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A systematic review and meta-analysis of observational studies on the association between animal protein sources and risk of rheumatoid arthritis

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Running title: Animal protein and rheumatoid arthritis

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Abstract

Objective: The aim of this study was to investigate the linear and nonlinear dose-response associations of animal-based dietary protein intake and risk of developing rheumatoid arthritis (RA).

Methods: A systematic search of MEDLINE, Scopus and Embase was conducted up to October 2020. Observational studies that report risk estimates of RA for animal-based protein consumption were included. We calculated pooled relative risks (RRs) by using a random-effects model. Linear and non-linear dose-response analyses were performed to examine the dose-response relations between animal-based protein consumption and RA.

Results: Seven cohort studies (n = 457,554) with 3,545 incident cases and six case-control studies with 3,994 cases and 5,252 controls were identified. Highest compared with the lowest category of fish consumption was inversely associated with risk of RA (RR: 0.89; 95% CI, 0.80 to 0.99; $I^2 = 0\%$, n=10). Also, a 100 g/day increment in fish intake was associated with a 15% decreased risk of RA. Dose-response analysis showed a modest U-shaped association between fish consumption and incidence of RA, with the lowest risk at a fish intake of 20-30 g/day ($P_{\text{non-linearity}} = 0.04$). We found no significant association between consumption of red meat, poultry or dairy and the risk of RA.

Conclusion: The present study revealed a significant reverse association between fish consumption and risk of RA. While we observed no association between red meat, dairy or poultry consumption and risk of RA. Further well-designed prospective studies are needed to support our findings.

Keywords: rheumatoid arthritis, animal protein, fish, meta-analysis
Introduction

Rheumatoid arthritis (RA) is a chronic disease characterized by systemic inflammation and progressive erosion of the joints (1). Pain and functional limitations are the most common complications of RA and significant causes of morbidity and mortality in these patients (2). RA affects around 0.5–1.0% of adults in developed countries, with a yearly incidence of 5-50 cases per 100,000 individuals (3).

Both genetic and environmental factors have a role in the pathogenesis of RA (4-10). However, the exact pathogenesis is not yet fully known (1). An unhealthy diet may be involved in the development of RA, as well as following a healthy diet is a protective factor (3, 9, 10). Dietary protein is an essential nutrient for the production of hormones and enzymes, fluid balance, blood clotting, vision and cell repair (11). The current Recommended Daily Allowance (RDA) for protein is 0.8–1.2 g/kg bodyweight per day for both younger and older adults (12). The choice of protein sources can inevitably affect health outcomes by affecting other components of the diet, including phytochemicals, nutrients and micronutrients. Although research into this field is relatively recent, studies have indicated that there might be potential differences in the association between intake of either animal- or plant-based dietary proteins and the risk of type II diabetes, cardiovascular disorder, and all-cause mortality, with some suggestions of a beneficial effect of plant-based dietary protein sources and detrimental effect of animal-based protein sources (13-16). Studies have suggested that higher consumption of red meat and total proteins, and lower consumption of fruits, vegetables and vitamin C may be associated with a higher risk of RA (17). It has been reported that there is an inverse association between dietary intake of mushrooms, beans, citrus fruits, poultry, fish and dairy products and the risk of RA (18). In two
case reports, dairy products, especially milk, have been suggested as risk factors for developing RA due to hypersensitivity reactions (19, 20).

A case-control study, by Pattison et al., suggested that a higher intake of red meat is associated with increased risk of inflammatory arthritis (21). However, in a large cohort of women, dietary intake of red meat and dairy were not related to the risk of RA (22). Also, a dose-response meta-analysis from 2014 showed a non-statistically significant negative association between fish intake and RA (23).

To our knowledge, there is no study that attempted to quantitatively synthesize the evidence on the relationship between different animal-based dietary protein sources and risk of RA in the general population. This study was therefore performed to quantify the associations using a dose-response meta-analysis of observational studies.

**Methods**

The present study was reported based on the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guideline (24).

**Search strategy**

A comprehensive systematic search was conducted up to October 2020 in MEDLINE (via PubMed), Scopus and Embase (via. Ovid) for observational studies that examined the association between dietary intake of animal protein and incidence of RA. Search strategies, including the key terms and the queries for each database, are presented in the supplementary Table 1. No limitation on language or time of publication were applied. We also checked the reference lists of eligible studies and recent reviews.

**Inclusion and exclusion criteria**
Publications were included in our synthesis if they were observational studies, conducted in the general population, and reported effect sizes including hazard ratios (HR), relative risks (RR) or odds ratios (OR) with corresponding 95% confidence intervals (CIs) for the relationship between intake of animal-based dietary proteins as the exposure of interest, and RA as the outcome of interest. Animal-based dietary proteins were categorized as fish (such as tuna, shellfish, and shrimps), poultry (such as chicken and turkey), dairy (such as milk, yoghurt, cheese, cream), or red meat (such as beef, lamb, pork, unprocessed red meat, and processed meat including various kinds of sausages, cold cuts, liver pate and bacon). Animal studies, reviews, meta-analyses, letters, comments, cross-sectional and ecological studies were excluded.

**Study selection and data abstraction**

The screening of titles and abstracts and the subsequent full-text assessment were conducted by two independent authors (FA and ZK). We also checked the reference lists of included studies and recent reviews. Disagreements were resolved through discussion by third author (HM). Two authors (FA and ZK) extracted the following data from included studies: first author’s name, publication year, country, age range or mean age of the participants, gender, follow-up period, number of cases, number of participants (cohort studies) or controls (case-control studies), exposure assessment method, exposure type, comparison, the maximally adjusted ORs, RRs or HRs with corresponding 95% CIs and covariates that were adjusted for in the statistical analysis. Accuracy of extracted data from each study was checked by third author (HM).

**Statistical analysis**

RRs and 95% CIs were used as the effect size for all studies. We considered the reported HRs in cohort studies equal to RRs (25). Since the outcome is rare (average event rate in included cohort studies: 0.75%), the ORs were considered equal to RR. Meta-analyses were conducted separately.
according to different animal-based dietary protein sources, including red meat, fish, poultry, and dairy, when at least two studies were available. For the main analyses, the reported effect sizes for the highest compared with the lowest category of animal-based dietary protein sources were combined. In the analyses, random-effects models or fixed-effects models were performed using maximally adjusted OR or RR with corresponding 95% CI (26). Random-effects models were used when there was significant heterogeneity between studies and fixed-effects model when heterogeneity was negligible (less than 50%). For studies that reported continuous estimation from the associations, we converted per-unit increment risk estimates to the high compared with the low RR by using the average difference between the midpoints of the upper and lower categories in other studies included in the analysis. Between-studies heterogeneity was evaluated by $I^2$ (27). There was between-study heterogeneity if the $I^2$ value was greater than 50% and $p<0.1$ for the result of the Q test (27). We combined cohort and case-control studies in the main analyses, and we performed subgroup analysis by study design to determine whether the results have been influenced by study design. Publication bias was examined using Egger’s test and Begg’s test and visual inspection of funnel plot (28, 29). Also, we used trim-and-fill method to detect the effect of probable missing studies on the overall effect. Sensitivity analysis was conducted to evaluate the effect of removing any of the studies or group of studies on overall estimate.

We performed dose–response meta-analysis using the method suggested by Berlin et al. (30) and Orsini et al. (31) to assess the dose–response association between animal-based protein sources and risk of RA. The log-transformed RRs and their CIs among categories of animal proteins were used to compute study-specific slopes (linear trends). In this method, we required the distribution of cases and the RRs with the variance estimates for more than three quantitative
categories of exposure. For studies that reported the animal-based protein sources as a range, the
median in each category was estimated by calculating the midpoint of the lower and upper
bounds. When the highest and lowest categories were open-ended, the length of these open-
ended intervals was assumed to be the same as those of the adjacent intervals. To examine
potential nonlinear dose–response associations of animal-based protein sources and risk of RA,
restricted cubic splines (three knots at fixed percentiles of 10%, 50%, and 90% of the distribution
were used (32)). For the study of Di Giuseppe et al. (33), the mean fish intake within each
exposure level was obtained from the primary data reported in another published meta-analysis
(23). We performed all statistical analyses using Stata software version 14 (Stata Corp, College
Station, Texas, USA) and p-values <0.05 were considered statistically significant.

**Risk of bias and credibility of the evidence assessment**

We assessed the risk of bias for each study using the non-randomised studies of exposures
(ROBINS-E) tool (34). This tool includes 7 domains of bias due to confounding, selection of
participants, assessment of exposure, misclassification during follow-up, missing data,
measurement of the outcome, and selective reporting of the results. Each domain was assessed as
at low, moderate, serious, or critical risk of bias. Studies were categorized as at least the same
severity of the highest risk of bias of a single domain.

We also used the NutriGrade tool to quantify the certainty of evidence for the association
between animal protein sources and RA (35). The measurement score has been calculated and
interpreted as follows: very low (0 to less than 4 points), low (4 to less than 6 points), moderate
(6 to less than 8 points) or high (8 to 10 points) certainty of the evidence. Separate judgments on
certainty of evidence were made for fish, meat, dairy and poultry.
Results

Study selection

Among the 3,260 retrieved reports, 1,006 studies were duplicates and 2,169 publications were excluded during screening of titles and abstracts (Fig. 1). After reading the full texts of the remaining articles, 73 studies were excluded due to following reasons: evaluated other dietary components than animal protein sources (n = 40), protocols (n = 4), insufficient data (n=14), provided effect estimates for other autoimmune disease than RA (n = 15), and review articles (n = 10). Finally, 13 studies involving seven cohorts (22, 33, 36-40) and six case-control studies (18, 41-45) were included for meta-analysis.

Characteristics of included studies

Table 1 shows the characteristics of the included studies. The studies were performed between 1991 and 2020 and included a total of 466,800 participants (457,554 in cohort studies and 9,246 in case-control studies). All studies were conducted on adults. Total number of cases with RA was 7,539 (3,545 in cohort studies and 3,994 in case-control studies). Participant’s age ranged from 18 to 89 years old. The studies were conducted in Sweden (22, 33, 44), USA (36, 40, 45), Denmark (38, 39), Greece (41, 42), France (37), China (18) and Iran (43). The median follow-up duration of the cohort studies varied from 5.3 to 30 years. To assess the exposure, 10 studies used food frequency questionnaire (FFQ) (18, 22, 33, 36-40, 43, 45) and three studies used dietary questionnaire (41, 42, 44). In terms of exposure, seven articles reported effect sizes for red meat intake (18, 22, 36-39, 45), three for poultry intake (18, 22, 36), 10 for fish intake (18, 33, 36-38, 40-42, 44, 45) and five for dairy intake (18, 22, 37, 43, 45). Six studies enrolled only women (22, 33, 36, 37, 40, 45) and the rest of them were carried out on both sexes (18, 38, 39, 41-44).
The covariates most commonly adjusted in the included studies were age (n=11), smoking (n=7), alcohol consumption (n=6), sex (n=5), BMI (n=5) and energy intake (n=5). Other studies also controlled for meat (n=2) and fish consumption (n=2).

**Fish consumption and risk of RA**

Five cohort studies (399,628 participants and 2,380 incident cases) (33, 36-38, 40) and five case-control studies (3,494 cases and 4,752 controls) (18, 41, 42, 44, 45) were included in the analysis of fish consumption and risk of RA. Groups with the lowest intake ranged between 0 and 10 g/day and the groups with the highest intake ranged between 33 and 67.85 g/day. The relative risk of RA for the highest compared with the lowest category of fish intake was 0.89 (95% CI, 0.80 to 0.99), with no evidence of between-study heterogeneity, $I^2=0.0\%$, $P_{\text{heterogeneity}} = 0.71$ (Supplementary Figure 1; Table 2). Subgroup analyses revealed a significant negative association between fish consumption and risk of RA in case-control studies (OR: 0.82; 95% CI, 0.68 to 0.99), however in cohort studies the association was not significant (RR: 0.93; 95% CI, 0.82 to 1.05). Sensitivity analysis, initially including all 10 studies, showed that exclusion of the studies by Rosell et al. (44) and Di Giuseppe et al. (33) from the analysis influenced the estimate, leading to slightly smaller effect sizes (RR: 0.91; 95% CI, 0.81 to 1.01 and RR: 0.90; 95% CI, 0.81 to 1.00, respectively), indicating our results should be interpreted with caution (Supplementary Figure 2). There was no evidence of publication bias ($P = 0.06$ for Begg’s test and $P = 0.05$ for Egger’s test). But the funnel plot seemed asymmetrical (Supplementary Figure 3).

The linear trend estimation revealed that a 100 g/d increment in fish intake was associated with 15% lower risk of RA (RR: 0.85; 95% CI, 0.73 to 0.98) (Supplementary Figure 4; Table 2). Non-linear dose-response meta-analysis showed a modest U-shaped association between fish
intake with the risk of RA, with the lowest risk at fish intake of approximately 25 g/d ($P_{\text{non-linearity}} = 0.04$; Fig. 2A).

**Red meat consumption and risk of RA**

Four cohort studies (228,912 participants and 1,780 incident cases) (36-39, 46) and one case-control studies (968 cases and 1,037 controls) (18) were included in the analysis of red meat consumption and risk of RA. Groups with the lowest intake ranged between 35.71 and 53 g/day and the groups with the highest intake ranged between 164.28 and 409.82 g/day. The pooled effect size for risk of RA comparing the highest versus lowest red meat intake was 0.96 (95% CI, 0.85 to 1.07), without heterogeneity among studies (Supplementary Figure 5; Table 2). Similar result was found after subgroup analysis by study design for case-control (OR: 1.07; 95% CI, 0.88 to 1.30) and cohort studies (RR: 0.90; 95% CI, 0.78 to 1.04). Sensitivity analysis demonstrated that no particular study influenced the overall estimate (Supplementary Figure 6). Also, there was no evidence for publication bias ($P = 0.33$ Begg’s test and $P = 0.40$ Egger’s test) and the shape of the funnel plot seems symmetrical (Supplementary Figure 7).

The linear dose response indicated that a 100 g/d increase in red meat intake was not associated with the risk of RA (RR: 0.98; 95% CI, 0.93 to 1.02) (Supplementary Figure 8; Table 2). In addition, a non-significant linear inverse association between red meat intake and RA was found ($P_{\text{non-linearity}} = 0.19$, Fig. 2B).

**Dairy consumption and risk of RA**

Two cohort studies (98,229 participants and 848 incident cases) (37, 46) and three case-control studies (18, 43, 45) (1,792 cases and 2,782 controls) were included in the analysis of dairy consumption and risk of RA. Groups with the lowest intake ranged between 60 and 98.57 g/day and the groups with the highest intake ranged between 192.85 and 548.57 g/day. The pooled
effect size for risk of RA comparing the highest versus lowest categories of dairy intake was 0.95 (95% CI, 0.70 to 1.28) (Supplementary Figure 9; Table 2), with significant heterogeneity across included studies ($I^2 = 66.0\%, P = 0.01$). Similar result was found after subgroup analysis by case-control (OR: 0.85; 95% CI, 0.50 to 1.44) and cohort studies (RR: 1.11; 95% CI, 0.92 to 1.34). Sensitivity analysis showed no particular study had a significant influence on the summary effect (Supplementary Figure 10). Also, no evidence of publication bias was found ($P = 0.62$ for Begg’s test and $P = 0.91$ for Egger’s test). But the funnel plot seemed to be slightly asymmetrical (Supplementary Figure 11). Linear dose response meta-analysis showed no association between 200 grams per day increment of dairy intake and risk of RA (RR: 1.00; 95% CI, 0.85 to 1.17) (Supplementary Figure 12; Table 2). There was no association between dairy consumption and risk of RA in the nonlinear dose-response analysis ($P_{\text{non-linearity}} = 0.01$, Fig. 2C).

**Poultry consumption and risk of RA**

Two cohort studies (117,663 participants and 914 incident cases) (36, 46) and one case-control study (968 cases and 1,037 controls) were included in the analysis of poultry consumption and risk of RA. Groups with the lowest intake ranged between 0 and 9 g/day and the groups with the highest intake ranged between 21.42 and 48.00 g/day. The highest category of poultry intake compared with the lowest one was not associated with the risk of RA (RR: 1.05; 95% CI, 0.84 to 1.31), with no evidence of heterogeneity (Supplementary Figure 13; Table 2). Similar result was found after subgroup analysis by case-control (OR: 0.72; 95% CI, 0.21 to 2.52) and cohort studies (RR: 1.06; 95% CI, 0.84 to 1.33). No particular study had a remarkable effect on overall summary estimate (Supplementary Figure 14). There was no evidence for publication bias ($P = 0.60$ for Begg’s test and $P = 0.51$ for Egger’s test). The shape of funnel plot seemed symmetrical.
(Supplementary Figure 15). Linear dose-response meta-analysis showed no significant association between each 100 grams per day increment in poultry intake and risk of RA (RR: 1.03; 95% CI, 0.40 to 2.68) (Supplementary Figure 16; Table 2)

Risk of bias and certainty of the evidence

Based on the ROBINS-E tool, 9 studies categorized as moderate risk of bias and 4 studies rated as serious risk of bias because the serious risk of bias was found in at least one domain (Supplementary Table 2).

NutriGrade scores for included studies showed a moderate credibility of evidence for fish consumption and risk of RA. Low credibility of evidence was established for meat consumption. The credibility of findings for poultry and dairy consumption was considered very low (Supplementary Table 3).

Discussion

This systematic review and meta-analysis showed a negative significant dose-response association between consumption of fish and risk of developing RA. However, we did not observe any significant association between red meat, poultry or dairy consumption and risk of RA.

Our findings showed that fish intake was correlated with reduced risk of RA. These results complement the previous systematic review and meta-analysis (23). Giuseppe et al. showed that consuming one to three servings of fish per week was associated with a 20-24% lower the risk (23). Possible mechanisms for these results might be associated with anti-inflammatory properties of the omega-3 fatty acids in fish. In fact, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) could compete for residency in membrane phospholipids with
arachidonic acid. As a result they could reduce the production of effective mediators in inflammation (47, 48).

Eicosanoids produced by the omega-3 fatty acid metabolism pathway, such as leukotriene, thromboxane and prostaglandins have less pro-inflammatory properties than eicosanoids synthesized from arachidonic acid (49, 50). A number of studies have also shown that these omega-3 metabolites can prevent the proliferation of human T cells and IL-2 production in culture, which itself plays an important protective role in RA (48, 51). On the other hand, previous studies showed an inverse association between omega-3 fatty acids and anti-cyclic citrullinated peptide (anti-CCP) autoantibodies (52). Citrullinated proteins are found in inflamed and arthritic joints, while their detection in healthy joints is rare (53). The antibodies against these citrullinated proteins (ACPA) plays an important role in the pathogenesis of RA and is detected in the serum of RA patients prior to the clinical onset of arthritis (54). Also, fish intake is positively related to healthy dietary pattern and healthy lifestyle factors like higher levels of exercise and little or no smoking (55).

With regards to red meat consumption and risk of RA, no significant association between red meat consumption and risk of RA was found. However, some clinical trials have shown that reducing meat consumption is associated with improved disease activity in RA patients (56, 57). Also, in a cohort study, it has been reported that participants with self-reported arthritis had higher intake of meat (58). Our results showed no significant association between poultry consumption and risk of RA. This is inconsistent with a case-control study by Sanghi et al., investigating that meat and poultry consumption might have a protective effect on subjects with osteoarthritis (59). Studies suggest that meat-rich diets, like the Western diet, might have pro-inflammatory properties and thereby be associated with the risk of RA, type 2 diabetes, and
cardiovascular disease (60). In addition, increased consumption of red meat might be associated with weight gain (61, 62). Obesity and excess fat mass leads to reduction in adiponectin production and increment in leptin production and inflammatory markers (63). The arachidonic acid content of meat causes arachidonic acid cascade and eicosanoids production with pro-inflammatory properties such as Prostaglandin E2 (PGE2) (64). Iron content of meat is another possible risk factors that has been suggested to increase oxidative stress (65, 66). Moreover, iron from red-meat might accumulate in the rheumatoid synovia membrane and cause tissue damage (67). However, Pattison et al. showed that the association between meat intake and the incidence of arthritis was independent of iron content (68). Also, Benito-Garcia et al. showed that there was no association between iron intake with risk of RA (36). The inconsistency regarding meat consumption and incidence of RA could be attributed to the variety in methodological approaches and limited numbers of conducted studies. Therefore, further studies in this context are needed.

With regards to dairy consumption, our results suggested that dairy consumption was not significantly associated with risk of RA. Some studies have suggested that dairy consumption has a detrimental effect on the incidence of RA due to allergic or hypersensitivity reactions to cow's milk protein (20, 69, 70), while Liden et al. showed that allergic reactions to cow's milk were observed just in a minor fraction of subjects with RA (71). On the other hand, some dairy nutrients, especially vitamin D, could have a protective effect on RA (72).

**Strengths and limitations**

The present systematic review and meta-analysis has some advantages. This is the first attempt to examine the association of dietary animal protein sources with risk of RA. Also, we performed linear and non-linear dose-response analyses to clarify the exact associations between animal
protein sources and risk of RA. Furthermore, the sample size was relatively large (466,800 participants, 7,539 cases) and two investigators conducted the study selection and data extraction.

Also, our study has some limitations. First, the included observational studies could be affected by selection, recall and reverse causality biases, which could influence the results of our synthesis. Second, included studies used different tools for evaluating dietary intakes and used different units for animal-based protein sources. Third, the number of included studies reporting on some animal protein sources, such as poultry and dairy, were low, therefore, the results should be interpreted with caution. Fourth, due to relatively low number of included studies (n<10), the results of the publication bias tests may be due to chance. Fifth, moderate heterogeneity existed in the analysis of red meat intake which may be largely explained by differences in study design of included studies. Finally, no pre-defined protocol exists for this study.

**Recommendations for future research**

The relationship between consumption of different types of fish, whether saltwater or freshwater fish, and risk of RA is lacking in the current literature and should ideally be evaluated in future studies separately, because they have different nutrients. Also, well-designed studies to examine the association between different dairy sources like milk, cheese and yogurt with risk of RA are needed. Moreover, future randomized clinical trials should shed light on the effect of animal protein sources on ACPA and RF as diagnostic factors in the development of the disease.

**Conclusion**
Finally, the results of the present comprehensive dose-response meta-analysis on 13 observational studies revealed a significant reverse association between fish intake and risk of RA. While we observed no association between red meat, dairy or poultry consumption and risk of RA. Present findings highlight the potential role of diet to reduce the risk of RA.
Authors’ contributions

Conception and design: FA, HM

Data collection and analysis of data: FA, SEM.

Interpretation of data: All authors.

Critical revision of study material: All authors.

Drafting of the article: FA, ZK

Critical revision of the article for important intellectual content and final approval of the article: All authors.

Authors who take responsibility for the integrity of the work as a whole: HM

Funding

None

Conflict of interest

None

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References


Legends of figures:

**Figure 1.** Study selection process

**Figure 2.** Nonlinear dose–response relationship between (A) fish intake and risk of RA, (B) red meat intake and risk of RA, (C) dairy intake and risk of RA.
<table>
<thead>
<tr>
<th>Author (year, Country)</th>
<th>Age</th>
<th>Sex</th>
<th>Follow up</th>
<th>Cases/cohort size or controls</th>
<th>Exposure assessment (items)</th>
<th>Outcome assessment</th>
<th>Exposure type</th>
<th>Comparison</th>
<th>RR (95% CI), Highest Versus Lowest</th>
<th>Covariates</th>
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<tr>
<td><strong>Cohort studies</strong></td>
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<tr>
<td>Rubin et al. (2020, Denmark)</td>
<td>50-64</td>
<td>Both</td>
<td>22.2 y</td>
<td>797/54,558</td>
<td>FFQ (192)</td>
<td>ICD8 or ICD10</td>
<td>Red meat</td>
<td>T3 versus T1</td>
<td>0.84 (0.69-1.02)</td>
<td>age, sex, energy, alcohol intake, smoking status, education, civil status, and co-morbidity</td>
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<tr>
<td>Nguyen et al. (2020, France)</td>
<td>52.5</td>
<td>Women</td>
<td>11.7 y</td>
<td>480/62,629</td>
<td>FFQ (208)</td>
<td>ACR criteria</td>
<td>Fish Dairy</td>
<td>&gt;25 g/d versus &lt;9 g/d &gt;253 g/d versus &lt;120 g/d</td>
<td>0.99 (0.80-1.22) 1.12 (0.90-1.41)</td>
<td>total daily intake except alcohol, and age, BMI, smoking status, passive smoking in childhood, gastrointestinal transit, educational level, physical activity</td>
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<td>Sundström et al. (2019, Sweden)</td>
<td>54–89</td>
<td>Women</td>
<td>12 y</td>
<td>368/35,600</td>
<td>FFQ 1987 (67) FFQ 1997 (96)</td>
<td>ICD10</td>
<td>Red meat Poultry Dairy</td>
<td>&gt;10 servings/week versus ≤4 servings/week &gt;1 serving/week versus 0 servings/week &gt;6 servings/week versus ≤3 servings/week</td>
<td>1.08 (0.77-1.50) 0.88 (0.60-1.31) 1.09 (0.76-1.55)</td>
<td>age, alcohol intake, smoking, energy intake, dairy, and fish consumption</td>
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<td>Sparks et al. (2019, USA)</td>
<td>NHS:30-55 NHSII: 24-42</td>
<td>30 y</td>
<td>24 y</td>
<td>1080/166,013</td>
<td>FFQ (133)</td>
<td>ACR criteria</td>
<td>Fish</td>
<td>≥4 serving /week versus none to &lt; 1 serving /month</td>
<td>0.93 (0.67-1.28)</td>
<td>age, questionnaire period, cohort, total energy intake, median household income, cigarette smoking, BMI, and alcohol intake</td>
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<td>Sample Size</td>
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<td>Outcome</td>
<td>Odds Ratio (95% CI)</td>
<td>Adjusted Factors</td>
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<tr>
<td>Di Giuseppe et al. (2014, Sweden)</td>
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<td>7.5</td>
<td>FFQ 1987 (67)</td>
<td>Fish</td>
<td>&lt;1 serving/week versus ≥1 serving/week</td>
<td>0.75 (0.53-1.06)</td>
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</tr>
<tr>
<td>Benito-Garcia et al. (2007, USA)</td>
<td>Women</td>
<td>30–55</td>
<td>22</td>
<td>FFQ (147)</td>
<td>Red meat, Poultry, Fish</td>
<td>Q5 versus Q1, Q5 versus Q1, Q5 versus Q1</td>
<td>0.86 (0.64-1.16), 1.17 (0.88-1.55), 0.96 (0.72-1.26)</td>
<td>age, body mass index, smoking, and total lifetime, breastfeeding</td>
<td></td>
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</tr>
<tr>
<td>Pedersen et al. (2005, Denmark)</td>
<td>Both</td>
<td>50-64</td>
<td>5.3</td>
<td>FFQ (NR)</td>
<td>Red meat, Fish</td>
<td>Per 100 g/day, Per 30 g/day</td>
<td>1.79 (0.57-4.65), 0.90 (0.67-1.23)</td>
<td>age and gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rambod et al. (2018, Iran)</td>
<td>Both</td>
<td>≥18</td>
<td>500/500</td>
<td>FFQ (168)</td>
<td>Dairy</td>
<td>One cup per month</td>
<td>1.96 (1.22-7.44)</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>He et al. (2016, China)</td>
<td>Both</td>
<td>50.9±14.3</td>
<td>NA</td>
<td>FFQ (NR)</td>
<td>Red meat, Poultry, Fish, Dairy</td>
<td>Highest versus lowest category, Highest versus lowest category, Highest versus lowest category</td>
<td>1.07 (0.89-1.32), 0.72 (0.34-4.18), 0.62 (0.24-1.58), 0.57 (0.38-0.85)</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosell et al. (2009, Sweden)</td>
<td>Both</td>
<td>18-70</td>
<td>NA</td>
<td>Dietary questionnaire</td>
<td>Fish</td>
<td>1–7 times/week versus seldom or never</td>
<td>0.80 (0.60-1.00)</td>
<td>Age, residential area, smoking, gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linos et al. (1999, Greece)</td>
<td>Both</td>
<td>18-84</td>
<td>NA</td>
<td>dietary questionnaire</td>
<td>Fish</td>
<td>Q4 versus Q1</td>
<td>0.95 (0.46-1.96)</td>
<td>age, sex, BMI, years of schooling, olive oil, meat, fish, shellfish, dairy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Age/Gender</td>
<td>NA</td>
<td>Sample Size</td>
<td>Instrument</td>
<td>ACR criteria</td>
<td>Outcome</td>
<td>Cut-off</td>
<td>RR</td>
<td>95% CI</td>
<td>Variables</td>
</tr>
<tr>
<td>---------------------</td>
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<td>------------------------------------------------------</td>
</tr>
<tr>
<td>Shapiro et al.</td>
<td>18-64 Women</td>
<td>NA</td>
<td>324/1245</td>
<td>FFQ (NR)</td>
<td>ACR criteria</td>
<td>Fish</td>
<td>≥2 serving/week versus &lt;1 serving/week Q4 versus Q1</td>
<td>0.92 (0.67-1.25)</td>
<td>Reference age, reference year, education, race, total caloric intake</td>
<td></td>
</tr>
<tr>
<td>Linos et al.</td>
<td>24-89 Both</td>
<td>NA</td>
<td>168/137</td>
<td>dietary questionnaire (&gt; 100)</td>
<td>ACR criteria</td>
<td>Fish</td>
<td>&gt;12 times/month versus 1-2 times/month</td>
<td>0.37 (0.13-1.05)</td>
<td>Age, gender, occupation, residence, marital status, body mass index, adherence to lent</td>
<td></td>
</tr>
</tbody>
</table>

FFQ=food frequency questionnaire; NA=not applicable; NR=not reported; RR=risk ratio; ICD= International Classification of Diseases; ACR= American College of Rheumatology; NOS= Newcastle-Ottawa Scale; Q, quantile; T, tertile; BMI, body mass index.
### Table 2. Animal protein sources and risk of Rheumatoid arthritis

<table>
<thead>
<tr>
<th></th>
<th>Highest vs. lowest category meta-analysis</th>
<th>Dose-response meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Studies, n</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fish</td>
<td>10</td>
<td>0.89 (0.80, 0.99)</td>
</tr>
<tr>
<td>Red meat</td>
<td>5</td>
<td>0.96 (0.85, 1.07)</td>
</tr>
<tr>
<td>Dairy</td>
<td>5</td>
<td>0.95 (0.70, 1.28)</td>
</tr>
<tr>
<td>Poultry</td>
<td>3</td>
<td>1.05 (0.84, 1.31)</td>
</tr>
<tr>
<td><strong>Cohort studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fish</td>
<td>5</td>
<td>0.93 (0.82, 1.05)</td>
</tr>
<tr>
<td>Red meat</td>
<td>4</td>
<td>0.90 (0.78, 1.04)</td>
</tr>
<tr>
<td>Dairy</td>
<td>2</td>
<td>1.11 (0.92, 1.34)</td>
</tr>
<tr>
<td>Poultry</td>
<td>2</td>
<td>1.06 (0.84, 1.33)</td>
</tr>
<tr>
<td><strong>Case-Control studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fish</td>
<td>5</td>
<td>0.82 (0.68, 0.99)</td>
</tr>
<tr>
<td>Red meat</td>
<td>1</td>
<td>1.07 (0.88, 1.30)</td>
</tr>
<tr>
<td>Dairy</td>
<td>3</td>
<td>0.85 (0.50, 1.44)</td>
</tr>
<tr>
<td>Poultry</td>
<td>1</td>
<td>0.72 (0.21, 2.52)</td>
</tr>
</tbody>
</table>

Abbreviation: RR
Figure 1.