DR. WENDY MARDER (Orcid ID : 0000-0001-7963-4206)

DR. EMILY C SOMERS (Orcid ID : 0000-0001-5234-3978)

Article type : Original Article

Dietary omega polyunsaturated fatty acid intake and patient-reported outcomes in systemic lupus erythematosus: The Michigan Lupus Epidemiology & Surveillance (MILES) Program

Prae Charoenwoodhipong, MS [1], Sioban D. Harlow, PhD [2], Wendy Marder, MD MS[3,4], Afton L. Hassett, PsyD [5], W. Joseph McCune, MD [3], Caroline Gordon, MD [6], Charles G. Helmick, MD [7], Kamil E. Barbour, PhD [7], Lu Wang, PhD [8], Peter Mancuso, PhD [1], Emily C. Somers, PhD ScM [3,4,9]*, Suzanna M. Zick [1,10]*

1. University of Michigan, Department of Nutritional Sciences, Ann Arbor, MI
2. University of Michigan, Department of Epidemiology, Ann Arbor, MI
3. University of Michigan, Department of Internal Medicine, Division of Rheumatology, Ann Arbor, MI
4. University of Michigan, Department of Obstetrics & Gynecology, Ann Arbor, MI
5. University of Michigan, Department of Anesthesiology, Ann Arbor, MI
6. Rheumatology Research Group, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK
7. Centers for Disease Control and Prevention, Atlanta, GA
8. University of Michigan, Department of Biostatistics, Ann Arbor, MI
9. University of Michigan, Department of Environmental Health Sciences, Ann Arbor, MI
10. University of Michigan, Department of Family Medicine, Ann Arbor, MI

**Co-senior authors*

Corresponding author:
Emily C Somers, PhD ScM
Associate Professor of Medicine, Environmental Health & OB/GYN
University of Michigan Schools of Medicine & Public Health
North Campus Research Complex – Bldg 14, Rm G236
2800 Plymouth Road | Ann Arbor, MI 48109-2800
emsomers@umich.edu | phone +1 734-936-3257

ABSTRACT

Objective:

To examine associations between dietary intake of omega-3 (n-3; generally anti-inflammatory) and omega-6 (n-6; generally pro-inflammatory) fatty acids and patient-reported outcomes in systemic lupus erythematosus (SLE).

Methods:

This study was based on the population-based Michigan Lupus Epidemiology & Surveillance (MILES) Cohort. Estimates of n-3 and n-6 intake were derived from Diet History Questionnaire II items (DHQ II; past year with portion size version). Patient-reported outcomes included self-reported lupus activity (Systemic Lupus Activity Questionnaire/SLAQ). Multivariable regression, adjusted for age, sex, race, and body mass index, was used to assess associations between absolute intake of n-3 and n-6, as well as the n-6:n-3 ratio, and patient-reported outcomes.

Results:

Among 456 SLE cases, 425 (93.2%) were female, 207 (45.4%) were black, and mean age was 52.9±12.3 years. Controlling for potential confounders, the average SLAQ score was significantly higher by 0.3 points [(95% CI 0.1, 0.6); p=0.013] with each unit increase of the n-6:n-3 ratio. Both lupus activity and PROMIS-Sleep Disturbance scores were lower with each 1g/1000 Kcal increase of n-3 fatty acids [SLAQ regression coefficient β=-0.8 (95% CI -1.6, 0.0), p=0.055; PROMIS-Sleep β=-1.1 (95% CI -2.0, -0.2), p=0.017]. Higher n-3 intakes were non-significantly associated with lower levels of depressive symptoms and comorbid fibromyalgia, and higher quality of life, whereas results for the n6:n3 ratio trended in the opposite direction.

Conclusion:

This population-based study suggests that higher dietary intake of n-3 fatty acids, and lower n-6:n-3 ratios, are favorably associated with patient-reported outcomes in SLE, particularly self-reported lupus activity and sleep quality.

SIGNIFICANCE AND INNOVATION

- This is the first study to show that lower dietary intake levels of omega-6 (pro-inflammatory) fatty acids, and higher dietary intake levels of omega-3 (anti-inflammatory) fatty acids, are favorably associated with patient-reported outcomes in lupus, including decreased lupus activity and better sleep quality.

- The finding that dietary intake levels of omega-6 and omega-3 fatty acids appeared to oppose one another, including after adjustment for omega-3 supplement use (fish

and/or flaxseed oil), suggests that use of supplements alone might be less likely than a broader dietary approach to influence patient-reported outcomes in lupus.

- This study should prompt health care providers to consider reviewing the USDA 2015-2020 Dietary Guidelines for Americans with their lupus patients to promote intake of fatty fish, nuts, and seeds, thereby encouraging a better balance of fatty acids from dietary sources.

INTRODUCTION

Systemic lupus erythematosus (SLE) is one of a number of rheumatic and musculoskeletal diseases (1), and is associated with substantial comorbidities, including renal impairment and premature cardiovascular disease (2,3). In general, advances in diagnosis and management have led to improved outcomes for SLE patients (4). However, fatigue, poor sleep, chronic and often widespread pain, depression, and diminished quality of life remain challenging and prevalent issues for SLE patients. As many as 85% of SLE patients report significant levels of persistent fatigue (5), 57% ongoing issues with sleep (6), 75% depressive disorders (7), and over 20% chronic pain pervasive enough to meet criteria for comorbid fibromyalgia (8). Non-pharmacological interventions that address these persistent symptoms could have a significant impact on quality of life for lupus patients. Modification of dietary polyunsaturated fatty acid (PUFA) intake could be one such approach.

Omega-3 (n-3) PUFA, found in fatty fish, nuts, seeds and oils, and consumed at relatively low levels in the US diet, have been found to have anti-inflammatory and immunomodulatory effects (9,10). In contrast, omega-6 (n-6) PUFA, including linoleic acid and arachidonic acid, are generally considered pro-inflammatory (9,10) and are ubiquitous

in the US food supply (*e.g.*, corn and soybean oils) (11). Due to the uneven distribution of n-6 and n-3 fatty acids in the food supply, the ratio of n-6 to n-3 consumption in the US is as high as 15:1 (11). The substantially higher intake of n-6 fatty acids is thought to adversely impact health; products derived from n-6 fatty acids include inflammatory eicosanoids (*i.e.*, prostaglandin E2), as compared to eicosanoids derived from n-3s, which are considered anti-inflammatory substances (*i.e.*, prostaglandin E3) (10–12). As n-6 and n-3 compete for the same desaturation and elongation enzymes (13), both high absolute levels of n-6 consumption, as well as high ratios of n-6 relative to n-3, may contribute to a systemic pro-inflammatory state and immune dysfunction (13–15). Studies in lupus-prone mouse models have reported favorable effects associated with n-3 fatty acid consumption, including reduced levels of autoantibodies, proteinuria and glomerulonephritis, as well as down-regulation of relevant CD4+ T cell-associated genes (16). An intriguing study found that dietary enrichment with the n-3 fatty acid docosahexaenoic acid (DHA) in lupus-prone NZBWF1 mice suppressed crystalline silica-induced autoimmunity in a dose-response fashion, including inhibition of proinflammatory cytokines and reduced glomerulonephritis (17). However, precise mechanisms concerning PUFA-related immunomodulation and lupus outcomes require further elucidation.

Four human studies of n-3 supplementation have reported improved lupus disease activity compared to placebo groups (18–21), while others have detected no differences (22–24). One of the clinical trials examined the impact of n-3 supplementation on quality of life and common symptoms such as pain and fatigue in SLE, and found trends toward improvement (21). However, studies in SLE have focused primarily on n-3 supplementation, not dietary intake of fatty acids. In contrast to trials of individual supplements, measures of routine dietary intake allow for more comprehensive profiling of

nutrient exposures (including n-6 fatty acids and the n-6 to n-3 ratio), and may reflect more stable or habitual patterns of exposure over time.

We performed a cross-sectional study within the population-based Michigan Lupus Epidemiology & Surveillance (MILES) Cohort, to assess the association between dietary intake of n-3 and n-6 fatty acids and their ratio on patient-reported outcomes of SLE disease activity, quality of life, fatigue, pain, depression, and sleep. We anticipated that higher dietary intakes of n-3 fatty acids and lower ratios of n-6 to n-3 would be associated with more favorable patient-reported outcomes.

METHODS

Study population

This study was based on data from the MILES Cohort, a population-based cohort of persons with SLE from southeastern Michigan. Ethics approval was obtained from the Institutional Review Boards of the University of Michigan and Michigan Department of Health and Human Services, and cohort participants signed written, informed consent. Lupus cases for the MILES Cohort were recruited from the MILES Surveillance Registry, one of the National US Lupus Registries supported by the Centers for Disease Control & Prevention (CDC) and described elsewhere (2,25). In brief, the MILES Registry included persons who were residents of Wayne or Washtenaw Counties in Michigan (encompasses a source population ~2.4 million, and includes the cities of Detroit and Ann Arbor) during 2002-2005, and with a new or existing diagnosis of SLE during this calendar period. Baseline enrollment for the MILES Cohort was conducted between February 2014 – September 2015.

Baseline characteristic variables

Sociodemographic variables (*e.g.*, race, ethnicity) were based on self-report. Height and weight were measured at the research clinic visit, and body mass index (BMI) computed as weight (kg) divided by height squared (m^2).

Dietary assessment and omega fatty acid variables

Dietary intake was assessed using an abbreviated version of the Diet History Questionnaire II (DHQ II; past year version, with portion size) by the National Cancer Institute (NCI) Epidemiology and Genomic Research Program, that focused on fatty foods (**Supplemental Table S1**) (26). Diet*Calc software v.1.5.0 (27) was used to link dietary data to nutrient databases from the U.S. Department of Agriculture (USDA) (for n-6) and the Nutrition Data System for Research (NDSR) (for n-3) for generation of nutrient intake estimates (28). The Diet*Calc/NDSR n-3 fatty acid variable represented the sum of the following fatty acids: alpha-linolenic acid (ALA, 18:3n-3), parinaric acid (18:4n-3), eicosapentaenoic acid (EPA, 20:5n-3), docosapentaenoic acid (DPA, 22:5n-3) and docosahexaenoic acid (DHA, 22:6n-3) (29). Omega-6 was calculated as total octadecadienoic acid or linoleic acid [LA, 18:2n-6].

Total n-3 and n-6 were adjusted for fat calorie intake (per 1,000 Kcal) to remove extraneous variation and control for confounding (30). The fat energy-adjusted n-3 and n-6 variables were used as independent variables in the multivariable models, and to compute the n-6:n-3 ratio. While the dietary assessment did not include quantification of supplement use, omega-3 supplements (fish oil and flaxseed oil) were recorded as yes/no if used more than once per week. Thus, in secondary models, we included omega-3 supplement use as a binary covariate.

Patient-reported outcomes (PRO) measures

Detailed sociodemographic and patient-reported outcome data were collected at baseline, and included the measures described below.

The Systemic Lupus Activity Questionnaire (SLAQ) (31) was used to assess SLE disease activity. The SLAQ is a self-administered tool developed for epidemiologic studies and not intended for clinical management. It includes 24 symptom questions and a numerical rating scale assessing disease activity during the past three months. The SLAQ yields scores ranging from 0-47, with higher scores indicating greater disease activity.

The Survey Criteria for Fibromyalgia (FM Scale) (32) was used to assess the presence of fibromyalgia/widespread pain. The FM Scale consists of the Widespread Pain Index (WPI) that provides a count of the number of body regions reported as painful by the patient (range: 0-19) and the Symptom Severity (SS) scale that assesses fatigue, non-refreshing sleep, cognitive problems, and the extent of somatic symptoms (range: 0-12). Based on the FM Scale, participants were classified as fulfilling criteria for fibromyalgia if the following were met: (1) WPI ≥7 and SS ≥5, or (2) WPI 3-6 and SS ≥9; and with symptoms present at a similar level for at least 3 months in the absence of a disorder that would otherwise explain the pain.

PROMIS-Depression Short Form v1.0 is an 8-item measure used to assess self-reported negative mood, views of self, and social cognition, as well as positive affect and engagement. Scores can range from 37.1 to 81.1, with higher scores representing worse depressive symptoms (33).

The PROMIS-Sleep Disturbance Short Form v1.0 is an 8-item measure used to assess perception of sleep quality, which includes sleep depth and restoration associated with

sleep. Scores range from 28.9 to 76.5, with higher scores representing worse sleep disturbance (34).

The RAND Medical Outcomes Study 36-Item Short-Form Survey Instrument (MOS SF-36) (35) was used to measure health-related quality of life (HRQOL). It is a self-report questionnaire consisting of 36 items aggregated to score 8 subscales related to physical and mental health. Subscales include Physical Functioning, Role Physical, Bodily Pain, General Health, Energy/Fatigue, Social Function, Role Emotional and Mental Health. The subscale scores are normalized for a mean of 50 with a standard deviation of 10; higher scores indicate better HRQOL.

The Lupus Quality of Life Questionnaire (LQoL) (36) was used to assess disease-specific quality of life. The LQOL is a 34-item scale, and scores are aggregated into eight subscales including Physical Health, Emotional Health, Body Image, Pain, Planning, Fatigue, Intimate Relationships, and Burden to Others. Scores range from 0 to 100, with higher scores indicating better HRQOL.

Statistical analyses

Descriptive statistics were computed, with mean and standard deviation for continuous variables, and frequency and percentage for categorical variables. Univariate logistic or linear regression was performed for dichotomous and continuous outcomes, respectively, to examine the associations between fat energy-adjusted fatty acid intake (n-3, n-6, and the ratio of n-6:n-3) and patient-reported outcomes. Outcomes for linear regression models were normally distributed. Separate models were constructed for each patient-reported outcome. Multivariable models adjusted for covariates determined *a priori* to be relevant to the exposures and outcomes based on prior research (age, sex, race,

and BMI in primary models; secondary models also included n-3 supplement use) (37–40). Effect estimates from the multivariable logistic (odds ratios) and linear regression (beta coefficients, mean outcome changes associated with one-unit change of the covariate) models with 95% confidence intervals are presented. Electronic data capture and management utilized the REDCap tools hosted at the University of Michigan (41). Statistical analysis was conducted using SPSS Statistics, v.23 (IBM Corp, Armonk, NY) and Stata v.14 (StataCorp, College Station, TX).

RESULTS

At the baseline visit, 462 lupus cases were enrolled, of whom 456 completed the dietary questionnaire and were included in this study. Characteristics of the study population are presented in **Table 1**. Over 93% of the participants were female, average age was 53 years, and self-identified race was primarily white (52%) or black (45%).

PUFA intake

Fat energy-adjusted dietary intake of n-3 (mean ± SD) was 3.1 g/1000 Kcal ± 0.9 (range 0.7 to 7.2). The mean n-6 intake was 20.1 g/1000 Kcal ± 7.5 (range 5.0 to 36.7). The mean n-6:n-3 ratio was 6.9 ± 2.9, with ratios ranging from 1.2 to 18.0. Use of flaxseed and/or fish oil supplements was reported in 112 of 456 (26.8%) of the participants.

PUFA intake and patient-reported outcomes

Estimated associations between PUFA intake and patient-reported outcomes from the primary models are depicted in forest plots (**Figures 1—4**). These models adjusted for

sex, age, race, and body mass index. Self-reported lupus disease activity was significantly associated with PUFA intake (**Figure 1**): for each unit increase in the ratio of n-6 to n-3, the mean SLAQ score was correspondingly higher by 0.3 points [(95% CI 0.1, 0.6); p=0.013]. Further, an association between greater absolute n-3 intake and reduced SLE activity bordered on significance, where for each unit increase of n-3 intake the SLAQ score was lower by 0.8 points [regression coefficient β= -0.8 (95% CI -1.6, 0.0); p=0.055]. Cut-points for 'clinically meaningful' changes on the SLAQ have not been defined, but as a patient-reported outcome measure, scores represent activity perceptible to the patient and thus potentially meaningful from the patient perspective.

Perceived sleep quality (**Figure 1**) was also significantly associated with PUFA intake, whereby each unit increase of n-3 intake was associated with a lower mean PROMIS-Sleep Disturbance score by -1.1 points [(95% CI -2.0, -0.2); p=0.017]. However, the ratio of n6:n3 was not significantly associated with sleep disturbance [β=0.2 (95% CI -0.1, 0.5); p=0.111]. We did not detect significant associations for depression and PUFA intake [**Figure 1;** n-3, β= -0.9 (95% CI -1.9, 0.1); p=0.093; ratio n6:n3, β=0.1 (95% CI -0.2, 0.5), p=0.369).

We assessed three dimensions of pain – fibromyalgia/widespread pain as a dichotomous measure representing fulfillment of the Survey Criteria for Fibromyalgia (FM Scale) (**Figure 2**), and the continuous pain subscales of the MOS SF-36 (**Figure 3**) and LQOL (**Figure 4**). There were not significant associations between PUFAs and the three pain measures. However there was an inverse association between n-3 intake and comorbid FM that bordered on significance, such that with each unit increase of n-3 intake, fulfillment of FM survey criteria was approximately 20% lower [OR 0.82 (95% CI 0.66, 1.02), p=0.07].

For general- and disease-specific quality of life measures (MOS SF-36 and LQOL, respectively) (**Figures 3 & 4**), significant associations were not detected for any of the PUFA

measures. However, a general trend was observed for the majority of subscales (14 of 16), whereby higher n-3 intakes were associated with higher subscale scores, higher ratios of n-6:n-3 were negatively associated, and absolute n-6 intake remained around a null association.

For the MOS SF-36, subscale scores that deviate from the mean of 50 by one standard deviation (SD=10) are generally thought to be clinically relevant. PROMIS measures similarly are standardized with a mean of 50.

Secondary models were constructed including n-3 supplement use (flaxseed and/or fish oil), in addition to the other covariates from the main models (**Supplemental Table S2**). There were no substantive changes to results. However, the association between absolute n-3 intake and reduced SLE activity, which bordered on significance in the main model, now reached significance [β= -0.8 (95% CI -1.7, -0.0); p=0.049].

DISCUSSION

In this population-based, cross-sectional study, lower ratios of n-6 (inflammatory) to n-3 (anti-inflammatory) fatty acids, and higher levels of n-3 fatty acid intake, were significantly associated with improved self-reported lupus disease activity. Higher levels of n-3 intake were also significantly associated with better perceived sleep quality. Absolute intake levels of n-6 fatty acids, without accounting for n-3 fatty acid intake, were not independently associated with any of the patient-reported outcomes.

Across the remaining outcomes – depression, fibromyalgia, pain and health-related quality of life – although results did not reach statistical significance, the direction and magnitudes of association were generally consistent in that increased n-3 intake and

decreased ratios of n-6 to n-3 appeared favorable, whereas n-6 intake alone hovered around a null association.

Our findings of associations between PUFA intake and patient-reported SLE disease activity are consistent with some prior studies in lupus patients. A cross-sectional study of lupus patients found that adipose tissue levels of EPA and DHA were negatively correlated with disease activity (42). A 4-month open-label trial of fish oil supplementation (3 g/day) (20), as well as three ~6-month trials of fish oil supplementation (3-4.5 mg/day) versus olive oil placebo, found decreases in SLE activity (18,19,21). However, a 12-week trial of fish oil (3g/day) versus corn starch placebo (22) and two small trials (one in pediatric lupus, the other in lupus nephritis) failed to detect improvement in lupus activity (23,24). With the positive trials having intervention periods of approximately four to six months, it is possible that shorter interventions may be insufficient to impact lupus activity. It should be noted that supplement trials are not directly comparable to studies of dietary intake, and n-3 doses in clinical trials often exceed dietary intake levels (the average n-3 dietary intake in our lupus population was 0.42 g/day, unadjusted for energy intake).

In terms of health-related quality of life, one of the above referenced trials in SLE found that none of the RAND SF-36 subscales were significantly improved after 6 months of fish oil supplementation compared to placebo, though there were non-significant trends of improvement in the Energy/Fatigue and Emotional Well-Being subscales in the fish oil group compared to placebo group (21). We likewise observed non-significant associations of benefit in these domains.

Our finding of a small but significant association between n-3 intake and sleep quality is compatible with findings from a study from coastal Ecuador, in which higher DHA blood levels and oily fish consumption were significantly associated with improved sleep

quality (43). Another study in which male forensic patients were randomized to consumption of fatty fish versus meat three times per week for 6 months found significantly improved sleep and daily functioning in the fish group (44). Further, n-3 levels in red blood cells have been found to be inversely associated with obstructive sleep apnea severity (45). Although the mechanisms of how n-3 fatty acids impact sleep quality are unclear, (43) it has been suggested that such effects might be due to the role that n-3s, particularly EPA and DHA, play in increasing serotonin secretion (46); low serotonin levels result in sleep disruption and sleep disorders, including insomnia.

There are several limitations in our study. First, the abbreviated dietary questionnaire that we used mainly captured PUFA intake from cooking oil, seafood, beans and eggs, which could underestimate absolute PUFA intake. Although cooking oils and marine products are the main dietary sources of n-3 and n-6, we were unable to capture data on PUFA intake from other sources such as leafy greens, nuts, seeds, and meat. Quantification of n-3 supplement use was not possible given the yes/no format for supplements in the dietary questionnaire; however, we included n-3 supplement use as a binary variable in secondary models. Thus, we likely underestimated both n-3 and n-6, though underestimation of n-6 was more likely given its greater presence in the food supply. The average n-6:n-3 ratio in our study population (roughly 7:1) is lower than that expected from the standard American diet (up to 15:1) (11). In comparison, a larger cohort study in Detroit, MI of colorectal cancer cases and controls that used a food frequency questionnaire assessing the entire diet, found the ratio of n-6:n-3 to be approximately 10:1 (47); while this is higher than the ratio in our lupus population from the same region, it is still lower than typically reported for the US population. There is some evidence for a downward shift of n-

6:n-3 in recent years due to increased use of canola oil (which is n-3 rich) in the American food supply (9).

A second limitation is that the brief dietary questionnaire limited us from calculating a global measure of diet quality, or to estimate total energy intake from all the food groups that can be used for energy adjustment. The energy adjustment from only fat intake might overestimate the energy-adjusted absolute amount of PUFAs. Dietary questionnaires are also subject to recall bias and are less quantitative than biomarker measurements. However, a strength of dietary questionnaires is that they cover average intake over preceding months and not exposure at a single time point. Another limitation was that our outcome measure for lupus activity (SLAQ) was based on self-report. While this tool has been validated for epidemiologic research and is a preferred tool for self-reported lupus activity measurement, tools that incorporate rheumatologist assessment and laboratory findings are the gold-standard for use in a clinical setting. Unfortunately, the clinician-centric tools are rarely feasible in epidemiologic field research. Also, while we adjusted for potential confounders in multivariable models, it is possible that unrecognized confounders were not accounted for, which would result in residual confounding. Finally, the cross-sectional nature of our study did not allow for exploration of temporality or causal effects of variations in PUFA intake on disease outcomes.

Future research should focus on examination of PUFA intake from all dietary sources and supplements, and should also incorporate objective measurement of PUFAs in blood. More refined PUFA measurement would increase the accuracy and precision of estimated relationships between PUFA and outcomes in SLE. Randomized clinical trials of n-3 rich diets are also warranted in order to assess causality.

In the absence of dietary trials manipulating PUFA levels in SLE, review of the USDA 2015-2020 Dietary Guidelines for Americans might be considered as part of patient education. These guidelines recommend that adults eat at least 8 ounces of seafood per week, with a target intake of at least 250 mg per day of the omega-3 fatty acids EPA and DHA. However, awareness of seafood advisories and U.S. Food and Drug Administration/Environmental Protection Agency advice on best seafood choices should be included (48), so that species most likely to be contaminated with toxicants such as mercury can be avoided. While the seafood guidelines are targeted to children and women of reproductive age, they may also be of particular relevance to lupus and autoimmune populations, as even low-levels of methylmercury exposure (for which the primary route of exposure is ingestion of contaminated seafood) have been associated with autoantibody positivity (49). Species of fish high in omega-3 and low in mercury include salmon and sardines. The USDA Dietary Guidelines also recommend consuming 1 oz per day (~1/4 cup) of nuts and seeds, with particular emphasis on those high in n-3s, such as flaxseeds, walnuts, and chia seeds, and shifting to canola oil in cooking (50). Adherence to the above guidelines would be expected to favorably shift personal n-6:n-3 ratios.

In conclusion, lower ratios of n-6 to n-3 and higher absolute levels of n-3 fatty acids in the diet of individuals with SLE were significantly associated with lower self-reported lupus disease activity scores and better sleep quality, and trended towards favorable associations with a range of patient-reported outcomes of clinical importance in SLE, including pain, depression and quality of life. Given that treatment of lupus frequently requires multiple pharmacologic agents, a non-pharmacologic intervention which could target various comorbidities is a particularly attractive prospect. Future studies are needed to help elucidate the mechanisms by which PUFAs impact outcomes in lupus, and to assess if

dietary manipulation of PUFAs can translate into clinically meaningful disease control. In the meantime, nutritional education on omega-3 rich seafood (low-mercury species), nuts, seeds and seed oils may be beneficial for SLE patients.

ACKNOWLEDGEMENTS

This work was supported by the Centers for Disease Control and Prevention (1U01 DP006265, 1U01 DP003250, U58 CCU522826, U58 DP001441) and the National Institutes of Health (NIH/NIEHS K01ES019909, NIH/NIEHS P30ES017885, and NIH/NCRR UL1RR024986). PC was supported by the Royal Thai Government Scholarship. We thank the Michigan Department of Health and Human Services for their expertise during the development of the MILES Program. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC, NIH, or the Department of Health and Human Services.

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Table 1. Baseline characteristics and patient-reported outcome (PRO) scores among SLE patients (n=456)

	Mean ± SD [range] or n (%)
Age (years)	52.9 ± 12.3
Female	425 (93.2)
Race	
White	235 (51.5)
Black	207 (45.4)
Asian	4 (0.9)
Other/unspecified	10 (2.2)
Hispanic ethnicity	17 (3.7)
Body mass index (kg/m^2)	30.0 ± 8.0
Fat energy intake (Kcal)	131.0 ± 151.4
Dietary n-3 intake (g/1000 Kcal)	3.1 ± 0.9 [0.7, 7.2]
Dietary n-6 intake (g/1000 Kcal)	20.1 ± 7.5 [5.0, 36.7]
Flaxseed and/or fish oil supplement use	112 (26.8%)
Patient-reported outcomes	
SLAQ	13.0 ± 8.0 [0, 38]
FM Scale positive	188 (41.2)
PROMIS-Depression	51.8 ± 9.9 [37.1, 81.1]
PROMIS-Sleep Disturbance	56.5 ± 8.8 [28.9, 76.5]
MOS SF-36 subscales	
Physical functioning	56.2 ± 30.2 [0, 100]
Role functioning/physical	41. 8 ± 42.5 [0, 100]
Role functioning/emotional	58.1 ± 43.5 [0, 100]
Energy/fatigue	39.8 ± 21.9 [0, 100]
Emotional/well-being	69.5 ± 19.2 [4, 100]
Social functioning	64.3 ± 29.0 [0, 100]

Pain	51.8 ± 27.0 [0, 100]
General health	42.1 ± 23.8 [0, 100]
LupusQoL domains	
Physical health	65.0 ± 27.3 [0, 100]
Pain	63.7 ± 28.6 [0, 100]
Planning	74.4 ± 28.3 [0, 100]
Intimate relationships	70.7 ± 33.7 [0, 100]
Burden to others	65.5 ± 31.9 [0, 100]
Emotional health	80.7 ± 20.0 [8.3, 100]
Body image	74.8 ± 24.6 [0, 100]
Fatigue	61.6 ± 26.5 [0, 100]

Abbreviations: SLAQ=Systemic Lupus Activity Questionnaire; FM=fibromyalgia; PROMIS=Patient-Reported Outcome Measurement Information System; MOS SF-36=RAND Medical Outcomes Study 36-Item Short-Form Survey Instrument; LupusQoL=Lupus Quality of Life Questionnaire

Sample sizes for variables with >1% missing: LQOL-intimate relationships, n=392; LQOL-body image, n=402

Figure 1. Associations between dietary polyunsaturated fatty acid intake (n-3, n-6 and n-6:n-3) and patient-reported outcome measures for lupus activity (SLAQ), sleep quality (PROMIS-Sleep Disturbance), and depression (PROMIS-Depression), from separate multivariable models.

Symbol markers designate regression (beta) coefficients, which represent mean outcome changes associated with each one-unit increase of the respective PUFA variable; horizontal lines designate 95% confidence intervals. Lower scores for the SLAQ and PROMIS measures indicate better outcomes (coefficients below 0 indicate "favorable" associations, and above 0 indicate "unfavorable" associations). The n-3 and n-6 fatty acid variables were fat energy-adjusted (g/1000 Kcal). Multivariable models adjusted for the following covariates: sex, age, race, and body mass index.

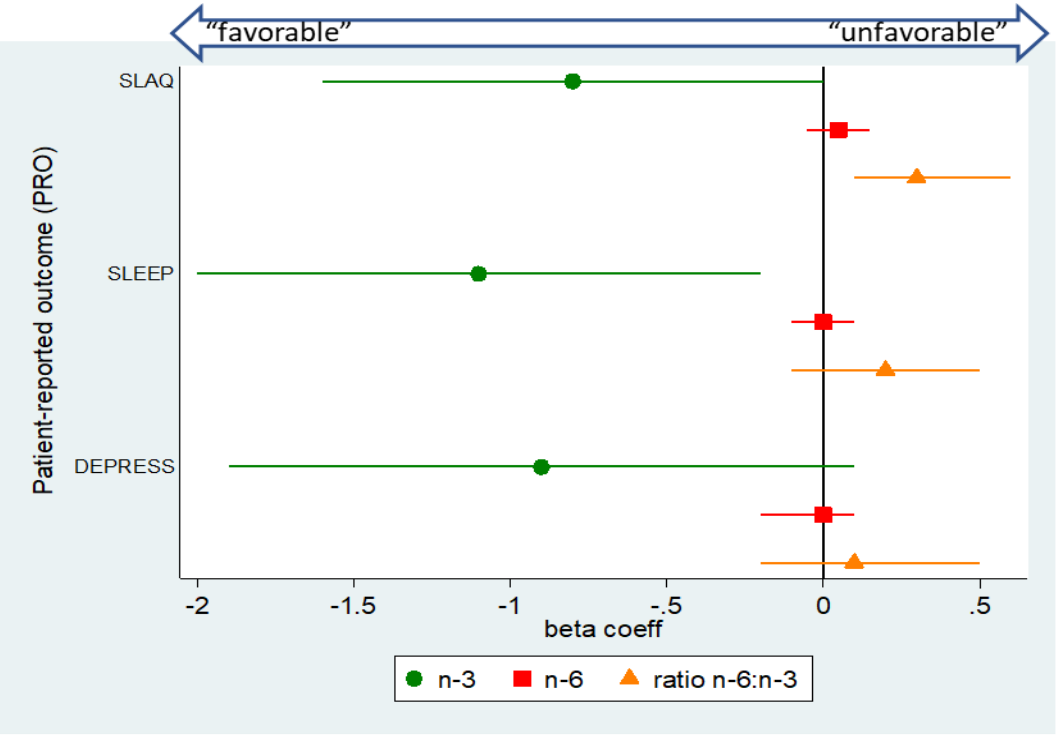

Figure 2. Associations between dietary fatty acid intake (n-3, n-6 and n-6:n-3) and fulfillment of fibromyalgia (FM) survey criteria, from separate multivariable models.

Symbol markers designate odd ratios (ORs), and horizontal lines designate 95% confidence intervals. ORs below 1 indicate "favorable" associations, and above 1 indicate "unfavorable" associations. The n-3 and n-6 fatty acid variables were fat energy-adjusted (g/1000 Kcal). Multivariable models adjusted for the following covariates: sex, age, race, and body mass index.

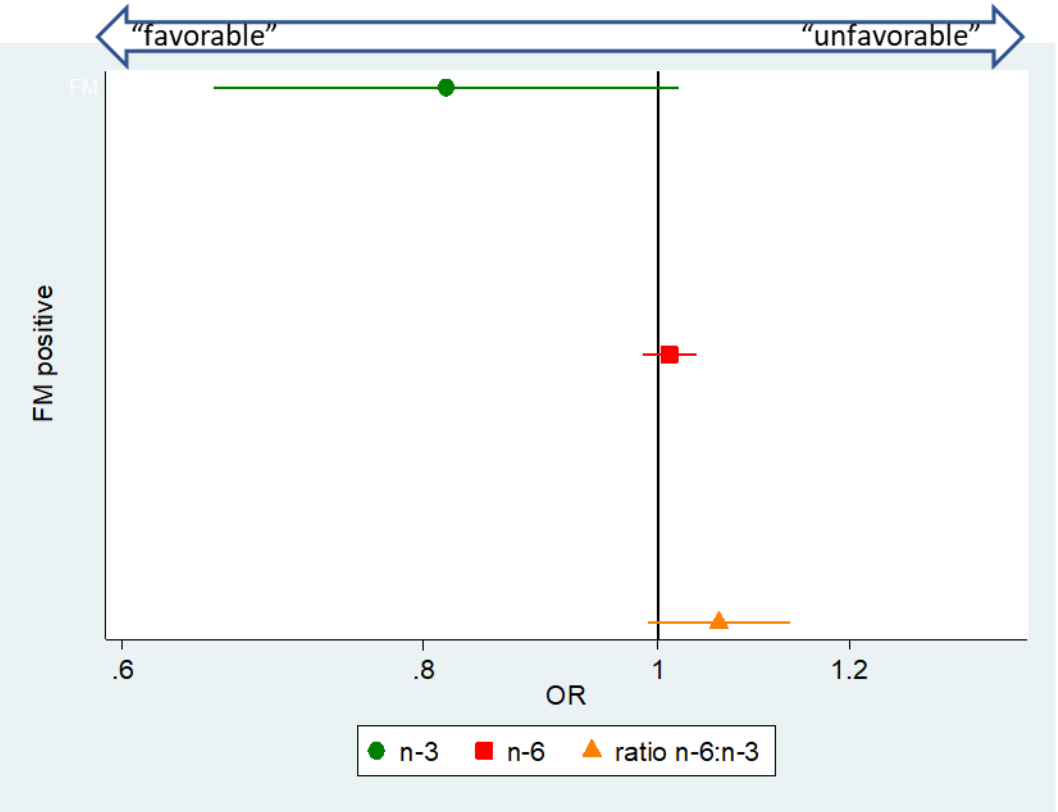

Figure 3. Associations between dietary fatty acid intake (n-3, n-6 and n-6:n-3) and health related quality of life, measured by MOS SF-36, from separate multivariable models.

Symbol markers designate regression (beta) coefficients, which represent mean outcome changes associated with each one-unit increase of the respective PUFA variable; horizontal lines designate 95% confidence intervals. Higher scores indicate better HRQOL. The n-3 and n-6 fatty acid variables were fat energy-adjusted (g/1000 Kcal). Multivariable models adjusted for the following covariates: sex, age, race, and body mass index.

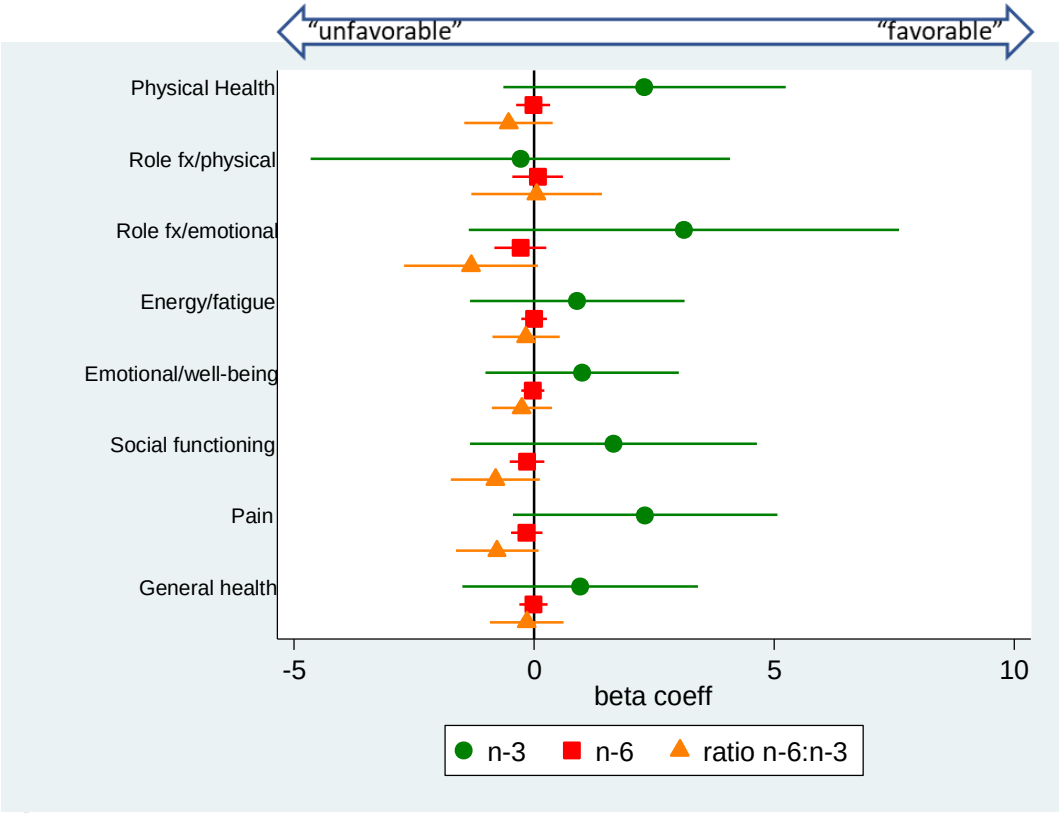

Figure 4. Associations between dietary fatty acid intake (n-3, n-6 and n-6:n-3) and lupus-specific quality of life, measured by the LupusQoL Questionnaire, from separate multivariable models.

Symbol markers designate regression (beta) coefficients, which represent mean outcome changes associated with each one-unit increase of the respective PUFA variable; horizontal lines designate 95% confidence intervals. Higher scores indicate better HRQOL. The n-3 and n-6 fatty acid variables were fat energy-adjusted (g/1000 Kcal). Multivariable models adjusted for the following covariates: sex, age, race, and body mass index.