The Role of Diet in Susceptibility to Rheumatoid Arthritis: A Systematic Review

DOROTHY J. PATTISON, ROGER A. HARRISON, and DEBORAH P.M. SYMMONS

ABSTRACT. ***Objective.*** Many studies have examined the role of diet in the management of established rheumatoid arthritis (RA), warranting several recent reviews. However, none have considered the possible link between diet and the onset of RA in detail. Studies investigated a possible effect of individual components of diet and the development of RA, but the lack of a systematic review means there is no unbiased assessment of the evidence.

Methods. We systematically reviewed studies with comparison groups that examined dietary intake or biological markers prior to the onset of RA. Four electronic databases were searched to identify relevant reports. Six quality criteria were agreed, against which the studies were assessed. The main outcome measure was a diagnosis of RA according to the ARA 1958 or revised ACR 1987 classification criteria.

Results. Fourteen reports were included in the review. There was evidence of a protective effect of higher consumption of olive oil, oil-rich fish, fruit, vegetables and ß-cryptoxanthin. Lower serum concentrations of antioxidants were associated with an increased risk of RA in 3 studies. Due to the heterogeneity of study designs and analyses, the results could not be pooled.

Conclusion. Evidence exists that diet may play a role in the etiology of RA, but it is inconclusive due to the small number of studies available and variation in study design. (J Rheumatol 2004; 31:1310–9)

Key Indexing Terms:

DIET	RHEUMATOID ARTHRITIS	ETIOLOGY
SYSTEMATIC REVIEW	CASE-CONTROL	COHORT

The cause of rheumatoid arthritis (RA) is still unknown. It is likely to involve both genetic susceptibility and environmental factors such as diet. There are leads from the investigation of other chronic diseases and from the treatment of RA that may be worth following. For example, fruit and vegetable consumption has been shown to have an important role in the etiology of other chronic diseases, such as cardiovascular disease[1,2] and some cancers[3]. Given that cardiovascular disease shares similar inflammatory and immunologic pathways with those observed in RA[4], it is reasonable to hypothesize that a higher intake of fruit and vegetables may influence the etiology of inflammatory joint disease. A metaanalysis of 10 trials of dietary fish oil supplementation compared to placebo in patients with established RA showed that fish oil has a modest effect in reducing the tender joint count and morning stiffness[5], but it is not known whether fish oils can reduce the risk of developing the disease.

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Submitted June 9, 2003; revision accepted January 14, 2004.

A number of epidemiological studies have examined the role of diet in the etiology of RA, but these have not been subjected to systematic review. Consequently, it is difficult to obtain a robust and unbiased assessment of the evidence linking diet and RA onset[6]. Such information would be of value in terms of public health education, and could also inform the development of preventive strategies.

We systematically reviewed studies that examined the association between diet and RA onset.

MATERIALS AND METHODS

Identification of studies. We used the following databases to conduct literature searches: the Cochrane Database of Systematic Reviews, Medline OVID citations (1966 to 2003), Embase (1980 to 2003), and the ISI Web of Science (1981 to 2003). We used the following search criteria: ("diet" or "nutrition" or "food" or "antioxidant" or "alcohol" or "lifestyle") combined with ("arthritis" or "rheumatoid arthritis") and ("aetiology" or "etiology" or "cohort" or "risk" or "onset") or ("case" and "control") to identify studies that examined the association between dietary factors and RA onset. Searches were restricted to English language publications, but no date restrictions were imposed. The reference lists of reports obtained were also searched to identify other relevant reports. We also searched journal supplements of abstracts from the American College of Rheumatology (ACR), the British Society for Rheumatology (BSR), and the European Congress of Rheumatology (EULAR) annual scientific meetings, from 2001 and 2002, assuming that abstracts presented prior to 2001 would have been published as scientific reports by the time of this review.

Inclusion and exclusion criteria. All relevant reports of studies with comparison groups, that is, case-control and cohort studies, were reviewed. We focused on studies that measured dietary intake and reported associa-

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tions between food and/or nutrients and the onset of RA. We also included studies that assessed nutrient exposure using biological markers of dietary nutrient intake. Ecological and cross-sectional studies were excluded because these study designs are inappropriate for estimating disease risk[7]. The primary outcome was onset of RA, according to the 1958 American Rheumatism Association (ARA) criteria[8] or the revised 1987 ARA classification criteria for RA[9]. These criteria were initially derived from the consensus opinion of experts and were developed to discriminate between patients with established RA and those with other defined musculoskeletal syndromes attending hospital clinics. However, by using these criteria, studies undertaken before 1958 were automatically excluded from the review.

Quality assessment and data extraction. Six criteria were used to assess study quality. The criteria were based on methodological issues relevant to nutritional epidemiology, expert knowledge, and published guidelines[10]. These criteria assessed whether: (1) an *a priori* hypothesis was given; (2) cases were ascertained using the ARA 1958[8] or 1987[9] criteria for diagnosis of RA; (3) cases and controls were comparable at baseline; (4) controls were randomly selected from the source of the population of the cases; (5) dietary assessment was undertaken prior to onset of symptoms, using a "validated" method of assessment and the same method was used for cases and controls; and (6) potential confounding factors were accounted for.

Two of the authors (DJP and RAH) independently reviewed the identified papers and extracted the data using a form designed specifically for this purpose. The results were compared and any discrepancies were discussed, but there were no disagreements that required adjudication by the third author (DPMS).

RESULTS

A search of the Cochrane Database of Systematic Reviews (and protocols) confirmed that no similar review had been done or was in progress. Using the search strategy as described, Medline produced 309 results, Embase 478, and Web of Science 499. After initial screening only 15 reports were included in the next phase of the review, and 13 of these met our inclusion criteria. An additional 3 abstracts were identified from searching conference abstracts, but only one[11] met our inclusion criteria. Five case-control studies[12-16] and 3 cohort studies of diet[11,17-21] (one cohort study produced 3 papers and one abstract) and 3 case-control studies of serum biomarkers[22-24] were included in the final review. Four studies were excluded because of the study design or outcome measures used[25-28]. There was some uncertainty whether 2 hospital-based case-control studies were actually independent of each other[13,16], and 2 population-based case-control studies appeared to have investigated a geographically very similar population[14,15]. However, all 4 studies were included. Eight reports were from the USA, 3 from Finland, 2 from Greece, and one from The Netherlands. The methods and results of the case-control and cohort studies of dietary intake are summarized in Tables 1 and 2, and the studies of serum biomarkers of nutrient intake are summarized in Table 3.

Study characteristics. A number of important factors distinguished the studies from one another, for example, restriction to one sex, different age ranges, and various methods of dietary assessment. The use of subgroup analysis, for example, seropositive compared with seronegative cases, was not universal, and finally, few foods or nutrients were examined in more than one study. Therefore, it was not possible to pool the data because of heterogeneity across study designs.

Specific foods and nutrients. In the following section we report the results of this review according to food and nutrient groups investigated.

Oils

A protective effect against RA onset was observed with higher fish consumption in 2 studies[13,15], although in one the association was significant only for broiled or baked fish, and a stronger effect was seen in seropositive compared to seronegative cases[15]. Shapiro and colleagues also estimated omega-3 fatty acid intake from fish consumption and found an inverse association between the highest quartile of intake compared to the lowest[15], but this association was only significant in seropositive cases. Two case-control studies in Greece found that higher olive oil consumption was associated with a statistically significant reduced risk of developing RA (top quintile compared to bottom)[13,16].

Coffee, tea, caffeine

In adult men and women (> 16 years of age) in Finland, high caffeinated coffee consumption was associated with an increased risk of seropositive RA[18]. However, in the Iowa Women's Health Study, a cohort of North American women aged between 55 and 69 years at baseline assessment, higher consumption of decaffeinated coffee was associated with an increased risk of RA, particularly in seropositive cases[20], but no clear association was found with caffeinated coffee. In the same study, women who drank more tea (> 3 cups/day) were found to be at a lower risk of RA than those who drank none, but there were very few subjects in the highest group of tea consumption, and no trend was observed across increasing tertiles of intake (Table 2). In the Nurses Health Study, a cohort of younger women, no association was found between coffee, decaffeinated coffee, tea or caffeine intake and RA onset[17], using cumulative followup data collected every 4 years since 1980. Interestingly, after multivariate analysis using baseline data only, greater caffeinated coffee consumption was associated with a statistically significant increase in the risk of RA (Table 2).

Alcohol

The association between alcohol consumption and the risk of developing RA has been investigated in 3 studies, all of women only. A hospital-based case-control study in The Netherlands reported a significant, protective effect against RA onset in women with the highest current intakes of alcohol compared to none[12], whereas no significant associations between total alcohol or different types of alcohol and the risk of developing RA were found in the prospective Iowa Women's Health Study[19]. No association between

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Table 1. Case-control studies reporting measures of association between dietary factors and RA.

Study (exposure)	Age, yrs Sex	Study Population	Cases/ Recruitment Period	Controls	Exposure Measure	Confounders	Association with RA
Hazes[12] (alcohol)	16–50 F	Hospital-based outpatients	1982–86 Prevalent cases 135 definite or classical RA† Onset of symptoms within 5 yrs of 1st clinic visit	378 outpatients with soft tissue rheumatism or OA. Matched for age and date of 1st clinic visit	In-person interview Daily number alcohol consumptions at time of 1st clinic visit	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 = 0.1 for linear trend
Linos[13] (olive oil, fish)	24–89 M + F	Hospital-based in & outpatients	Recruited over 1 yr Prevalent cases 168 definite or classical RA† 90% outpatients 37% definite RA 80.9% women median age 56 71% RF+	137 in & outpatients excluding metabolic disease Group matched for sex and age ± 5 yrs 5% RF+	Interview administered 100 item FFQ Lifelong dietary intake prior to diagnosis	Age, sex, occupation, residence, marital status, BMI Adherence to Lent, consumption of major food groups (adjusted data not presented)	Olive oil consumption × per month–unadjusted RR (95% CI) ≤ 6 1.00 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) chi-square for trend 6.3; p = 0.01 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) chi-square for trend 4.7; p = 0.03
Linos[16] (olive oil, vegetables	18–84 M + F	Hospital-based in & outpatients	145 prevalent RA† cases Clinical & radiological examination 83.5% women mean age 54.9 (± 14.5) 75% RF+	188 in & outpatients excluding metabolic disease, serially matched for age ± 5 yrs, sex & health care facility 78.2% women mean age 54.5 (± 12.9)	Interview administered 100 item FFQ of lifelong dietary intake, prior to disease diagnosis	BMI, consumption of major food groups	Adjusted OR (95% CI); p for trend Olive oil consumption–quartiles of intake 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 Cooked vegetables–quartiles of intake Lowest 1.00 2nd 0.55 (0.28, 1.08) 3rd 0.41 (0.20, 0.87) Highest 0.24 (0.11, 0.53) p = 0.003
Voigt[14] (alcohol)	15–64 F	Population-based	1986–91 Prevalent cases 349 probable, definite or classical RA† Clinical exam, medical record review 92% definite or classical, 50% RF+ 55.9% < 45 yrs at symptom onset	1457 randomly selected from community 55.4% < 45yrs at reference date	In-person interview No. of alcoholic drinks over different periods in lifetime 1 year prior to symptom onset	Age at reference, smoking history, BMI	Postmenopausal Premenopausal Lifetime alcoholic drinks per week–adjusted OR (95% CI) None 1.0 1.0 1 1.2 (0.6, 2.1) 1.1 (0.7, 1.7) 1–5 1.1 (0.6, 2.0) 0.9 (0.6, 1.5) 5–14 0.7 (0.3, 1.5) 0.7 (0.4, 1.3) > 14 0.5 (0.2, 1.7) 1.1 (0.5, 2.2) Lifetime total alcoholic drinks–adjusted OR (95% CI) None 1.0 1.0 < 800 1.3 (0.7, 2.5) 1.1 (0.7, 1.8) 800–2,500 1.1 (0.5, 2.2) 0.9 (0.5, 1.5) 2,500–7,500 1.1 (0.6, 2.2) 0.9 (0.5, 1.5) > 7,500 0.7 (0.4, 1.3) 0.9 (0.5, 1.5) Postmenopausal RF+ Premenopausal RF+ Lifetime alcoholic drinks per week – adjusted RR (95% CI) ≥ 14 v none 0.4 (0.1, 1.6) 0.7 (0.2, 1.9)

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Table 1. Continued.

Study (exposure)	Age, yrs Sex	Study Population	Cases/ Recruitment Period	Controls	Exposure Measure	Confounders	Association with RA		
Shapiro[15] (fish, omega-3 fatty acids)	15–64 F	Population-based	1986–91 Prevalent cases 324 probable, definite or classical RA[†] Clinical exam, medical record review	1243 randomly selected from community and frequency matched on age and reference year	Self-administered semiquantitative FFQ (2 versions) Usual diet 5 years prior to date of symptom onset	Reference age, year, race, education, total energy intake		All cases	RF+ cases
							All fish items including shellfish (servings/wk)–adjusted OR (95% CI)		
							< 1	1.00	1.00
							1–2	0.87 (0.62, 1.21)	0.85 (0.55, 1.32)
							≥ 2	0.92 (0.67, 1.25)	0.78 (0.51, 1.19)
Shapiro[15] con't			92.6% definite or classical 50.3 RF+ 54.9% < 45 yrs at onset of symptoms	53.9% < 45 yrs at reference date			Broiled or baked fish (servings/wk)		
							< 1	1.00	1.00
							1–2	0.78 (0.53, 1.14)	0.65 (0.38, 1.12)
							≥ 2	0.57 (0.35, 0.93)	0.32 (0.14, 0.72)
							Omega-3 fatty acids (g/day)–quartiles of intake		
							Lowest (≤ 0.2 g/day)		1.00 1.00
							2nd	1.10 (0.78, 1.56)	1.10 (0.71, 1.71)
							3rd	1.01 (0.70, 1.44)	0.76 (0.47, 1.24)
							Top 10–25%	1.02 (0.67, 1.55)	0.70 (0.39, 1.25)
							Top 10% (> 1.6 g/day) (of highest quartile)	0.77 (0.46, 1.27)	0.43 (0.21, 0.91) p = 0.01 for trend
							Macronutrients–adjusted OR (95% CI)		
							Total calories (kcal)		% calories from protein
							1 (≤ 1294.5)	1.00	1 (≤ 14.1) 1.00
							2 (> 1,294.5–1,674.7)	0.83 (0.57, 1.21)	2 (14.1–16.1) 0.90 (0.65, 1.25)
							3 (> 1,674.7–2,146.3)	1.01 (0.70, 1.46)	3 (> 16.1–17.9) 0.69 (0.48, 1.00)
							4 (> 2146.3)	1.62 (1.15, 2.28) p = 0.002 trend	4 (> 17.9) 0.65 (0.46, 0.94) p = 0.008 trend

[†] ARA 1958 criteria[8]. BMI: body mass index, FFQ: food frequency questionnaire, RF+: rheumatoid factor positive, RR: relative risk.

current alcohol intake and RA was found in a population-based case-control study in Washington state, USA[14], although in women with the highest weekly and total lifetime alcohol consumption (compared to none) the risk of developing RA was reduced, but only in postmenopausal women and not significantly so. The association was stronger in seropositive postmenopausal women.

Fruit, vegetables, antioxidant vitamins

Higher intakes of fruit[15,21], cooked (but not raw) vegetables[16], and cruciferous vegetables[21] were associated with lower risk of developing RA in 3 studies. In 2 of these, ß-cryptoxanthin, a carotenoid found in fruits and vegetables, and vitamin C were also found to be strongly protective against developing RA (top tertile vs bottom)[15,21]. In an abstract from the Iowa Women's Health Study the highest tertile of dietary vitamin D intake compared to the lowest was associated with a lower (but nonsignificant) risk of RA[11]. We found no evidence for associations between the dietary intake of other antioxidants or carotenoids and the risk of RA.

Other nutrients

No association was found between calcium intake and RA onset in the Iowa Women's Health Study[11]. However, in a population-based case-control study modest inverse associations were observed between the highest intakes of both calcium and phosphorus when compared to the lowest (highest vs lowest quartile)[15]. In the same study, significant associations were found between the highest quartile of energy intake (compared to the lowest) and an increased risk of developing RA, although the highest quartile of protein intake (adjusted for energy intake) compared to the lowest was associated with a reduced risk of RA. Consumption of other macronutrients or minerals (carbohydrate, fat, fiber, cholesterol, calcium, iron) was not associated with the onset of RA.

Other food groups

Again, Shapiro and colleagues found no significant associations between various food groups and developing RA, although a higher intake of meat (top quartile vs bottom) was associated with a modest reduction in the risk of developing RA. Dairy foods, milk on its own, and high fiber cereals were not associated with the risk of RA in this study[15], whereas in the Iowa Women's Health Study a summary score of servings of dairy foods was calculated and a protective effect observed for those in the highest tertile compared with the lowest tertile of intake[11].

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Table 2. Prospective studies reporting measures of association between diet and arthritis.

Study (exposure)	Sample size, Recruitment Period	Age yrs, Sex	Exposure Measure	Confounders	Followup	Case Ascertainment	No. Events	Association with RA (all are adjusted RR with 95% CI; p for trend)
Heliövaara[18] Finland, Mobile Clinic Health Examination Survey (coffee)	18,981 1973–76 83% response rate	20–98, mean 45, M + F	Self-administered, postal questionnaire & interview, prior to diagnosis	Sex, age, level of education, BMI, serum cholesterol, smoking, alcohol	1973–89	Record linkage & medical certificate against criteria**	126 incident RA cases 70.6 RF+	Caffeinated coffee consumption–cups/day RF+ RA ≤ 3 1.00 ≥ 4 v < 4 2.20 (1.13, 4.27); p = 0.01
[w]Mikuls[20] Iowa Women's Health Study, USA (coffee, decaffeinated coffee, tea & caffeine)	[w, x]31,336 [w,x,y,z] 1986	[w,x,y,z] 55–69 mean 61.1 (± 3.9) F	[w,x,y,z] Self-administered, postal 127-item semi-quantitative FFQ at baseline only, included use of supplements [w]mean time-lag from baseline assessment to symptom onset 6.1 ± 3 yrs	[w] Age, alcohol, marital status, smoking history, age at menopause, use of HRT	[w,x,y,z]1986–97 [w,x] 334,463 person-yrs	[w,x,y,z] Self-report of RA in 1992 & or 1997 Validated against medical records, lab results, X-rays & physician questionnaire, by 2 trained reviewers*	[w,x] 158 incident RA cases 60% RF+ Mean age at symptom onset 67.8 (± 4.9)yrs	[w] Total coffee–cups/day 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 [w] Decaffeinated coffee–cups/day None 1.00 ≤ 1 1.13 (0.74, 1.72) 2–3 1.11 (0.67, 1.84) ≥ 4 2.44 (1.52, 3.89); p = 0.003 ≥ 4 v < 4 2.48 (1.64, 3.74) [w] Caffeinated coffee–cups/day None 1.00 ≤ 1 1.23 (0.80, 1.88) 2–3 0.72 (0.43, 1.20) ≥ 4 0.98 (0.60, 1.61); p = 0.46 ≥ 4 v < 4 1.04 (0.69, 1.56) [w] Tea–cups/day 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 [w] Caffeine–mg/day < 29.1 1.00 29.2–153.7 1.28 (0.81, 2.01) 153.8–376.5 0.69 (0.41, 1.17) > 376.5 0.94 (0.58, 1.52); p = 0.33 [w] RF+ cases (n = 94) Decaffeinated coffee–cups/day None 1.00 ≤ 1 1.25 (0.74, 2.11) 2–3 1.25 (0.68, 2.33) ≥ 4 2.64 (1.46, 4.79); p = 0.006 [w] Tea–cups/day None 1.00 < 0.6 1.06 (0.64, 1.76) 0.6–3.0 1.20 (0.72, 2.02) > 3.0 0.26 (0.06, 1.09); p = 0.43

Biomarkers of nutrient intake. Three studies found lower serum levels of the antioxidants ß-carotene, retinol, α-tocopherol, and selenium in RA cases[22-24]. In a small, community-based prospective case-control study of blood donors to a serum bank, Comstock, *et al*[23] found that, in samples collected prior to the onset of symptoms, new cases of RA had lower serum concentrations of α-tocopherol, retinol, and ß-carotene than matched controls, but the difference

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Table 2. Continued.

Study (exposure)	Sample size, Recruitment Period	Age yrs, Sex	Exposure Measure	Confounders	Followup	Case Ascertainment	No. Events	Association with RA (all are adjusted RR with 95% CI; p for trend)
[x] Cerhan[19] (alcohol)	31,336 1986	55–69 Mean age 61.5 F	Self-administered postal 127-item semi-quantitative FFQ at baseline only, included use of supplements to measure average alcohol consumption over past year	Age	1986–97 334,463 person-years	Self-report of RA in 1992 & or 1997, validated against medical records, lab results, X-rays & physician questionnaire, by 2 trained reviewers	158 incident cases 61% RF+ Mean age at symptom onset 67.8 (± 4.9) yrs	Age-adjusted RR with 95% CI Total alcohol g/day None 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 Beer: 1 glass, bottle, can < 1/mo or never 1.00 < 1/week 1.08 (0.62, 1.88) ≥ 1/week 0.88 (0.49, 1.50); p = 0.76 Red wine: 4oz glass < 1/mo or never 1.00 < 1/week 0.99 (0.64, 1.53) ≥ 1/week 0.93 (0.49, 1.78); p = 0.84 White wine: 4oz glass < 1/mo or never 1.00 < 1/week 0.92 (0.57, 1.48) ≥ 1/week 1.04 (0.61, 1.79); p = 0.99 Liquor: 1 shot/drink < 1/mo or never 1.00 < 1/week 0.78 (0.45, 1.37) ≥ 1/week 1.03 (0.67, 1.60); p = 0.92
[y] Merlino[11] (vitamin D, calcium) Abstract	[y] 29,369 w, x, y, z		w, x, y, z	[y] Total energy intake, age, smoking, use of HRT, decaffeinated coffee & ß-cryptoxanthin intake	w, x, y, z	w, x, y, z	[yz] 152 RA	[yz] Highest v lowest tertile of intake Vitamin D–diet 0.72 (0.46, 1.17); p = 0.16 Calcium in diet+ calcium suppls No association found Summary score of servings of dairy foods 0.66 (0.42, 1.02); p = 0.06
[z] Cerhan[21] (antioxidant nutrients*)	[z] 29,368 w, x, y, z	[z] mean age 61.4	w, x, y, z	[z] Age, total energy at intake, marital status, smoking, age at menopause, HRT use, tea & decaffeinated coffee consumption	314,181 person yrs Median time from baseline to symptom onset 5.9yrs (0.9-12)	w, x, y, z	[z] Mean age at symptom onset 68 (57–79yrs) 62% RF+	[z]ß-cryptoxanthin µg/day (tertiles of intake) < 40.0 (ref) 1.00 40.0–86.9 0.73 (0.49, 1.10) > 86.9 0.59 (0.39, 0.90); p = 0.01 Cruciferous vegetables (servings/mo) < 6 (ref) 1.00 6–11 0.73 (0.48, 1.12) > 11 0.65 (0.42, 1.01); p = 0.07

was significant only for ß-carotene. By contrast, in 2 studies of Finnish adults, where lower serum levels of α-tocopherol, ß-carotene, and selenium (collected prior to symptom onset) were associated with a modest increase in the risk of RA[22,24], the strongest association was found with a combined "antioxidant index" rather than individual nutrients.

DISCUSSION

From the 14 articles reviewed, there is evidence that various aspects of diet may influence the etiology of RA in either positive or negative ways (Tables 1 to 3). The findings are not consistent across the individual studies, and in some instances associations are only present depending on

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Table 2. Continued.

Study (exposure)	Sample Size, Recruitment Period	Age yrs, Sex	Exposure Measure	Confounders	Followup	Case Ascertainment	No. Events	Association with RA (all are adjusted RR with 95% CI; p for trend)
Karlson[17] Boston, USA, Nurses Health Study (coffee, decaffeinated coffee, total coffee, tea, caffeine)	121,701 1976 83,124 with completed FFQ	34–59 yrs mean 46.9 F	Self-reported postal FFQ prior to onset of RA-baseline (1980) & every 4 years Coffee questions modified in FFQ used after 1980	Age, smoking, BMI, alcohol, age at menarche, parity, age at first birth, breast feeding, OCP use, age at menopause, use of HRT	1980–98	Connective tissue disease screening questionnaire & medical record review**	480 RA incident cases (with complete FFQ) Mean age at diagnosis 53.7 yrs 77% RF+	Caffeinated coffee ≥ 4 cups/day v none Baseline data 1.4 (1.0, 1.8) Followup data 1.1 (0.8, 1.6) Decaffeinated coffee ≥ 4 cups/day v none Baseline 1.0 (0.6, 1.7) Total coffee, ≥ 4 cups/day vs none Baseline 1.2 (0.9, 1.7) Tea > 3 cups/day v none 1.1 (0.7, 1.6) Caffeine, mg/day > 700 v < 142 1.2 (0.9, 1.6)

* Results shown for dietary intake not supplements. ** ACR 1987 revised criteria[9], BMI: body mass index, FFQ: food frequency questionnaire, HRT: hormone replacement therapy, OCP: oral contraceptive pill, RF+: rheumatoid factor positive, RR: relative risk; suppls: supplements.

rheumatoid factor (RF) status (seropositive) or menopausal status (postmenopausal). The studies included in this review vary extensively in design, exposure(s) measured, measurement tools, period of followup, analytical methods, and the interpretation of results. However, by virtue of our selection criteria, the outcome measures used[8,9] were consistent.

Several studies found that associations were present in seropositive but not seronegative RA, or that the associations were stronger in seropositive compared to seronegative disease, suggesting that diet might play a role in the etiology and even contribute to a more severe disease course. In patients presenting with seronegative RA the clinical diagnosis is more open to misclassification, and it may transpire that these patients have an alternative diagnosis.

The number of studies we identified that had investigated the relationship between diet and RA was small, which may simply reflect the complexity of nutritional epidemiology. However, this has not prevented diet being actively examined with respect to other chronic diseases such as cancer and cardiovascular disease. Given that RA is not a rare disease, with a prevalence of RA in developed countries of around 1.0% of the adult population[29], further research in this area would seem warranted.

Potential bias within the review. Despite attempting to include published abstracts, our review may be limited by publication bias[10], in that studies with negative findings have not been published or that we have not been able to identify all conference abstracts that remain unpublished as scientific reports. We also limited our search to publications in the English language and will have missed reports published in other languages.

Internal validity of reviewed studies. Selection of the comparator group is critical to the internal validity of case-control studies[30]. Both hospital-based case-control studies from Greece[13,16] excluded from the control group patients with arthritis and those with metabolic conditions that could affect dietary intake. However, in the study from The Netherlands the control group comprised patients with osteoarthritis or other soft tissue rheumatism[12]. The onset of other rheumatic conditions may have led to patients altering their diet, thus affecting the relationship between disease onset and dietary exposure. In all 3 studies, control subjects were believed to be free of RA (at least) and came from the same source as cases and so were considered representative of the unaffected members of the eligible population. The use of random-digit dialing to recruit healthy controls in 2 community-based studies[14,15] could have introduced selection bias if people who do not have a telephone are more likely to be in a lower social class.

Diet was assessed prior to onset of RA in the prospective studies, but retrospectively in the case-control studies. It is well recognized that in studies of environmental risk factors and RA, retrospective assessment of the exposure of interest will introduce recall bias. This is particularly relevant to the assessment of past dietary intake. In addition, when assessing dietary risk factors in prevalent cases of RA, it is difficult to distinguish whether diet is influencing the development of RA or the course of the disease. It is also common for people to change their diets soon after the onset of RA, and since current dietary intake strongly influences dietary recall, retrospective dietary assessment in prevalent cases may not actually represent past dietary intake.

Food frequency questionnaires were used in 3 of the case-control studies[13-16], the Iowa Women's Health Study[19–21], and in the Nurses Health Study[17]. The remaining studies relied on a single or series of questions[14,18]. From the information provided in the reports or the abstract, it appeared that not all studies had attempted to validate the

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Table 3. Case-control studies reporting measures of association between biomarkers of nutrient intake and RA.

Study, (exposure)	Age, Sex	Study Design/ Recruitment Period	Cases/ Ascertainment	Controls	Exposure Measure	Confounders	Association with RA
Heliövaara[22] Finland, Mobile Clinic Health Examination Survey (serum antioxidants)	28–73 yrs M + F	Nested case-control	14 RA Prevalent cases Median followup 20 yrs 42.9%women, mean age 55 yrs Medical record linkage & medical certificate**	27 controls matched for age, sex, municipality 44.4% women, mean age 55 yrs	Prediagnostic serum concentrations of antioxidants (α-tocopherol, ß-carotene & selenium) Samples collected 1968–72 & frozen until 1984 Antioxidant index- the product of the molar concentrations of α-tocopherol, ß-carotene & selenium	None given	Lowest tertile v highest–RR (95% CI); p for linear trend α-tocopherol 1.88 (0.40, 8.92); p = 0.24 ß-carotene 2.30 (0.43, 12.24); p = 0.13 Retinol 1.00 (0.18, 5.46); p = 0.96 Selenium 1.63 (0.57, 4.69); p = 0.11 Antioxidant index 8.34 (0.98, 71.0); p = 0.03
Comstock[23] Washington County, USA (serum antioxidants)	M + F	Prospective case-control 1974–75 20,305 30% response rate	21 RA† Prevalent cases (6 SLE) 1976–1989 71.4% women median age 41 yrs median age at RA onset 52 yrs Medical record review	84 Controls matched for age, sex, municipality 24 controls (SLE)	Prediagnostic serum concentrations of antioxidants Samples collected & frozen in 1974 & July 1975	None given	Difference in mean serum concentrations between cases and controls (cases lower than controls) α-tocopherol –0.05 (–0.20, 0.10) ß-carotene –6.9 (–13.1, –0.6) retinol –4.3 (–10.0, 1.4)
Knekt[24] Finland, Mobile Clinic Health Examination Survey (serum selenium & α-tocopherol)	20–98 yrs M + F	Nested, case-control 1973-77 19,518 83% response rate	122 RA** Prevalent cases 1973–1989 72.1% RF+ 68.9% women mean age 45.8 yrs Medical record linkage & medical certificate	357 controls matched for age, sex, municipality (3 per case for most) 68.9% women, mean age 45.8 yrs	Prediagnostic serum concentrations of selenium & α-tocopherol Samples frozen & stored until 1994	Smoking, serum total cholesterol	Highest tertile v lowest–adjusted RR (95% CI) Selenium All cases / RF+ cases / RF– cases Lowest 1.00 / 1.00 / 1.00 Middle 1.02 (0.61, 1.72) / 1.16 (0.62, 2.15) / 0.56 (0.18, 1.77) Highest 0.65 (0.36, 1.16) / 0.96 (0.49, 1.90) / 0.16 (0.04, 0.69) α-tocopherol Lowest 1.00 / 1.00 / 1.00 Middle 0.60 (0.35, 1.05) / 0.81 (0.43, 1.54) / 0.23 (0.07, 0.79) Highest 0.90 (0.48, 1.68) / 1.03 (0.48, 2.23) / 0.76 (0.24, 2.35)

† ARA 1958 criteria[8]; ** ACR 1987 revised criteria[9]. RF+/–: rheumatoid factor positive/negative; RR: relative risk, SLE: systemic lupus erythematosus.

dietary question or questionnaire within the study population[12-14,16], and in one case-control study, 2 different versions of the same questionnaire were used during the study period[15]. These factors could all have affected the reliability and validity of the dietary data collected. There is extensive debate about which dietary assessment method should be used in epidemiological studies but further discussion is out of the scope of this review.

The effects of confounding by factors such as smoking, which has been identified as a risk factor for RA[14,31,32], had been controlled for in most, but not all studies. It appears that Linos, *et al*[13,16] did not consider smoking in their analyses, which could have confounded the apparent associations between diet and RA onset. It is also important to note that none of the prospective studies were set up primarily to study RA incidence, thus case ascertainment was retrospective and based on case-note review and medical certificates, with no clinical examination. Only one study[21] met all our quality criteria, thus the results must be treated with caution.

External validity. The prospective studies, 2 case-control studies of dietary intake (Tables 1 and 2), and the studies of biological markers (Table 3) were population-based, thus increasing the generalizability of findings. The remaining studies of dietary intake recruited participants through hospital populations[12,13,16], which will limit the extrapolation of results. Four studies[12,14,15,17] and the Iowa Women's

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Health Study recruited women only, with considerable variation in age between study groups. Given that the average age of onset of RA in women is around 55 years[33], it would appear that the outcome being measured in the Iowa Women's cohort could be "older age onset" RA, whereas the Nurses Health Study is a cohort of younger women health professionals. There is some debate about the occurrence of RA in these different age groups and whether there are actually 2 different diseases[34]. It could also be argued that the Nurses Health Study is examining a select, well-informed group of young women, which is likely to influence the dietary and other lifestyle information provided. The Finnish cohort study was based on a population sample of adult men and women aged between 16 and 72 years. In terms of age and sex these cohort studies are very heterogeneous, making comparison of the results difficult and limiting the generalizability of the findings.

Biological plausibility

Oils. The relationship between the intake of fish oils and the risk of developing RA is not well researched. However, dietary supplementation with encapsulated fish oils has been found to reduce pain and symptoms in established, but milder cases of RA[5], possibly due to the antiinflammatory effects of omega-3 polyunsaturated fatty acids. Plant oils, for example olive oil, may also confer antiinflammatory benefits due to a high content of omega-9 polyunsaturated fatty acids. It is reasonable to hypothesize that these oils may also confer a protective effect against onset of RA, but it is certainly not clear whether the active mechanism in prevalent disease would be similar prior to onset.

Coffee, tea, alcohol. We are not aware of any biological findings that have been reported of an association between coffee and other diseases, and it was difficult to identify a clear *a priori* hypothesis in any of these studies[17,18,20]. As described, there were major differences in study design, and as the results were inconsistent across all of the studies, the findings cannot be regarded as definitive. The associations found between alcohol intake and RA onset were also inconsistent and despite mechanisms being suggested for this, the relationship remains unclear.

Fruit, vegetables, antioxidant vitamins. Fruit and vegetables are the main source of antioxidants in our diet. Antioxidants act as efficient scavengers of free-radical oxidation products in the bloodstream, thus preventing oxidative damage to tissues and other substrates[35]. The studies measuring biological markers were supportive of a protective role for antioxidants. However, serum antioxidants may not reflect dietary intake accurately, except possibly for ß-carotene[36], and as these were all prospective case-control studies that required serum samples to be stored for long periods of time (12 to 16 years), this could have affected the stability of the antioxidants, and thus true associations may have been underestimated.

In this systematic review, we have identified, from a small number of studies, that the evidence for diet having a role in the etiology of RA is limited. Higher intakes of fish and olive oil, both rich sources of antiinflammatory fatty acids, have been found to protect against RA onset, although we have highlighted important weaknesses in the studies reviewed. The evidence for a role for coffee is unclear. Despite 3 prospective studies finding associations, they were not consistent for one type of coffee, and a plausible reason for such an association is difficult to find. However, this is an intriguing area and may be worthy of further investigation. RA is less common and the disease less severe in the Southern Mediterranean countries, such as Italy and Greece[37,38], where inhabitants consume much higher quantities of oil-rich fish, fruit, vegetables, and olive oil[39]. There is also evidence in support of this type of diet in the primary and secondary prevention of cardiovascular disease[40]. As discussed, cardiovascular disease shares some commonalities to RA in relation to biological mechanisms[4], lending further support to the idea that these foods may play a clinically relevant role in determining the onset of RA. Ideally, further prospective, population-based studies using robust dietary assessment methods are necessary to determine whether diet plays a role in susceptibility to RA.

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