Clinically suspect arthralgia: unraveling the development of rheumatoid arthritis

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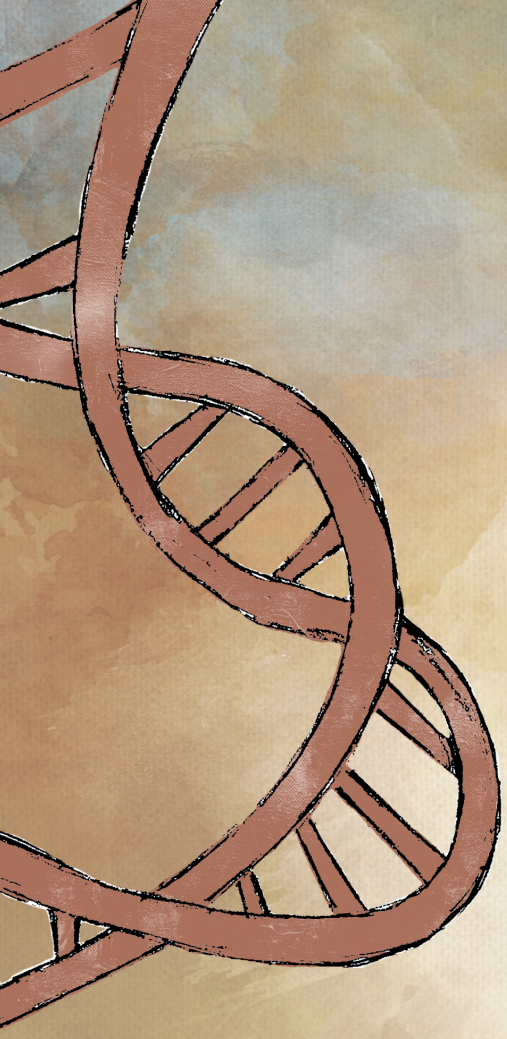

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Subclinical synovitis in arthralgia: how often does it result in clinical arthritis? Reflecting on starting points for disease-modifying anti-rheumatic drug treatment

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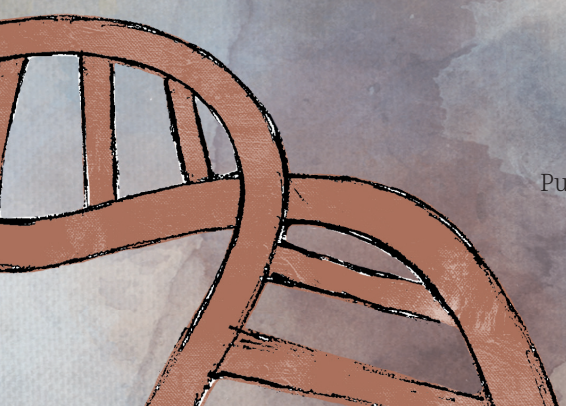


Published as *Concise Report* in Rheumatology (Oxford)
2021 Aug 2;60(8):3872-3878.
doi:10.1093/rheumatology/keaa774.

Abstract

Objectives

According to guidelines, clinical arthritis is mandatory for diagnosing rheumatoid arthritis (RA). However, in the absence of clinical synovitis, imaging-detected subclinical synovitis is increasingly used instead, and considered as starting point for DMARD-therapy. To search for evidence, we studied the natural course of arthralgia-patients with subclinical synovitis from three longitudinal cohorts and determined the frequencies of non-progression to clinically apparent inflammatory arthritis (IA) (i.e. 'false-positives').

Methods

Subclinical synovitis in hands or feet of arthralgia-patients was visualized with ultrasound (two cohorts, subclinical synovitis definition: greyscale ≥2 and/or power doppler ≥1) or MRI (one cohort, definition: synovitis score ≥1 by two readers). Patients were followed for 1-year on IA-development; two cohorts also had 3-year data. Analyses were stratified for anti-citrullinated protein antibody (ACPA).

Results

Subclinical synovitis at presentation was present in 36%, 41% and 31% in the three cohorts. Of the ACPA-positive arthralgia-patients with subclinical synovitis 54%, 44% and 68%, respectively, did not develop IA. These percentages were even higher in the ACPA-negative arthralgia-patients: 66%, 85% and 89%. Similar results were seen after 3-years follow-up.

Conclusion

Replacing clinical arthritis by subclinical synovitis to identify RA introduces a high false positive rate (44-89%). These data suggest an overestimation regarding the value of ACPA-positivity in combination with the presence of subclinical synovitis in patients with arthralgia, which harbors the risk of overtreatment if DMARDs are initiated in the absence of clinical arthritis.

Introduction

Early start with disease modifying anti-rheumatic drugs (DMARDs) has become key in the treatment of rheumatoid arthritis (RA), because of its association with improved disease outcomes.[1] It has also fueled research that aims to identify patients at risk for RA in the symptomatic phase preceding clinically apparent arthritis, in the hope that even earlier treatment may prevent the development of RA. At present clinically apparent arthritis is mandatory for diagnosing RA and according to current guidelines it is the regular starting point for DMARD-treatment.[1]

However, this basic notion seems to be shifting at some places. A recent Dutch study showed that rheumatologist are increasingly willing to initiate 'preventive' treatment in the absence of clinical arthritis.[2] Likewise, a survey in the UK demonstrated that up to 73% of consulting rheumatologists would start DMARD-treatment in anti-citrullinated protein antibody (ACPA)-positive patients with musculoskeletal symptoms and power Doppler on ultrasound(US) in the absence of clinically apparent arthritis.[3]

Subclinical synovitis has indeed been consistently reported as a predictor for RA-development, however not all patients with this feature will develop RA.[4,5] Although others and we have published about predictive models, the risk of patients with subclinical synovitis to progress to RA, especially in the presence of ACPA , cannot be easily deduced from these studies, while this is the clinical situation were DMARDs are increasingly considered in clinical practice. Therefore, the question remains how often DMARD-treatment in such patients would be correct, and how frequently patients will be overtreated, because they would not have developed RA in the absence of DMARD-treatment.

It is also suggested to apply the 2010-classification criteria for RA in patients with subclinical inflammation, thus replacing the entry-criterion of clinical arthritis by subclinical synovitis. It is then conceptualized that subclinical synovitis and ≥6 points allow for an earlier classification of RA and could result in less overtreatment than treatment of subclinical synovitis alone.

Therefore, we set out to search for evidence of the natural course and determined in arthralgia-patients with subclinical synovitis, from three longitudinal cohorts, the frequencies of non-progression to clinically apparent inflammatory arthritis (IA) (i.e patients that could be considered as 'false-positives'), both in the presence and absence of ACPA. Furthermore, we explored if applying the 2010-criteria in patients with subclinical synovitis in the absence of clinical arthritis, thus broadening the entry-criterion, diminished the false-positive rate.

Methods

Cohorts

Data from three independent Dutch cohorts of arthralgia-patients with ≥1 year of follow-up for IA-development were used. The cohorts have been described previously.[6-8] Details of cohorts and imaging are presented in supplementary material.

In short, cohort 1 is the SONAR-study, a multicenter observational inflammatory arthralgia cohort. At baseline a bilateral ultrasound(US) was made of metacarpophalangeal(MCP)-joints 2-5, metatarsophalangeal(MTP)-joints 2-5 and wrists. Subclinical synovitis was defined as greyscale ≥2 and/or power doppler ≥1.

Cohort 2 is the clinically suspect arthralgia(CSA)-cohort. Patients underwent contrast-enhanced 1.5T MRI of the wrists, MCP 2-5 and MTP 2-5. Scans were independently scored by two trained readers for subclinical synovitis according to RAMRIS and a synovitis-score ≥1 by both readers was used as cutoff.[9]

Cohort 3 is the seropositive arthralgia cohort that included patients positive for ACPA and/or RF. A bilateral US of wrists, MCP 2-3 and MTP 2, 3 and 5 was made at baseline, according to a predefined US protocol.[4,7] Subclinical synovitis definition was similar to the SONAR study.

In all three cohorts the imaging examiners were blinded to the clinical details and the treating rheumatologists were blinded to the imaging results.

Outcome

The primary outcome of all three cohorts was development of IA after one year, determined by physical examination of the treating rheumatologist. In cohorts 2 and 3 the outcome was also assessed after three years. Importantly, DMARD treatment (including glucocorticoid injections) were not initiated in the phase of arthralgia and only prescribed after a patient had developed clinically apparent arthritis.

Analysis

The true and false positive rates were determined. These were respectively the percentages of patients that developed and did not develop IA, from all patients with a positive test. Analyses were stratified for ACPA-status. For our second aim we applied the 2010-criteria at baseline in patients with subclinical synovitis. The entry-criterion that requires presence of clinical arthritis was replaced by presence of ≥1 joint with subclinical synovitis in patients with arthralgia. The item 'number of involved joints' was solely based on the tender joint count (44-joints) and not by imaging.

Several sensitivity analyses were performed. First, the abovementioned analyses in cohort 2 and 3 were repeated when IA was assessed after 3-years of follow-up. Secondly, the definition of subclinical synovitis was evaluated in three ways. Because it is known that power Doppler could be a stronger predictor, progression to IA was shown for patients who had greyscale ≥2 or power doppler ≥1 separately.[6,10] In addition, multiple imaging studies in the general population showed that symptom-free persons can have inflammatory features.[11,12] Because this could affect the false-positive rate, analyses were repeated when features found in the general population were considered in the definition of the presence of subclinical synovitis. MRI detected subclinical synovitis was considered present if it occurred in <5% in the healthy population of the same age-category at the same joint (see Supplementary Methods for further explanation).[11,13] Similarly, the definition of US detected subclinical synovitis included the results from a large US study carried out on a symptom free population;[12] based on these results the cut-off value for MTP 2-3 was adjusted and subclinical synovitis was considered present in MTP 2-3 if GS≥3 and/or PD≥1, whilst the cut-off in MCP, wrist and MTP 4,5 joints remained unchanged (GS≥2 and/or power doppler ≥1). Finally, although the threshold for US detectable subclinical synovitis GS≥2 and/or PD≥1 is most frequently used in current literature,[4,6,10] we also evaluated the effect of a more stringent threshold (GS≥3 and/or PD≥2) on the false positivity rates.

STATA software V.15 and SPSS V25 were used.

Results

Baseline characteristics

166, 473 and 162 patients were included in cohort 1, 2 and 3. Table 1 presents the baseline characteristics. The percentage of ACPA-positives was 22% in cohort 1, 14% in cohort 2 and 56% in cohort 3. At baseline 36%, 41% and 31% of patients had subclinical synovitis. After one year 22%, 15% and 18% had developed IA, respectively.

False positive rates

Of the ACPA-positive patients with subclinical synovitis 54%, 44% and 68% did not develop IA in cohorts 1, 2 and 3 respectively (Figure 1A). In the ACPA-negative patients with subclinical synovitis, 66%, 85% and 89% did not progress to IA (Figure 1A).

Evaluation of use of subclinical synovitis as entry-criterion for the 2010-criteria

The analyses were also performed within arthralgia patients in whom subclinical synovitis was used as entry-criterion and who also had ≥6 points on the 2010-criteria

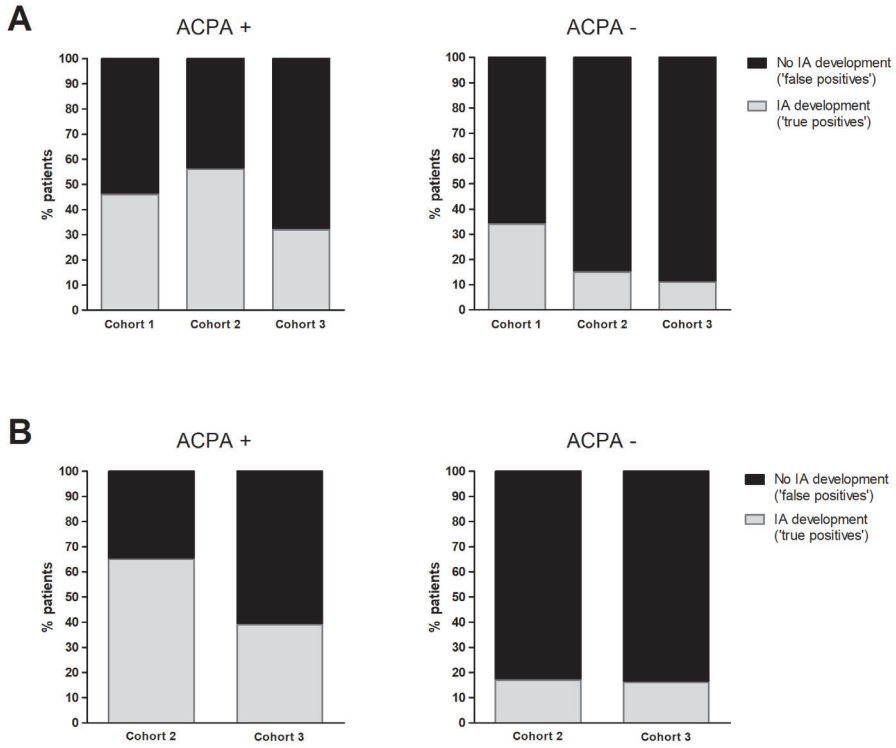
Table 1. Baseline characteristics of arthralgia-patients included in the three cohorts, also stratified for ACPA status

	All arthralgia patients			ACPA positive			ACPA negative		
	Cohort 1 (n=166)	*Cohort 2 (n=473)*	*Cohort 3 (n=162)*	*Cohort 1 (n=37)*	*Cohort 2 (n=64)*	*Cohort 3 (n=90)*	*Cohort 1 (n=129)*	*Cohort 2 (n=409)*	*Cohort 3 (n=72)*
Age in years, mean (SD)	45 (12)	44 (13)	51 (11)	45 (11)	48 (13)	51 (11)	45 (12)	43 (13)	52 (11)
Female, n (%)	136 (82)	366 (77)	120 (74)	32 (86)	52 (81)	67 (74)	104 (81)	314 (77)	53 (74)
Symptom duration in weeks, median (IQR)	29 (19-40)	19 (9-44)	57 (26-157)	28 (17-40)	24 (13-53)	52 (26-137)	29 (20-39)	18 (9-41)	83 (30-209)
TJC44, median (IQR)	5 (3-8)	5 (2-9)	1 (0-5)	4 (2-7)	3 (1-7)	1 (0-5)	5 (3-8)	5 (2-10)	1 (0-5)
ACPA positivity, n (%)	37 (22)	64 (14)	90 (56)	NA	NA	NA	NA	NA	NA
RF positivity, n (%)	49 (30)	95 (20)	119 (74)	22 (59)	49 (77)	47 (52)	27 (21)	46 (11)	72 (100)
Increased CRP, n (%)	39 (23)	101 (22)	12 (7)	11 (30)	20 (32)	8 (9)	28 (22)	81 (20)	4 (6)
Presence of local subclinical synovitis[a], n (%)	60 (36)	193 (41)	50 (31)	13 (35)	36 (56)	31 (34)	47 (36)	157 (38)	19 (26)

[a] Presence of Ultrasound (cohort 1 and cohort 3) or MRI (cohort 2) -detected subclinical synovitis. Joints screened for cohort 1 and cohort 2; metacarpophalangeal 2-5, radiocarpal, intercarpal, radioulnar (cohort 2) and metatarsophalangeal 2-5. Joints screened for cohort 3; metacarpophalangeal 2-3, metatarsophalangeal 2, 3, 5 and wrist.

Abbreviations: SD: standard deviation, IQR: interquartile range, TJC: tender joint count, ACPA: anti-citrullinated protein antibody, RF: rheumatoid factor, CRP: c-reactive protein, NA: not applicable

Figure 1. Percentage of arthralgia-patients with subclinical synovitis at baseline that did and did not develop inflammatory arthritis after 1-year (A) and 3-years follow-up (B), stratified for ACPA-status.



(A) ACPA-positive patients; (cohort 1 n=37, cohort 2 n=64, cohort 3 n=90). Patients with subclinical synovitis at baseline; n=13, n=36, n=31, respectively. Of these n=6, n=20, n=10 patients developed IA after one year follow-up, respectively. ACPA-negative patients; (cohort 1 n=129, cohort 2 n=409, cohort 3 n=72). Patients with subclinical synovitis at baseline; n=47, n=157, n=19, respectively. Of these n=16, n=23, n=2 patients developed IA after one year of follow-up, respectively.
(B) ACPA-positive patients; (cohort 2 n=43, cohort 3 n=90). Patients with subclinical synovitis at baseline; n=26, n=31, respectively. Of these n=17, n=12 patients developed IA after three years of follow-up, respectively. ACPA-negative patients; (cohort 2 n=292, cohort 3 n=72). Patients with subclinical synovitis at baseline; n=121, n=19, respectively. Of these n=20, n=3 patients developed IA after three years of follow-up, respectively.

(hereby imaging was not used to evaluate the number of involved joints). Within the ACPA-positive patients, 45%, 37% and 63% did not progress to IA (Supplementary Figure 1A). Within the ACPA-negative patients 67%, 82% and 89% did not progress. Hence in both ACPA-groups the false positive rates did not diminish when the 2010-criteria were used in arthralgia patients with subclinical synovitis.

Sensitivity analyses

First analyses were repeated for cohort 2 and 3 with IA-development after 3-year of follow-up. Similar false positive rates were observed (Figure 1B). Also the results of the use of the 2010-criteria in patients with subclinical synovitis after 3-years were similar (Supplementary Figure 1B).

Secondly, the results for progression to IA were shown separately for patients having greyscale ≥2 and patients having power doppler ≥1. No important differences were seen in patients having greyscale ≥2 compared to the main analysis (Supplementary Figure 2A/3A). The false positive rate for PD did diminish somewhat in subgroups of cohort 1 and 3 compared to the main analyses, but remained substantial (Supplementary Figure 2B/3B).

Additionally, imaging findings observed in symptom-free persons were considered in the definition of subclinical synovitis. When using a more stringent definition for MRI-detected synovitis 37% of ACPA-positive patients and 80% of ACPA-negative patients with subclinical synovitis did not progress to IA after 1 year (Supplementary Figure 4). Also when a more stringent definition for US-detected synovitis was used, a considerable proportion of ' false positives' remained, as 50% of the ACPA-positive and 71% of the ACPA-negative patients with subclinical synovitis did not progress to IA after 1 year (Supplementary Figure 5).

Finally, an even more stringent threshold for subclinical synovitis was studied (GS≥3 and/or PD≥2). Although the number of patients with arthralgia that had subclinical synovitis according to this definition decreased, the high false positive rates persisted (Supplementary Figure 6).

Discussion

Although daily practice most likely differs per region, there is an increasing tendency to start DMARD-treatment in arthralgia-patients with subclinical synovitis, at least in some places.[3] This is based upon the assumption that the clinical presentation of subclinical synovitis in ACPA-positive arthralgia is equivalent to imminent RA. The lack of evidence for this notion prompted us to perform a study in multiple cohorts. We observed that replacing clinical arthritis by subclinical synovitis for identification of IA introduced a high false-positive rate; as 44-68% of ACPA-positive and 66-89% of ACPA-negative arthralgia-patients with subclinical synovitis did not develop IA. These results on the natural disease course of arthralgia patients with subclinical synovitis imply that starting DMARD-treatment within these patients would lead to considerable overtreatment, as they would also not progress to IA without DMARD-therapy. Another argument is the lack of evidence that starting DMARD-treatment in this phase will prevent the development of RA. However, this is currently being investigated in several trials and is outside the scope of this study.[14]

Although the inclusion criteria of the three cohorts were somewhat different, the

primary results were comparable and this strengthens the validity of the results.

US and MRI are both suitable for detecting subclinical inflammation in arthralgia.[5,6,10] Although MRI is more sensitive than US, the decrease in sensitivity (with MRI as reference) is less for the detection of synovitis than for tenosynovitis and osteitis.[15,16] Interestingly, the results for the false positive rates of the two imaging modalities were not importantly different. However, for clinical purposes MRI can be less attractive since it is less easily available, is more expensive and requires intravenous contrast administration compared to US.[15] With respect to US, a limitation is that different machines were used in the two US studies. Nonetheless, the results were comparable and different machines are also used in daily clinical practice.

Ideally the definition of subclinical inflammation incorporates correction for the symptom-free population to prevent false-positive findings.[11,12] For MRI, reference values were available and considered. For US, we used the results of Padovano et al.[12] and the results with and without correction were similar. In, cohort 3 the false-positive rate reduced slightly but remained considerable. This suggests that signs of inflammation found in the normal population do not explain the observed false-positive rates.

The 2010-criteria are intended for classification and not for diagnosis/treatment start. Furthermore, to prevent false-positive classifications the 2010-criteria should only be applied in case of a clinical diagnosis of RA with ≥1 clinical swollen joint. Nonetheless in the 'pre-RA field' it is suggested that applying the 2010-criteria to patients with subclinical inflammation can be helpful. Previous studies that evaluated imaging as entry-criterion for the 2010-criteria were done in patients with clinically apparent arthritis or in mixed population with arthralgia and arthritis.[17,18] Our data from three cohorts with arthralgia patients and subclinical synovitis revealed that a high proportion of patients with subclinical synovitis and ≥6 points did not develop IA/RA. Consequently, there is currently no evidence to change the entry-criterion of clinical synovitis into subclinical synovitis, as the false positive rate remained substantial.

Furthermore the additional benefit of applying imaging in the 2010-criteria in patients with clinical arthritis to determine the number of involved joints has also been studied.[13] This is different from the current research where imaging detected subclinical synovitis replaces the entry-criterion of clinical arthritis.

In clinical practice, rheumatologists may be inclined to start DMARDs in ACPA-positive arthralgia-patients with subclinical synovitis. The current data from three cohorts suggests that ACPA-positivity in combination with subclinical synovitis is

overestimated in their ability to indicate the future development of IA/RA. Also in our sensitivity analysis where more stringent definitions of subclinical synovitis were used, high false positive rates remained. Altogether, this emphasizes the need for other biomarkers, in addition to ACPA and subclinical synovitis, to enhance risk stratification in patients with arthralgia. For example, imaging-detected tenosynovitis has been shown to be a better predictor than imaging-detected synovitis.[5,19] Combining imaging with other predictors (e.g. clinical, genetic and serological data) will presumably result in higher positive predictive values and true positive rates.[14,19]

A recent study on long-term outcomes of arthralgia-patients with subclinical inflammation that did not progress to IA showed that 33-38% of these patients, including those with ACPA-positivity, had symptom resolution.[20] Interestingly, this was also associated with reduction of subclinical inflammation, illustrating that a combination of symptoms, inflammation and presence of autoantibodies can be self-limiting.

In conclusion, our results showed that presence of subclinical synovitis and ACPA-positivity is not equal to RA-development. Therefore, in our view, further observational studies on the natural disease course are necessary to derive accurate and validated risk stratification for patients presenting with arthralgia. So that, when randomized clinical trials have shown that treatment of arthralgia patients prevents progression to IA, we can apply this treatment to the right patients and avoid significant overtreatment.

References

1. Combe B, Landewe R, Daien CI et al. 2016 update of the EULAR recommendations for the management of early arthritis. Ann Rheum Dis. 2017;76:948-59.

2. Van Boheemen L, Bolt JW, Ter Wee M et al. THU0117 PERSONS AT RISK OF RHEUMATOID ARTHRITIS OR AXIAL SPONDYLOARTHRITIS HAVE DIFFERENT PERCEPTIONS ON PREVENTIVE INTERVENTION THAN RHEUMATOLOGISTS. Annals of the Rheumatic Diseases. 2020;79:269-70.

3. Mankia K, Briggs C, Emery P. How Are Rheumatologists Managing Anticyclic Citrullinated Peptide Antibodies-positive Patients Who Do Not Have Arthritis? J Rheumatol. 2019.

4. 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.

5. van Steenbergen HW, Mangnus L, Reijnierse M et al. Clinical factors, anticitrullinated peptide antibodies and MRI-detected subclinical inflammation in relation to progression from clinically suspect arthralgia to arthritis. Ann Rheum Dis. 2016;75:1824-30.

6. van der Ven M, van der Veer-Meerkerk M, Ten Cate DF et al. Absence of ultrasound inflammation in patients presenting with arthralgia rules out the development of arthritis. Arthritis Res Ther. 2017;19:202.

7. 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.

8. van Steenbergen HW, van Nies JA, Huizinga TW et al. Characterising arthralgia in the preclinical phase of rheumatoid arthritis using MRI. Ann Rheum Dis. 2015;74:1225-32.

9. Ostergaard M, Peterfy C, Conaghan P et al. OMERACT Rheumatoid Arthritis Magnetic Resonance Imaging Studies. Core set of MRI acquisitions, joint pathology definitions, and the OMERACT RA-MRI scoring system. J Rheumatol. 2003;30:1385-6.

10. Nam JL, Hensor EM, Hunt L et al. Ultrasound findings predict progression to inflammatory arthritis in anti-CCP antibody-positive patients without clinical synovitis. Ann Rheum Dis. 2016;75:2060-7.

11. Mangnus L, van Steenbergen HW, Reijnierse M et al. Magnetic Resonance Imaging-Detected Features of Inflammation and Erosions in Symptom-Free Persons From the General Population. Arthritis Rheumatol. 2016;68:2593-602.

12. Padovano I, Costantino F, Breban M et al. Prevalence of ultrasound synovial inflammatory findings in healthy subjects. Ann Rheum Dis. 2016;75:1819-23.

13. Boer AC, Boeters DM, van der Helm-van Mil AHM. The use of MRI-detected synovitis to determine the number of involved joints for the 2010 ACR/EULAR classification criteria for Rheumatoid Arthritis - is it of additional benefit? Ann Rheum Dis. 2018;77:1125-9.

14. van Steenbergen HW, da Silva JAP, Huizinga TWJ et al. Preventing progression from arthralgia to arthritis: targeting the right patients. Nat Rev Rheumatol. 2018;14:32-41.

15. Ohrndorf S, Boer AC, Boeters DM et al. Do musculoskeletal ultrasound and magnetic resonance imaging identify synovitis and tenosynovitis at the same joints and tendons? A comparative study in early inflammatory arthritis and clinically suspect arthralgia. Arthritis Res Ther. 2019;21:59.

16. Wakefield RJ, O'Connor PJ, Conaghan PG et al. Finger tendon disease in untreated early rheumatoid arthritis: a comparison of ultrasound and magnetic resonance imaging. Arthritis Rheum. 2007;57:1158-64.

17. 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;65:890-8.

18. Tamai M, Kita J, Nakashima Y et al. Combination of MRI-detected bone marrow oedema with 2010 rheumatoid arthritis classification criteria improves the diagnostic probability of early rheumatoid arthritis.

Ann Rheum Dis. 2014;73:2219-20.

19. Matthijssen XME, Wouters F, Boeters DM et al. A search to the target tissue in which RA-specific inflammation starts: a detailed MRI study to improve identification of RA-specific features in the phase of clinically suspect arthralgia. Arthritis Res Ther. 2019;21:249.

20. Ten Brinck RM, Boeters DM, van Steenbergen HW et al. 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.

Supplementary Methods

Details about inclusion, clinical examination and follow-up of the cohorts have been described in detail previously.[1-3]

Cohort 1 SONAR, Rotterdam The Netherlands

Design of cohort

The first cohort consisted of data from the sonographic evaluation of hands, feet and shoulders in patients with inflammatory arthralgia (SONAR) study.[1] This is a multicenter observational cohort to identify subclinical inflammation in patients with inflammatory arthralgia symptoms using ultrasound (US). Patients were followed for one year on the development of inflammatory arthritis (IA) with scheduled visits after 6 and 12 months. At each visit, patients were seen by the research nurse, who performed the physical examination and took blood samples. Observed soft tissue swelling was always confirmed as an arthritis by the treating rheumatologist. At baseline a bilateral US was made of metacarpophalangeal (MCP)-joints 2-5, metatarsophalangeal (MTP)-joints 2-5 and radiocarpal (RC) and intercarpal (IC) joints.

The medical ethics committee of Erasmus University Medical Center (Erasmus MC), Rotterdam, The Netherlands approved the study protocol (MEC-2010–353). Furthermore, the study was assessed for feasibility by the local ethical bodies of the other two participating hospitals (Maasstad Hospital and Vlietland Hospital). All patients gave written informed consent before inclusion.

ACPA-testing

ACPA levels (EliA cyclic citrullinated peptide (anti-CCP2), Phadia, Nieuwegein, the Netherlands) were tested in the hospital of inclusion. For Erasmus MC and Vlietland hospital ACPA levels were considered positive if levels ≥10U/mL, for Maasstad Hospital ACPA levels were considered positive if levels ≥5U/mL.

Imaging protocol (Ultrasound)

A MyLab60(Esaote, Genoa, Italy) with a high-frequency linear array probe(LA435, 10–18 MHz) was used. Two trained ultrasonographers, who were blinded for the clinical details, performed the US. To minimize inter-observer variability, the scanning was performed according to a standardized protocol with fixed patient position and scanning planes, in accordance to EULAR guidelines.[4]

Joints scanned for the detection of US abnormalities were metatarsophalangeal joints (MTP) 2–5 (dorsal aspect), metacarpophalangeal joints (MCP) 2–5 (dorsal and palmar aspects), and the wrist (radiocarpal and intercarpal joints). As advised a single midline

(longitudinal 12 o'clock position) scan perpendicular to the bone surface was used.[5]

Evaluation of the US images was done as recommended by a modified version of the previously developed OMERACT.[6] A semi-quantitative scoring system of Szkudlarek (0–3) was used for both greyscale (GS) and Power Doppler (PD) images. For GS, all joints were graded as follows: 0 = no capsular distention; 1 = hypoechoic material only at the level of the joint margins; 2 = partial distention of the whole capsule, which appears mostly concave or flat; and 3 = complete distention of the whole capsule, which appears mostly convex. PD was only measured if GS≥1 and was graded as follows: 0 = absent, 1 = mild single-vessel signal or isolated signal, 2 = moderate confluent vessels, and 3 = marked vessel signals in more than half of the intra-articular area.[7] Subclinical synovitis was defined as GS≥2 and/or PD≥1.

Cohort 2 CSA cohort, Leiden, The Netherlands

Design of cohort

The second cohort consisted of patients from the clinically suspect arthralgia (CSA)-cohort in Leiden.[3] Patients had recent-onset (<1 year) arthralgia of small joints and were, according to the clinical expertise and pattern recognition of the treating rheumatologist, suspected for progression to RA. Patients were followed for the development of IA with scheduled visits after 4, 12 and 24 months, with additional visits in between or thereafter if patients experienced an increase in symptoms. Patients underwent a contrast-enhanced 1.5T MRI of the wrist, MCP 2-5 and MTP 2-5 at baseline.

Ethics approval was obtained from the medical ethics committee of the Leiden University Medical Center, Leiden, The Netherlands.

ACPA-testing

ACPA levels (EliA cyclic citrullinated peptide (anti-CCP2), Phadia, Nieuwegein, the Netherlands) were considered positive if levels ≥7U/mL.

Imaging protocol (MRI)

MRI was performed on a MSK-extreme 1.5T extremity MRI system (GE, Wisconsin, USA) using a 145mm coil for the foot and a 100mm coil for the hand. The patient was positioned in a chair beside the scanner, with the hand or foot fixed in the coil with cushions.

In the hand (metacarpophalangeal (MCP) joints 2-5 and wrist) the following sequence was acquired before contrast administration: T1-weighted fast spin-echo (FSE) sequence in the coronal plane (repetition time (TR) 575 ms, echo time (TE) 11.2 ms, acquisition matrix 388×288, echo train length (ETL) 2). After intravenous injection

of gadolinium contrast (gadoteric acid, Guerbet, Paris, France, standard dose of 0.1 mmol/kg) the following sequences were obtained: T1-weighted FSE sequence with frequency selective fat saturation (fatsat) in the coronal plane (TR/TE 700/9.7ms, acquisition matrix 364×224, ETL 2), T1-weighted FSE fatsat sequence in the axial plane (wrist: TR/TE 540/7.7 ms; acquisition matrix 320x192; ETL 2 and MCP-joints: TR/TE 570/7.7 ms; acquisition matrix 320x192; ETL 2).

The obtained sequences of the forefoot (metatarsophalangeal (MTP) joints 2-5) were for the first 77 patients before contrast administration: T1-weighted FSE sequence in the axial plane (TR/TE 650/17ms; acquisition matrix 388x288, ETL 2); and T2-weighted FSE fatsat sequence in the axial plane (TR/TE 3000/61.8; acquisition matrix 300x224, ETL 7). Imaging of the foot was initially limited to pre-contrast axial sequences. For the latter 396 patients post-contrast sequences were included: T1-weighted FSE fatsat sequence in the axial plane (TR/TE 700/9.5ms; acquisition matrix 364x224, ETL 2) and: T1-weighted FSE fatsat sequence in the coronal plane (perpendicular to the axis of the metatarsals) (TR/TE 540/7.5ms; acquisition matrix 320x192, ETL 2).

Field-of-view was 100mm for the hand and 140mm for the foot. Coronal sequences of the hand had 18 slices with a slice thickness of 2mm and a slice gap of 0.2mm. Coronal sequences of the foot had 20 slices with a slice thickness of 3mm and a slice gap of 0.3mm. All axial sequences had a slice thickness of 3mm and a slice gap of 0.3mm with 20 slices for the wrist, 16 for the metacarpophalangeal-joints and 14 for the foot.

All joints were scored semi-quantitatively according to the validated RA MRI scoring system (RAMRIS). Synovitis was scored on a range 0-3 based on the volume of enhancing tissue in the synovial compartment (none, mild, moderate, severe).[8]

Scoring was performed independently by two trained readers. Interreader and intrareader intraclass correlation coefficients were ≥0.91 and ≥0.92, respectively.

Mean scores from both readers were used. For the main analyses synovitis was considered present when at least one joint had a mean synovitis score of ≥1.

For the subanalysis concerning the symptom-free population, it is known that MRI-detected synovitis can also be present in the general population, scores were dichotomized with MRI-data of symptom-free controls as reference (n=193, as published previously).[9] Then, synovitis was considered present if the feature (with the observed severity) was present in <5% of symptom-free controls at the same location and in the same age category (<40, 40-59, ≥60).

Cohort 3 Seropositive arthralgia cohort, Amsterdam, The Netherlands

Design of cohort

Data from the third cohort derived from Amsterdam was also described in detail previously.[2] This study consecutively included seropositive arthralgia-patients (positive for ACPA and/or RF) from March 2009 till December 2015. Patients were followed on IA-development with scheduled visits every 12 months and additional visits in case of suspected arthritis for up to 5 years. An US of bilateral wrists, MCP 2-3 and MTP 2, 3 and 5 was made at baseline.

Study was approved by the Slotervaart ethics committee. Signed informed consent was obtained from all patients prior to inclusion.

ACPA-testing

ACPA levels (EliA cyclic citrullinated peptide (anti-CCP2), Phadia, Nieuwegein, the Netherlands) were considered positive if levels ≥10U/mL.

Imaging protocol (Ultrasound)

The Acuson Antares ultrasound system, premium edition (Siemens, Malvern, PA, USA) using linear array transducers VF 13–5 SP for finger and toe joints (operating at 11.43 MHz for grayscale and 8.9 MHz for PD) and VF 13–5 for larger joints (operating at 11.43 MHz for grayscale and 7.3 MHz for PD), was used for all scans. A single radiologist experienced in musculoskeletal US, blinded to the clinical data, did all the US examinations. Joints scanned for the detection of US abnormalities were metatarsophalangeal joints (MTP) (dorsal site) 2, 3 & 5, metacarpophalangeal joints (MCP) 2–3 (palmar and dorsal site), and the wrists (radiocarpal and intercarpal joints and ulnocarpal joint including the ulnar styloid process). This was based on a predefined standard US protocol.[2,10]

The semi-quantitative scale (0–3) of Szkudlarek was used for both GS and PD images.[7] Subclinical synovitis was defined as GS≥2 and/or PD≥1.

References

1. van der Ven M, van der Veer-Meerkerk M, Ten Cate DF et al. Absence of ultrasound inflammation in patients presenting with arthralgia rules out the development of arthritis. Arthritis Res Ther. 2017;19:202.

2. 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.

3. van Steenbergen HW, van Nies JA, Huizinga TW et al. Characterising arthralgia in the preclinical phase of rheumatoid arthritis using MRI. Ann Rheum Dis. 2015;74:1225-32.

4. Backhaus M, Burmester GR, Gerber T et al. Guidelines for musculoskeletal ultrasound in rheumatology. Ann Rheum Dis. 2001;60:641-9.

5. Naredo E, Moller I, Moragues C et al. Interobserver reliability in musculoskeletal ultrasonography: results from a "Teach the Teachers" rheumatologist course. Ann Rheum Dis. 2006;65:14-9.

6. Wakefield RJ, Balint PV, Szkudlarek M et al. Musculoskeletal ultrasound including definitions for ultrasonographic pathology. J Rheumatol. 2005;32:2485-7.

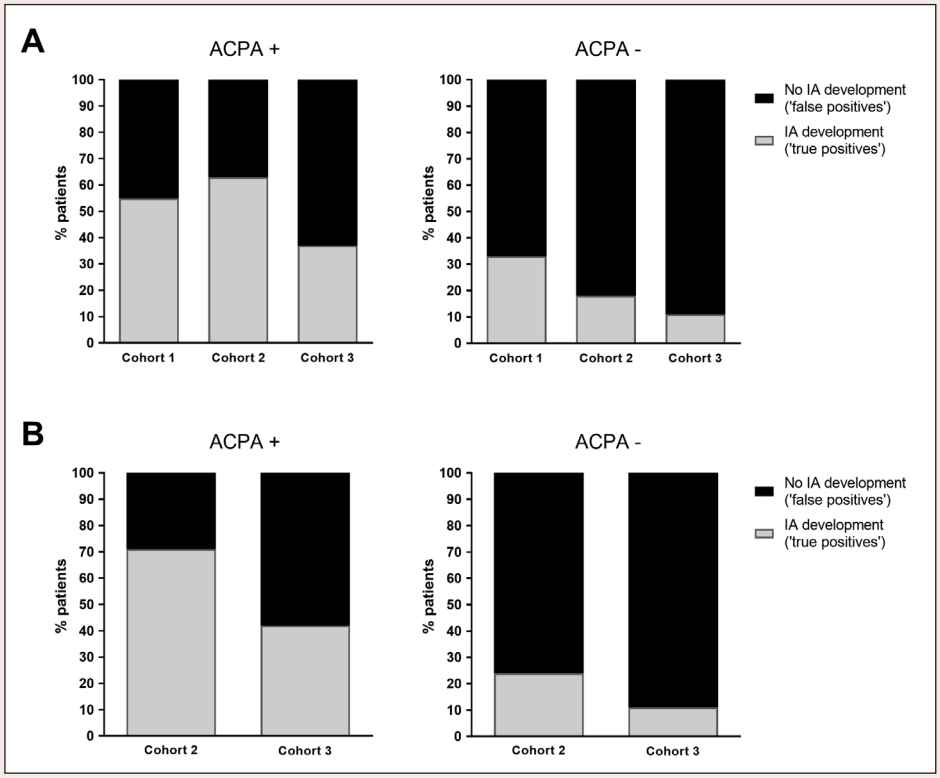
7. Szkudlarek M, Court-Payen M, Jacobsen S et al. Interobserver agreement in ultrasonography of the finger and toe joints in rheumatoid arthritis. Arthritis Rheum. 2003;48:955-62.

8. Ostergaard M, Peterfy C, Conaghan P et al. OMERACT Rheumatoid Arthritis Magnetic Resonance Imaging Studies. Core set of MRI acquisitions, joint pathology definitions, and the OMERACT RA-MRI scoring system. J Rheumatol. 2003;30:1385-6.

9. Mangnus L, van Steenbergen HW, Reijnierse M et al. Magnetic Resonance Imaging-Detected Features of Inflammation and Erosions in Symptom-Free Persons From the General Population. Arthritis Rheumatol. 2016;68:2593-602.

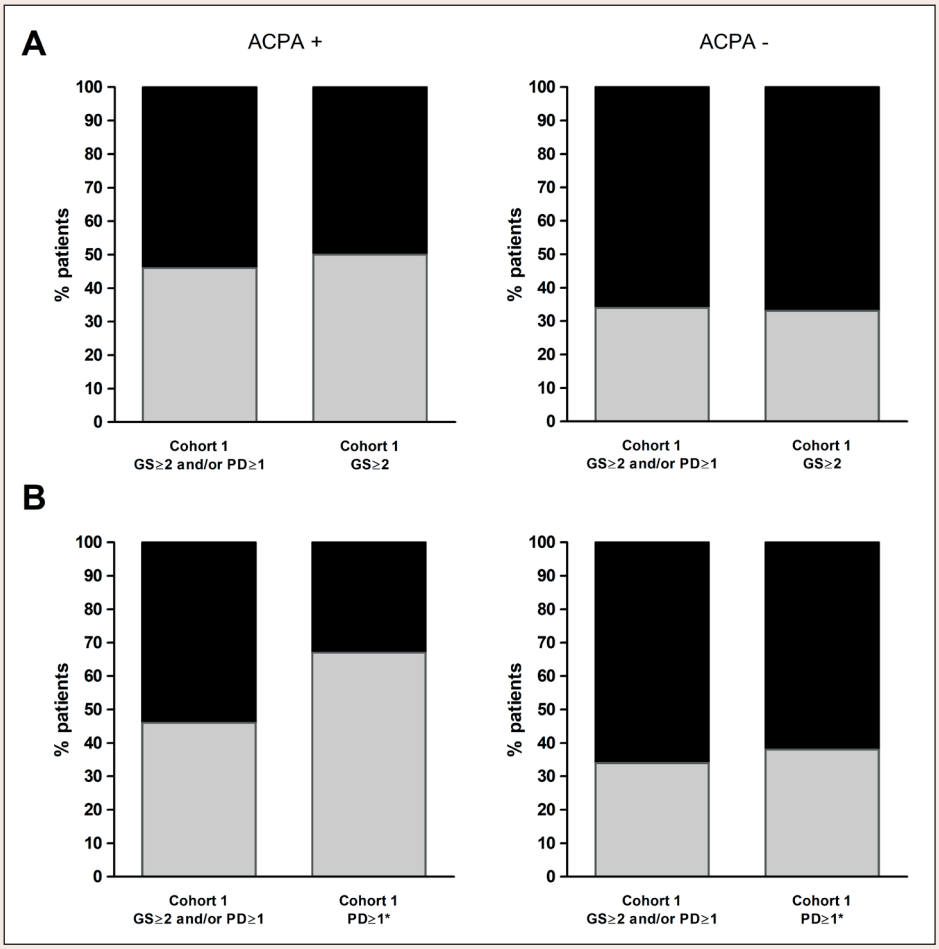
10. van de Stadt LA, Bos WH, Meursinge Reynders M et al. The value of ultrasonography in predicting arthritis in auto-antibody positive arthralgia patients: a prospective cohort study. Arthritis Res Ther. 2010;12:R98.

Supplementary Figure 1. Percentage of arthralgia-patients with subclinical synovitis (subclinical synovitis as entry-criterion) and ≥6 points on the 2010-criteria at baseline that did and did not develop inflammatory arthritis after 1-year (A) and 3-years follow-up (B) stratified for ACPA-status.



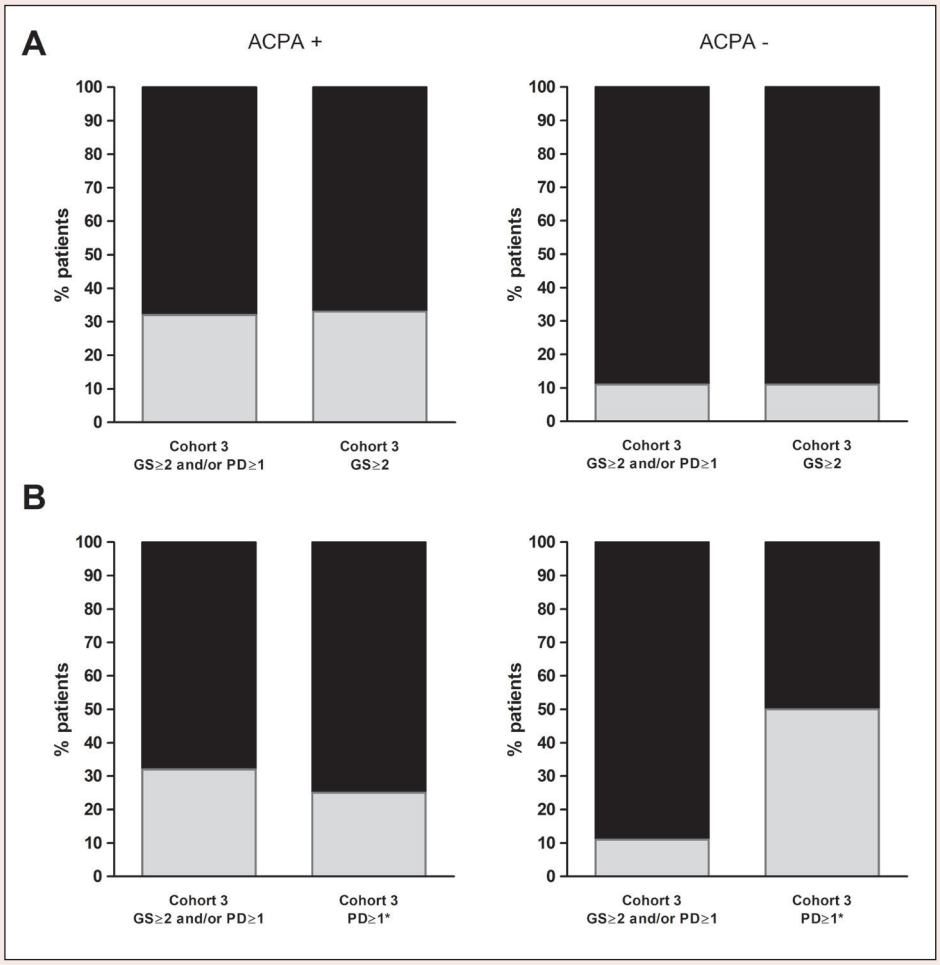
(A) ACPA-positive patients; (cohort 1 n=13, cohort 2 n=36, cohort 3 n=31). Patients with subclinical synovitis at baseline; n=11, n=27, n=19, respectively. Of these n=6, n=17, n=7 patients developed IA after one year of follow-up, respectively. ACPA-negative patients; (cohort 1 n=47, cohort 2 n=157, cohort 3 n=19). Patients with subclinical synovitis at baseline; n=12, n=39, n=9, respectively. Of these n=4, n=7, n=1 patients developed IA after one year of follow-up, respectively.
(B) ACPA-positive patients; (cohort 2 n=26, cohort 3 n=31). Patients with subclinical synovitis at baseline; n=21, n=19, respectively. Of these n=15, n=8 patients developed IA after three years of follow-up, respectively. ACPA-negative patients; (cohort 2 n=121, cohort 3 n=19). Patients with subclinical synovitis at baseline; n=29, n=9, respectively. Of these n=7, n=1 patients developed IA after three years of follow-up, respectively.

Supplementary Figure 2. Percentage of arthralgia-patients in cohort 1 with subclinical synovitis at baseline that did and did not develop inflammatory arthritis after 1-year, stratified for ACPA, when subclinical synovitis was defined as grey scale ≥2 and/or power Doppler ≥1 (as in the main analyses) and when grey scale ≥2 or power Doppler ≥1 were used separately.



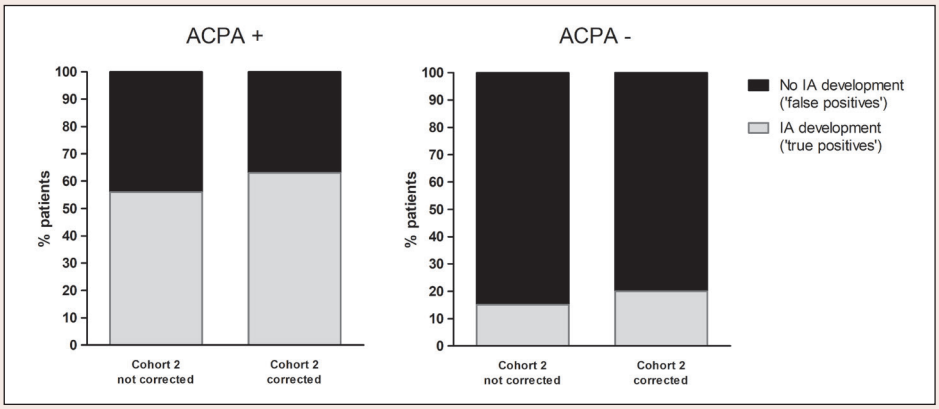
(A) ACPA-positive patients; (cohort 1 n= 37). Patients with subclinical synovitis at baseline; GS and/or PD n=13 , GS≥2 n=10. Of these n=6, n=5 patients developed IA after one year of follow-up, respectively. ACPA-negative patients; (cohort 1 n=129). Patients with subclinical synovitis at baseline; GS and/or PD n=47 , GS≥2 n=40. Of these n=16, n=13 patients developed IA after one year of follow-up, respectively.
(B) ACPA-positive patients; (cohort 1 n= 37). Patients with subclinical synovitis at baseline; GS and/or PD n=13 , PD≥1 n=9. Of these n=6, n=6 patients developed IA after one year follow-up, respectively. ACPA-negative patients; (cohort 1 n=129). Patients with subclinical synovitis at baseline; GS and/or PD n=47 , PD≥1 n=16. Of these n=16, n=6 patients developed IA after one year follow-up, respectively.
* PD≥1 and GS=1

Supplementary Figure 3. Percentage of arthralgia-patients in cohort 3 with subclinical synovitis at baseline that did and did not develop inflammatory arthritis after 1-year, stratified for ACPA, when subclinical synovitis was defined as grey scale ≥2 and/or power Doppler ≥1 (as in the main analyses) and when grey scale ≥2 or power Doppler ≥1 were used separately.



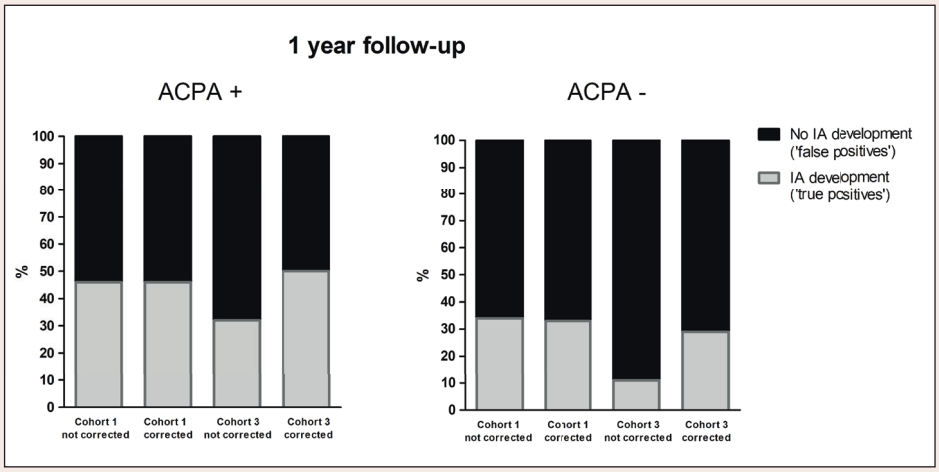
(A) ACPA-positive patients; (cohort 3 n=90). Patients with subclinical synovitis at baseline; GS and/or PD n=31 , GS≥2 n=30. Of these n=10, n=10 patients developed IA after one year of follow-up, respectively. ACPA-negative patients; (cohort 3 n=72). Patients with subclinical synovitis at baseline; GS and/or PD n=19 , GS≥2 n=19. Of these n=2, n=2 patients developed IA after one year of follow-up, respectively.
(B) ACPA-positive patients; (cohort 3 n=90). Patients with subclinical synovitis at baseline; GS and/or PD n=31 , PD≥1 alone n=4. Of these n=10, n=1 patients developed IA after one year follow-up, respectively. ACPA-negative patients; (cohort 3 n=72). Patients with subclinical synovitis at baseline; GS and/or PD n=19 , PD≥1 n=2. Of these n=2, n=1 patients developed IA after one year follow-up, respectively.
* PD≥1 and GS=1

Supplementary Figure 4. Percentage of arthralgia-patients with subclinical synovitis at baseline that did and did not develop inflammatory arthritis after 1-year, stratified for ACPA, before and after correcting the definition of subclinical synovitis for MRI-findings obtained in an age-matched symptom-free population.



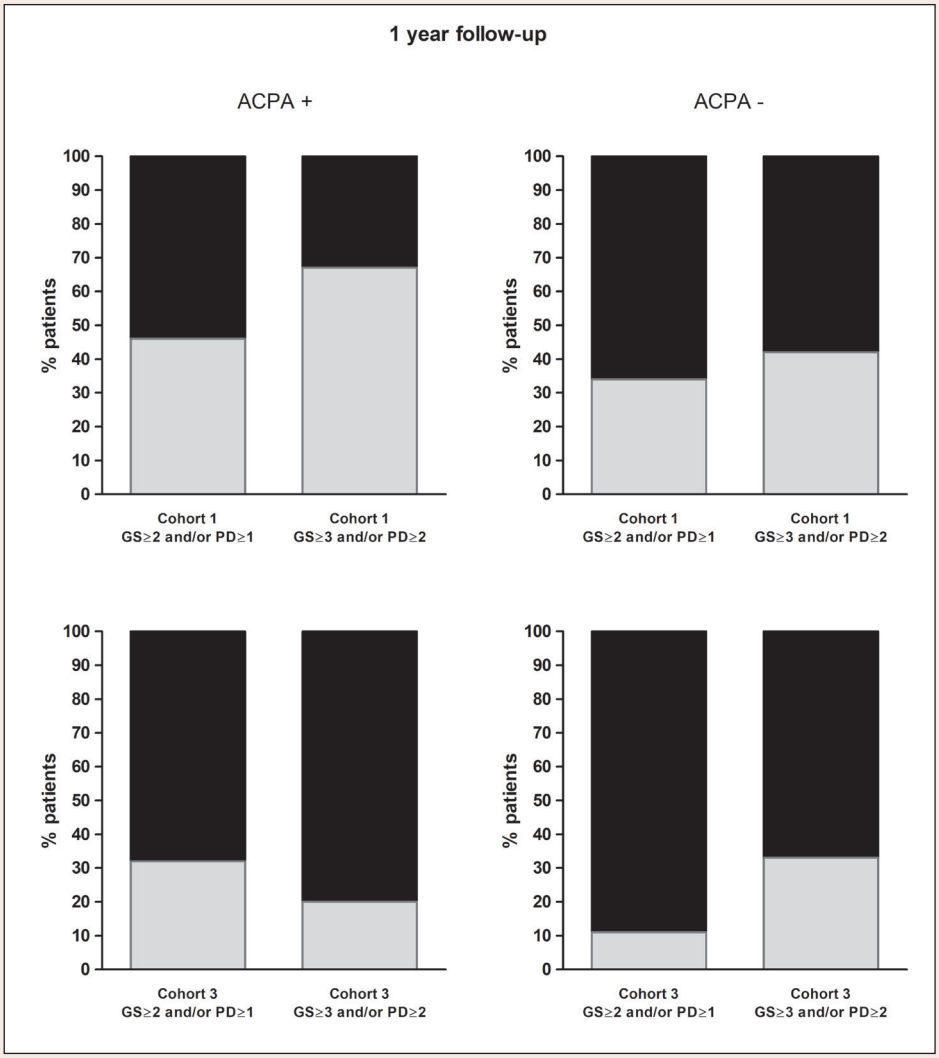
ACPA-positive patients; (cohort 2 n=64). Patients with subclinical synovitis at baseline; not corrected n=36, corrected n=24. Of these n=20, n=15 patients developed IA after one year follow-up, respectively. ACPA-negative patients; (cohort 2 n=409). Patients with subclinical synovitis at baseline; not corrected n=157, corrected n=70, respectively. Of these n=23, n=14 patients developed IA after one year follow-up, respectively.

Supplementary Figure 5. Percentage of arthralgia-patients with subclinical synovitis at baseline that did and did not develop inflammatory arthritis after 1-year, stratified for ACPA, before and after correcting the definition of subclinical synovitis for US-findings obtained in a symptom-free population.



ACPA-positive patients; (cohort 1 n=37). Patients with subclinical synovitis at baseline; n=13 not corrected, n=13 corrected. Of these n=6, n=6 patients developed IA after one year follow-up, respectively. (Cohort 3 n=90). Patients with subclinical synovitis at baseline; n=31 not corrected, n=16 corrected. Of these n=10, n=8 patients developed IA after one year follow-up, respectively. ACPA-negative patients; (cohort 1 n=129). Patients with subclinical synovitis at baseline; n=47 not corrected, n=42 corrected. Of these n=16, n=14 patients developed IA after one year follow-up, respectively. (Cohort 3 n=72). Patients with subclinical synovitis at baseline; n=19 not corrected, n=7 corrected, respectively. Of these n=2, n=2 patients developed IA after one year follow-up, respectively.

Supplementary Figure 6. Percentage of arthralgia-patients in two independent cohorts with subclinical synovitis at baseline that did and did not develop inflammatory arthritis after 1-year, stratified for ACPA, when subclinical synovitis was defined as grey scale ≥2 and/or power Doppler ≥1 (as in the main analyses) and as grey scale ≥3 and/or power Doppler ≥2 (more stringent threshold).



(A) ACPA-positive patients; (cohort 1 n=37). Patients with subclinical synovitis at baseline; GS≥2/PD≥1 n=13, GS≥3/PD≥2 n=6. Of these n=6, n=4 patients developed IA after one year of follow-up, respectively. ACPA-negative patients; (cohort 1 n=129). Patients with subclinical synovitis at baseline; GS≥2/PD≥1 n=47, GS≥3/PD≥2 n=12. Of these n=16, n=5 patients developed IA after one year follow-up, respectively.
(B) ACPA-positive patients; (cohort 3 n=90). Patients with subclinical synovitis at baseline; GS≥2/PD≥1 n=31, GS≥3/PD≥2 n=5. Of these n=10, n=1 patients developed IA after one year follow-up, respectively. ACPA-negative patients; (cohort 3 n=72). Patients with subclinical synovitis at baseline; GS≥2/PD≥1 n=19, GS≥3/PD≥2 n=3. Of these n=2, n=1 patients developed IA after one year follow-up, respectively.