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ORIGINAL RESEARCH

Hand function is already reduced before RA development and reflects subclinical tenosynovitis

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ABSTRACT

Background Clinically suspect arthralgia (CSA) is characterised by arthralgia of small joints and considered a risk stage for development of rheumatoid arthritis (RA). However, it remains unknown if the function of the hands is already affected and what mechanisms underlie impaired hand-function in CSA.

Methods We studied various measures of hand function in two CSA populations. CSA patients in the TREAT EARLIER-trial (n=236) were evaluated at baseline for: grip strength on a dynamometer (GS), patient-reported difficulties in the grip domain of the Health Assessment Questionnaire (HAQ) questionnaire and incomplete fist closure at physical examination. Findings were validated in an independent CSA cohort (n=600) where hand function was measured as: GS evaluated by squeezing the examiner's fingers, grip domain of the HAQ questionnaire and fist closure. Contrast-enhanced MRI of the hands measured synovitis, tenosynovitis and bone marrow oedema (summed as subclinical inflammation) in both cohorts.

Results GS (on a dynamometer) was reduced in 75% compared with reference values in healthy controls, 60% reported grip difficulties and 13% had incomplete fist closure. Reduced GS was associated with subclinical inflammation (−0.38 kg/point inflammation, 95% CI −0.68 to −0.08). Studying separate MRI features, GS reduction was independently associated with tenosynovitis, decreasing with −2.63 kg (95% CI −2.26 to −0.33)/point tenosynovitis (range observed tenosynovitis scores: 0–20). Similar relations with tenosynovitis were seen for patient-reported grip difficulties (OR 1.12/point, 95% CI 1.07 to 1.42) and incomplete fist closure (OR 1.36/point, 95% CI 1.03 to 1.79). In the validation cohort, 36% had decreased examiner-assessed GS, 51% reported grip difficulties and 14% incomplete fist closure: all were associated with tenosynovitis. Decreased dynamometer-measured GS was most sensitive for detecting tenosynovitis (75%), while incomplete fist closure was most specific (88%–90%).

Conclusion Hand function is already often affected before RA development. These limitations are related to subclinical inflammation and tenosynovitis in particular.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with clinically suspect arthralgia (CSA), who are at risk of developing rheumatoid arthritis (RA), often have hand symptoms.
⇒ It is unknown to what extent the function of the hands is affected in CSA patients, whether that would reflect underlying subclinical inflammation, and if it can be of value in clinical practice.

WHAT THIS STUDY ADDS

⇒ Hand function is already often affected in individuals at-risk of RA.
⇒ Reduced hand function reflects underlying subclinical inflammation, in particular subclinical tenosynovitis.
⇒ A dynamometer is most sensitive to measure this in clinical practice, while incomplete fist closure gives the clinician a high specificity for underlying tenosynovitis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study deepens our understanding of the already considerable burden of disease in CSA patients, and provides proof that subclinical joint involvement can have clinical consequences for hand function. Testing hand function in CSA patients could conveniently objectify early functional limitations in clinical practice.

INTRODUCTION

Rheumatoid arthritis (RA) is often preceded by an identifiable symptomatic phase with subclinical joint inflammation in the absence of clinical arthritis. In this phase of clinically suspected arthralgia (CSA), patients already have physical impairments, which can be as severe as at RA diagnosis.[1] These functional limitations already lead to work-related problems, and thus also have societal consequences.[2] However, the nature of functional disabilities and the underlying mechanisms in the CSA phase remains barely studied. Given the known large attribution of hand function to functional disability in established RA, hand function is likely to play an important

role in CSA.[3] In addition, previous research revealed that subclinical inflammation of the hand joints can already be present in the CSA phase.[4] Nevertheless, the prevalence of reduced function of the hands and the underlying mechanism remain elusive.

Multiple measurement modalities exist, assessing different aspects of hand function, such as grip strength (GS), range of motion of hand joints or impairments as perceived by patients themselves. GS is frequently measured using a dynamometer, especially in research setting, as this is a reliable and sensitive method.[5] Dynamometer-measured GS can also easily be analysed in comparison to age-specific/sex-specific reference-values in healthy controls.[6] In clinical practice, physicians often determine GS and range of motion by asking a patient to squeeze their fingers to and close their fist. Furthermore, functional disabilities of the hands as experienced by patients themselves can be measured with questionnaires.[7] Although hand function can be assessed in numerous ways, these measures described above are all easily measured in clinical practice, with limited need for additional equipment/time.

We studied these various hand function measures in two independent CSA populations where subclinical inflammation was sensitively measured with MRI. We hypothesised that different aspects of hand function, that is, grip strength, range of motion of hand joints and patient-reported impairments, are reduced in CSA, and that reduced hand function in this disease phase reflects subclinical joint inflammation. In addition, we evaluated which hand function measure can best be used in clinical practice to assess subclinical inflammation in a practical way.

METHODS

Study population

Two populations of CSA patients were studied (described in more detail in online supplemental methods p.2). In both, CSA was characterised by recent onset (<1 year) arthralgia of the small joints suspicious for progression to RA according to their rheumatologist, regardless of autoantibody status. Per definition, clinical arthritis or another explanation for the arthralgia was absent.

Our derivation cohort existed of the participants in the TREAT EARLIER trial that tested whether treatment in CSA patients with subclinical MRI inflammation (synovitis, tenosynovitis or bone marrow oedema (BME)) induced sustained disease modification.[8]

We validated our findings in the Leiden CSA cohort, a population-based inception-cohort of individuals consecutively presenting with CSA.[9] These patients also underwent an MRI, but in contrast to the TREAT EARLIER trial, presence of subclinical MRI inflammation was not necessary to participate.

Grip strength measures

In the derivation cohort, hand function was measured in three ways on inclusion (figure 1A). First, GS was measured

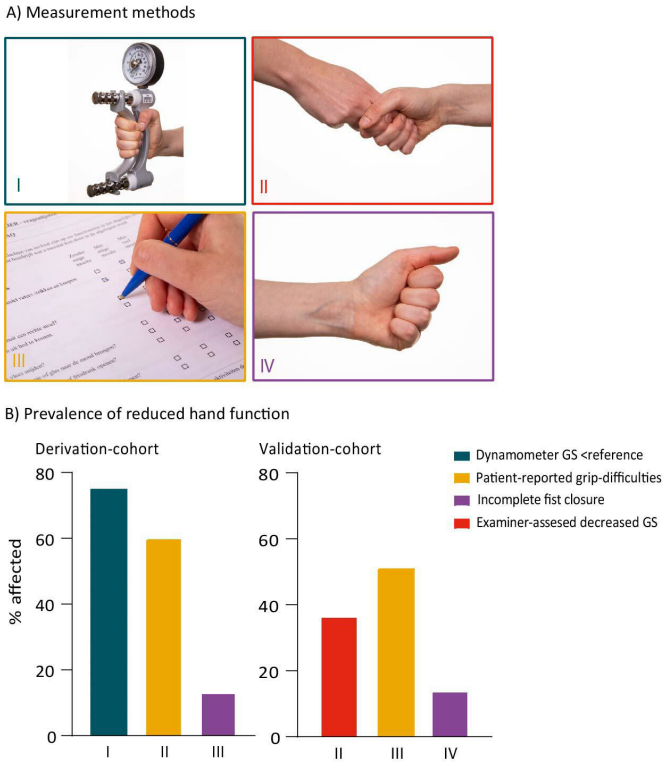

Figure 1 Assessment and prevalence of reduced hand function in the CSA phase. (A) Depicts the different measures of hand function used: I dynamometer-measured GS, II patient-reported grip difficulties in the HAQ grip domain, III fist closure, IV examiner-assessed GS. (B) Dynamometer-measured GS was compared with the mean GS in healthy individuals of the same age and sex as reported by Günther *et al*.[6] Patient-reported grip difficulties were defined as a score of 1 or higher (ie, individuals indicating some difficulty, much difficulty or unable to perform a task) in the HAQ grip domain. I, III and IV were assessed in the derivation cohort, II, III and IV in the validation cohort. GS, grip strength; HAQ, Health Assessment Questionnaire.

using a Jamar dynamometer (in kilograms (kg)). Patients squeezed the dynamometer 3 times per hand as hard as possible, alternating sides after each try. In this study, the highest GS of the strongest hand was used, which is less likely than the mean to be affected by the number of attempts.[10] Measurements were compared with mean reference values in healthy controls of Caucasian ethnicity per age and sex category, previously reported in literature.[6] Second, all patients filled in the Health Assessment Questionnaire Disability Index (HAQ). Out of the eight HAQ-domains, the grip domain (opening front door/jars/faucet, see also online supplemental files p.4) was chosen to measure patient-reported hand disabilities, because activities in this domain require the least locomotor activity of elbow/shoulder, lower extremities and trunk compared with other domains.[11] The presence of patient-reported grip difficulties was defined as any difficulty or inability to perform a task in the grip domain. Third, fistclosure (ability to actively close the fist with all fingertips touching the palm (yes/no)) was determined

on physical examination as an easily performed measure of range of motion of the hand joints.

In the validation cohort, patient-reported grip difficulties and fist closure were determined in the same way as in the derivation cohort. Instead of using a dynamometer, GS was assessed on inclusion by a patient squeezing the examiner's fingers and described as normal or decreased (figure 1A).

Assessment of subclinical joint inflammation

In both populations, a gadolinium-enhanced 1.5T-MRI of metacarpophalangeal and wrist of the most painful side, or the dominant side in case of symmetrically severe symptoms, was performed on inclusion.

Two independent, trained readers scored the MRIs, blinded to clinical data. MRIs were evaluated for BME, synovitis and tenosynovitis, in line with the OMERACT RA-MRI scoring system (RAMRIS). BME, synovitis and tenosynovitis were summed as total inflammation.

Since synovitis, tenosynovitis and BME may be seen on MRI to some extent in the general population, positivity for these features was determined as present <5% of age-matched symptom-free controls. The elaborate MRI (scoring) protocol can be found in online supplemental methods p.3.

Assessors of hand function and patients themselves were blinded to MRI-data.

Statistical analyses

Prevalence of reduced hand function was assessed, also after stratification for age and sex. In a cross-sectional design, linear or logistic regression (as appropriate), adjusted for age and sex, assessed associations of MRI-detected total inflammation and synovitis/tenosynovitis/BME separately with hand function (dependent variable). Diagnostic characteristics were determined for the presence of MRI-detected inflammation. Interobserver agreement was evaluated for examiner-assessed GS and fist closure. A sensitivity analysis on the different inclusion criteria between the derivation and validation cohort, assessed the prevalence of reduced hand function in the validation cohort after stratifying for the presence of MRI-detected inflammation. IBM SPSS V.25 was used. P values <0.05 were considered statistically significant.

RESULTS

A total of 236 CSA patients in the derivation cohort, and 600 CSA patients in the validation cohort were studied. Sixty-five per cent and 78% were women, median 68 tender joint count was 3 (IQR 1–9) and 5 (2-10), 33% and 22% were anti-citrullinated protein antibody (ACPA) positive and/or rheumatoid factor (RF) positive in the derivation and validation cohort, respectively (online supplemental table S1). The majority of participants reported a Caucasian ethnicity: 83% in the derivation and 94% in the validation cohort. Subclinical inflammation was present in all patients in the derivation cohort (since this was an inclusion criterium), and in 41% in the validation cohort.

Prevalence of reduced hand function

In the derivation cohort, GS was measured continuously using a dynamometer (figure 1B). Mean GS in CSA patients was 29.8 kg (SD 14.0). Across all age and sex categories, mean GS was lower than mean reference values from healthy controls (online supplemental figure S1). We then dichotomised GS using these reference values.[6] Seventy-five per cent (n=177) of patients had a GS below the reference. Fifty-six per cent (n=136) of patients had a GS of 1 SD or more below the reference (compared with 16% in the reference population), 30% (n=71) had a GS 2 SDs below the reference (compared with 2.5% in the reference population). Continuing with the other two hand function measures; 60% (n=137) of patients reported hand disability and 13% (n=31) was not able to close their fist completely (figure 1B, online supplemental table S2).

Stratification for sex revealed that women more often had reduced GS than men, after comparison with sex-matched and age-matched reference values.[6] Women also more often reported grip difficulties. Prevalence of incomplete fist closure was not clearly different between men and women (figure 2). Whereas GS in healthy controls is known to decreased with age (reference of 54 kg for <40 years, to 45 kg for >60 years), this age-related decline was not clearly seen in CSA patients, especially not in women (mean GS of 24 kg <40 years and 23 kg >60 years) (figure 2).[6] Similarly, grip difficulties and incomplete fist closure were prevalent in comparable proportions of patients in different age categories (figure 2A).

We then studied the prevalence of reduced hand function in the validation cohort. Here, 36% (n=214) had decreased examiner-assessed GS. The proportion of patients who reported grip difficulties (51% (n=269)) and who had incomplete fist closure (14% (n=80)) was comparable to the derivation cohort (figure 1), as well as results of age and sex stratification (figure 2B).

Associations with MRI detected subclinical joint inflammation

Next, we studied the associations between different hand-function assessments and subclinical joint inflammation, as sensitively detected by MRI. Total inflammation scores, which summed synovitis, tenosynovitis and BME, were observed to a maximum score of 42 points, BME to 21, synovitis to 19 and tenosynovitis to 20. Higher total inflammation scores were related to lower dynamometer-measured GS (−0.38 kg/point inflammation (95% CI −0.68 to −0.08)) and more grip difficulties (OR 1.12 (95% CI 1.04 to 1.20)) (table 1). We then studied the role of synovitis, tenosynovitis and BME separately. Synovitis and tenosynovitis were associated with dynamometer-measured GS in univariable analyses (online supplemental table S3). Multivariable analysis showed that individuals had a loss of −2.63 kg GS (95% CI −2.26 to −0.33)

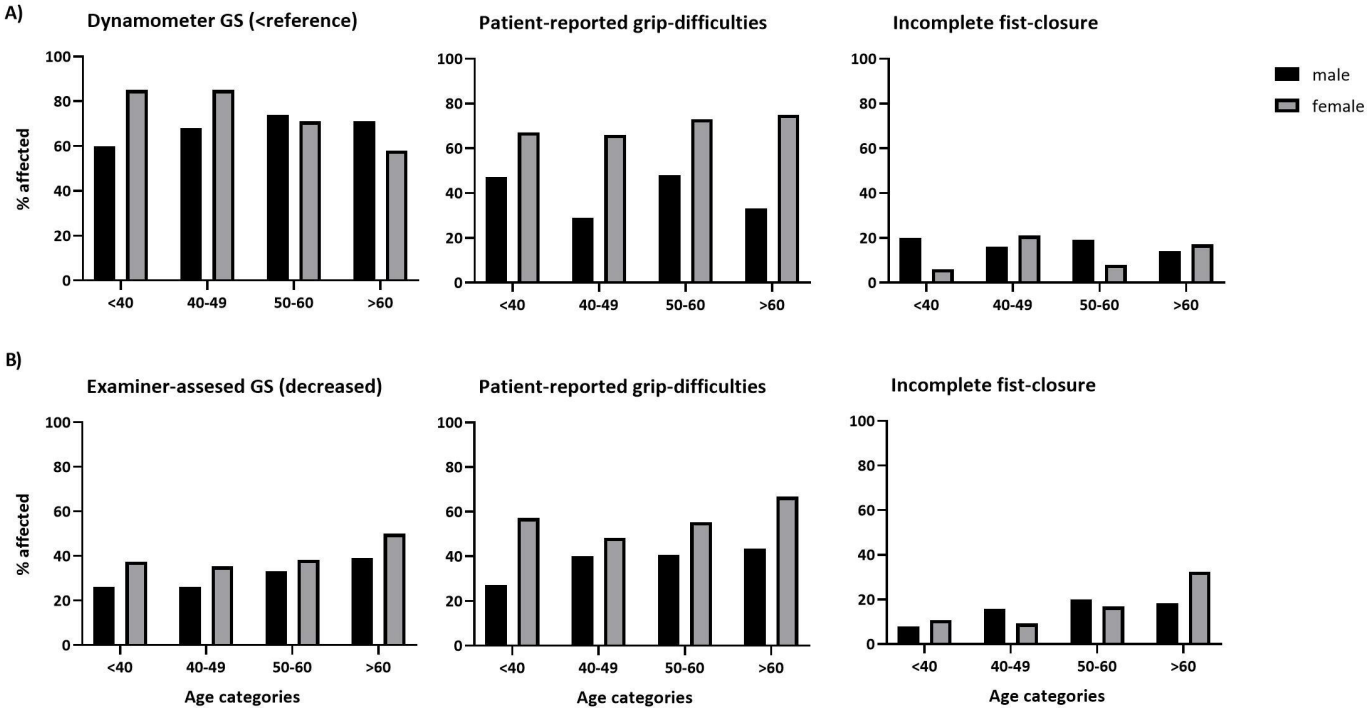

Figure 2 Age-stratified and sex-stratified prevalence of reduced hand function in the derivation cohort (A) and validation cohort (B). Dynamometer-measured GS was assessed with dynamometer (maximum of left or right hand) and dichotomised using reference values in healthy controls as reported by Günther *et al*.[6] Patient-reported grip difficulties were defined as a score of 1 or higher (ie, individuals indicating some difficulty, much difficulty or unable to perform a task) in the HAQ grip domain. Examiner-assessed GS was evaluated by squeezing the examiners fingers. GS, grip strength; HAQ, Health Assessment Questionnaire.

per point tenosynovitis when squeezing a dynamometer, independent of synovitis and BME. Likewise, tenosynovitis was independently associated (OR 1.12 (95% CI 1.07 to 1.40)) with grip difficulties in multivariable analysis. This was also found for incomplete fist closure (OR 1.36 (95% CI 1.03 to 1.79)) (table 1).

In the validation cohort, we found comparable associations between tenosynovitis and examiner-assessed GS (OR 1.20 (95% CI 1.02 to 1.40)), grip difficulties (OR 1.17 (95% CI 1.01 to 1.36)) and incomplete fist closure (OR 1.40 (95% CI 1.13 to 1.74)) (table 1).

With the mounting evidence on the predictive value of MRI-detected tenosynovitis for RA development in mind, and realising that hand function is more easily evaluated than performing an MRI, we evaluated diagnostic characteristics of the different hand function measures for the presence of subclinical tenosynovitis.[12] Dynamometer-measured GS below the reference had the highest sensitivity for the presence of tenosynovitis on MRI (75%). Thus, among the measures evaluated, the dynamometer missed the least patients with subclinical tenosynovitis. However, this was at the cost of low specificity (25%). This means that reduced dynamometer-measured GS is also often found in individuals without subclinical tenosynovitis. When using more strict thresholds for dynamometer-measured GS, we observed a classic trade-off between sensitivity and specificity: using >1 SD under the mean reference value as a threshold, specificity of GS increased to 44% (with sensitivity of 56%), for >2 SD under the mean specificity further increased to 71% (with a sensitivity of 31%). Incomplete fist had a high specificity (88%). However, this was accompanied by low sensitivity (14%) (table 1). The highest specificity was achieved when combining fist closure and a threshold of GS of 2SD under the reference value; specificity was 97% is both were positive (with a sensitivity of 11%).Finally, examiner-assessed GS and fist closure were assessed by different observers consecutively in a subset of patients in the validation cohort (n=315). Interobserver agreement (Cohen's kappa) was 0.31 for examiner-assessed GS and 0.59 for fist closure.

In a sensitivity analysis exploring the effect of different inclusion criteria between the derivation and validation cohort (ie, the obligation to have an MRI with more subclinical inflammation than 95% of symptom-free controls), we stratified the validation cohort in patients with and without subclinical inflammation on MRI, after adjusting for findings in symptom-free controls. We then found that reduced hand function was more prevalent in patients with subclinical inflammation on MRI, compared with patients without (online supplemental figure S2).

DISCUSSION

CSA patients are at-risk of RA development. It has been described that functional limitations in the CSA phase can be as severe as at RA diagnosis.[1] However, the nature and underlying explanation of these functional

Table 1 Associations between subclinical joint inflammation scores and hand function measures, and their diagnostic characteristics for the presence of tenosynovitis

(A) Derivation cohort			
Association with subclinical joint inflammation (semiquantitative score; per point)			
	Dynamometer-measured GS (in kg)	Patient-reported grip difficulties (OR)	Incomplete fist closure (OR)
Total inflammation score	−0.38 (−0.68 to −0.08)*	1.12 (1.04 to 1.20)*	0.98 (0.89 to 1.07)
Individual features (multivariable):			
Synovitis score	0.27 (−1.02 to 1.35)	1.15 (0.89 to 1.50)	0.67 (0.46 to 0.98)
Tenosynovitis score	−2.63 (−2.26 to −0.33)*	1.12 (1.07 to 1.40)*	1.36 (1.03 to 1.79)*
BME score	0.96 (−0.36 to 1.04)	1.03 (0.87 to 1.22)	0.91 (0.68 to 1.23)
Diagnostic characteristic for the presence of tenosynovitis			
Sensitivity (%)	75 (67 to 83)	54 (45 to 67)	14 (8 to 22)
Specificity (%)	25 (18 to 34)	45 (35 to 54)	88 (80 to 93)
(B) Validation cohort			
Associations with subclinical joint inflammation (semiquantitative; per point)			
	Examiner-assessed decreased GS (OR)	**Patient-reported grip difficulties (OR)**	**Incomplete fist closure (OR)**
Total inflammation score	1.06 (1.02 to 1.11)*	1.08 (1.02 to 1.13)*	1.11 (1.05 to 1.17)*
Individual features (multivariable):			
Synovitis score	0.93 (0.77 to 1.12)	0.97 (0.80 to 1.18)	0.86 (0.67 to 1.11)
Tenosynovitis score	1.20 (1.02 to 1.40)*	1.17 (1.01 to 1.36)*	1.40 (1.13 to 1.74)*
BME score	1.28 (0.99 to 1.48)	1.13 (0.94 to 1.36)	1.14 (0.98 to 1.34)
Diagnostic characteristic for the presence of tenosynovitis			
Sensitivity (%)	40 (32 to 49)	57 (48 to 67)	22 (14 to 30)
Specificity (%)	65 (60 to 69)	52 (46 to 57)	90 (87 to 93)

Total inflammation score is the sum of synovitis, tenosynovitis and BME scores. Measures of hand function were analysed as the dependent variable with linear/logistic regression including total inflammation or the three separate MRI features, adjusted for age and sex. Tenosynovitis was considered present if scored by two independent readers and if detected in <5% of age-matched healthy controls as described in online supplemental appendix. For the diagnostic characteristics of tenosynovitis, dynamometer-measured GS was compared with the mean GS in healthy individuals of the same age and sex as reported by Günther *et al*.[6]
95% CI is given between the brackets.
*Denotes statistical significance.
BME, bone marrow oedema; GS, grip strength.

disabilities had been scarcely studied. In this in-depth study in two CSA-cohorts, addressing different aspects of hand-function, we found that hand function is already frequently affected in CSA. Depending on the assessment method it is reduced in up to 75% of CSA patients. Reduced hand function was associated with the presence of subclinical joint inflammation and tenosynovitis in particular, indicating that limitations in hand function in CSA may find their origin in subclinical tenosynovitis.

Functional disability is one of the most important aspects of disease activity for RA patients.[13] Our study adds to the mounting evidence that functional disability is already commonly prevalent in the phase preceding clinical arthritis and has consequences in daily life even before an RA diagnosis is made.[1 2] Our study suggests that subclinical tenosynovitis lies at the base of these functional disabilities.

We studied several aspects of MRI detected subclinical inflammation. Subclinical tenosynovitis seemed to attribute most to functional disabilities of the hand. This is in line with earlier findings linking tenosynovitis to general functional disabilities, walking disabilities and joint tenderness at physical examination.[1 14 15] Together with previous research, the current study supports the role of tenosynovitis in explaining symptoms and signs of patients with CSA and early RA.[12]

Reduced GS and patient-reported difficulties were more prevalent in women than in men, also after adjustment for age-matched/sex-matched reference values. This is in line with studies in established RA stating that women with RA have worse levels of disease activity and functioning compared with male patients.[16] To our best knowledge, the current study is the first to describe a comparable sex-related difference in functional

limitations in patients with in arthralgia at-risk of RA. Reasons for this have to be further elucidated. Besides stratifying for sex, we also compared hand disabilities across age categories. GS is known to decrease with age in healthy individuals.[6] Interestingly, after correction for age-adjusted reference values, we found that CSA patients across all age categories had comparable prevalence of hand disabilities.

A strength of the current study is that we used two independent CSA populations to derive and validate our findings. A possible limitation could be that GS was measured in two different ways. GS measurement with a dynamometer (as performed in the derivation cohort) is presumably more sensitive than by squeezing the examiners fingers (as performed in the validation cohort). This is reflected in the higher prevalence of reduced GS in the derivation cohort compared with the validation cohort and the finding that dynamometer-measured GS was most sensitive for subclinical tenosynovitis.

Furthermore, inclusion criteria differed between the derivation and validation cohort, as the presence of subclinical inflammation on MRI was required in the derivation cohort. After stratification of patients with and without subclinical inflammation in the validation cohort, we observed that patients with subclinical inflammation more often had reduced hand function. This further underlines the association found between MRI-detected subclinical inflammation and GS.

A limitation of this study was that data on hand dominance was unavailable, as it is known to affect GS.[10] We therefore, studied the maximum attained value on the dynamometer of the left and right hand. We considered this most fair to analyse, since it reflects the 'best-case scenario'. The fact that the highest attained value in CSA patients is already often lower than reference values of healthy individuals, underlines the robustness of the finding that GS is already affected in the CSA phase.

This study covered various aspects of hand function: GS, patient-reported hand disabilities and inability to close the fist. Each test has advantages and disadvantages. While examiner-assessed GS has the advantage that it does not require any additional equipment, it only had fair interobserver reliability (Cohen's kappa 0.31).[17] Questionnaires have the benefit that they can be answered by patients themselves, even from home, without additional equipment or observation. While more dedicated questionnaires on hand disabilities exist and the HAQ grip domain is not specifically validated for measuring hand function, the grip domain has the advantage that it takes little time to answer three questions, and the HAQ questionnaire is very widely used and available.[7] Range of motion of hand joints can also be measured in multiple ways. Using a goniometer, range of motion can be measured more precisely compared with fist closure, but this method is less convenient. Besides, fist closure actually has a substantial interobserver agreement (Cohen's kappa 0.59).[17] The aim and setting of hand function assessment may determine what method is most suitable; for example, a dynamometer may be best suited in research for its sensitivity, while incomplete fist closure easily feasible to consider in clinical practice. More strict thresholds for dynamometer-measured GS or combining the two tests can be helpful in situations when high specificity is favoured over high sensitivity.

Future research questions include evaluations on the course of hand function over time during progression to RA or symptom resolution. In addition, the effect of treatment in the arthralgia phase on hand function remains to be established.

Concluding, this is the first elaborate study on hand function in symptomatic individuals at-risk of RA, before developing clinical arthritis, deepening our understanding of the considerable functional limitations experienced by these patients. We found that various aspects of hand function are already reduced in the CSA phase. These limitations are related to subclinical inflammation and tenosynovitis in particular.

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Contributors DIK and AvdHvM designed the study. DIK, SJHK, XMEM, RMtB and FJvdG collected the data. DIK analysed the data and acted as guarantor. All authors interpreted the data and wrote the report. AvdHvM was the principal investigator. All authors approved the final version of the manuscript.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The studies were approved by the medical ethical committee of the Leiden University Medical Centre (LUMC). Participants gave informed consent to participate in the study before taking part. The TREAT EARLIER trial is registered with the Netherlands Trials Registry (NTR4853-trial-NL4599).

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