Dietary Patterns and Risk of Systemic Lupus Erythematosus in Women

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Abstract

Objective—Dietary intake is a complex exposure and a potential risk factor for SLE due to its impact on lipid and glucose metabolism, oxidative stress, and the intestinal microbiome. To test whether a prudent dietary pattern is associated with lower risk of systemic lupus erythematosus (SLE), and whether a Western dietary pattern is associated with higher risk of SLE.

Methods—We prospectively investigated two dietary patterns and SLE risk among women in the Nurses' Health Study (NHS, 1984–2014) and Nurses' Health Study II (NHSII, 1991–2015). Food frequency questionnaires were completed every four years. Congruent with prior work in NHS and NHSII, we derived two separate dietary patterns (prudent and Western) using principal component analysis within each cohort. Incident SLE was confirmed by ACR 1997 criteria. We estimated hazard ratios (HR) and 95% confidence intervals (CI) for SLE by dietary pattern quartiles using Cox models adjusted for time-varying covariates. Models were performed separately in each cohort and results were meta-analyzed. Stratified analyses tested the association of dietary patterns with anti-dsDNA positive SLE and anti-dsDNA negative SLE.

Results—We confirmed 82 NHS incident SLE cases and 98 NHSII SLE cases during 3,833,054 person-years of follow-up. A higher (healthier) prudent dietary pattern score was not associated with SLE risk (meta-analyzed $HR_{Q4 \text{ vs. } Q1}$ 0.84 [95% CI 0.51, 1.38]). Women with higher (less healthy) Western dietary pattern scores did not have a significantly increased risk for SLE (meta-analyzed $HR_{Q4 \text{ vs. } Q1}$ 1.35 [95% CI 0.77, 2.35]). Results were similar after further adjustment for

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body mass index. Incident anti-dsDNA positive SLE and anti-dsDNA negative SLE were not associated with either dietary pattern.

Conclusion—We did not observe a relationship between prudent or Western dietary pattern score and risk of SLE.

INTRODUCTION

Systemic lupus erythematosus (SLE) develops in genetically susceptible individuals in concert with environmental exposures that trigger autoimmunity. Exposures that alter fatty acid and glucose metabolism and increase oxidative stress can dysregulate lymphocytes and alter gene expression, leading to autoantibody formation.(1) Several previously identified SLE risk factors, including ultraviolet radiation and cigarette smoking, increase oxidative stress and raise the possibility that other exposures increasing oxidative stress could influence the risk for SLE.(2) The risk for anti-dsDNA positive SLE is particularly high among current smokers, akin to increased risk for seropositive rheumatoid arthritis in smokers.(3) Dietary intake, a complex exposure that impacts lipid and glucose metabolism, oxidative stress, and the intestinal microbiome, might potentially impact risk for SLE through these pathways.

Dietary factors have been associated with risk for several autoimmune diseases but have not been well-studied in SLE. Fish consumption has been inconsistently associated with a lower risk for rheumatoid arthritis, for example.(4) However, evaluating individual foods as risk factors for rheumatic disease does not consider the broader context in which those foods are consumed; higher fish consumption may be paired with greater intake of other foods that influence risk of developing a disease.

Dietary pattern scores provide a relative measure of the healthfulness of an individual's diet. Prudent and Western dietary patterns scores characterize an individual's diet from self-reported consumption of hundreds of individual food items.(5–7) Higher prudent pattern scores reflect a diet higher in vegetables, fruit, legumes, fish, tomatoes, poultry, and whole grains. By contrast, higher Western pattern scores indicate a diet higher in refined grains, desserts and sweets, processed meat, red meat, French fries, condiments, potatoes, and pizza. These scores have been associated with cardiovascular disease and mortality risk in large, prospective cohort studies.(6) Diets high in fiber, short-chain fatty acids, and omega-3 fatty acids—which characterize the prudent pattern—are thought to protect against developing autoimmunity.(8) The Mediterranean dietary pattern, alternative healthy eating index score, and inflammatory dietary pattern have each been associated with risk for rheumatoid arthritis.(9)

We aimed to estimate the effect of two previously identified dietary patterns on the risk for SLE among women: the prudent pattern, considered a healthy diet pattern, and Western pattern, considered an unhealthy diet pattern.(7) We hypothesized that a higher prudent pattern score (healthy diet) would be associated with a lower risk for incident SLE and a higher Western pattern score would be associated with a higher risk for incident SLE. We tested this hypothesis in two prospective U.S. cohort studies: the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII).

METHODS

Study design and population

The NHS enrolled 121,700 women ages 30–55 in 1976; the NHSII enrolled 116,430 women ages 25–42 in 1989. Participants completed mailed questionnaires at baseline and every subsequent two years in follow-up regarding lifestyle factors, health behaviors, and the development of new diseases. A comprehensive Food Frequency Questionnaire (FFQ) was mailed every four years starting in 1984 in NHS and 1991 in NHSII. The current analysis includes participants who completed the baseline FFQ (in 1984 or 1991), provided baseline height and weight, and did not have prevalent SLE or connective tissue disease at baseline: 79,397 women in NHS (followed 1984–2014) and 93,283 women in NHS III (followed 1991–2015). Follow-up rates have been high and only 5% of person-time has been lost to follow-up.(10) This study was approved by the Partners' HealthCare Institutional Review Board.

SLE identification

Two rheumatologists independently reviewed medical records for participants who self-reported SLE or another connective tissue disease on biennial questionnaires to confirm whether Updated American College of Rheumatology (ACR) 1997 SLE Classification Criteria were fulfilled.(11) We excluded participants with self-reported SLE or other connective tissue diseases (CTD) at baseline. We censored participants during follow-up upon self-report of a non-SLE CTD, or upon SLE self-report not confirmed by medical record review.

Dietary patterns

Participants completed a 133-item semi-quantitative FFQ at baseline and approximately every four years. The FFQ assessed frequency and quantity of consumption, providing a measure of average dietary intake in the past year. Prior validation studies showed high correlation between the FFQ and dietary records.(12) Participants who reported total energy intake <500 kcal/day or >3500 kcal/day or with >70 missing items were considered extreme outliers and were excluded. Foods and beverages listed on the FFQ were categorized into 38 groups based on nutrient profiles or usage; beer, wine, and liquor were separate groups.(5, 6)

For this study, following prior work in the cohorts, prudent and Western dietary patterns were re-derived in the current analytic samples (separately in NHS and NHSII) using principal component analysis (PCA) based on cumulative average consumption of the 38 food/beverage groups, following previously published methods.(5) We used an orthogonal rotation procedure to create uncorrelated patterns and retained patterns with eigenvalue >1. We calculated dietary pattern scores as the weighted sum of consumption of each of the 38 food/beverage groups. The weight for each food/beverage group was the correlation coefficient of that group with the dietary pattern. Each score was standardized to have a mean of 0 and standard deviation of 1. We derived quartiles of prudent and Western dietary pattern scores separately in NHS and NHSII for the analysis. Higher prudent pattern scores (i.e. prudent Q4) were considered healthier as they reflect a diet more rich in vegetables, fruit, legumes, fish, tomatoes, poultry, and whole grains. Higher Western pattern scores (i.e.

Western Q4) were considered less healthy as they reflect a diet more rich in refined grains, desserts and sweets, processed meat, red meat, French fries, condiments, potatoes, and pizza. (7)

Time-varying covariates

Demographic, behavioral, and clinical data were updated on biennial questionnaires. Race was treated as binary (Caucasian vs. non-Caucasian). Body mass index (BMI) (kg/m^2) was calculated using self-reported height and weight and treated as continuous. A previous NHS validation study found self-reported weight and measured weight to be strongly correlated (r=0.97).(13) For questionnaire cycles in which women reported pregnancy, we carried forward BMI from the prior cycle. Cigarette smoking was categorized as never, past, or current. Recreational physical activity was treated as a continuous variable in metabolic equivalents (METS) per week. Household median income for each U.S. Census-tract was dichotomized at the sample median (< vs. $60,000). Oral contraceptive use was categorized as never vs. ever. Menopausal status was categorized as pre-menopausal, post-menopausal/never used post-menopausal hormones (PMH), and post-menopausal/ever used PMH. Missing covariates were imputed by assigning the last value carried forward for up to two consecutive questionnaire cycles. Total average energy intake in kcal/day, updated based on the FFQ every four years, was treated as a continuous variable.

Statistical methods

Baseline characteristics were reported by baseline quartile of Western and prudent dietary pattern scores. Cox proportional hazards models estimated hazard ratios (HR) and 95% confidence intervals (CI) for SLE risk separately in NHS and NHSII by quartile of Western and prudent dietary pattern score. The least healthy prudent pattern quartile (Q1) and most healthy Western pattern quartile (Q1) served as the reference groups. All models were adjusted for total energy intake to mitigate confounding by total energy intake. Base models were adjusted for age. Model 1 was further adjusted for race and time-varying smoking. We did not include BMI in Model 1 due to the possibility that BMI may be a mediator between dietary pattern and risk of SLE. We further adjusted for time-varying BMI in Model 2. Models further adjusting for physical activity, socioeconomic status, oral contraceptive use, and menopausal status were performed but did not change the estimates (see Supplementary Table 1), so these covariates were not included in the final models. We performed stratified analyses in each cohort to evaluate the association of dietary patterns with the risk for phenotypes of anti-dsDNA positive SLE and anti-dsDNA negative SLE.

We tested for a linear trend in SLE risk across quartiles in all analyses, using the median dietary pattern score in each quartile as a continuous variable. Meta-analysis of NHS and NHSII HRs was performed using a DerSimonian-Laird random effects model, further adjusted for cohort. The threshold for significance was p<0.05 in all models. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

We confirmed 82 incident NHS SLE cases and 98 incident NHSII SLE cases during 3,833,054 person-years of follow-up. Baseline characteristics are presented in Table 1. Mean age at baseline was 50.5 (SD 7.2) years in NHS and 36.2 (4.7) years in NHSII. Participants with the least healthy dietary patterns in each cohort had higher BMI, more frequently smoked, and were less physically active. Characteristics of 180 SLE cases at the time of diagnosis are presented in Table 2.

A higher (healthier) prudent dietary pattern score was not associated with SLE risk in NHS or NHSII (Table 3). The risk for SLE was lowest in the highest prudent quartile, though this was not statistically significant (meta-analyzed $HR_{Q4 \text{ vs. } Q1}$ 0.84 [95% CI 0.51, 1.38]). Women with higher (less healthy) Western dietary pattern scores had an increased point estimate for SLE risk that was not statistically significant (meta-analyzed $HR_{Q4 \text{ vs. } Q1}$ 1.35 [95% CI 0.77, 2.35]). We did not observe a trend for SLE risk across prudent or Western pattern quartiles. Results were similar after further adjustment for BMI.

In analyses stratified by anti-dsDNA positive SLE and anti-dsDNA negative SLE, prudent and Western pattern scores were not associated with SLE risk (Table 4).

DISCUSSION

We did not identify an association between either prudent or Western dietary pattern scores and risk of SLE among women in a large prospective cohort study with >3.8 million person-years of follow-up. Women with the healthiest prudent dietary pattern scores had non-significantly lower risk for SLE compared to women with the least healthy scores. Women with the least healthy Western dietary pattern scores had a non-significant increased risk for SLE compared to women in the healthiest quartile. Further adjustment for BMI did not alter results, suggesting that BMI does not play a significant role as a mediator of the relationship between dietary pattern and SLE risk. The risk of anti-dsDNA positive SLE and anti-dsDNA negative SLE also did not differ based on prudent or Western dietary patterns.

The scant literature on diet and risk of SLE focuses on possible dietary approaches to improve SLE disease activity, or to prevent or treat comorbidities such as cardiovascular disease; few studies have focused on dietary risk factors for incident SLE. In past work, SLE disease activity was worse in patients with lower omega-3 fatty acid and higher carbohydrate intake.(14) Moderate alcohol intake (versus none) was associated with lower risk for incident SLE in a prior study in NHS and NHSII, but antioxidant intake was not.(15, 16)

Dietary quality, which is associated with risk for cardiovascular disease and death, is also thought to affect the immune system. The intestinal microbiome has been proposed as a link between dietary patterns and development of autoimmunity. Greater consumption of short-chain fatty acids, which characterizes the prudent pattern, is thought to maintain intestinal epithelial integrity and prevent translocation of immunogenic bacteria and/or bacterial metabolites into the bloodstream, and to promote Treg formation.(8) This in turn may prevent the development of mimicry-induced autoimmunity. In murine models of lupus, intestinal colonization with *Lactobacillus reuteri* led to worsened lupus manifestations;

subsequently consuming a high-fiber diet decreased the number of plasmacytoid dendritic cells, lowered interferon expression, and reduced mortality.(17) In other lupus murine models, diets poor in methyl donor groups have been related to lupus disease activity via T cell DNA methylation, causing overexpression of normally silenced genes.(18) Consumption of vitamin A, which is found in many vegetables and fruits, may directly impact SLE pathogenesis through downregulation of interferon-gamma, interleukin-4, and upregulation of TGF-beta (19).

We hypothesized that women with a prudent dietary pattern (healthy) would have lower SLE risk, and women with a Western dietary pattern (unhealthy) would have greater SLE risk. The point estimates for SLE risk could support this directionality, but the hazard ratios and tests for trend were not statistically significant. Women in the least healthy prudent quartile had lower total average energy intake than the healthiest prudent quartile suggesting the total energy could be a confounder. We adjusted for total energy intake to mitigate confounding by total energy intake. Our findings do not entirely rule out the possibility that diet may influence SLE risk, but do suggest that dietary patterns do not have a large influence on SLE risk among women in their late 20s and older.

This study has some limitations, including a relatively small number of incident SLE cases despite up to 30 years of follow-up limiting the ability to examine more extreme categories such as the top decile of dietary patterns. The study population was predominantly Caucasian and all participants were female nurses; their dietary intake likely differs from that of other ethnic populations. Perhaps relatedly, the prudent and Western dietary pattern quartiles permitted comparison within each cohort, but do not provide absolute scores or a threshold above which a diet is considered "healthy"; this is an inherent limitation to studies using dietary pattern scores derived through principal component analysis and may be a particular issue within a more homogenous, largely healthy cohort. Finally, although weight and height were self-reported, raising potential for BMI misclassification, prior validation work in the NHS identified self-reported weight as highly accurate.

CONCLUSION

We did not identify an association between prudent or Western dietary pattern quartile and risk for SLE in a large prospective cohort of female nurses. Future work evaluating dietary patterns in a larger, multi-ethnic prospective cohort is needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Table 1.

Age-standardized characteristics of 79,397 Nurses' Health Study (NHS) participants (1984) and 93,283 Nurses' Health Study II (NHSII) participants (1991) by lowest and highest quartiles of prudent and Western dietary pattern scores

	Prudent pattern				Western pattern			
	Nurses' Health Study		Nurses' Health Study II		Nurses' Health Study		Nurses' Health Study II	
	Q1 Least healthy	Q4 Most healthy	Q1 Least healthy	Q4 Most healthy	Q1 Most healthy	Q4 Least healthy	Q1 Most healthy	Q4 Least healthy
Mean age, years (SD) *	48.9 (7.1)	51.8 (7.0)	35.5 (4.8)	36.7 (4.5)	52.4 (6.9)	48.8 (7.1)	36.5 (4.7)	35.8 (4.7)
Caucasian, %	93.5	93.2	92.3	92.8	91.6	94.8	91.7	93.7
African American, %	1.1	1.2	2.0	1.2	2.0	0.7	1.8	1.3
Other, %	5.4	5.6	5.7	6.0	6.4	4.5	6.5	5.0
Mean BMI, kg/m^2 (SD)	24.9 (4.8)	25.2 (4.8)	24.9 (5.8)	24.4 (5.1)	24.6 (4.3)	25.6 (5.3)	23.6 (4.5)	25.6 (6.2)
Current smoking, %	32.4	17.8	17.3	9.6	18.7	29.5	9.7	15.6
Physical activity, METs/week (SD) **	10.2 (16.7)	18.9 (26.3)	14.6 (21.6)	29.1 (34.3)	17.4 (25.7)	11.7 (18.8)	26.1 (32.5)	17.6 (24.2)
Census tract median household income by zip code < $60,000, %	56.6	46.1	61.8	49.4	45.9	55.6	47.8	62.1
Oral contraceptive use, %	47.7	48.3	86.3	82.2	47.9	47.7	83.8	84.9
Pre-menopausal, %	42.7	40.9	91.2	92.8	40.1	43.1	92.4	91.8
Post-menopausal, never used post-menopausal hormones, %	32.5	31.3	4.3	3.2	32.0	32.5	3.6	3.7
Post-menopausal, ever used post-menopausal hormones, %	24.8	27.8	4.5	4.0	27.9	24.4	4.1	4.5
Mean energy intake, kcal/day (SD)	1452 (470)	2060 (523)	1524 (518)	2130 (522)	1288 (362)	2286 (453)	1352 (395)	2345 (469)

Values are standardized to the age distribution of the study population. METs: metabolic equivalents

*
Not age-standardized

**
Data missing for physical activity (12.4% NHS, 0.3% NHSII)

Table 2.

Characteristics of 180 SLE cases at diagnosis

	NHS (n=82)	NHSII (n=98)
Age in years	58 (10)	44 (7)
Race		
White	92.7	92.7
African American	0	0
Other	7.3	7.3
Hispanic	2.4	1.0
ANA positive	97.6	99.0
Anti-dsDNA positive	41.5	52.0
Malar rash	50.0	37.8
Discoid rash	11.0	6.1
Photosensitivity	51.2	46.9
Nasopharyngeal ulcer	29.3	53.1
Arthritis	75.6	69.4
Serositis	28.1	32.7
Renal involvement	17.1	6.1
Neurologic involvement	0	6.1
Hematologic involvement	59.8	67.4

Presented as mean (SD) or percentage

Table 3.

Hazard ratios (95% CI) for systemic lupus erythematosus (SLE) by prudent and Western dietary pattern quartiles

	Prudent pattern quartiles					Western pattern quartiles				
	Q1	Q2	Q3	Q4	p trend	Q1	Q2	Q3	Q4	p trend
	Least healthy			Most healthy		Most healthy			Least healthy	
Nurses' Health Study (NHS)										
Cases/person-years	18/464,970	22/500,232	24/502,584	18/473,470		17/452,968	14/497,549	26/506,705	25/484,034	
Age-adjusted#	1.00 (ref)	1.15 (0.61,2.17)	1.29 (0.68,2.46)	1.01 (0.49,2.10)	0.96	1.00 (ref)	0.68 (0.33,1.40)	1.12 (0.57,2.20)	1.04 (0.46,2.35)	0.38
Model 1 *	1.00 (ref)	1.18 (0.63,2.22)	1.33 (0.70,2.54)	1.05 (0.50,2.19)	0.89	1.00 (ref)	0.67 (0.33,1.39)	1.11 (0.56,2.20)	1.01 (0.44,2.31)	0.42
Model 2 **	1.00 (ref)	1.18 (0.63,2.23)	1.33 (0.70,2.54)	1.05 (0.50,2.19)	0.89	1.00 (ref)	0.67 (0.32,1.39)	1.11 (0.56,2.20)	1.00 (0.43,2.32)	0.42
Nurses' Health Study II (NHSII)										
Cases/person-years	24/448,243	29/481,584	28/486,180	17/475,791		19/460,436	29/483,659	23/484,510	27/463,194	
Age-adjusted#	1.00 (ref)	1.15 (0.67,1.99)	1.09 (0.62,1.91)	0.70 (0.36,1.37)	0.25	1.00 (ref)	1.55 (0.86,2.81)	1.29 (0.67,2.50)	1.72 (0.82,3.62)	0.23
Model 1 (main) *	1.00 (ref)	1.16 (0.67,2.00)	1.09 (0.62,1.92)	0.70 (0.35,1.37)	0.24	1.00 (ref)	1.55 (0.86,2.81)	1.29 (0.67,2.50)	1.70 (0.81,3.61)	0.25
Model 2 **	1.00 (ref)	1.19 (0.69,2.07)	1.13 (0.64,2.00)	0.74 (0.37,1.45)	0.31	1.00 (ref)	1.49 (0.82,2.70)	1.20 (0.62,2.33)	1.50 (0.70,3.22)	0.42
Meta-analysis (NHS+NHSII)										
Cases/person-years	42/913,213	51/981,816	52/988,764	35/949,261		36/913,404	43/981,208	49/991,215	52/947,228	
Age-adjusted#	1.00 (ref)	1.15 (0.76,1.74)	1.17 (0.77,1.79)	0.83 (0.51,1.36)	0.39	1.00 (ref)	1.05 (0.47,2.37)	1.21 (0.75,1.93)	1.37 (0.79,2.37)	0.14
Model 1 *	1.00 (ref)	1.17 (0.77,1.77)	1.19 (0.78,1.82)	0.84 (0.51,1.38)	0.42	1.00 (ref)	1.05 (0.46,2.38)	1.20 (0.75,1.93)	1.35 (0.77,2.35)	0.16
Model 2 **	1.00 (ref)	1.19 (0.78,1.80)	1.22 (0.79,0.86)	0.87 (0.53,1.43)	0.49	1.00 (ref)	1.03 (0.47,2.25)	1.15 (0.72,1.86)	1.25 (0.71,2.20)	0.27

Adjusted for age and total average energy intake

* Model 1: Adjusted for age, total average energy intake, race, smoking. Meta-analysis further adjusted for cohort.

** Model 2: Model 1 additionally adjusted for BMI. Meta-analysis further adjusted for cohort.

Table 4.

Meta-analyzed hazard ratios (95% CI) for SLE in the Nurses' Health Study and Nurses' Health Study II by dietary pattern quartiles, stratified by anti-dsDNA antibody status

	Prudent pattern quartiles					Western pattern quartiles			
	Q1 Least healthy	Q2	Q3	Q4 Most healthy	p trend	Q1 Most healthy	Q2	Q3	Q4 Least healthy	p trend
Anti-dsDNA positive SLE (n=84 cases)									
Adjusted model*	1.00 (ref)	1.04 (0.57,1.90)	1.19 (0.60,2.36)	0.72 (0.35,1.49)	0.40	1.00 (ref)	0.88 (0.32,2.42)	0.89 (0.44,1.79)	1.26 (0.57, 2.79)	0.37
Anti-dsDNA negative SLE (n=96 cases)									
Adjusted model*	1.00 (ref)	1.29 (0.73,2.29)	1.21 (0.66,2.19)	0.95 (0.48,1.89)	0.75	1.00 (ref)	1.25 (0.55,2.85)	1.52 (0.79,2.93)	1.42 (0.37, 5.46)	0.54

*
Adjusted for age, cohort, total average energy intake, race, smoking