Supplementary material

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Study populations

Derivation cohort: the TREAT EARLIER trial

Our derivation-cohort existed of the participants in the TREAT-EARLIER (TE)-trial, a randomized placebo-controlled trial.(1) The TREAT EARLIER trial studied the hypothesis that intervention in the symptomatic phase preceding clinical arthritis is more often successful in permanent disease modification because of less matured underlying disease processes in this early at risk stage. A two-level definition was used to identify patients eligible for trial inclusion. First, patients needed to have recent-onset arthralgia (< 1 year) that was suspect to progress to RA according to the expertise of the treating rheumatologist (clinically suspect arthralgia; CSA). Second, patients needed to have subclinical inflammation of the hand or forefoot joints at 1.5 T MRI, after correction for MRI-findings in healthy controls. At baseline, hand function, other clinical parameters and laboratory testing was performed. Intervention (methotrexate and a single intramuscular glucocorticoid injection, or placebo) was started after the baseline visit, so the intervention could not have influenced measurements in the current study. 236 patients were included between April 2016 an September 2019.

Validation cohort: the Leiden CSA-cohort

The CSA-cohort of the Leiden University Medical Centre (LUMC) enrolled patients with recent-onset (symptom-duration <1 year) arthralgia of small joints in whom their rheumatologist suspected an increased risk of developing RA based on clinical expertise and pattern recognition.(2) Patients were included disregarding the results of laboratory investigations, including the presence of auto-antibodies. In line with Dutch guidelines for general practitioners these are generally not tested in primary care.[13] Notably, patients in whom clinical arthritis was already present or in whom alternative causes of arthralgia were more likely (e.g. osteoarthritis, fibromyalgia) were not included in the CSA-cohort. At inclusion, physical joint-examination and blood-tests were conducted, including IgG anti-citrullinated protein antibodies (ACPA) and IgM rheumatoid factor (RF). Patients also underwent an MRI if no contra-indications were present. The presence of MRI-detected subclinical inflammation however was not mandatory for participation in the cohort. For the current study, we studied all 600 consecutive CSA-patients with available data on MRI and hand-function included between April 2012-May 2020.

MRI-protocol

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.

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).

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, 16 for the metacarpophalangeal-joints.

All bones, joints and tendons were scored semi-quantitatively according to the validated RA MRI scoring system (RAMRIS). Bone marrow edema (BME) was scored on a scale 0-3 based on the affected volume of the bone (no BME, >0-33%, >33-66%, >66%) and synovitis was scored on a range 0-3 based on the volume of enhancing tissue in the synovial compartment (none, mild, moderate, severe).(2) Similar to methods described by Haavardsholm et al the tenosynovitis-score was based on the thickness of peritendinous effusion or synovial proliferation with contrast enhancement (normal, <2mm, 2-5mm, >5mm (range 0-3)).(3) Total inflammation score summed the scores of synovitis, tenosynovitis and BME scores.

MRI-scores were dichotomized into presence or absence of an inflammatory feature. Scans were considered positive if a feature was scored by both readers and present in <5% of age-matched healthy volunteers. These reference scores were developed in a previous analysis of RAMRIS-features in the same 193 symptom-free controls.(4)

Questions in the HAQ grip-domain

The HAQ grip-domain consistent of these three questions, asked in Dutch.

Were you able to:

A) Open the front door?
B) Open jars which have been previously opened?
C) Turn faucets on and off?

The questions were scored by patients on a 4-point scale representing the degree of difficulties experienced when performing the activity concerned, with '0' indicating no difficulties, '1' indicating some difficulty, '2' much difficulty and '3' indicating full disability. Patient-reported difficulties in the current study were defined as a score of 1 or higher.

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Supplementary Table S1. Baseline characteristics of the derivation and validation cohort

	Derivation: TREAT EARLIER (n=236)	**Validation: Leiden CSA (n=600)**
Age	47 (12)	44 (13)
Female	154 (65%)	469 (78%)
Symptom duration in weeks	27 (15-47)	19 (9-44)
TJC-68	3 (1-9)	5 (2-10)
Pain	50 (30-70)	50 (30-65)
HAQ total score	0.63 (0.19-1.13)	0.63 (0.25-1.00)
ACPA-positive and/or RF-positive	77 (33%)	133 (22%)
Increased CRP (≥5 mg/L)	68 (29%)	130 (22%)
Presence of any subclinical inflammation	236 (100%)	231 (41%)
MRI-detected subclinical inflammation	4.5 (2.5-7.5)	1.5 (0-4.0)
Synovitis	2.0 (0.5-3.0)	0.5 (0-2.0)
Tenosynovitis score	1.5 (0.5-3.0)	0 (0-1.5)
BME score	1.0 (0-2.0)	0 (0-1.0)

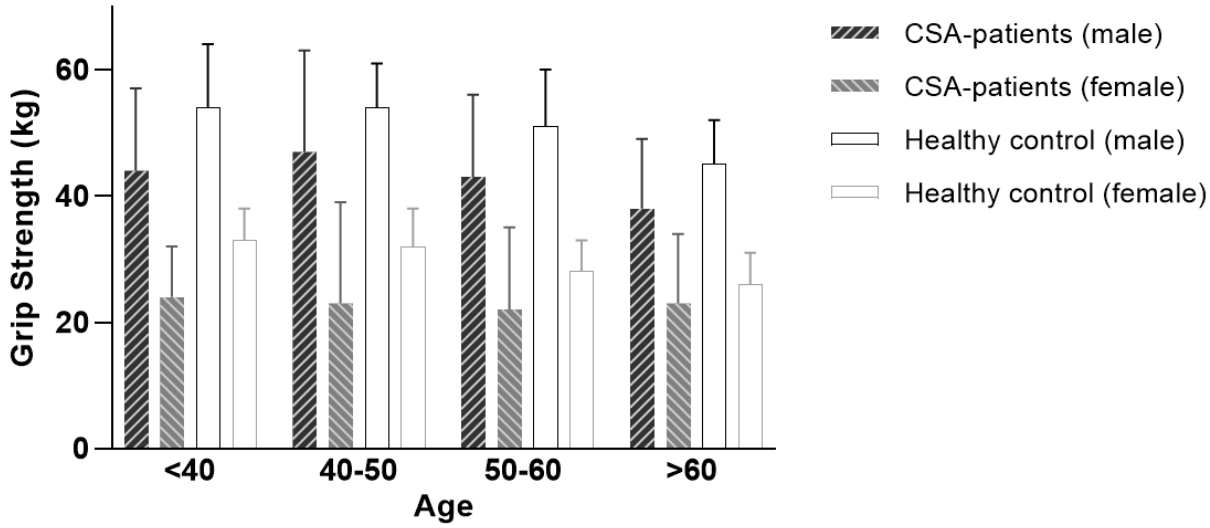
Legend supplementary table S1.
Data are n (%), mean (SD) or median (IQR). Subclinical inflammation was considered present if found in <5% of age-matched healthy controls. Presence of subclinical inflammation in hand or forefoot was an inclusion criterium for the TREAT EARLIER trial. MRI-detected subclinical inflammation summed the scores on synovitis, tenosynovitis and BME in the wrist and MCP-regions. TJC-68: tender joint count involving 68 joints, ACPA: anti-citrullinated protein antibodies (positive if >7 U/ml, anti-CCP; Phadia, Netherlands), RF: rheumatoid factor (positive if >3.5 IU/ml, in-house ELISA), BME: bone marrow edema.

Supplementary Table S2. Hand function in the derivation and validation cohort

	Derivation (n=236)	**Validation: (n=600)**
Dynamometer-measured GS in kg, mean ± SD	29.8 (14.0)	-
Dynamometer-measured GS <reference, n (%)*	177 (75%)	-
HAQ, domain grip, median score (IQR) (range 0-3)	1 (0-1)	1 (0-1)
Any difficulty with grip, n(%)	137 (60%)	269 (51%)
Question 'Opening the front door', median score (IQR)	0 (0-0)	0 (0-0)
Any difficulty with 'Opening the front door', n(%)	38 (17%)	97 (19%)
Question 'Opening a lid', median score (IQR)	0 (0-1)	0 (0-1)
Any difficulty with 'Opening a lid', n(%)	105 (46%)	201 (38%)
Question 'Opening a tap', median score (IQR)	0 (0-1)	0 (0-1)
Any difficulty with 'Opening a tap', n(%)	87 (38%)	155 (30%)
Incomplete fist closure, n (%)	31 (13%)	80 (14%)
Examiner-assessed GS	-	214 (36%)

Legend Supplementary Table S2.
Any difficulty in the HAQ domain or separate questions was defined as a score of 1 or higher (i.e. individuals indicating some difficulty, much difficulty or unable to perform a task). Dynamometer-measured GS was assessed with dynamometer (maximum of left or right hand). *: reference values in healthy controls were used as reported by Gunther et al.(5) Examiner-assessed GS was evaluated by squeezing the examiners fingers.
GS: grip strength, -: outcome was not assessed in this cohort.

Supplementary figure S1. Dynamometer-measured grip strength in kg, compared to healthy controls of same age and gender



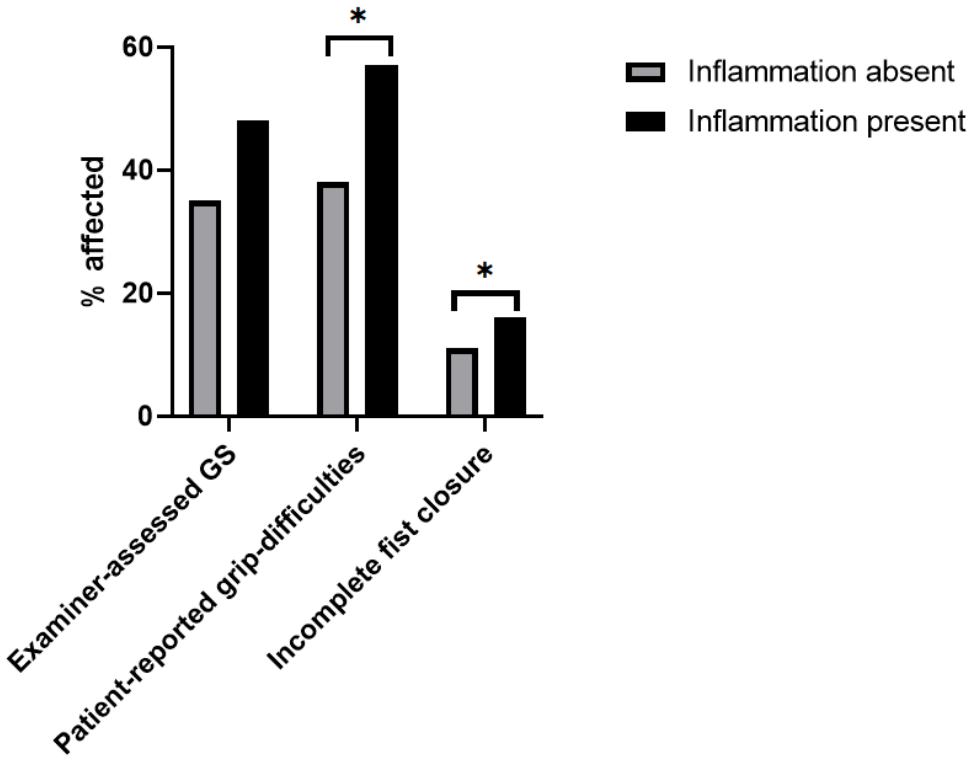
Legend supplementary figure S1
Dynamometer-measured grip strength was assessed with dynamometer (maximum of left or right hand) and dichotomized using reference values in healthy controls as reported by Gunther et al.(5)

Supplementary Table S3. Univariable associations between reduced hand function and subclinical inflammation on MRI

Derivation-cohort:			
	Dynamometer-measured GS (in kg)	**Patient-reported grip-difficulties (OR)**	**Incomplete fist closure (OR)**
Total inflammation score (per point)	-0.38 (-0.68; -0.08)*	1.12 (1.04; 1.20)*	0.98 (0.89; 1.07)
Individual features (univariable):			
Synovitis score (per point)	-0.96 (-1.69; -0.23)*	1.29 (1.09; 1.52)*	0.90 (0.72; 1.12)
Tenosynovitis score (per point)	-1.20 (-1.80; -0.61)*	1.23 (1.07; 1.42)*	1.07 (1.01; 1.26)*
BME score (per point)	0.43 (-0.25; 1.01)	1.04 (0.90; 1.21)	0.84 (0.62; 1.13)
Validation-cohort:			
	Examiner-assessed decreased GS (OR)	**Patient-reported grip-difficulties (OR)**	**Incomplete fist closure (OR)**
Total inflammation score (per point)	1.06 (1.02; 1.11)*	1.08 (1.02; 1.13)*	1.11 (1.05; 1.17)*
Individual features (univariable):			
Synovitis score (per point)	1.11 (1.00; 1.22)*	1.13 (1.02; 1.27)*	1.22 (1.08; 1.39)*
Tenosynovitis score (per point)	1.13 (1.02; 1.27)*	1.14 (1.03; 1.28)*	1.29 (1.15; 1.45)*
BME score (per point)	1.14 (1.02; 1.27)*	1.20 (1.04; 1.38)*	1.17 (1.03; 1.33)*

Legend table S3.
Total inflammation score is the sum of synovitis, tenosynovitis and BME. Analyses were adjusted for age and gender. Measures of hand function were analyzed as the dependent variable. GS: grip strength, BME: bone marrow edema, *: denotes statistical significance.

Supplementary figure S2. Reduced hand function in the CSA-cohort, stratified for patients in whom MRI-detected subclinical inflammation is absent or present



Legend supplementary figure S2. MRI was positive for subclinical inflammation in 231 (41%) of CSA-patients. Subclinical inflammation summed the scores on synovitis, tenosynovitis and BME. A feature was considered present if scored by two readers independently and detected in <5% of age-match healthy controls (as described by previously (4)). If one or more features were present, the MRI was considered positive for subclinical inflammation. * Indicate p-values <0.05.

References in supplementary materials

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