Published in final edited form as:

Arthritis Care Res (Hoboken). 2018 March ; 70(3): 327–332. doi:10.1002/acr.23295.

The relationship between fish consumption and disease activity in rheumatoid arthritis

Sara K. Tedeschi, MD, MPH[1], **Joan M. Bathon, MD**[2], **Jon T. Giles, MD, MPH**[2], **Tzu-Chieh Lin, PhD**[1], **Kazuki Yoshida, MD, MPH, MS**[1,3], and **Daniel H. Solomon, MD, MPH**[1]

[1]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital and Harvard Medical School, Boston, USA

[2]Division of Rheumatology, Columbia University College of Physicians & Surgeons and New York-Presbyterian Hospital, New York, USA

[3]Departments of Epidemiology & Biostatistics, Harvard T.H. Chan School of Public Health, Boston, USA

Abstract

Objective—To assess whether more frequent fish consumption is associated with lower RA disease activity scores among participants in an RA cohort.

Methods—We conducted a cross-sectional analysis using baseline data from participants in the Evaluation of Subclinical Cardiovascular Disease and Predictors of Events in RA (ESCAPE-RA) cohort study. Frequency of fish consumption was assessed by a baseline food frequency questionnaire assessing usual diet in the past year. Multivariable, total energy-adjusted linear regression models provided effect estimates and 95% confidence intervals (CI) for frequency of fish consumption (never to <1/month, 1/month to <1/week, 1/week, and ≥2/week) on baseline DAS28-CRP. We also estimated the difference in DAS28-CRP associated with increasing fish consumption by one serving per week.

Results—Among 176 participants, median DAS28-CRP was 3.5 (interquartile range 2.9–4.3). In an adjusted linear regression model, subjects consuming fish ≥2 times/week had a significantly lower DAS28-CRP compared with subjects who ate fish never to <1/month (difference −0.49 [95% CI −0.97, −0.02]). For each additional serving of fish per week, DAS28-CRP was significantly reduced by 0.18 (95% CI −0.35, −0.004).

Conclusions—Our findings suggest that higher intake of fish may be associated with lower disease activity in RA patients.

Keywords

diet; disease activity; rheumatoid arthritis

Corresponding author: Sara K. Tedeschi, MD, MPH, Brigham and Women's Hospital, Division of Rheumatology, Immunology and Allergy, 60 Fenwood Road, Suite 6016, Boston, Massachusetts 02115 USA, Telephone: +1-617-732-5325 Fax: +1-617-732-5766, stedeschi1@partners.org.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by synovial inflammation leading to pain, functional impairment, and joint erosions. Use of disease modifying anti-rheumatic drugs (DMARDs) reduces systemic inflammation, improves symptoms, and prevents long-term joint damage. While DMARDs are standard-of-care for RA, other anti-inflammatory therapies have been studied. Omega-3 fatty acids downregulate pro-inflammatory cytokines, thus have been of interest for decades.[1–4] Several randomized trials tested the effect of fish oil supplements on RA disease activity,[5–7] using doses of omega-3 fatty acids (≥3 grams/day eicosapentaenoic acid [EPA] + docosahexaenoic acid [DHA]) exceeding the omega-3 content in one serving of fish.[8] In double-blind, placebo-controlled trials, subjects receiving fish oil had improved tender joint counts,[7] and higher rates of remission on triple non-biologic (nb)DMARD therapy.[6] While those nutrient-focused interventions showed benefit on disease activity, potential benefits of eating whole fish could not be detected given the study design.

We hypothesized that greater fish consumption would be associated with lower RA disease activity scores and tested this hypothesis in an RA cohort.

METHODS

Study design and population

We conducted a cross-sectional analysis using baseline data from participants in the Evaluation of Subclinical Cardiovascular Disease and Predictors of Events in Rheumatoid Arthritis (ESCAPE-RA) cohort study, which investigated subclinical cardiovascular disease in RA.[9] From October 2004 to May 2006, ESCAPE-RA enrolled adults aged 45–84 years meeting American College of Rheumatology 1987 RA classification criteria,[10] living near Baltimore, USA. Entry criteria for ESCAPE-RA mirrored entry criteria for the Multi-Ethnic Study of Atherosclerosis (MESA);[11] thus, subjects with a prior cardiovascular event or weighing >300 pounds were excluded. All study procedures were approved by the appropriate Institutional Review Boards.

Outcome

Disease Activity Score in 28 Joints with CRP (DAS28-CRP) was calculated at baseline using joint counts performed by a single trained assessor, and was normally distributed based on the Shapiro-Wilk test ($p=0.14$).[12,13]

Food frequency questionnaire and exposure

At baseline, participants completed a 120-item food frequency questionnaire (FFQ) assessing usual diet in the past year. This FFQ was originally developed for MESA and was modeled on a validated FFQ.[14] For each item, participants recorded frequency of use on a nine-point scale ranging from “never to <1/month” to “≥2/day”. Participants indicated small, medium, or large serving size for each item. Missing frequency was assigned never to <1/month. Missing serving size was assigned medium. For each food item, the product of frequency of consumption and serving size represented the average energy/day from that

item.[15] Total average energy/day was calculated as the sum of average energy/day from all 120 items. Participants reporting extreme total average energy/day (men <800 kcal/day or >4200 kcal/day, women <600 kcal/day or >3500 kcal/day) were excluded (n=10).[16,17] Thus, the range of total average energy intake/day was 800–4200 kcal/day for men, and 600–3500 kcal/day for women.

Frequency of fish consumption was calculated as the sum of frequencies of two items in units of times per day: "tuna fish, salmon, sardines (cooked or raw including sashimi or sushi)," and "other broiled, steamed, baked or raw fish (trout, sole, halibut, poke, grouper, etc.)". These two items represented non-fried fish consumption, and were selected due to higher omega-3 fatty acid content compared to the other seafood items included on the MESA FFQ.[15,18] Among MESA study participants, plasma EPA + DHA levels were significantly correlated with non-fried fish consumption ($r=0.38$, $p<0.05$) but not with consumption of fried fish, non-fried shellfish, or fish in mixed dishes (such as "stir-fried shrimp or fish with vegetables").[15] Therefore, we did not include fried fish, non-fried shellfish, or fish in mixed dishes in our assessment of fish intake.

Fish consumption was categorized in four groups using cutoffs representing meaningful differences in frequency of consumption. These four categories were: never to <1/month (FFQ category: never to <1/month), 1/month to <1/week (FFQ categories: 1/month and 2–3/month), 1/week (FFQ category: 1/week), and ≥2/week (FFQ categories: 2/week, 3–4/week, 5–6/week, 1/day, ≥2/day). Prior studies using MESA FFQ data have also focused on frequency of consumption of food items of interest, rather than serving size.[15,19] In sensitivity analyses we evaluated three groups of consumption, as studies of fish and RA risk have tested various categorizations.[20] The three groups were: never to <1/month, 1/month to <1/week, and ≥1/week (FFQ categories: 1/week, 2/week, 3–4/week, 5–6/week, 1/day, ≥2/day).

Covariates

Baseline covariates included race, dichotomized as White/non-White, and body mass index assessed as continuous (kg/m^2) and categorical (<25, 25 to <30, and ≥30 kg/m^2). Education, smoking, annual income, employment status, marital status, depression symptoms, and Charlson comorbidity score were reported.

RA features included anti-cyclic citrullinated protein antibody, rheumatoid factor, *HLA*-shared epitope, symptom duration, years since RA diagnosis, and functional status (Health Assessment Questionnaire).[21] Current use of nbDMARDs, biologic (b)DMARDs, glucocorticoids, and fish oil supplements were recorded.

Statistical methods

Baseline characteristics were summarized by fish consumption categories using descriptive statistics. Univariate linear regression models were constructed to assess the relationship between covariates and DAS28-CRP. Covariates with two-sided p-value <0.20 were tested for confounding (>10% change in coefficient for fish consumption) using linear regression models, adjusted for total average energy per day and fish consumption.

Linear regression models were constructed to test the relationship between frequency of fish consumption and DAS28-CRP. For each category of fish consumption we reported the mean difference in DAS28-CRP (beta-coefficient and 95% confidence interval [CI]) compared to consuming fish never to <1/month. All models were adjusted for total average energy consumed per day.[22] Multivariable models first included age and sex, followed by additional adjustment for confounders. To test for trend across categories of fish consumption, we calculated the difference in DAS28-CRP associated with increasing fish consumption (an increase of one serving/week) by including a term representing median frequency of fish consumption/week in each category. The coefficient and 95% CI of this term represented the difference in mean DAS28-CRP per one additional serving of fish/week.

Pre-specified sensitivity analyses adjusted for bDMARDs, fish oil supplements, and pack-years; excluded subjects taking fish oil supplements; and evaluated three categories of fish consumption. We also examined the impact of outliers, defined as DAS28-CRP >95th percentile of each fish consumption group, on the primary analysis by excluding those subjects in a sensitivity analysis. Simple imputation was performed by assigning zero for categorical variables or the sample median for continuous variables. Seven subjects (4.0%) had missing data for “tuna fish, salmon, sardines (cooked or raw including sashimi or sushi)” and six (3.4%) lacked data for “other broiled, steamed, baked or raw fish (trout, sole, halibut, poke, grouper, etc.).” For the variable representing overall frequency of non-fried fish consumption, obtained by summing the frequencies of these two food items, nine subjects (5.1%) had missing data. For each of the covariates included in multivariable models, fewer than five subjects had missing data.

RESULTS

We included 176 ESCAPE-RA participants in this analysis; Table 1 presents baseline traits. The majority were middle-aged, college-educated White females taking DMARDs for seropositive, longstanding RA. Thirty-five subjects (19.9%) reported infrequent fish consumption (never to <1/month) while 31 (17.6%) were frequent consumers (≥2 times/week). Pack-years were highest, and depression scores lowest (best), among the most frequent consumers. Median (interquartile range [IQR]) DAS28-CRP was 3.5 (2.9–4.3) among all participants, reflecting moderate disease activity.[23] Distribution of DAS28-CRP by fish consumption group is presented in Supplemental Figure 1. Fish oil supplement use was most frequent (20%) among subjects eating fish never to <1/month.

Adjusting for age and sex, DAS28-CRP was significantly lower by an average of 0.65 (95% CI −1.15, −0.15) among subjects consuming fish ≥2 times/week compared to those eating fish never to <1/month (Table 2). With additional adjustment for confounders, subjects consuming fish ≥2 times/week had significantly lower DAS28-CRP compared with never to <1/month by an average of 0.49 (95% CI −0.97, −0.02). For each additional serving of fish/week, DAS28-CRP was significantly reduced by an average of 0.18 (95% CI −0.35, −0.004).

In sensitivity analyses, we obtained similar results after additional adjustment for bDMARDs and fish oil supplements (Table 2). Upon excluding outliers of DAS28-CRP3

(n=6), we obtained similar results; subjects consuming fish ≥2 times/week had significantly lower DAS28-CRP by an average of 0.54 (95% CI −0.99, −0.09) compared to those eating fish never to <1/month. Fish oil supplement use itself was also associated with lower DAS28-CRP (−0.22, 95% CI −0.72, +0.29). Further adjustment for smoking produced similar results; subjects consuming fish ≥2 times/week had significantly lower DAS28-CRP by an average of 0.49 (95% CI −0.98, −0.003) compared with never to <1/month. Among 160 subjects not using fish oil supplements, DAS28-CRP was lower by an average of 0.41 (95% CI −0.92, +0.11) among those eating fish ≥2 times/week compared with never to <1/month. In this subgroup, each additional serving of fish/week was associated with a lower DAS28-CRP of 0.14 (95% CI −0.32, +0.04).

In analyses evaluating fish in three groups, subjects consuming fish ≥1 time/week had significantly lower mean DAS28-CRP by 0.44 (95% CI −0.85, −0.04) compared with never to <1/month in the fully-adjusted model (Table 3). For each additional serving of fish/week, the difference in mean DAS28-CRP was significantly lower by 0.26 (95% CI −0.51, −0.02).

DISCUSSION

In this cross-sectional analysis of fish consumption in a cohort of RA patients, DAS28-CRP was significantly lower among subjects consuming fish ≥2 times per week compared with those eating fish <1/month after adjusting for confounders. One additional serving of fish/week was associated with significantly lower DAS28-CRP. Further adjustment for bDMARDs, fish oil supplements and pack-years, and excluding outliers, produced similar results.

The observed difference in mean DAS28-CRP between the highest and lowest categories of fish consumption is of clinically important magnitude. During the SWEFOT trial run-in period, mean DAS28 decreased by 1.2 among 258 subjects after 3–4 months of methotrexate. In a cohort of 307 longstanding RA patients with moderate-to-high disease activity treated with methotrexate (without bDMARDs), mean DAS28 decreased by 1.6 after six months.[24] Our observed difference of 0.49 between the highest and lowest categories of fish consumption is approximately one-third the magnitude of these observed differences in DAS28 among methotrexate users.

In a recent randomized controlled trial of fish oil supplementation among RA subjects with disease duration <12 months and on triple DMARD therapy, treatment with high-dose fish oil (EPA + DHA 5.5 g/day) vs. low-dose fish oil (EPA + DHA 0.4 g/day) produced no significant difference in the change in DAS28-ESR over 12 months.[6] At 12 months, both groups had a significant decrease in DAS28-ESR compared to baseline, which may account for the fact that a between-group difference in DAS28-ESR was not observed. Nonetheless, the time to remission was significantly shorter in the high-dose vs. low-dose fish oil group. Earlier studies of fish oil supplementation in RA were conducted in decades before the DAS28 was commonly used; thus we are unable to compare outcomes between our analysis and those studies.

In our analysis, omega-3 fatty acid consumption among subjects in the highest group of fish consumption (≥2 times per week) was almost certainly less than 5.5 g/day, given that one 8 ounce (225 gram) serving of fatty fish generally provides around 2–4 g EPA + DHA.[8] Our analysis focused on two FFQ items describing non-fried fish, which have the highest omega-3 content of the FFQ fish items; we excluded fried seafood and shellfish due to lower omega-3 content. Potential reasons for lower omega-3 fatty acid content in fried fish include low omega-3 content of the fish selected for frying, and deterioration of long-chain fatty acids during the frying process.[15] Our observation that baseline consumption of fish ≥2 times per week was associated with lower DAS28-CRP at the same point in time may either reflect a generally healthier lifestyle among those who eat fish most often, or may reflect an effect of consuming fish as a whole food that contains various macronutrients and micronutrients in addition to omega-3 fatty acids. While the group consuming fish ≥2 times per week had some baseline traits that might be associated with improved disease activity, such as lower BMI and higher socioeconomic status, the prevalence of smoking was also highest in this group, making it difficult to draw conclusions about the way that these potential confounders could affect the relationship between fish consumption and DAS28-CRP. However, we must also bear in mind that causal inferences are always limited in cross-sectional, non-randomized studies.

In the primary analysis we divided subjects into four groups reflecting realistic differences in fish consumption. In a study of MESA subjects who completed the same FFQ as ESCAPE-RA subjects, a threshold effect of fish consumption on plasma levels of EPA + DHA was observed for fish intake ≥2 times per week,[15] providing rationale for our highest category in the primary analysis. Multiple studies have reported decreased risk of incident RA associated with greater fish consumption, although categorizations of fish intake varied.[20] In a sensitivity analysis, we categorized fish consumption into three groups and observed similar results to the primary analysis. Meta-analysis of seven studies found a non-significant decreased risk of developing RA for each additional serving of fish/week.[20] While beyond the scope of the present analysis, some have wondered if lower RA incidence rates in some countries may be related to cultural or environmental differences, including differences in frequency of fish consumption. In our cross-sectional analysis, each additional serving of fish/week was associated with 0.18 lower DAS28-CRP.

We observed the highest percentage of smokers and longer disease duration among subjects consuming fish most frequently, which one might expect to be associated with worse disease activity scores. However, despite increased prevalence of these potential confounders, the group consuming fish ≥2 times/week had significantly lower DAS28-CRP scores compared to the reference group, stimulating further interest regarding the importance of fish consumption as it relates to lower disease activity. While the magnitude of difference in DAS28-CRP was striking between the highest and lowest categories of fish consumption, this was a cross-sectional study and we cannot draw firm conclusions about the impact of frequent fish consumption on RA disease activity. Reverse causation is a possible explanation for observing an association between frequent fish intake and lower disease activity, thus prospective studies are needed to minimize this potential source of bias. Cohort studies cannot control for unmeasured confounders, and a randomized controlled trial would be required to provide firm evidence that greater fish consumption lowers RA disease

activity. The ESCAPE-RA cohort was predominantly White, well-educated, married patients with longstanding RA, thus our results may not generalize to other populations.

In conclusion, we observed significantly lower DAS28-CRP among subjects consuming fish ≥2 times/week compared to those eating fish never or <1/month. Prospective assessment of disease activity in relationship to fish consumption is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors would like to thank the ESCAPE-RA study participants, Majken K. Jensen, PhD and Eric Rimm, ScD of the Departments of Epidemiology & Nutrition, Harvard T.H. Chan School of Public Health, Boston, USA, for their assistance with the Multi-Ethnic Study of Atherosclerosis (MESA) FFQ and analysis plan, and the MESA Data Coordinating Center.

Funding: Dr. Tedeschi's work on this project was supported by NIH-NIAMS T32AR007530 and L30AR070514. Dr. Solomon's work on this project was supported by NIH-NIAMS K24AR055989. Funding for the ESCAPE-RA cohort was provided by NIH-NIAMS AR050026 to Dr. Bathon. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. Tedeschi SK, Costenbader KH. Is there a role for diet in the therapy of rheumatoid arthritis? Current Rheumatology Reports. 2016; 18:23. [PubMed: 27032786]
2. Lee TH, Hoover RL, Williams JD, et al. Effect of dietary enrichment with eicosapentaenoic and docosahexaenoic acids on in vitro neutrophil and monocyte leukotriene generation and neutrophil function. The New England Journal of Medicine. 1985; 312:1217–24. [PubMed: 2985986]
3. Kremer JM, Bigauoette J, Michalek AV, et al. Effects of manipulation of dietary fatty acids on clinical manifestations of rheumatoid arthritis. Lancet. 1985; 1:184–7. [PubMed: 2857265]
4. Darlington LG. Do diets rich in polyunsaturated fatty acids affect disease activity in rheumatoid arthritis? Annals of the Rheumatic Diseases. 1988; 47:169–72. [PubMed: 3281607]
5. Berbert AA, Kondo CR, Almendra CL, Matsuo T, Dichi I. Supplementation of fish oil and olive oil in patients with rheumatoid arthritis. Nutrition. 2005; 21:131–6. [PubMed: 15723739]
6. Proudman SM, James MJ, Spargo LD, et al. Fish oil in recent onset rheumatoid arthritis: a randomised, double-blind controlled trial within algorithm-based drug use. Annals of the Rheumatic Diseases. 2015; 74:89–95. [PubMed: 24081439]
7. Kremer JM, Lawrence DA, Petrillo GF, et al. Effects of high-dose fish oil on rheumatoid arthritis after stopping nonsteroidal antiinflammatory drugs. Clinical and immune correlates. Arthritis and Rheumatism. 1995; 38:1107–14. [PubMed: 7639807]
8. Health.gov. Dietary Guidelines. EPA and DHA Content of Fish Species (Data from NDB SR 16-1). (Accessed June 8, 2015, 2015, at http://www.health.gov/dietaryguidelines/dga2005/report/HTML/table_g2_adda2.htm.)
9. Giles JT, Ling SM, Ferrucci L, et al. Abnormal body composition phenotypes in older rheumatoid arthritis patients: association with disease characteristics and pharmacotherapies. Arthritis and Rheumatism. 2008; 59:807–15. [PubMed: 18512711]
10. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis and Rheumatism. 1988; 31:315–24. [PubMed: 3358796]
11. Nettleton JA, Steffen LM, Mayer-Davis EJ, et al. Dietary patterns are associated with biochemical markers of inflammation and endothelial activation in the Multi-Ethnic Study of Atherosclerosis (MESA). The American Journal of Clinical Nutrition. 2006; 83:1369–79. [PubMed: 16762949]

12. Paulus HE, Ramos B, Wong WK, et al. Equivalence of the acute phase reactants C-reactive protein, plasma viscosity, and Westergren erythrocyte sedimentation rate when used to calculate American College of Rheumatology 20% improvement criteria or the Disease Activity Score in patients with early rheumatoid arthritis. Western Consortium of Practicing Rheumatologists. The Journal of Rheumatology. 1999; 26:2324–31. [PubMed: 10555885]
13. DAS and DAS28. (Accessed 6 October 2016, 2016, at http://www.das-score.nl/das28/en/difference-between-the-das-and-das28/how-to-measure-the-das28/how-to-calculate-the-das28/alternative-validated-formulae.html.)
14. Mayer-Davis EJ, Vitolins MZ, Carmichael SL, et al. Validity and reproducibility of a food frequency interview in a Multi-Cultural Epidemiology Study. Ann Epidemiol. 1999; 9:314–24. [PubMed: 10976858]
15. Chung H, Nettleton JA, Lemaitre RN, et al. Frequency and type of seafood consumed influence plasma (n-3) fatty acid concentrations. The Journal of Nutrition. 2008; 138:2422–7. [PubMed: 19022967]
16. Virtanen JK, Mozaffarian D, Chiuve SE, Rimm EB. Fish consumption and risk of major chronic disease in men. The American Journal of Clinical Nutrition. 2008; 88:1618–25. [PubMed: 19064523]
17. Hu Y, Costenbader KH, Gao X, Hu FB, Karlson EW, Lu B. Mediterranean diet and incidence of rheumatoid arthritis in women. Arthritis Care & Research. 2014
18. Wall R, Ross RP, Fitzgerald GF, Stanton C. Fatty acids from fish: the anti-inflammatory potential of long-chain omega-3 fatty acids. Nutrition Reviews. 2010; 68:280–9. [PubMed: 20500789]
19. Nettleton JA, Lutsey PL, Wang Y, Lima JA, Michos ED, Jacobs DR Jr. Diet soda intake and risk of incident metabolic syndrome and type 2 diabetes in the Multi-Ethnic Study of Atherosclerosis (MESA). Diabetes Care. 2009; 32:688–94. [PubMed: 19151203]
20. Di Giuseppe D, Crippa A, Orsini N, Wolk A. Fish consumption and risk of rheumatoid arthritis: a dose-response meta-analysis. Arthritis Research & Therapy. 2014; 16:446. [PubMed: 25267142]
21. Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: A review of its history, issues, progress, and documentation. The Journal of Rheumatology. 2003; 30:167–78. [PubMed: 12508408]
22. Willett, WC. Nutritional Epidemiology. 3. Oxford University Press; 2012.
23. Wells G, Becker JC, Teng J, et al. Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. Annals of the Rheumatic Diseases. 2009; 68:954–60. [PubMed: 18490431]
24. Santos-Moreno PI, de la Hoz-Valle J, Villarreal L, Palomino A, Sanchez G, Castro C. Treatment of rheumatoid arthritis with methotrexate alone and in combination with other conventional DMARDs using the T2T strategy. A cohort study. Clinical Rheumatology. 2015; 34:215–20. [PubMed: 25318612]

SIGNIFICANCE AND INNOVATION

- This is a novel analysis of the relationship between consuming fish as a whole food, rather than consuming fish oil supplements, and rheumatoid arthritis disease activity
- We report a statistically and clinically significant reduction in DAS28-CRP among subjects with rheumatoid arthritis who consumed fish ≥2 times/week compared to those who consumed fish never or <1/month, after adjustment for confounders
- Our observed difference in DAS28-CRP of 0.49 between the highest and lowest categories of fish consumption is approximately one-third the magnitude of previously reported pre- and post-treatment differences in DAS28 among methotrexate users

Table 1

Characteristics of 176 subjects by frequency of fish consumption

	Frequency of fish consumption			
	Never to <1/month ***n=35***	**1/month to <1/week** ***n=72***	**1/week** ***n=38***	**≥2/week** ***n=31***
Demographics and comorbidities	*Median (interquartile range) or percent*			
Age, years	59.0 (52.0–65.0)	60.5 (52.0–66.0)	60.0 (57.0–64.0)	57.0 (51.0–63.0)
Female (%)	60.0	56.9	71.1	51.6
White (%)	91.4	91.7	76.3	83.9
Body mass index, kg/m^2	29.1 (26.3–32.0)	28.2 (25.5–30.9)	27.2 (24.1–31.7)	26.9 (24.0–31.1)
Some college or greater [*] (%)	74.3	76.4	65.8	71.0
Married [*] (%)	85.3	86.1	73.7	80.7
Income <USD$50,000/year [*] (%)	34.3	40.3	39.5	32.3
Employed full- or part-time [*] (%)	37.1	44.4	42.1	67.7
Current smoker (%)	8.6	11.1	10.5	19.4
Pack-years [*]	1.3 (0–37.5)	10.2 (0–30.0)	8.4 (0–25.5)	11.7 (0–38.0)
CES-Depression scale [*^]	6.5 (4.0–11.0)	5.5 (2.0–10.5)	6.0 (3.0–14.0)	4.0 (2.0–9.0)
Charlson comorbidity score [*]	1.0 (1.0–1.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)
Rheumatoid arthritis features				
DAS28-CRP	3.8 (3.2–4.6)	3.6 (2.9–4.2)	3.5 (2.9–4.3)	3.1 (2.8–3.9)
Seropositive (anti-CCP and/or RF)	80.0	77.8	81.6	77.4
Anti-CCP positive [*] (%)	68.6	70.4	73.7	71.0
RF positive (%)	65.7	65.3	76.3	51.6
HLA-SE present [*] (%)	68.6	69.0	68.4	77.4
RA symptom duration, years	11.0 (6.0–24.0)	10.5 (6.0–20.5)	10.0 (6.0–23.0)	15.0 (3.0–23.0)
RA duration, years	8.0 (5.0–17.0)	8.5 (5.0–16.5)	9.0 (3.0–21.0)	11.0 (3.0–17.0)
Health Assessment Questionnaire	0.9 (0.5–1.3)	0.6 (0.1–1.4)	0.6 (0.1–1.5)	0.6 (0–1.3)
Current medications				
None [*] (%)	2.9	2.8	5.3	3.2
Methotrexate [*+] (%)	64.7	73.6	60.5	64.5
Non-biologic DMARD [*+] (%)	79.4	87.5	89.5	90.3
Biologic DMARD [*+] (%)	55.9	44.4	47.4	35.5
Glucorticoids [+] (%)	51.4	36.1	44.7	22.6
Fish oil supplement (%)	20.0	6.9	5.3	6.5

Abbreviations: RF: rheumatoid factor. CCP: cyclic citrullinated protein. *HLA-SE*: *HLA*-shared epitope, either 1 or 2 alleles present.

[^] CES-Depression scale: range 0-60. Higher scores indicate greater depressive symptoms; >16 indicates clinically significant depressive symptoms.

[*] Data missing for education (n=1), married (n=1), income (n=4), employment (n=3), pack-years (n=5), CES-Depression score (n=1), Charlson comorbidity score (n=1), anti-CCP (n=1), *HLA-SE* (n=1), no current medications (n=1), methotrexate (n=1), non-biologic DMARD (n=1), biologic DMARD (n=1)

[+]Monotherapy or combination therapy. Non-biologic DMARDs include methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, azathioprine, and minocycline. Biologic DMARDs include TNF-alpha inhibitors, rituximab, and anakinra.

Table 2

Linear regression model estimates of difference in DAS28-CRP3 compared to eating fish never to <1/month

	Frequency of fish consumption				
	Never to <1/month ***n=35***	**1/month to <1/week** ***n=72***	**1/week** ***n=38***	**≥2/week** ***n=31***	**Difference in DAS28-CRP3 per 1 additional serving of fish/week[+]**
Model adjusted for:[*]	*β-coefficient (95% confidence interval)*				*β-coefficient (95% CI)*
Age and sex	0 (ref)	−0.32 (−0.73, 0.10)	−0.32 (−0.79, 0.15)	−0.65 (−1.15, −0.15)	−0.22 (−0.40, −0.04)
Age, sex, body mass index, depression, married	0 (ref)	−0.23 (−0.62, 0.16)	−0.36 (−0.81, 0.08)	−0.49 (−0.97, −0.02)	−0.18 (−0.35, −0.004)
Age, sex, body mass index, depression, married, bDMARD, fish oil	0 (ref)	−0.24 (−0.64, 0.15)	−0.39 (−0.85, 0.06)	−0.51 (−0.99, −0.02)	−0.18 (−0.35, −0.003)

[*] All models are adjusted for total energy intake. Covariates: age in decades, sex, body mass index in kg/m^2 (<25, 25 to <30, ≥30), CES-Depression score (continuous), married (yes/no), biologic DMARD use (yes/no), fish oil supplement use (yes/no)

[+] β-coefficient (95% CI) from linear regression models including a term representing the median frequency of fish consumption per week in each exposure group

Table 3

Linear regression model estimates of difference in DAS28-CRP3 compared to eating fish never to <1/month, with 3 categories of fish consumption

	Frequency of fish consumption			
	Never to <1/month ***n=35***	**1/month to <1/week** ***n=72***	**≥1/week** ***n=69***	**Difference in DAS28-CRP3 per 1 additional serving of fish/week** [+]
Model adjusted for: [*]	*β-coefficient (95% confidence interval)*			*β-coefficient (95% CI)*
Age and sex	0 (ref)	−0.32 (−0.73, 0.10)	−0.47 (−0.88, −0.05)	−0.26 (−0.51, −0.01)
Age, sex, body mass index, depression, married	0 (ref)	−0.23 (−0.62, 0.16)	−0.42 (−0.82, −0.02)	−0.25 (−0.49, −0.01)
Age, sex, body mass index, depression, married, bDMARD, fish oil	0 (ref)	−0.24 (−0.64, 0.15)	−0.44 (−0.85, −0.04)	−0.26 (−0.51, −0.02)

[*] All models are adjusted for total energy intake. Covariates: age in decades, sex, body mass index in kg/m^2 (<25, 25 to <30, ≥30), CES-Depression score (continuous), married (yes/no), biologic DMARD use (yes/no), fish oil supplement use (yes/no)

[+] β-coefficient (95% CI) from linear regression models including a term representing the median frequency of fish consumption per week in each exposure group