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Dietary long-chain omega-3 fatty acid intake and arthritis risk in the Women's Health Initiative

Jessica L. Krok-Schoen, PhD^{1,2,*}, Theodore M. Brasky, PhD^{1,*}, Rebecca P. Hunt, PhD³, Thomas E. Rohan, PhD, DHSc⁴, Tamara A. Baker, PhD⁵, Wenjun Li, PhD⁶, Laura Carbone, MD⁷, Rachel H. Mackey, PhD⁸, Linda Snetselaar, PhD⁹, Maryam Lustberg, MD¹, and Marian L. Neuhouser, PhD³

¹The Ohio State University-James Comprehensive Cancer Center, Columbus, OH USA

²School of Health and Rehabilitation Sciences, The Ohio State College of Medicine, Columbus, OH USA

³Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA USA

⁴Department of Epidemiology and Population Health, Albert Einstein College of Medicine, New York City, NY USA

⁵University of Kansas Department of Psychology, Lawrence, KS USA

⁶University of Massachusetts School of Medicine, Boston, MA USA

⁷Medical College of Georgia at Augusta University, Augusta, GA USA

⁸University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA USA

⁹The University of Iowa College of Public Health, Iowa City, IA USA

Abstract

Background—The prevalence of arthritis in the United States is substantial and on the rise. Long-chain omega-3 polyunsaturated fatty acids (LCω-3PUFA), which have anti-inflammatory properties, have been shown to provide therapeutic benefit to arthritis patients; however, to date, few have examined these associations with arthritis risk.

Objective—The study objective was to examine the associations of LCω-3PUFA intake with osteoarthritis (OA) and rheumatoid arthritis (RA) risk among postmenopausal women.

Correspondence: Theodore M. Brasky, 1590 N High St., Suite 525, Columbus, OH 43201, Theodore.Brasky@osumc.edu, Phone: 614-293-3722, Fax: 614-293-5611.

*Equal contribution

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Conflict of Interest Statement

None of the authors have any conflict of interests to report.

Design—This was a prospective cohort study.

Participants—The sample for this analysis consisted of 80,551 postmenopausal women, ages 55-79 years and with no history of arthritis, recruited into the Women's Health Initiative Observational Study and Clinical Trials cohort between 1993 and 1998. Women completed a 120-item food frequency questionnaire at baseline.

Main outcome measures—After a median follow-up of 8 years, 22,306 incident OA and 3,348 RA cases were identified.

Statistical analyses performed—Adjusted Cox regression models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the associations between dietary LC ω -3PUFA intake and OA and RA risk.

Results—Individual and total LC ω -3PUFA (Quintile 5 vs 1: HR 1.04, 95% CI: 0.99-1.09 for OA; HR 1.01, 95% CI: 0.90-1.13 for RA) were not associated with OA and RA risk. Further, no associations were observed between ω -6 PUFA and either arthritis outcome.

Conclusions—This study is the first to examine associations of LC ω -3PUFA intake with OA risk and the largest to examine associations with RA risk. Despite their therapeutic potential, the study provides no evidence of benefit of these nutrients in relation to arthritis risk.

Keywords

arthritis; LC ω -3PUFA; osteoarthritis; rheumatoid arthritis; Women's Health Initiative

Introduction

Arthritis is a general term for >100 rheumatic diseases and conditions that affect the joints and synovial tissues¹. The most common types of arthritis include osteoarthritis (OA), a degenerative joint disease, and rheumatoid arthritis (RA), an autoimmune disease¹ which affects over 30 million and 1.28 million U.S. adults, respectively^{1,2}. Risk factors associated with the development of OA include older age, female sex, obesity, family history, and joint injury or overuse^{1,3}. The risk factors associated with the development of RA similar to OA include older age, female sex, and family history, but also include smoking^{1,4}.

The specific causes of OA are unknown, but it is hypothesized to result from both mechanical and molecular events in the affected joint, traditionally classified as a noninflammatory arthritis^{5,6}. In contrast, RA is an autoimmune chronic inflammatory arthritis that typically occurs in multiple joints⁷. However, there is increasing evidence that inflammation plays an important role not only in RA, but in OA as well^{8,9}. In OA, the synovia of joints are often inundated with inflammatory cytokines that contribute to cartilage damage, which is OA's signature pathologic feature^{8,10}. Furthermore, previous studies have found that early stage OA is an inflammatory disease before visible cartilage degeneration has occurred^{9,11}.

Inhibition of inflammation is important for treatment of both OA and RA, yet relatively little attention has been given to whether anti-inflammatory treatment is associated with reduced incidence of these conditions^{8,12}. Long-chain omega-3 polyunsaturated fatty acids

(LC ω -3PUFA), which derive primarily from consumption of oily fish and fish oil supplements, have been shown in human studies to have anti-inflammatory properties¹³⁻¹⁶, possibly through inhibition of NF- κ B and COX pathways¹⁷. Conversely, arachidonic acid (20:4 ω 6), which competes with LC ω -3PUFA on cell phospholipid membranes and is a precursor to COX-derived eicosanoids, is thought to increase inflammation, although results from human studies are inconsistent¹⁸⁻²⁰. Given the multifactorial etiology of arthritis, any association between diet and risk may be expected to be small. Only one prior study has examined associations between LC ω -3PUFA and (rheumatoid) arthritis risk. Di Giuseppe et al.²¹, reported that intakes of LC ω -3PUFA 210 mg/day were associated with a 35% (RR 0.65, 95% CI: 0.48-0.90) reduced RA risk in a prospective study among Swedish women.

This study sought to examine the associations of LC ω -3PUFA intake with osteoarthritis (OA) and rheumatoid arthritis (RA) risk among postmenopausal women. Herein, this study describes the investigation of dietary LC ω -3PUFA and risk of OA and RA in the Women's Health Initiative (WHI), a large, prospective cohort of postmenopausal women in the U.S. To our knowledge, this study is the first to examine these associations with OA risk, and the largest to examine associations with RA risk.

Materials and Methods

Women's Health Initiative

The WHI is a large, prospective study of 161,808 postmenopausal women that was designed to examine common causes of morbidity and mortality among postmenopausal women, including cancer, cardiovascular disease, and osteoporosis²². WHI methods are detailed elsewhere²²⁻²⁴. Briefly, the study consists of a multi-component (hormone therapy, dietary modification, and/or calcium and vitamin D supplementation) clinical trial (CT) and an observational study (OS). Postmenopausal women, ages 50 to 79 years were recruited at 40 US clinical centers between September 1, 1993 and December 31, 1998. The WHI CT included three overlapping components: two placebo controlled hormone therapy trials; a low-fat dietary modification trial with a control group; and a placebo-controlled calcium/vitamin D supplementation clinical trial²⁵⁻²⁷. Women who were screened for participation in the CT but were ineligible or unwilling to participate were offered participation in the OS²⁸. Women provided written informed consent for participation. Human Subjects Review Committees at all participating institutions approved the WHI study protocol (clinicaltrials.gov identifier: NCT00000611). This study was deemed exempt by the Ohio State University Institutional Review Board. This study was deemed exempt under federal regulation 45 46.101 (b) CFR.

Data collection

WHI participants attended baseline screening visits, during which they completed self-administered questionnaires that collected detailed information on demographics, medical and reproductive history, leisure physical activity, lifestyle habits such as smoking and alcohol use, and other risk factors. Height and weight were measured by clinic staff and used to compute body mass index (BMI; kg/m²). Although women were asked about dietary supplement use, they were not asked specifically about consumption of fish oil.

Women also completed at baseline a semi-quantitative food frequency questionnaire (FFQ)²⁹. Participants reported their usual frequency of intake and portion size (small, medium, or large, relative to the stated medium portion size and to photographs of portion sizes) of 122 foods and beverages consumed during the 3 months prior to baseline. The questionnaire was designed specifically to improve measurement of fat intake by including questions about food preparation and types of fats added in cooking or at the table. The average daily intake of specific fatty acids was calculated by multiplying the frequency times portion size for each specific food by its fatty acid content, as determined by the University of Minnesota's Nutrient Data System for Research (NDS-R®, version 2007)³⁰. Average daily intakes of PUFAs were estimated in this manner. Variables representing total LC ω -3PUFA [mg/d; defined here as eicosapentaenoic acid (EPA; 20:5 ω 3) + docosapentaenoic acid (DPA; 22:5 ω 3) + docosahexaenoic acid (DHA; 22:6 ω 3)] and total ω -6PUFA [defined as linoleic acid (LA; 18:2 ω 6) + arachidonic acid (AA; 20:4 ω 6)] were created. The majority of EPA, DPA, and DHA consumed came from fish intake, with the largest contributions from dark, oily fish, and minor amounts contributed through consumption of poultry and lunchmeats. α -linolenic acid (ALA; 18:3 ω 3) was not included in the summary of LC ω -3PUFA as it does not hold significant anti-inflammatory properties³¹. Total fruit intake was calculated as the sum of: 1) a question which queried participants on their usual overall intake of fruits; 2) intakes of orange juice; and 3) other fruit juices. Total vegetable intake was calculated in a similar manner, combining data on the usual intakes of: 1) vegetables (other than salad, potatoes, or dried beans); 2) lettuce; 3) mixed lettuce with vegetables; and 4) potatoes. Red meat was summarized as intakes of ruminant animals (beef, pork, lamb) as well as: 1) lunch meats; 2) liver; 3) bacon; 4) sausage; and 5) intakes of several additional meat-containing foods (e.g., chili, burritos, meat sauces on pasta, etc.).

Follow-up for incident arthritis and censoring

Incident arthritis (OA or RA) was self-reported annually in the WHI-OS and semiannually in the WHI-CT. Participants were asked on follow-up questionnaires: "has a doctor told you for the first time that you have any of the following specific conditions?", among which "Osteoarthritis or arthritis associated with old age" and "Rheumatoid Arthritis (not including rheumatism)" were response options. After a mean follow-up of 8.0 years (interquartile range 7.0-8.9), $n=22,306$ and $n=3,348$ cases of OA and RA were identified, respectively. Aside from a diagnosis of arthritis, participants were right-censored from the analysis at the earliest of the following occurrences: withdrawal from the study ($n=4,457$), death ($n=10,052$), loss of contact ($n=2,726$), or April 8, 2005 ($n=63,316$), the last date of follow-up of the original study.

Statistical analyses

The original WHI sample included 161,808 women. In the present analysis, exclusions were made for women who reported at baseline: a positive or missing history of any arthritis ($n=77,640$), or positive/missing history of systemic lupus erythematosus ($n=1,067$). Out of the 83,101 remaining women, those who did not complete a baseline FFQ or whose FFQ energy intake was <600 kcal/day or $>5,000$ kcal/day ($n=2,550$) were also excluded, leaving $n=80,551$ postmenopausal women available for study.

Dietary fatty acid intakes were energy-adjusted using the residual method³² and categorized into fifths. Discrete time Cox regression models using baseline age as the time variable were used to estimate hazards ratios (HR) and 95% confidence intervals (CI) for associations of participants' baseline characteristics with OA and RA risk. Cox regression models were also used to estimate associations of ω -3 and ω -6 fatty acid intakes with risks of OA and RA.

For each fatty acid variable, the results of two regression models are presented as: 1) minimally-adjusted, which included age (time variable), WHI study component (OS, or CT randomization assignment), and total energy intake; and 2) multivariable-adjusted, which resulted from backward selection and began with a "saturated" model that included all baseline factors associated with arthritis risk at $P < 0.05$ in age-adjusted Cox models (Table 1). Variables in the minimally-adjusted model (i.e., WHI study component and total energy) were forced into the final multivariable-adjusted model. The resulting model included those factors that remained associated with arthritis risk at $P < 0.05$. The backward selection procedure was performed separately for OA and RA. The final multivariable model for OA included adjustment for age (time variable), WHI study component, total energy intake, race/ethnicity, BMI, smoking, multivitamin use, duration of combined hormone therapy, duration of estrogen-alone hormone therapy, prevalent diabetes, prevalent cardiovascular disease, and nonsteroidal anti-inflammatory drug (NSAID) use. The final multivariable model for RA included age (time variable), WHI study component, total energy intake, education, race/ethnicity, BMI, memory loss, and fruit intake. All reported P values are 2-sided, and a $P < 0.05$ was considered statistically significant. P values for trend (P_{trend}) were calculated across quintiles of dietary fatty acid intake by treating ordinal categorical fatty acid variables as continuous in Cox models. Statistical analyses were performed using SAS v9.3 (Cary, NC)³³.

BMI is positively correlated with inflammation³⁴ and was recently reported to be a strong risk factor for arthritis in women³⁵. Therefore, in an exploratory analysis, this study examined whether associations between LC ω -3 PUFA intake and arthritis risk were modified by participants' body size, by stratifying analyses on BMI (<25, 25-29, 30 kg/m²). P values for interaction ($P_{\text{interaction}}$) were calculated using a likelihood ratio test of a model with and without a cross-product term.

A series of sensitivity analyses were conducted. Because self-reported RA has been shown to be an error-prone measure³⁶, RA was defined as the use of post-baseline disease-modifying anti-rheumatic drugs (DMARDs; including hydroxychloroquine, sulfasalazine, minocycline, methotrexate, leflunomide, cyclosporine, azathioprine, gold compounds, cyclophosphamide, anti-tumor necrosis factor medications, and oral steroids) combined with self-reported RA. Since medication data were updated after year 3 in the WHI CT only, the sensitivity analysis was restricted to the CT (n=35,212; n cases=125). In a separate validation study within the WHI, combining DMARDs with self-reported RA resulted in moderate agreement ($\kappa=0.53$) with RA determined from medical chart review³⁶. Additional sensitivity analyses for both RA and OA risk were conducted to assess the impact of diet quality (adjustment for Healthy Eating Index (HEI)), a 2-year lag analyses, and truncation of follow-up to the year 2000.

Results

Women who were overweight, were the least physically active, had 5 pregnancies, had prevalent heart disease, reported memory loss, or consumed the most red meat had elevated risks of both OA and RA (Table 1). Women of Hispanic ethnicity, those who smoked, consumed the most calories, experienced moderate to severe memory loss, or used multivitamins, menopausal hormones, or NSAIDs had elevated risks of OA. In contrast, Black, Hispanic, and American Indian women, women with prevalent diabetes, those who did not use multivitamins, and those who consumed the least alcohol, fruit, or vegetables, or who consumed the most red meat had elevated risks of RA. With the exception of associations of non-white race and ethnicity, moderate to severe memory loss, and obesity with RA risk, most associations were relatively weak.

Self-reported dietary intakes of LC ω -3PUFA were not associated with the risk of OA (Table 2) or RA (Table 3) in multivariable-adjusted models. Point estimates for individual and total LC ω -3PUFA (Q5 vs Q1: HR 1.04, 95% CI: 1.00-1.09 for OA; HR 1.01, 95% CI: 0.90-1.13 for RA), individual and total ω -6 PUFA (HR 0.98, 95% CI: 0.94-1.03 for OA; HR 0.96, 95% CI: 0.85-1.08 for RA), and the LC ω -6 to ω -3 ratio, each approximated the null value. *P* values for tests of linear trend across quintiles of PUFA intake were statistically non-significant. In a sensitivity analysis redefining RA as self-reported with DMARD use, results for LC ω -3PUFA were unchanged (data not shown). Additional sensitivity analyses including adjustment for HEI, 2-year lag analyses, and truncation of follow-up also had no effect on OA and RA estimates. The null association between LC ω -3PUFA intake and arthritis risk did not differ when the data were stratified on BMI (*P*interaction: 0.71 for OA; 0.87 for RA) (Table 4).

Discussion

In this prospective study of 80,551 postmenopausal women, dietary intakes of LC ω -3PUFA were not associated with incident OA or RA. Although prior studies have explored associations of fish intake with RA risk^{37,38}; only one published report has examined intakes of specific LC ω -3PUFA²¹. To our knowledge, no prior study has examined these associations with OA risk.

The underlying etiologic mechanisms for OA and RA differ. Unlike the concentrated, progressive cartilage loss within one joint in OA, RA's chronic inflammatory process simultaneously affects multiple joints and other organs¹. In RA, the inflamed synovium leads to an erosion of cartilage and bone, resulting in pain, swelling, redness, and joint deformity. RA is also characterized by elevated inflammatory cytokines in the synovial joints³⁹. Similar to OA, the etiology of RA is unclear but RA is believed to be the result of both genetic and environmental factors⁴⁰. Although few modifiable risk factors have been identified, smoking⁴¹⁻⁴³ and obesity^{35,42,44} are suspected to increase RA risk; notably both are associated with increased inflammation and obesity was associated with RA risk in this study. Results indicated weak positive associations between red meat and NSAIDs and OA and RA risk, several such associations have been reported previously⁴². Results also indicated weak positive associations of several additional factors such as multivitamins and

menopausal hormones with OA risk. Conversely, there were negative associations for multivitamin use, alcohol, fruit, and vegetable intake and RA risk.

The PUFA intake among women reported in this sample are slightly lower compared to other studies^{21,38,45}, particularly in relation to the upper quintiles of intake. For example, the first four quintiles of intake reported in the current study contain the first four average intakes from the Nurses Health Study II, accounting for 80% of their sample⁴⁵. In the only study to examine associations between LC ω -3PUFA intake and RA risk, Di Giuseppe et al.²¹ recently reported that intakes >210mg/day, similar to the upper quintile of intake in the present study, was associated with a 35% reduced RA risk (RR 0.65, 95% CI: 0.48-0.90) among 32,232 women in the Swedish Mammography Cohort.

A few other prospective studies examined associations between fish intake and RA risk^{46,47}. Pederson et al.⁴⁶ reported that intakes of fatty fish were associated with 49% statistically non-significant reduced RA risk (incidence rate ratio= 0.51, 95% CI: 0.25-1.03) among 57,053 male and female participants of a Danish cohort study. In addition, fish intake was not associated with RA risk in the Nurses' Health Study cohort (n=82,063)⁴⁷. Case-control studies of fish intake and RA risk have largely not reported an association³⁸. To our knowledge, the present study is the first to report on associations between LC ω -3PUFA intake and OA risk.

Despite the failure to observe an association between dietary LC ω -3PUFA and arthritis risk, there is evidence of therapeutic benefit of supplemental LC ω -3PUFA treatment in both RA and OA. Meta-analyses of randomized controlled trials^{48,49} reported that LC ω -3PUFA reduced NSAID use, patient-reported pain intensity, morning stiffness, and the number of painful and/or tender joints among RA patients. Studies of LC ω -3PUFA and OA therapy are less common and results have been inconsistent⁵⁰. However, a recent randomized trial reported, somewhat inexplicably, that OA patients randomized to *low-dose* supplemental LC ω -3PUFA had improved pain and function scores, relative to those randomized to a higher dose supplement.⁵¹

Despite limited preclinical data suggesting that ω -6 PUFAs may be important in promoting RA²⁰, to the authors' knowledge, there are a paucity of studies that have examined associations for RA or OA risk in humans. Data from the Swedish Mammography Cohort found no association between n-6 PUFAs (LA Q5 vs Q1: HR 0.91, 95% CI: 0.59-1.40; AA Q5 vs Q1: HR 1.10, 95% CI: 0.66-1.82) and RA risk (personal communication: Alicja Wolk, 5/2017). The current study's data do not support any such role.

The present study has a number of strengths. With 80,551 participants and 22,306 incident OA and 3,348 incident RA cases, there was ample statistical power to examine low to moderate associations with risk. Furthermore, this study controlled for a number of potential confounding factors. Nevertheless, this study was limited by the potential for non-differential measurement error: 1) OA and RA were not adjudicated. Prior studies have demonstrated that basing arthritis status solely on self-reported RA is error-prone^{36,52}; however, in a sensitivity analysis in which RA status was additionally classified with DMARD use, the findings were unchanged. 2) RA diagnosis was not serologically

confirmed. 3) Dietary data in this study were also self-reported in a single baseline measurement. Self-reported diet is subjective and prone to measurement error⁵³, especially since diet is susceptible to change over time. 4) Lastly, supplement sources of LC ω -3PUFA (i.e., fish oil) were not systematically collected in the WHI, potentially contributing to measurement error. Therefore, it remains possible that the null associations reported herein are the result of such errors. Future studies would benefit by measuring biomarkers of LC ω -3PUFA intake, which are considered more objective.

Conclusion

In summary, in this large, prospective study of postmenopausal women, there was no evidence to suggest that dietary intakes of LC ω -3PUFA are associated with the risk of OA or RA. Given the relative paucity of data examining the associations between LC ω -3PUFA and arthritis risk, and evidence of therapeutic benefit among patients, additional prospective studies with robust measurement of dietary and supplement sources of intake and arthritis outcomes are needed.

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RESEARCH SNAPSHOT**Research Question**

Is there an association between long-chain omega-3 polyunsaturated fatty acids (LC ω -3PUFA) and arthritis (rheumatoid (RA) and osteoarthritis (OA)) risk?

Key Findings

There was no evidence to suggest that dietary intakes of LC ω -3PUFA are associated with the risk of OA or RA in this large, prospective study of postmenopausal women from the Women's Health Initiative.

Age-adjusted associations of participants' baseline characteristics with arthritis risk, stratified by arthritis type, in the WHI Observational Study and Clinical Trials ($n=80,551$).

Table 1

Characteristic	Osteoarthritis, $n=22,306$			Rheumatoid Arthritis, $n=3,348$		
	Cases	HR	(95% CI)	Cases	HR	(95% CI)
<i>Demographics and anthropometrics</i>						
Education						
High school graduate	4,542	1.00	(reference)	869	1.00	(reference)
Some college	8,343	1.01	(0.97, 1.05)	1,263	0.78	(0.71, 0.85)
College or advanced degree	9,279	0.96	(0.93, 1.00)	1,189	0.63	(0.57, 0.68)
Race and Ethnicity						
Non - Hispanic White	18,767	1.00	(reference)	2,499	1.00	(reference)
Non-Hispanic Black	1,608	0.99	(0.94, 1.05)	415	1.89	(1.70, 2.10)
Hispanic/Latina	905	1.19	(1.11, 1.28)	267	2.50	(2.20, 2.84)
American Indian	61	0.79	(0.61, 1.03)	17	1.72	(1.07, 2.78)
Asian/Pacific Islander	649	0.93	(0.86, 1.01)	78	0.87	(0.69, 1.09)
Unknown	316	1.08	(0.96, 1.21)	72	1.87	(1.48, 2.37)
Body mass index, kg/m ²						
<25	7,960	1.00	(reference)	1,070	1.00	(reference)
25–<30	7,876	1.14	(1.10, 1.17)	1,192	1.24	(1.15, 1.35)
30	6,287	1.37	(1.32, 1.42)	1,061	1.59	(1.45, 1.73)
<i>Lifestyle characteristics</i>						
Leisure Physical activity, MET ^a -hrs/week						
Inactive	3,026	1.00	(reference)	507	1.00	(reference)
<7.34	6,185	0.99	(0.95, 1.04)	970	0.95	(0.85, 1.05)
7.34–<17.5	5,905	0.94	(0.89, 0.98)	822	0.81	(0.73, 0.91)
17.5	6,036	0.95	(0.90, 0.99)	846	0.83	(0.74, 0.93)
Smoking, pack-years						
Non-smoker	11,043	1.00	(reference)	1,727	1.00	(reference)
<7	3,313	1.07	(1.03, 1.11)	493	1.00	(0.90, 1.10)
7–<24	3,669	1.12	(1.07, 1.16)	505	0.95	(0.86, 1.05)

Characteristic	Osteoarthritis, <i>n</i> =22,306			Rheumatoid Arthritis, <i>n</i> =3,348		
	Cases	HR	(95% CI)	Cases	HR	(95% CI)
24	3,561	1.10	(1.06, 1.14)	516	1.01	(0.91, 1.11)
Multivitamin use						
No	13,392	1.00	(reference)	2,170	1.00	(reference)
Yes	8,913	1.09	(1.07, 1.13)	1,177	0.90	(0.83, 0.96)
<i>Medical history</i>						
Duration of estrogen + progesterone use, years						
None	15,577	1.00	(reference)	2,446	1.00	(reference)
<5	3,325	1.09	(1.04, 1.13)	492	0.94	(0.85, 1.04)
5-<10	1,951	1.18	(1.12, 1.24)	253	0.93	(0.81, 1.06)
10-<15	1,027	1.20	(1.12, 1.28)	105	0.80	(0.66, 0.98)
15	426	1.13	(1.02, 1.25)	52	0.96	(0.73, 1.27)
Duration of unopposed estrogen use, years						
None	14,620	1.00	(reference)	2,258	1.00	(reference)
<5	2,966	1.12	(1.07, 1.17)	454	1.05	(0.95, 1.16)
5-<10	1,640	1.18	(1.12, 1.24)	230	1.01	(0.88, 1.16)
10-<15	1,209	1.13	(1.06, 1.20)	159	0.97	(0.82, 1.14)
15	1,871	1.09	(1.04, 1.15)	247	1.00	(0.87, 1.14)
History of diabetes						
No	21,328	1.00	(reference)	3,175	1.00	(reference)
Yes	959	0.99	(0.93, 1.06)	172	1.25	(1.07, 1.46)
History of heart disease						
No	17,749	1.00	(reference)	2,666	1.00	(reference)
Yes	3,329	1.18	(1.13, 1.23)	481	1.15	(1.04, 1.26)
NSAID use						
No	15,187	1.00	(reference)	2,374	1.00	(reference)
Yes	7,119	1.21	(1.17, 1.24)	974	1.04	(0.97, 1.13)
Memory loss						
None	8,973	1.00	(reference)	1,314	1.00	(reference)
Mild	11,105	1.23	(1.20, 1.27)	1,620	1.20	(1.12, 1.29)
Moderate	1,898	1.56	(1.48, 1.64)	325	1.49	(1.49, 1.90)

Characteristic	Osteoarthritis, <i>n</i> =22,306			Rheumatoid Arthritis, <i>n</i> =3,348		
	Cases	HR	(95% CI)	Cases	HR	(95% CI)
Severe	204	1.80	(1.55, 2.08)	51	2.75	(2.07, 3.66)
<i>Usual diet</i>						
Alcohol consumption, drinks/week						
0	8,527	1.00	(reference)	1,456	1.00	(reference)
>0-<0.85	4,640	1.01	(0.98, 1.05)	660	0.83	(0.76, 0.91)
0.85-<3.74	4,505	1.00	(0.96, 1.03)	604	0.78	(0.71, 0.86)
3.74	4,624	1.02	(0.98, 1.06)	624	0.81	(0.73, 0.89)
Fruit consumption, medium servings/day						
<0.994	5,564	1.00	(reference)	975	1.00	(reference)
0.994-<1.64	5,479	0.96	(0.92, 1.00)	860	0.88	(0.80, 0.97)
1.64-<2.53	5,624	0.98	(0.95, 1.02)	760	0.79	(0.72, 0.87)
2.53	5,639	1.00	(0.96, 1.04)	753	0.79	(0.72, 0.87)
Vegetable consumption, medium servings/day						
<1.261	5,508	1.00	(reference)	956	1.00	(reference)
1.261-<1.921	5,534	0.96	(0.93, 1.00)	869	0.90	(0.82, 0.98)
1.921-<2.855	5,592	0.98	(0.94, 1.02)	779	0.81	(0.73, 0.89)
2.855	5,672	1.00	(0.96, 1.04)	744	0.78	(0.71, 0.87)
Red meat consumption, medium servings/day						
<0.303	5,411	1.00	(reference)	817	1.00	(reference)
0.303-<0.562	5,549	1.01	(0.97, 1.05)	773	0.93	(0.84, 1.02)
0.562 - <0.932	5,545	1.02	(0.98, 1.06)	815	0.96	(0.87, 1.06)
0.932	5,801	1.10	(1.05, 1.14)	943	1.13	(1.02, 1.24)
Energy, calories/day						
<1,177.4	5,308	1.00	(reference)	849	1.00	(reference)
1,177.4-<1,524.56	5,380	1.01	(0.97, 1.05)	809	0.95	(0.86, 1.05)
1,524.56-<1,946.35	5,783	1.10	(1.05, 1.14)	799	0.93	(0.84, 1.02)
1,946.35	5,835	1.14	(1.09, 1.18)	891	1.03	(0.93, 1.13)

^aMetabolic Equivalent

Table 2

Associations between dietary long-chain ω -3 PUFA^a intake and osteoarthritis risk in the WHI Observational Study and Clinical Trials ($n=80,551$).

Fatty acid	Energy - adjusted quintiles of fatty acid intake					P trend ^b
	1	2	3	4	5	
N-3 fatty acids						
EPA C ₁ +DPA C ₂ +DHA C ₃ , mg/d	<56.2	56.2–90.2	90.3–132.4	132.5–203.3	>203.3	
Cases, <i>n</i>	4,444	4,501	4,444	4,423	4,494	
HR (95% CI) ^f	1.00 (reference)	1.05 (1.01, 1.10)	1.03 (0.99, 1.08)	1.02 (0.98, 1.07)	1.04 (1.00, 1.09)	0.30
HR (95% CI) ^g	1.00 (reference)	1.06 (1.01, 1.11)	1.04 (0.99, 1.09)	1.04 (1.00, 1.09)	1.04 (0.99, 1.09)	0.26
EPA (20:5ω3), mg/d	<15.4	15.4–27.2	27.3–41.1	41.1–63.2	>63.2	
Cases, <i>n</i>	4,446	4,455	4,457	4,439	4,509	
HR (95% CI) ^f	1.00 (reference)	1.04 (0.99, 1.08)	1.03 (0.98, 1.07)	1.03 (0.98, 1.07)	1.04 (1.00, 1.09)	0.12
HR (95% CI) ^g	1.00 (reference)	1.04 (0.99, 1.09)	1.04 (0.99, 1.09)	1.04 (1.00, 1.09)	1.04 (0.99, 1.09)	0.14
DPA (22:5ω3), mg/d	<6.7	6.7–10.6	10.6–15.0	15.0–21.9	>21.9	
Cases, <i>n</i>	4,478	4,377	4,450	4,464	4,537	
HR (95% CI) ^f	1.00 (reference)	1.00 (0.96, 1.05)	1.01 (0.97, 1.06)	1.02 (0.97, 1.06)	1.04 (1.00, 1.09)	0.03
HR (95% CI) ^g	1.00 (reference)	1.00 (0.95, 1.04)	1.03 (0.98, 1.08)	1.02 (0.98, 1.07)	1.04 (0.99, 1.08)	0.07
DHA (22:6ω3), mg/d	<32.4	32.4–51.4	51.4–75.8	75.8–119.5	>119.5	
Cases, <i>n</i>	4,483	4,483	4,449	4,406	4,485	
HR (95% CI) ^f	1.00 (reference)	1.04 (1.00, 1.09)	1.03 (0.98, 1.07)	1.01 (0.96, 1.05)	1.03 (0.99, 1.08)	0.62
HR (95% CI) ^g	1.00 (reference)	1.04 (0.99, 1.09)	1.03 (0.99, 1.08)	1.02 (0.98, 1.07)	1.03 (0.98, 1.08)	0.42
ALA ^h (18:3ω3), mg/d	<916.9	916.9–1,125.1	1,125.1–1,326.8	1,326.8–1,632.2	>1,632.2	
Cases, <i>n</i>	4,495	4,397	4,418	4,505	4,491	
HR (95% CI) ^f	1.00 (reference)	1.00 (0.96, 1.05)	1.01 (0.97, 1.06)	1.03 (0.98, 1.07)	1.00 (0.96, 1.04)	0.69
HR (95% CI) ^g	1.00 (reference)	1.00 (0.96, 1.05)	1.00 (0.96, 1.05)	1.02 (0.97, 1.07)	0.99 (0.95, 1.04)	>0.99
N-6 fatty acids						
LA ⁱ +AA ^j , mg/d	<8,271.1	8,271.1–9,993.2	9,993.2–11,466.8	11,466.8–13,435.0	>14,435.0	
Cases, <i>n</i>	4,470	4,417	4,392	4,476	4,551	
HR (95% CI) ^f	1.00 (reference)	1.01 (0.97, 1.05)	1.01 (0.96, 1.05)	1.02 (0.98, 1.07)	1.02 (0.97, 1.06)	0.42

Fatty acid	Energy - adjusted quintiles of fatty acid intake					P trend ^b
	1	2	3	4	5	
HR (95% CI) ^g	1.00 (reference)	1.00 (0.95, 1.05)	0.98 (0.93, 1.03)	1.00 (0.95, 1.04)	0.98 (0.94, 1.03)	0.44
LA (18:2 ω 6), mg/d	<8,180.2	8,180.2–9,9896.5	9,9896.5–11,366.9	11,366.9–13,329.8	>13,329.8	
Cases, <i>n</i>	4,475	4,410	4,398	4,464	4,559	
HR (95% CI) ^f	1.00 (reference)	1.01 (0.96, 1.05)	1.01 (0.96, 1.05)	1.01 (0.97, 1.06)	1.01 (0.97, 1.06)	0.44
HR (95% CI) ^g	1.00 (reference)	0.99 (0.95, 1.04)	0.98 (0.94, 1.03)	1.00 (0.95, 1.04)	0.98 (0.94, 1.03)	0.44
AA (20:4 ω 6), mg/d	<60.8	60.8–80.1	80.1–99.0	99.0–126.2	>126.2	
Cases, <i>n</i>	4,480	4,414	4,398	4,434	4,580	
HR (95% CI) ^f	1.00 (reference)	1.00 (0.96, 1.04)	1.01 (0.97, 1.05)	1.02 (0.98, 1.06)	1.06 (1.01, 1.10)	0.01
HR (95% CI) ^g	1.00 (reference)	0.99 (0.94, 1.03)	0.99 (0.95, 1.04)	0.99 (0.94, 1.03)	1.01 (0.97, 1.06)	0.59
Ratio of LA+AA to EPA+DPA+DHA, mg/d	<44.32	44.33–75.02	75.03–114.46	114.47–183.77	>183.77	
	4,517	4,471	4,400	4,448	4,470	
	1.00 (reference)	1.00 (0.96, 1.05)	0.98 (0.94, 1.03)	1.00 (0.96, 1.05)	0.98 (0.94, 1.03)	0.46
	1.00 (reference)	1.00 (0.96, 1.05)	0.98 (0.94, 1.03)	0.99 (0.94, 1.03)	0.97 (0.92, 1.01)	0.10

^a Polyunsaturated fat^b P trend calculated by treating ordinal categorical fatty acid variables as continuous in regression model^c Eicosapentaenoic acid^d Docosapentaenoic acid^e Docosahexaenoic acid^f Derived from Cox proportional hazards models adjusted for age (time variable), WHI study component, and energy^g Further adjusted for race/ethnicity, BMI, pack-years of smoking, multivitamin use, durations of estrogen plus progesterone and estrogen-alone use, diabetes, history of CVD, and NSAID use^h Alpha-linolenic acidⁱ Linoleic acid^j Arachidonic acid

Associations between dietary long-chain ω -3 PUFA^a intake and rheumatoid arthritis risk in the WHI Observational Study and Clinical Trials ($n=80,551$).

Table 3

Fatty acid	Energy - adjusted quintiles of fatty acid intake					P trend ^b
	1	2	3	4	5	
N-3 fatty acids						
EPA C ₁₈ +DPA C ₂₂ +DHA C ₂₂ , mg/d	<56.2	56.2–90.2	90.3–132.4	132.5–203.3	>203.3	
Cases, <i>n</i>	690	681	671	666	640	
HR (95% CI) ^f	1.00 (reference)	1.01 (0.90, 1.12)	1.00 (0.90, 1.12)	0.99 (0.89, 1.10)	0.96 (0.86, 1.07)	0.44
HR (95% CI) ^g	1.00 (reference)	1.00 (0.90, 1.12)	1.01 (0.91, 1.13)	1.03 (0.92, 1.15)	1.01 (0.90, 1.13)	0.72
EPA (20:5 ω 3), mg/d	<15.4	15.4–27.2	27.3–41.1	41.1–63.2	>63.2	
Cases, <i>n</i>	666	701	662	677	642	
HR (95% CI) ^f	1.00 (reference)	1.08 (0.96, 1.20)	1.02 (0.91, 1.14)	1.04 (0.93, 1.16)	0.99 (0.89, 1.11)	0.72
HR (95% CI) ^g	1.00 (reference)	1.07 (0.96, 1.20)	1.04 (0.93, 1.16)	1.09 (0.98, 1.22)	1.03 (0.92, 1.16)	0.51
DPA (22:5 ω 3), mg/d	<6.7	6.7–10.6	10.6–15.0	15.0–21.9	>21.9	
Cases, <i>n</i>	704	667	657	630	690	
HR (95% CI) ^f	1.00 (reference)	0.96 (0.86, 1.08)	0.95 (0.85, 1.06)	0.91 (0.82, 1.02)	1.01 (0.91, 1.13)	0.82
HR (95% CI) ^g	1.00 (reference)	0.97 (0.87, 1.08)	0.96 (0.86, 1.07)	0.93 (0.83, 1.04)	1.00 (0.90, 1.12)	0.81
DHA (22:6 ω 3), mg/d	<32.4	32.4–51.4	51.4–75.8	75.8–119.5	>119.5	
Cases, <i>n</i>	696	684	676	662	630	
HR (95% CI) ^f	1.00 (reference)	1.00 (0.90, 1.11)	1.00 (0.89, 1.11)	0.98 (0.88, 1.09)	0.93 (0.84, 1.04)	0.21
HR (95% CI) ^g	1.00 (reference)	0.98 (0.88, 1.10)	1.00 (0.89, 1.12)	1.02 (0.91, 1.14)	0.99 (0.88, 1.11)	0.93
ALA ^h (18:3 ω 3), mg/d	<916.9	916.9 – 1,125.1	1,125.1 – 1,326.8	1,326.8 – 1,632.2	>1,632.2	
Cases, <i>n</i>	625	655	659	707	702	
HR (95% CI) ^f	1.00 (reference)	1.06 (0.95, 1.19)	1.07 (0.95, 1.20)	1.14 (1.02, 1.28)	1.11 (1.00, 1.24)	0.03
HR (95% CI) ^g	1.00 (reference)	1.03 (0.91, 1.15)	0.97 (0.86, 1.09)	1.04 (0.92, 1.16)	1.00 (0.89, 1.12)	0.98
N-6 fatty acids						
LA ⁱ +AA ^j , mg/d	<8,271.1	8,271.1–9,993.2	9,993.2–11,466.8	11,466.8–13,435.0	>13,435.0	
Cases, <i>n</i>	632	623	646	697	750	
HR (95% CI) ^f	1.00 (reference)	0.99 (0.88, 1.10)	1.02 (0.91, 1.15)	1.09 (0.98, 1.23)	1.16 (1.04, 1.30)	0.001

Fatty acid	Energy - adjusted quintiles of fatty acid intake					P trend ^b
	1	2	3	4	5	
HR (95% CI) ^g	1.00 (reference)	0.95 (0.84, 1.06)	0.93 (0.83, 1.05)	0.95 (0.84, 1.07)	0.96 (0.85, 1.08)	0.64
LA (18:2 ω 6), mg/d	<8,180.2	8,180.2–9,989.5	9,989.5–11,366.9	11,366.9–13,329.8	>13,329.8	
Cases, <i>n</i>	631	629	642	697	749	
HR (95% CI) ^f	1.00 (reference)	0.99 (0.89, 1.11)	1.01 (0.90, 1.14)	1.09 (0.98, 1.23)	1.16 (1.04, 1.30)	0.002
HR (95% CI) ^g	1.00 (reference)	0.96 (0.85, 1.08)	0.93 (0.82, 1.04)	0.95 (0.84, 1.07)	0.96 (0.85, 1.08)	0.59
AA (20:4 ω 6), mg/d	<60.8	60.8–80.1	80.1–99.0	99.0–126.2	>126.2	
Cases, <i>n</i>	654	630	635	663	766	
HR (95% CI) ^f	1.00 (reference)	0.96 (0.86, 1.08)	0.98 (0.88, 1.10)	1.02 (0.91, 1.14)	1.19 (1.07, 1.33)	<0.001
HR (95% CI) ^g	1.00 (reference)	0.93 (0.83, 1.04)	0.91 (0.81, 1.02)	0.92 (0.82, 1.04)	1.00 (0.89, 1.12)	0.94
Ratio of LA+AA to EPA+DPA+DHA, mg/d	<44.32	44.33–75.02	75.03–114.46	114.47–183.77	>183.77	
Cases, <i>n</i>	656	653	633	693	713	
HR (95% CI) ^f	1.00 (reference)	0.99 (0.88, 1.10)	0.96 (0.86, 1.07)	1.04 (0.93, 1.16)	1.05 (0.94, 1.17)	0.21
HR (95% CI) ^g	1.00 (reference)	0.98 (0.87, 1.09)	0.90 (0.80, 1.01)	0.95 (0.85, 1.07)	0.96 (0.86, 1.07)	0.43

^a Polyunsaturated fat^b P trend calculated by treating ordinal categorical fatty acid variables as continuous in regression models^c Eicosapentaenoic acid^d Docosapentaenoic acid^e Docosahexaenoic acid^f Derived from Cox proportional hazards models adjusted for age (time variable), WHI study component, and energy^g Further adjusted for education, race/ethnicity, BMI, memory loss, and fruit intake^h Alpha-linolenic acidⁱ Linoleic acid^j Arachidonic acid

Table 4

Associations between dietary LCn-3PUFA^a intake and arthritis risk, stratified by BMI (in kg/m²) and arthritis type in the WHI Observational Study and Clinical Trials (*n*=80,551).

	Energy adjusted quintiles of EPA ^b + DPA ^c + DHA ^d , mg/d					<i>P</i> trend ^e
	<56.2	56.2 – 90.2	90.3 – 132.4	132.5 – 203.3	>203.3	
Osteoarthritis						
BMI<25.0 kg/m ²						
Cases, <i>n</i>	1,512	1,587	1,581	1,602	1,678	
HR (95% CI) ^h	1.00 (reference)	1.03 (0.96, 1.11)	1.02 (0.95, 1.11)	1.05 (0.98, 1.14)		0.26
BMI 25.0-29.9						
Cases, <i>n</i>	1,488	1,632	1,610	1,592	1,554	
HR (95% CI) ^h	1.00 (reference)	1.11 (1.03, 1.20)	1.10 (1.01, 1.18)	1.07 (0.99, 1.16)		0.19
BMI 30						
Cases, <i>n</i>	1,408	1,246	1,223	1,184	1,226	
HR (95% CI) ^h	1.00 (reference)	1.04 (0.95, 1.13)	1.03 (0.95, 1.12)	1.01 (0.92, 1.10)	0.98 (0.90, 1.07)	0.52
						<i>P</i> _{Interaction} ^g = 0.71
Rheumatoid arthritis						
BMI<25.0 kg/m ²						
Cases, <i>n</i>	217	212	215	223	203	
HR (95% CI) ^h	1.00 (reference)	0.96 (0.79, 1.17)	0.99 (0.81, 1.20)	1.03 (0.85, 1.25)	0.95 (0.78, 1.16)	0.86
BMI 25.0-29.9						
Cases, <i>n</i>	226	246	244	247	229	
HR (95% CI) ^h	1.00 (reference)	1.05 (0.87, 1.27)	1.07 (0.88, 1.29)	1.14 (0.95, 1.38)	1.09 (0.90, 1.32)	0.25
BMI 30						
Cases, <i>n</i>	242	218	207	190	204	
HR (95% CI) ^h	1.00 (reference)	0.99 (0.81, 1.20)	0.98 (0.81, 1.20)	0.91 (0.75, 1.12)	0.98 (0.81, 1.20)	0.63
						<i>P</i> _{Interaction} ^g = 0.87

^aLong-chain omega-3 fatty acids

^bEicosapentaenoic acid

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c_p Docosapentaenoic acid
 p_p Docosahexaenoic acid

p trend calculated by treating ordinal categorical fatty acid variables as continuous in regression models

f_j Derived from Cox proportional hazards models adjusted for age (time variable), WHI study component, energy, race/ethnicity, BMI, pack-years of smoking, multivitamin use, durations of estrogen plus progesterone and estrogen-alone use, diabetes, history of CVD, and NSAID use

g_p p interaction calculated by likelihood ratio test

h_j Derived from Cox proportional hazards models adjusted for age (time variable), WHI study component, energy, education, race/ethnicity, BMI, memory loss and fruit intake