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ORIGINAL ARTICLE

Functional limitations in the phase of clinically suspect arthralgia are as serious as in early clinical arthritis; a longitudinal study

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ABSTRACT

Introduction A phase of arthralgia may precede the emergence of rheumatoid arthritis (RA). Although several studies have focused on biomarkers, the relevance of this phase for patients is less studied. It is unknown if patients already have functional limitations and if this is correlated to the extent of subclinical inflammation. Therefore, we assessed functional disability in patients with clinically suspect arthralgia (CSA), its association with MRI-detected subclinical inflammation and its course during progression to clinical arthritis.

Methods From April 2012 to March 2015, 241 patients had arthralgia for <1 year and were, based on clinical presentation, considered at risk for RA by their rheumatologists. At baseline, Health Assessment Questionnaire (HAQ) scores were determined and unilateral 1.5 T MRI of metacarpophalangeal, wrist and metatarsophalangeal joints were made. Presence of MRI-detected subclinical inflammation was assessed by summing synovitis, tenosynovitis and bone marrow oedema scores (range 0–189). Patients were followed on arthritis development and HAQ scores were repeated when clinical arthritis had developed.

Results The median HAQ score at presentation with CSA was 0.50. Higher MRI-inflammation scores were associated with higher HAQ scores ($\beta=0.017$, 95% CI=0.004 to 0.030). During median 103 weeks follow-up, 44 patients progressed to clinical arthritis. HAQ scores ≥ 1.0 were associated with arthritis development (HR=2.50, 95% CI=1.03 to 6.10). Within converters, median HAQ scores did not increase from presentation with CSA to arthritis development (0.88 and 0.75, $p=0.36$).

Conclusions HAQ scores ≥ 1.0 at presentation were associated with the development of clinical arthritis. Functional limitations in the prearthritis phase of CSA were as serious as in the early clinical phase, demonstrating the relevance of CSA from patients' perspectives.

INTRODUCTION

Within rheumatoid arthritis (RA), a symptomatic phase may precede the development of clinical arthritis.¹ A broad range of symptoms

Key messages**What is already known about this subject?**

Within rheumatoid arthritis, a symptomatic phase may precede the development of clinical arthritis with a broad range of symptoms and signs.

What does this study add?

Functional disabilities exist already in the symptomatic prearthritis phase, with (on group level) a similar severity as when presenting with clinical arthritis.

How might this impact on clinical practice?

Although occurrence of clinically detectable arthritis is a major event from the rheumatologist's perspective (as this is mostly the moment of initiation of disease-modifying antirheumatic drug therapy), it is of less importance for patients from a functional perspective.

and signs has been described in this phase.² In addition, it has been established that presence of autoantibodies,^{3 4} increased levels of acute phase reactants⁵ and MRI-detected subclinical inflammation⁶ are associated with progression to clinical arthritis. Although several biomarkers have been studied, it is still unknown to what extent patients with arthralgia at risk for RA experience functional disability. In addition, it is undetermined if functional disability in this disease stage is associated with subclinical inflammation and if the functional disability increases during progression to clinical arthritis.

The Health Assessment Questionnaire (HAQ) is a commonly used instrument to measure self-reported functional disability in patient groups.⁷ From the general population, it is known that HAQ scores increase with age⁸ and are higher for women.⁹ The median HAQ score for patients presenting

with RA is generally 1.0.^{9,10} It has been demonstrated that MRI-detected inflammation in RA was associated with increased functional impairment at 6 years follow-up.¹¹

In order to increase the comprehension of patients' experiences on physical functioning in a symptomatic prearthritis stage, this study evaluated patients without clinical arthritis but with arthralgia that were considered at risk for progression to RA by their rheumatologists (clinically suspect arthralgia (CSA)). This study assessed 1) the level of functional disability measured with HAQ scores in CSA, 2) the association of functional disability with the severity of MRI-detected subclinical inflammation, 3) the association of functional disability with progression to clinical arthritis and 4) the course of HAQ scores during progression from CSA to clinical arthritis.

METHODS

Patients

Two hundred and forty-one patients were consecutively included between April 2012 and March 2015 in the Leiden CSA cohort. Patients with CSA had recent-onset (<1 year) arthralgia of hand or feet joints and were considered at risk for RA based on the clinical expertise of the rheumatologists.⁶ Per definition CSA was not present if patients presented with clinical arthritis or if another explanation for the symptoms (eg, osteoarthritis or fibromyalgia) was more likely than imminent RA. Hence, as described previously,⁶ inclusion was mainly based on clinical expertise and patients with evident other diagnoses were not studied. Furthermore, laboratory results were largely unknown at first visit as general practitioners were discouraged to perform additional tests, hence inclusion in the cohort was largely based on the findings obtained at history taking and physical examination. At baseline, questionnaires were completed, among which were HAQ and Visual Analogue Scale (VAS, range 0–10) for pain. Within 2 weeks after inclusion, an MRI was performed. The design of the cohort is further described in reference 6. Baseline HAQ scores were missing in 37 patients (15.4%). No differences were found in baseline characteristics for the patients with known and unknown HAQ scores (see online supplementary file 2).

Health Assessment Questionnaire

The HAQ-Disability Index (HAQ-DI) was used.¹² The HAQ is a well-validated questionnaire,¹³ which comprises 20 questions, covering 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip and activities of daily living. Scores for each category consist of a scale, ranging 0–3, with 0 being no disability and 3 representing full disability. When patients require extra devices for certain HAQ activities, like a raised toilet or crutches, a lower score for that specific question is increased to 2. When a question was already scored with a 2 or 3 that score remains unchanged. Each category contains at least two questions. The scoring system is based on the highest abnormal response in each category.

The total HAQ score consists of an average of the eight categories ranging from 0 to 3 as well, with 3 indicating complete disability.

Subclinical inflammation detected by MRI

Unilateral contrast-enhanced MRIs were made of the second to fifth metacarpophalangeal (MCP), wrist and first to fifth metatarsophalangeal joints of the most painful side, or the dominant side in case of equally severe symptoms at both sides. Patients were instructed not to use non-steroidal anti-inflammatory drugs (NSAIDs) 24 hours prior to MRI as it has been suggested that NSAIDs can lower the extent of MRI-detected synovitis.^{14,15} An MSK-extremity 1.5 T MRI scanner was used. The detailed MR protocol is provided in online supplementary file 1. In short, before contrast-enhancement a T1-weighted sequence was acquired of MCP and wrist joints in the coronal plane. Postcontrast, T1-weighted, fat saturated sequences were acquired in coronal and axial planes. The foot was scanned with two protocols. In the first 78 patients, a T1-weighted sequence and a T2-weighted fat saturated sequence were acquired in the axial plane (relative to the anatomical position), before contrast agent administration. In the remaining 163 patients, postcontrast, T1-weighted, fat saturated sequences were acquired in axial and coronal planes. This provided more information while reducing scanning times. MRIs were scored for bone marrow oedema (BME) and synovitis as defined by the OMERACT Rheumatoid Arthritis MRI Scoring system.¹⁶ Tenosynovitis was scored as described by Haavardsholm *et al* (also applied at flexor and extensor tendons of second to fifth MCP joints).¹⁷ The sum of scores for synovitis, tenosynovitis and BME yielded the total MRI-inflammation score; the total score ranged between 0 and 189. Scoring was performed by two independent trained readers (HWvS, LM) blinded to clinical data. Within-reader intraclass correlation coefficients for the total MRI-inflammation score were 0.98 and 0.99; between-reader interclass correlation coefficient was 0.96. Mean scores of the two readers were used in analyses.

Follow-up

Scheduled follow-up visits were performed at 4, 12 and 24 months. Additional visits took place at indication; either if preferred by the patient (because of an increase in symptoms) or if felt necessary by the rheumatologist). The patients included in this study were all followed for development of clinically apparent arthritis for ≥ 1 year. Medical files were studied for established arthritis until 22 April 2016. Patients were not treated with disease-modifying anti-rheumatic drug (DMARDs) (including steroids) in the phase of CSA; NSAIDs were allowed. Time to clinical arthritis was defined as time from inclusion in the cohort to the date of first detection of clinical arthritis. Patients who did not develop arthritis were censored at the date that all medical files were studied on arthritis development or at the last follow-up

visit. If patients developed clinical arthritis, the HAQ was repeated at that visit. DMARDs (steroids, conventional synthetic DMARDs) were only initiated after the identification of clinical arthritis. DMARDs were initiated either directly at the visit when clinical arthritis was identified or at subsequent visits.

Sensitivity analyses

Recently, a European League Against Rheumatism (EULAR) definition for arthralgia suspicious for progression to RA was developed.¹⁸ Patients fulfilled this definition (with a high sensitivity), if three out of seven items were present. The associations between HAQ and subclinical inflammation at baseline and between HAQ and the development of clinical arthritis were also studied in the subgroup of patients that also fulfilled the EULAR definition.

Statistical analyses

Univariable linear regression models were used to investigate the association between subclinical MRI inflammation and HAQ scores; models were adjusted for age at inclusion. Univariable Cox proportional hazards regression analyses were used to calculate HRs for HAQ scores in relation to arthritis development. Patients were appointed into quartiles according to their total HAQ score to create four subgroups with equal numbers. Cox regression was repeated with development of RA according to the 2010 classification criteria¹⁹ as outcome. In multivariable Cox regression, the analysis was adjusted for age, gender, presence of MRI-subclinical inflammation and anticitrullinated peptide antibody (ACPA) status. A paired t-test was performed to compare HAQ and VAS scores for pain at presentation with CSA and after conversion to clinical arthritis; patients who completed the HAQ or VAS score ≥ 1 week after DMARD prescription were excluded from these analyses. SPSS V.23.0 was used; p values < 0.05 were considered to be statistically significant.

RESULTS

Patients with CSA

Baseline characteristics of the 241 patients included are shown in [table 1](#). The mean age was 44.3 years, 78% were female. The median HAQ score of the total group of patients at baseline was 0.50 (IQR: 0.25–0.88). Thirty-three patients reported the use of extra devices for certain HAQ activities, mostly for the categories arising, walking and grip.

HAQ score and MRI-detected subclinical inflammation at presentation

The association between severity of MRI-detected subclinical inflammation and functional disability was corrected for age. Patients with CSA who presented with higher total MRI-inflammation scores had higher HAQ scores ($\beta=0.017$, 95% CI=0.004 to 0.030, $p=0.010$); β indicates the per point increase in MRI-inflammation

Table 1 Patient characteristics at baseline presentation with CSA

Patient characteristic	n=241
Age in years, mean (SD)	44.3 (12.9)
Female sex, n (%)	187 (77.6)
Family history of RA, n (%)	71 (29.5)
Symptom duration in weeks, median (IQR)	18.4 (9.7–48.2)
Presence of morning stiffness ≥ 60 min * †, n (%)	80 (33.2)
BMI in kg/m ² , median (IQR)	26.1 (23.6–29.9)
68-TJC, median * (IQR)	6 (3–10)
Current smoker, n (%)	54 (22.4)
Autoantibody status	
ACPA-positive (>7 U/mL), n (%)	32 (13.3)
IgM-RF-positive (>3.5 IU/mL), n (%)	51 (21.2)
Increased CRP (>10 mg/L), n (%)	53 (22.0)
Daily use of NSAIDs, n (%)	57 (23.6)
Positive for EULAR definition for arthralgia suspicious for progression to RA, ¹⁸ n (%)	178 (74)
Baseline VAS pain score, median (IQR)	5 (3–7)
Baseline HAQ score *	
First quartile (n=44)	<0.25
Second quartile (n=62)	0.25–0.50
Third quartile (n=51)	0.63–0.88
Fourth quartile (n=47)	≥ 1.0

Symptoms were noted by rheumatologists as reported by the patients.

*Missing data were as follows: morning stiffness (27), 68-TJC (4), HAQ score (37).

†The presence of symptoms refers to the presence of symptoms at the baseline visit.

ACPA, anticitrullinated peptide antibody; BMI, body mass index; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; HAQ, Health Assessment Questionnaire; NSAIDs, non-steroidal anti-inflammatory drugs; RF, rheumatoid factor; RA, rheumatoid arthritis; TJC, tender joint count; VAS, Visual Analogue Scale.

score, the HAQ score increased with 0.017 (for interpretation the MRI-inflammation score ranges between 0 and 189). The synovitis, tenosynovitis and bone marrow oedema scores were also studied separately. Of the individual types of inflammation, the tenosynovitis score showed the strongest association with functional disability ($\beta=0.046$, 95% CI=0.017 to 0.076) vs $\beta=0.024$, 95% CI=–0.008 to 0.057) and $\beta=0.026$ (95% CI=–0.004 to 0.057) for synovitis and bone marrow oedema, respectively.

HAQ scores at presentation and progression to clinical arthritis

During a median follow-up period of 103 weeks, 44 patients progressed to clinical arthritis. The patients who

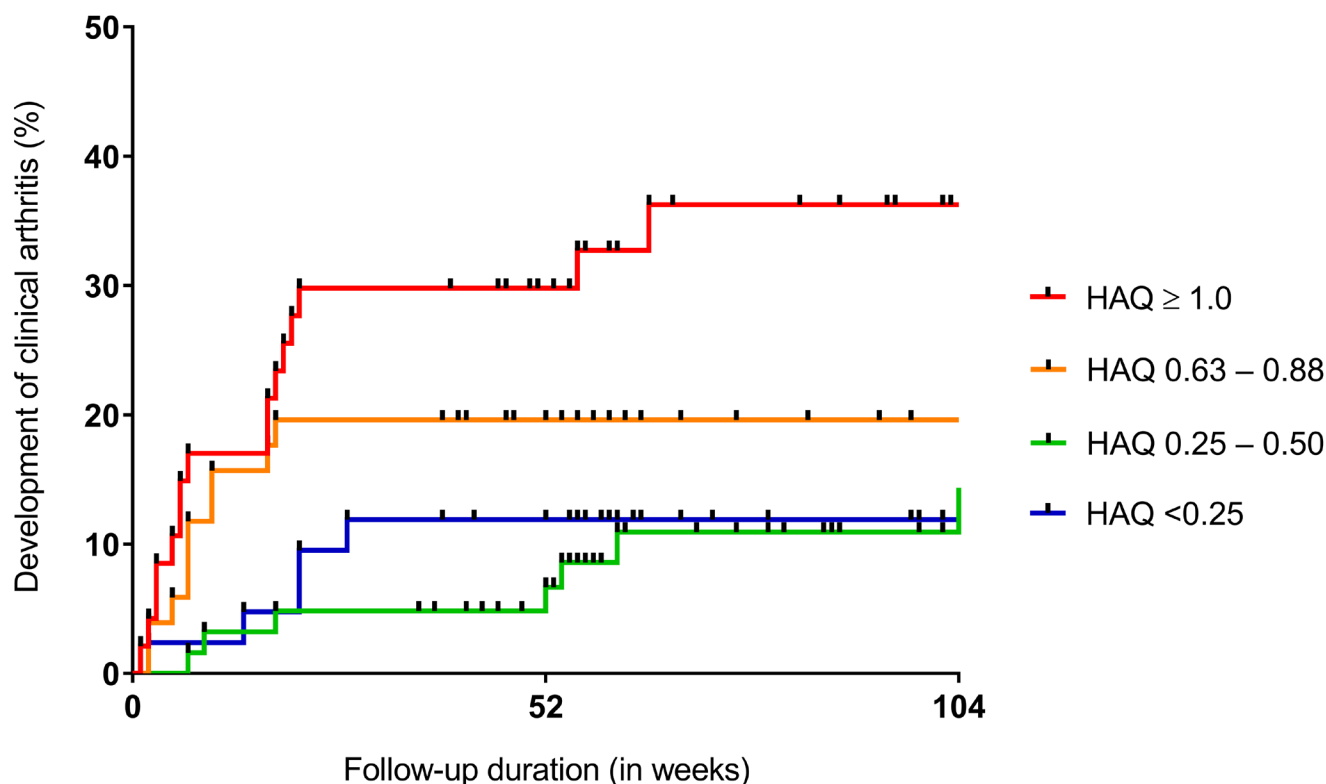


Figure 1 Kaplan-Meier One Minus Survival plot showing cumulative progression to clinical arthritis for patients with clinically suspect arthralgia divided in four groups based on their baseline Health Assessment Questionnaire (HAQ) score. Patients were appointed into quartiles according to their total HAQ score to create four subgroups with equal numbers (see online supplementary file 3). Each line represents one HAQ score quartile and cumulative progression to clinical arthritis. The lowest quartile contains patients with HAQ scores <0.25 with $n=44$ as the reference group. The second quartile contains HAQ scores $0.25-0.50$ ($n=62$), with an HR for progression to clinical arthritis of 0.67 (95% CI=0.24 to 1.9). Patients in the third quartile had HAQ scores $0.63-0.88$ ($n=51$), with an HR for progression to clinical arthritis of 1.3 (95% CI 0.49 to 3.4). Finally, the quartile with the highest HAQ scores contains HAQ scores ≥ 1.0 ($n=47$). The HR for this quartile (HR=2.50, 95% CI=1.03 to 6.10) was significantly elevated compared with the lowest quartile.

progressed presented with higher baseline HAQ scores than patients with CSA who did not progress (median 0.88 vs 0.50). Four subgroups with equal numbers were created to study the association between HAQ scores and progression to clinical arthritis in more detail (the quartiles contained four groups with HAQ scores of <0.25 , $0.25-0.50$, $0.63-0.88$ and ≥ 1.0 , see online supplementary file 3). Patients with HAQ scores ≥ 1.0 had a significantly increased hazard on developing clinical arthritis (HR=2.50, 95% CI=1.03 to 6.10), compared with the patients with HAQ scores <0.25 (figure 1).

Multivariable Cox regression was performed to investigate the association between HAQ scores and arthritis development, adjusting for age, gender, ACPA status and presence of MRI-detected subclinical inflammation. Higher HAQ scores remained significantly associated with arthritis development with HAQ scores <0.25 as reference: HR 2.6 (95% CI=1.05 to 6.6) for HAQ scores ≥ 1.0 . The presence of a positive ACPA test and the presence of MRI-detected subclinical inflammation were also significantly associated with arthritis development in this model (HR=6.7, 95% CI=3.4 to 13.8

and HR=3.3, 95% CI=1.4 to 8.0, respectively). No significant associations were observed for age (HR=0.98, 95% CI=0.95 to 1.01) or gender (HR=0.88, 95% CI=0.40 to 2.0).

At the time that clinical arthritis was identified, 27 of the 44 patients with clinical arthritis also fulfilled the 2010 criteria for RA at that visit.¹⁹ Online supplementary file 4 provides the results of subanalyses with RA as outcome. Similar findings were obtained with the highest HR for the group of patients with a HAQ >1.0 (HR 2.7, 95% CI 0.85 to 8.5).

Sensitivity analyses in patients fulfilling the EULAR definition of arthralgia suspicious for progression to RA

Out of 241 patients, 178 who were identified as CSA by their rheumatologists also fulfilled the EULAR definition of arthralgia suspicious for progression to RA. Also in this subgroup the total MRI inflammation scores were associated with the HAQ scores ($\beta=0.015$, 95% CI=0.001 to 0.029, $p=0.047$) and also here a HAQ scores ≥ 1 were associated with progression to clinical arthritis; HR 2.9 (95% CI 1.2 to 7.2).

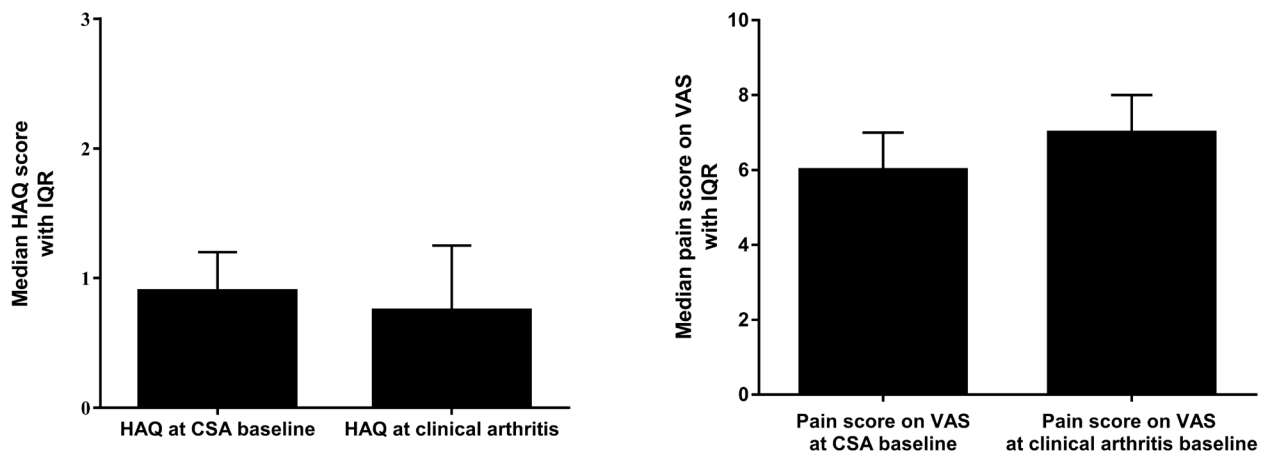


Figure 2 Column bar graphs showing Health Assessment Questionnaire (HAQ) scores and pain score on Visual Analogue Scale (VAS) (scale 0–10) that were collected at presentation with clinically suspect arthralgia (CSA) and after progression to clinical arthritis but before disease-modifying antirheumatic drug (DMARD) initiation. Column bar graphs showing HAQ scores and pain score on VAS (scale 0–10) of 25 patients that were serially collected at presentation with CSA (left bar) and after progression to clinical arthritis but before DMARD initiation (right bar). A paired t-test for comparisons of median HAQ scores and pain scores on VAS (scale 0–10) at both time points (CSA baseline inclusion and the moment of established arthritis) revealed no differences ($p=0.36$ and $p=0.11$, respectively).

HAQ and VAS for pain at presentation with CSA and at arthritis development

HAQ scores at clinical presentation with CSA and after arthritis development (and <7 days of DMARD prescription) were available in 25 patients. On group level, median HAQ scores did not differ between the time of presentation with CSA and the time of presentation with clinically apparent arthritis: median 0.88 (IQR 0.38–1.2) vs 0.75 (IQR 0.38–1.3), respectively, $p=0.36$ (figure 2). Intra-individual changes in HAQ scores over time are shown in online supplementary file 5. When the analysis was repeated within the patients who completed the HAQ at the day, they received a prescription for DMARDs ($n=19$), also no difference in HAQ was observed: median 1.1 (IQR 0.45–1.2) when presenting with arthralgia and 0.75 (IQR 0.5–1.3) at clinical arthritis (p value=0.59). Furthermore, also in the subgroup of patients that fulfilled the 2010 criteria for RA ($n=21$), the median HAQ did not increase between presentation with CSA and clinical arthritis development (0.82 and 0.75, $p=0.47$).

The progression from CSA to clinical arthritis is based on an increase in local joint inflammation. As functional limitations may associate with inflammation and be a direct consequence of pain, we also explored the overall level of pain (measured on a VAS ranging 0–10) in CSA and at conversion to clinical arthritis. The VAS score for pain showed a non-significant tendency towards an increase between the phase of CSA and that of early clinical arthritis (median 6.0 and 7.0, respectively, $p=0.11$, figure 2). Thus, despite an increase in inflammation and pain, functional disability was already maximal in the phase of CSA.

DISCUSSION

This longitudinal study showed that patients who develop clinical arthritis already have functional limitations in the phase of arthralgia. HAQ scores at group level were similar at the time of presenting with CSA and after emergence of clinical arthritis. Furthermore, severity of MRI-detected subclinical inflammation is associated with the severity of functional impairments. Together, these data demonstrate the functional relevance of the HAQ and MRI-detected subclinical inflammation in symptomatic patients in the prearthritis stage. This suggests that, although occurrence of clinically detectable arthritis is a major event from the rheumatologist's perspective (as this is mostly the moment of initiation of DMARD therapy), it is of less importance for patients from a functional perspective.

Patients with CSA with HAQ scores ≥ 1.0 in particular were at increased risk of progression to clinical arthritis. Interestingly, previous studies in early RA cohorts have shown that mean HAQ scores at presentation were 1.0.^{9 10} This suggests that functional impairments in the symptomatic prearthritis and early clinical phases are of similar severity. A previous study comparing patients diagnosed with early RA and patients with arthralgia showed similar burden of disease among the two groups.²⁰ The presumption of similar burden of disease during the pre-RA phase and early RA is further supported by our findings that the patients with CSA who progressed to clinical arthritis did not experience an increase in functional disability; in other words, the maximal level of disability was already present when presenting with CSA.

Patients who presented with CSA but did not progress to clinical arthritis presumably also had more functional impairments than the general population, as their median HAQ was 0.50 and mean HAQ score of an age-related normal population (women aged 40–44 years) is approximately 0.08.⁸

We observed that a HAQ ≥ 1.0 was associated with progression to clinical arthritis, independent of other predictors (age, gender, ACPA, MRI-detected inflammation). This study was not aimed at identifying novel markers for progression from CSA to RA, it aimed to explore the level of functional disability in patients with CSA and during progression to clinical arthritis. The question if a HAQ score is valuable for diagnostic or prognostic purposes needs to be studied in further, larger studies. Furthermore, future studies can explore if specific functional limitations are most predictive. Previous qualitative studies have shown the breadth of symptoms present in the early phase of RA²¹; further explorations on measures for recognising symptom patterns that are specific for pre-RA that include functional limitations are warranted.

The severity of functional disability was associated with the severity of MRI-detected subclinical inflammation, indicating that the functional impairments were in part related to (subclinical) inflammation. Previous studies in early arthritis or in RA also showed an association between MRI-detected inflammation and HAQ scores within RA.^{11,22} In one of these studies, it was observed that MRI-detected tenosynovitis had the strongest association with functional disability in early arthritis.¹⁵ Interestingly, also in patients with CSA we observed that tenosynovitis had the strongest association with functional disability. The beta of MRI-detected tenosynovitis of 0.046 indicates that a MRI-inflammation score of 6 associated with an increase in HAQ of 0.27. Although statistically significant, the relatively small effect size indicates that the functional disability in CSA is only partly explained by (MRI-detected) subclinical inflammation.

A potential weakness is that 37 patients did not complete the baseline HAQ. Because the baseline characteristics of the patients who had HAQ data and those without HAQ data were similar, we believe that there is no important bias.

A previous study explored the impact of symptoms on daily functioning within antibody-positive patients with arthralgia.²³ Our sets of patients is slightly different as autoantibody negative patients at risk for RA were also included and because patients were not included if the treating rheumatologist considered another explanation for the arthralgia (eg, osteoarthritis or fibromyalgia) more likely than imminent RA. In addition, analyses were also repeated in the patients with arthralgia fulfilling the EULAR definition of arthralgia at risk for RA. These showed similar results. Importantly, as patients who had other explanations for the arthralgia were not included, we think it is unlikely that patients with forms of (chronic) pain syndromes might have skewed the data

towards higher HAQ scores. Comparisons were based on medians of HAQ and VAS scores as these are more resistant against outliers.

Another potential limitation for the analyses is that both HAQ scores and MRI-inflammation scores are assessed at semi-quantitative scales. However, the HAQ is one of the most important and validated patient-reported outcomes in RA.¹²

Finally, it should be taken into consideration that the sample size of patients converting to clinical arthritis is relatively small. Our study is nevertheless the largest to date to investigate functional disability in patients with CSA.

Ideally, to fully evaluate the burden of clinically suspect arthralgia on functional disability, the functional status of the patients with CSA included in this study should be compared with age-matched and sex-matched controls from the general population. As such references were not available for the Dutch population, we could not perform such comparison.

In conclusion, functional disabilities exist already in the symptomatic prearthritis phase, with (on group level) a similar severity as when presenting with clinical arthritis. The occurrence of clinically detectable arthritis is a major event from the rheumatologist's perspective as all trials in RA are performed in patients with clinically apparent arthritis. Hence, as soon as arthritis is clinically evident initiation of DMARD therapy may be warranted. Currently, several trials are being performed to investigate if treatment initiation in the phase of arthralgia is effective. As long as these trials have not reported positive results, there is no scientific evidence to start DMARD therapy in patients without clinical arthritis. Nonetheless, the present data illustrate that, from the patients' perspective, the burden of disease is already severe in pre-RA. Acknowledging the importance of the symptomatic prearthritis phase from a functional perspective underlines the necessity of further studies to better identify patients with RA in the phase of arthralgia, and to verify the concept of very early treatment in these patients.

Contributors RMTB and AHMvdH-vM contributed to the conception and study design. RMTB analysed the data. RMTB, HWvS, LM, LEB, MR, TWJH and AHMvdH-vM contributed to interpretation of the data. HWvS and LM contributed to acquisition of the data. RMTB and AHMvdH-vM wrote the first version of the manuscript and RMTB, HWvS, LM, LEB, MR, TWJH and AHMvdH-vM revised it critically. RMTB, HWvS, LM, LEB, MR, TWJH and AHMvdH-vM read and approved the final manuscript.

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Competing interests None declared.

Ethics approval The study was approved by the medical ethical committee of the Leiden University Medical Center. All patients signed informed consent.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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Functional limitations in the phase of clinically suspect arthralgia are as serious as in early clinical arthritis; a longitudinal study

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