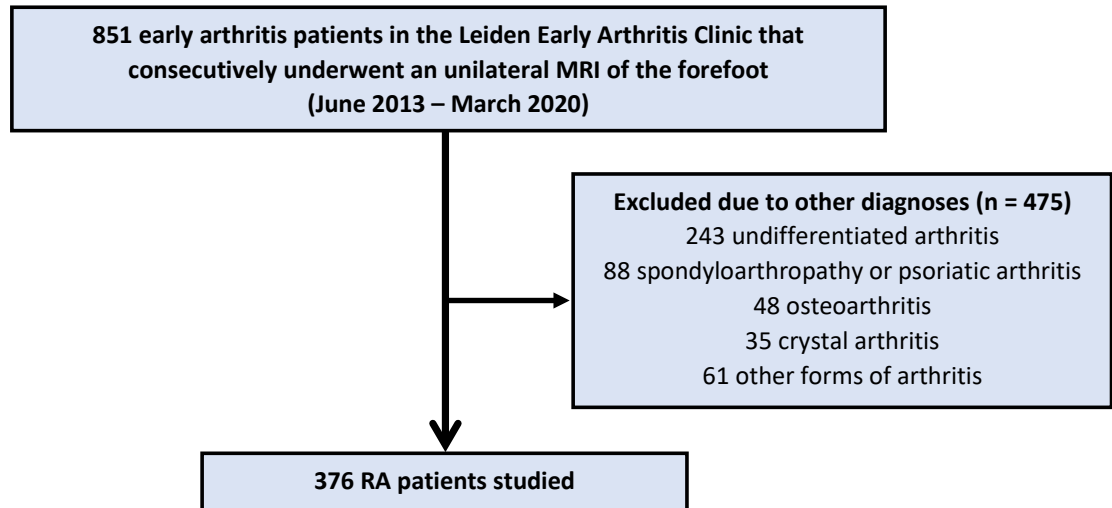


## Supplementary files

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**Supplementary Figure S1. Flowchart of patient selection.**

**Supplementary Data S2. MRI protocol and scoring.**

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

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 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 140mm. The coronal sequence had 20 slices and the axial sequence had 14 slices, both with a slice thickness of 3mm and a slice gap of 0.3mm. As part of the Leiden Early Arthritis Cohort, MRIs of the hands were acquired in the same session as those of the foot, but the hands were not evaluated in the current study.

We used the contrast enhanced T1-weighted fat suppressed sequence to assess osteitis in the forefoot. According to the 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 osteitis. However, three previous studies have demonstrated that a contrast enhanced T1-weighted fat suppressed sequence has a strong correlation with T2-weighted fat suppressed sequences (1-3). 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 osteitis (4). 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 (1, 2). Based on these results osteitis 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. In addition, because T2-weighted fat suppressed sequences could be omitted, coronal sequences of the foot could be added. In total this resulted in a shorter total scan time and more information.

The bones, joints and tendons of the metatarsophalangeal (MTP)-joints were scored semi-quantitatively according to the validated RA MRI scoring system (RAMRIS). Osteitis was scored on a scale 0-3 based on the affected volume of the bone (no osteitis, >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) (5). 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)) (6). Erosions were scored as well but these are beyond the scope of this article.

**Supplementary Table S3. Characteristics of selected RA patients with and without assessment of IMB.**

	With IMB assessment n = 242	Without IMB assessment n = 134	P-value
Age in years, mean (SD)	60 (14)	60 (15)	0.72
Female, n (%)	152 (63)	87 (65)	0.68
ACPA positivity ( $\geq 7$ IU/mL), n (%)	115 (48)	56 (42)	0.25
RF-positivity, ( $\geq 3.5$ IE/mL), n (%)	130 (55)	63 (52)	0.51
Increased CRP ( $\geq 10$ mg/L), n (%)	115 (48)	67 (50)	0.65
SJC-66, median [IQR]	6 [3-11]	5 [2-10]	0.14
TJC-68, median [IQR]	8 [4-13]	7 [3-12]	0.14
Any walking disability, n (%)	125 (57)	67 (52)	0.40
Sum of RAMRIS inflammation at MTP-level, median [IQR]	3.5 [1-7.5]	2 [0.5-6]	0.10

**Legend**

Unpaired t-test, Mann-Whitney U test, and Chi<sup>2</sup>-test were used for normal distributed continuous, non-normal distributed continuous, and categorical data. Abbreviations: HAQ = Health Assessment Questionnaire, ACPA = anti-citrullinated peptide antibodies, SD = standard deviation, IQR = interquartile range, IgM RF = immunoglobulin M rheumatoid factor, CRP = C-reactive protein, TJC-68 = 68 tender joint count, SJC-66 = 66 swollen joint count, RAMRIS = Rheumatoid Arthritis Magnetic Resonance Imaging Scoring system, MTP = metatarsophalangeal.

**Supplementary Table S4. Reference values of IMB-size used to define positivity for IMB, based on the 95<sup>th</sup> percentile of IMB-measurements in healthy controls who were described previously (7, 8)**

<u>Intermetatarsal space</u>				
Age group	1 <sup>st</sup> (MTP 1–2)	2 <sup>nd</sup> (MTP 2–3)	3 <sup>rd</sup> (MTP 3–4)	4 <sup>th</sup> (MTP 4–5)
<40 years	any size	any size	≥ 4 mm	any size
40–59 years	≥ 10 mm	≥ 9 mm	≥ 11 mm	any size
≥60 years	≥ 12 mm	≥ 3 mm	≥ 11 mm	any size

**Legend**

Size was measured in dorsoplantar direction.

Abbreviations: IMB = intermetatarsal bursitis; MTP = metatarsophalangeal joint.

**Supplementary Table S5. Characteristics of selected RA patients with and without assessment of walking disabilities.**

	With assessment n = 350	Without assessment n = 26	P-value
Age in years, mean (SD)	60 (14)	58 (15)	0.43
Female, n (%)	223 (64)	16 (62)	0.82
Increased CRP ( $\geq 10$ mg/L), n (%)	167 (48)	15 (60)	0.25
ACPA positivity ( $\geq 7$ IU/mL), n (%)	159 (46)	12 (48)	0.82
RF-positivity, ( $\geq 3.5$ IE/mL), n (%)	180 (54)	13 (57)	0.81
SJC-66, median [IQR]	6 [3-10]	6 [2-11]	0.99
TJC-68, median [IQR]	8 [4-12]	6 [2-16]	0.44
Total RAMRIS inflammation at MTP-level, median [IQR]	3 [1-6.5]	4.5 [1-8.5]	0.53

**Legend**

Unpaired t-test, Mann-Whitney U test, and Chi<sup>2</sup>-test were used for normal distributed continuous, non-normal distributed continuous, and categorical data. Abbreviations: CRP = C-reactive protein, ACPA = anti-citrullinated peptide antibodies, SD = standard deviation, IQR = interquartile range, IgM RF = immunoglobulin M rheumatoid factor, TJC-68 = 68 tender joint count, SJC-66 = 66 swollen joint count, RAMRIS = Rheumatoid Arthritis Magnetic Resonance Imaging Scoring system, MTP = metatarsophalangeal.

**Supplementary Table S6. Frequencies (%) of tender and swollen joints, and inflamed joint tissues detected by MRI of the MTP joints in ACPA-positive (A) and ACPA-negative RA (B) patients.**

<b>A</b>	<b>ACPA-positive RA</b>				
<b>Clinical signs</b>	<b>MTP 1</b>	<b>MTP 2</b>	<b>MTP 3</b>	<b>MTP 4</b>	<b>MTP 5</b>
Tenderness	10	27	28	25	15
Swelling	2	21	22	17	7
<b>Imaging</b>	<b>MTP 1</b>	<b>MTP 2</b>	<b>MTP 3</b>	<b>MTP 4</b>	<b>MTP 5</b>
Synovitis	8	22	25	21	29
Flexor tenosynovitis	12	14	16	11	5
Extensor tenosynovitis	17	1	5	3	6
Osteitis	6	18	17	14	24
<b>Intermetatarsal space</b>	<b>First</b>	<b>Second</b>	<b>Third</b>	<b>Fourth</b>	
IMB	20	38	46	19	
<b>B</b>	<b>ACPA-negative RA</b>				
<b>Clinical signs</b>	<b>MTP 1</b>	<b>MTP 2</b>	<b>MTP 3</b>	<b>MTP 4</b>	<b>MTP 5</b>
Tenderness	8	27	29	21	12
Swelling	2	17	21	14	3
<b>Imaging</b>	<b>MTP 1</b>	<b>MTP 2</b>	<b>MTP 3</b>	<b>MTP 4</b>	<b>MTP 5</b>
Synovitis	3	22	19	20	21
Flexor tenosynovitis	10	18	16	12	7
Extensor tenosynovitis	13	3	5	2	3
Osteitis	2	7	5	6	7
<b>Intermetatarsal space</b>	<b>First</b>	<b>Second</b>	<b>Third</b>	<b>Fourth</b>	
IMB	26	30	27	14	

#### Legend

Frequencies of clinical signs are the average of both sides, frequencies of imaging are unilateral and performed at the most painful side or dominant side if both sides were equally painful. The findings depicted were corrected for findings in a healthy symptom-free population, as described previously.(7, 8) Abbreviations: ACPA = anti-citrullinated peptide antibodies, IMB = intermetatarsal bursitis, MTP = metatarsophalangeal.



**Supplementary Table S7. Sensitivity analysis showing the association of presence of MRI-detected inflammation with adjacent MTP joint swelling, excluding MTP1, in ACPA-positive and ACPA-negative RA patients.**

	Univariable	P-value	Multivariable	P-value
Joint swelling	OR (95% CI)		OR (95% CI)	
<b>ACPA-positive</b>				
Synovitis	3.0 (1.8 – 4.9)	<0.001	1.8 (0.9 – 3.5)	0.09
Tenosynovitis	4.0 (2.2 – 7.0)	<0.001	1.9 (0.9 – 3.9)	0.09
IMB	3.2 (1.7 – 5.9)	<0.001	2.4 (1.2 – 4.8)	0.01
<b>ACPA-negative</b>				
Synovitis	2.2 (1.2 – 4.1)	0.01	2.2 (1.0 – 4.9)	0.06
Tenosynovitis	1.6 (0.8 – 3.2)	0.15	1.0 (0.5 – 2.0)	0.96
IMB	1.8 (0.9 – 3.4)	0.09	1.3 (0.6 – 2.7)	0.47

#### Legend

Odds ratios were calculated using GEE and represent joint swelling as dependent variable.

Multivariable joint-level analyses were performed in 438 MTP joints of ACPA-positive and 499

MTP joints of ACPA-negative RA patients. Abbreviations: GEE = generalized estimating

equations, MRI = magnetic resonance imaging, ACPA = anti-citrullinated peptide antibodies,

OR = odds ratio, 95% CI = 95% confidence interval, MTP = metatarsophalangeal, IMB =

intermetatarsal bursitis.

**Supplementary Table S8. Sensitivity analysis showing the association of presence of MRI-detected inflammation with adjacent MTP joint swelling in autoantibody-positive and -negative RA patients.**

	<b>Univariable</b>	<b>P-value</b>	<b>Multivariable</b>	<b>P-value</b>
<b>Joint swelling</b>	OR (95% CI)		OR (95% CI)	
<b>ACPA and/or RF positive</b>				
<b>Synovitis</b>	3.6 (2.3 – 5.6)	<0.001	2.5 (1.4 – 4.6)	0.002
<b>Tenosynovitis</b>	2.9 (1.8 – 4.8)	<0.001	1.8 (1.0 – 3.3)	0.052
<b>IMB</b>	3.1 (1.8 – 5.1)	<0.001	2.2 (1.3 – 3.9)	0.005
<b>ACPA and RF negative</b>				
<b>Synovitis</b>	2.7 (1.3 – 5.7)	0.009	2.7 (1.4 – 4.6)	0.02
<b>Tenosynovitis</b>	1.2 (0.5 – 3.0)	0.67	0.6 (0.2 – 1.5)	0.26
<b>IMB</b>	2.0 (0.9 – 4.3)	0.08	1.6 (0.7 – 3.6)	0.22

#### **Legend**

Odds ratios were calculated using GEE and represent joint swelling as dependent variable.

Multivariable joint-level analyses were performed in 722 MTP joints of ACPA and/or RF positive RA patients and 444 MTP joints of double negative RA patients (ACPA and RF negative).

Abbreviations: GEE = generalized estimating equations, MRI = magnetic resonance imaging,

ACPA = anti-citrullinated peptide antibodies, RF = rheumatoid factor, OR = odds ratio, 95% CI =

95% confidence interval, MTP = metatarsophalangeal, IMB = intermetatarsal bursitis.

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