Factors associated with resolution of ultrasound subclinical synovitis in anti-CCP-positive individuals with musculoskeletal symptoms: a UK prospective cohort study

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Summary

Background Subclinical synovitis occurs in a third of individuals at risk of rheumatoid arthritis. The objective of this study was to assess the reversibility of subclinical synovitis in individuals at risk of rheumatoid arthritis who are positive for anti-cyclic citrullinated peptide (CCP) antibody with musculoskeletal symptoms and investigate factors associated with its resolution within 12 months.

Methods We conducted a single-centre, prospective, cohort study in the UK, recruiting individuals aged 18 years or older who were anti-CCP-positive with a new non-specific musculoskeletal symptom but no clinical synovitis. Referrals were made through primary or secondary care. Participants attended a baseline visit, which included a clinical assessment, blood tests, patient questionnaires, and a musculoskeletal ultrasound scan (ie, of wrists and metacarpophalangeal, proximal interphalangeal, and metatarsophalangeal joints), and then follow-up visits every 3 months for the first year, with a repeat ultrasound scan every 12 months. Participants with subclinical synovitis (ie, grey scale ≥1 and power Doppler ≥1) in at least one joint at baseline were selected for this analysis. Investigation of good prognostic factors by 12 months was done first using univariable analysis to identify significant factors in participants with no missing data. Then receiver operating characteristic (ROC) curves were used to establish the optimal cutoffs for significant continuous variables. Finally, a modified Poisson regression approach was performed to identify the best prediction model and was adjusted for confounders, using data from all participants, with missing values imputed. This study is registered with ClinicalTrials.gov, NCT02012764.

Findings Between June 30, 2008, and Feb 24, 2020, 451 participants consented to participate in the CCP study and 122 (27%) individuals had subclinical synovitis at baseline, of whom 90 (74%) had data available at 12 months. Mean age was 54·1 years (SD 12·5), and 63 (70%) of 90 participants were women and 27 (30%) were men. Subclinical synovitis resolved in 43 (48%) of 90 participants, whereas subclinical synovitis persisted in 47 (52%) participants, 27 (57%) of whom developed clinical synovitis within 12 months. In the multivariable analysis, low anti-CCP titre (relative risk [RR] 1·52, 95% CI 1·04–2·22), negative rheumatoid factor (1·54, 0·92–2·58), subclinical synovitis in only one joint (1·62, 1·04–2·50), and an erythrocyte sedimentation rate of 15 mm/h or lower (1·82, 1·15–2·87) were predictors of subclinical synovitis resolution within 12 months (ie, good prognostic factors). ROC curve showed an area under the curve of 0·84 (95% CI 0·76–0·92; p<0·0001). Resolution occurred in seven (100%) of seven participants with all four factors present, and in only one (7%) of 14 participants with none of the factors present.

Interpretation In individuals who were anti-CCP-positive, subclinical synovitis disappeared in approximately half of the participants by 12 months and was associated with the presence of good prognostic factors. Subclinical synovitis should be interpreted in the context of these additional factors.

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Introduction

The sensitivity of musculoskeletal ultrasound for the detection of synovitis is considerably superior to physical examination and x-rays.[1] Due to its wide availability and low cost, ultrasound is often used to aid in the diagnosis and management of rheumatoid arthritis.[2] Ultrasound is also capable of detecting local joint inflammation before clinical synovitis has developed (ie, subclinical synovitis), which makes this tool extremely useful for the investigation of the preclinical phase of the rheumatoid arthritis disease continuum.[3]

Many studies have assessed the role of subclinical synovitis on ultrasound in individuals at risk of rheumatoid arthritis. Whereas most of these studies agree that the presence of subclinical synovitis has a predictive value for the development of inflammatory arthritis, with some suggesting that subclinical synovitis is the inevitable prelude to clinical synovitis, controversy

Research in context

Evidence before this study

To assess the reversibility of subclinical synovitis in anti-CCP-positive individuals, we searched PubMed, Cochrane Library, and Google Scholar, without language restriction, for articles published from inception to March 10, 2023, using the terms (("subclinical" OR "ultrasound") AND ("synovitis" OR "power doppler" OR "inflammation" OR "arthritis" OR "disease") AND ("at-risk" OR "arthralgia" OR "anti-CCP" or "ACPA")), appearing either in the title or abstract. Individual searches were also performed. Subclinical synovitis is found in approximately a third of individuals who are at risk of rheumatoid arthritis, which makes it a common clinical scenario for rheumatologists. Subclinical synovitis is associated with an increased risk of progression to an inflammatory arthritis; however, in many people, disease does not develop, meaning that these subclinical inflammatory changes might resolve. Data are scarce regarding the evolution of subclinical synovitis in individuals who are at risk of rheumatoid arthritis, and to our knowledge, no data exist from an ultrasound point of view. The window of opportunity (ie, a disease stage that allows modulation of biological processes while they are in a less mature and more reversible phase) and the good long-term outcomes that are associated with early treatment have been important promoters of the use of musculoskeletal ultrasound to detect inflammation at early stages and facilitate treatment. However, there are no clinical guidelines regarding how soon disease-modifying antirheumatic drugs should be administered. As a result, 73% of rheumatologists are willing to initiate immunosuppressant treatment in individuals with subclinical synovitis despite the fact that these inflammatory changes might resolve in some people.

Added value of this study

To our knowledge, this study provides the most complete data on the natural history of subclinical synovitis that has been published so far and is the only study focusing on the evolution of subclinical synovitis on ultrasound in individuals who are anti-CCP positive and at risk of rheumatoid arthritis with non-specific musculoskeletal symptoms. Understanding the evolution of subclinical synovitis is essential to improve clinical practice. This study has identified good prognostic factors that are associated with resolution of subclinical synovitis within 12 months.

Implications of all the available evidence

Assessment of the presence of good prognostic factors can be incorporated into standard clinical practice, allowing identification of individuals whose subclinical synovitis is likely to resolve without clinical intervention, preventing unnecessary immunosuppressant treatment.

still exists due to some studies showing little predictive value.[4–7] Results also vary regarding whether ultrasound is predictive of arthritis at the joint level versus at the patient level.[4,5] These discrepancies are probably due to the heterogeneity of studies, using different populations of participants at risk of rheumatoid arthritis (eg, participants with clinically suspect arthralgia or participants who are rheumatoid factor-positive), and different cutoffs for clinically relevant ultrasound synovitis (ie, grey scale changes ≥1 *vs* grey scale changes ≥2, with or without power Doppler signal). Little is known about the evolution of subclinical synovitis in individuals at risk of rheumatoid arthritis. Few studies have assessed the reversibility of these changes and short-term (ie, ≤12 months) and long-term (ie, >12 months) longitudinal data are scarce.[8] Thus, the relevance of a positive ultrasound finding in these individuals is uncertain.

Anti-cyclic citrullinated peptide (anti-CCP) antibodies have a high sensitivity and specificity for the diagnosis of rheumatoid arthritis.[9] These antibodies can be detected in the blood years before clinical disease appears and can also predict rheumatoid arthritis development and a subsequent aggressive phenotype.[10] The presence of subclinical synovitis in this population is a relatively frequent finding, so studying these individuals is a logical way to investigate the evolution of subclinical synovitis.[4]

The objective of this study was to assess the reversibility of subclinical synovitis in anti-CCP-positive individuals with musculoskeletal symptoms who are at risk of rheumatoid arthritis and investigate factors associated with its resolution within 12 months.

Methods

Study design and participants

We invited individuals aged 18 years or older who were anti-CCP positive with a new non-specific musculoskeletal symptom and no evidence of clinical synovitis to take part in a single-centre, prospective, cohort study for individuals at risk of developing rheumatoid arthritis (ie, Coordinated Programme to Prevent Arthritis—Can We Identify Arthritis at a Pre-clinical Stage? [CCP study]). The patient and public involvement group organised by the Leeds Biomedical Research Centre have played an active role in the CCP study. A number of meetings took place where patients and public partners had the opportunity to discuss the importance of the use of clinical practical biomarkers for the risk stratification of individuals at risk of an inflammatory arthritis. Feedback from patient and public involvement group members was requested at different stages of the process and their input was taken into consideration for the development and design of the study.

Referral could be made through primary or secondary care. In primary care, eligible candidates were identified by general practitioners or by other health professionals. Participants gave written informed consent to take part in the study. Individuals were tested for the presence of anti-CCP antibodies, and those with a positive result were

invited to attend a dedicated rheumatology research clinic in Chapel Allerton Hospital, Leeds, UK. In secondary care, anti-CCP-positive individuals with a new musculoskeletal symptom and no clinical synovitis could be referred by rheumatology colleagues. Potential candidates were then seen in the CCP research clinic and, if eligible, gave written informed consent to take part in the study.

Participants were enrolled consecutively and had a baseline visit, which included a clinical assessment, blood tests, patient questionnaires, and a musculoskeletal ultrasound scan. Participants were followed up every 3 months for the first year and had the ultrasound scan repeated every 12 months. Participants with subclinical synovitis (ie, grey scale ≥1 and power Doppler ≥1) in at least one joint at baseline were selected for this analysis. Resolution of subclinical synovitis was assessed at 12 months (plus or minus 2 months). Participants who were diagnosed with clinical synovitis before 12 months by a rheumatologist were withdrawn from the study and their ultrasound scan was not repeated at the 12-month timepoint. For analysis purposes, these individuals were included in the group of participants whose subclinical synovitis did not resolve by 12 months.

Ethical approval was obtained from Leeds West Research Ethics Committee (REC reference number 06/Q1205/169). Participants gave written informed consent to participate in the CCP study and for publication of their anonymised data. This study is registered with ClinicalTrials.gov, NCT02012764.

Procedures

The following data were collected by rheumatologists, including LG-M, LD, ADM, JLN, KH, RC, and KM, at the baseline visit performed at the CCP research clinic in Chapel Allerton Hospital, Leeds, UK: age, sex (assigned at birth), smoking exposure, and minutes of early morning stiffness. Additionally, a physical examination was done to assess the number of tender joints (ie, proximal interphalangeal and metacarpophalangeal joints, wrists, elbows, shoulders, hips, knees, ankles, and metatarsophalangeal joints) and confirm the absence of clinical synovitis. Ethnicity data were not specifically collected for this study as it did not have ethics approval to do so; however, the population from this region is demographically and ethnically representative of the UK as a whole. Patient questionnaires included a mannequin, where participants would indicate the joints where they had experienced pain for the past week (ie, fingers, wrists, elbows, shoulders, hips, knees, ankles, or feet). Blood samples were tested for the presence of a range of biomarkers, including rheumatoid factor (initial positivity cutoff ≥40 IU/mL and later ≥20 IU/mL), presence of antinuclear antibodies, anti-CCP antibody titre (initially analysed with ImmunoCAP 250 [Phadia, Uppsala, Sweden] with positive cutoff being >7 IU/mL, and later Bioplex 2200 CCP [BioRAD, Hercules, CA, USA] with positive cutoff >2·99 IU/mL; high titre was defined as at least three times the upper limit of normal), the presence of shared epitope (ie, HLA DRB01*01, DRB01*04, DRB01*10, or a combination), and increases in inflammatory markers (C-reactive protein [CRP] in mg/dL and erythrocyte sedimentation rate [ESR] in mm/h).

Ultrasound scans of hands (ie, wrists, proximal interphalangeal joints, and metacarpophalangeal joints) and feet (ie, metatarsophalangeal joints) were performed by an ultrasonographer who was masked to all participant details except study number and initials and trained in the study protocol using the following ultrasound machine models throughout the duration of the study: Philips (ATL HDI 5000, Bothell, WA, USA) with 5–12 MHz and 8–15 MHz transducers, General Electric S7 (Milwaukee, WI, USA) with a 6–15 MHz transducer, and General Electric Logiq E9 (Milwaukee, WI, USA) with a 6–15 MHz transducer. Power Doppler was set up with a pulse repetition frequency of 700–1000 Hz and a Doppler frequency of 6 MHz for the Philips model and 10 MHz for the two GE models.[4,11]

Ultrasound scans were assessed using a semiquantitative method initially proposed by the European League Against Rheumatism (now the European Alliance of Associations for Rheumatology [EULAR]), with scores ranging from 0 to 3 for grey scale and power Doppler,[12] and more recently following the EULAR–Outcome Measures in Rheumatology (OMERACT) scoring system.[13] Ultrasound images were scored at the time of data acquisition. The presence of subclinical synovitis was defined as both grey scale changes of at least 1 and power Doppler signal of at least 1. Resolution of subclinical synovitis was defined as disappearance of power Doppler (power Doppler=0), regardless of the grey-scale grading. The presence of bone erosions was defined according to OMERACT.[14] Participants with isolated subclinical synovitis in the first metatarsophalangeal joint were not included in our analysis due to the likelihood of it being secondary to wear and tear.

None of the participants received any disease-modifying antirheumatic drugs (DMARDs) during the study. Pain management included painkillers, physiotherapy, wrist splints, insoles, and non-steroidal anti-inflammatory drugs as appropriate and did not change over time. Participants were warned not to take non-steroidal anti-inflammatory drugs before their ultrasound scan.

Statistical analysis

Descriptive statistics were used for dichotomous and continuous variables. The following variables were recorded as dichotomous and frequencies and percentage were calculated: female (yes or no), rheumatoid factor (positive or negative), antinuclear antibodies (positive or negative), shared epitope (present or absent), smoking exposure (yes or no), and anti-CCP antibodies (high [ie, at least three times the upper limit

of normal] or low [ie, less than three times the upper limit of normal]). The decision to dichotomise these variables was made on the basis of a review of the literature, expert opinion, and international cutoffs. Continuous variables included age, CRP concentration, ESR, early morning stiffness, tender joint count, number of painful joints reported by the patient, number of joints with subclinical synovitis, and number of erosions on ultrasound, which were reported as either mean and SD or median and IQR.

Association between patient status at 12 months (ie, resolution of subclinical synovitis [yes or no], defined as disappearance of power Doppler) and dichotomised variables was assessed using either χ^2 test or Fisher's exact test, as appropriate (χ^2 if expected counts in each cell were 5 or greater, otherwise Fisher's exact test). For continuous variables, we used either an independent t-test or Mann-Whitney U test depending on the data distribution and homogeneity of variance between comparison groups using Levene's test. Normality of continuous variables was assessed by use of a Shapiro-Wilk test.

Significant continuous variables were further dichotomised using receiver operating characteristic (ROC) curves to establish the most appropriate cutoff values. The optimal cut points for ROC curves were established by maximising the difference between sensitivity and 1-specificity (ie, false positive rate); which is known as the Youden Index. Then, a modified Poisson regression approach was used including all significant variables from the univariable analysis and further adjustment for additional confounding factors: age (rheumatoid arthritis has a peak incidence at age 50 years and was also significant in the univariable analysis), sex (rheumatoid arthritis is more common in women), and smoking status (the presence of anti-CCP antibodies is increased in smokers).[15] The coefficient of each factor was expressed as a risk ratio (RR) and 95% CI. A final ROC curve was performed to assess the model's discrimination.

Spearman correlation coefficient was used to assess the association between the number of joints with subclinical synovitis at baseline and the number of prognostic factors for resolution and the association between the number of joints with subclinical synovitis at baseline and the number of factors traditionally identified as predictive of clinical synovitis.

Only available data were included in the univariable analysis. Missing data for ESR were imputed using expectation maximisation method in the modified Poisson regression model. A sensitivity analysis was performed comparing the imputed variable with the original variable data, showing similar results for the factors associated with resolution of subclinical synovitis by 12 months.

Statistical analyses were performed using SPSS (version 28.0.1.1) and R Studio (version 2023.09.0+463) with various packages. Significance level was set at 0·05.

Role of the funding source

The funder of the study funded the infrastructure and the patient and public involvement group, which played an active role in the design of the study. The funder had no role in data collection, data analysis, data interpretation, or writing of the report.

Results

Recruitment took place between June 30, 2008, and Feb 24, 2020. Participants were recruited nationally (ie, those referred from primary care) but mainly across West Yorkshire (ie, referred from secondary care). Of the 699 participants assessed for eligibility at Chapel Allerton Hospital, Leeds, UK, 451 participants were recruited for the CCP study and 122 (27%) had subclinical synovitis at baseline (figure 1; appendix p 3). Subclinical synovitis status at 12 months (ie, ultrasound scan or confirmation of clinical synovitis at 12 months) was available for 90 (74%) of 122 individuals, who were subsequently

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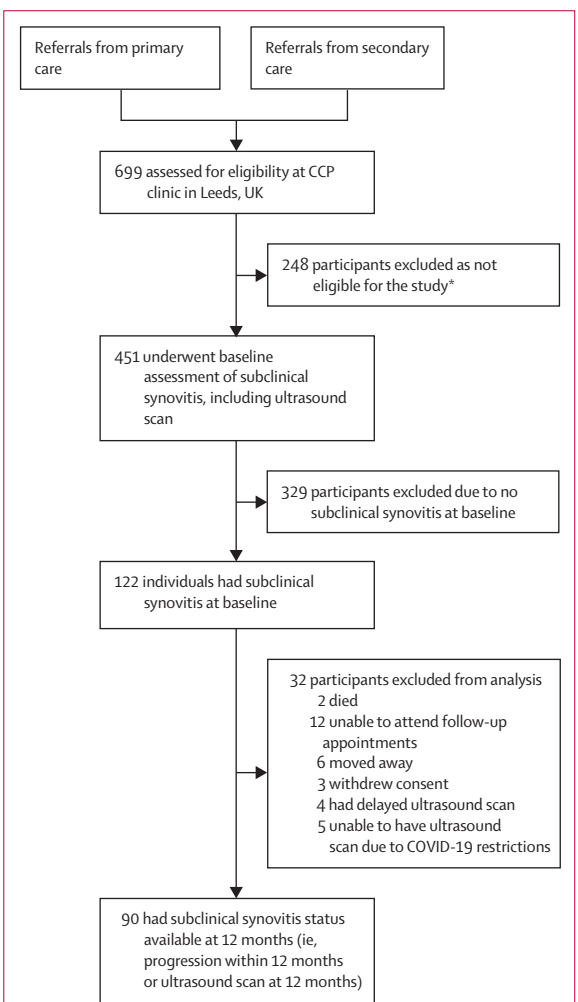

Figure 1: **Study profile**
CCP=cyclic citrullinated peptide. *Reasons were not recorded because participants referred from secondary care had not yet signed a consent form.

included in the analysis (table; figure 1). In some individuals, ultrasound status beyond 12 months were documented. The date of last follow-up was Nov 3, 2022. Sex disaggregated data can be found in the appendix (p 4).

Baseline characteristics of the 32 individuals with subclinical synovitis who could not be included in this analysis due to lack of follow-up data are shown in the appendix (p 5). Differences existed between these individuals and those included in the analysis: a higher proportion of individuals without follow-up data had a low anti-CCP titre and were negative for rheumatoid factor compared with the individuals included in the analysis.

Of the 90 participants analysed in the study, subclinical synovitis resolved within 12 months in 43 (48%) participants (table). Regarding the 47 (52%) participants whose subclinical synovitis did not resolve by 12 months, 27 (57%) developed clinical synovitis within 12 months and 20 (43%) continued to have persistent subclinical synovitis.

Univariable analysis showed that low anti-CCP titre, negative rheumatoid factor, young age, low ESR, few joints with subclinical synovitis, and few bone erosions at baseline were associated with resolution of subclinical synovitis within a year (table). Importantly, the prevalence of ultrasound bone erosions in this population was remarkably high, being present in 28 (31%) of 90 participants. Even though the prevalence of shared epitope, smoking exposure, and early morning stiffness were substantially higher in individuals whose subclinical synovitis persisted, the differences were not significant.

After performing ROC curves, the cutoffs for the significant continuous variables were established (ie, age ≤55 years, ESR ≤15 mm/h, only one joint with subclinical synovitis, and no bone erosions). These variables were then dichotomised and included in the multivariable analysis alongside categorical significant variables (ie, anti-CCP and rheumatoid factor) and confounding factors (ie, sex and smoking exposure).

Modified Poisson regression showed that a low anti-CCP titre (Relative risk [RR] 1·52, 95% CI 1·04–2·22), a negative rheumatoid factor result (1·54, 0·92–2·58), only one joint with subclinical synovitis (1·62, 1·04–2·50), and an ESR of less than or equal to 15 mm/h (1·82, 1·15–2·87) were predictors of subclinical synovitis resolution (ie, good prognostic factors). ROC curve showed an AUC of 0·84 (95% CI 0·76–0·92; p<0·0001) obtained from Mann-Whitney U test, testing the significance of forecast event probabilities for cases where events actually occurred with those where events did not occur (figure 2).[16]

Resolution occurred in seven (100%) of seven participants with four factors present, 14 (78%) of 18 participants with three factors, 14 (61%) of 23 participants with two factors, seven (25%) of 28 participants with one factor, and only one (7%) of 14 participants with no factors (figure 3). The number of joints with subclinical synovitis at baseline was negatively associated with the number of good prognostic factors at baseline (r=–0·408; p<0·0001).

The number of joints with subclinical synovitis at baseline was positively associated with the number of

	Overall cohort (n=90)	Subclinical synovitis persisted (n=47)	Subclinical synovitis resolved (n=43)	p value
Sex	..	..	..	0·38
Female	63 (70%)	31 (66%)	32 (74%)	..
Male	27 (30%)	16 (34%)	11 (26%)	..
Age, years	54·1 (12·5)	57·1 (13·0)	51·0 (11·3)	0·023
Anti-CCP low titre	28 (31%)	8 (17%)	20 (47%)	0·0030
Rheumatoid factor negative	44 (49%)	15 (32%)	29 (67%)	<0·0001
Antinuclear antibody negative	69/88 (78%)	36/46 (78%)	33/42 (79%)	0·97
Shared epitope negative	25/86 (29%)	12/46 (26%)	13/40 (33%)	0·51
Never smoked	35 (39%)	15 (32%)	20 (47%)	0·16
CRP concentration, mg/dL	55·0 (46·0–63·3)	4·0 (4·0–10·0)	4·0 (0·1–4·4)	0·095
Early morning stiffness, min	10·0 (0·0–30·0)	10·0 (0·0–60·0)	0·0 (0·0–30·0)	0·21
ESR, mm/h	15·0 (7·5–25·0)	20·0 (11·3–30·5)	9·0 (4·0–19·0)	0·0020
Number of joints with subclinical synovitis in hands or feet	2·0 (1·0–3·0)	2·0 (1·0–5·0)	1·0 (1·0–2·0)	0·0020
Number of tender joints	1·0 (0·0–3·3)	2·0 (0·0–4·0)	1·0 (0·0–2·0)	0·54
Number of painful joints	5·0 (3·0–8·0)	5·0 (2·0–8·0)	4·0 (3·0–8·0)	0·51
Number of joints with erosions	0·0 (0·0–1·0)	0·0 (0·0–1·0)	0·0 (0·0–0·0)	0·018

Data are n (%), n/N (%), mean (SD), or median (IQR). Data were missing for antinuclear antibody (two [2%] of 90 participants), shared epitope (four [4%]), CRP concentration (one [1%]), early morning stiffness (six [7%]), erythrocyte sedimentation rate (five [6%]), and number of painful joints (18 [20%]). CCP=cyclic citrullinated peptide. CRP=C-reactive protein. ESR=erythrocyte sedimentation rate. Ethnicity data were not collected.

Table: **Baseline clinical and demographic characteristics**

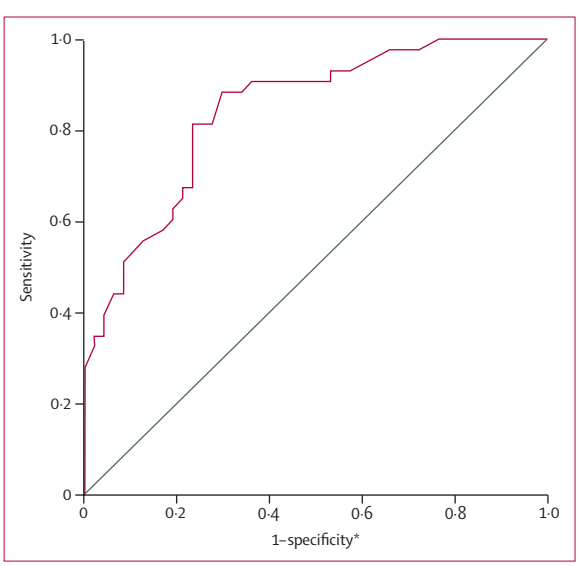

Figure 2: **Receiver operating characteristic curve for resolution of subclinical synovitis within 12 months**
Diagonal segments are produced by ties. *Also known as the false positive rate.

factors traditionally identified as predictive for clinical synovitis development, such as a high anti-CCP titre, rheumatoid factor positivity, smoking exposure, and presence of shared epitope (r=0·543; p<0·0001).[17–19] The mean baseline number of subclinical synovitis joints for participants with subclinical synovitis resolution was 1·77 (SD 1·23) compared with a mean of 3·28 (SD 2·49) for participants with persistent subclinical synovitis.

The most common joints presenting subclinical synovitis were the wrists (53 [59%] of 90 individuals) and the least common were the fourth proximal interphalangeal (one [1%] individual) and fourth metatarsophalangeal joints (one [1%] individual) (appendix p 6). One (100%) of one participant with subclinical synovitis in the fourth proximal interphalangeal joint had resolution and zero of one participant with subclinical synovitis in the fourth metatarsophalangeal joint had resolution; however, considering the few participants with involvement in these joints, resolution rates in these locations should be interpreted with caution.

For the remaining joints, the highest resolution rates were seen in the second metatarsophalangeal joint (six [55%] of 11 participants) and the second metacarpophalangeal joint (seven [54%] of 13 participants; appendix p 6). The lowest resolution rates (apart from the previously mentioned fourth metatarsophalangeal joint) were documented for the third proximal interphalangeal joint (two [29%] of seven participants) and the fifth metatarsophalangeal joint (four [31%] of 13 participants). Univariable analysis showed that presence of subclinical synovitis in the fifth metatarsophalangeal joint was associated with persistence of subclinical synovitis at 12 months at the patient level (RR 5·03, 95% CI 1·18–21·43). As mentioned, subclinical synovitis in the fifth metatarsophalangeal joint was among the least likely to resolve.

Regarding evolution of subclinical synovitis after 12 months, we can distinguish different outcomes for the two groups of participants (figure 4). Of the 43 participants whose subclinical synovitis resolved within 12 months, seven (16%) did not have further scans because they were either not due yet or the participant was lost to follow-up. Of the remaining 36 participants, 25 (69%) with resolved subclinical synovitis did not develop any further anomalies in consecutive ultrasound scans. Subclinical synovitis reappeared later in five (14%) of 36 participants. The same joints (with or without additional joints) as previously affected were affected again in three of these participants. For the other two participants, the joints involved in the recurrence were different. Six (17%) of 36 participants developed clinical synovitis eventually (good prognostic factors are shown in appendix p 8).

In the 20 participants who did not progress to clinical synovitis within 12 months but had persistent subclinical synovitis, two participants did not have further follow-up. Of the remaining 18 individuals, subclinical synovitis subsequently resolved in three (17%) participants, and eight (44%) participants continued to have persistent subclinical synovitis in consecutive scans (figure 4). The same joints (with or without additional joints) as those affected at baseline were still affected in four of these eight participants, whereas different joints were involved in the other four participants. Seven (39%) of 18 participants developed clinical synovitis later on.

Discussion

To our knowledge, this study provides the most complete data on the natural history of subclinical synovitis in individuals at risk of rheumatoid arthritis. Many studies have investigated the role of ultrasound as a predictor for inflammatory arthritis development in populations at risk;[4,6] however, this is the first study to assess the evolution and reversibility of subclinical synovitis detected by ultrasound. Subclinical synovitis was present in 122 (27%) of 451 participants at baseline, confirming that subclinical synovitis is a common clinical scenario, and hence emphasising the importance of assessing its evolution and the practical implications of its resolution or persistence.

We show that by 12 months, subclinical synovitis resolved in 43 (48%) of 90 participants and identified four good prognostic factors (ie, a low anti-CCP titre, a negative rheumatoid factor, subclinical synovitis in only one joint, and ESR ≤15 mm/h) for subclinical synovitis resolution. The proportion of participants with resolution of subclinical synovitis at 12 months correlated with the number of good prognostic factors at baseline.

A study from the Netherlands investigated the frequency of spontaneous improvement of symptoms and its relationship with the course of MRI-detected subclinical inflammation in patients with clinically suspect arthralgia.[8] Participants had a baseline MRI, which was repeated after 2 years. In contrast to the baseline MRI results of people who did not have symptom improvement after 2 years, the

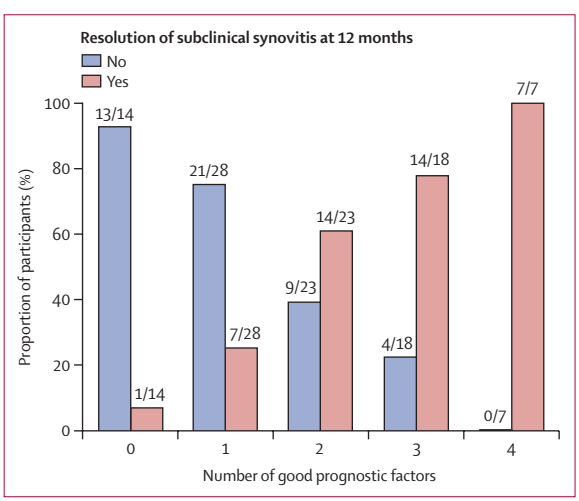

Figure 3: **Proportion of patients with resolution of subclinical synovitis at 12 months based on the number of good prognostic factors at baseline**

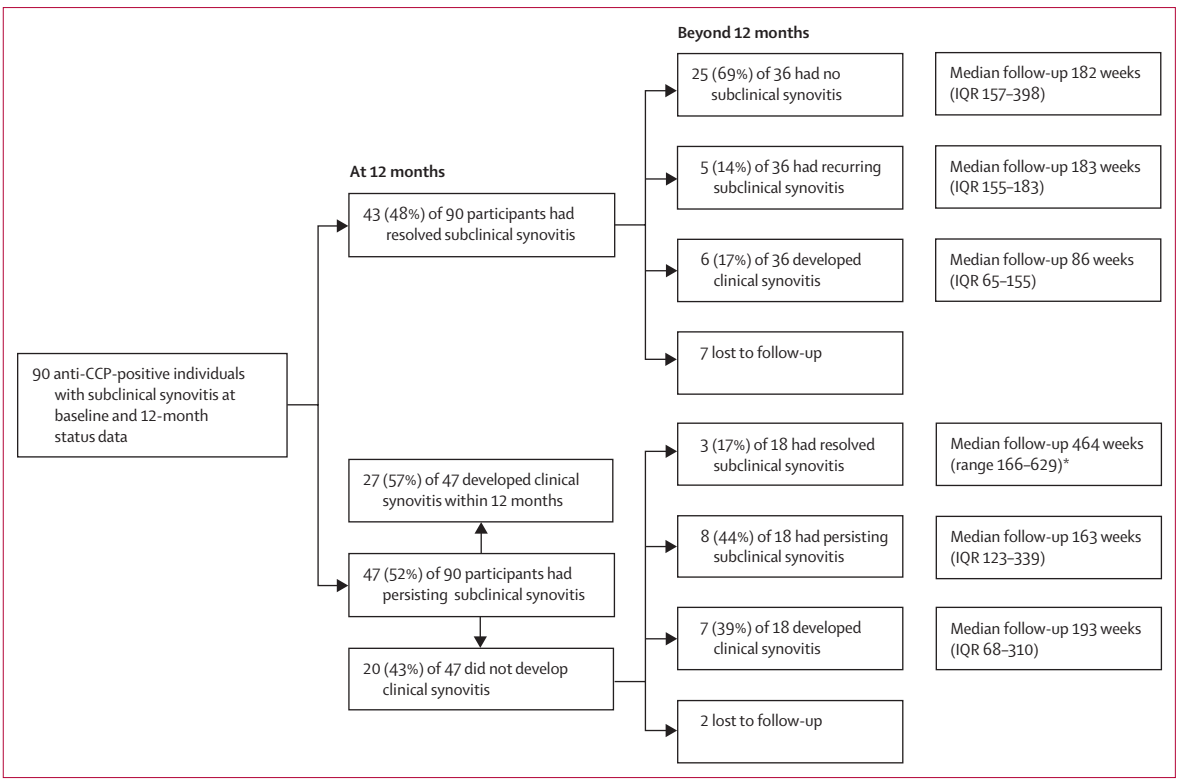

Figure 4: **Diagram of subclinical synovitis evolution in anti-CCP-positive individuals at risk of rheumatoid arthritis**
CCP=cyclic citrullinated peptide. *Range is provided rather than IQR because there were only three participants.

baseline MRI results of participants who did have spontaneous improvement (including the subset of seropositive individuals) showed subclinical inflammation, and their MRI inflammatory scores decreased significantly during the 2 year follow-up, suggesting that symptoms might have been secondary to the inflammatory changes detected on MRI. However, these results are not directly comparable to our study, because only people without disease progression were included and no data were provided regarding reversibility of MRI inflammation, only of improvement of imaging scoring in the context of the symptoms.

Whereas the definition of synovitis by OMERACT requires only the presence of synovial hypertrophy (ie, grey scale) regardless of the presence of power Doppler,[13] in our study, subclinical synovitis was defined as the combination of grey scale of at least 1 and power Doppler of at least 1 rather than separate entities, because their combination increases specificity. The implications of grey scale in people at risk of inflammatory arthritis are not clearly defined, and grey scale alone can often be found in healthy individuals;[20] by contrast, power Doppler is a more specific feature of active joint inflammation.

There are many causes of joint synovitis, with or without hypervascularity (ie, power Doppler), and the frequency of synovitis with or without power Doppler is influenced by the location or area affected. Causes of synovitis can be classified as mechanical, which is the result of structural damage secondary to mechanical forces (eg, post-traumatic synovitis, osteoarthritis, or repeated movements or overuse), or inflammatory, which is typical of autoimmune conditions (eg, rheumatoid arthritis, psoriatic arthritis), but microcrystalline arthropathies and infectious arthritis are also potential causes.

Another particularity of this study is the assessment of all, as opposed to specific, metatarsophalangeal joints.[21] The metatarsophalangeal joints are a key site for erosions in rheumatoid arthritis, and erosions in these joints are predictive of arthritis development.[11] Considering that persistent inflammation is required for a bone erosion to appear, it is reasonable to look for power Doppler in these joints.[22] Univariable analysis showed that absence of erosions was associated with resolution of subclinical synovitis at 12 months; however, this was not supported by the modified Poisson regression, probably because the prevalence of ultrasound erosions in the study population (all of whom had subclinical synovitis) was much higher than in unselected anti-CCP-positive individuals (ie, 28 [31%] of 90 participants *vs* 41 [10%] of 419 participants).[11]

Early DMARD initiation in the so-called window of opportunity (ie, a disease stage that allows modulation of biological processes while they are in a less mature and more reversible phase) has become a priority because of its

association with improved outcomes in the long term.[23] Due to the sensitivity of ultrasound for detecting inflammatory changes even at a subclinical stage, it has been proposed in various studies and by EULAR congresses that, when applying the 2010 American College of Rheumatology (ACR)–EULAR criteria,[24] ultrasound findings could be used to increase the number of joints involved and facilitate fulfilling criteria if a clinically swollen joint was present;[1,23,25] however, a study showed that substituting clinical arthritis in the 2010 ACR–EULAR criteria for subclinical synovitis in hands or feet detected either by ultrasound or MRI led to a high false-positive rate, ranging from 44–68% in anti-CCP-positive individuals.[26]

Although algorithms for the use of ultrasound in people at risk of rheumatoid arthritis with no clinical arthritis have been proposed, directions are vague for people with subclinical inflammation, leaving it up to the clinician to make a decision on the basis of the presence of poorly specified risk factors.[27] A UK survey showed that 27 (73%) of 37 rheumatologists would be willing to initiate treatment (usually DMARDs) in symptomatic anti-CCP-positive individuals with subclinical synovitis on ultrasound.[28] Given the high rates of subclinical synovitis resolution, this finding is a concern because the absence of precise guidelines could result in some people being prescribed DMARDs, which are frequently continued in the long term, even before clinical disease is established.[28,29]

Although subclinical synovitis alone is predictive of disease progression,[4,6] this outcome is not universal, as subclinical synovitis resolved in almost half of participants in the study. The identification of favourable factors that are predictive of subclinical synovitis resolution might be useful to help to identify participants who are unlikely to benefit from preclinical therapy, and hence prevent overtreatment. Development of persistent synovitis is an endpoint of an accumulation of risk factors, which are necessary but not sufficient for progression to an inflammatory arthritis.

This study has some limitations. Firstly, the findings are applicable only to anti-CCP-positive individuals with subclinical synovitis. Another limiting factor is the relatively small sample size, which is a result of the scarcity of anti-CCP-positive individuals with subclinical synovitis and the variability in the length of follow-up beyond 12 months. Another potential bias is that individuals without follow-up data had a higher prevalence of good prognostic factors for subclinical synovitis resolution; therefore, rates of subclinical synovitis resolution at 12 months might have been underestimated.

As an observational study, there are some inevitable limitations, such as the presence of unmeasured confounding factors or the inability to show causality. Also, the categorisation of quantitative variables might have resulted in loss of power and residual confounding; however, it will facilitate clinical decisions. The absence of cross validation, especially when using AUC to identify prognostic factors, is also a limitation because it is overly optimistic. The use of univariable screening on the basis of significance for variable selection does not follow the recommended analysis practices for predictive model development,[30] meaning that this study is an exploratory risk factor study, and hence these findings require further validation in larger cohorts to offer evidence for clinical guidance.

Finally, there are limitations related to ultrasound, such as the exclusion of tendon imaging (which was not assessed in the initial study protocol). Another limitation was that the severity of power Doppler and the improvements (as opposed to resolution) were not analysed. The reasons for these factors not being analysed were the variable power Doppler sensitivity of ultrasound machines combined with the understanding that the presence of power Doppler, even if grading has reduced to 1, remains clinically relevant. Resolution of grey scale was not assessed because it is unlikely that clinicians would commence treatment with neither clinical synovitis nor power Doppler present, and therefore, these findings would not increase the usefulness of the study.

In conclusion, subclinical synovitis was identified in a third of anti-CCP-positive individuals at risk of rheumatoid arthritis but resolved in approximately half of these participants by 12 months. The presence of good prognostic factors (ie, low anti-CCP titre, negative rheumatoid factor, subclinical synovitis limited to one joint, and ESR ≤15 mm/h) were predictive of subclinical synovitis resolution by 12 months. If all four of these factors were present, resolution occurred in all participants (seven [100%] of seven participants), whereas if none were present, resolution of subclinical synovitis occurred in only one (7%) of 14 participants. Subclinical synovitis should always be interpreted within the context of the individual's risk factors. These data should improve management, particularly by preventing potential overtreatment.

Contributors

LG-M was responsible for conceptualisation, data curation, formal analysis, investigation, methodology, software, and writing of the original draft. JK was responsible for conceptualisation, data curation, formal analysis, methodology, software, validation, supervision, and reviewing and editing the manuscript. LG-M and JK accessed and verified the underlying data. LD was responsible for data curation, investigation, software, and reviewing and editing the manuscript. ADM, JLN, KH, and RC were responsible for data curation, investigation, and reviewing and editing the manuscript. KM was responsible for conceptualisation, data curation, funding acquisition, investigation, project administration, resources, supervision, visualisation, and reviewing and editing the manuscript. PE was responsible for conceptualisation, funding acquisition, project administration, resources, supervision, visualisation, and writing the original draft. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

KM has received grants from Lilly, Gilead, and Serac Life Sciences; consulting fees from Serac Life Sciences; and honoraria from AbbVie, Lilly, and Galapagos. PE has received grants from Lilly and Samsung; received consulting fees from AbbVie, AnaptysBio, BMS, Gilead, Lilly, and Novartis; received honoraria from AbbVie, BMS, Gilead, Lilly, Novartis, and Sandoz;

received support for attending meetings from Lilly; and reports participation on data safety monitoring or advisory board by AstraZeneca. LG-M, JK, LD, ADM, JLN, KH, and RC declare no competing interests.

Data sharing

The data underlying this Article will be shared on reasonable request while preserving patient anonymity. A proposal with a detailed description of study objectives and statistical analysis plan will need to be provided to the corresponding author and be approved by the sponsor of the CCP study.

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References

1 Wakefield RJ, Gibbon WW, Conaghan PG, et al. The value of sonography in the detection of bone erosions in patients with rheumatoid arthritis: a comparison with conventional radiography. *Arthritis Rheum* 2000; **43:** 2762–70.

2 Joshua F, Edmonds J, Lassere M. Power Doppler ultrasound in musculoskeletal disease: a systematic review. *Semin Arthritis Rheum* 2006; **36:** 99–108.

3 Di Matteo A, Duquenne L, Cipolletta E, et al. Ultrasound subclinical synovitis in anti-CCP-positive at-risk individuals with musculoskeletal symptoms: an important and predictable stage in the rheumatoid arthritis continuum. *Rheumatology (Oxford)* 2022; **61:** 3192–200.

4 Nam JL, Hensor EM, Hunt L, Conaghan PG, Wakefield RJ, Emery P. Ultrasound findings predict progression to inflammatory arthritis in anti-CCP antibody-positive patients without clinical synovitis. *Ann Rheum Dis* 2016; **75:** 2060–67.

5 van de Stadt LA, Bos WH, Meursinge Reynders M, et al. The value of ultrasonography in predicting arthritis in auto-antibody positive arthralgia patients: a prospective cohort study. *Arthritis Res Ther* 2010; **12:** R98.

6 Molina Collada J, López Gloria K, Castrejón I, et al. Ultrasound in clinically suspect arthralgia: the role of power Doppler to predict rheumatoid arthritis development. *Arthritis Res Ther* 2021; **23:** 299.

7 Di Matteo A, Corradini D, Mankia K. What is the value of ultrasound in individuals 'at-risk' of rheumatoid arthritis who do not have clinical synovitis? *Healthcare (Basel)* 2021; **9:** 752.

8 Ten Brinck RM, Boeters DM, van Steenbergen HW, van der Helm-van Mil AHM. Improvement of symptoms in clinically suspect arthralgia and resolution of subclinical joint inflammation: a longitudinal study in patients that did not progress to clinical arthritis. *Arthritis Res Ther* 2020; **22:** 11.

9 Quinn MA, Gough AK, Green MJ, et al. Anti-CCP antibodies measured at disease onset help identify seronegative rheumatoid arthritis and predict radiological and functional outcome. *Rheumatology (Oxford)* 2006; **45:** 478–80.

10 Rantapää-Dahlqvist S, de Jong BA, Berglin E, et al. Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. *Arthritis Rheum* 2003; **48:** 2741–49.

11 Di Matteo A, Mankia K, Duquenne L, et al. Ultrasound erosions in the feet best predict progression to inflammatory arthritis in anti-CCP positive at-risk individuals without clinical synovitis. *Ann Rheum Dis* 2020; **79:** 901–07.

12 D'Agostino M, Wakefield R, Filipucci E, et al. Intra- and inter-observer reliability of ultrasonography for detecting and scoring synovitis in rheumatoid arthritis: a report of a EULAR ECSISIT task force. EULAR Congress; June 8–11, 2005 (abstr OP0019).

13 D'Agostino MA, Terslev L, Aegerter P, et al. Scoring ultrasound synovitis in rheumatoid arthritis: a EULAR-OMERACT ultrasound taskforce—part 1: definition and development of a standardised, consensus-based scoring system. *RMD Open* 2017; **3:** e000428.

14 Wakefield RJ, Balint PV, Szkudlarek M, et al. Musculoskeletal ultrasound including definitions for ultrasonographic pathology. *J Rheumatol* 2005; **32:** 2485–87.

15 van der Woude D, van der Helm-van Mil AHM. Update on the epidemiology, risk factors, and disease outcomes of rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2018; **32:** 174–87.

16 Mason SJ, Graham NE. Areas beneath the relative operating characteristics (ROC) and relative operating levels (ROL) curves: statistical significance and interpretation. *Q J R Meteorol Soc* 2002; **128:** 2145–66.

17 Bos WH, Wolbink GJ, Boers M, et al. Arthritis development in patients with arthralgia is strongly associated with anti-citrullinated protein antibody status: a prospective cohort study. *Ann Rheum Dis* 2010; **69:** 490–94.

18 del Puente A, Knowler WC, Pettitt DJ, Bennett PH. The incidence of rheumatoid arthritis is predicted by rheumatoid factor titer in a longitudinal population study. *Arthritis Rheum* 1988; **31:** 1239–44.

19 Wouters F, Maurits MP, van Boheemen L, et al. Determining in which pre-arthritis stage HLA-shared epitope alleles and smoking exert their effect on the development of rheumatoid arthritis. *Ann Rheum Dis* 2022; **81:** 48–55.

20 Padovano I, Costantino F, Breban M, D'Agostino MA. Prevalence of ultrasound synovial inflammatory findings in healthy subjects. *Ann Rheum Dis* 2016; **75:** 1819–23.

21 van Beers-Tas MH, Blanken AB, Nielen MMJ, et al. The value of joint ultrasonography in predicting arthritis in seropositive patients with arthralgia: a prospective cohort study. *Arthritis Res Ther* 2018; **20:** 279.

22 Sreerangaiah D, Grayer M, Fisher BA, Ho M, Abraham S, Taylor PC. Quantitative power Doppler ultrasound measures of peripheral joint synovitis in poor prognosis early rheumatoid arthritis predict radiographic progression. *Rheumatology (Oxford)* 2016; **55:** 89–93.

23 Nell VP, Machold KP, Eberl G, Stamm TA, Uffmann M, Smolen JS. Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with early rheumatoid arthritis. *Br J Rheumatol* 2004; **43:** 906–14.

24 Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010; **62:** 2569–81.

25 Nakagomi D, Ikeda K, Okubo A, et al. Ultrasound can improve the accuracy of the 2010 American College of Rheumatology/European League against rheumatism classification criteria for rheumatoid arthritis to predict the requirement for methotrexate treatment. *Arthritis Rheum* 2013; **65:** 890–98.

26 Rogier C, Wouters F, van Boheemen L, van Schaardenburg D, de Jong PHP, van der Helm-van Mil AHM. Subclinical synovitis in arthralgia: how often does it result in clinical arthritis? Reflecting on starting points for disease-modifying anti-rheumatic drug treatment. *Rheumatology (Oxford)* 2021; **60:** 3872–78.

27 D'Agostino MA, Terslev L, Wakefield R, et al. Novel algorithms for the pragmatic use of ultrasound in the management of patients with rheumatoid arthritis: from diagnosis to remission. *Ann Rheum Dis* 2016; **75:** 1902–08.

28 Mankia K, Briggs C, Emery P. How are rheumatologists managing anticyclic citrullinated peptide antibodies-positive patients who do not have arthritis? *J Rheumatol* 2020; **47:** 305–06.

29 Verstappen M, van der Helm-van Mil AHM. Sustained DMARD-free remission in rheumatoid arthritis - about concepts and moving towards practice. *Joint Bone Spine* 2022; **89:** 105418.

30 Zamanipoor Najafabadi AH, Ramspek CL, Dekker FW, et al. TRIPOD statement: a preliminary pre-post analysis of reporting and methods of prediction models. *BMJ Open* 2020; **10:** e041537.