3	0.2
P trend[d]				0.9					0.1		0.5		0.1
FRAP score													
Fifth 1	7	101	375,636	1.0 (referent)		5	28	212,129	1.0 (referent)		1.0 (referent)		
Fifth 2	10	133	386,913	1.2	0.9, 1.6	8	34	214,811	1.2	0.7, 1.9	1.2	1.0, 1.5	0.9
Fifth 3	12	127	387,566	1.1	0.9, 1.5	10	42	214,978	1.4	0.9, 2.3	1.2	0.9, 1.5	0.4
Fifth 4	15	131	385,807	1.1	0.9, 1.5	13	35	214,410	1.1	0.7, 1.9	1.1	0.9, 1.4	0.9
Fifth 5	20	127	377,414	1.1	0.9, 1.5	18	29	212,071	0.9	0.5, 1.5	1.1	0.8, 1.4	0.4
P trend[d]				0.9					0.5		0.8		0.5

Abbreviations: CI, confidence interval; FRAP, ferric-reducing ability of plasma; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; RR, relative risk.

[a] The multivariable model was adjusted for age at menarche, oral contraceptive use (never, past, current), menopausal status, postmenopausal hormone use (never, past, current), pack-years of cigarette smoking, physical activity (hours per week), body mass index, and race (Caucasian, other).

[b] *P* for test of heterogeneity (het) between the 2 cohorts. Risk estimates were pooled by using a DerSimonian and Laird random-effects model.

[c] Cumulatively averaged energy-adjusted intake from food and supplements.

[d] *P*-for-trend test using the midpoints of each fifth.

Table 4. Cohort-specific and Pooled Analyses of Antioxidants in Relation to Risk of Systemic Lupus Erythematosus in US Women in NHS (1980–2004) and NHSII (1991–2003)

	NHS					NHSII					Pooled RR[a]	95% CI	*P* het[b]
	Median Value	No. of Cases	No. of Person-Years	Multivariable RR[a]	95% CI	Median Value	No. of Cases	No. of Person-Years	Multivariable RR[a]	95% CI			
Vitamin A intake, IU/day[c]													
Fifth 1	670	19	375,812	1.0 (referent)		606	15	200,486	1.0 (referent)		1.0 (referent)		
Fifth 2	1,020	25	386,849	1.3	0.7, 2.4	924	11	203,961	0.8	0.3, 1.6	1.1	0.6, 1.8	0.3
Fifth 3	1,420	22	385,433	1.2	0.6, 2.1	1,317	13	207,226	0.9	0.4, 1.8	1.0	0.6, 1.7	0.6
Fifth 4	2,019	29	381,113	1.5	0.8, 2.7	1,922	19	205,299	1.3	0.7, 2.6	1.4	0.9, 2.2	0.8
Fifth 5	3,236	23	371,612	1.2	0.7, 2.3	3,012	16	201,575	1.2	0.6, 2.4	1.2	0.8, 1.9	1.0
P trend[d]				0.6					0.3		0.3		0.6
Vitamin C intake, mg/day[c]													
Fifth 1	90	22	375,225	1.0 (referent)		83	12	200,258	1.0 (referent)		1.0 (referent)		
Fifth 2	141	24	385,243	1.0	0.6, 1.8	127	15	203,593	1.2	0.6, 2.6	1.1	0.7, 1.7	0.7
Fifth 3	195	26	381,608	1.1	0.6, 2.0	172	12	206,602	1.0	0.5, 2.3	1.1	0.7, 1.7	0.9
Fifth 4	307	24	384,245	1.0	0.5, 1.8	250	23	204,224	2.1	1.1, 4.3	1.4	0.7, 3.0	0.1
Fifth 5	720	22	374,499	1.0	0.5, 1.8	610	12	203,870	1.1	0.5, 2.5	1.0	0.6, 1.7	0.8
P trend[d]				0.9					0.9		0.9		0.9
Vitamin E intake, mg/day[c]													
Fifth 1	6	27	364,183	1.0 (referent)		7	15	200,048	1.0 (referent)		1.0 (referent)		
Fifth 2	8	21	381,451	0.7	0.4, 1.2	8	14	201,303	0.9	0.4, 1.8	0.8	0.5, 1.2	0.6
Fifth 3	11	16	384,506	0.5	0.3, 1.0	11	14	204,219	0.9	0.4, 1.9	0.7	0.4, 1.1	0.3
Fifth 4	19	35	389,899	1.1	0.7, 1.9	17	16	205,890	1.1	0.5, 2.2	1.1	0.7, 1.7	0.9
Fifth 5	128	19	380,782	0.6	0.3, 1.1	98	15	207,087	1.0	0.5, 2.1	0.8	0.5, 1.2	0.3
P trend[d]				0.3					0.8		0.5		0.4
α-Carotenoid intake, mg/day[c]													
Fifth 1	282	25	372,746	1.0 (referent)		194	19	200,637	1.0 (referent)		1.0 (referent)		
Fifth 2	458	18	378,093	0.8	0.4, 1.4	423	10	204,594	0.5	0.2, 1.1	0.7	0.4, 1.1	0.5
Fifth 3	623	28	385,108	1.1	0.7, 2.0	615	17	205,665	0.9	0.5, 1.8	1.0	0.7, 1.6	0.6
Fifth 4	913	22	388,041	0.9	0.5, 1.6	869	11	205,155	0.6	0.3, 1.2	0.8	0.5, 1.2	0.4
Fifth 5	1,506	25	376,833	1.1	0.6, 1.9	1,452	17	202,496	1.0	0.5, 1.9	1.0	0.7, 1.6	0.8
P trend[d]				0.7					0.8		0.6		0.9
β-Carotenoid intake, mg/day[c]													
Fifth 1	1,924	21	370,652	1.0 (referent)		1,670	15	200,985	1.0 (referent)		1.0 (referent)		
Fifth 2	2,948	31	382,873	1.4	0.8, 2.4	2,708	16	204,507	1.1	0.5, 2.2	1.3	0.8, 2.0	0.6
Fifth 3	3,956	18	384,256	0.8	0.4, 1.5	3,652	12	205,482	0.8	0.4, 1.8	0.8	0.5, 1.3	1.0
Fifth 4	5,266	20	384,662	1.0	0.5, 1.8	4,865	13	204,788	0.9	0.4, 2.0	1.0	0.6, 1.5	1.0
Fifth 5	7,806	28	378,378	1.4	0.8, 2.4	7,438	18	202,785	1.3	0.6, 2.7	1.4	0.9, 2.1	1.0
P trend[d]				0.5					0.4		0.3		0.8

β-Cryptoxanthin intake, mg/day													
Fifth 1	88	18	381,456	1.0 (referent)		51	15	201,231	1.0 (referent)		1.0 (referent)		
Fifth 2	149	31	387,266	1.8	1.0, 3.2	86	18	204,488	1.2	0.6, 2.3	1.5	1.0, 2.3	0.4
Fifth 3	201	25	386,508	1.4	0.8, 2.6	121	13	205,012	0.9	0.4, 1.9	1.2	0.7, 1.9	0.3
Fifth 4	255	26	381,504	1.5	0.8, 2.8	167	13	204,872	0.9	0.4, 1.9	1.2	0.7, 2.0	0.3
Fifth 5	359	18	364,087	1.1	0.6, 2.2	254	15	202,943	1.1	0.5, 2.3	1.1	0.7, 1.8	1.0
P trend[d]				0.9					1.0		0.9		0.9
Lycopene intake, mg/day[c]													
Fifth 1	1,497	23	340,907	1.0 (referent)		3,660	17	198,189	1.0 (referent)		1.0 (referent)		
Fifth 2	3,235	14	384,056	0.5	0.3, 1.0	5,194	13	204,775	0.7	0.3, 1.5	0.6	0.4, 1.0	0.5
Fifth 3	4,269	28	390,415	1.0	0.6, 1.7	6,616	14	205,901	0.8	0.4, 1.6	0.9	0.6, 1.4	0.6
Fifth 4	5,421	29	393,193	1.0	0.6, 1.7	8,607	16	206,064	0.9	0.4, 1.7	0.9	0.6, 1.5	0.8
Fifth 5	7,390	24	392,251	0.8	0.4, 1.4	12,379	14	203,618	0.8	0.4, 1.7	0.8	0.5, 1.3	1.0
P trend[d]				1.0					0.8		0.8		0.9
Lutein/zeaxanthin intake, mg/day[c]													
Fifth 1	1,499	17	378,054	1.0 (referent)		1,039	17	202,613	1.0 (referent)		1.0 (referent)		
Fifth 2	2,301	30	382,929	1.7	1.0, 3.2	1,710	11	205,110	0.6	0.3, 1.3	1.1	0.4, 2.9	0.04
Fifth 3	3,047	24	384,461	1.3	0.7, 2.5	2,360	15	204,957	0.9	0.5, 1.9	1.1	0.7, 1.8	0.5
Fifth 4	4,318	21	386,038	1.2	0.6, 2.2	3,166	14	204,129	0.9	0.4, 1.8	1.0	0.6, 1.7	0.5
Fifth 5	6,971	26	369,338	1.6	0.8, 2.9	4,883	17	201,738	1.1	0.6, 2.3	1.4	0.9, 2.2	0.5
P trend[d]				0.5					0.4		0.3		0.7
FRAP score													
Fifth 1	7	30	372,957	1.0 (referent)		5	14	202,530	1.0 (referent)		1.0 (referent)		
Fifth 2	10	21	384,512	0.7	0.4, 1.3	8	20	205,249	1.5	0.7, 2.9	1.0	0.5, 2.0	0.1
Fifth 3	12	20	385,278	0.7	0.4, 1.2	10	16	204,768	1.2	0.6, 2.6	0.9	0.5, 1.6	0.2
Fifth 4	15	27	383,243	0.9	0.5, 1.6	13	10	204,884	0.8	0.3, 1.8	0.9	0.6, 1.4	0.7
Fifth 5	20	20	374,831	0.7	0.4, 1.3	18	14	201,116	1.1	0.5, 2.5	0.8	0.5, 1.3	0.3
P trend[d]				0.5					0.7		0.4		0.8

Abbreviations: CI, confidence interval; FRAP, ferric-reducing ability of plasma; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; RR, relative risk.

[a] The multivariable model was adjusted for age at menarche, oral contraceptive use (never, past, current), menopausal status, postmenopausal hormone use (never, past, current), pack-years of cigarette smoking, physical activity (hours per week), body mass index, and race (Caucasian, other).

[b] *P* for test of heterogeneity (het) between the 2 cohorts. Risk estimates were pooled by using a DerSimonian and Laird random-effects model.

[c] Cumulatively averaged energy-adjusted intake from food and supplements.

[d] *P*-for-trend test using the midpoints of each fifth.

RESULTS

The mean follow-up times for women in the NHS and NHSII cohorts were 21.1 years (range, 2–24) and 11.4 years (range, 2–12), respectively. Characteristics of the women participating in NHS (1990) and NHSII (1991) are shown in Table 1 according to the lowest and highest fifths of vitamins A, C, and E intakes. Most participants in both cohorts are Caucasian. Women with higher antioxidant vitamin intakes had other markers of a healthy lifestyle: fewer were current smokers, they were more physically active, and they had lower intakes of alcohol and caffeine and higher intakes of calcium and protein. Only 3%–4% of participants in NHSII were postmenopausal in 1991. We found no important differences in the demographic characteristics of women who responded to our additional mailings concerning connective tissue disease reports compared with those who did not respond (data not shown).

Characteristics at diagnosis of the RA and SLE cases included in these analyses in each of the cohorts are shown in Table 2. Incident RA cases were aged 29–81 years, and incident SLE cases were aged 31–77 years. Fifty-seven percent of RA cases were rheumatoid factor positive at diagnosis, and 97% of SLE cases had antinuclear antibodies present at diagnosis. A physician who was an American College of Rheumatology member diagnosed the majority of cases in both cohorts.

Results of age-adjusted and multivariable Cox proportional hazards models of the relative risks of developing RA and SLE are shown in Tables 3 and 4, respectively, according to fifths of cumulative intakes of antioxidants from food and supplements combined. We observed no associations between intakes of these antioxidants and subsequent risks of developing either RA or SLE. There was little evidence of heterogeneity between the 2 cohorts of women regarding the associations between antioxidant vitamin intakes and risk of RA or SLE. For the highest category of vitamin C intake, the pooled relative risk, for example, was 1.0 (95% confidence interval: 0.8, 1.3) and for SLE was 1.0 (95% confidence interval: 0.6, 1.7). Additional adjustments for body mass index at age 18 years, alcohol intake, and husband's educational level did not affect the relative risks in any of the multivariable models in either cohort, so these variables were not included in the final models. We observed no associations between cumulatively averaged vitamin A, C, or E intake, defined in different models as vitamin from food and supplements combined, or from food and from supplements separately (data not shown), or when vitamin intakes were divided into fifths or used as continuous measures.

In sensitivity analyses, baseline intakes of antioxidant vitamins from the first year of dietary assessments in the cohorts were not associated with risks of either RA or SLE, nor did we find any associations when we evaluated antioxidant intake in a simple updated (not cumulatively updated) model. In sensitivity analyses excluding women who reported cancer at baseline or during follow-up, results for both cohorts and for both outcomes were unchanged (data not shown). When stratifying by those who used vitamin C or vitamin E supplements and those who did not, we did not find increased intake of either vitamin to be associated with increased risk of RA or SLE in supplement users or nonusers. Finally, in analyses investigating antioxidant intake and risk of RA, stratified by fewer than or more than or equal to 10 pack-years of cigarette smoking, no associations were observed in either cohort (data not shown). We did not stratify analyses of the risk of SLE by smoking status given the insufficient number of incident cases.

DISCUSSION

In our prospective analyses involving women followed for up to 24 years, we found no evidence of associations between intake of antioxidants from foods and supplements and the risks of RA and SLE. No clear trends of increasing or decreasing risk of either of these autoimmune diseases were found in relation to a range of antioxidant intakes nor to a summary measure of antioxidant intake. In our sensitivity analyses, we investigated whether the timing of nutrient intake, either remote intake from cohort baseline only or more recent intake in the most current questionnaire cycle only, could be related to risk, but we found no indication that either was true.

The impetus for this study was that, in several past studies, blood levels of antioxidants were found to have decreased in RA and SLE subjects both before and after diagnosis (15–18, 38, 46), and an inverse relation between systemic inflammation and antioxidant blood levels has been reported (16). Associations between baseline intake of antioxidant nutrients from foods and supplements and RA development up to 11 years later were investigated in the Iowa Women's Health Study, a prospective cohort study involving 29,368 women aged 55–69 years when the study started (19). High intakes of β-cryptoxanthin and supplemental (but not total) zinc were found to be potentially protective against RA. In the Norfolk Arthritis Registry, those in the highest compared with the lowest tertiles of zeaxanthin and β-cryptoxanthin were at lower risk of developing inflammatory polyarthritis (20). However, in the Women's Health Study, a randomized, double-blind, placebo-controlled trial of 39,876 female health professionals, supplementation with 600 IU of vitamin E a day for a mean of 10.1 years was not associated with a significant reduction in the risk of developing RA (47).

Our study included a large number of incident cases, as well as detailed, repeated assessments of exposures, allowing for assessment of average and more recent diet, time-varying covariates, prospective assessment of most exposures, and long follow-up. The accuracy and validity of the semiquantitative FFQ have been well studied, and, in past NHS and NHSII analyses, associations between antioxidant intake and risks of lung cancer (48) and breast cancer (49) have been observed. Our 2-stage validation process includes careful medical record reviews, and all women who self-reported any connective tissue disease not confirmed as definite RA or SLE were excluded to reduce misclassification. We controlled for cigarette smoking, alcohol intake, and physical activity; none were related to RA or SLE risk, and none confounded observed associations. We examined antioxidant intakes individually and calculated an overall antioxidant FRAP score. We performed a variety of sensitivity analyses, including stratifying

the RA analyses by pack-years of smoking. Smoking creates oxidative stress, inducing free radicals and decreasing blood antioxidant levels (50), which could modify the relation between antioxidant intake and risk of disease. No associations between intakes of any of these vitamins and risks of these autoimmune diseases were found, however.

Potential limitations of the current study include the observational study design and use of self-reported exposure data; low correlations between FFQ-based intakes of lycopene, lutein, and β-carotene and plasma levels in past validation studies; and limited generalizability of results to non-Caucasian or male populations. With 787 validated cases of incident RA and 192 cases of incident SLE, we had limited power to detect small effects of antioxidant intake, and these results do not rule out the possibility that profound deficiencies of one or more of these antioxidants contribute to the pathogenesis of these autoimmune diseases. Similarly, many factors other than dietary intake (such as genetic differences in absorption or homeostatic mechanisms, and environmental exposures) may influence between-person variations in plasma antioxidant levels and oxidative stress (51).

Oxidative stress may be involved in the pathogenesis of one or both of these diseases. However, the current prospective, longitudinal cohort study does not support the hypothesis that regular intake of a range of antioxidants in foods and supplements is related to future risk of developing either RA or SLE in women.

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