Supplementary file 1 – Detailed description of methods

Patients

Between April 2012 and October 2018, 613 patients were included in the Leiden CSA cohort. CSA-patients had recent-onset (<1 year) arthralgia in the small joints, which was likely to progress to RA based on the clinical expertise of the rheumatologist. Per definition, patients were excluded if arthritis was detected upon physical examination or if a different explanation for the joint pain (e.g. osteoarthritis, fibromyalgia) was more likely than imminent RA. Baseline visit consisted of physical examination, questionnaires, blood sampling and MRI. Follow-up visits were scheduled at 4, 12 and 24 months. When necessary, for instance in case of an increase of symptoms or when patients experienced joint swelling, additional visits were planned. Follow-up ended when patients developed arthritis (determined at physical examination of joints by the treating rheumatologist), or else after 2-years. The cohort has been described in detail previously.[1]

During follow-up treatment with disease-modifying antirheumatic drugs (DMARDs, including steroids) was not allowed. Since April 2015, CSA-patients with MRI-detected subclinical inflammation could participate in a randomized double-blind placebo-controlled trial (RCT; Treat Earlier, trial registration number: NTR4853), studying the effect of Methotrexate in preventing progression to RA. This RCT is still ongoing; patients enrolled in this trial (n=88) were excluded from longitudinal follow-up in the CSA cohort because of the 50% chance of DMARD-use (Supplementary Figure 1).

Assessment and reliability of difficulties making a fist

At baseline the ability to completely close the fist and fist strength were assessed in both hands. Complete fist closure was defined as the ability to actively close the fist, with all fingertips touching the palm, and was assessed by visual inspection. Fist strength was measured by trained research nurses (RNs) while a patient squeezed the 2nd and 3rd finger of the RN. To investigate reliability of the measures for fist closure and fist strength, tests were also performed and documented by

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rheumatologists in a subset of patients (n=324 and n=318, respectively). Measure of agreement between RN and rheumatologist were determined for both tests.

Fist strength can also be measured with a hand held dynamometer. Strength measured with a dynamometer in e.g. clinical trials is mainly used to evaluate continuous strength measures over time within persons, or to compare strength between groups. To use strength as a diagnostic factor within individuals, a single measure ought to be dichotomized according to norm values. Norm values have a wide range, also within age and gender categories.[2] As single measures with a handheld dynamometer also introduce interobserver variation and reference values show a large distribution, reliability of the measure would remain questionable. Most importantly, as hand held dynamometers are not always available in clinical practice, the present used method reflects daily clinical practice best. For these reasons we chose not to use a handheld dynamometer.

MRI scanning and scoring protocol

Within two weeks after inclusion, CSA-patients underwent contrast-enhanced MRI of wrist and 2^{nd}-5^{th} metacarpophalangeal (MCP) joints of the most painful side (in case of equally severe symptoms on both sides, the dominant side was scanned).

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

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

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(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).

Field-of-view was 100mm. Coronal sequences had 18 slices with a slice thickness of 2mm and a slice gap of 0.2mm. Axial sequences had a slice thickness of 3mm and a slice gap of 0.3mm with 20 slices for the wrist and 16 for the MCP-joints.

We used the contrast enhanced T1-weighted fat suppressed sequence to assess bone marrow edema (BME). According to the RA MRI scoring system (RAMRIS)-method, T2-weighted fat suppressed sequences, or when this sequence is not available a short tau inversion recovery (STIR) sequence, should be used to assess BME. However, three previous studies have demonstrated that a contrast enhanced T1-weigthed fat suppressed sequence has a strong correlation with T2-weighted fat suppressed sequences.[3-5] Furthermore, the arthritis subcommittee of the European Society of Musculoskeletal Radiology (ESSR) also recommends the use of contrast enhanced T1-weighted fat suppressed sequences for depicting BME.[6] The T2-weighted image shows increased water signal and a contrast-enhanced T1-weighted sequence shows increased water content and the increased perfusion and interstitial leakage. A strong correlation has been shown in arthritis patients and in patients without inflammatory diseases such as bone bruises, intraosseous ganglions, bone infarcts and even nonspecific cases.[4, 5] Based on these results BME was assessed on contrast enhanced T1-weighted fat suppressed sequences as it has a higher signal to noise ratio and allowed a shorter scan time for patients.

All bones (with the exception of metacarpal base 1 and the trapezium), joints and tendons were scored semi-quantitatively according to the validated RAMRIS. Bones were scored separately for BME on a scale 0-3 based on the affected volume of the bone (no BME, >0-33%, >33-66%, >66%). Synovitis was scored on a range 0-3 based on the volume of enhancing tissue in the synovial compartment (none, mild, moderate, severe).[7] Similar to the scoring method described by Haavardsholm et al., tenosynovitis at the flexor and extensor sides of the wrist, flexor side of MCP joints and MCP extensor peritendinitis

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were scored based on the thickness of peritendinous effusion or synovial proliferation with contrast enhancement (normal, <2mm, 2-5mm, >5mm (range 0-3)).[8]

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

MRI-detected subclinical inflammation

Mean scores from both readers were used to determine presence of subclinical inflammation (synovitis, BME, tenosynovitis and MCP extensor peritendinitis) for the wrist- and MCP-joints separately. As MRI-detected subclinical inflammation also can be present in the general population, scores were dichotomized with MRI-data of symptom-free controls as reference (n=193, as published previously).[9] Patients were considered positive for an inflammatory feature if it is uncommon in symptom-free controls, i.e. present in <5% of symptom-free controls at the same location and in the same age category (<40, 40-59, ≥60).

Outcome

The main outcome for longitudinal analyses was development of clinical arthritis, determined by the rheumatologist at physical examination. The secondary outcome was RA-development (fulfilment of 1987- or 2010-criteria).[10, 11]

Statistics

Cox regression was used to investigate predictive value of difficulties making a fist for the development of inflammatory arthritis (IA) and RA. Time-to-event was determined as the time from inclusion until the first time clinical IA (or RA) was observed by the rheumatologist. Patients who did not develop IA (or RA) were censored at the date of their 2-year visit, or, when current follow-up was shorter than 2

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years, at the date all medical files were last checked for IA (or RA) development (8 October 2018). Multivariable Cox regression was corrected for regular predictors (age, gender, CRP-status (normal/increased) and ACPA-status (anti-CCP2 positive/negative). Analyses were done with IA-development as primary outcome, and thereafter done with RA-development as outcome.

Associations between difficulties making a fist and subclinical inflammation in the same hand at baseline were assessed with logistic regression. Inflammatory MRI-features (from both wrist- and MCP joints) with associations of $p<0.1$ in univariable logistic regression were included together with age and gender in multivariable logistic regression.

The measure of agreement between RN and rheumatologists for tests of fist closure and fist strength was determined with the Cohen's Kappa.

P-values <0.05 were considered statistically significant. IBM SPSS Statistics Version 23 was used.

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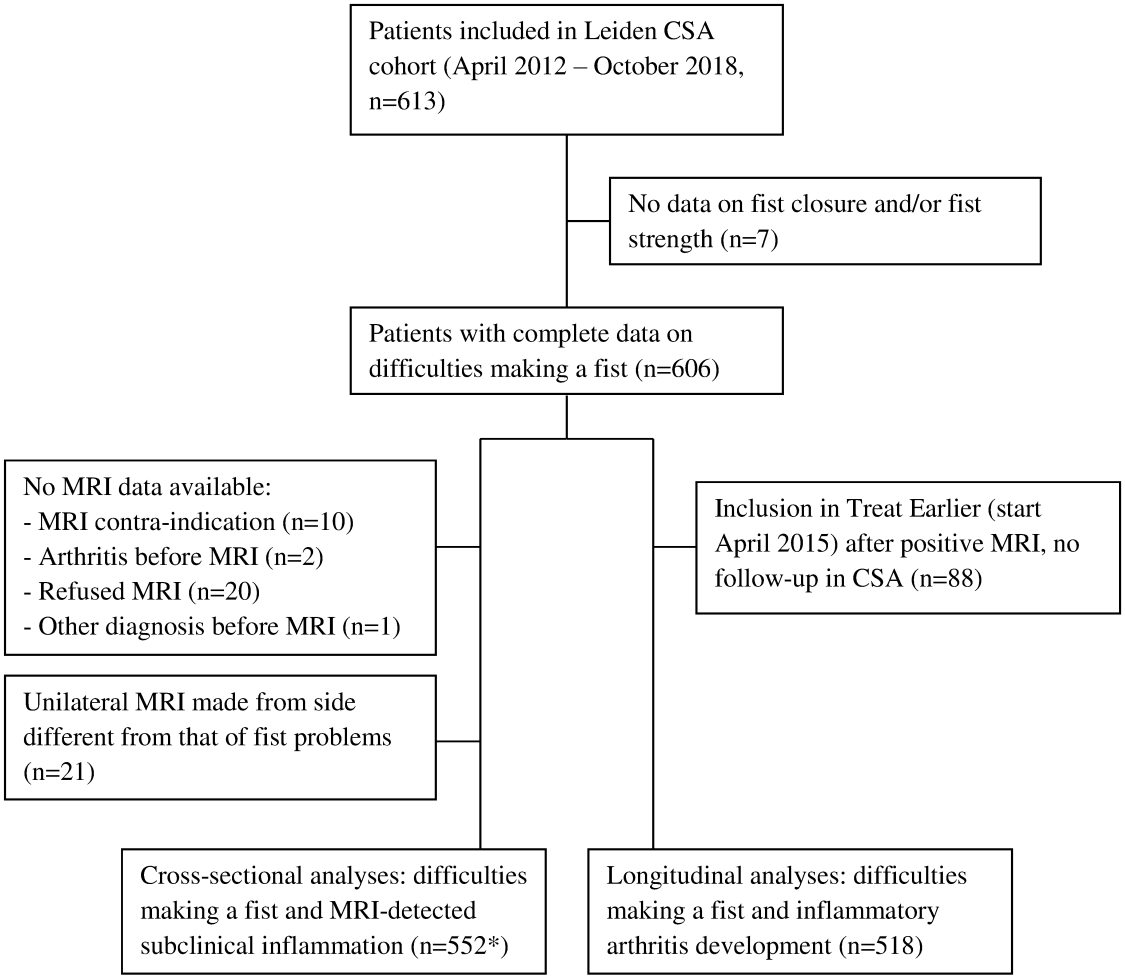
Supplementary Figure 1 – Patient selection flowchart



Patients used for longitudinal analyses (n=518) had a median follow-up of 16 months (IQR 4-25), 85 (16%) developed inflammatory arthritis. *Fist closure and fist strength were observed by both RN and rheumatologist in 324 and 318 patients, respectively.

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Supplementary Table 1 Baseline characteristics of the studied CSA-patients

	Cross-sectional: difficulties making a fist and MRI-detected subclinical inflammation (n=552)	**Longitudinal: difficulties making a fist and inflammatory arthritis development (n=518)**
Age in years, mean (SD)	44.0 (12.8)	43.5 (12.6)
Female, n (%)	411 (74.5)	404 (78.0)
Symptom duration in weeks, median (IQR)	19 (9-41)	19 (9-44)
68-TJC , median (IQR)	5 (2-10)	5 (2-10)
MRI inflammation score wrist and MCP, median (IQR)	1.8 (0.5-4.5)	1.5 (0.5-4.0)
ACPA positivity (≥7 U/mL), n (%)	76 (13.8)	68 (13.1)
RF positivity (≥3.5 IU/mL), n (%)	112 (20.3)	103 (19.9)
Increased CRP (≥5 mg/L), n (%)	117 (22.4)	104 (21.2)

CSA: clinically suspect arthralgia, SD: standard deviation, IQR: interquartile range, TJC: tender joint count, ACPA: anti-citrullinated protein antibody, RF: rheumatoid factor, CRP: c-reactive protein

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Supplementary Table 2 Predictive value of difficulties making a fist for the development of RA

	Univariable Cox regression		**Multivariable Cox regression [a]**	
	HR (95% CI)	*P-value*	*HR (95% CI)*	*P-value*
Incomplete fist closure with one or both hands	2.18 (1.22-3.90)	0.009	2.55 (1.38-4.71)	0.003
Decreased fist strength in one or both hands	1.29 (0.78-2.14)	0.328	1.76 (1.04-2.98)	0.036

[a] Adjusted for age, gender, CRP-status and ACPA-status

RA: rheumatoid arthritis, HR: hazard ratio, CI: confidence interval

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Supplementary Table 3 Measure of agreement between assessors of fist closure

Fist closure		**According to the rheumatologist**		
		Complete	Incomplete	Total
According to the research nurse	Complete	278	4	282
	Incomplete	20	22	42
	Total	298	26	324
Cohen's Kappa		0.61		

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Supplementary Table 4 Measure of agreement between assessors of fist strength

Fist strength		**According to the rheumatologist**		
		Not decreased	Decreased	Total
According to the research nurse	Not decreased	163	23	186
	Decreased	81	51	132
	Total	244	74	318
Cohen's Kappa		0.28		

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