Targeting long non-coding RNA MALAT1 preserves endothelial cell integrity and protects against kidney fibrosis

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Comparison of findings on contrast-enhanced MRI of the hand, wrist, and forefoot in healthy controls, two at-risk groups, and patients with rheumatoid arthritis: a cohort study

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Summary

Background The sensitivity of MRI in detecting joint inflammation in rheumatoid arthritis is well known but its specificity is less discussed. It is important to prevent false positive results and consequent overdiagnosis. Therefore, we aimed to examine MRI-detected inflammation that is less specific for rheumatoid arthritis by evaluating the frequencies of inflammation in healthy controls and in two at-risk groups who have not developed rheumatoid arthritis, compared with patients with rheumatoid arthritis.

Methods In this cohort study, we performed contrast-enhanced MRIs of the second to fifth metacarpophalangeal, wrist, and first to fifth metatarsophalangeal joints of two at-risk groups (individuals with clinically suspect arthralgia and patients with undifferentiated arthritis who have not developed rheumatoid arthritis within a 2-year and 1-year follow-up period, respectively), and patients with rheumatoid arthritis, from two longitudinal observational cohort studies at Leiden University Medical Centre, Netherlands; the Leiden Early Arthritis Clinic (EAC) and the clinically suspect arthralgia (CSA) cohort. Healthy volunteers were also recruited as controls from Leiden University Medical Centre. MRIs were evaluated for synovitis, tenosynovitis, and osteitis using the Rheumatoid Arthritis MRI Scoring system. Intermetatarsal bursitis was also evaluated. All MRIs were scored by two readers independently of each other and who were blinded for clinical data. Each site was graded 0 (no inflammation), 1 (low), 2 (moderate), or 3 (severe). Increased signal intensity of joints, tendon sheaths, and bones were considered as less specific for rheumatoid arthritis if a similar signal intensity grade was present in more than 5% of the reference group. Comparisons were made in the following age-strata: <40 years, 40–59 years, and ≥60 years. Patient partners were involved in the design of the EAC and CSA cohorts.

Findings Participants with valid MRI data from the EAC cohort (enrolled Aug 24, 2010, to March 9, 2020]) and the CSA cohort (enrolled April 3, 2012, to April 29, 2021), and 193 healthy volunteers (enrolled between Nov 15, 2013, to Dec 2, 2014) were included. At follow-up, 516 patients had rheumatoid arthritis, 305 had undifferentiated arthritis, and 598 had clinically suspect arthralgia. Of all participants, 1089 (68%) of 1612 were female and 523 (32%) were male, 1105 (94%) of 1160 were White, and mean age was 51 years (SD 14). Grade 2 and 3 synovitis, tenosynovitis, or osteitis did not occur in more than 5% of healthy controls and clinically suspect arthralgia non-converters (of all ages), therefore grade 1 inflammation in these reference populations versus patients with rheumatoid arthritis was evaluated. Grade 1 inflammation was found at a number of sites in the hand, wrist, and forefoot in more than 5% in all reference populations across all age groups, and these locations of inflammation were also frequently seen in patients with rheumatoid arthritis. The frequency of inflammation across all cohorts increased with age. Grade 2 inflammation that occurred in more than 5% was only present in patients with non-progressing undifferentiated arthritis aged 60 years or older.

Interpretation We describe several low-grade MRI-detected inflammatory findings of the hand, wrist, and forefoot that are less specific for rheumatoid arthritis. These include locations that are regularly inflamed in rheumatoid arthritis. These findings could assist in avoiding overinterpretation when using contrast-enhanced MRI.

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Introduction

MRI is a sensitive modality for detecting joint inflammation and its use is recommended by the European Alliance of Associations for Rheumatology (EULAR) in the diagnostic trajectory of rheumatoid arthritis when in diagnostic doubt.[1] MRI has a superior sensitivity to detect synovitis, compared with both physical examination and ultrasound.[2] It is also very

Research in context

Evidence before this study

Although studies on MRI findings in healthy volunteers and patients with rheumatoid arthritis have been performed previously, none made direct comparisons between rheumatoid arthritis and other reference populations. This is required to evaluate the specificity of MRI. We searched PubMed between database inception and April 11, 2024, with no language restrictions, using the search terms "Arthritis, Rheumatoid"[Mesh]) AND "Magnetic Resonance Imaging"[Mesh] AND ("Hand"[Mesh] OR "Foot"[Mesh]) AND ("Healthy"[tiab] OR "Volunteer"[tiab] OR "Arthralgia"[tiab] OR "Undifferentiated*"[tiab] OR "Unclassified*"[tiab]). Our search indicated that nine studies focused on MRI findings in patients with rheumatoid arthritis and healthy controls. However, in those studies, the maximum number of healthy controls studied was 31. Furthermore, age-matched comparisons were impossible with these small sample sizes. Studies directly comparing their findings on joint level with other reference populations (ie, clinically suspect arthralgia and patients with undifferentiated arthritis who have not developed rheumatoid arthritis) were absent. Therefore, with the ultimate aim to avoid overdiagnosis by MRI findings, direct comparisons between healthy controls, and patients with clinically suspect arthralgia and undifferentiated arthritis who have not developed rheumatoid arthritis with patients with rheumatoid arthritis are needed to provide a clear overview for rheumatologists in clinical practice and future research.

Added value of this study

To our knowledge, this is the first extensive study where MRI findings of three reference groups were directly compared with findings in patients with rheumatoid arthritis across three age-strata. We found several locations of inflammation that are less specific for rheumatoid arthritis, especially in participants aged 60 years and older. Some are known predilection places for degeneration. Furthermore, several locations with low-grade (grade 1) inflammation found on MRI in the general population also appear to be frequently inflamed in rheumatoid arthritis. People in the reference populations at older ages often had more than one inflammatory lesion that was less specific for rheumatoid arthritis. In addition, synovitis was found more often in these reference populations than osteitis or tenosynovitis. This study contributes to improved interpretation of MRI findings for clinical practice and research by showing that, contrary to general belief, not all positive MRI findings should be considered rheumatoid arthritis-specific.

Implications of all the available evidence

The less-specific locations for rheumatoid arthritis we describe should be considered in future trials or in clinical practice to ensure a high specificity of MRI. This can avoid overdiagnosis when using contrast-enhanced MRI in the diagnostic trajectory. The fact that subtle inflammation in the healthy population and inflammation in patients with rheumatoid arthritis can occur at the same sites (at different severity) warrants further studies into underlying processes to understand why local homeostasis is maintained in healthy people and not in patients with rheumatoid arthritis.

sensitive in detecting tenosynovitis and is the only modality to depict osteitis.[1–3] Despite its focus on sensitivity, the specificity of MRI is less discussed. High specificity prevents false positive test results, and thereby overdiagnosis. The issue of specificity and preventing overdiagnosis is of increasing importance as recent data suggest that MRI is helpful in the early identification of at-risk individuals who will progress to rheumatoid arthritis and treatment in such patients could reduce the disease burden.[4–6]

In general, the specificity encompasses the percentage of true negative tests in the group of individuals without the disease. When assessing the specificity for rheumatoid arthritis in case-control settings, the general population is often considered as the reference without the disease. However, in longitudinal studies in populations at-risk for a disease, the reference is the at-risk population with similar characteristics who do not develop the disease. In the setting of rheumatoid arthritis, the reference could consist of patients with clinically suspect arthralgia or undifferentiated arthritis who do not progress to rheumatoid arthritis. In medicine, a positive (abnormal) test result is typically based on reference values from the general population. For example, autoantibody test thresholds, like anti-citrullinated protein antibodies, are determined using general population data.[7] Some laboratory tests' reference has shown to be age-dependent, for example, erythrocyte sedimentation rate (ESR) has a higher cutoff for people older than 50 years.[8] However, in the field of imaging, the use of (age-matched) references is less common. It is often assumed that healthy individuals show normal images, and consequently, observed abnormalities are interpreted as pathological. However, a recent ultrasound study in healthy individuals showed a higher frequency of inflammation-like features at increasing age.[9] For conventional contrast-enhanced MRI of joints, inflammation-like findings have been found in healthy individuals and including an age-matched reference population increases the specificity of MRI of hands and feet.[10,11]

A large-scale study directly comparing healthy controls with patients with rheumatoid arthritis, and those in its at-risk stages, including clinically suspect

arthralgia and undifferentiated arthritis, is still needed. Due to the increasing interest in very early identification of patients with imminent rheumatoid arthritis and with the ultimate aim to reduce overdiagnosis, we aimed to evaluate the locations in hands and forefeet where inflammation is less specific for rheumatoid arthritis. We therefore did a large cross-sectional MRI study at joint level to compare healthy individuals, patients with clinically suspect arthralgia and undifferentiated arthritis who have not developed rheumatoid arthritis over time, and patients with early rheumatoid arthritis.

Methods

Study design and participants

In this study, we examined MRI scans of the metacarpophalangeal, wrist, and metatarsophalangeal joints from patients with rheumatoid arthritis, clinically suspect arthralgia who have not progressed to rheumatoid arthritis within a 2-year follow-up period and patients with undifferentiated arthritis who have not progressed to rheumatoid arthritis within a 1-year follow-up period, from two longitudinal observational cohort studies at Leiden University Medical Centre, Netherlands: the Leiden Early Arthritis Clinic (EAC) and the clinically suspect arthralgia (CSA) cohort. Healthy volunteers were also recruited as controls from Leiden University Medical Centre.

Patients with rheumatoid arthritis were from the Leiden EAC. The EAC is a population-based inception cohort consisting of patients with recent-onset arthritis who have been recruited consecutively since 1993. Patients were included if clinical arthritis was present at physical examination by a rheumatologist and symptom duration was less than 2 years. Patients were excluded if they previously used disease-modifying antirheumatic drugs (DMARDs). The EAC study design has been extensively described elsewhere.[12] Since the inception of the cohort, patients referred with suspicion of early arthritis were seen with priority, generally within 2 weeks. Diagnoses were determined at baseline and verified after 1 year based on routinely available data (MRI findings were not reported to rheumatologists). Rheumatoid arthritis was defined as a clinical diagnosis by the rheumatologist and fulfilment of the 1987 American College of Rheumatology (ACR) or 2010 ACR–EULAR rheumatoid arthritis classification criteria within the first year of follow-up.[13,14]

When defining specificity, individuals at risk of, but have not yet developed rheumatoid arthritis can also be considered as a reference population. Therefore, we evaluated the MRI-scans of patients presenting with undifferentiated arthritis and clinically suspect arthralgia who have not progressed to rheumatoid arthritis.

Patients in the EAC presenting with recent-onset arthritis who did not fulfil the 1987 ACR or 2010 ACR–EULAR rheumatoid arthritis classification criteria and had no other classified diagnosis within 1-year follow-up, were considered as undifferentiated arthritis non-progressors. MRI was added to the EAC study protocol from Aug 24, 2010 until March 9, 2020. Consecutively included patients with rheumatoid arthritis and undifferentiated arthritis that had not progressed to rheumatoid arthritis are included in this study.

Patients with clinically suspect arthralgia were from the CSA cohort, a population-based inception cohort that was initiated in April, 2012 at the rheumatology outpatient clinic in Leiden, Netherlands. Patients with recent-onset (<1 year) arthralgia of the small joints that due to the nature of the symptoms was considered suspicious to progress to arthritis over time by the rheumatologist were recruited to this cohort. Patients were excluded if clinical arthritis was present at physical examination or when the arthralgia was better explained by another diagnosis such as osteoarthritis or fibromyalgia, as other explanations preclude the presence of clinically suspect arthralgia. The CSA cohort has been extensively described previously.[15] Follow-up ended when a patient with clinically suspect arthralgia developed clinically apparent inflammatory arthritis. For this study, we included patients with clinically suspect arthralgia and who did not develop clinically apparent inflammatory arthritis during a 2-year follow-up. These patients were considered as clinically suspect arthralgia non-converters.

Healthy volunteers were recruited from local newspapers and the hospital website, as previously described.[10,11] Participants were included if they were aged 18 years or older, had no history of rheumatoid arthritis or other inflammatory rheumatic diseases, no joint symptoms during the previous month, and no clinically detectable arthritis at physical joint examination. Exclusion criteria included clinically detectable arthritis at physical joint examination and a history of inflammatory arthritis. Screening for inclusion and exclusion criteria took place by phone, followed by a subsequent visit at the rheumatology outpatient clinic at Leiden University Medical Centre. Here, information was collected including age, sex, dominant hand, smoking history, comorbidities, and medical history. Physical examination of the hands and feet was done by a rheumatologist to exclude presence of arthritis. Asymptomatic Heberden or Bouchard nodes or hallux valgus were evaluated and noted. Participants with these stigmata in the absence of joint symptoms were not excluded to prevent selection bias. It was reasoned that osteoarthritis is associated with joint symptoms and that individuals who show signs without causing symptoms do not have disease, and these processes might be related to ageing or age-related degeneration. Participants received a €20 voucher after the second visit as compensation for their time and travel costs.

	Rheumatoid arthritis (n=516)	Undifferentiated arthritis non-progressors (n=305)	Clinically suspect arthralgia non-converters (n=598)	Healthy controls (n=193)
Age, years	59 (14)	54 (15)	43 (13)	50 (16)
Sex				
Female	330 (64%)	163 (53%)	460 (77%)	136 (70%)
Male	186 (36%)	142 (47%)	138 (23%)	57 (30%)
Ethnicity*				
African	0/443	1/256 (<1%)	2/461 (<1%)	NA
Asian	8/443 (2%)	5/256 (2%)	0/461	NA
Hindustani	6/443 (1%)	2/256 (1%)	2/461 (<1%)	NA
Moroccan	0/443	2/256 (1%)	8/461 (2%)	NA
Multi-ethnic	4/443 (1%)	0/256	3/461 (1%)	NA
Turkish	1/443 (<1%)	0/256	5/461 (1%)	NA
White	418/443 (94%)	246/256 (96%)	441/461 (96%)	NA
Symptom duration, weeks	11 (6–28)	8 (4–22)	104 (112–136)	NA
66 swollen joint count	5 (2-10)	2 (1–3)	NA	NA
68 tender joint count	8 (4-13)	2 (1–4)	5 (2–10)	NA
Rheumatoid factor-positivity	278 (54%)	11 (4%)	78 (13%)	NA
ACPA-positivity	235 (46%)	4 (1%)	41 (7%)	NA
VAS general health	43 (25)	34 (22)	36 (24)	NA
Physical functioning (HAQ-DI)	1·0 (0·5–1·5)	0·5 (0·1–1·0)	0·5 (0·3–0·9)	NA

Data presented are n (%), n/N (%) if missing data, mean (SD), or median (IQR). ACPA=anti-citrullinated protein antibodies. HAQ-DI=Health Assessment Questionnaire Disability Index. NA=not applicable. VAS=visual analogue scale. *Ethnicity was self-reported and not collected for healthy controls.

Table: **Baseline characteristics**

The local medical ethics committee approved each study (Commisie Medische Ethiek B19.008 and P11.210). All participants provided written informed consent. Patient partners were involved in the design of the EAC and CSA cohorts and were informed on study results.

Procedures

All cohorts used the same MRI machine and protocol throughout the study periods (1·5 Tesla extremity-MRI, GE Healthcare, Madison, WI, USA). At the baseline visit of each cohort, unilateral MRI of the second to fifth metacarpophalangeal, wrist, and first to fifth metatarsophalangeal joints of the most painful side or dominant side (in case of symmetrical symptoms or for healthy controls) was done. After enrolment into the study, MRI was done within a mean of 7 days in the EAC and CSA cohorts. Patients were asked not to use non-steroidal anti-inflammatory drugs during 24 h before the MRI. Further details on the MRI protocol are described in the appendix (pp 4–5).

Synovitis and osteitis were evaluated according to the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) Rheumatoid Arthritis MRI Scoring system (RAMRIS).[16] Tenosynovitis was evaluated according to Haavardsholm and colleagues.[17] Each site was evaluated by grade (0, 1, 2, or 3) of synovitis, tenosynovitis, and osteitis based on the severity of inflammation. We assessed intermetatarsal bursitis because the intermetatarsal bursae have a synovial lining similar to those of synovial joints. All MRIs were scored by two readers independently of each other and who were blinded for clinical data. Scoring of RAMRIS inflammation was done by trained medical doctors. Inter-reader intraclass correlation coefficients (ICC) were greater than 0·91. Scoring of inflammation of the intermetatarsal bursae (intermetatarsal bursitis) is not part of RAMRIS and so was done by a musculoskeletal radiologist with more than 20 years of experience and a trained medical doctor with more than 2 years of experience in RAMRIS scoring (inter-reader ICC was 0·90), as described previously.[18] An overview of the inter-reader reliability of each pair of readers is shown in the appendix (p 6). Grade 1 inflammation was present if both readers scored 1 or more. If only one reader scored 1 and the other 0, grade 1 inflammation was considered to be absent. If both readers scored inflammation but with a discrepancy in its grade, then the lower grade was used for analysis (eg, one reader scored grade 2, and the other grade 3, then grade 2 was used). Missing values on MRI evaluation due to impossible scoring were generally low (<5%) and often explained by fat-suppression issues. Further details on MRI scoring are described in appendix pp 5–6.

See Online for appendix

The joints, bones, and tendon sheaths that were assessed are schematically depicted in the appendix (p 8). The wrist bones included were distal radius, distal ulna, scaphoid, lunate, triquetrum, pisiform, hamate, capitate, trapezoid, trapezium, and first to fifth metacarpal bases. Of the bones of the second to fifth

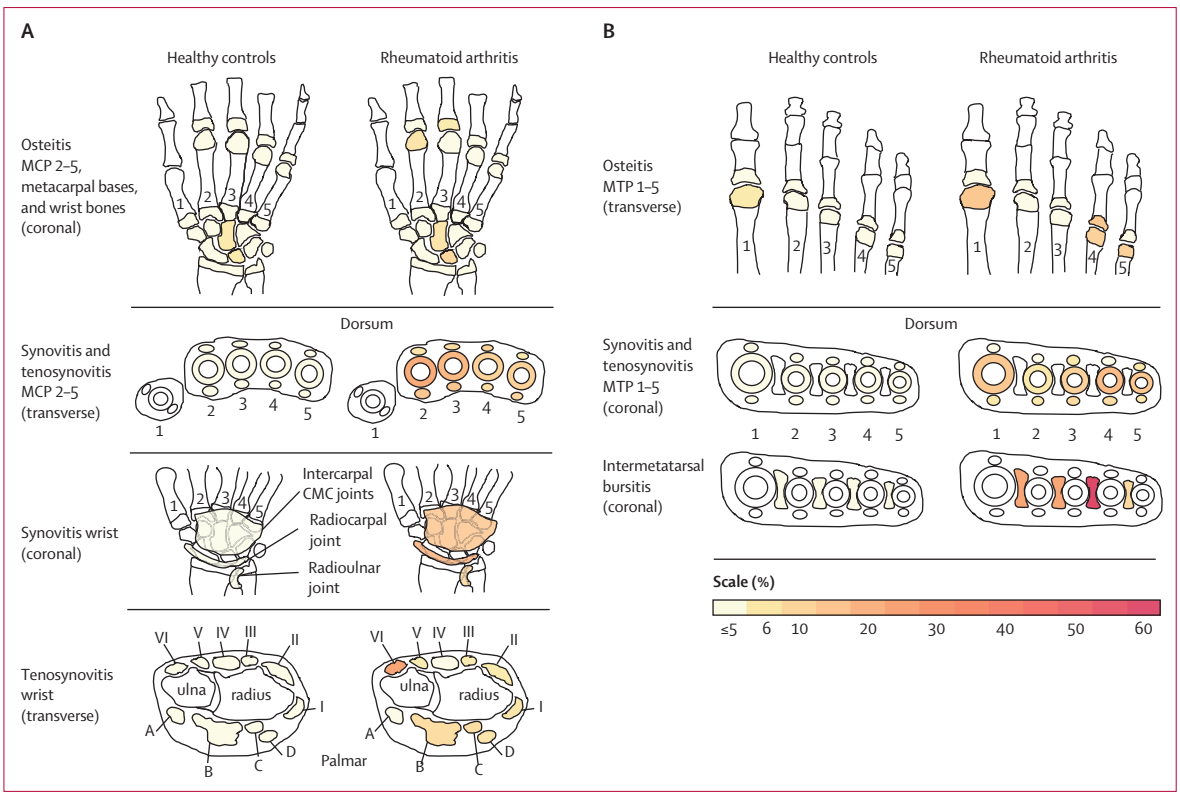

Figure 1: **Prevalence of healthy controls and patients with rheumatoid arthritis younger than 40 years with grade 1 MRI-detected signal intensities**
Prevalence (%) of healthy controls (n=51) and patients with rheumatoid arthritis (n=55) younger than 40 years with grade 1 MRI-detected signal intensities in the hand, wrist (A) and forefoot (B). All frequencies of 5% or less are light yellow, and frequencies of more than 5% are in darker shades. MCP=metacarpophalangeal. MTP=metatarsophalangeal. CMC=carpometacarpal. 1–5 represent first–fifth MCP or MTP joints. I–VI represent wrist extensor compartments. A–D represent wrist flexor compartments. n/N (%) are in the appendix (p 9).

metacarpophalangeal joints these included the heads of the metacarpals and the bases of the proximal phalanges. Of the bones of the first to fifth metatarsophalangeal joints these included the heads of the metatarsals and bases of proximal phalanges. The wrist joint included the distal radioulnar joint, the radiocarpal joint, and the intercarpal-carpometacarpal joints.

Outcomes

To identify less-specific lesions for rheumatoid arthritis with increased signal intensity, we assessed inflammatory findings that were also relatively frequent in the reference populations. For this, we used a cut-off of greater than 5% per feature, which is a commonly used cut-off in laboratory tests such as ESR.[8] This equals a threshold of 95% specificity for each joint, bone, and tendon sheath. Since increased signal intensities are correlated with age, we did all comparisons by the following age-strata, thereby obtaining age-specific cut-offs for people aged <40, 40–59, and ≥60 years.[10] The phrase less specific for rheumatoid arthritis was considered preferable compared with nonspecific or aspecific for rheumatoid arthritis, as terminology and interpretation could depend on the threshold that is taken (in our case 5%, but not 0%).

Statistical analysis

Frequencies at the joint level were calculated and Clopper–Pearson exact binomial 95% CIs were reported to measure accuracy. Frequencies of each reference group were compared with frequencies of rheumatoid arthritis, yielding prevalence ratios, and heatmaps were constructed. Findings scored as grade 2 or 3 were evaluated separately as the heatmaps would depict the frequencies of each grade (and not all grades together). However, grade 2 occurred rarely and therefore no heatmaps were generated for this grade. After assessing the frequencies of less-specific lesions, we evaluated the number of less-specific findings on MRI per healthy control within each age-stratum. SPSS version 29.0 was used.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

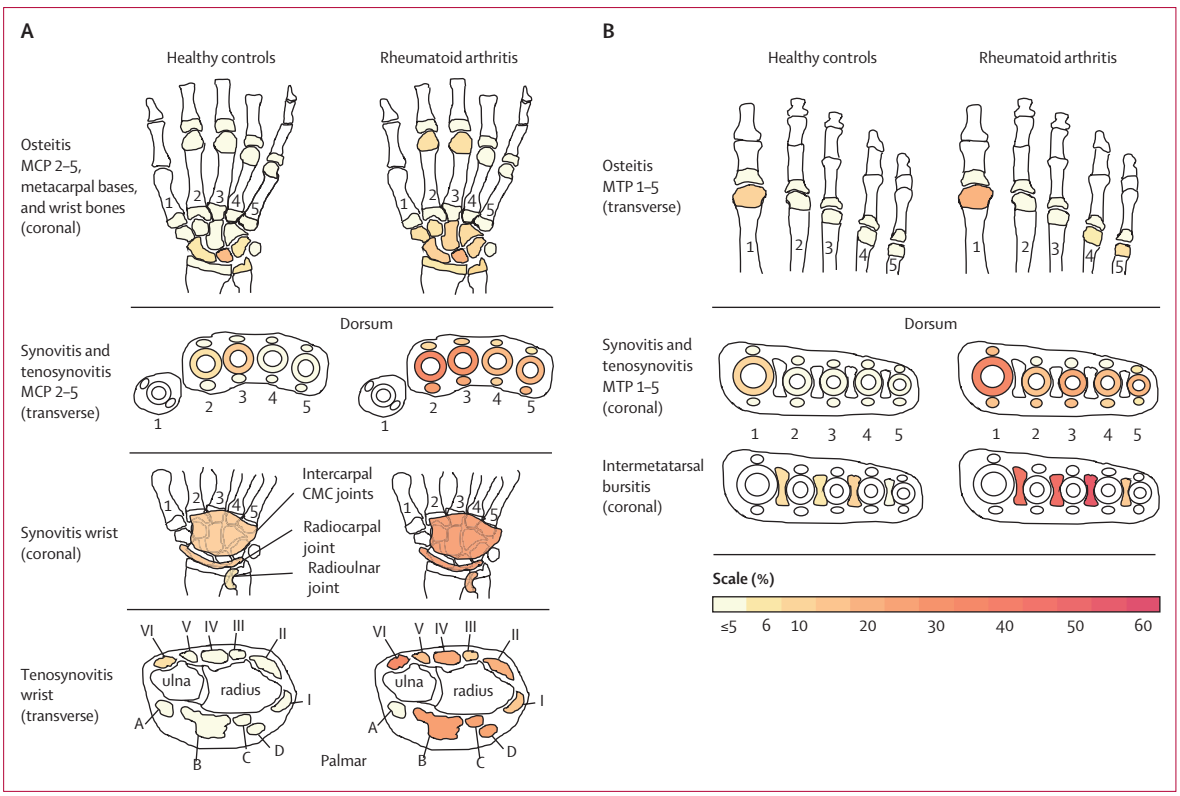

Figure 2: **Prevalence of healthy controls and patients with rheumatoid arthritis aged 40–59 years with grade 1 MRI-detected signal intensities**
Prevalence (%) of healthy controls (n=90) and patients with rheumatoid arthritis (n=194) aged 40–59 years with grade 1 MRI-detected signal intensities in the hand, wrist (A) the forefoot (B). All frequencies of 5% or less are light yellow, and frequencies of more than 5% in darker shades. MCP=metacarpophalangeal. MTP=metatarsophalangeal. CMC=carpometacarpal. 1–5 represent first-fifth MCP or MTP joints. I–VI represent wrist extensor compartments. A–D represent wrist flexor compartments. n/N (%) are in the appendix (p 10).

Results

Between Aug 24, 2010, and March 9, 2020, 1692 consecutive patients were enrolled in the EAC cohort, 1178 (70%) of whom had valid MRI data (appendix p 2). At baseline, 445 (38%) of 1178 patients had rheumatoid arthritis and 408 (35%) had undifferentiated arthritis. At 1 year, 516 (44%) patients had rheumatoid arthritis, 305 (26%) were undifferentiated arthritis non-converters (ie, had undifferentiated arthritis), and 357 (30%) had other diagnoses. 330 (64%) of 516 patients with rheumatoid arthritis were female and 186 (36%) were male, 418 (94%) of 443 were White, and the mean age was 59 years (SD 14; table). Of the 305 patients with undifferentiated arthritis (ie, undifferentiated arthritis non-progressors), 163 (53%) were female and 142 (47%) were male, 246 (96%) of 256 were White, and the mean age was 54 years (SD 15; table).

Between April 3, 2012, and April 29, 2021, 774 consecutive patients with clinically suspect arthralgia were enrolled in the CSA cohort, of whom 723 (93%) underwent MRI (appendix p 3). At 2 years, 598 (77%) of 774 patients were clinically suspect arthralgia non-converters and selected as the reference group (ie, had clinically suspect arthralgia). 460 (77%) of 598 patients with clinically suspect arthralgia were female and 138 (23%) were male, 441 (96%) of 461 were White, and the mean age was 43 years (SD 13; table). In addition, 193 healthy volunteers were recruited between Nov 15, 2013, and Dec 2, 2014, of whom 136 (70%) were female and 57 (30%) were male, and the mean age was 50 years (SD 16; table). No data on ethnicity were collected for the healthy controls.

Grade 2 and 3 synovitis, tenosynovitis, or osteitis did not occur in more than 5% of healthy controls (of all ages). Therefore, we continued studying grade 1 inflammation in healthy controls per age category and compared this with patients with rheumatoid arthritis.

In participants younger than 40 years, lunate, capitate, and first metatarsal phalanx osteitis occurred in three (6%) of 51 healthy controls and these frequencies were similar in patients with rheumatoid arthritis (n=55; prevalence ratios: 1·2 [95% CI 0·3–5·3] to 2·7 [0·7–10·4]; figure 1 and appendix p 9). Synovitis, tenosynovitis, and intermetatarsal bursitis were infrequent in healthy controls at all locations (<5%).

In participants aged 40–59 years, synovitis was present at the second metacarpophalangeal joint in seven (8%) of 90 healthy controls, the third metacarpophalangeal joint in 13 (14%), the radioulnar joint in seven (8%), the

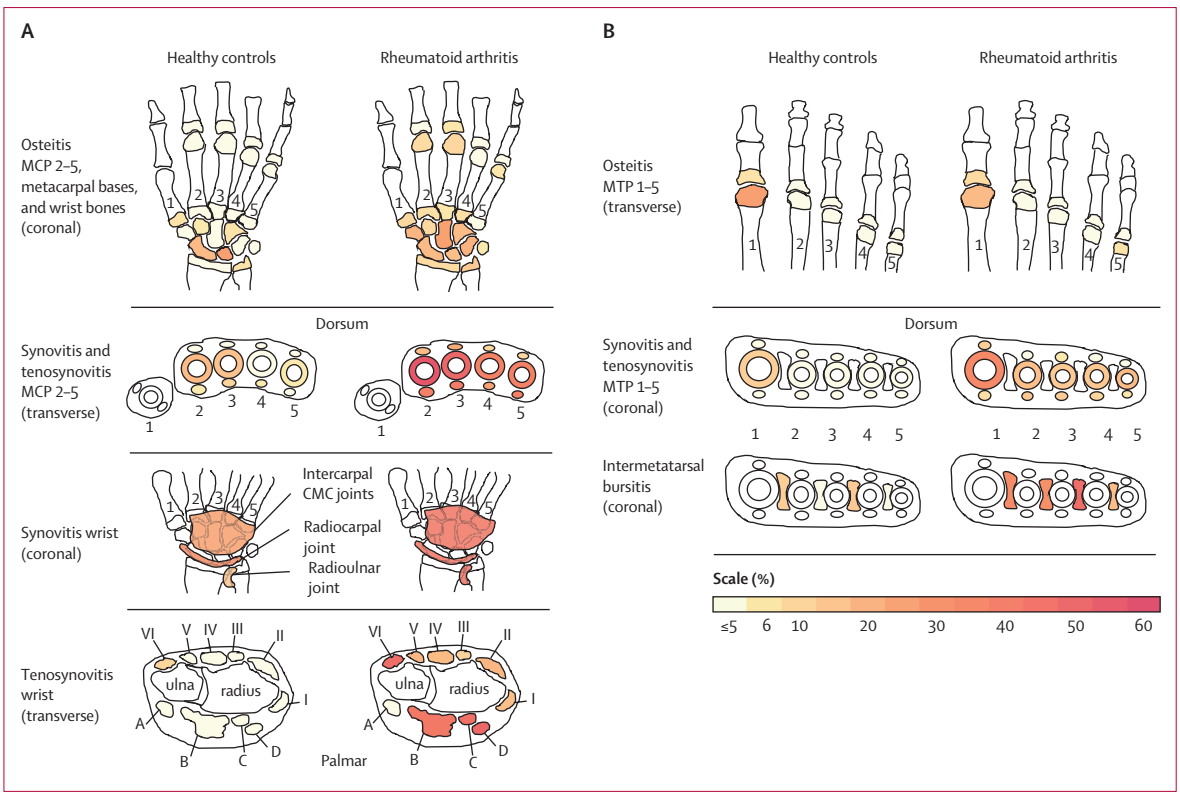

Figure 3: **Prevalence of healthy controls and patients with rheumatoid arthritis older than 60 years with grade 1 MRI-detected signal intensities**
Prevalence (%) of healthy controls (n=52) and patients with rheumatoid arthritis (n=267) older than 60 years with grade 1 MRI-detected signal intensities in the hand, wrist (A) the forefoot (B). All frequencies of 5% or less are light yellow, and frequencies of more than 5% in darker shades. MCP=metacarpophalangeal. MTP=metatarsophalangeal. CMC=carpometacarpal. 1–5 represent first-fifth MCP or MTP joints. I–VI represent wrist extensor compartments. A–D represent wrist flexor compartments. n/N (%) are in the appendix (p 11).

radiocarpal joint in 15 (17%), the intercarpal-carpometacarpal joint in 14 (16%), and the first metatarsophalangeal joint in ten (11%) (figure 2). In patients with rheumatoid arthritis (n=194), synovitis was also frequently present at these locations, however, with prevalence ratios of 1·8 (95% CI 1·1–3·0) to 4·5 (2·2–9·4; figure 2 and appendix p 10).

Tenosynovitis was present in the wrist at extensor compartment VI (extensor carpi ulnaris) in eight (9%) of 90 healthy controls aged 40–59 years (figure 2) and was also frequently found in patients with rheumatoid arthritis (prevalence ratio 3·8 [95% CI 1·9–7·6]).

Osteitis was present at the triquetrum in five (6%), lunate in 17 (19%), scaphoid in six (7%), distal ulna in six (7%), and first metatarsal head in 11 (12%) in 90 healthy controls aged 40–59 years (figure 2). Osteitis was present in patients with rheumatoid arthritis at the same locations in prevalence ratios of 1·1 (95% CI 0·7–1·9) to 1·9 (0·8–5·0; figure 2 and appendix p 10). Intermetatarsal bursitis was found in the first intermetatarsal spaces in eight (9%), in the second intermetatarsal spaces in six (7%), and in the third intermetatarsal spaces in 11 (12%) of 90 healthy controls aged 40–59 years (figure 2). Intermetatarsal bursitis was present in patients with rheumatoid arthritis at the same locations, however, in prevalence ratios of 4·3 (95% CI 2·4–7·7) to 6·6 (2·9–14·8); figure 2 and appendix p 10).

In participants aged 60 years or older, synovitis was present at the second metacarpophalangeal joint in ten (19%) of 52 healthy controls, the third metacarpophalangeal joint in nine (17%), the fifth metacarpophalangeal joint in three (6%), the radioulnar joint in nine (17%), the radiocarpal joint in 18 (35%), the intercarpal-carpometacarpal joint in 14 (27%), and the first metatarsophalangeal joint in seven (14%; figure 3). Synovitis was present at the same locations in patients with rheumatoid arthritis (n=267) in prevalence ratios of 1·2 (95% CI 0·8–1·9) to 6·6 (2·2–20; figure 3 and appendix p 11).

Tenosynovitis was present at the extensor carpi ulnaris in six (12%), the metacarpophalangeal flexor 3 in six (12%), and in three (6%) of both flexor 2 and flexor 4 in 52 healthy controls (figure 3). Patients with rheumatoid also had tenosynovitis at these locations; this occurred between 3·5 (95% CI 1·6–7·5) and 6·6 (2·2–20·1; figure 3 and appendix p 11).

Osteitis was present at the base of the first metacarpal phalanx, first proximal phalanx of the foot, distal ulna,

and hamate in four (8%) of 52 healthy controls. Osteitis was present in the trapezoid in three (6%), scaphoid in ten (19%), lunate in 14 (27%), and first metatarsal phalanx in 14 (27%) of 52 healthy controls (figure 3 and appendix p 11). Osteitis was also present in these locations in patients with rheumatoid arthritis in prevalence ratios of 0·7 (95% CI 0·4–1·1) to 2·4 (0·9–6·4; figure 3 and appendix p 11).

Intermetatarsal bursitis was present at the first intermetatarsal space in seven (14%) and at the third intermetatarsal space in eight (15%) of 52 healthy controls (figure 3). Patients with rheumatoid arthritis also had intermetatarsal bursitis at these locations, but occurred more regularly with prevalence ratios between 2·5 (95% CI 1·2–5·2) and 2·9 (1·5–5·7; figure 3 and appendix p 11).

We next studied the two at-risk groups who have not developed rheumatoid arthritis. Locations of grade 1 inflammation at baseline in patients with clinically suspect arthralgia who have not developed rheumatoid arthritis (ie, clinically suspect arthralgia non-converters) are shown in the appendix (pp 12–17). In clinically suspect arthralgia non-converters, grade 2 and grade 3 inflammation did not occur.

Patients with undifferentiated arthritis who have not developed rheumatoid arthritis (ie, undifferentiated arthritis non-progressors) more frequently showed inflammation in more than 5% of individuals compared with the other reference populations. Locations of grade 1 inflammation that did not occur in healthy controls were as follows: tenosynovitis at the third metacarpophalangeal joint extensor, wrist extensors, and flexors (appendix pp 18–23). Additionally, several locations in 123 patients with undifferentiated arthritis aged 60 years or older showed grade 2 inflammation: osteitis of triquetrum in eight (7%) individuals, synovitis of the second metacarpophalangeal joint in nine (7%), the third metacarpophalangeal joint in ten (8%), radioulnar joint in 15 (12%), radiocarpal joint in 28 (23%), and intercarpal-carpometacarpal joint in 20 (16%).

Finally, we studied the number of less-specific features within each healthy control (figure 4). Of the healthy controls younger than 40 years, 42 (82%) of 51 did not have a less-specific finding, and none showed more than one such lesion. Of the healthy controls aged 40–59 years, 36 (40%) of 90 had more than one less-specific finding and the median number of less-specific findings was 1 (IQR 1–3). In healthy controls aged 60 years or older, 37 (71%) of 52 had more than one less-specific finding and the median number of less-specific findings was 3 [IQR 1–5]. Hence, the number of less-specific locations in healthy controls also increased with age.

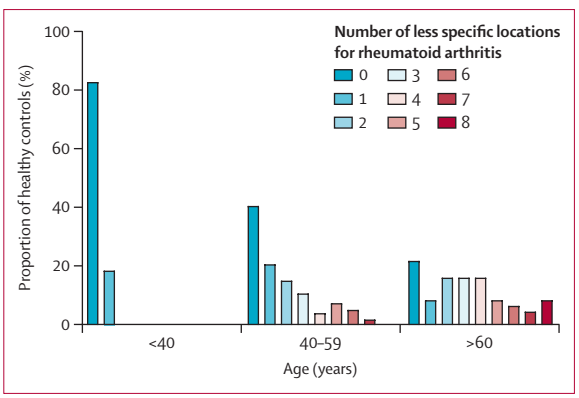

Figure 4: **Number of less specific locations for rheumatoid arthritis at the person-level within each age-category**
Bars represent the proportion (%) of healthy controls with a corresponding total number of grade 1 less specific locations on MRI.

Discussion

In this imaging study, we found that several MRI-detected locations with low-grade synovitis, tenosynovitis, osteitis, and intermetatarsal bursitis can be considered less specific for rheumatoid arthritis since they also occur in healthy controls, and patients with clinically suspect arthralgia, and undifferentiated arthritis who have not developed rheumatoid arthritis, and appear to increase with age. To our knowledge, this study is the first to directly compare MRI findings of healthy controls and patients with rheumatoid arthritis, and to include other at-risk groups without rheumatoid arthritis as a reference, thereby providing a clear overview of MRI-detected (subclinical) joint inflammation that is less specific for rheumatoid arthritis.

Although the healthy population is the most stringent reference in terms of defining specificity, the expectation that MRIs of healthy controls would show nothing was not true; more MRI abnormalities were visible with increasing age. MRIs do not inform about the nature of increased signal intensity. Our interpretation is that different factors might play a role. First, some findings occurred across most age-strata (eg, lunate and scaphoid osteitis and synovitis in the first metatarsophalangeal joint) and occurred as often in patients with rheumatoid arthritis (prevalence ratio close to 1 or below 1). Hence, these findings can be considered nonspecific for rheumatoid arthritis. Second, some signal intensity occurred with increasing age at locations that are known predilection places for degeneration, such as the first carpometacarpal joint. Finally, some inflammation was present in healthy controls at locations that are known to be often inflamed in patients with rheumatoid arthritis (eg, wrist, second metacarpophalangeal joint, and third metacarpophalangeal joint). These locations are possibly prone to some subtle inflammation whereby homeostasis (eg, balance between tissue microdamage and repair) is maintained in the healthy setting, but this homeostasis is lost in rheumatoid arthritis. Hypothetically, local triggers such as mechanical stress could disrupt the local homeostasis between microtrauma and repair mechanisms at increasing age, which could contribute to

disease development.[19] It is interesting to further investigate this hypothesis of insufficient repair as part of rheumatoid arthritis pathophysiology.

These data are of importance for rheumatologists or radiologists who evaluate MRI in the setting of early recognition of (imminent) rheumatoid arthritis to prevent overinterpretation. Reducing false positive findings has become of extra importance since prevention trials in patients with arthralgia who are at-risk for rheumatoid arthritis showed beneficial effects of DMARD-treatment in patients with arthralgia and subclinical joint inflammation.[5,6] Previous studies by our research group studied the value of MRI in clinically suspect arthralgia and undifferentiated arthritis by including a reference to normality when defining an abnormal (positive) MRI,[5,20–23] and showed that this increases the specificity of MRI in clinically suspect arthralgia and undifferentiated arthritis, without decreasing the sensitivity of MRI.[11] This latter study was longitudinal in nature, assessed the value of MRI findings for future rheumatoid arthritis development, and provided test characteristics on the patient level. The current study is cross-sectional in nature and compared patients with rheumatoid arthritis with healthy controls, patients with clinically-suspect arthralgia, and patients with undifferentiated arthritis that did not progress to rheumatoid arthritis at tissue and location level. Therefore, this overview contributes to improved location-level interpretation of MRI findings and reducing overdiagnosis when MRI is used.

Furthermore, findings at the group level might not always apply to individual patients. For example, when a 65-year-old woman has symptoms of the third metacarpophalangeal joint and synovitis is observed on MRI, it is possible that the synovitis is pathological. Though if this is the only MRI-detected inflammatory feature present, clinicians should be aware that this is also quite common in the general population and that this might not be highly specific for rheumatoid arthritis. Even if there is increased signal intensity at several places it can be normal. A reference to age-matched and location-matched reference values is needed to obtain MRI results with higher specificity. An estimation of location-specific specificities per MRI inflammatory features can be deduced using the data from the figures in this study of the reference groups by subtracting the proportion of that feature at that location from 100%. However, if an individual shows a combination of normal and abnormal findings, a combined evaluation is needed to determine how specific these are. This could be more challenging compared with defining a cutoff for laboratory tests with numerical values such as ESR.

Importantly, the observations of less-specific inflammation apply to grade 1 inflammation; grade 2 inflammation did not occur in healthy controls or clinically suspect arthralgia non-converters and could therefore be regarded as rheumatoid arthritis-specific. Grade 2 did occur in undifferentiated arthritis non-progressors who did not develop rheumatoid arthritis within 1 year follow-up, though these patients have clinical arthritis too. Previous studies showed that most patients with clinically-suspect arthralgia and undifferentiated arthritis who convert do so during the first year of follow-up, thereby confirming that it is highly unlikely that the reference populations studied contained patients with rheumatoid arthritis.[24] It is known that only a proportion of patients with undifferentiated arthritis develop rheumatoid arthritis, and a large proportion remain unclassified.[25] These patients do have an inflammatory autoimmune disease and are a different reference group than healthy controls or clinically suspect arthralgia non-converters (without or with subclinical joint inflammation).

This study also had some limitations. First, although contrast-enhanced MRI is recommended by the OMERACT MRI in Arthritis Working Group, these findings cannot be generalised to MRI protocols without contrast-enhancement. Fluid-sensitive MRI sequences that do not require contrast, like the modified Dixon, were recently developed.[26] A reference of normality should be developed for such sequences. Second, we focussed on findings with a prevalence of more than 5%, which is in line with 95% specificity, a cutoff that is often used for defining abnormal (positive) laboratory tests. However, if another cutoff, such as 10%, had been chosen, less findings could be considered as less specific for rheumatoid arthritis (findings that are considered as less specific can be deduced from figures 1–3 and from appendix pp 9–23). Third, there was very minimal data about MRI findings in the healthy population before this study was done and an age-effect was not hypothesised. As such, the sample size calculation was not done for the three age strata; this might have led to imprecision in determining whether the prevalence of an abnormality is truly below or above 5%. Larger studies on healthy controls are required for a higher level of precision. Finally, grading has been done according to the RAMRIS method, which is validated for research purposes but was not derived for use in clinical practice. Whether an alternative scoring system that incorporates age-specific and location-specific weights of MRI findings would improve specificity or feasibility of MRI in clinical practice is subject to future studies.

A major strength of this study is the large number of MRIs of healthy and at-risk individuals who did not develop rheumatoid arthritis that were compared to findings done at rheumatoid arthritis diagnosis in different age-categories.

In summary, this study comprised hand, wrist, and forefoot MRIs of more than 1600 individuals. The value of MRI is related to its high sensitivity in detecting joint inflammation; it can detect inflammation even before it is detectible with physical joint examination. Furthermore, the type of inflamed tissue can be

appreciated on MRI. Previous studies showed that tenosynovitis is a strong predictor for rheumatoid arthritis development in patients with clinically suspect arthralgia and undifferentiated arthritis, and osteitis is a strong predictor for development of bone erosions in patients with rheumatoid arthritis.[25,27–29] Although synovitis is generally considered a hallmark of rheumatoid arthritis, synovitis at MRI was also regularly present in the reference populations studied here.[30] In conclusion, not all MRI findings are highly specific for rheumatoid arthritis, as these data show. Assuming that MRI will be increasingly used in research and clinical practice in the future, we believe that this study can contribute to reducing overinterpretation of MRI findings, so that MRI will not only have a high sensitivity but also a high specificity.

Contributors

All authors contributed to the conception and study design. NKdH contributed to data collection. DAT analysed the data. All authors contributed to the interpretation of the data. DAT wrote the first version of the manuscript, HWvS and AHMvdH-vM revised it critically. All authors read and approved the final submitted manuscript. All authors had full access to all the data and all authors had final responsibility in the decision to submit the manuscript for publication. DAT and AHMvdH-vM directly assessed and verified the underlying data.

Declaration of interests

We declare no competing interests.

Data sharing

Data are available upon reasonable request to the corresponding author.

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