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Research on TCM Theory

Possible Roles of Diet in the Etiology of Rheumatoid Arthritis: A Systematic Review

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ABSTRACT

Background: There is a growing interest in the possible role of diet in the prevention of rheumatoid arthritis (RA). However, the evidence for diet having a role in the etiology of RA is inconsistent, sometimes conflicting.
Objective: To critically appraise the literature to pool the results of studies to clarify the relation between diet risk and RA.
Methods: We performed a systematic review using guideline-recommended methodology to evaluate the association between pre-illness diet or diet pattern and the risk of subsequent RA diagnosis.
Results: A total of 25 studies met the inclusion criteria. They include 13 cohort studies, 10 case-control studies and 2 nested case-control studies, with a total of 1279810 participants. There were new evidences of a protective effect of long term consumption of alcohol. High sodium intake was associated with an increased risk of RA. Fish intake has consistently been shown to have no effect on the development of RA. Mediterranean diet pattern, Vitamin D intake, and the consumption of long-chain omega-3 acids were not associated with an increased/decreased risk of RA in every two studies. There were non-statistically significant association between RA and sugar-sweetened soda, red meat, vegetable and fruits in each single study. The association between coffee, tea and RA was consistent, and here exists an inverse relationship between olive oil and RA. Due to the heterogeneity of study designs and analyses, the results could not be pooled.
Conclusion: The results of this SR indicate that alcohol consumption and sodium intake may be associated with RA risk, especially evidence from recent studies. Because of some discordant results, the debate continues on whether some other dietary intakes increase or decrease RA risk.
Key words: Diet, Rheumatoid Arthritis, Systematic review
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BACKGROUNDS

Rheumatoid arthritis (RA) causes disability and lowers the quality of life[1]. Although genetic factors play a part in susceptibility to RA, the etiology of RA remain elusive[2-3]. Now, there is much conflicting information on the internet about whether patients' diet has a role in the etiology of RA. The majority of intervention studies of diet and RA were published prior to the start of the twenty-first century. In 2009, a review of the effect of diets for people with RA was conducted by researchers in the Cochrane Collaboration[4]. By contrast, new clinical evidences to explore correlations between diet and RA onset are developing in the late years. Furthermore, the microbiota of the human gut is gaining broad attention owing to its association with RA and the potential uses of complementary and alternative medicine in RA[5-6], there is a growing interest in the role of diet in the prevention of RA[7-8].

A number of observational studies have examined the role of different diet factors in the etiology of RA. Cohort and case control studies have shown positive effects of a variety of daily food and nutrients on RA. Examples include alcohol[9] and fish[10]. But other authors report negative results. In 2004, a first publication of systematic review (SR) of the role of diets in susceptibility to RA summarized the previous available evidence[3]. Consequently, 12 years later, it is difficult to refer such SR as there is an unbiased assessment of the evidence linking diet and RA onset. For instance, two new studies, presented at the American College of Rheumatology Annual Meeting in San Francisco, show a person's diet can significantly affect his or her chance of developing RA[11]. The first study found that typical Western diets can increase a person's risk of developing RA in comparison to Prudent diets. The second study showed that following the Dietary Guidelines for Americans can also lower one's chance of developing the disease. Such information would be of value in terms of current public health education, and could also inform the development of preventive strategies.

Obviously, the evidence for diet having a role in the etiology of RA is inconsistent, sometimes conflicting. Now, it is a good chance to summarize new evidence and explore confounder adjustment in analysis. Here, we performed a SR using guideline-recommended methodology to evaluate the association between pre-illness diet and the risk of subsequent RA diagnosis.

MATERIALS AND METHODS

Searches

Two authors (CZ and KMC) searched the following electronic databases from their inception to April 2016: PubMed, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library. Search strategy example Pubmed (((arthritis, rheumatoid[MeSH Terms]) OR rheumatoid arthritis[Title])) AND ((((((((((((((((diet[Title/Abstract]) OR Nutrient[Title/Abstract]) OR nutritional[Title/Abstract]) OR food[Title/Abstract]) OR vitamin[Title/Abstract]) OR fatty acids[Title/Abstract]) OR fish oil[Title/Abstract]) OR fish[Title/Abstract]) OR coffee[Title/Abstract]) OR alcohol[Title/Abstract]) OR tea[Title/Abstract]) OR sodium [Title/Abstract]) OR sugar[Title/Abstract]) OR meat[Title/Abstract]) OR vegetable[Title/Abstract]) OR fruit[Title/Abstract]) OR olive oil[Title/Abstract]) Filters: Humans. For others, these terms were slightly modified. There is no language restriction. Search strategy available on request.

Inclusion and excluded criteria

Observational studies were included that:

- were case control studies, cohort studies, or nested case control studies.
- examined the relationship between diet/diet pattern and the risk of RA development.
- patients with RA, as defined by the American College of Rheumatology (ACR) (1987) or other acceptable criteria.

The manuscripts with the following criteria will be excluded: intervention trials, case reports and animal studies. Additional studies evaluating the same cohort (the largest study with the most complete information was included) were also excluded.

Study selection

All studies were assessed and was performed by pairs of investigators (KMC and CZ), working independently. Studies were included if they investigated diet of interest. When studies were reported in several publications, we analyzed only the most complete set of data to avoid double counting cases.

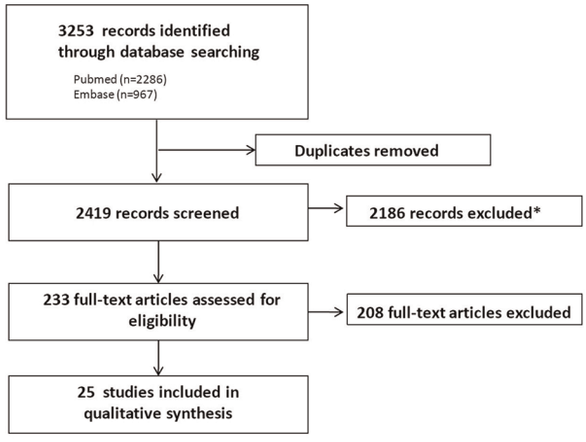
Data extraction

The following data were extracted from the selected studies: (1) study design; (2) country; (3) number of participants; (4) characteristics of participants; (5) factors adjusted for in analyses; (6) Outcomes. Risk of bias for included studies was assessed by two authors (CZ and KMC) according to Newcastle-Ottawa Quality Assessment Scale (NOQAS)[12].

RESULTS

Study characteristics

Figure 1 illustrates the flow chart for search process and study selection. The electronic searches identified 3253 studies. All of the studies were judged, on the basis of titles and abstracts, as not relevant. We include 13 cohort studies, 10 case-control studies and 2 nested case-control studies, with a total of 1279810 participants. Characteristics of the included studies are showed in Table 1. The number of papers from US and northern Europe mainland still comprises a very large proportion of the total number of papers (Figure 2). The majority (57.7%) of included studies were published in recent ten years.



***Case reports, letters, reviews and studies in animals or did not evaluate outcomes of interest reviews were excluded.**

Figure 1. Flow of papers through review.

Methodological quality

According to the predefined quality assessment criteria, the general methodological quality of the majority of studies was good (Table 2). The score ranged from 5 to 8. The quality is good (7.15±0.91). Some cohort studies were not allocated points because they used semi questionnaires to evaluate exposures; additionally one study failed to adjust for confounders. Some case control studies were not allocated points because they captured information on diet exposures from unblinded interviews, did not fully report response rates or had differing response rates between cases and controls.

Some daily foods or nutrients and the risk of RA

1. Alcohol consumption

Ten studies[13-22] met our inclusion criteria, comprising five case control studies (3584 cases, 8477 controls) and three cohort studies (935 RA cases, 303608 individuals) and two nested case control studies (558 RA cases, 2574 individuals). The data for six studies were collected from women. Rest four studies include both men and women. Significant protective effects of long term modest alcohol consumption on RA risk were observed in five studies after 2009 (Figure 3). In one recent study, although some trends could be seen in subgroup analyses as standard glasses. This is inconsistent with the previous five studies. One reason to this discrepancy could be that the consumption of alcohol in these patients and controls was lower than those in previous studies showing associations.

Table 1 Studies reporting measures of association between dietary factors and rheumatoid arthritis (RA)

	Study ID	Age	Sex	Study design	Cases	Factors adjusted for in analyses	Association with RA
Alcohol							
	Hazes et al 1990 The Netherlands	16–50	F	Case control	135/378	Year of birth, age at onset of symptoms, parity, number cigarettes, marital status, menopause, oral contraceptive use	Alcohol consumptions per day adjusted OR (95% CI) None 1.00 ≥1 0.54 (0.35, 0.82) 1–2 0.62 (0.40, 0.98) ≥3 0.31 (0.13, 0.74) *P* = 0.10
	Voigt et al 1994 US	15–64	F	Case control	349/1457	Age, smoking history, BMI	Lifetime alcoholic drinks per week adjusted OR (95% CI) Premenopausal / Postmenopausal None 1.00 / 1.00 1 1.20 (0.60, 2.10) / 1.1 (0.70, 1.70) 1–5 1.10 (0.60, 2.0) / 0.9 (0.60, 1.50) 5–14 0.70 (0.30, 1.50) / 0.7 (0.40, 1.30) >14 0.50 (0.20, 1.70) / 1.1 (0.5, 2.20)
	Cerhan et al 2002 US	55–69	F	Cohort	158/31336	Age	Total alcohol g/day adjusted RR (95% CI) None 1.00 1.00 <2 0.77 (0.46, 1.27) 2–7 1.21 (0.80, 1.83) >7 0.86 (0.51, 1.36) *P* = 0.85
	Rodríguez et al 2009 UK	20–79	F	Case control	579/4234	Age, sex, smoking, BMI	Alcohol intake (units per week) OR (95% CI) 0–1 1.00 2–20 0.94 (0.76, 1.17) 21–36 1.37 (0.81, 2.33) >37 1.06 (0.46, 2.45)
	Källberg et al 2009 Sweden & Denmark	51.1 (12.5) 52.1 (11.7) 49.1 (11.1) 49.8 (10.5)	F+M	Case control	1204/871 444/533	Age, sex, smoking and residential area (EIRA only)	Alcohol consumption per week OR (95% CI) EIRA, OR = 0.50 (95% CI 0.40 to 0.60); CACORA, OR = 0.60 (95% CI 0.40 to 0.90)
	Maxwell et al 2010 UK	61.4 (12.2) 48.0 (13.9)	F+M	Case control	873/1004	Age, gender and smoking	Never- vs ever-regular alcohol consumption, adjusted OR (95% CI) Yes 1 No 2.31 (1.73, 3.07)
	Giuseppe et al 2012 Sweden	48–83	F	Cohort	197/34141	Age, smoking, current cigarettes/day, BMI, educational, parity, menopausal status, and consumption of meat and dairy products	No of glasses of alcohol/week adjusted RR (95% CI) <1 or never 1.00 1–2 0.86 (0.56 to 1.33) >2–4 0.99 (0.67 to 1.46) >4 0.63 (0.42 to 0.96) *P* = 0.04

Table 1 (Continued)

	Study ID	Age	Sex	Study design	Cases	Factors adjusted for in analyses	Association with RA
	Bergström et al 2012 Sweden	63.4 (8.0)	F+M	Nested case control	172/688	Smoking, formal education, and consumption	Alcohol consumption per week OR (95% CI) Lowest quartile 1 Moderate quartiles 2–3 0.52 (0.25–1.07) Highest quartile 0.75 (0.33–1.69)
	Lu et al 2014 US	30–55	F	Cohort	580/238131	Age, community median income, smoking, BMI, physical activity, menarche age, breastfeeding, menopausal status, post-menopausal hormone use, and total calories intake	Total alcohol use of 5.0–9.9 grams/day multivariable adjusted hazard ratios (HR) (95% CI) 0.78 (0.61–1.00)
	Sundström et al 2015 Sweden	30–61	F+M	Nested case control	386/1886	None	Glasses of alcohol per week OR (95% CI) 1 1 1–2 1.03 (0.78–1.36) 2–4 0.88 (0.65–1.20) >4 0.84 (0.54–1.31)
Coffee							
	Heliövaara et al 2000 Finland	20–98	F+M	Cohort	126/18981	Age, sex, BMI, education, serum cholesterol, smoking, alcohol	Caffeinated coffee consumption–cups/day ≤3 1 ≥4 2.20 (1.13, 4.27) *P* = 0.01
	Mikuls et al 2002 US	55–69	F	Cohort	158/31336	Age, sex, education, HRT use, smoking, alcohol, marital status	Total coffee cups/day adjusted RR (95% CI) None 1.00 ≥1 1.39 (0.68, 2.82) 2–3 1.10 (0.52, 2.32) ≥4 1.56 (0.80, 3.06); *P* = 0.21
	Karlson et al 2003 US	34–59	F	Cohort	480/83124	Age, sex, BMI, education, oral contraceptive use, parity, breastfeeding, smoking, alcohol, HRT use	Total coffee cups/day adjusted RR (95% CI) None 1.00 ≤1 0.6 (0.9, 1.3) 2–3 1.1 (0.8, 1.5) ≥4 1.2 (0.9, 1.7)
	Pedersen et al 2005 Finland	50–64	F+M	Cohort	69/56691	Age, sex, smoking, education	Coffee per 200 g/day Incidence rate ratios (IRR) (95% CI) 1.10 (0.99–1.21) *P* = 0.07
Tea							
	Mikuls et al 2002 US	55–69	F	Cohort	158/31336	Age, sex, education, HRT use, smoking, alcohol, marital status	Tea cups/day adjusted RR (95% CI) None 1.00 <0.6 1.09 (0.73,1.63) 0.6–3.0 1.23 (0.81,1.87) >3.0 0.35 (0.13,0.97); *P* = 0.50

Table 1 (Continued)

	Study ID	Age	Sex	Study design	Cases	Factors adjusted for in analyses	Association with RA
	Karlson et al 2003 US	34–59	F	Cohort	480/83124	Age, sex, BMI, education, oral contraceptive use, parity, breastfeeding, smoking, alcohol, HRT use	Tea cups/day adjusted RR (95% CI) None 1.00 >3 1.1 (0.7, 1.6)
Sodium							
	Salgado et al 2015 Spain	mean age 38	F+M	cross-sectional	392/18555	Age, sex, prevalent diabetes, prevalent cardiovascular disease, prevalent cancer, dietary habits, BMI, smoking, alcohol	Total sodium intake adjusted OR (95% CI) 1.5 (1.1–2.1) $P = 0.02$
Sugar-sweetened soda							
	Hu et al 2014 US	30–55	F	Cohort	857/238131	Age, sex, BMI, family income, physical activity, alcohol, smoking habit, multivitamin use, age of menarche, parity, breastfeeding, menopausal status, current hormone use, total energy intake	Sugar-sweetened soda consumption multivariable adjusted HRs (95% CIs) <1 serving/mo 1 (Reference) 1–4 servings/mo 1.18 (0.88, 1.59) 2–6 servings/wk 0.85 (0.64, 1.15) ≥1 servings/d 0.90 (0.52, 1.53) $P = 0.44$
Fish							
	Linos et al 1991 Greece	24–89	F+M	Case control	168/137	Age, sex, occupation, residence, marital status, BMI, Adherence to Lent, consumption of major food groups	Fish consumption per month unadjusted RR (95% CI) 1–2 1.00 4–10 0.64 (0.38, 1.08) ≥12 0.37 (0.13, 1.05) $P = 0.03$
	Shapiro et al 1996 US	15–64	F	Case control	324/1243	Age, race, education, total energy intake	Fish consumption (servings/day) adjusted OR (95% CI) <1 1.00 1–2 0.87 (0.62, 1.21) ≥2 0.92 (0.67, 1.25)
	Linos et al 1999 Greece	18–84	F+M	Case control	145/188	Age and sex	Fish consumption (median 3 s/w) RR (95% CI) Q1: 1.00 (ref) Q2 (4 s/w): 1.21 (0.64, 2.29) Q3 (6 s/w): 0.90 (0.47, -1.71) Q4 (10 s/w): 0.95 (0.46, 1.96)
	Pedersen et al 2005 Denmark	50–64	F+M	Cohort	69/56691	Age, sex, smoking, education	Fish per 30 g/day Incidence rate ratios (IRR) (95% CI) 0.91 (0.68–1.23) $P = 0.55$
	Benito-Garcia et al 2007 US	30–55	F	Cohort	546/82063	Age, BMI, smoking	Fish consumption (servings/day) adjusted RR (95% CI) 0.07 1.00 0.13 0.94 (0.73–1.23) 0.17 1.09 (0.81–1.47) 0.25 1.06 (0.80–1.40) 0.44 0.96 (0.72–1.26) $P = 0.88$

Table 1 (Continued)

	Study ID	Age	Sex	Study design	Cases	Factors adjusted for in analyses	Association with RA
	Rosell et al, 2009 Sweden	18–70	F+M	Case control	1889/2145	Age, residential area, smoking, sex	Fish consumption RR (95% CI) Never/seldom: 1.00 1–3 s/m: 0.8 (0.7, 1.0) 1–7 s/w: 0.8 (0.6, 1.0)
	Giuseppe et al 2014 Sweden	54–89	F	Cohort	205/32232	Age, smoking, alcohol, use of aspirin, intake energy	Fish consumption RR (95% CI) <1 s/w 1 ≥1 s/w 0.71 (0.48, 1.04)
	Sundström et al 2015 Sweden	30–61	F+M	Nested case control	386/1886	None	Fish consumption (servings/day) OR (95% CI) Lowest tertile 1 Intermediate tertile 0.95 (0.73–1.24) Highest tertile 0.92 (0.70–1.22)
	Hu et al 2015 US	30–55	F	Cohort	913/174638	Age, sex, BMI, family income, physical activity, alcohol, smoking habit, multivitamin use, age of menarche, parity, breastfeeding, menopausal status, current hormone use, total energy intake	Fish consumption (servings/day) HR (95% CI) Q1 1.00 Q2 1.01 (0.83–1.23) Q3 1.03 (0.85–1.26) Q4 1.15 (0.95–1.40) *P* = 0.12
Red meat							
	Pedersen et al 2005 Denmark	50–64	F+M	Cohort	69/56691	Age, sex, smoking, education	Red meat per 100 g/day Incidence rate ratios (IRR) (95% CI) 1.36 0.75–2.47 *P* = 0.31
	Benito-Garcia et al 2007 US	30–55	F	Cohort	546/82063	Age, BMI, smoking	Red meat consumption (servings/day) adjusted RR (95% CI) 0.53 1.00 0.89 0.92 (0.71–1.19) 1.21 0.95 (0.73–1.23) 1.57 0.82 (0.62–1.09) 2.22 0.86 (0.64–1.16) *P* = 0.35
Vegetable							
	Linos et al 1999 Greece	18–84	F+M	Case control	145/188	Consumption of major food groups, BMI	Vegetable consumption–quartiles of intake adjusted OR (95% CI) Lowest 1.00 2nd 0.67 (0.34, 1.28) 3rd 0.89 (0.47, 1.61) Highest 0.85 (0.44, 1.67) *P* = 0.78
	Hu et al 2015 US	30–55	F	Cohort	913/174638	Age, sex, BMI, family income, physical activity, alcohol, smoking habit, multivitamin use, age of menarche, parity, breastfeeding, menopausal status, current hormone use, total energy intake	Vegetable consumption (g/1000kcal) HR (95% CI) Q1 1.00 Q2 0.94 (0.78–1.14) Q3 0.96 (0.79–1.17) Q4 1.13 (0.92–1.38) *P* = 0.15

Table 1 (Continued)

	Study ID	Age	Sex	Study design	Cases	Factors adjusted for in analyses	Association with RA
Fruit							
	Hu et al 2015 US	30–55	F	Cohort	913/174638	Age, sex, BMI, family income, physical activity, alcohol, smoking habit, multivitamin use, age of menarche, parity, breastfeeding, menopausal status, current hormone use, total energy intake	Fruit consumption (g/1000kcal) HR (95% CI) Q1 1.00 Q2 0.96 (0.80–1.16) Q3 1.16 (0.96–1.40) Q4 0.95 (0.77–1.17) $P = 0.86$
Olive oil							
	Linos et al 1991 Greece	24–89	F+M	Case control	168/137	Age, sex, occupation, residence, marital status, BM, Adherence to Lent, consumption of major food groups	Olive oil consumption per month unadjusted RR (95% CI) 8–14 0.90 (0.38, 2.25) 16–24 0.90 (0.19, 4.05) 28–30 0.50 (0.29, 0.99) >30 0.26 (0.07, 0.98) $P = 0.01$
	Linos et al 1999 Greece	18–84	F+M	Case control	145/188	Consumption of major food groups, BMI	Olive oil consumption–quartiles of intake adjusted OR (95% CI) Lowest 1.00 2nd 0.60 (0.30, 1.22) 3rd 0.95 (0.48, 1.91) Highest 0.38 (0.17, 0.85) $P = 0.02$
Long-chain omega-3 acids							
	Giuseppe et al 2014 Sweden	54–89	F	Cohort	205/32232	Age, smoking, alcohol, use of aspirin, intake energy	Consumption (g/day) adjusted RR (95% CI) ≤0.21 1 0.21–0.29 0.62 (0.41, 0.95) 0.30–0.37 0.50 (0.46, 1.07) 0.38–0.49 0.67 (0.44, 1.03) >0.49 0.26 (0.07, 0.98) $P = 0.30$
	Sundström et al 2015 Sweden	30–61	F+M	Nested case control	386/1886	None	Long-chain omega-3 acids (E%) OR (95% CI) Lowest tertile 0–0.04 (Men),0–0.04 (women) 1 Intermediate tertile 0.04–0.10, 0.04–0.10 0.83 (0.63–1.09) Highest tertile 0.10–0.95, 0.10–0.11 1.03 (0.79–1.35)
Vitamin D							
	Merlino et al 2004 US	55–69	F	Cohort	152/29368	Age, caloric intake, smoking, hormone replacement therapy, decaffeinated coffee, β-cryptoxanthin intake	Vitamin D from food and supplements (IU/day) adjusted RR (95% CI) <221.4 1.00 221.4–467.6 0.67 (0.45–1.01) ≥467.7 0.67 (0.44–1.00) $P = 0.05$

Table 1 (Continued)

Study ID	Age	Sex	Study design	Cases	Factors adjusted for in analyses	Association with RA
Costenbader et al 2008 US	22–55	F	Cohort	722/186389	Age, oral contraceptive use, menopausal status, postmenopausal hormone use, smoking, latitude of residence at age 15, physical activity in metabolic equivalent hours per week, BMI and race.	Vitamin D intake (IU/day) adjusted RR (95% CI) Quintile 1 1.00 (Ref.) Quintile 2 1.50 (0.9, 2.5) Quintile 3 1.20 (0.7, 2.1) Quintile 4 1.30(0.8, 2.2) Quintile 5 1.40 (0.8, 2.3) *P* = 0.30
Mediterranean diet						
Hu et al 2015 US	30–55	F	Cohort	913/174638	Age, sex, BMI, family income, physical activity, alcohol, smoking habit, multivitamin use, age of menarche, parity, breastfeeding, menopausal status, current hormone use, total energy intake	aMed score adjusted HR (95% CI) Q1 1.00 Q2 0.81 (0.67–0.98) Q3 0.97 (0.80–1.18) Q4 0.98 (0.80–1.20) *P* = 0.85
Sundström et al 2015 Sweden	30–61	F+M	Nested case control	386/1886	None	Mediterranean diet score (MDS) OR (95% CI) Lowest tertile (0–2) 1 Intermediate tertile (3–4) 0.81 (0.62–1.07) Highest tertile (5–8) 0.82 (0.60–1.12)

BMI: body mass index.

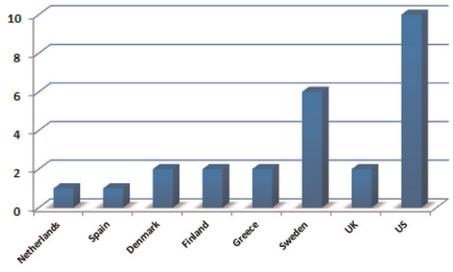


Figure 2. Distributions of countries in 25 studies that reporting measures of association between dietary factors and risk of rheumatoid arthritis onset.

2. Coffee intake

This was evaluable in four studies[23-26] (Table 1). One reported a significant inverse risk relationship between coffee intake and RA development. The remainder showed no relationship.

3. Tea

The situation was similar in the tea assessment studies. One cohort study evaluated the impact of tea on RA risk with significant adjusted risk reductions RR (95%CI) (0.35 (0.13, 0.97))[24]. However, another cohort study with no risk reduction observed RR (95%CI) 1.1 (0.7, 1.6)[25].

4. Daily sodium intake

Salgado et al, 2015[27] showed a dose-dependent relationship between daily sodium intake and the diagnosis of RA. The study also demonstrates that the association between sodium intake and RA is more significant in nonsmokers than in smokers; as the risk of RA is already high in smokers. RA patients should be aware of high sodium intake and smoking which are both preventable. But this linkage needs further investigation to understand the theory behind.

Table 2. Quality of studies evaluating the impact of diet on the risk of rheumatoid arthritis with Newcastle-Ottawa Quality Assessment Scale (score from 0 as poor to 9 as excellent)

Study ID	Total score
Hazes et al 1990[13]	7
Voigt et al 1994[14]	7
Cerhan et al 2002[15]	7
Rodríguez et al 2009[16]	7
Källberg et al 2009[17]	7
	7
Maxwell et al 2010[18]	7
Giuseppe et al 2012[19]	7
Bergström et al 2012[20]	7
Lu et al 2014[21]	8
Heliövaara et al 2000[23]	8
Mikuls et al 2002[24]	8
Karlson et al 2003[25]	7
Pedersen et al 2005[26]	6
Salgado et al 2015[27]	8
Hu et al 2014[28]	8
Linos et al 1991[29]	5
Shapiro et al 1996[30]	8
Linos et al 1999[31]	5
Benito-Garcia et al 2007[33]	7
Rosell et al 2009[32]	6
Giuseppe et al 2014[34]	8
Sundström et al 2015[22]	8
Hu et al 2015[35]	8
Merlino et al 2004[41]	8
Costenbader et al 2008[42]	8

5. Sugar-sweetened soda consumption

Hu and his colleagues have performed a large prospective cohort study to prove that women who consumed ≥1 serving of sugar-sweetened soda/d had a 63% (HR: 1.63; 95% CI: 1.15, 2.30; P = 0.004) increased risk of developing seropositive RA compared with those who consumed no sugar-sweetened soda or who consumed <1 serving/mo[28].

6. Fish consumption

Nine studies[22,26,29-35] (four case-controls, four prospective cohorts and one nested case control study) involving a total of 4645 RA cases were included. Four of the studies analyzed RA risk only among women, while the remaining analyzed both men and women. Two studies adjusted only for age and gender, while other took into account other possible confounding factors, such as body mass index (BMI) and total energy intake. Four studies adjusted for other dietary factors, such as smoking and alcohol consumption. Using the NOQAS quality assessment, the nine studies were assessed to have moderate to high quality.

7. Vegetable and fruit

913 incident cases of RA were documented in two cohorts, the Nurses' Health Study (NHS; 1980–2008) and NHS II (1991–2009). The Alternate Mediterranean Diet Score (aMed), a modified version of the Mediterranean diet scale, consist 9 components including vegetables and fruits. Results from Hu et al 2015 study[35], the largest study to date, did not observe a significant association for vegetable, fruit intake and RA.

8. Mediterranean diet

Same as above, according to Hu et al, 2015[35], there is no significant association found between an overall Mediterranean dietary pattern and RA risk. The same year, the results of a nested case control indicated that no significant association was found in the highest tertile of Mediterranean diet score among the cases and control OR (95%) 0.82 (0.60–1.12)[22].

DISCUSSION

In 2004 SR[36], the authors have identified 14 studies that the evidence for diet having a role in the etiology of RA is limited. In this SR, we found 25 studies meeting the inclusion criteria, nearly doubled in amount. They include 13 cohort studies, 10 case-control studies and 2 nested case-control studies. There were new evidences of a protective effect of long term consumption of alcohol (Figure 3). Fish intake has consistently been shown to have no effect on the development of RA. Similar findings to ours were presented in SRs 2 to 3 years ago[10,37]. High sodium intake was associated with

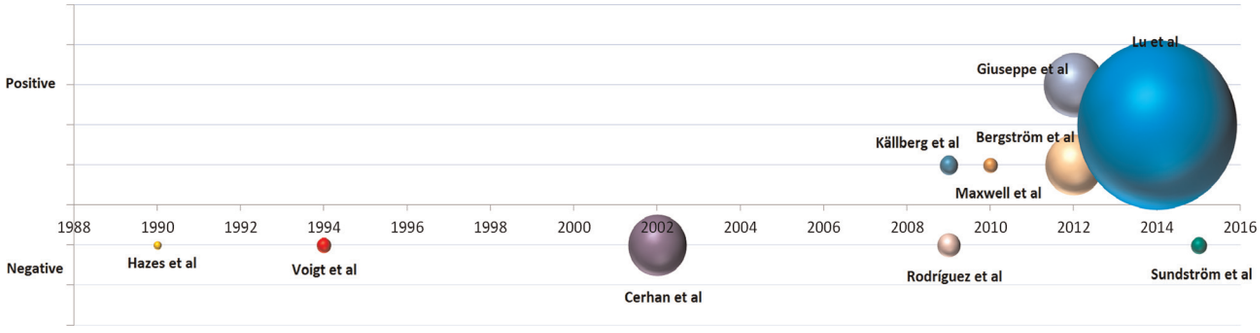


Figure 3. Bubble chart for positive (+)/negative (-) results from studies that reporting measures of association between Alcohol intake and risk of rheumatoid arthritis onset. Data were from ten studies published in the past twenty years. The size of each bubble represents the total number of sample size of each study. More recently, study with larger sample size suggested significant risk relationship between alcohol intake and RA onset.

an increased risk of RA. Mediterranean diet pattern, Vitamin D intake, and the consumption of long-chain omega-3 acids were not associated with an increased/decreased risk of RA in every two studies. There were non-statistically significant association between RA and sugar-sweetened soda, red meat, vegetable and fruits in each single study. The association between coffee, tea and RA was consistent, and here exists an inverse relationship between olive oil and RA.

Databases are an important source for risk studies. However, sometimes they lack information on some potential confounders for specific diseases. Of nearly two dozen variables, 3-10 commonly used factors were adjusted to estimate relative risk in these studies. In some studies, coffee consumption itself has an association on the initiation of RA, but greater coffee drinking is associated with smoking, which has been shown to be a risk factor for RA. That is the difficulty in post hoc analysis. Individuals with a family history of RA are known to have an approximately two-fold increased risk of the disease[38]. It is difficult to interpret whether this increased risk is due to genetic or environmental effects such as diet pattern. Hence, family history can be used as a factor in questionnaire design and data analysis. Fortunately, there is an NIH-funded prospective, Personalized Risk Estimator for RA (PRE-RA) Family Study (ClinicalTrials.gov NCT02046005) designed to understand how personalized risk factors for RA may impact willingness to change behaviors associated with RA. There's a lot can be expected[39].

There are several limitations of the present review. Most of the studies used many different outcome measures, increasing the probability of detecting remarkably differences in some of them by chance. Standardized terminology may facilitate RA case identification and questionnaire application since semi food frequency questionnaire (FFQ) is a frequently used tool to assess dietary patterns in these included original studies[40]. Participants in prospective cohort studies received the FFQ when they were pre-disease, while in retrospective case control studies, some RA patients received the FFQ after identification, leading to a possible recall bias. On the other hand, a SR conclusion is influenced by the quality of the studies included. Results could be over- or underestimated due to residual confounding. In our study, although there were non-statistically significant associations between RA and sugar-sweetened soda, red meat, vegetable and fruits, but the results were only from single or two studies. Additionally, all researches were from US and European, it limited generalizability of the studies' findings. Actually, many diet factors and patterns from worldwide are not explored until now. As we known, in Chinese medicine, as with most autoimmune diseases, proper diet is extremely important to prevent RA. More researches around the world are expected to develop tests that will show the association of diet and RA onset. Moreover, although microbial involvement has been suggested in RA as well, no definitive link has been established in nationwide cohort studies that assess long-term outcomes after some diet factors. Further studies are clearly required.

CONCLUSION

The results of this SR indicate that alcohol consumption and sodium intake may be associated with RA risk, especially evidence from recent studies. Because of some discordant results, the debate continues on whether some other dietary intakes increase or decrease RA risk.

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AUTHOR CONTRIBUTIONS

Designers: CZ and APL; Searchers: CZ and KMC; Studies appraisers: CZ, KMC and APL; Data extractors: CZ and KMC; Analyzer: CZ, KMC and APL; Writers: CZ and KMC.

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