



The relationship between fish consumption and rheumatoid arthritis; a systematic review and meta-analysis

Moloud Fakhri¹, Hossein Azadeh², Assie Jokar³, Mahmood Moosazadeh⁴, Hafez Fakheri⁵, Melina Ramezanzpour⁶

¹Traditional and Complementary Medicine Research Center, Addiction Institute, Mazandaran University of Medical Sciences, Sari, Iran

²Department of Internal Medicine, Rheumatology Division, Orthopedic Research Center, Mazandaran University of Medical Sciences, Sari, Iran

³Persian Medicine Department, Traditional and Complementary Medicine Research Center, Addiction Institute, Mazandaran University of Medical Sciences, Sari, Iran

⁴Gastrointestinal Cancer Research Center, Non-communicable Diseases Institute, Mazandaran University of Medical Sciences, Sari, Iran

⁵Gut and Liver Research Center, Non-communicable Disease Institute, Mazandaran University of Medical Sciences, Sari, Iran

⁶Medical School, Mazandaran University of Medical Sciences, Sari, Iran

*Correspondence to

Moloud Fakhri,

Email: mmfir@yahoo.com, m.fakhri@mazums.ac.ir and Hossein Azadeh, Email: hosein.azade@gmail.com, hosein.azade@yahoo.com

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Abstract

Introduction: Rheumatoid arthritis is a chronic autoimmune disease with numerous side effects. Since long ago, the impact of fish consumption on treating this disease has been of researchers' interest. Hence, this study aims to examine the relationship between fish consumption and the risk of rheumatoid arthritis through a systematic review and a meta-analysis method.

Materials and Methods: For this meta-analysis to reach the research related to the case study, the following databases: PubMed, Scopus, Web of Science, Cochrane, and the Google Scholar search engine were conducted. The data were analyzed using the STATA 14, and the significance level of the tests was $P < 0.05$.

Results: There were 2166980 people (20218 cases and 2146762 controls) in this case study, and the age range of the patients was between 18 and 89. The studies were published between 1991 and 2022 and estimated the odds ratio (OR) of fish consumption and rheumatoid arthritis as (OR=0.83; 95% CI: 0.78, 0.89). This measure was (OR=0.79; 95% CI: 0.72, 0.87) in six case-control studies and (OR=0.86; 95% CI: 0.78, 0.94) in 7 cohort studies. In addition, the effect of fish consumption on reducing the rheumatoid arthritis development was more in people who had consumed fish 2 or less than 2 times a week compared to people who consumed fish more than 2 times every week.

Conclusion: Fish consumption reduces the rheumatoid arthritis extension; therefore, these patients are advised to include fish in their diet.

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Introduction

Rheumatoid arthritis is the most common autoimmune arthritis whose incidence is up to one percent (1). In this disease, the interaction between the genetic and environmental factors can lead to autoimmunity (2). Rheumatoid arthritis is diagnosed by synovial inflammation, which causes pain, functional dysfunction, and joint erosion. It significantly affects the patient's physical, emotional, and social activity. It can also lead to cardiovascular disease, severe inability and premature death (3).

The standard treatment of this disease includes disease-modifying antirheumatic drugs, which can reduce systematic inflammation, improve the symptoms and

Key point

There were 2166980 people (20218 cases and 2146762 controls) in this case study, and the age range of the patients was between 18 and 89. The studies were published between 1991 and 2022 and estimated the odds ratio of fish consumption and rheumatoid arthritis as [OR=0.83 (95% CI: 0.78, 0.89)]. This measure was [OR=0.79 (95% CI: 0.72, 0.87)] in six case-control studies and [OR=0.86 (95% CI: 0.78, 0.94)] in seven cohort studies. In addition, the effect of fish consumption on reducing the rheumatoid arthritis risk factor was more in people who had consumed fish two or less than two times a week compared to people who consumed fish more than two times every week.

prevent long-term joint injuries (4,5). However, these drugs come with many side effects (6). Therefore, researchers are now looking for other methods. The diet pattern

called “the western diet” can increase rheumatoid arthritis development in two ways: on the one hand, directly by amplifying the inflammation, and on the other hand, indirectly and by increasing resistance to insulin and fatness (7). On the contrary, fish consumption can reduce rheumatoid arthritis progression because of the anti-inflammatory properties of Omega-3 polyunsaturated fatty acids (PUFAs) (8).

Various studies have evaluated the relationship between fish consumption and rheumatoid arthritis, but the results have been contradictory (9-12). In a study published by Ariza-Ariza and colleagues to examine the background, medicinal properties, action mechanism, and the clinical experience of using Omega-3 PUFAs to treat rheumatoid arthritis, it was concluded that treatment with Omega-3 unsaturated fatty acids could improve some measurements taken for rheumatoid arthritis treatment. The researchers said further was needed to see whether treatment with Omega-3 unsaturated fatty acids can replace non-steroidal anti-inflammatory drugs in particular circumstances or not (13).

Some previous studies have concluded that fish consumption does not affect rheumatoid arthritis, and some have considered fish consumption a factor that can improve rheumatoid arthritis disease. Therefore, the present study examines the relationship between fish consumption and the risk of rheumatoid arthritis through a systematic review and meta-analysis. Of course, a meta-analysis study on this topic was published in 2014 (14) and showed that fish consumption does not affect rheumatoid arthritis. However, since 2014, numerous studies have been conducted on this topic; we therefore decided to conduct a new meta-analysis on this topic to be able to evaluate this issue more comprehensively.

Materials and Methods

Study design

The present study is a meta-analysis examining the relationship between fish consumption and rheumatoid arthritis. The present study is written based on the PRISMA statement on the systematic review and meta-analysis studies.

Studies outcomes

The most crucial purpose was to examine the relationship between fish consumption and the rheumatoid arthritis development.

Search strategy

In this meta-analysis, the following international databases were used without time or language limits: PubMed, Scopus, Web of Science, Cochrane, and the Google Scholar search engine. The research was done using the following valid keywords: [Rheumatoid Arthritis; Arthritis, Rheumatoid; Autoimmune Diseases; Fishes, and their Persian equivalents and Mesh.] (Updated until 02/05/2022). Also,

the combination of keywords was searched in the databases using the (AND and OR) operators. The reference list of every preliminary study that entered the meta-analysis was searched to operate a manual search. The search strategy in the PubMed database is shown below as an example: (((Rheumatoid Arthritis[Title/Abstract]) OR (Arthritis, Rheumatoid[Title/Abstract])) OR (Autoimmune Diseases[Title/Abstract])) AND (Fishes[Title/Abstract]).

PICO (population–intervention–comparison–outcome) components

Study population: rheumatoid arthritis patients; Intervention: rheumatoid arthritis patients who had fish alongside their routine treatment; Comparison: rheumatoid arthritis patients under regular treatment; Outcome: the odds ratio (OR) between fish and rheumatoid arthritis.

Inclusion criteria

In this meta-analysis, cohort and case-control studies that examined the effect of fish consumption on rheumatoid arthritis entered.

Exclusion criteria

Studies that explained the effect of fish consumption on rheumatoid arthritis qualitatively, studies that demonstrated the effect of fish oil consumption on rheumatoid arthritis, the low- quality of the studies based on the quality control checklist, case report studies, absence of the report of the needed information to analyze the data, lack of the complete text of some of the studies.

Qualitative assessment of studies

The two independent researchers evaluated the quality of the studies from different methodological perspectives using the STROBE (strengthening the reporting of observational studies in epidemiology) checklist (15). The STROBE checklist has 22 sections that cover other parts of a report, and the scoring of this report is maximally 44. Scores 1-15 indicate poor quality, scores 16-30 indicate mediocre quality, and scores 31-44 indicate excellent quality. The cutoff point of this study is considered 15. Then all matters of disagreement were introduced to a single point using the agreement of the two previous authors.

Data extraction

First, a form was designed. After completing this form based on at least one study, to ensure the quality of the predicted data, two copies of this were made and were presented to two reviewers per each primary study. The researchers entered the extracted data into a checklist, including the name of the researcher, type of study, subject of the study, the year of the study, place of the study, the age range of the patients, the duration of the fish consumption, the dose of fish consumption, the total number of the samples,

number of the men and women, the OR factors between fish consumption and rheumatoid arthritis and its upper and lower limits. The third researcher also examined the data extracted by the other two previous researchers to remove the deficiencies in case of discrepancy.

Statistical analysis

To examine the relationship between fish consumption and rheumatoid arthritis extension, the OR was conducted. To combine the conclusions of the studies, the OR logarithm was used in each study, and the I^2 index and the Q statistics were used to examine the heterogeneity between studies. Because this meta-analysis had a medium heterogeneity ($I^2=30.3\%$), the random effect model was employed. The data were analyzed using STATA 14 software. The significance level of the tests was $P<0.05$.

Results

In the first stage, 495 articles were found. With the examination of the subjects of the articles, 206 repeated articles were deleted. The abstracts of the papers were studies, and another seven of them were deleted since their full texts were unavailable. Another 283 articles were deleted because of other output criteria. In the end, 12 articles entered the quality evaluation phase, all of which had the desirable quality, and the meta-analysis phase (Figure 1).

In the 13 studies under examination with a sample of 2166980 people whose studies were published in 1991-2022, the age range of the patients was 18-89. Around 20218 of these people were in the case group, and 2146762 were in the control group. It should be noted that six of these 13 studies were case-control and seven were cohort studies (Table 1).

Figure 2 shows that fish consumption reduces the rheumatoid arthritis development (OR=0.83; 95% CI: 0.78, 0.89), and this relationship is statistically significant. Fish consumption reduces the rheumatoid arthritis progression by 17%. In the analysis based on the type of studies, we realized that the OR between fish consumption and rheumatoid arthritis was (OR=0.86; 95% CI: 0.78, 0.94) in the cohort studies and (OR=0.79; 95% CI: 0.72, 0.87) in case-control studies. In both studies, fish consumption had reduced the rheumatoid arthritis extension.

The relationship between fish consumption and rheumatoid arthritis based on the place of study, amount of fish consumption, and the place where the study was conducted can be found in Table 2. On the other hand, the case studies were related to England, America, France, Japan, China, Denmark, Sweden, and Greece, and the information on the other countries was unavailable.

Discussion

This meta-analysis showed that fish consumption

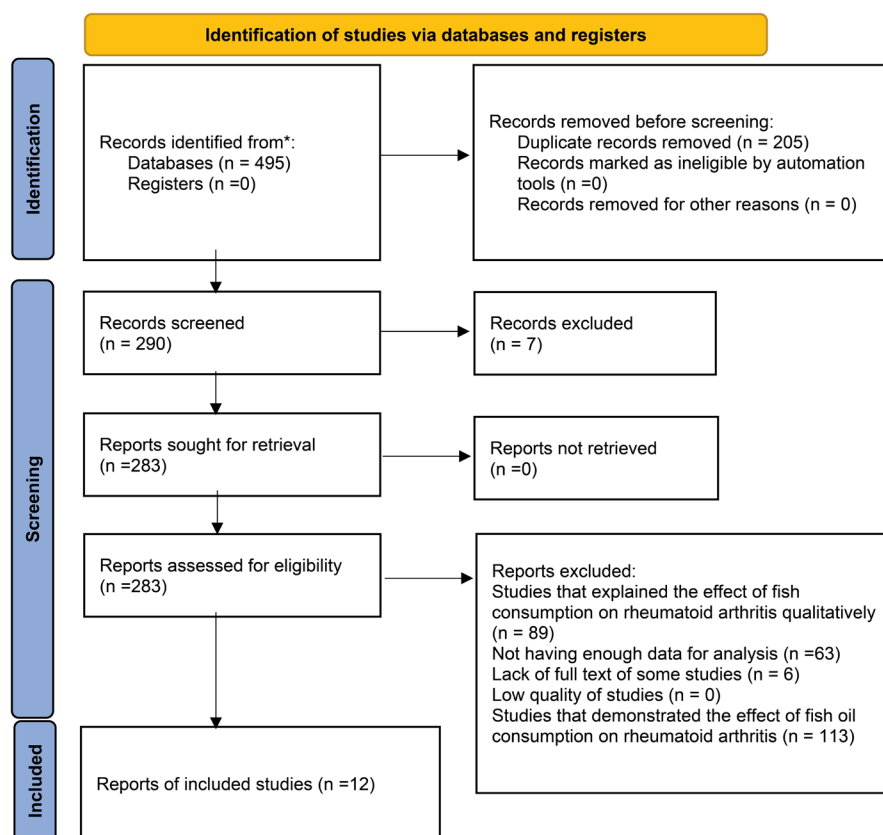


Figure 1. The process of entering the studies into the systematic review and meta-analysis.

Table 1. Information of articles entered into the meta-analysis process

First author, year	Country	Type of study	Mean age (y)	No. of cases	No. of control	Time	Duration, years	Dosage	Compared
Mazzucca, 2022 (9)	UK	Cohort	40-69	2819	476 675	In 2006 (pilot phase) and 2007–2010 (main phase)	8.15	Less than once a week	Compared to no consumption,
Mazzucca, 2022 (9)	UK	Cohort	40-69	2819	476 675	In 2006 (pilot phase) and 2007–2010 (main phase)	8.15	Once a week	Compared to no consumption,
Mazzucca, 2022 (9)	UK	Cohort	40-69	2819	476 675	In 2006 (pilot phase) and 2007–2010 (main phase)	8.15	At least two times a week	Compared to no consumption,
Nguyen, 2022 (10)	France	Cohort	52.5	480	62 149	Since 1990	-	1 to 2 servings/week	Compared with low fish consumption
Nguyen Y, 2022 (10)	France	Cohort	52.5	480	62 149	Since 1990	-	>1 to 2 servings/week	Compared with low fish consumption
Minamino, 2021(16)	Japan	Cohort	53-71	306	-	Between 1st May and 31st December 2014	9	> 2 times/week	Two times/week or less
Sparks, 2019 (17)	USA	Cohort	25-55	1080	164 933	(NHS, 1984–2014) and NHSII (1991–2015)		≥4 servings/week	< 1 serving/month
He, 2016 (18)	China	Case-Control	52.1	968	1037	Between May 2012 and September 2013	2	High intakes of fish	-
Sundstrom, 2015(19)	Sweden	Case-Control	58	386	1886	-	-	Moderate intakes of fish	-
Sundström B, 2015(19)	Sweden	Case-Control	58	386	1886	-	-	High intakes of fish	-
Di Giuseppe, 2014 (14)	Sweden	Cohort	≤63, 64–71 and ≥72	205	-	1 January 2003 to 31 December 2010	7.5	≥1 serving per week	Compared with<1
Rosell, 2009 (20)	Sweden	Case-Control	18-70	1899	2145	Between May 1996 and December 2005	-	1–3 Times/Month	Compared to no consumption,
Rosell, 2009 (20)	Sweden	Case-Control	18-70	1899	2145	Between May 1996 and December 2005	-	1–7 Times/Week	Compared to no consumption,
Benito-Garcia, 2007 (21)	USA	Cohort	30–55	546	82 063	From 1980 to 2002	-	0.13 s/d	-
Benito-Garcia, 2007 (21)	USA	Cohort	30–55	546	82 063	From 1980 to 2002	-	0.17 s/d	-
Benito-Garcia, 2007 (21)	USA	Cohort	30–55	546	82 063	From 1980 to 2002	-	0.25 s/d	-
Benito-Garcia, 2007 (21)	USA	Cohort	30–55	546	82 063	From 1980 to 2002	-	0.44 s/d	-
Pedersen, 2005 (22)	Denmark	Cohort	50-64	69	56 691	Between 1993 and 1997	5.3	30 g/day	-
Linos, 1999 (23)	Greece	Case-Control	18-80	145	188	-	-	4 servings/week	-
Linos, 1999 (23)	Greece	Case-Control	18-80	145	188	-	-	6 servings/week	-
Linos, 1999 (23)	Greece	Case-Control	18-80	145	188	-	-	10 servings/week	-
Shapiro, 1996 (12)	USA	Case-Control	18-64	324	1245	1986-1991	-	1- <2 servings/week	<1 servings/week
Shapiro, 1996 (12)	USA	Case-Control	18-64	324	1245	1986-1991	-	≥ 2 servings/week	<1 servings/week
Linos, 1991 (11)	Greece	Case-Control	24-89	168	137	-	-	4-10 servings/Month	1-2 servings/Month
Linos, 1991 (11)	Greece	Case-Control	24-89	168	137	-	-	>12 servings/Month	1-2 servings/Month

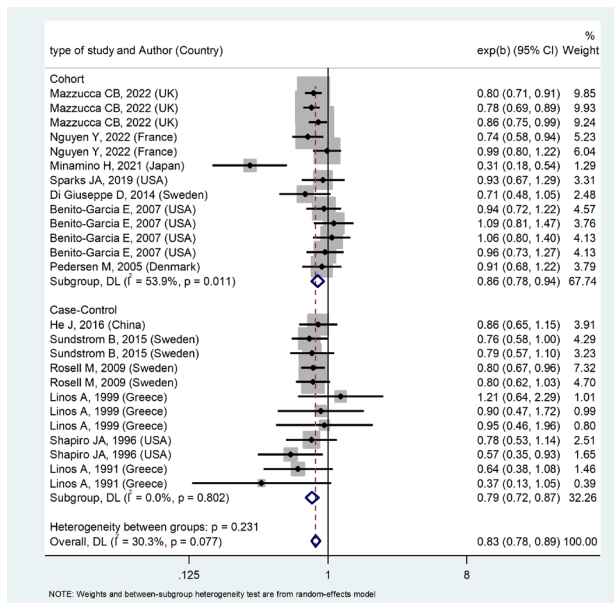


Figure 2. Odds ratio between fish consumption and rheumatoid arthritis development.

reduces the rheumatoid arthritis development, and this relationship is statistically significant (OR=0.83; 95% CI: 0.78, 0.89). As we saw in the analysis of the subgroups, the influence of fish consumption on reducing the rheumatoid arthritis progression has been less in case-control studies compared with the cohort studies. In addition, the effect of fish consumption on reducing the rheumatoid arthritis extension was more in people who had consumed fish 2 or less than 2 times a week compared to people who consumed more than 2 every week. Even though in both cases, fish consumption had significantly reduced the rheumatoid arthritis development. These results showed that consuming a high dose of fish may not influence rheumatoid arthritis greatly.

In five of eight of the examined countries, the relationship between fish consumption and rheumatoid arthritis was not significant and only in England (OR=0.81; 95% CI: 0.75, 0.88), Japan (OR=0.31; 95% CI: 0.18, 0.54), and

Sweden (OR=0.78; 95% CI: 0.80, 0.88) fish consumption reduced the rheumatoid arthritis progression. Lack of uniform distribution in the examined countries, differences in dose, and the type of consumed fish can explain why the results differ.

Chen and colleagues conducted a study to evaluate the effect of red meat on Rheumatoid arthritis using the meta-analysis method. This meta-analysis consisted of four cohort and seven case-control studies. Based on the conclusions of this study, the rheumatoid arthritis extension for people who consume red meat all the time was 0.94 (95% CI: 0.77 to 1.15) compared with those who do not consume red meat or only sometimes consume it. A high dose of red meat increased the rheumatoid arthritis progression (OR: 1.26, 95% CI: 1.07 to 1.50) (24). Di Giuseppe and colleagues examined the relationship between fish consumption and rheumatoid arthritis development in a meta-analysis, which included 7 studies (4 case-control studies and 3 prospective studies), 174701 participants and 3346 case studies. Based on their conclusion, for each meal of fish consumption in a week, the relative risk (RR) of the rheumatoid arthritis extension was 0.96 (95% CI: 0.91 to 1.01). Besides, RR of the rheumatoid arthritis progression was 0.76 (95% CI: 0.57 to 1.02) for 1 to three meals a week. This meta-analysis did not indicate a significant relationship between fish consumption and rheumatoid arthritis (14).

The conclusions of the current meta-analysis contradict the previous meta-analysis. The conclusion of the studies published in 2014-2022 might be responsible for this contradiction. Since our study is more comprehensive than the previous research, the present conclusion is, to some extent, more reliable. In a meta-analysis of the findings of rheumatoid arthritis patients, Barkoot and colleagues showed that omega 3's PUFAs have a significant influence on non-steroidal anti-inflammatory drug (NSAID) consumption (Standardized mean differences -0.52, 95% CI: -0.92 to -0.12, $P = 0.01$) and pain (Standardized mean differences -0.55, 95% CI: 0.17-0.027, $P = 0.57$). Hence, consuming omega 3's PUFAs in doses higher

Table 2. Relationship between fish consumption and rheumatoid arthritis based on the sub-groups under examination

Subgroup	OR	Low- OR	Up- OR	P-value	I ² (%)
Total	0.83	0.78	0.89	0.077	30.3
Type of study					
Cohort	0.86	0.78	0.94	0.011	53.9
Case-control	0.79	0.72	0.87	0.802	0
Dosage					
≤ 2 time per week	0.77	0.70	0.85	0.981	0
>2 time per week	0.81	0.68	0.95	0.019	53.2
Countries					
UK	0.81	0.75	0.88	0.582	0
France	0.86	0.65	1.14	0.072	69.2
Japan	0.31	0.18	0.54	---	0
USA	0.94	0.83	1.06	0.357	9.4
China	0.86	0.65	1.15	---	0
Sweden	0.78	0.70	0.88	0.984	0
Denmark	0.91	0.68	1.22	---	0
Greece	0.81	0.58	1.12	0.313	15.9

than 2/7 daily for more than 3 months effectively reduces consuming NSAIDs in rheumatoid arthritis patients (25). Lee and colleagues conducted a meta-analysis to evaluate the effects of omega 3 PUFAs on the clinical results of rheumatoid arthritis patients. In the 10 clinical trials studied in this research, which included 183 rheumatoid arthritis patients in the Intervention group and 187 rheumatoid arthritis patients in the control group (under placebo treatment), the results showed that consuming omega 3 PUFAs in doses higher than 2/7 daily and for more than three months decreases the consumption of non-steroidal anti-inflammatory drugs in rheumatoid arthritis patients (26). The results of the current meta-analysis are in line with these two meta-analyses and are a confirmation of the present meta-analysis.

Gioxari and colleagues conducted research that included 20 RCT studies (717 rheumatoid arthritis patients were in the intervention group, and 535 rheumatoid arthritis patients were in the control group). The results indicated that despite some evidence suggesting the low- quality of the trials, consuming omega 3 PUFAs can improve the symptoms indicating the disease's action (27). A meta-analysis conducted by Fortin et al, which aimed to determine the effectiveness of fish oil in rheumatoid arthritis showed that consuming fish oil supplement in the diet for three months can reduce the number of sensitive joints (rate difference = -2.9; 95% CI: -3.8 to -2.11, $P = 0.001$) morning dryness (rate difference = -25.9; 95% CI: -44.3 to -7.51, $P < 0.01$) significantly compared to the control group (28). As you can see in this research, even consuming fish oil supplements can improve the symptoms of rheumatoid arthritis and reduce its extension.

Conclusion

In this meta-analysis, we realized that fish consumption could reduce rheumatoid arthritis development, and consuming higher doses compared to lower doses less influences the disease progression. It is advised that studies in this field will be conducted in Asian countries like Iran, India and Iraq. The results should be evaluated based on different sub-groups like age group, gender, consumption dose, and the fish type therefore the limitations of the meta-analysis are removed, and we can have more detailed results.

Limitations of the study

(A) Since there was considerable overlap between the patients' age groups, we did not have an analysis based on the age group because we could not code the age group variable. (B) Since the studies did not report the OR factor based on gender, we were also unable to analyze based on the patient's sex. (C) The type of fish and how it was cooked were not reported in the studies. (D) In some of the studies, the duration of fish consumption was not indicated, thereby we did not manage to analyze based on "consumption duration."

Authors' contribution

Conceptualization: AJ, HF, HA, MM and MF.

Methodology: MF, HA and MM.

Formal analysis: HA and MF.

Resources: MF.

Writing—original draft preparation: All authors.

Writing—review and editing: All authors.

Funding Acquisition: MF.

Conflicts of interest

The authors declare that they have no conflict of interest regarding the contents of this article.

Ethical issues

This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (International Prospective Register of Systematic Reviews) website (ID: CRD42022332694, https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022332694). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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