Supplementary materials for 'Joint involvement in RA starts predominantly in the hands: functional, clinical and imaging studies in clinically suspect arthralgia'

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Supplementary Data S1. CSA cohort Leiden

Patients with CSA were included in the cohort at their first visit at the outpatient clinic, before any blood tests had been performed.[1] In line with national guidelines for general practitioners (GPs), GPs are discouraged to perform ACPA-testing themselves but are encouraged to refer patients in case of any suspicion on imminent RA. Hence inclusion was mostly done without knowledge of the results of additional investigations. At each study visit (0,4,12,24 months), physical joint examination was performed, and blood samples were taken for routine laboratory screening, including immunoglobulin M-rheumatoid factor (RF) (positive ≥3.5 IU/mL); and ACPA (anti-CCP2, EliA CCP, Phadia, the Netherlands, positive ≥7 U/mL).

Supplementary Data S2. Protocol for Magnetic Resonance Imaging (MRI)

Patients who were included in the Leiden CSA-cohort, underwent a unilateral MRI of wrist, metacarpophalangeal (MCP)-, and metatarsophalangeal (MTP)-joints with gadolinium contrast enhancement on an MSK-extreme 1.5T extremity MR imaging system (GE, Wisconsin, USA), using a 145mm coil for the foot and a 100mm coil for the hand. The MRI was made on the side with the most symptoms, or the dominant side when symptom severity was symmetrical. Patients were instructed not to use NSAIDs 24 hours prior to MRI. Patient were positioned in a chair beside the scanner, with the hand or foot fixed in the coil with cushions. In the hand (MCP 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) 575ms, echo time (TE) 11.2ms, acquisition matrix 388×288, echo train length (ETL) 2). After intravenous injection of gadolinium contrast (gadoteric acid, Guerbet, Paris, France, standard dose of 0.1mmol/kg) the following sequences were obtained: T1-

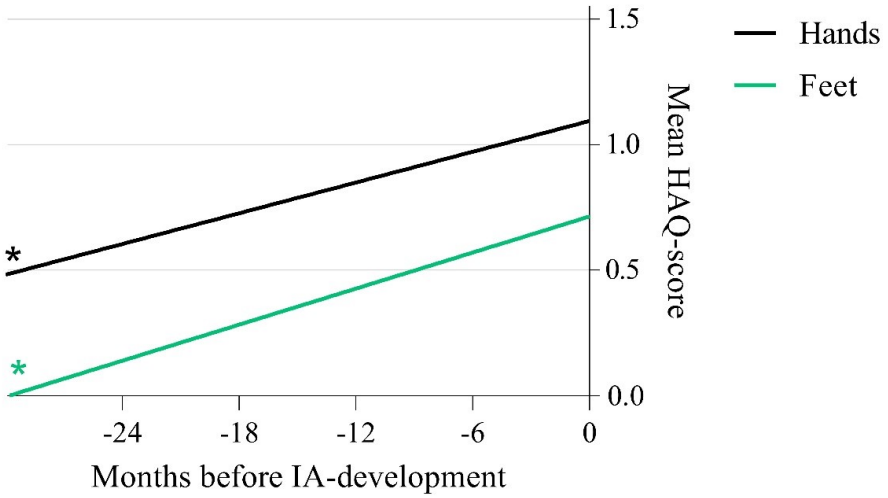
weighted FSE sequence with frequency selective fat saturation (fatsat) in the coronal plane (TR/TE 700/9.7ms, acquisition matrix 364×224, ETL 2), T1-weighted FSE sequence with frequency selective fat saturation in the axial plane (wrist: TR/TE 540/7.7ms; acquisition matrix 320x192; ETL 2 and MCP-joints: TR/TE 570/7.7ms; acquisition matrix 320x192; ETL 2). The obtained sequences of the forefoot (MTP 1-5 joints) concerned post-contrast images of the foot: 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 MTP-joints) (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 MCP-joints and 14 for the foot.

Supplementary Data S3. MRI-inflammation; scoring and dichotomization

Synovitis was scored in line with the Outcome Measures in Rheumatology Clinical Trials (OMERACT) RA MRI scoring (RAMRIS)-method.[2] RAMRIS was not developed to score MTP-joints, however others have previously adapted the RAMRIS to score MTP-joints as well.[3] Tenosynovitis was scored according to the method described by Haavardsholm (also applied at the flexor and extensor tendons at the 2-5 MCP-joints; range 0-3).[4] The synovitis score (range 0-3) was scored based on the volume of enhancing tissue in the synovial compartment (none, mild, moderate, severe) and the tenosynovitis-score (ranged 0-3) was based on the thickness of peritendinous effusion or synovial proliferation with contrast enhancement (normal, <2mm, 2-5mm, >5mm). Presence of inflammation was dichotomized per feature of inflammation (synovitis, tenosynovitis, osteitis) and per location; if the

inflammation-score of any feature was higher than present in <5% of age matched healthy controls at the same location, the joint was scored positive for inflammation.[5] Baseline MRIs were scored by two experienced readers, blinded to any clinical data. The mean scores of two readers were calculated and in case of disagreement the lower score was used. Inter- and intrareader intraclass correlation coefficients were ≥0.90, as published previously.[3]

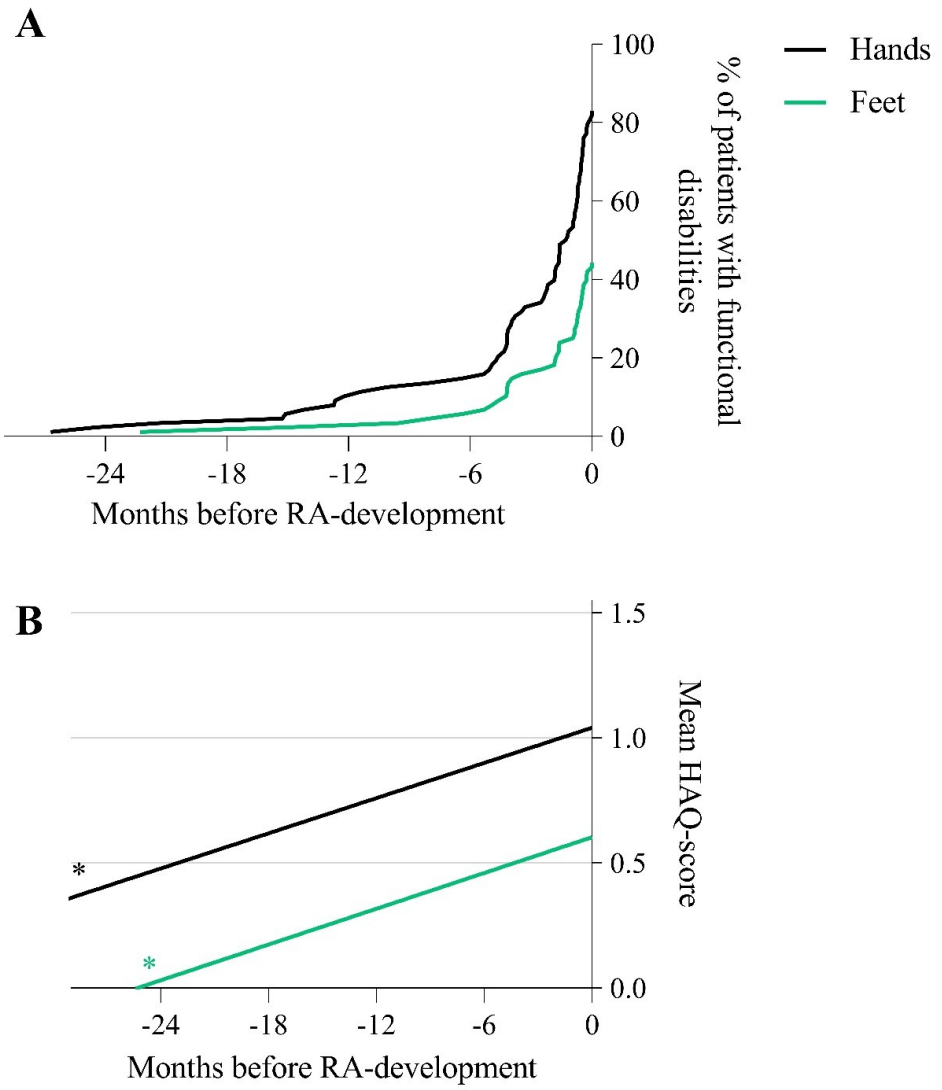
Supplementary Figure S1. Severity of functional disabilities (mean HAQ-score) involving hands and feet in CSA-patients during the trajectory towards development of inflammatory arthritis, with correction for age



Legend: lines depict the course of functional disabilities involving the hands (average of dressing, eating, grip; range 0-3) and feet (walking; range 0-3) with correction for age, derived from linear mixed model analyses and including all HAQ-measurements prior to development of inflammatory arthritis. In these analyses, the moment of inflammatory arthritis is considered as t=0. *Statistically significant increases in mean HAQ-scores.

Abbreviations: CSA=clinically suspect arthralgia; HAQ=Health Assessment Questionnaire Disability-Index; IA=inflammatory arthritis.

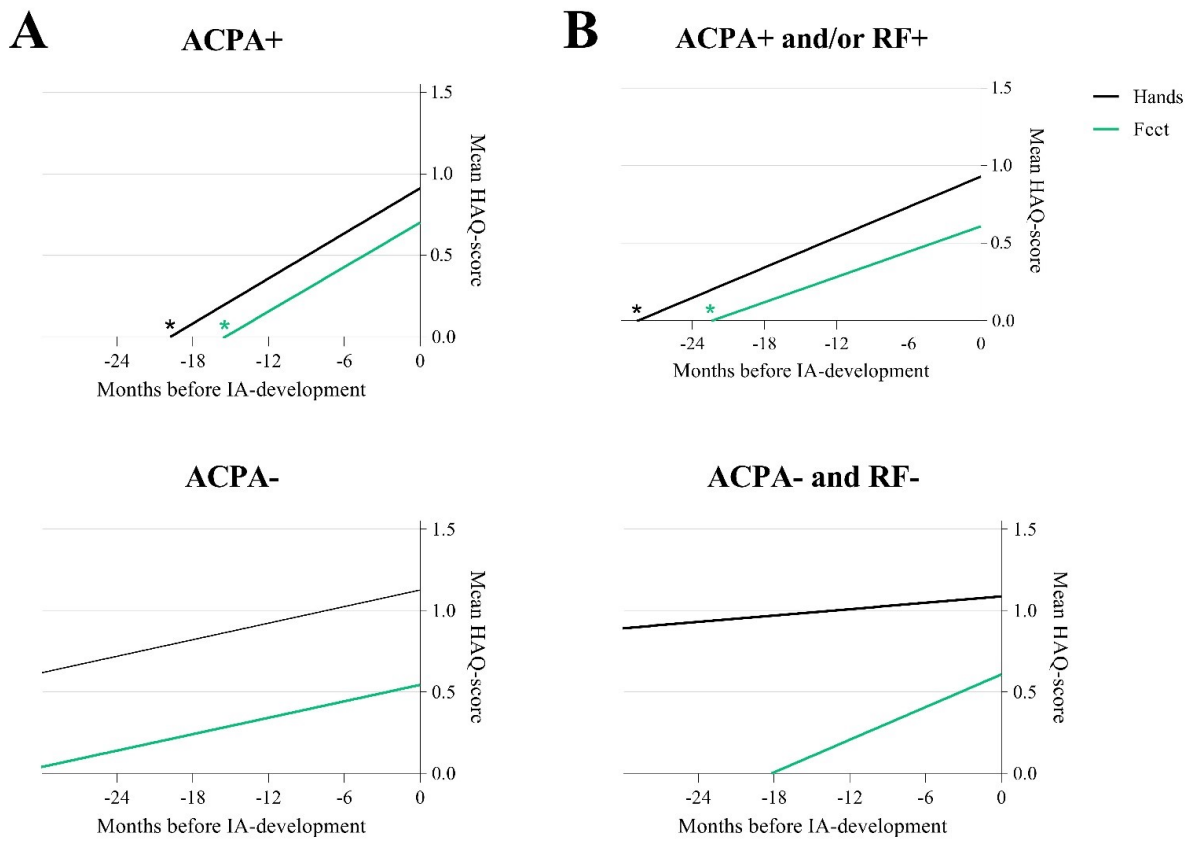
Supplementary Figure S2. A) Increasing incidence of functional disabilities and B) severity of functional disabilities (mean HAQ-score) involving hands and feet in CSA-patients during the trajectory towards RA-development



Legend: A: lines depict the increasing incidence of functional disabilities involving the hands and feet prior to development of RA (considered as t=0), including all HAQ-measurements. Hand- and foot-disabilities were defined as a score >0 on the hand-domain and foot-domain of the HAQ, both having a range of 0-3. B: lines depict the course of functional disabilities involving the hands (average of dressing, eating, grip; range 0-3) and feet (walking; range 0-3), derived from linear mixed model analyses and including all HAQ-measurements prior to development of RA. In both A and B, moment of RA-development is defined as t=0 and all HAQ-measurements prior to RA-development were used to analyse the course of functional disabilities towards RA-development. *Statistically significant increases in HAQ-scores.

Abbreviations: CSA=clinically suspect arthralgia; HAQ=Health Assessment Questionnaire Disability-Index; RA=rheumatoid arthritis.

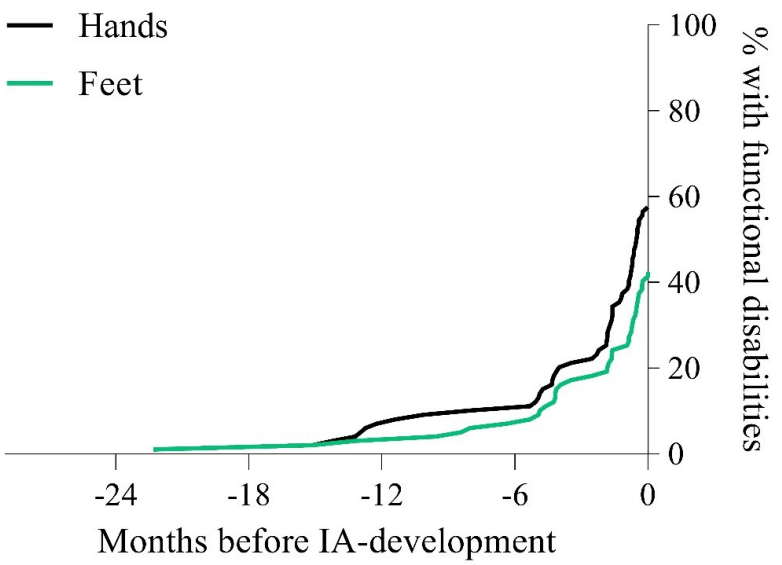
Supplementary Figure S3. The severity of functional disabilities (mean HAQ-score) involving hands and feet in CSA-patients during the trajectory towards development of inflammatory arthritis stratified for A) ACPA and B) ACPA and/or RF



Legend: lines depict the course of functional disabilities involving the hands (average of dressing, eating, grip; range 0-3) and feet (walking; range 0-3), derived from linear mixed model analyses and including all HAQ-measurements prior to development of inflammatory arthritis. In these analyses, the moment of inflammatory arthritis is considered as t=0. *Statistically significant increases in HAQ-scores.

Abbreviations: ACPA=anti-citrullinated protein antibody; CSA=clinically suspect arthralgia; HAQ=Health Assessment Questionnaire Disability-Index; IA=inflammatory arthritis; RF=rheumatoid factor.

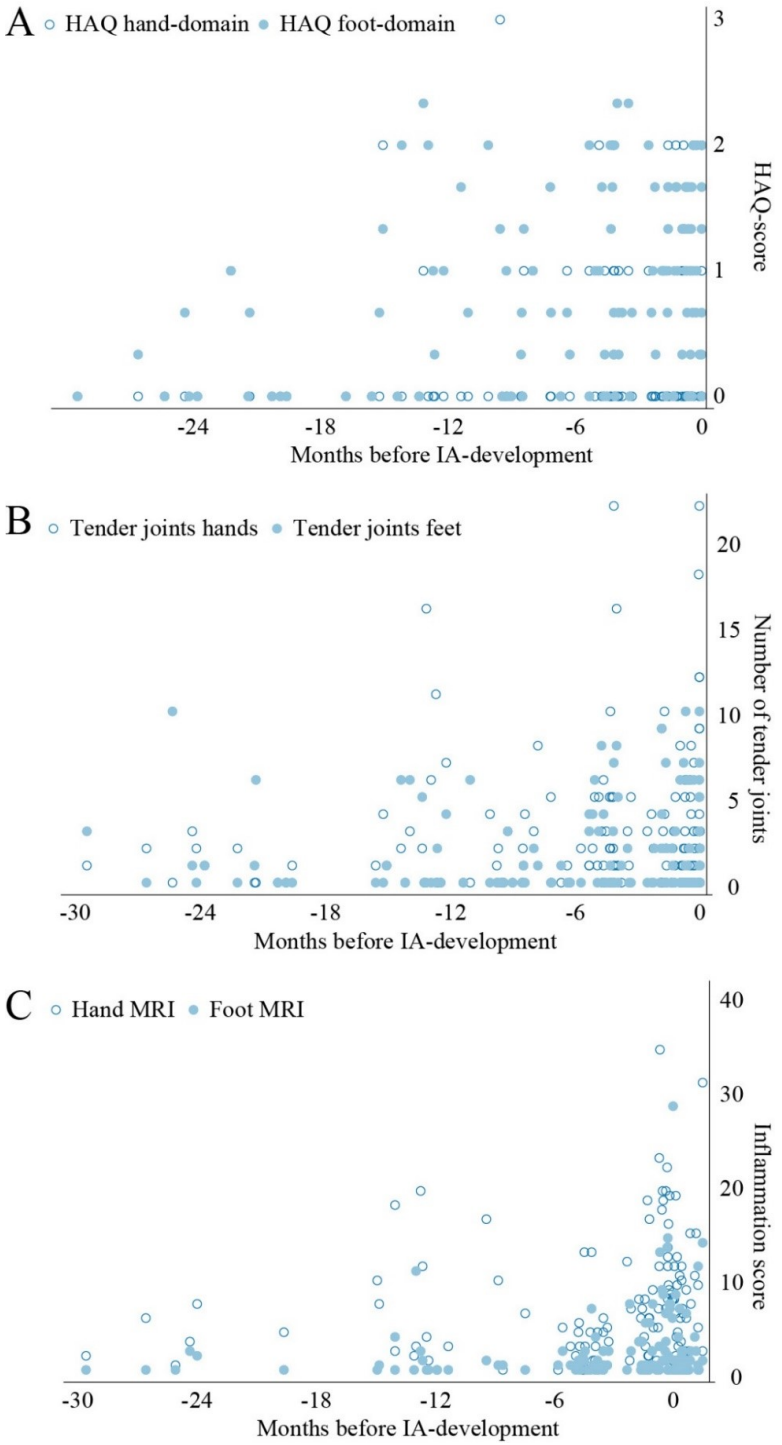
Supplementary Figure S4. Increasing incidence of functional disabilities involving hands≥1 and feet in CSA-patients during the trajectory towards development of inflammatory arthritis



Legend: lines depict the increasing incidence of functional disabilities involving the hands and feet prior to development of inflammatory arthritis (considered as t=0), including all HAQ-measurements. Foot-disabilities were defined as a score>0 on the foot-domain of the HAQ, and hand-disabilities were defined as a score≥1. Thus, a more stringent definition of hand-disabilities was used in this figure. Both the hand- and foot-domain have a range of 0-3.

Abbreviations: CSA=clinically suspect arthralgia; HAQ=Health Assessment Questionnaire Disability-Index; IA=inflammatory arthritis.

Supplementary Figure S5. Raw data on A) functional disabilities, B) tender joints and C) subclinical joint-inflammation involving hands and feet prior to development of IA



Abbreviations: HAQ=Health Assessment Questionnaire Disability-Index; IA=inflammatory arthritis; MRI=magnetic resonance imaging.

Supplementary Table S1. Baseline characteristics of CSA-patients with and without baseline data on HAQ

	Patients with HAQ-data (n=524)	Patients without HAQ-data (n=76)	P-value
Female	411 (78)	58 (76)	0.68
Age in years	44 ± 13	41 ± 11	0.049
Symptom duration in days	149 (68-344)	105 (61-183)	0.018
TJC-68	5 (2-10)	6 (3-12)	0.35
TJC-group*			0.46
• TJC: hands+ feet-	215 (41)	37 (49)	
• TJC: hands- feet+	43 (8)	4 (5)	
• TJC: hands+ feet+	194 (37)	27 (36)	
• TJC: hands- feet-	66 (13)	6 (8)	
ACPA-positive	65 (12)	14 (18)	0.15
RF-positive	98 (19)	17 (22)	0.45
CRP increased (≥5 mg/L)	112 (21)	18 (24)	0.68
ESR increased**	75 (14)	13 (17)	0.58
IA-development	91 (17)	8 (11)	0.13

Legend: data are n (%), mean ± SD or median (IQR). *TJC of the hands involved: wrist, metacarpophalangeal (MCP) joints 1-5, proximal interphalangeal (PIP) joints 2-5 and interphalangeal (IP) joints of the thumb. TJC of the feet involved: metatarsophalangeal (MTP) joints 1-5. **ESR was considered elevated with a reference for age and sex (<50 years: male>15 mm/h, female>20mm/h; >50 years: male>20mm/h, female>30mm/h).

Abbreviations: ACPA=anti-citrullinated protein antibody; CRP=c-reactive protein; CSA=clinically suspect arthralgia; ESR=erythrocyte sedimentation rate; HAQ=Health Assessment Questionnaire Disability-Index; IA=inflammatory arthritis; RF=rheumatoid factor; TJC=tender joint count.

References

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2. Østergaard, M., 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**(6): p. 1385-6.
3. Dakkak, Y.J., et al., *Reliability of Magnetic Resonance Imaging (MRI) Scoring of the Metatarsophalangeal Joints of the Foot according to the Rheumatoid Arthritis MRI Score.* J Rheumatol, 2020. **47**(8): p. 1165-1173.
4. Haavardsholm, E.A., et al., *Introduction of a novel magnetic resonance imaging tenosynovitis score for rheumatoid arthritis: reliability in a multireader longitudinal study.* Ann Rheum Dis, 2007. **66**(9): p. 1216-20.
5. Mangnus, L., et al., *Magnetic Resonance Imaging-Detected Features of Inflammation and Erosions in Symptom-Free Persons From the General Population.* Arthritis Rheumatol, 2016. **68**(11): p. 2593-2602.