RHEUMATOLOGY

Original article

Modifiable risk factors for RA: prevention, better than cure?

Manjari Lahiri[1,2], Catharine Morgan[1], Deborah P. M. Symmons[1] and Ian N. Bruce[1,3]

Abstract

Objective. To perform a meta-synthesis of the evidence for modifiable lifestyle risk factors for inflammatory polyarthritis (IP) and RA.

Methods. We performed a MEDLINE literature search. Case–control and cohort studies and systematic reviews published from 1948 through February 2011 and studying modifiable risk factors for RA were retrieved. The main outcome measure was diagnosis of RA according to the standard criteria.

Results. Smoking contributes up to 25% of the population burden of RA. The risk is dose related, stronger in males and especially strong for anti-citrullinated peptide antibody positive (ACPA[+]) RA through an interaction with the shared epitope. After smoking cessation, there is, however, a latency of up to 20 years to return to baseline risk. Other associations are less definitive; however, prospective studies suggest that dietary antioxidants and breastfeeding may be protective and that high coffee consumption may increase RA risk. An inverse association with alcohol intake (especially in smokers) and with education/ social class (especially seropositive RA) and an increased risk with obesity (seronegative RA) is also noted.

Conclusion. There is a need for further large-scale prospective studies with a consistent definition of RA phenotype (undifferentiated IP through to ACPA[+]/RF[+] disease). This will ultimately afford the opportunity to evaluate preventative population strategies for RA akin to the well-established programmes for cardiovascular disease and cancer, targeting common risk factors.

Key words: rheumatoid arthritis, review, risk factors, epidemiology, lifestyle, environment, smoking, alcohol, diet, social class.

CLINICAL SCIENCE

Introduction

The aetiology of RA remains an area of intense interest. In recent years, there have been major advances in our understanding of genetic risk, aided by the genome-wide association studies. There has also been renewed interest in environmental triggers and their potential interactions with these susceptibility genes [1, 2]. In the absence of a diagnostic test for RA, the 1987 ACR criteria have until recently been the gold standard for disease definition [3, 4]. However, RA is part of a continuum from undifferentiated inflammatory polyarthritis (IP) to classical RA and evolution of disease may take up to 5 years [5]. The RA phenotype may be a final pathway of a number of different combinations of risk factors and an emerging concept is that anti-citrullinated peptide antibody positive (ACPA[+]) disease may be a more homogenous entity with distinct aetiological factors [6–10]. Diet and lifestyle factors are of particular interest as they are, at least in theory, modifiable. The aim of this review is to summarize current knowledge of lifestyle factors implicated in the aetiology of RA and consider how these can contribute to disease prevention strategies.

[1]Arthritis Research UK Epidemiology Unit, School of Translational Medicine, Manchester Academic Health Science Centre, The University of Manchester, Manchester, UK, [2]Division of Rheumatology, University Medicine Cluster, National University Health System, Singapore and [3]The Kellgren Centre for Rheumatology, Manchester NIHR Biomedical Research Centre, Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK
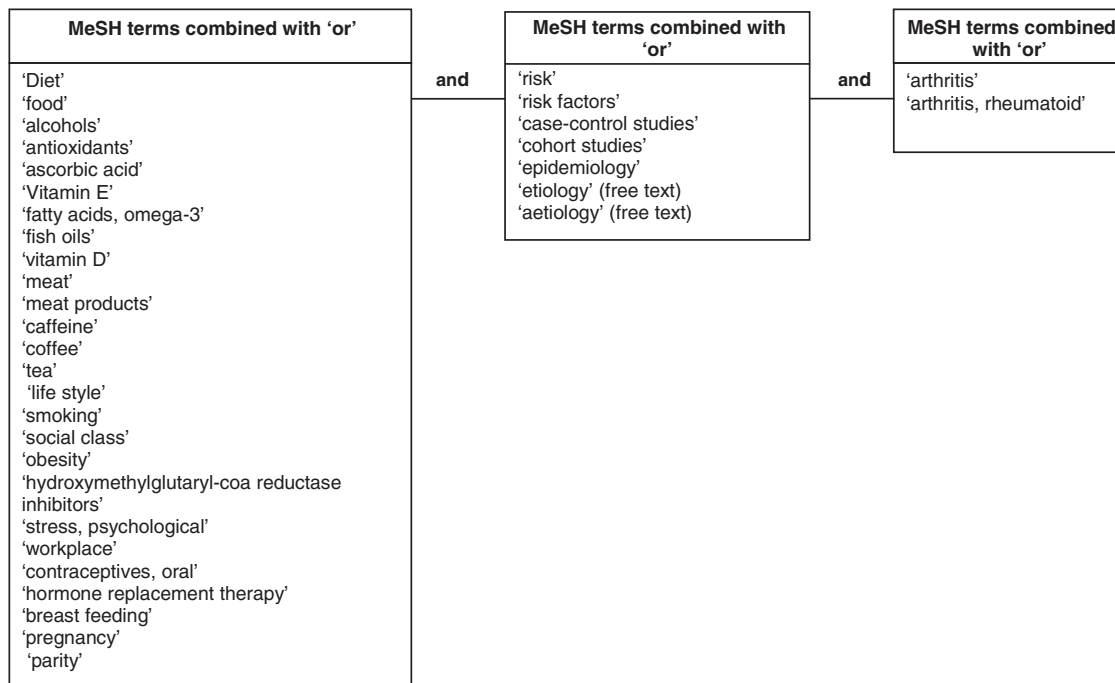
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Correspondence to: Ian N. Bruce, Arthritis Research UK Epidemiology Unit, School of Translational Medicine, Manchester Academic Health Science Centre, The University of Manchester, Stopford Building, Oxford Road, Manchester M13 9PT, UK.
E-mail: ian.bruce@manchester.ac.uk

Methods

We conducted a MEDLINE literature search in February 2011 with the MeSH search terms in Fig. 1. Search

Fɪɢ. 1 Search terms and strategy.

MeSH terms combined with 'or'		MeSH terms combined with 'or'		MeSH terms combined with 'or'
'Diet' 'food' 'alcohols' 'antioxidants' 'ascorbic acid' 'Vitamin E' 'fatty acids, omega-3' 'fish oils' 'vitamin D' 'meat' 'meat products' 'caffeine' 'coffee' 'tea' 'life style' 'smoking' 'social class' 'obesity' 'hydroxymethylglutaryl-coa reductase inhibitors' 'stress, psychological' 'workplace' 'contraceptives, oral' 'hormone replacement therapy' 'breast feeding' 'pregnancy' 'parity'	**and**	'risk' 'risk factors' 'case-control studies' 'cohort studies' 'epidemiology' 'etiology' (free text) 'aetiology' (free text)	**and**	'arthritis' 'arthritis, rheumatoid'

headings were pre-defined from previous knowledge of the literature. Abstracts of case–control studies, cohort studies and systematic reviews were screened, and suitable full-text articles were retrieved. The main outcome measure was a diagnosis of RA according to the ARA 1958 or revised ACR 1987 classification criteria or by expert opinion. Studies only published in abstract form were excluded. Selection of articles for inclusion was done by a single author (M.L.). No additional quality criteria, date or language limits were imposed. Studies using hospitalization or death due to RA or erosive RA as the primary outcome were excluded as these relate to RA severity rather than incidence. Relevant studies from reference lists of retrieved articles were also included (Fig. 2). Results for some of the major studies as presented by the authors were extracted [odds ratio (OR), relative risk (RR), incidence rate ratio (IRR) or hazard ratio (HR) with 95% CI in parentheses].
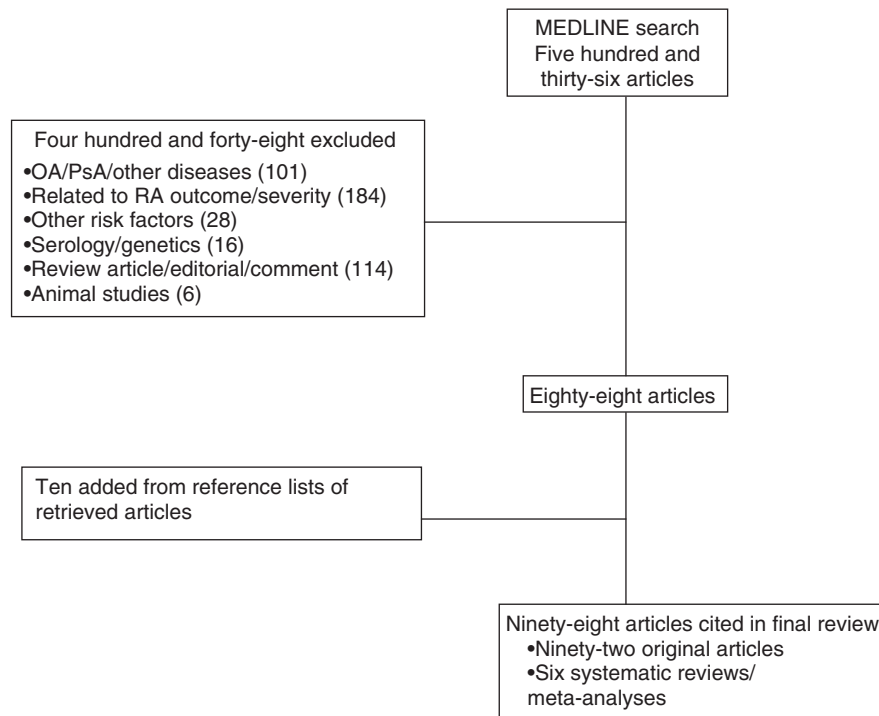
Results

Smoking

Smoking is the best-studied preventable risk factor for RA. Initial twin studies were suggestive of an elevated risk [11]. In a meta-analysis of 11 case–control studies [7, 12–22] and 5 cohort studies [23–27] smoking was consistently found to be a risk factor especially in males and for RF[+] RA [OR for RF[+] RA 3.91 (2.78, 5.50) for male and 1.29 (0.94, 1.77) for female current smokers] [28]. The Nurses' Health Study and the Nurses' Health Study II are two large US-based cohorts following a total of 238 308 female nurses aged 25–42 years since 1976 and 1989, respectively. Data from these cohorts suggest a dose-dependent effect of pack-years of smoking, and a threshold dose of 10 pack-years before an elevated risk becomes evident [RR 1.35 (1.04, 1.74) for 11–20 pack-years compared with never-smokers]. The Iowa Women's Health Study (Iowa WHS), a prospective cohort of older, post-menopausal Caucasian women, corroborated these results [25]. It is estimated that smoking contributes 18–25% of the population-attributable risk of RA [24, 25]. There is a long latency, up to 20 years after smoking cessation, to return to the risk level of a non-smoker [24]. Klareskog and colleagues [29] proposed that smoking may be a specific risk factor for only ACPA[+] RA. In a national register-based case–control study of incident RA [the Epidemiological Investigation of RA (EIRA) in Sweden], it was noted that smoking interacts with all alleles of the shared epitope (SE) to exponentially increase the risk for RA [10]. Ever-smokers with two copies of the SE had an RR of 21.0 (11.0, 40.2) for ACPA[+] RA as compared with non-smokers with no SE [10], a finding supported by the Danish Case–Control Study of RA (CACORA), the Nurses' Health Study and a case-only analysis from the Netherlands [7, 30–32]. The population attributable risk was much higher in this group, at 35% for ACPA[+] RA and up to 55% in individuals with two copies of the HLA-DRB1 SE [30, 33]. Importantly, there may be ethnic and geographical variations in the association. A North American case-only analysis did not support the smoking–SE interaction [34] and studies among Korean and African American subjects have argued against its

Fig. 2 Algorithm for selection of articles for review.

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                         │   MEDLINE search    │
                         │   Five hundred and  │
                         │  thirty-six articles│
                         └─────────────────────┘
┌────────────────────────────────────┐
│ Four hundred and forty-eight excluded│
│ •OA/PsA/other diseases (101)        │
│ •Related to RA outcome/severity (184)│
│ •Other risk factors (28)            │
│ •Serology/genetics (16)             │
│ •Review article/editorial/comment (114)│
│ •Animal studies (6)                 │
└────────────────────────────────────┘
                         ┌─────────────────────┐
                         │  Eighty-eight articles│
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│ Ten added from reference lists of   │
│ retrieved articles                  │
└────────────────────────────────────┘
                  ┌──────────────────────────────┐
                  │ Ninety-eight articles cited in final review│
                  │  •Ninety-two original articles│
                  │  •Six systematic reviews/     │
                  │   meta-analyses               │
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specificity for ACPA$^+$ RA [35, 36]. It has also been suggested that smoking specifically increases the risk in subjects without the SE [37], that the risk may differ with different SE alleles [38] and that there may be other mechanisms of pathogenesis [39]. Results from selected studies on the influence of smoking on risk of RA are summarized in Table 1. The interaction of smoking with other RA-associated genes such as protein tyrosine phosphatase N22 (PTPN22), peptidyl arginine deiminase type-4 (PADI-4) and cytotoxic T-lymphocyte antigen-4 (CTLA-4) is less clear, but data are rapidly emerging [8, 40, 41]. For example, the Nurses' Health Study found an OR of 3.27 (1.74, 6.15) for RF$^+$ RA in smokers of >10 pack-years who were carriers of the *PTPN22* gene as compared with non-carriers who smoked <10 pack-years [40]. Passive smoking and smokeless tobacco have not been found to be associated with RA risk [24, 42].

Diet

Omega-3 fatty acids

Omega-3 fatty acids have been shown in a number of studies to ameliorate clinical symptoms of RA [43–49] and ecological studies in Japan and among Eskimos have suggested that they may decrease the risk of RA [50–52]. Early retrospective case–control studies supported this [OR for the top *vs* the lowest quartile of olive oil consumption 0.49 (0.30, 0.81) and for increase in consumption by more than twice a week 0.38 (0.17, 0.85) in two studies from Greece] [53, 54], especially for seropositive disease [OR for two or more *vs* less than one serving/week of baked or broiled fish 0.57 (0.35, 0.93) for RA, 0.32 (0.14, 0.72) for RF$^+$ RA in an American study] [55]. The only prospective study to examine these factors was the Danish Diet, Cancer and Health (DCH) population-based cohort of 57 053 individuals. This study of incident RA failed to confirm a protective effect of olive oil [IRR 1.00 (0.92, 1.08) per gram consumption]. Consumption of oily fish did, however, show a trend towards a protective effect [(IRR per 30 g/day 0.51 (0.25, 1.03)] [56].

Antioxidants

A variety of health benefits have been attributed to consumption of fruits and vegetables and are hypothesized to be largely due to their antioxidant properties, which are contributed by vitamins C and E, lycopene, caroteinoids, flavonoids and possibly fructose-mediated urate production [57]. Vitamin C and β-cryptoxanthin (a carotenoid) have been demonstrated to be protective in a systematic review [58]. The Norfolk arm of the multicentre population-based European Prospective Investigation of Cancer (EPIC) study has followed about 25 000 mainly Caucasian participants aged >40 years since 1993 [59, 60]. Linkage with the Norfolk Arthritis Register (NOAR)—a primary-care-based register of incident IP with an overlapping catchment area [5] has given the opportunity for a prospective study of risk factors for IP. In this study, there was an inverse association between consumption of β-cryptoxanthin and vitamin C and RA risk [OR 0.48 (0.24, 0.94) and 0.51 (0.25, 1.02) for the top *vs* the bottom tertile of zeaxanthin and β-cryptoxanthin,

TABLE 1 Summary of selected studies on smoking and risk of RA (meta-analysis, recent prospective cohort studies and studies on interaction with the shared epitope)

Name of study/ origin	Meta-analysis	Nurses' Health Study (USA)	Iowa WHS (USA)	Finland	GPRD (UK)	EIRA (Sweden)	CACORA (Denmark)	CLEAR (USA)	Korea
Author	Sugiyama et al. [28]	Costenbader et al. [24], Karlson et al. [31]	Criswell et al. [25, 37]	Heliövaara et al. [26]	Rodriguez et al. [76]	Klareskog, Källberg, Stolt, Padyukov and colleagues [10, 18, 19, 33]	Pedersen et al. [7, 30]	Mikuls et al. [36]	Bang et al. [35]
Type	Meta-analysis	Cohort	Cohort	Cohort	Cohort, nested CC	CC	CC	CC	CC
Source	Observational Studies	Nurses	Pop	Pop	GP registers	Pop	Hosp	Hosp	Hosp
Age, years	Adult	30–55, 25–42	55–69	Adult	Adult	≥18	18–65	Adult	Adult
Ethnicity	Caucasian Asian (Korean)	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian		
African-American									
Case ascertainment attendance	Literature review	Questionnaire, chart review	Questionnaire, chart review	Registry	Chart review	Registry	Referral, chart review	Outpatient attendance	Outpatient
Diagnosis	As per original study	ARA 58, expert opinion	ACR 87	ACR 87	Physician diagnosed	ACR 87	ACR 87	ACR 87	ACR 87
Sex	Both	Female	Female	Male, both	Both	Both	Both	Both	Both
No. of patients (RA)		82 063–186 389 (480–722)	29 368–31 336 (152–158)	9777–18 981 (30–126)	579, i	1204, i	445–515, i, ep	605	1482
Risk in RA									
Overall	▲			▲	▲	▲	▲	▲	▲
Males	▲	▲		▲		▲	▲		
Females	▲*		▲	–		▲	▲		
Specificity for seropositive RA	Yes	Yes		Yes		Yes	Yes	No	No
Interaction with the SEa	Yes	Yes	Inverse			Yes	Yes	Yes	Yes

*Non-significant for RF positive disease. aIn addition, there are two case-only analyses of interaction of smoking with the SE, one supporting and one refuting a significant interaction [32, 34]. GPRD: the general practice research database; CLEAR: Consortium for the Longtidunal Evaluations of African Americans with Early Rheumatoid Arthritis; CC: Case control study; GP: general practitioner; Pop: Population based; Hosp: Hospital based; ACR 87: American College of Rheumatology 1987 criteria for Classification of Rheumatoid Arthritis; ARA 58: American Rheumatism Association 1958 criteria for Rheumatoid Arthritis; i: incident cases; ep: early prevalent cases; SE: Shared epitope; –: no effect on risk; ▲: increased risk; ▼: decreased risk.

respectively, and 3.3 (1.4, 7.9) for the lowest *vs* the highest tertile of vitamin C consumption] [61, 62]. Similar results were obtained in the Iowa WHS [RR for highest *vs* lowest tertile of β-cryptoxanthin intake 0.59 (0.39, 0.90)], which also found a protective effect of dietary zinc supplements [RR 0.39 (0.17, 0.88) for 15 mg/day compared with non-users] [63] and in a nested case–control study within a Finnish cohort, which found an increased risk associated with low pre-disease serum levels of selenium or a composite antioxidant measure [64, 65]. However, the DCH study and the Nurses' Health Study found no benefit of antioxidants, in spite of testing multiple parameters of antioxidant content [56, 66] and a large randomized double-blind placebo-controlled trial of vitamin E supplements, the Women's Health Study, which recruited 39 876 female health professionals and followed them for 10 years, showed no efficacy in the prevention of RA, though there was a non-significant trend in RF$^+$ cases [RR for vitamin E (600 IU every other day) *vs* placebo 0.64 (0.39, 1.06)] [67]. However, there is poor generalizability between trials of a single vitamin and the effects of whole fruit and vegetable consumption. Observational studies have attempted to examine whole foods. There was a protective effect for cooked vegetables [OR for highest *vs* lowest quartile 0.39 (0.20, 0.77)] in a Greek case–control study [54] and of fruit intake in a nested case–control study from the EPIC-NOAR [OR for lowest *vs* highest tertile of fruit consumption 2.1 (1.1, 4.2)] ; however, other studies have shown no association. For example, OR for the highest *vs* lowest tertile of fruit consumption was 0.72 (0.46, 1.12) in the Iowa WHS and IRR per 100 g of fruit consumption 0.93 (0.79, 1.09) in the DCH study [56, 63].

Red meat

There is a north–south gradient in RA prevalence in Europe and this may be associated with a protective effect of the Mediterranean diet, or might be due to the difference in per-capita red meat intake as suggested in an ecological study [69]. Red meat consumption may be inversely related to that of fruits, vegetables and oily fish. It may also be associated with a higher overall fat and calorie intake or lower fibre intake; and may indeed be a surrogate marker for an unhealthier lifestyle. There have been contradictory results from three prospective studies. Whereas the EPIC-NOAR study found a positive association with IP [OR 2.3 (1.1, 4.9) for the highest *vs* lowest tertile of meat and meat products combined], the subsequent Danish DCH study and the Nurses' Health Study did not show any effect [56, 68, 70].

Alcohol

Moderate consumption of alcohol, especially red wine, is proposed to protect against coronary heart disease, possibly because of its flavonoid content and antioxidant properties [71]. Red wine is an inherent component of the Mediterranean diet and may specifically act by counteracting post-prandial oxidative stress [72]. Three retrospective case–control studies have suggested that alcohol is associated with a decreased risk of RA [7, 12, 30,

73]. The risk reduction was confined to ACPA$^+$ RA in the CACORA study [OR 0.6 (0.4, 0.9) for the highest quartile of consumption *vs* low consumers ($>$0 to 50th centile)], but for all RA in the Swedish EIRA study [OR 0.5 (0.4, 0.6) for the same comparison] with the greatest risk reduction in smokers carrying the SE [73]. Other studies have found only a weak association [22]. A differential recall due to reduced consumption of alcohol after diagnosis, especially in seropositive cases treated with MTX, may have affected the results in these retrospective studies. Prospective cohort studies do not thus far support a protective role of alcohol. The Iowa WHS, the EPIC-NOAR study, the General Practice Research Database (GPRD) (a population-based database of about 5 million patients registered with selected general practitioners in the UK since 1987) and a population-based male Finnish cohort with 9777 participants did not find any association between alcohol consumption and the risk of RA, although in the Iowa WHS alcohol did attenuate the increased risk associated with smoking [68, 74–76].

Caffeine

Coffee consumption has been studied as a risk determinant of RA because of its association with smoking and other potential dietary risk factors. A prospective study of 19 000 subjects in Finland found that drinking four or more cups coffee per day was associated with RF$^+$ but not RF$^-$ RA [RR 2.20 (1.13, 4.27) for RF$^+$ RA as compared with those who drank three or less cups] [77]. In the Iowa WHS, the association was limited to decaffeinated coffee consumption [RR 2.64 (1.46, 4.79) for RF$^+$ RA for four or more cups/day *vs* none]. This study also found a trend towards an inverse association with tea consumption [RR for RF$^+$ RA 0.26 (0.06, 1.09) for consuming more than 3 cups/day *vs* none] [78]. With an increased prevalence of atherosclerosis risk factors in the RA group, subjects may adopt presumed healthier practices and consumption of decaffeinated coffee may be a marker of this effect [79]. Subsequent studies such as the Nurses' Health Study, the DCH and EPIC-NOAR studies have not found a link between coffee, total caffeine or decaffeinated coffee and RA [56, 68, 80]. These negative studies may, of course, need to be examined separately for ACPA$^+$ subsets; indeed, the CACORA study found a strong association in 515 prevalent ($<$5 years) cases with ACPA$^+$, but not ACPA$^-$ RA [OR 2.18 (1.07, 4.42) for more than 10 *vs* no cups of coffee/day for ACPA$^+$ RA and OR 1.23 (0.48, 3.16) for ACPA$^-$ RA] [7] and especially in carriers of the SE [OR 53.3 (15.5, 183) for more than five cups/day in SE homozygotes as compared with non-drinkers with no SE; OR for non-drinker SE homozygotes is 13.0 (3.3, 50.8)], an effect size similar in strength to smoking in this study [30].

Vitamin D

Vitamin D deficiency is implicated in the pathogenesis of several autoimmune conditions including multiple sclerosis and Type 1 diabetes by its proposed role as an immunoregulatory hormone [81]. Its role in RA has been investigated by measuring dietary intake in a number of

prospective studies, most of which, other than the Iowa WHS [RR for highest *vs* lowest tertile 0.67 (0.44, 1.00)] have been negative [56, 68, 82, 83]. Dietary intake is, however, a poor estimate of vitamin D status as levels are predominantly affected by latitude and sunlight exposure. A small retrospective case–control study of 79 patients from the Netherlands failed to show an association between serum levels in blood donors and subsequent development of RA [84].

Results from various studies on the dietary influences on RA risk are summarized in Table 2. There is some support for the protective role of antioxidant containing foods, oily fish and alcohol and a possible increased risk with coffee. The effect of vitamin D deficiency and red meat remains unclear. Methodological differences may explain some of the apparently contradictory findings. For example, the 7-day diary method used in the EPIC study correlates better with biomarkers of diet than does the more widely used food frequency questionnaire (FFQ). The presence of dietary measurement error inherent in the FFQ attenuates the estimates of disease relative risk [85–87]. There may also be residual confounding from a healthy lifestyle effect, which is difficult to fully account for in epidemiological studies. Randomized trials tend to be reductionist in their nature, focusing on a small number of candidate elements and cannot examine the holistic effects of whole foods. As we have seen, however, there is also evidence that some risk factors have significant associations only with specific ACPA subsets.

Obesity

Obesity increases the amount of available oestrogen through increased conversion of androstenedione to oestrone and decreased sex hormone binding globulin, especially in post-menopausal women [88]. Leptin, an adipocyte-secreted hormone, has an increasingly recognized role in regulating immune responses [89]. Elevated levels of circulating leptin tend to drive immune responses to a Th1 phenotype and increase production of pro-inflammatory cytokines such as TNF-α and IL-1. This may contribute to a common pathway leading towards both RA and cardiovascular disease (CVD). Obesity was associated with RA risk in three population based case–control studies [OR for BMI $\geqslant$30 *vs* <25 = 3.74 (1.14, 12.27) in the NOAR study, for the highest *vs* lowest quartile of BMI 1.4 (1.0, 2.0) in an American case–control study and for BMI $\geqslant$30 *vs* 18.5 to <25 = 3.45 (1.73, 6.87) for ACPA$^-$ RA in the CACORA study] [7, 20, 22]. Others, including prospective studies, have found no association of obesity with RA risk [21, 74, 76, 90]. The apparent contradiction may be explained by the findings in the prospective EPIC-NOAR study, where obesity was a risk factor only when measured in proximity to the onset of IP [OR 4.79 (1.17, 19.6) for IP onset $\leqslant$18 months of questionnaire], and not in the remote past [91]. Only two studies have assessed the effect of physical activity and with conflicting results [7, 74].

Statins

The proposed anti-inflammatory effects of statins may play a role in reducing RA risk [92–94]. A nested case–control study from the GPRD suggested that statins may reduce the risk of RA in patients with hyperlipidaemia [OR 0.59 (0.37, 0.96) for statin users compared with untreated patients with hyperlipidaemia and OR 0.88 (0.55, 1.40) compared with non-hyperlipidaemic controls] [92]. Subsequent studies in the same population showed no association [76, 93]. A cohort study of 211 627 individuals followed for >10 years with 2578 incident cases of RA from a health maintenance organization in Israel found that high adherence to statins lowered the risk of RA [HR 0.58 (0.52, 0.65) for those with $\geqslant$80% *vs* <20% adherence] [94], but while they controlled for a healthy user effect, they did not account for smoking as a confounder.

Social class

Social class (SC) or education may be a marker for unmeasured lifestyle variables and is associated with a poorer outcome in established RA [95], so it is attractive to postulate that it may influence RA risk. The NOAR study found no association between SC (defined by occupation and areal housing indices of deprivation) and incident RA, nor did a population-based study of 361 prevalent cases in Norway [21, 96]. In contrast, a Swedish study found an inverse association between higher education and incident RA, especially RF$^+$ disease [OR 0.3 (0.2, 0.7) for men with schooling beyond compulsory education] [17]. This was supported by the EIRA study where subjects without a university degree had an increased risk compared with degree holders [OR for RF$^+$ RA 1.7 (1.2, 2.2)]. The association with occupational class was less clear [OR for RF$^+$ RA for lower *vs* higher class 1.5 (1.0, 2.1)] [97]. A similar inverse association with education was found in the CACORA study [98]. Methodological differences may explain some of these conflicting results, especially variation of definition and ascertainment of SC based on occupational class, educational attainment or area-level deprivation indices.

Psychosocial factors

Work stress defined by low decision latitude, was associated with an increased risk for RA in the EIRA study [OR 1.6 (1.2, 2.2) *vs* workers with high decision latitude] as was shift work in a prospective Finnish study of 70 000 mainly female government employees [OR 1.36 (1.02, 1.82)] [99]. The NOAR investigators have suggested that reduced adaptation scores, implying a reduced ability to cope with stress may be an important factor [100].

Hormonal factors

RA is three times more common in women than in men, and so it is intuitive that hormonal factors may play a role in aetiology. Modifiable lifestyle factors involving hormonal manipulation include the use of oral contraceptives (OCs) and HRT, parity and breastfeeding.

TABLE 2 Dietary risk factors for RA: summary of key studies

Name of study/origin	EIRA (Sweden)	Seattle (USA)	CACORA (Denmark)	Greece	The Netherlands	EPIC/ NOAR (UK)	DCH (Denmark)	Finland	Iowa WHS (USA)	Nurses' Health Study (USA)	WHS (USA)
Author	Källberg et al. [73]	Voigt et al. [22], Shapiro et al. [55]	Pedersen et al. [7, 30], Källberg et al. [73]	Linos et al. [53, 54]	Hazes et al. [12]	Pattison et al. [61, 62, 68]	Pedersen et al. [56]	Aho, Heliövaara and colleagues [64, 65, 75, 77]	Mikuls, Cerhan, Merlino and colleagues [63, 74, 78, 82]	Karlson, Costenbader, Benito-Garcia and colleagues [66, 70, 80, 83]	Karlson, et al. [67]
Type	CC	CC	CC	CC	CC	Cohort, Nested CC	Cohort	Cohort, Nested CC	Cohort	Cohort	RCT
Source	Pop	Pop	Hosp	Hosp	Hosp	Pop	Pop	Pop	Pop	Nurses	Pop
Age, years	≥18	18–64	18–65	Adult	≥20	45–74	50–64	Adult	55–69	30–55, 25–42	≥45
Case ascertainment	Registry	Direct assessment, chart review	Referral, chart review	Outpatient attendance	Outpatient attendance	Registry, direct assessment	Registry	Registry	Questionnaire, chart review	Questionnaire, chart review	Questionnaire, chart review
Diagnosis	ACR 87	ACR 87	ACR 87	ACR 87	ARA 58	IP (subset ACR 87)	ACR 87, expert opinion	ACR 87	ACR 87	ARA 58, expert opinion	ARA 58, expert opinion
Sex	Both	Female	Both	Both	Female	Both	Both	Male, Both	Female	Female	Female
No. of patients (RA)	1204, i	324–349, i	445–515, i; ep	168, 145, p	135, ep	25 630 (73–88)	57 053 (69)	9777– 18 981 (30–126)	29 368– 31 336 (152–158)	82 063– 186 389 (480–722)	39 144 (106)
Oily fish		▼		▲			–				
Red meat						▲ ▼	–			–	
Dairy					▲	–	–			–	
Alcohol	▼	–	▲			–	–	–		–	
Coffee			▲			–	–	▲	▲ decaf	–	
Tea						–	–		▼ *	–	
Fruit						▼ ▼	–	▲			
Antioxidants		–				–	–		▼	–	–
Vitamin D						–	–	▼	▼	–	–

WHS: Women's Health Study; CC: Case control study; RCT: Randomized controlled trial; Pop: Population based; Hosp: Hospital based; ACR 87: American College of Rheumatology 1987 criteria for Classification of Rheumatoid Arthritis; ARA 58: American Rheumatism Association 1958 criteria for Rheumatoid Arthritis; i: incident cases; ep: early prevalent cases; p: prevalent cases; –: no effect on risk; ▲: increased risk; ▼: decreased risk. *Non-significant.

OCs

A possible inverse association between OC use and the risk of RA has been the subject of debate since the 1970s [23, 101–113] and remains unresolved [114–117]. More recent large prospective cohorts such as the Nurses' Health Study, the Malmö Study (a prospective cohort of 18 326 women in Sweden with 136 cases of incident RA), the GPRD and the Iowa WHS have examined ever-use of OC and showed no association with RA risk [76, 118–122]; although other studies have suggested a dose-dependent risk reduction [123, 124]. Few population-based studies of incident RA have included enough current users of OC. The NOAR study found a protective effect limited to current use [OR for current *vs* never-users 0.22 (0.06, 0.85), OR for ever *vs* never-users 0.88 (0.47, 1.64)] [125]. This was not replicated in the CACORA study [OR 1.0 (0.57, 1.76) for current *vs* never use] or the GPRD [7, 76]. Interestingly, the CACORA study found an increased risk of ACPA+ RA among ever-users of OC [OR 1.65 (1.06, 2.57) *vs* never users], with additive risk in SE carriers [OR 2.27 (0.85, 6.04) for ever-users with no SE, OR 32.3 (9.93, 105) for non-users with SE homozygosity and OR 44.6 (15.2, 131) for SE homozygous ever-users; all compared with non-users with no SE] [7, 30].

HRT

Though HRT involves supplementation of exogenous hormones similar to OC, the dose of oestrogen is much reduced, and the target population is of a different age and menopausal status. Results have been consistently negative for any influence of HRT on RA risk [119, 121, 123, 125–127].

Pregnancy

Pregnancy classically results in amelioration of symptoms of established RA, which then often flare post-partum. Nulliparity could therefore be a risk factor for RA, either through increased time at-risk or through a true immunological mechanism [109, 128]. Recent studies have failed to show an association of pregnancy or parity with risk of RA [90, 103, 120–122, 125, 129, 130] and the association with age at first or last pregnancy is inconsistent (Table 3) [121, 128, 129, 131]. Pregnancy may, however, be a time-varying risk factor [132]. The GPRD showed a decreased risk of RA in the year following pregnancy [76] and a recent case–control study demonstrated a decrease in risk most pronounced at 1–5 years after the last child birth, which reduced with time [RR 0.29, $P < 0.001$ within 1–5 years of last child birth; RR 0.51, $P < 0.001$ within 5–15 years of last child birth and RR 0.76, $P = 0.18$ for >15 years since last child birth, all relative to nulliparous women] [131].

Breastfeeding

Despite many health benefits, early evidence suggested that RA risk was increased by breastfeeding, especially after the first pregnancy, possibly due to a surge in the pro-inflammatory hormone prolactin [133]. Another small study found an increased risk associated with the duration of breastfeeding especially in carriers of the PTPN22 allele [OR 5.7 (1.25, 26.52) for breastfeeding ⩾11 months and no T-variant, OR 3.6 (0.44, 28.89) for no breastfeeding and T-variant+ and OR 14.0 (2.83, 69.24) for breastfeeding ⩾11 months and T variant+] [124]. Prospective studies have, however, found a dose-dependent inverse association with duration of breastfeeding and RA risk [120–122, 125]. These results may not, however, be absolutely contradictory. The first episode of breastfeeding may produce a prolactin surge and unmask latent RA in a susceptible individual. If this first episode is survived from an RA perspective, then the individual may breastfeed longer and in subsequent pregnancies. Thus, the protection afforded by longer duration of breastfeeding may in part be an example of depletion of susceptibles. Results from selected studies on modifiable hormonal influences and RA risk are summarized in Table 3.

Conclusions

It is therefore clear that lifestyle can influence the risk of RA. We have, however, identified variability in many epidemiological factors, some of which can be explained by study design (case–control *vs* prospective cohort studies), definition of exposure, definition of outcome, serological subsets and time-varying risk. Smoking is the most consistent association, in both case–control and prospective studies, and contributes up to 25% of the population burden of RA. The risk is dose related, stronger in males and especially strong in SE carriers for ACPA+ RA. Unfortunately, there is a latency of up to 20 years after smoking cessation to return to baseline risk. From a public health perspective, this is yet another reason to advise young adults not to start smoking. Prospective studies also support a protective role of antioxidants and breastfeeding and an increased risk with coffee intake. There are also at least three case–control studies suggesting an inverse association with alcohol intake and higher education/SC and an increased risk with obesity. Obesity and pregnancy may exert an effect in proximity to disease onset, which reduces with time. Smoking, alcohol, coffee and SC are all more consistently associated with seropositive (RF+ or ACPA+) disease, whereas obesity and breastfeeding may be particularly relevant in seronegative disease. Further characterizing gene–environment interactions in the development of RA within this paradigm will be a key priority and combining genetic and environmental data in the same cohorts will be crucial to advancing our understanding of the disease. Some of the factors identified already form part of the healthy lifestyle advice given for CVD and cancer prevention, and prevention of RA may be a bystander motivating factor in high-risk individuals such as those with first-degree relatives with RA. Formalizing this into a focused prevention programme is more challenging but may be a highly cost-effective public health initiative.

Future perspectives

Many of the remaining questions regarding environmental risk of RA will almost certainly require pooling results from

TABLE 3 Modifiable hormonal risk factors of RA: summary of key studies

Name of study/origin	NOAR (UK)	Sweden	Seattle (USA)	Mayo Clinic (USA)	CACORA (Denmark)	The Netherlands	Oxford-FPA (UK)	Finland	RCGP/GPRD	Iowa WHS (USA)	MDCS (Sweden)	Nurses' Health Study (USA)
Author	Brennan et al. [125]	Olsson et al. [16, 17]	Guthrie, Koepsell, Moskowitz and colleagues [110, 118, 127, 131]	Doran et al. [123]	Pedersen et al. [7, 30]	Hazes et al. [106, 128]	Vessey et al. [23]	Heliövaara et al. [130]	Hannaford et al. [102, 103]	Merlino et al. [121]	Pikwer et al. [120]	Karlson, Hernandez-Avila and colleagues [90, 119, 122]
Type	CC	CC	CC	CC	CC	CC	Cohort	Cohort	Cohort	Cohort	Cohort	Cohort
Source	Pop	Pop	Pop	Pop	Hosp	Hosp	Pop	Pop	Pop	Pop	Pop	Nurses
Diagnosis	IP (Subset ACR 87)	ACR 87	ACR 87	ACR 87	ACR 87	ARA 58	Self-reported	Physician certified	ICD8	ACR 87	ACR 87	IP; ARA 58, expert opinion
Case ascertainment	Registry, direct assessment	Chart review	Direct assessment, chart review	Records linkage system	Referral, chart review	Outpatient attendance	Questionnaire/interview	Registry	Chart review	Questionnaire, chart review	Registry	Questionnaire, chart review
Age, years	16–80	25–75	18–64	≥18	18–65	≥20	25–39	≥30	All	55–69	≥44	30–55, 25–42
No. of patients (RA)	115, i	422, p	135–310, i	445, i	445, ep	135, ep	17 032 (78)	15 441–19 072 (116–269)	46 000 (276)	31 336 (158)	18 326 (136)	116 779–121 700 (217–674)
OC current	▼					▼	–		▼/–	–	–	–
OC ever	–	–	▼ –	▲	◀	▼	–		–	–	–	–
Early age at first pregnancy		–	▼ –			▼				–	–	–
Later age at last pregnancy										▼		
Breastfeeding	–	▼	▼			▼					▼	▼
Parity	–	–	–						–	–	–	–
HRT current	–		–							–		–
HRT ever	–		–	–				–		–		–

Oxford-FPA: Oxford Family Planning Association contraceptive study; WHS: Women's Health Study; MDCS: Malmö Diet and Cancer Study; CC: Case control study; Pop: Population based; Hosp: Hospital based; ACR 87: American College of Rheumatology 1987 criteria for Classification of Rheumatoid Arthritis; ARA 58: American Rheumatism Association 1958 criteria for Rheumatoid Arthritis; i: incident cases; ep: early prevalent cases; p: prevalent cases; OC: Oral contraceptive; –: no effect on risk; ▲: increased risk; ▼: decreased risk.

large prospective cohorts and include common definitions of exposures, disease phenotype and serological subtypes. However, we are close to being able to combine risk factors to develop a Framingham-style risk prediction model for RA. It remains to be seen whether we will need completely separate risk models for ACPA$^+$ and ACPA$^-$ disease. Clearly, there are several common risk factors between RA and CVD and pathways contributing to early low-grade inflammation deserve further study. It also affords the opportunity to evaluate the potential to draw together preventative health messages for RA with those for CVD and cancer for which such programmes are now well established.

> ### Rheumatology key messages
>
> - Lifestyle risk factors for RA are potentially modifiable.
> - Smoking remains the most consistent environmental risk factor for RA across studies.
> - We are at the threshold of being able to risk-stratify populations for RA prevention.

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