RMD Open
Rheumatic & Musculoskeletal Diseases

REVIEW

A core set of risk factors in individuals at risk of rheumatoid arthritis: a systematic literature review informing the EULAR points to consider for conducting clinical trials and observational studies in individuals at risk of rheumatoid arthritis

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To cite: Mankia K, Siddle H, Di Matteo A, *et al*. A core set of risk factors in individuals at risk of rheumatoid arthritis: a systematic literature review informing the EULAR points to consider for conducting clinical trials and observational studies in individuals at risk of rheumatoid arthritis. *RMD Open* 2021;**7**:e001768. doi:10.1136/rmdopen-2021-001768

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/rmdopen-2021-001768).

Received 10 June 2021
Accepted 1 September 2021

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ABSTRACT

Background There is significant interest in determining risk factors in individuals at risk of rheumatoid arthritis (RA). A core set of risk factors for clinical arthritis development has not been defined.

Methods A literature search and systematic literature review (SLR) was conducted to identify risk factors in individuals at risk of RA using Medline, Embase, PubMed and Central databases.

Results 3854 articles were identified by the literature search. After screening of titles, 138 abstracts were reviewed and 96 articles finally included. Fifty-three articles included data on risk factors including autoantibodies, subclinical inflammation on imaging, clinical features, serum and cellular biomarkers and genetic markers. Risk factors were dependent on the at-risk population. There was good evidence for serum anticitrullinated protein antibodies (ACPA) levels, as risk factors for arthritis in all at-risk populations (n=13 articles). Subclinical inflammation on ultrasound (n=12) and MRI (n=6) was reported as a risk factor in multiple studies in at-risk individuals with musculoskeletal (MSK) symptoms and undifferentiated arthritis (UA). Clinical features were reported as a risk factor in at-risk individuals with MSK symptoms and UA (n=13). Other risk factors, including serum and cellular markers were less frequently reported.

Conclusions Risk factors for arthritis development in RA are specific to the at-risk population. Serum ACPA confers risk in all populations; subclinical inflammation on imaging and clinical features confer risk in at-risk individuals with MSK symptoms. This SLR informed the EULAR taskforce for points to consider on conducting clinical trials and studies in individuals at risk of RA.

Key messages

- Risk factors for arthritis development in rheumatoid arthritis (RA) are specific to the at-risk population.
- Serum anticitrullinated protein antibodies (ACPA) confer risk of RA in both asymptomatic and symptomatic at-risk populations.
- Serum ACPA, clinical features and subclinical inflammation on imaging should be considered as 'core risk factors' in individuals at risk of RA who have symptoms without clinical arthritis.

INTRODUCTION

Furthering our understanding of the preclinical phase of rheumatoid arthritis (RA) is likely to hold the key to disease prevention. The identification, follow-up and scrutiny of individuals at risk of RA is a central part of this approach. At-risk populations have been identified based on the presence of a few well-recognised risk factors for the development of RA. These include a family history of RA, the presence of anticitrullinated protein antibodies (ACPA) and certain musculoskeletal (MSK) symptoms. Within the different at-risk populations, data on several other risk factors have also been reported. These include different RA-related autoantibodies, imaging biomarkers, various clinical features and serological markers. Typically the risk factors collected vary in different observational studies and clinical trials. Consequently, the relative importance of these risk factors in

at-risk populations can be difficult to interpret. There is also variation in which risk factors are used to select at-risk individuals for clinical trials.

The EULAR task force for conducting clinical trials and studies in individuals at risk of RA was convened to help align future work in this area through the provision of data-driven guidance and consensus. The task force agreed that population-specific core sets of risk factors should be stipulated for inclusion in future observational studies an clinical trials. The task force also felt that the frequency at which risk factor assessment should be repeated was an important question to be addressed. When defining the points to consider, participants of the EULAR task force were guided by the findings of this systematic literature review.

METHODS

An international multidisciplinary EULAR task force was convened to define points to consider for conducting clinical trials and studies in individuals at risk of RA (co-convened by KM and PE). At the first meeting (October 2019 in Amsterdam, The Netherlands), the task force agreed on four key questions to be addressed by systematic literature reviews (SLR). A key question agreed and prioritised by the task force was: *'In individuals at risk of rheumatoid arthritis (RA), is there core set of risk factors and how frequently should they be measured?'* The results of the corresponding SLR are presented in the current manuscript. Three other questions were also proposed and are addressed in the EULAR points to consider. However, the SLR on risk factors was deemed the most novel and contained the most data. The task force agreed that this SLR should be submitted for independent publication.

Study protocol

A literature search was carried out by two of the authors (KM and HS) and the expert health librarian (JK), following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[1] For the literature search, relevant keywords determined by the librarian were used in Medline, Embase, PubMed and Central databases (searched from 1944 to October 2019); see online supplemental materials for full search strategy.

Inclusion criteria

We included studies, which demonstrated risk factors for arthritis development in individuals at risk of RA. Studies identifying risk factors in the following at-risk populations were eligible for inclusion: first-degree relatives (FDRs) of RA probands, indigenous North American populations, ACPA-positive individuals with/without MSK symptoms, seropositive arthralgia, clinically suspect arthralgia, undifferentiated arthritis (UA), palindromic rheumatism (PR). Abstracts published from January 2018 onwards were included. This was to ensure important recent data, yet to be published in full articles, were also included. Articles not published in English were excluded. Duplicates were excluded. Meta-analyses were included but all other reviews and study protocols were excluded. Manually searched articles either from the references of selected manuscripts or identified by task force members could also be included.

Study selection

Studies retrieved from the searches were recorded on a central database. After removing conference abstracts (pre-2018), two investigators (KM and HS) independently screened all titles. Abstracts of titles identified as potentially eligible for inclusion were then independently assessed against the inclusion and exclusion criteria by the two investigators. Disagreements were settled by discussion between the two investigators and through discussion with a third investigator (ADM) where required. Discussions were held with the expert EULAR task force members to ensure additional relevant articles could also be identified ('hand searched').

Quality assessment

Quality assessment of studies was performed using the Newcastle-Ottowa Scale (NOS) for assessing the quality of non-randomised studies in meta-analysis.[2] This was conducted by two of the investigators independently (ADM and DA-R). Any disagreement between the two investigators was resolved by a third independent investigator (KM). The NOS scores studies according to three items: selection, comparability and outcome. The final score (range 0–9) is a sum of the item scoring. The higher the score, the better the methodological quality and the lower risk of bias (RoB); studies with ≥6 stars were considered low RoB, those with 4 or 5 stars intermediate RoB and those with <4 stars at high RoB.

RESULTS

A total of 3854 articles were identified by the librarian search. A further 38 articles were identified by hand searches. No specific pattern was identified by the health librarian to explain why these articles were missed by the searches. After screening of titles, 176 abstracts and/or articles were reviewed and 96 articles were evaluated in detail (figure 1).

Articles identifying risk factors for the development of RA fell into one of two categories: (1) risk factors identified in prospective cohorts of individuals at risk of developing RA, or (2) risk factors for development of RA in the general population using retrospective (predominantly case-control) studies. As the research question specifies risk factors in at-risk individuals, rather than the background population, articles which were in the first category were reviewed in detail.

Of the 96 articles evaluated in detail, 53 studies identifying risk factors in at-risk individuals were grouped according to the specific risk factor(s) identified in the study (table 1). All but two of the articles assessed were of high quality, that is, low RoB according to the NOS score (see online supplemental tables 1–4). Seven articles were

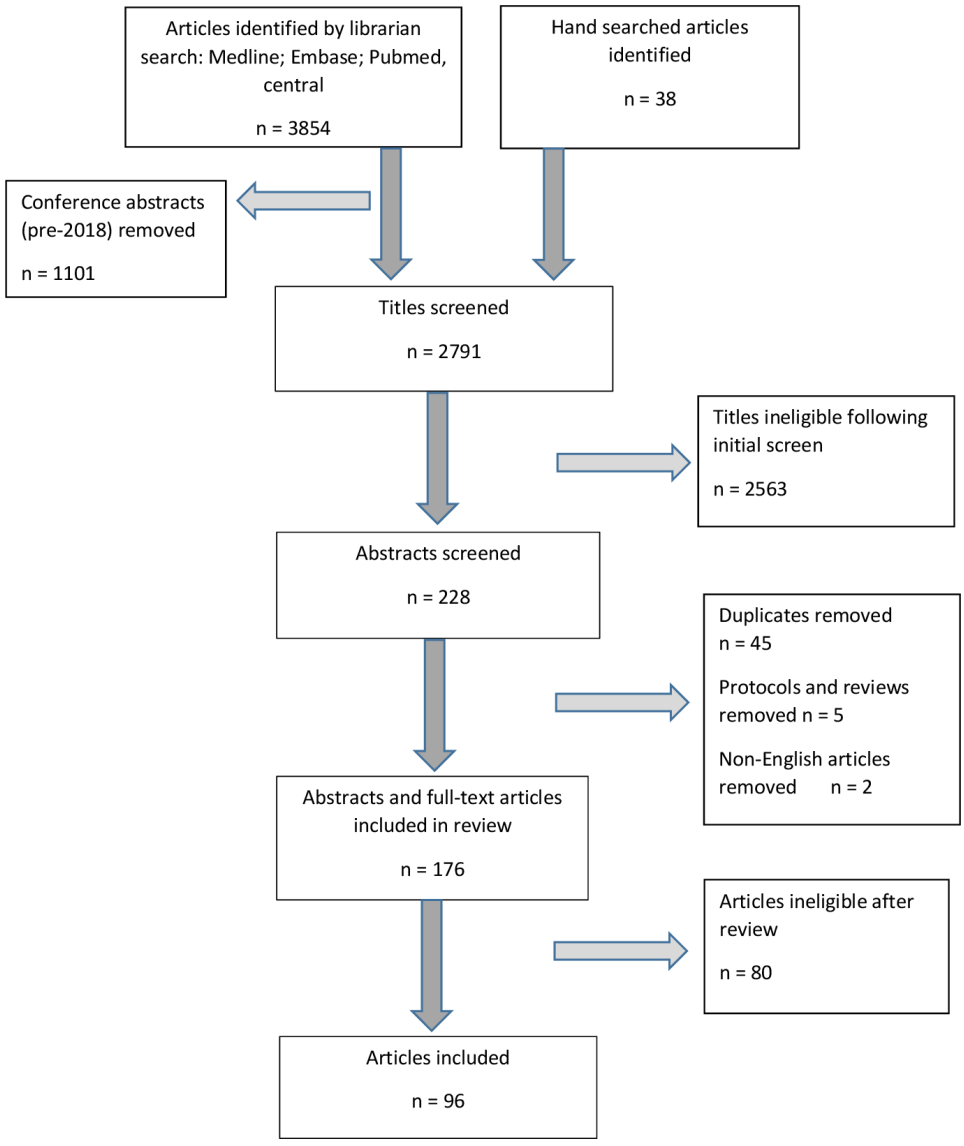

Figure 1 Flow chart for article selection according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

abstracts or letters and two were meta-analyses. These studies could not be assessed for RoB.

In these studies, risk factors are usually considered in a population-specific manner; for example, risk factors such as clinical features and subclinical inflammation on imaging are relevant in at-risk individuals with MSK symptoms but not in asymptomatic populations such as FDRs of RA probands.

ACPA and other autoantibodies

Thirteen articles specifically addressed ACPA and other autoantibodies as risk factors for arthritis development; 10/13 had a low RoB and 2/13 had intermediate RoB. One article was a systematic review and meta-analysis.

Presence of RA-related autoantibodies, especially ACPAs, is the best characterised risk factor for arthritis development across the various at-risk populations, from those without symptoms through to those with early synovitis (table 2). Indeed, serum ACPAs were identified prior to the onset of arthritis in multiple seminal studies in this field.[3–5] Considering asymptomatic populations (ie, without MSK symptoms), ACPA-positive individuals may be identified by screening in the general population or testing individuals with a heightened genetic risk of RA, that is, relatives of RA probands or Indigenous North American (INA) populations. There is good evidence that the latter groups are at higher risk of RA development, whereas there are relatively few published longitudinal data on arthritis development in ACPA-positive individuals screened from the general population. In a large Mexican cohort study, 819 healthy relatives (79% FDRs) of RA probands were followed prospectively for 5 years to investigate for RA development.[6] RA developed in 17 (2.1%) of the relatives, with a positive predictive value (PPV) of 64% when both anti-CCP and rheumatoid factor (RF) were present, and 58% when only anti-CCP was positive.[6] In a recent longitudinal study of healthy

Table 1 Research articles identified by the literature search according to the different at-risk populations

	At-risk population			
Risk factor	Asymptomatic*	MSK symptoms without clinical arthritis	UA/PR	Total
Subclinical inflammation on ultrasound	0	8	4	12
Subclinical inflammation on MRI	0	4	2	6
BMD	0	1	1	2
ACPA/RF/Other autoantibodies	6	4	3	13
Clinical features	0	4	9	13
Demographic features	0	1	0	1
Serum markers	1	2	1	4
Cellular markers	0	2	0	2
Genetic markers	0	1	1	2
Total	7	27	21	53

Fifty-three articles were identified: one article reported on both clinical and genetic risk factors; one article reported on both autoantibodies and serum markers.
*Including relatives of patients with RA.
ACPA, anticitrullinated protein antibodies; BMD, bone mineral density; MSK, musculoskeletal; PR, palindromic rheumatism; RA, rheumatoid arthritis; RF, rheumatoid factor; UA, undifferentiated arthritis.

relatives of INAs with RA, in which autoantibody levels were serially measured, 4.8% developed inflammatory arthritis (IA) during follow-up. All were seropositive at IA onset. Thirty per cent of anti-CCP/RF double positive individuals developed IA. Interestingly, there was a 71% likelihood of an ACPA-positive state reverting to seronegative after 5 years.[7] Furthermore, glycosylation of the IgG ACPA variable domain is present in FDRs of INAs with RA and is strongly associated with the future development of RA (HR 6.1, 95% CI 1.5 to 25.2, p=0.01).[8] Prior to the availability of ACPA testing, a large longitudinal study of >2000 INAs monitored bi-annually for 19 years revealed a highly significant association between RF level and RA development (p<0.01, controlling for age and sex).[9] In a recent study of anti-CCP3-positive individuals identified by population screening at health fairs in the USA, 35 of 250 individuals who tested anti-CCP3 positive were recruited and followed longitudinally for mean of 2.56 years.[10] Forty per cent of these subjects developed IA.[10]

In at-risk individuals with MSK symptoms (seropositive arthralgia, clinically suspect arthralgia, ACPA positive with MSK symptoms), ACPA levels are also strongly associated with progression to IA. In a Dutch seropositive (anti-CCP + and/or RF+) arthralgia cohort, positive anti-CCP antibodies were associated with progression to IA (HR 6.0, 95% CI 1.8 to 19.8, p<0.01). Within anti-CCP-positive subjects, a high level of anti-CCP antibodies and/or the additional presence of IgM RF were further associated with progression to IA (HR 1.7, 95% CI 1.1 to 2.5, p<0.01 and HR 3.0, 95% CI 1.4 to 6.9, p=0.01, respectively).[11] In a subsequent study from the same group, higher anti-CCP levels were associated with a broader ACPA repertoire; patients recognising ≥2 of 5 candidate ACPAs were at higher risk of IA development (p=0.04).[12] In the Dutch clinically suspect arthralgia (CSA) cohort, where subjects are recruited based on their symptoms alone rather than serological status, anti-CCP positivity, but not RF or anti-carbamylated protein antibodies (anti-CarP), was associated with development of IA (HR 5.1) in the multivariable analysis. However, in addition to anti-CCP positivity, lone RF positivity was also associated with IA development compared with seronegative individuals (HR 2.6).[13] High anti-CCP level was also the strongest risk factor in two clinical prediction rules in Dutch seropositive patients with arthralgia[14] and the Leeds cohort of ACPA-positive individuals with non-specific MSK symptoms.[15] One study has demonstrated a positive association between serum anti-CarP antibodies and IA development in a cohort of anti-CCP/RF-positive patients with arthralgia (HR 1.6, p=0.02).[16] This association remained positive in the anti-CCP-positive subgroup (OR 2.2, p<0.01).

In patients with early UA, anti-CCP antibodies are also a strong risk factor for disease progression to RA.[17–19] Anti-CCP2 antibodies were the strongest predictive biomarker for progression to RA in a Japanese cohort of patients with UA, with other diagnostic biomarkers (including IgM RF and C reactive protein) adding minimal additional value.[17] Anti-CCP2 antibodies were compared with anti-CCP3, RF and antimutated citrullinated vimentin (MCV) antibodies in a prospective study of 625 patients with UA.[19] Overall, anti-CCP2 antibodies had the highest PPV for RA development (67.1%), followed by anti-CCP3 (64%), RF (61.7%) and anti-MCV (56.3%).

In 376 Norwegian early arthritis clinic patients, the association between anti-CCP and RF levels and arthritis persistence was tested.[18] Almost 50% of these patients had persistent arthritis at 1 year. Sensitivity/Specificity for persistent arthritis was 28%/95% for RF alone, 30%/95% for anti-CCP alone and 37%/92% for both autoantibodies. Likelihood of persistent arthritis increased with increasing levels of both RF and anti-CCP.[18]

One important caveat when interpreting these studies is that patients were classified as UA based on failure to meet now outdated RA classification criteria. It is therefore likely that a significant proportion of these patients with UA would actually classify as RA based on contemporary criteria.[20]

Clinical features

Thirteen articles addressed clinical features as risk factors for arthritis development; 11/13 had a low RoB. Of the

Table 2 Articles reporting on RA-related autoantibodies as isolated risk factors in individuals at risk of RA

Study	Population studied	Cohort size	Risk factor	Frequency assessed	Main outcome
Asymptomatic					
del Puente *et al*[9]	Healthy NAN	2712	RF	Multiple: bi-annually	RA development Incidence of RA (cases per 1000 person-years) increased according to RF titre (p<0.001): cases per 1000 person-years=2.4 (RF titre <1:2); 6.7 (titre 1:2–1:16); 11.0 (titre 1:32–1:256); 48.3 (titre >1:256)
Ramos-Remus *et al*[6]	FDRs and relatives of RA probands	819 relatives of 252 RA probands	Relatives of RA probands	Once (BL)	Development of RA *All relatives* Anti-CCP2+/RF + versus seronegative: HR 52.5 (95% CI 19.1 to 144.1), p<0.01 *Offspring versus other relatives* HR 3.1 (95% CI 1.2 to 8.1)
Gan *et al*[52]	Anti-CCP3-positive individuals screened from the general population	35	Anti-CCP3	Once (BL)	Development of IA Anti-CCP3: 14/35 (40%) of anti-CCP3 + individuals developed IA at 2.56 years follow-up
Verheul *et al*[60]	Pre-RA individuals, FDRs	379 (pre-RA) 246 (FDR)	Anti-CCP RF Anti-CarP	Meta-analysis	Development of RA *Number of different autoantibodies present:* one antibody: OR 12 (95% CI 6 to 21) two antibodies: OR 30 (95% CI 11 to 83) three antibodies: OR 112 (95% CI 6 to 2122)
Tanner *et al*[7]	Unaffected relatives of NAN RA-probands in Canada and Alaska	374	ACPA RF	Multiple: BL and annually	Development of IA *Cases of IA per 1000 person-years:* ACPA+/RF + 97.1 ACPA–/RF + 7.2 ACPA+/RF– 36.4
Hafkenscheid *et al*[8]	ACPA-positive FDRs of patients with RA, in NANs	126	IgG ACPA V-domain glycosylation		Development of RA IgG ACPA variable-domain glycosylation: HR=6.07 (95% CI 1.46 to 25.2, p=0.013)
MSK symptoms without arthritis					
Bos *et al*[11]	Seropositive arthralgia (ACPA and/or RF)	147 (50 ACPA+, 52 RF+, 45 ACPA+/RF+)	Anti-CCP2 IgM RF	Once (BL)	Development of IA *Compared with RF:* anti-CCP: HR 6.0 (95% CI 1.8 to 19.8); p=0.004 *In anti-CCP + only:* anti-CCP+/IgM RF+: HR 3.0 (95% CI 1.4 to 6.9), p=0.01. High anti-CCP level: HR 1.7; (95% CI 1.1 to 2.5), p=0.008
van de Stadt *et al*[12]	Seropositive arthralgia (ACPA and/or RF)	244	Reactivity to five citrullinated peptides: cFib1 cFib2 cFib3 enolase vimentin	Once (BL)	Development of IA Recognition of 2–5 additional citrullinated peptides: HR 1.7 (95% CI 0.93 to 3.16), p=0.08
Shi *et al*[16]	Seropositive arthralgia (anti-CCP2 and/or RF)	340	Anti-CarP Ab	Once (BL)	Development of IA Anti-CarP antibodies: HR=1.56 (95% CI 1.06 to 2.29), p=0.003. *In anti-CCP + subgroup only:* anti-CarP antibodies: HR=2.23 (95% CI 1.31 to 3.79), p=0.003
Ten Brinck *et al*[13]	CSA	241	ACPA, RF and anti-CarP Ab	Once (BL)	Development of IA Anti-CCP2: HR=5.1 (95% CI 2.0 to 13.2) RF: 2.0 (95% CI 0.81 to 4.9) Anti-CarP: 1.04 (95% CI 0.46 to 2.4)
Early clinical arthritis					

Continued

Table 2 Continued

Study	Population studied	Cohort size	Risk factor	Frequency assessed	Main outcome
Kudo-Tanaka *et al*[17]	Recent-onset (<2 years) UA (arthritis in ≥2 joints not meeting RA or other classification criteria)	146	Anti-CCP IgM RF MMP3 CARF	Once (BL)	RA development (PPV, NPV and diagnostic accuracy) anti-CCP2: 65.2%, 97.2%, 91.7%, respectively; IgM RF: 34.1%, 95.6%, 76.3%, respectively; CARF: 30.2%, 97.5%, 70.5%, respectively; MMP3: 25.0%, 91.5%, 69.0%, respectively
van der Linden *et al*[19]	Early (<2 years) UA	625	Anti-CCP2 Anti-CCP3 Anti-MCV	Once (BL)	RA development (PPV) Anti-CCP2: 67.1% Anti-CCP3: 64% Anti-MCV: 56.3%
Mjaavatten *et al*[18]	UA (≥1 clinically swollen joint of ≤16 weeks duration)	376	Anti-CCP2 IgM RF Anti-CCP2+/IgM RF+	Once (BL)	Development of persistent IA Anti-CCP: OR 3.567 (95% CI 1.572 to 8.094) IgM RF: OR 2.716 (95% CI 1.189 to 6.202) Anti-CCP+/RF+: OR 7.948 (95% CI 2.659 to 23.752)

HR/OR and 95% CIs have been reported where available.
+, positive; Ab, antibodies; ACPA, anticyclic citrullinated peptide antibodies; BL, baseline; CARF, anti-agalactosyl IgG antibodies; CarP, carbamilated protein; CCP, cyclic citrullinated peptide; CCP2, second-generation anti-CCP Ab; CCP3, third-generation anti-CCP Ab; CSA, clinically suspect arthralgia; FDRs, first-degree relatives; IA, inflammatory arthritis; MCV, mutated citrullinated vimentin; MMP-3, matrix metalloproteinase 3; NAN, native American nations; NPV, negative predictive value; PPV, positive predictive value; RA, rheumatoid arthritis; RF, rheumatoid factor; UA, undifferentiated arthritis.

two articles without low RoB, one article was an abstract and one was a systematic review and meta-analysis.

Clinical features have not been well characterised in at-risk populations who do not have MSK symptoms (ie, FDRs and INA populations). A range of clinical features related to the MSK system have been characterised in ACPA-positive individuals with MSK symptoms, patients with seropositive arthralgia, patients with CSA and patients with early arthritis (ie, UA and PR) (table 3). Whether non-MSK symptoms, for example, fatigue, are relevant to disease progression will be an important area for future research. Composite risk prediction tools incorporating multiple clinical features have been reported for seropositive arthralgia[14] and ACPA-positive individuals with MSK symptoms.[15] The Dutch risk prediction tool was based on an analysis of 374 patients with seropositive arthralgia, 254 (68%) of whom were anti-CCP positive. One hundred thirty-one (35%) patients developed arthritis after a median of 12 months. In the multivariate Cox regression analysis, six clinical MSK features were associated with arthritis development: duration of symptoms <12 months, intermittent symptoms, location of symptoms in the upper and lower extremities, visual analogue scale (VAS) pain ≥50, early morning stiffness (EMS) ≥1 hour, swollen joints reported by the patient. Of these, VAS pain ≥50 had the strongest association with progression (HR 2.3) and was given two points in the risk score while all other clinical features were given one point.[14] A subsequent UK risk prediction tool (Leeds CCP cohort) was based on a cohort of 100 anti-CCP-positive individuals with non-specific MSK symptoms, of whom 50 developed arthritis after a median of 7.9 months.[15] In this study, only two clinical features were associated with arthritis development, tenderness of small joints and EMS (≥30 min and ≥60 min). Pain VAS ≥50, intermittent symptoms and symptoms in the upper and lower extremities were not predictive.[15] In both risk prediction tools, autoantibody status had a far stronger association with arthritis development than any clinical feature.[14 15] The EULAR definition of arthralgia suspicious for progression to RA (ie, the accepted case definition of CSA) is a set of six clinical features (and one genetic factor) deemed by rheumatologists to represent an increased risk for arthritis development.[21] These include symptoms duration <1 year, metacarpophalangeal (MCP) joint symptoms, EMS ≥60 min, most severe symptoms in morning, difficulty making a fist, positive MCPJ squeeze test. This definition was subsequently validated in two independent cohorts of patients with CSA from Leiden (The Netherlands) and Umea (Sweden).[22] Recruitment into these cohorts preceded the EULAR definition. Individuals meeting criteria for a positive definition of CSA (≥3 of the above listed factors present) had an increased risk of developing arthritis compared with definition-negative patients (HR 2.1, 95% CI 0.9 to 4.7), although statistical significance was not reported. The sensitivity was 84% and the PPV was 30%.[22]

The majority of published data on clinical features as risk factors in at-risk individuals are reported in patients with early clinical arthritis, classifying as UA based on criteria that precede 2010 RA classification criteria.[23–30] The clinical parameters used in these studies are summarised in table 3.

In patients with PR, clinical features have also been demonstrated to be risk factors for RA development. In a retrospective review of 127 Spanish patients with PR, 36

Table 3 Articles reporting clinical features alone, or as part of a risk prediction tool, as risk factors in individuals at risk of RA

Study	Population	Cohort size	Risk factor	Frequency	Part of composite risk prediction tool?	Outcome
MSK symptoms without arthritis						
van de Stadt *et al*[14]	Seropositive arthralgia (ACPA and/or RF)	374	Symptoms duration <12M Intermittent symptoms Symptoms in upper and lower extremities VAS pain ≥50 EMS >60 min Swollen joints reported	BL	Y	**Development of IA** Symptoms duration <12M: HR=1.72 (95% CI 1.39 to 2.15) Intermittent symptoms: HR=1.75 (95% CI 1.41 to 2.16) Symptoms upper and lower extremities: HR=1.37 (95% CI 1.12 to 1.68) VAS pain ≥50: HR=2.29 (95% CI 1.85 to 2.85) EMS >60 min: HR=1.67 (95% CI 1.29 to 2.15) Swollen joints reported: HR=1.78 (95% CI 1.46 to 2.20)
Rakieh *et al*[15]	Anti-CCP + individuals with non-specific MSK symptoms	100	EMS ≥30 min	BL	Y	**Development of IA** HR=1.85 (95% CI 1.02 to 3.35), p=0.043
Burgers *et al*[22]	CSA	354 (2 cohorts)	Positive definition of CSA (EULAR definition for suspicious arthralgia) ≥3 parameters present	BL	Y	**Development of IA** HR=2.1 (95% CI 0.9 to 4.7)
Nakajima *et al*[61]	ACPA + individuals without clinical synovitis	18	Tenderness of DAS-28 subject joints at the first visit	BL	N	**Development of IA** *Progressors versus non-progressors:* tenderness present in 10/10 patients vs 2/8 patients (p=0.0044)
Early clinical arthritis						
Gonzalez-Lopez *et al*[31]	PR—Gonzalez Lopez criteria	127	Frequency of PR attacks	BL	Y	Development of a chronic connective tissue disease HR 1.03 (95% CI 1.01 to 1.05), p=0.03
El Miedany *et al*[24]	UA—synovitis >2 joints for ≤6 months	173	EMS duration	BL	Y	Development of persistent arthritis OR 1.15 (95% CI 1.094 to 1.222), p<0.001
Kuriya *et al*[29]	UA—symptoms ≤12 months	105	TJC SJC HAQ score	BL	Y	Development of RA *Progressors versus non-progressors:* TJC (median 22 vs 4), p<0.001 SJC (median 12 vs 1), p<0.001 HAQ score (mean 0.94 vs 0.52), p=0.006
Salaffi *et al*[62]	UA—symptoms ≤16 weeks	149	Symptoms ≥6 weeks EMS >30 min	BL	Y	Development of RA Symptoms ≥6 weeks: OR=4.97 (95% CI 1.39 to 17.88), p=0.014 EMS >30 min: OR=3.16 (95% CI 1.06 to 9.46), p=0.039
Tamai *et al*[32]	PR—Gonzalez Lopez criteria	28	PIP joint involvement	BL	N	Development of RA HR 27.16 (95% CI 1.55 to 474.22), p=0.024
Ha *et al*[27]	UA—(not meeting 1987 RA criteria)	164	EMS >30 min SJC ≥4	BL	Y	Development of RA EMS >30 min: OR=11.9 (95% CI 2.0 to 71.7), p=0.007 SJC ≥4: OR=13.8 (95% CI 1.7 to 112.4), p=0.014
Bizzaro *et al*[26]	UA—symptoms ≤12 weeks	192	Hand joint arthritis	BL	Y	Development of RA HR=2.140 (95% CI 1.128 to 4.059) p=0.02

Continued

Table 3 Continued

Study	Population	Cohort size	Risk factor	Frequency	Part of composite risk prediction tool?	Outcome
McNally *et al*[25]	UA—up to 12M symptoms, synovitis in ≥1 joint	1084	Score of ≥8 on the Leiden Clinical Prediction Rule	Meta-analysis	Y	Development of RA at 1 year Specificity 95% (95% CI 92 to 97) and sensitivity 49% (95% CI 43 to 55)
Yiannopoulos *et al*[30]	UA	192	Disease duration	BL	N	Development of RA *Progressors versus non-progressors* Disease duration 28.5 months vs 45.3 months, p=0.018

HR/OR and CIs have been reported where available.
+, positive; A, abstract only; ACPA, anticyclic citrullinated peptide; BL, baseline; CCP, cyclic citrullinated peptide; CPR, clinical prediction rule; CRP, C reactive protein; CSA, clinically suspect arthralgia; DAS-28, Disease Activity Score-28 joints; EMS, early morning stiffness; ESR, erythrocyte sedimentation rate; FDRs, first-degree relatives; HAQ, Health Assessment Questionnaire; IA, inflammatory arthritis; M, months; MSK, musculoskeletal; PD, power Doppler; PIPs, proximal interphalangeal joints; PPV, positive predictive value; PR, palindromic rheumatism; RA, rheumatoid arthritis; RADAI, rheumatoid arthritis disease activity index; RF, rheumatoid factor; STJ, swollen joints count; TJC, tender joints count; UA, undifferentiated arthritis; US, ultrasound; VAS, visual analogue scale.

(28%) had subsequently developed RA and early involvement of the wrist and proximal interphalangeal (PIP) joints was associated with this progression.[31] However, the presence of RF was more strongly associated with development of RA compared with any clinical factors and this study predated the routine use of ACPA assays. In a subsequent Japanese cohort study, PIP joint involvement was again associated with arthritis development (OR 8.2). However, anti-CCP antibodies were much more predictive than clinical factors (OR 46.7).[32]

Imaging markers

Eighteen articles specifically addressed imaging markers as risk factors for arthritis development; 13/18 had a low RoB. The five articles without low RoB were abstracts, therefore RoB was not applicable.

In at-risk individuals with MSK symptoms, including anti-CCP + individuals with MSK symptoms and patients with seropositive arthralgia, joint abnormalities on high-resolution ultrasound (US) are associated with arthritis development (table 3). US abnormalities are also predictive of disease progression in patients with UA (table 4). In a UK cohort of 136 anti-CCP-positive individuals with MSK symptoms, US features were predictive of arthritis development at both joint and patient level.[33] US erosions and grey-scale (GS) synovitis were both predictive of arthritis at patient level, although intra-articular power Doppler (PD) signal had the highest predictive value (HR 3.7, 95% CI 2.0 to 6.9, p<0.01). There was an even stronger association with progression at joint level; PD grade ≥2 had an HR 31.3, 95% CI 15.6 to 62.9, p<0.01. In the same cohort, US scans acquired at multiple time points have been analysed to identify predictors of disease progression. In 44 subjects who had 3 serial US scans, those patients who developed arthritis had an increase in US inflammation (ie, total PD score) between scans 2 and 3 (preprogression and progression to arthritis) compared with the corresponding time points in non-progressors, suggesting US inflammation is a late feature which heralds the imminent onset of clinical arthritis.[34] In a subsequent analysis of 307 subjects, the frequency of US PD at patient level (ie, number of joints affected) increased in the 12 months prior to arthritis development.[35] In a Dutch seropositive arthralgia cohort, US changes (ie, PD signal, GS synovitis, erosions) were associated with arthritis development at joint level but not patient level, although the US protocol contained fewer joints compared with the UK cohort studies.[36] In a subsequent study, GS synovitis (grade ≥2) was associated with the development of arthritis and its timing at patient level (metatarsophalangeal (MTP) joints excluded); HR 3.4. Interestingly, there was no positive association with PD in this study and the predictive capacity of US was higher in individuals at higher risk of arthritis, based on a clinical prediction rule based on this cohort.[14 37] These data further emphasise the predictive utility of US in higher risk individuals with MSK symptoms. In a Swedish cohort of ACPA-positive individuals with MSK symptoms but no

Table 4 Articles reporting imaging findings alone as risk factors in individuals at risk of RA

Study	Population	Cohort size	Risk factor	Frequency	Outcome
Ultrasound alone					
MSK symptoms without arthritis					
van de Stadt *et al*[36]	Seropositive arthralgia (ACPA and/or RF)	192	US PD signal (joint level)	BL	Development of IA OR=2.9 (95% CI 4.65 to 360)
Nam *et al*[33]	Anti-CCP + with non-specific MSK symptoms	136	US PD signal (patient level) US BE (patient level) USGS ≥2 (patient level)	BL	Development of IA US PD signal: HR 3.7 (95% CI 2.0 to 6.9), p<0.001 US BE: HR 2.9 (95% CI 1.7 to 5.1), p<0.001 US GS ≥2: HR 2.3 (95% CI 1.0 to 4.9), p=0.038
Zufferey *et al*[40]	Anti-CCP-negative patients with arthralgia and no synovitis	80	US synovitis (SONAR score)	BL	Progression to RA OR=7.4 (95% CI 1.19 to 42.8), p=0.02
van Beers-Tas *et al*[37]	Seropositive arthralgia (ACPA and/or RF)	163	US GS ≥2 (excluding MTP joints) (patient level)	BL	Development of IA HR=3.4 (95% CI 1.6 to 6.8), p<0.01
Pentony *et al*[34]	Anti-CCP + with non-specific MSK symptoms	44	US total PD score in the wrists, MCPJs (1–5) and PIP joints (1–5)	BL Preprogression Progression	Development of IA 54.5% progressors had increased PD signal score longitudinally vs 9.1% non-progressors
Kisten *et al*[38]	Anti-CCP + with non-specific MSK symptoms but no clinical/US inflammation	66	US TSV (patient level)	BL or FU visits	Development of IA RR=3.0 (95% CI 1.8 to 4.8), p=0.001
Hensvold *et al*[39]	Anti-CCP + with non-specific MSK symptoms but no clinical/US inflammation	66	Combined US-TSV on US (patient level) and positive HLA-SE	BL	Development of IA HR=4.9 (95% CI 1.5 to 16), p=0.01
Duquenne *et al*[35]	Anti-CCP + with non-specific MSK symptoms	307	≥1 joint with PD signal	>12M before progression 3–12M before progression <3M before progression	Development of IA in the next 3 months OR=7.52
Early clinical arthritis					
Freeston *et al*[41]	UA ≤12W of inflammatory arthralgia ±synovitis	50	US GS score ≥3, PD signal ≥1, ≥1 BE	BL	Development of persistent arthritis Probability increased from 34% to 94%
Filer *et al*[42]	UA—early synovitis of ≥1 joint and symptom duration ≤3M	58	PD 10 index: summed PD grades of MCP joints 2–3, wrists and MTP joints 2–3	BL	Development of RA PD 10 index combined with Leiden prediction score: AUC 0.962, compared with AUC 0.905 (Leiden score alone), p<0.05
Sahbudin *et al*[43]	UA—early synovitis of ≥1 joint and symptom duration ≤3M	107	US digital flexor TSV Positive PD signal in MCP3	BL	Development of RA OR=4.066 (95% CI 1.444 to 11.444), p=0.008 OR=3.078 (95% CI 1.047 to 9.046), p=0.041
MRI±US					
MSK symptoms without arthritis					

Continued

Table 4 Continued

Study	Population	Cohort size	Risk factor	Frequency	Outcome
Kleyer *et al*[44]	ACPA-positive at-risk individuals	20	MRI TSV at ≥2 sites	BL	Development of RA 5/5 (100%) of individuals who developed RA had MRI TSV at ≥2 sites
Van Steenbergen *et al*[46]	CSA	150	Subclinical MRI inflammation	BL	Development of IA HR=5.07 (95% CI 1.77 to 14.50), p=0.002
Boer *et al*[63]	Patients with CSA and patients with UA (arthritis <2 years)	225 CSA +201 UA	MRI inflammation 'corrected' for MRI abnormalities in healthy individuals	BL	'Corrected' versus 'uncorrected' MRI inflammation Development of IA at 12 months Accuracy 60% (95% CI 54 to 67) vs 32% (95% CI 26–38) AUC 0.71 vs 0.55 Fulfilment of 1987 RA criteria at 12 months Accuracy 44% (95% CI 38 to 51) vs 22% (95% CI 17 to 29) AUC 0.65 vs 0.52
Hunt *et al*[45]	Anti-CCP + individuals with non-specific MSK symptoms	98	MRI TSV US PD+ ≥2 US GS ≥2	BL	Development of IA HR=4.02 (95% CI 1.91 to 8.44), p=0.002 HR=5.09 (95% CI 1.93 to 13.44), p=0.006 HR=2.69 (95% CI 1.14 to 6.34), p=0.059
Early clinical arthritis					
Navalho *et al*[49]	Untreated recent onset (<1 year) polyarthritis	32	MRI ECU TSV MRI FT2 TSV MRI synovitis of the radioulnar joint	BL	Development of RA OR=3.21 (95% CI 1.09 to 9.40), p=0.03 OR=9.6 (95% CI 1.17 to 78.93), p=0.03 OR=8.79 (95% CI 1.02 to 75.63), p=0.04
Navalho *et al*[47]	Untreated recent onset (<1 year) undifferentiated polyarthritis	4	MRI carpal joint synovitis MRI flexor tendon TSV MRI global joint and tendon count Global MRI and US scores	BL	Development of RA OR=3.64 (95% CI 1.19 to 11.84), p=0.032 OR=5.09 (95% CI 1.62 to 16.05), p=0.005 OR=2.77 (95% CI 1.249 to 6.139), p=0.012 AUC=0.959 and=0.853, respectively, p<0.05
Dakkak *et al*[48]	UA (arthritis in ≥1 joint, symptom duration <2 years)	123	MRI TSV in feet adjusted for BME and synovitis of the foot MRI TSV in feet adjusted for CRP and swollen joint count MRI TSV in hands independent of BME and synovitis	BL	Development of RA OR=3.29 (95% CI 1.03 to 10.53) OR=2.14 (95% CI 0.77 to 5.95) OR=3.99 (95% CI 1.64 to 9.69)

HR/OR and CIs have been reported where available.
+, positive; A, abstract only; ACPA, anticyclic citrullinated peptide antibodies; AUC, area under the curve; BE, bone erosions; BL, baseline; BME, bone marrow oedema; CCP, cyclic citrullinated peptide; CRP, C reactive protein; CSA, clinically suspect arthralgia; ECU, extensor carpi ulnaris; FDRs, first-degree relatives; FT, flexor tendons; FU, follow-up; GS, grey scale; IA, inflammatory arthritis; M, months; MCPs, metacarpophalangeal joints; MSK, musculoskeletal; MSUS, musculoskeletal ultrasound; MTPs, metatarsophalangeal joints; PD, power Doppler; PPV, positive predictive value; RA, rheumatoid arthritis; RF, rheumatoid factor; RR, relative risk; TSV, tenosynovitis; UA, unclassified/undifferentiated arthritis; US, ultrasound; W, weeks.

clinical or US synovitis, US tenosynovitis was associated with arthritis development (RR 3.0, 95% CI 1.8 to 4.8, p<0.01).[38 39]

In seronegative at-risk individuals with arthralgia, US synovitis (Swiss SONAR criteria positive) is also associated with arthritis development.[40] Furthermore, in seronegative patients with early UA, US synovitis and erosions were associated with development of persistent arthritis.[41] GS synovitis in the wrists and MCP joints and PD signal in the MTP joints were all associated with development of RA in a UK cohort of patients with very early UA.[42] In a subsequent analysis of 107 patients with UA by

the same group, US tenosynovitis was frequently identified and US finger flexor tenosynovitis was predictive of RA development (OR 3.1, 95% CI 1.05 to 9.05, p=0.04).[43]

In both ACPA-positive individuals with MSK symptoms and patients with CSA, subclinical inflammation on MRI has been associated with arthritis development[44–46] (table 4). In both populations, MRI tenosynovitis was the most prevalent MRI abnormality and also the most strongly associated with arthritis development. In a study of 150 Dutch patients with CSA, 31% of patients with baseline subclinical MRI inflammation (either synovitis, osteitis or tenosynovitis) had developed clinical arthritis at 1 year (71% of ACPA-positive patients with CSA with MRI inflammation had developed arthritis). MRI tenosynovitis was the only MRI feature independently associated with arthritis development in the multivariable analysis (HR 8.4, 95% CI 3.4 to 20.8, p<0.01).[46] Similarly, at patient level, MRI tenosynovitis was the only MRI feature associated with arthritis development in a UK cohort of 98 ACPA-positive individuals with MSK symptoms (HR 4.02, 95% CI 1.9 to 8.4, p<0.01).[45]

MRI findings in patients with UA are also associated with disease progression and specifically RA development.[47 48] In a small study of patients with recent-onset polyarthritis, MRI tenosynovitis of the finger flexor tendons and extensor carpi ulnaris, and synovitis of the radioulnar joint were associated with progression to RA.[49] In this study, MRI was more sensitive than US for joint and tendon inflammation. In a subsequent study comparing MRI and US in the same cohort, MRI was more accurate for predicting RA development.[47] In patients with UA, MRI tenosynovitis in the foot was also associated with development of RA, independent of bone marrow oedema (BME) and synovitis (OR 3.3, 95% CI 1.0 to 10.5).[48] However, in this study adding MRI of the foot did not improve the predictive accuracy compared with MRI of the hands alone.

Serum markers

Four articles specifically addressed serum markers as risk factors for arthritis development. Three of these articles had low RoB. The one article which did not have a low RoB was a research letter, therefore RoB could not be formally assessed.

The vast majority of published work on serum biomarkers as risk factors in at-risk individuals relates to autoantibodies. There are relatively few data on other serum biomarkers (table 5). In a Dutch seropositive arthralgia cohort, the serum inflammatory protein 14-3-3eta was detectable up to 5 years before the onset of clinical arthritis and was present more frequently and at higher levels in those who developed arthritis compared with those who did not.[50] However, it was not clear from this study whether 14-3-3eta levels could predict arthritis onset independently of autoantibodies. Serum dyslipidaemia was also investigated in the same cohort; of several lipid markers measured, lower baseline levels of apolipoprotein A1 were associated with an increased risk of arthritis development, even after adjustment for anti-CCP status (HR 0.5, 95% CI 0.3 to 0.9).[51]

In a small prospective cohort (n=35) of at-risk individuals identified by screening for anti-CCP3 antibodies at health fairs, increased levels of docosapentaenoic acid (a n-3 fatty acid) in red blood cells appeared to be protective for the development of IA (HR 0.5, 95% CI 0.3 to 1.0).[52]

Cellular markers

Two articles specifically addressed cellular markers as risk factors for arthritis development. Both had low RoB.

Circulating T-cell and B-cell biomarkers appear to be risk factors for arthritis development in at-risk individuals, although relatively few data have been published. In a UK cohort of anti-CCP positive individuals with MSK symptoms, frequencies of circulating T-naïve and T-reg cells were reduced, while inflammation-related cells were increased compared with controls.[53] The presence of two or more T cell abnormalities had high specificity for arthritis development and a prediction model combining clinical factors and T-cell subsets performed better than clinical factors alone (AUC 0.8, 95% CI 0.7 to 0.9).[53] In patients with seropositive arthralgia, the expansion of B-cell receptor clones (ie, presence of dominant clones) was associated with arthritis development. In both a test and validation cohort, the presence of ≥5 dominant B-cell clones was independently associated with arthritis development (Relative Risk 6.3, 95% CI 2.7 to 15, p<0.01).[54] Interestingly, when at-risk individuals developed arthritis, the dominant B-cell receptor clones appeared in synovial tissue but disappeared from peripheral blood, suggesting migration into target tissue in the at-risk phase.

Genotype, gene expression and other markers

Two articles specifically addressed genotype and gene expression as risk factors for arthritis development. Two articles addressed bone mineral density and one addressed demographic features. All of these articles were deemed to have a low RoB.

There is very limited published work on genetic markers (genotype or gene expression) as independent risk factors for arthritis in individuals at risk of RA. In the Leeds cohort of anti-CCP-positive individuals with MSK symptoms, one or more copies of HLA DR shared epitope (SE) alleles was associated with development of clinical arthritis (HR 2.5, 95% CI 1.0 to 5.9). Consequently, HLA DR SE was included in the Leeds risk prediction tool.[15] In a UK study of patients with very early UA, synovial mRNA expression of 117 cytokines was measured in synovitic joints. Higher mRNA levels of the inflammatory chemokines CXCL4 and CXCL7 were identified in individuals with very early RA (ie, in the early phase of persistent arthritis) compared with those with resolving arthritis.[55]

Two Dutch studies have demonstrated that bone mineral density (BMD) loss measured by X-ray is associated with disease progression, both in patients with CSA and patients with early UA.[5657] In 108 patients with CSA,

Table 5 Other risk factors which have been reported in individuals at risk of developing RA

Study	Population	Cohort size	Risk factor	Frequency	Outcome
BMI					
Deane *et al*[59]	ACPA + subjects without arthritis (some FDRs, some clinic patients and some health fares)	86	Those with incident RA had higher BMI (p=0.03)	BL	Development of IA Higher BMI in progressors versus non-progressors (32 vs 27), p=0.03
Serum/Cellular/Genetic					
Asymptomatic					
Gan *et al*[52]	Anti-CCP3 + individuals without IA (from health fairs)	35	Increased docosapentaenoic acid (n-3 FA)	BL and 6M assessments until IA development	Development of IA HR=0.52 (95% CI 0.27 to 0.98)
MSK symptoms without arthritis					
van Beers-Tas *et al*[50]	Seropositive arthralgia (ACPA and/or RF)	144	14-3-3eta	BL	Development of IA RR=2.5 (95% CI 1.2 to 5.6), p=0.02
van De Stadt *et al*[51]	Seropositive arthralgia (ACPA and/or RF)	348	Lower ApoA1 level	BL	Development of IA HR 0.52 (95% CI 0.29 to 0.92)
Rakieh *et al*[15]	Anti-CCP + individuals with non-specific MSK symptoms	100	HLA DR shared epitope	BL	Development of IA HR=1.84 (95% CI 1.02 to 3.32)
Hunt *et al*[53]	Anti-CCP + individuals with non-specific MSK symptoms	103	Combined clinical and T-cell subset parameters	BL and repeated at 1 year	Development of IA AUC 0.79. PPV 60% and NPV 95%
Early clinical arthritis					
Jacobsen *et al*[64]	Early (<2 years) polyarthritis	68	Homozygous for MBL variant alleles	BL	Development of RA OR 4.7 (95% CI 1.1 to 19), p=0.02
Yeo *et al*[55]	UA—early synovitis ≥1 joints with symptoms ≤3 months	48	Synovial mRNA and protein expression of CXCL4 and CXCL7	BL assessment	Development of RA at 18 months *Progressors versus non-progressors* Increased expression (trend) in progressors
BMD					
Mangnus *et al*[56]	CSA	108	BMD loss	BL and one subsequent visit	Development of IA HR 6.1 (95% CI 1.7 to 21.4), p=0.005
de Rooy *et al*[57]	Early UA	125	Highly elevated BMD loss (>2.5 mg/cm^2/month)	BL and 6 months	Development of RA OR 6.1 (95% CI 1.24 to 29.24)

HR/OR and CIs have been reported where available.
+, positive; ;A, abstract only; ACPA, anticyclic citrullinated peptide antibodies; ApoA1, apolipoprotein A1; AUC, area under the curve; BCR, B cell receptor; BL, baseline; BMD, bone mineral density; BMI, body mass index; CCP, cyclic citrullinated peptide; CRP, C-reactive protein; CXCL, C-X-C motif ligand; FA, fatty acid; FDRs, first-degree relatives; FU, follow-up; HLA-SE, human leucocyte antigen-shared epitope; hs-CRP, high-sensitive C reactive protein; M, months; MBL, mannose binding-lectine; MCP-1, monocyte chemotactic protein 1; MSK, musculoskeletal; NAN, native American nations; NPV, negative predictive value; PPV, positive predictive value; RA, rheumatoid arthritis; RF, rheumatoid factor; ROC, receiving operating characteristics; RR, relative risk.

BMD loss was associated with total MRI inflammation scores, and both factors were independently associated with arthritis development.[56] In a separate cohort of 101 patients with UA, highly elevated BMD loss (≥2.5 mg/cm^2/month) was associated with RA development (OR 6.1, 95% CI 1.2 to 29.2). Of the various demographic

factors measured in at-risk cohorts, elevated body mass index (BMI) has been demonstrated to be associated with progression to arthritis in cohorts of patients with seropositive arthralgia and ACPA-positive individuals (from health fairs, clinic patients and some FDRs).[58 59] In 83 ACPA-positive individuals recruited from health fairs, rheumatology clinics and FDRs, BMI was higher in the 10 individuals who progressed to arthritis compared with those that did not (32 vs 27, p=0.03).[59] In an early analysis of the Dutch seropositive arthralgia cohort, elevated BMI and smoking history were both independently associated with the development of arthritis in the 15/55 (27%) of individuals who progressed. Of the two, smoking had the stronger association with arthritis (HR 9.6, 95% CI 1.3 to 73, p=0.03 vs HR 5.6, 95% CI 1.3 to 25, p=0.02).[58]

Repeat assessment of risk factors

The large majority of the prospective studies described have evaluated risk factors for arthritis development at only the baseline time point (ie, the first assessment). There is, therefore, insufficient published data to indicate the optimum frequency at which risk factors should be measured in at-risk individuals, and whether and how specific risk factors may fluctuate over time. This is an important area for future research. The limited studies that have assessed risk factor(s) at multiple time points highlight the unique insights which may be derived from this approach; sequential US assessments in ACPA-positive individuals with MSK symptoms suggest the development of US inflammation is a relatively late event, which occurs when clinical arthritis is imminent.[34 35] Furthermore, serial autoantibody assessments in FDRs of INAs suggest that in many individuals, ACPA/RF resolve over time and individuals become seronegative.[7] The stability and timing of other risk factors in relation to the development of arthritis in at-risk individuals has not been reported.

DISCUSSION

This SLR was performed to address a key question raised by the EULAR task force for conducting clinical trials and studies in individuals at risk of RA. Where relevant, SLRs addressing other questions raised by the taskforce will be published separately. There is significant interest in the study of risk factors in at-risk individuals. Multiple risk factors have now been reported, across multiple biomarker modalities and in different at-risk populations. A key ambition of the task force was to provide evidence-based guidance on a 'core set' of risk factors for each at-risk population, so that investigators could include these in future observational studies and clinical trials. Of note, certain risk factors for RA have been identified in large case-control studies undertaken in the wider background population, but have not been identified in populations of at-risk individuals. A detailed discussion of all such risk factors was outside the scope of this review.

Across all at-risk populations, the most well-described risk factor for arthritis development is the presence of serum RA-related autoantibodies, in particular ACPA. The level of ACPA, and its combination with RF, has been consistently demonstrated to predict arthritis development in at-risk individuals across the continuum, from FDRs through to patients with UA. Imaging abnormalities (mainly on MRI and US) appear to be significant

Table 6 Core risk factors for development of arthritis in individuals at risk of RA according to population

At-risk population	Subpopulations	Core risk factors for arthritis
Asymptomatic at-risk individuals	Relatives of RA probands	Serum ACPA level±RF
	Indigenous at-risk populations	
	ACPA + individuals identified by population screening	
MSK symptoms without arthritis	ACPA + with MSK symptoms	Serum ACPA level±RF MSK symptoms Subclinical joint inflammation on US Subclinical joint and tendon inflammation on MRI
	ACPA+/RF + with arthralgia	Serum ACPA level±RF MSK symptoms Subclinical joint inflammation on US
	Clinically suspect arthralgia	Serum ACPA level±RF MSK symptoms Subclinical joint and tendon inflammation on MRI
Early clinical arthritis	Palindromic rheumatism	Serum ACPA level±RF MSK symptoms
	Undifferentiated arthritis	Serum ACPA level±RF MSK symptoms Subclinical joint inflammation on US Subclinical joint and tendon inflammation on MRI

ACPA, anticitrullinated protein antibodies; MSK, musculoskeletal; RA, rheumatoid arthritis; RF, rheumatoid factor; US, ultrasound.

risk factors for arthritis in *symptomatic* at-risk populations (ie, seropositive arthralgia, ACPA-positive individuals with MSK symptoms, CSA and UA). This includes recent MRI studies, which highlight tenosynovitis as a risk factor for disease progression. Of note, imaging abnormalities have not been well studied in *asymptomatic* at-risk populations (ie, FDRs, genetically predisposed individuals and ACPA + subjects screened from the general population) and further investigation is required. A range of clinical features also confer increased risk of arthritis in symptomatic at-risk populations; the majority of published data have been in UA cohorts and many describe clinical features as part of composite risk prediction tools, which also include autoantibodies. In at-risk individuals with MSK symptoms but without clinical arthritis, clinical features which indicate inflammatory type symptoms (eg, prolonged EMS duration) have been reported as risk factors for arthritis in several populations, and form important components of risk prediction tools (table 6). The significance of clinical symptoms in at-risk individuals without MSK symptoms has not been well studied.

While there are data suggesting other serum and cellular biomarkers may be associated with arthritis development in at-risk populations, these are far fewer and largely demonstrated in single studies without validation in other cohorts. Without further evidence, these would not yet be appropriate to consider as 'core' risk factors. The EULAR task force agreed a research agenda, which included several open questions related to risk factors in at-risk populations which should be addressed by future research (see 'Research agenda' section).

The strengths of this SLR include an expert librarian-led search and the review of all titles, relevant abstracts and papers by two investigators. We also benefitted from the expert knowledge of the EULAR task force; some additional relevant manuscripts, which were not identified in the literature search, have been included in the SLR. The risk of important articles being missed is therefore low. One limitation is that the SLR is restricted to narrative review as there was significant heterogeneity in the data and populations were not comparable between studies.

The identification of specific risk factors in at-risk populations is critical both on a pragmatic level, to improve the precision of risk prediction, and also on a scientific level, to improve our understanding of the pathobiology of RA. This SLR has served to bring together this information and has informed the guidance provided in the EULAR points to consider in this key area.

RESEARCH AGENDA

- Do the risk factors that drive RA autoimmunity and disease progression vary according to the ethnicity or geography of the population?
- Which biomarkers/risk factors change as individuals progress to IA?
- In individuals at risk of RA what is the sequence and timescale of the changes in biomarkers/risk factors?
- How frequently should we re-assess an individual's risk and is this subpopulation-dependent?
- Should interventions be personalised to an individual's risk factors? For example, smoking cessation, treatment of periodontitis, weight loss?
- In those at high risk, should multimodal intervention be considered according to risk factors? For example, immunomodulation combined with periodontal therapy/smoking cessation/weight loss as appropriate.
- Does reduction in one or more risk factors reduce the likelihood of progression?
- Can the quantification of an individual's risk be improved, and risk scores validated?
- Should individuals with mucosal inflammation/dysbiosis (periodontal, lung or gut) with or without genetic predisposition or serum autoantibodies be considered as an at-risk group?

Patient and public involvement

EULAR PARE members Marios Kouloumas and Codruta Zabalan were members of the EULAR task force (CLI 115) and were involved in determining the topic of focus for this SLR.

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Acknowledgements The authors would like to thank Leeds Teaching Hospitals library services for providing informatics support.

Contributors KM, HS and JK conducted the literature search. KM and HS reviewed and selected the articles. ADM and DA-R conducted the quality assessment. The manuscript was drafted by KM and PE. All authors commented on and revised the manuscript.

Funding EULAR grant CLI 115.

Competing interests KM: honoraria from AbbVie, Lilly, UCB; grants from Lilly, Gilead. HJS: none declared. AK: speakers bureau, consultancy: AbbVie, Bristol-Myers Squibb, Celgene, Eli-Lilly, Gilead, Merck Sharp and Dohme, Novartis and Pfizer. DA-R: scientific advisor for GSK. ADM: none declared. JK: none declared. DA: none declared. PE: expert advice to Pfizer, AbbVie, Amgen, MSD, Roche, Sanofi, BMS, Novartis, Lilly, Gilead, Samsung, Celltrion; grants from AbbVie, Lilly, BMS, Samsung. The review was not registered. Data collection forms and other materials used in the review available from authors on request.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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