Review

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Diet and rheumatoid arthritis development: what does the evidence say?

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Rheumatoid arthritis (RA), a chronic autoimmune disease, is related to both genetic and environmental factors. Among environmental factors, only smoking can be considered as an established risk factor for RA, while mixed results have been observed regarding other potential risk factors. Diet has been evaluated in several studies for its role in the management of established RA, while fewer studies have examined diet in relation to the development of RA. This review summarizes the published evidence on the association between diet and RA risk, with attention to specific foods and their nutrient content. Results stratified by types of RA are also presented.

Keywords: diet • review • rheumatoid arthritis

Rheumatoid arthritis (RA), an inflammatory autoimmune disease, is characterized by chronic, destructive, debilitating arthritis of the joints. RA affects approximately 1% of the adult population [1], and is caused by both genetic and environmental factors [2].

Among environmental factors, diet may play a fundamental role in the prevention of some chronic diseases owing to its potential as a modifiable risk factor. For this reason, it is of primary importance to study the role of diet in the etiology of RA in order to identify foods and dietary patterns that could help in reducing the risk of RA, as well as dietary factors that, on the contrary, may increase the risk. Diet has been evaluated in several studies for its role in the management of established RA [3], while fewer studies have examined diet in relation to the development of RA.

In this review, the authors will summarize available epidemiological evidence on the relationship between diet and risk of RA, with attention to specific foods (Table 1) and their nutrient content (Table 2).

Results from studies in which inflammatory polyarthritis was used as proxy of RA were also included [11,13,31].

Foods of animal origin

As part of diet, foods from both animal and plant origin have been investigated, as well as different beverages. The authors will first present published results for foods and nutrients from animal sources, including fish, meat and dairy products.

Fish

Fish consumption is considered protective against several chronic diseases, including cancer [34–36] and cardiovascular diseases [37,38]. Seven observational studies have analyzed the association between fish consumption and RA, and results are mixed [4–10]. Among the four case–control studies, two hospital-based case–control studies conducted in Greece by the same research group have reported a lack of association between fish consumption and RA [4,5]. A population-based case–control study conducted in western Washington (DC, USA) found no association between total fish (including shellfish) consumption and RA, while observing a 43% reduced risk (odds ratio [OR]: 0.57; 95% CI 0.35–0.93) of RA among women who consumed two or more servings of broiled or baked fish per week [6]. The inverse association was even

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Table 1. Summary of studies reporting measures of association between food consumptions and rheumatoid arthritis.

Study name or location	Publication year	Design	Number of cases vs controls/cohort size	Direction of association	Rheumatoid arthritis subtypes	Ref.
Fish						
Greece	1991	Hospital-based case–control	168/137	No association	–	[4]
Greece	1999	Hospital-based case–control	145/188	No association	–	[5]
Washington, DC, USA	1996	Population-based case–control	324/1245	Inverse	RF positive: inverse RF negative: no association	[6]
EIRA	2009	Population-based case–control	1889/2145	Inverse	ACPA positive: inverse ACPA negative: no association RF positive: inverse RF negative: no association	[7]
DCH	2005	Prospective cohort	69/57,053	No association	–	[8]
NHS	2007	Prospective cohort	546/82,063	No association	–	[9]
SMC	2013	Prospective cohort	205/32,232	Inverse	–	[10]
Meat						
Washington, DC, USA	1996	Population-based case–control	324/1245	No association	–	[6]
EPIC-Norfolk	2004	Nested case–control	88/176	Positive	–	[11]
DCH	2005	Prospective cohort	69/57,053	No association	–	[8]
NHS	2007	Prospective cohort	546/82,063	No association	–	[9]
Dairy products						
Washington, DC, USA	1996	Population-based case–control	324/1245	No association	–	[6]
EPIC-Norfolk	2004	Nested case–control	88/176	Positive	–	[11]
IWHS	2004	Prospective cohort	152/29,368	Inverse		[12]
Fruit						
Washington, DC, USA	1996	Population-based case–control	324/1245	No association	–	[6]
EPIC-Norfolk	2004	Nested case–control	73/146	Inverse	–	[13]
IWHS	2003	Prospective cohort	152/29,368	Inverse	–	[14]
DCH	2005	Prospective cohort	69/57,053	No association	–	[8]
Vegetables						
Greece	1999	Hospital-based case–control	145/188	Inverse	–	[5]
Washington, DC, USA	1996	Population-based case–control	324/1245	No association	–	[6]
EPIC-Norfolk	2004	Nested case–control	73/146	Inverse	–	[13]
IWHS	2003	Prospective cohort	152/29,368	Inverse	–	[14]
DCH	2005	Prospective cohort	69/57,053	No association	–	[8]

RF: Rheumatoid factor.

Table 1. Summary of studies reporting measures of association between food consumptions and rheumatoid arthritis (cont.).

Study name or location	Publication year	Design	Number of cases vs controls/cohort size	Direction of association	Rheumatoid arthritis subtypes	Ref.
Olive oil						
Greece	1991	Hospital-based case–control	168/137	Inverse	–	[4]
Greece	1999	Hospital-based case–control	145/188	Inverse	–	[5]
DCH	2005	Prospective cohort	69/57,053	No association	–	[8]
Coffee						
Denmark	2006	Population-based case–control	515/769	Positive	Anti-CCP positive: positive Anti-CCP negative: no association	[15]
EPIC-Norfolk	2004	Nested case–control	88/176	No association	–	[11]
Finland	2000	Prospective cohort	126/18,981	Positive	–	[16]
BWHS	2001	Prospective cohort	71/64,000	Positive only for decaffeinated coffee	–	[17]
IWHS	2002	Prospective cohort	158/31,336	Positive only for decaffeinated coffee	RF positive: positive RF negative: no association	[18]
NHS	2003	Prospective cohort	480/83,124	No association	RF positive: positive	[19]
DCH	2005	Prospective cohort	69/57,053	No association	–	[8]
Tea						
EPIC-Norfolk	2004	Nested case–control	88/176	No association	–	[11]
BWHS	2001	Prospective cohort	71/64,000	Positive	–	[17]
IWHS	2002	Prospective cohort	158/31,336	Inverse	RF positive: inverse RF negative: no association	[18]
NHS	2003	Prospective cohort	480/83,124	No association	RF positive: no association	[19]
Alcohol						
Leiden, The Netherlands	1990	Hospital-based case–control	135/378	Inverse	–	[20]
King County, WA, USA	1994	Population-based case–control	349/1457	No association	–	[21]
Denmark	2006	Population-based case–control	515/769	No association	Anti-CCP positive: inverse Anti-CCP negative: no association	[15]
EIRA	2009	Population-based case–control	1204/871	Inverse	ACPA positive: inverse ACPA negative: inverse	[22]
CACORA	2009	Population-based case–control	444/533	Inverse	ACPA positive: inverse ACPA negative: no association	[22]
Sheffield, UK	2010	Population-based case–control	873/1004	Inverse	Anti-CCP positive: inverse Anti-CCP negative: inverse	[23]

RF: Rheumatoid factor.

Table 1. Summary of studies reporting measures of association between food consumptions and rheumatoid arthritis (cont.).

Study name or location	Publication year	Design	Number of cases vs controls/cohort size	Direction of association	Rheumatoid arthritis subtypes	Ref.
EPIC-Norfolk	2004	Nested case–control	88/176	No association	–	[11]
Malmö Diet and Cancer Study	2013	Nested case–control	172/688	Inverse	RF positive: inverse RF negative: no association	[24]
Finland	2000	Prospective cohort	126/18,981	No association	–	[16]
IWHS	2002	Prospective cohort	158/31,336	No association	–	[25]
SMC	2012	Prospective cohort	197/34,141	Inverse	–	[26]

RF: Rheumatoid factor.

stronger for rheumatoid factor (RF)-positive RA risk (OR: 0.32; 95% CI 0.14–0.72). The EIRA study, a large population-based case–control study conducted in Sweden, found a modest decrease in risk of total RA and type-specific RA – including RF positive and negative, and ACPA positive and negative – associated with consumption of oily fish (OR: 0.8; 95% CI: 0.6–1.0, for one to seven servings/per week vs never/seldom) [7].

In addition, the three prospective cohort studies presented mixed results. An inverse association was observed in the DCH cohort in Denmark between oily fish and RA (relative risk [RR]: 0.51; 95% CI 0.25–1.03), while the association was positive between medium oily fish and RA (RR: 2.74; 95% CI 1.39–5.42) [8]. The researchers did not draw any conclusion regarding these discrepant results owing to the very limited number of cases (n = 69) identified in their large cohort (n = 56,691) during an average follow-up time of 5.3 years. Results from the NHS, a prospective cohort study in which nurses were asked about dietary intake every 4 years from 1980 to 1998, did not show an association between total fish and RA [9]. The SMC study analyzed the long-term consumption of fish and observed that women with consistent consumption of one or more servings of fish per week for a period of more than 10 years had a 30% decreased risk of RA (RR: 0.71; 95% CI: 0.18–1.04) [10].

As shown above, only one study analyzed the method of preparation of fish [6]. The difference in results between broiled or baked fish compared with fried fish, for which no association was observed, suggests that the method of preparation may influence the beneficial effects of fish.

Long-chain n-3 polyunsaturated fatty acids

The observed inverse association between fish consumption and RA risk has been attributed to their content of long-chain n-3 polyunsaturated fatty acids (PUFAs). The n-3 PUFA eicosapentaenoic acid and docosahexaenoic acid are metabolized to competitive inhibitors of n-6 PUFAs (prostaglandins and leukotrienes) and suppress the production of the inflammatory cytokines, such as TNF-α and IL-1β [39], involved in RA development. However, only three studies have directly examined these nutrients. The case–control study among women of western Washington (DC, USA) found no association between intake of long-chain n-3 PUFAs and total RA, while they observed an inverse association with RF-positive RA [6]. The study conducted in the DCH cohort (based on only 69 cases) also found no association with RA [8]. Results from the SMC showed a threshold effect of long-chain n-3 PUFAs on RA risk: an intake of more than 0.21 g per day (first quintile of the distribution in the study population) was associated with a decrease in RA risk of 35% (RR: 0.65; 95% CI: 0.48–0.90) [10]. Moreover, this study showed that a consistent long-term intake over more than 10 years of more than 0.21 g per day was associated with a 52% decrease in RA risk (RR: 0.48; 95% CI: 0.33–0.71).

Vitamin D

Fish is also the main dietary source of vitamin D. Some studies have shown that vitamin D may reduce the development of autoimmune diseases [40,41]. The first study that examined vitamin D in relation to RA risk was conducted in the prospective IWHS and showed an inverse association between vitamin D intake and RA (RR: 0.67; 95% CI: 0.44–1.00, for a daily intake of vitamin D of ≥467.7 vs <221.4 IU per day) [12]. The association was stronger for vitamin D from supplements (RR: 0.66; 95% CI: 0.43–1.00) than dietary vitamin D (RR: 0.72; 95% CI: 0.46–1.14). However, other studies were not able to confirm these findings. No associations were observed for dietary vitamin D intake in the DCH cohort [8], in the NHS nor in the

Table 2. Summary of studies reporting measures of association between nutrients intake and rheumatoid arthritis.

Study name or location	Publication year	Design	Number of cases vs controls/cohort size	Direction of association	Comments	Ref.
Long-chain n-3 polyunsaturated fatty acids						
Washington, DC, USA	1996	Population-based case–control	324/1245	Inverse	RF positive: inverse RF negative: no association	[6]
DCH	2005	Prospective cohort	69/57,053	No association		[8]
SMC	2013	Prospective cohort	205/32,232	Inverse		[10]
Vitamin D						
EPIC-Norfolk	2004	Nested case–control	88/176	No association		[11]
IWHS	2004	Prospective cohort	152/29,368	Inverse		[12]
DCH	2005	Prospective cohort	69/57,053	No association		[8]
NHS	2008	Prospective cohort	722/186,389	No association		[27]
NHS and NHS II	2012	Prospective cohort	800/119,173	No association	Intake during adolescence	[28]
Iron						
Washington, DC, USA	1996	Population-based case–control	324/1245	No association		[6]
EPIC-Norfolk	2004	Nested case–control	88/176	No association		[11]
DCH	2005	Prospective cohort	69/57,053	No association		[8]
NHS	2007	Prospective cohort	546/82,063	No association		[9]
Calcium						
Washington, DC, USA	1996	Population-based case–control	324/1245	No association		[6]
IWHS	2004	Prospective cohort	152/29,368	No association		[12]
Selenium						
Finland	1994	Nested case–control	14/28	Inverse		[29]
Finland	2000	Nested case–control	122/357	Inverse	RF positive: no association RF negative: inverse	[30]
EPIC-Norfolk	2004	Nested case–control	73/146	No association		[13]
Protein						
Washington, DC, USA	1996	Population-based case–control	324/1245	Inverse	RF positive: inverse RF negative: no association	[6]
EPIC-Norfolk	2004	Nested case–control	88/176	Positive		[11]
NHS	2007	Prospective cohort	546/82,063	No association		[9]
Vitamin C						
Washington, DC, USA	1996	Population-based case–control	324/1245	No association		[6]
EPIC-Norfolk	2004	Nested case–control	73/146	Inverse		[13]
EPIC-Norfolk	2005	Nested case–control	88/176	Inverse		[31]
IWHS	2003	Prospective cohort	152/29,368	Inverse		[14]
DCH	2005	Prospective cohort	69/57,053	No association		[8]

RA: Rheumatoid arthritis; RF: Rheumatoid factor.

Table 2. Summary of studies reporting measures of association between nutrients intake and rheumatoid arthritis (cont.).

Study name or location	Publication year	Design	Number of cases vs controls/cohort size	Direction of association	Comments	Ref.
NHS and NHS II	2010	Prospective cohort	787/18,4643	No association		[32]
α-tocopherol (vitamin E)						
Washington, DC, USA	1996	Population-based case–control	324/1245	No association		[6]
Finland	1994	Nested case–control	14/28	Inverse		[29]
Finland	2000	Nested case–control	122/357	Inverse	RF positive: no association RF negative: no association	[30]
EPIC-Norfolk	2004	Nested case–control	73/146	No association		[13]
IWHS	2003	Prospective cohort	152/29,368	No association		[14]
DCH	2005	Prospective cohort	69/57,053	No association		[8]
NHS and NHS II	2010	Prospective cohort	787/184,643	No association		[32]
The Women's Health Study	2008	Randomized, double-blind, placebo-controlled trial	106/39,144	No association	Seropositive RA: no association Seronegative RA: no association	[33]
Carotenoids (α-carotene)						
IWHS	2003	Prospective cohort	152/29,368	No association		[14]
NHS and NHS II	2010	Prospective cohort	787/184,643	No association		[32]
Carotenoids (β-carotene)						
Finland	1994	Nested case–control	14/28	Inverse		[29]
EPIC-Norfolk	2004	Nested case–control	73/146	No association		[13]
EPIC-Norfolk	2005	Nested case–control	88/176	No association		[31]
DCH	2005	Prospective cohort	69/57,053	No association		[8]
IWHS	2003	Prospective cohort	152/29,368	No association		[14]
NHS and NHS II	2010	Prospective cohort	787/184,643	No association		[32]
Carotenoids (β-crypthoxantin)						
EPIC-Norfolk	2005	Nested case–control	88/176	Inverse		[31]
IWHS	2003	Prospective cohort	152/29,368	Inverse		[14]
NHS and NHS II	2010	Prospective cohort	787/184,643	No association		[32]
Carotenoids (lycopene)						
EPIC-Norfolk	2005	Nested case–control	88/176	No association		[31]
IWHS	2003	Prospective cohort	152/29,368	No association		[14]
NHS and NHS II	2010	Prospective cohort	787/184,643	No association		[32]
Carotenoids (lutein/zeaxanthin)						
EPIC-Norfolk	2005	Nested case–control	88/176	No association		[31]
IWHS	2003	Prospective cohort	152/29,368	No association		[14]
NHS and NHS II	2010	Prospective cohort	787/184,643	No association		[32]
Carotenoids (retinol; vitamin A)						

RA: Rheumatoid arthritis; RF: Rheumatoid factor.

Table 2. Summary of studies reporting measures of association between nutrients intake and rheumatoid arthritis (cont.).

Study name or location	Publication year	Design	Number of cases vs controls/cohort size	Direction of association	Comments	Ref.
Washington, DC, USA	1996	Population-based case–control	324/1245	No association		[6]
Finland	1994	Nested case–control	14/28	No association		[29]
EPIC-Norfolk	2004	Nested case–control	73/146	No association		[13]
NHS and NHS II	2010	Prospective cohort	787/184,643	No association		[32]
DCH	2005	Prospective cohort	69/57 053	No association		[8]

RA: Rheumatoid arthritis; RF: Rheumatoid factor.

NHS II cohort, a second prospective cohort study of younger nurses aged 25–42 years in 1989, who completed nutritional questionnaires in 1991, 1995 and 2001 [27]. By contrast, an increased risk was observed for vitamin D supplements in the NHS II cohort [27]. No association was observed between dietary intake of vitamin D during adolescence and RA later in life in the NHS or NHS II [28]. A nested case–control study on inflammatory polyarthritis within the EPIC-Norfolk study reported a weak nonstatistically significant positive association between dietary intake of vitamin D and inflammatory polyarthritis [13].

Selenium

Fish is also rich in selenium. Adequate levels of selenium are important for immunity, and selenium is also involved in regulating excessive immune responses and chronic inflammation [42]. No association was observed between selenium intake and inflammatory polyarthritis risk in the EPIC-Norfolk study [13]. Two nested case–control studies conducted in Finland analyzed the serum concentrations of selenium in men and women with and without RA [29,30]. An elevated risk of RA was observed for low levels of selenium, but the association was not statistically significant.

Contaminants

Fish also contains persistent organic pollutants, such as polychlorinated biphenyls and methyl mercury, that could play a role in developing RA [43]. However, no studies have analyzed the influence of these contaminants on the risk of RA.

Meat

Meat consumption is an important dietary source of protein and essential nutrients including iron, zinc and vitamin B_{12}. However, there is accumulating evidence that red meat consumption increases the risk of cardiovascular diseases [44,45] and colon cancer [46,47]. Ecological studies have shown that the prevalence of RA is also higher in countries with higher consumption of red meat [48].

However, analytical epidemiological studies have reported a lack of association with RA. A case–control study of women conducted in Washington (DC, USA) showed no association between total meat consumption and risk of RA [6], as well as the study conducted in the Diet, Cancer and Health cohort that found no association between red meat and total meat with the risk of RA [8]. Meat intake was extensively analyzed in the NHS, where total meat, red meat and poultry were not associated with the development of RA [9].

However, another nested case–control study found an increased risk of inflammatory polyarthritis with high intake of red meat (OR: 1.9; 95% CI: 0.9–4.0, for >58 vs <25.5 g/day) and red meat combined with other meat products (OR: 2.3: 95% CI: 1.1–4.9, for >87.8 vs <49 g/day) [11].

Proteins

Studies have shown that low-protein diets may improve RA symptoms [49–51]. In line with this, the EPIC-Norfolk study observed a threefold increased inflammatory polyarthritis risk for high levels of protein intake (OR: 2.9; 95% CI: 1.1–7.5, for >75.3 vs <62.4 g/day) [11]. By contrast, a case–control study of women in Washington (DC, USA) reported that percentage of calories from protein was inversely associated with risk of RA (OR: 0.65; 95% CI 0.46–0.94, for >17.9 vs ≤14.1% of energy per day) [6]. The association with protein was even stronger for RF-positive RA (RR: 0.52; 95% CI: 0.32–0.86). A stratified analysis of protein intake by animal or vegetable source in the prospective NHS did not find any association [9].

Iron

Dietary iron intake has been linked with increased risk of inflammation [52]; however, results from

epidemiological studies on the association of dietary iron intake and risk of RA have shown no associations [6,8,9,11].

Dairy products

Dairy products is a broad term used to indicate milk and products derived from milk, including yogurt, cheese and butter. Dairy products have a high content of calcium, magnesium, vitamin D, and whey proteins. Some dairy products, such as cheese, cream and butter also have a high fat content that may offset any benefits of increased intake of calcium or other potentially beneficial dairy components.

There are only two studies examining dairy product consumption in relation to RA risk, and their results are not consistent. The case–control study conducted in Washington (DC, USA) showed no association between dairy products and milk beverages and risk of RA [6]. By contrast, the IWHS prospective cohort reported an inverse association between total milk products (including skim milk, whole milk, ice cream, yogurt, cottage cheese, cream cheese, and other cheese) and risk of RA (RR: 0.66; 95% CI: 0.42–1.01, for ≥68 vs 1–35 servings per month) [12]. In addition, the use of butter was reported to decrease the risk of RA, while no associations were found between the consumption of other individual dairy products and RA. Neither of the two studies observed any association with calcium intake [6,12]. Regarding inflammatory polyarthritis, the nested case–control study within the EPIC-Norfolk cohort found an increased risk associated with dairy product consumption (OR: 1.9; 95% CI: 0.9–4.2, for >260 vs <153 g/day) [11].

Thus, in summary, no conclusions can be made, owing to a very limited number of studies and mixed results.

Foods of plant origin

Studies regarding consumption of foods of plant origin in relation to RA risk are also limited.

Fruit & vegetables

Fruits and vegetables play an important role in diet owing to their protective action against several chronic diseases [53,54] – from cancer [55] to cardiovascular diseases [56]. Since cardiovascular diseases may have an inflammatory response similar to RA [57], fruits and vegetables could also prevent the development of RA, especially thanks to their high content of antioxidant nutrients.

Studies on the association between fruits and vegetables and RA are limited, and results from case–control and prospective studies are not concordant. A case–control study conducted in Washington (DC, USA) found no association between fruit and vegetable consumption and RA risk [6]. However, a more recent case–control study in Greece found an inverse association between cooked vegetables and RA (OR: 0.39; 95% CI: 0.20–0.77, for >85 vs <20 servings per month), but not for raw vegetables [5]. Among prospective studies, an inverse association, although not statistically significant, was observed in the IWHS between fruit (RR: 0.72; 95% CI: 0.46–1.12, for >83 vs <52 servings per month) and vegetable (RR: 0.74; 95% CI: 0.48–1.14 for >97 vs <60 servings per month) consumption and RA [14]. Among fruits, oranges and grapefruit juice consumption showed the lowest relative risks, while among vegetables, cruciferous vegetable consumption was associated with the lowest risk. No associations with fruits or vegetables were observed in the DCH cohort [8].

In line with the Iowa cohort study, the EPIC-Norfolk study showed that a low intake of fruits and vegetables (OR: 1.9; 95% CI: 1.0–4.0, for <167 vs >275 g/day) was associated with increased risk of inflammatory polyarthritis [13].

Antioxidants

Fruits and vegetables are rich in antioxidants that may protect against oxidative stress. Products of free radical oxidation are present in the synovial fluid of patients with RA, indicating a role of free radicals and oxidative stress in the RA inflammation process [58,59].

Among the four studies examining associations between antioxidants and RA, only one prospective study observed an inverse association. Several antioxidants were examined in the IWHS, where inverse associations were observed for vitamin C and β-cryptoxanthin (carotenoid) with RA, while no associations were found for vitamin E, or other specific carotenoids (α- and β-carotene, lycopene and lutein/zeaxanthin) and total carotenoids [14]. No association was observed in the DCH cohort [8] or in the NHS and NHS II [32] with antioxidant (vitamin A, C and E, α- and β-carotene, β-cryptoxanthin, lycopene, lutein and zeaxanthin) intake from foods and supplements.

No association was observed in the case–control study conducted in Washington (DC, USA) between vitamins A, C and E and RA risk [6]. The EPIC-Norfolk study reported that low intake of vitamin C (OR: 3.3; 95% CI: 1.4–7.9, for <55.7 vs >94.9 mg/day) was associated with increased risk of inflammatory polyarthritis [13], while the intake of vitamin E, β-carotene, and retinol were not associated with inflammatory polyarthritis. A subsequent study based on the new cases arising from the same cohort, confirmed the inverse association between vitamin C and inflammatory polyarthritis, and also showed a decreased risk associated with intake of β-cryptoxanthin [31].

The association between antioxidants and RA was also examined using serum antioxidant concentrations in three studies. Two nested case–control study conducted in Finland observed an elevated risk of RA for low levels of serum α-tocopherol, and β-carotene, but none of the associations were statistically significant [29,30]. A case–control study in Washington County (MD, USA) analyzed the difference in serum concentration of α-tocopherol and β-carotene between RA cases and controls, finding a statistically significant decrease only for β-carotene [60].

A randomized, double-blind, placebo-controlled trial conducted in USA, The Women's Health Study, also evaluated vitamin E supplementation and found no association with RA [33].

Cereals & legumes

Consumption of whole-grain cereals has been shown to reduce levels of inflammatory markers (C-reactive protein and IL-6) [61]. In addition, legumes have been found to decrease levels of inflammatory biomarkers (high-sensitive C-reactive protein, TNF-α and IL-6) [62]. However, only one case–control study has analyzed the association of high-fiber cereals with RA and observed no association [6], while no studies have analyzed the association of legume consumption with RA.

Olive oil

Olive oil is a major component of the Mediterranean diet and is considered to be associated with many health benefits [63]. The health-related effects of olive oil are attributed to its richness in oleic acid and natural antioxidants [64]. Oleic acid has been reported to have modulatory effects in a wide variety of physiological functions, and a beneficial effect on cancer, autoimmune and inflammatory diseases [65]. Oleic acid is a n-9 monounsaturated fatty acid that is converted to 8,9,11-eicosatrienoic acid under restriction of n-6 fatty acids [66]. Oleic acid and its metabolite 8,9,11-eicosatrienoic acid may have an anti-inflammatory effect with a mechanism similar to fish oil [5].

However, results from epidemiological studies are inconclusive. Two hospital-based case–control studies conducted in Greece found an inverse association between high consumption of olive oil and risk of RA (OR: 0.39; 95% CI: 0.19–0.82, for high vs low) [4,5]. However, this finding was not confirmed in the prospective DCH cohort [8].

Beverages

Coffee

Coffee and tea are two of the most consumed beverages in the world. The first study on coffee and RA was conducted in Finland [16], where the association between coffee and RA was examined in a prospective cohort. The researchers found an increase in RA risk associated with a high intake of coffee (RR: 2.20; 95% CI: 1.13–4.27, for ≥four vs ≤three cups per day). However, the three following US prospective studies failed to replicate this result. The BWHS [17], the IWHS [18] and the NHS [19] reported no association with RA for total or caffeinated coffee intake. A lack of association was also observed in the Danish DCH cohort with RA [8] and in the EPIC-Norfolk nested case–control study with inflammatory polyarthritis [11].

However, a matched case–control study conducted in Denmark among men and women reported an increased RA risk associated with high coffee consumption (OR: 2.33; 95% CI: 1.40–3.87, for >ten vs zero cups per day) [15]. This association was present among anti-CCP-positive cases, but not among anti-CCP-negative RA cases. Moreover, when the analysis was stratified by shared epitope carrier status, the risk increased only among shared epitope heterozygotes and homozygotes, but not among noncarriers [67].

Decaffeinated coffee

It has been hypothesized that solvents used in the decaffeination process of coffee beans may play a role in the development of RA [68]. Observational studies seem to confirm this hypothesis. Indeed, the BWHS reported a positive association for decaffeinated coffee (OR: 3.9; 95% CI: 1.8–8.3, for ≥one cup per day vs <one cup per week) [17]. Similar results have been observed in the IWHS, which reported an increased risk of RA for decaffeinated coffee (RR for ≥four cups per day vs none: 2.44; 95% CI: 1.52–3.89) [18]. However, the NHS found no association [19].

Tea

It is hypothesized that tea has both antioxidative and antiinflammatory properties [69], but results from observational studies on RA are mixed. The IWHS observed a decreased risk of RA with high consumption of tea (RR: 0.35; 95% CI: 0.13–0.97, for three cups per day vs none) [18]. The NHS found no association with tea consumption [19]. In addition, no association was observed with inflammatory polyarthritis risk in the EPIC-Norfolk study [11]. In contrast to the hypothesis, the BWHS found a positive association between tea consumption and RA (OR: 2.1; 95% CI: 1.0–4.2, for ≥one cup per day vs <one cup per week) [17].

Alcohol

Long-term consumption of alcohol in moderate amounts may affect immune function and could downregulate production of proinflammatory molecules involved in the development of RA [70–72].

Among dietary factors, alcohol has been the most studied in association with RA. The first epidemiological study to analyze a possible association between alcohol consumption and RA was a hospital based case–control study among women in The Netherlands [20]. Women who drank three or more servings of alcohol per day had a 69% reduced risk of RA compared with women who did not drink (OR: 0.31; 95% CI: 0.13–0.74). However, subsequent studies did not observe any association between alcohol and RA. A case–control study from Washington (DC, USA) considering lifetime average alcohol consumption observed no association among pre- or post-menopausal women [21]. In addition, a frequency-matched case–control study in Denmark found no association between alcohol consumption and RA in both men and women, but found a decreased risk of anti-CCP-positive RA among subjects with an alcohol consumption of more than 15 drinks per week compared with never drinkers (OR: 0.60; 95% CI: 0.35–1.04) [8]. Moreover, they showed that shared epitope homozygotes reporting no alcohol consumption had a higher risk of anti-CCP-positive RA compared with noncarriers who consumed one to ten alcoholic drinks per week, suggesting a strong gene–environment interaction [67]. The EPIC-Norfolk nested case–control study reported no association between alcohol intake and inflammatory polyarthritis [11]. In addition, two prospective studies, conducted in Finland and the IWHS cohort observed no association [16,25]. The IWHS analyzed specific types of alcoholic beverages (beer, red wine, white wine and liquor), and found no association by type.

In 2008, the Epidemiological Investigation of RA (EIRA) group examined the association of alcohol consumption with RA in both their case–control study and in the Danish CACORA [22]. The researchers observed an inverse association with RA in both EIRA (OR: 0.5; 95% CI: 0.4–0.6) and CACORA (OR: 0.6; 95% CI: 0.4–0.9) for high alcohol consumption (amount not specified) compared with nondrinkers. The inverse association was also present for anti-CCP-positive RA, while the association with anti-CCP-negative RA was inverse in only the EIRA study, but not in CACORA.

All the following studies found an inverse association as well. A case–control study conducted in Sheffield (UK) demonstrated a four-times higher RA risk among never drinkers compared with those who drank more than 10 days per month (OR: 4.17; 95% CI: 3.01–5.77) [23]. This study also reported an inverse association between alcohol and anti-CCP-positive and -negative RA, and also with measure of disease severity, including C-reactive protein, Disease Activity Score 28, pain Visual Analog Scale and modified Health Assessment Questionnaire. A nested case–control study from the MDCS found a decreased risk among men and women with moderate (3.67–15.21 g/day) versus low consumption (0.05–3.66 g/day) of alcohol (OR: 0.48; 95% CI: 0.22–1.05), but not among those with high consumption (15.22–194.00 g/day) [24]. A study from the SMC showed a nonlinear dose-response relationship between glasses of alcohol per week and risk of RA (RR for >four vs <one glasses/week or never: 0.63; 95% CI: 0.42–0.96) [26]. Specific types of alcohol (beer, wine and liquor) were also inversely associated with RA, although the estimates were not statistically significant. The authors also performed an analysis of long-term alcohol consumption, showing that consistent consumption of more than three glasses per week over a period of more than 10 years halved the risk of RA compared with never drinkers (RR : 0.48; 95% CI: 0.24–0.98).

The accumulated evidence on the association between alcohol consumption and RA risk has been quantitatively summarized in two recent meta-analyses and clearly indicates a protective role of moderate consumption of alcohol (<15 g/day) in the development of RA [73,74].

Methodological considerations

In general, the accumulated evidence regarding the associations between dietary factors and risk of RA is limited and results are not consistent. This may, in part, be related to the different methodologies that researchers have used in analyzing such a complex exposure as diet.

First of all, the results could be influenced by the choice of study design. Case–control studies may be affected by recall bias, a systematic error due to a different recall of the exposure status between cases and controls. Receiving a diagnosis of RA may cause a more accurate recall and better reporting of dietary habits compared with healthy controls who are not as focused on their health. Therefore it is difficult to draw conclusions based on findings from case–control studies that could either be an overestimate or underestimate of the true risk owing to this type of bias. The prospective cohort design is preferred as it is not affected by recall bias, since the collection of dietary information occurs when all members of the cohort are not affected by the disease. Moreover, cases included in a case–control design may have already changed their diet at the time of the interview owing to the developing of RA, leading to biased estimates of the risk. However, prospective, as well as retrospective, studies can be affected by nondifferential misclassification of the exposure. In fact, people tend to report their food consumption according to what they think is socially acceptable. For example, women tend to report a lower alcohol consumption since high

alcohol consumption is considered an unhealthy behavior, while they tend to report higher intake of fruits and vegetables that are considered healthy [75]. Such type of misclassification usually leads to biased estimates.

All studies included in this review used a food frequency questionnaire, with the exception of the studies conducted by Pattison *et al.* who used a 7-day food diary [11,13,31]. The food diary is a more precise way to collect information regarding daily diet, but the time period of only 1 week does not allow an assessment of long-term diet and seasonal changes. Moreover, to take into account changes in diet over time and better assess the influence of food consumption on the risk of a disease it is important to collect dietary information at different points in time. Of the studies presented in this review, only the SMC [10,26] and the NHS and NHS II collected information at two or more occasions using a food frequency questionnaire [27,32].

Incident cases of RA were identified in multiple ways by the studies. Case–control studies identified cases from the rheumatology or internal medicine departments of hospitals, while prospective cohort studies identified cases in two different ways: some studies linked the cohort to national registers [8,10,11,13,26,31], while other studies validated self-reported RA cases by collecting medical records [9,12,14,18,25,27,28,32,33]. The use of self-reported and subsequently validated RA avoids the inclusion of misclassified RA cases; however, true RA cases that have not self-reported their status are missed and included in the study as noncases.

The studies conducted in the EPIC-Norfolk cohort analyzed inflammatory polyarthritis cases, of which only 40% satisfied the ACR criteria for RA definition [11,13,31]. The authors argued that they decided to use inflammatory polyarthritis and not RA definition because the RA criteria did not perform well in the setting of early disease [76]. They conducted analysis stratified by RA status, which did not reveal any difference from the results reported for inflammatory polyarthritis [11].

Finally, some studies could have been affected by problems related to a low statistical power. One nested case–control study included as few as 14 cases [29], while the EPIC-Norfolk study identified only 73 [13], and later 88 cases of inflammatory polyarthritis [11,31]. Among prospective cohort studies, the DCH cohort identified only 69 RA cases in a cohort of 57,053 men and women during an average follow-up of 5.3 years [8]. The cohort with the largest number of cases was the NHS with 546 cases identified among 82,063 women (Tables 1 & 2) [9].

Studies on subtypes of RA, such as RF positive or negative and ACPA positive or negative, are also very limited. Only six studies stratified accordingly to subtypes of RA and found different results between positive and negative RA cases [6,7,15,18,23,24]. The reasons for this could be either the small number of RA cases identified may prevent further stratifications or problems in retrieving information regarding the subtype's classification for each case.

Conclusion

Studies on diet and risk of RA are limited and often have reported mixed results. It is, therefore, difficult to draw any firm conclusions on the association between different foods and nutrients and RA development and its subtypes (RF positive and negative, ACPA positive and negative). The accumulated evidence is most consistent regarding moderate alcohol consumption and decreased risk of RA. Emerging evidence may also indicate a potentially beneficial role of fish consumption in RA prevention.

Future perspective

Further well-designed prospective studies are needed to better understand the role of diet in the development of RA. Prospective cohort studies with repeated measurements of diet over time to assess not only short-term, but especially long-term, diet in relation to RA development should be preferred. In addition, since some previous studies have reported a different association with RA depending on method of preparation of foods (e.g., cooked/broiled fish, raw vs cooked vegetables), further studies are needed to analyze also how different methods of cooking influence the observed associations of foods on RA development. Moreover, more attention should be given to the association of diet with specific types of RA.

Single prospective studies may have low statistical power to perform subgroup analyses, for example, by a specific type of RA, or by presence of specific genetic factors. Therefore, analyses of pooled data from available prospective studies should be strongly encouraged. This could also allow the analysis of the interplay of dietary factors with genetic factors in a prospective setting.

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Executive summary

Background

- Rheumatoid arthritis (RA), an inflammatory autoimmune chronic disease that affects the joints, affects approximately 1% of the adult population.
- Only smoking has been identified as risk factor for RA, while other modifiable factors, such as diet, are less studied and published results are mixed.

Foods of animal origin

- Studies on the association between fish, meat and dairy products and RA are limited and results are mixed.
- There is some evidence that fish consumption and long-chain n-3 polyunsaturated fatty acids are inversely associated with RA risk.

Foods of plant origin

- Among the limited studies on fruits and vegetables, as well as olive oil, some studies, but not all, observed decreased risk of RA.
- Beverages
  - Moderate alcohol intake is inversely associated with RA.
  - Caffeinated coffee and tea appear not to be associated with RA risk.
  - Decaffeinated coffee has been linked to an increased risk of RA.

Methodological consideration

- The methodologies used in the different studies, such as different study designs, varying definition of the outcome and collection of self-reported exposure data, could have led to the differences in the reported results.

Conclusion

- Studies on diet and RA are limited and results are mixed.
- The accumulated evidence is most consistent regarding moderate alcohol consumption and decreased RA risk.
- Emerging evidence is also indicates a potentially beneficial role of fish consumption in prevention of RA.
- Further studies, preferably with prospective design, are necessary to better understand the role of diet in the development of RA.

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