Differences and similarities of autoantibody-positive and autoantibody-negative rheumatoid arthritis during the disease course: on our way to personalized medicine

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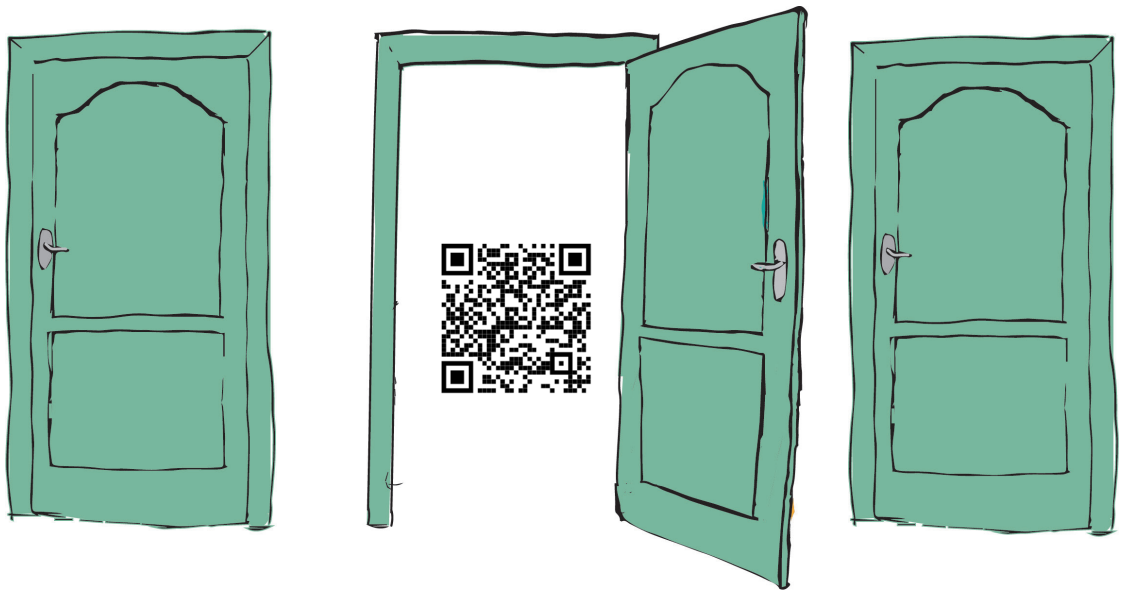

CHAPTER 5

The value of imaging detected joint inflammation in explaining fatigue in RA at diagnosis and during the disease course - a large MRI study

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ABSTRACT

Objective

Fatigue in rheumatoid arthritis (RA) is hypothesized to be caused by inflammation. Still ~50% of the variance of fatigue in RA cannot be explained by the disease activity score (DAS), nor by background or psychological factors. Since MRI can detect joint inflammation more sensitively than the clinical joint counts as incorporated in the DAS, we hypothesized that inflammation detected by MRI could aid in explaining fatigue in RA at diagnosis and during follow-up.

Methods

526 consecutive RA-patients were followed longitudinally. Fatigue was assessed yearly on a numerical rating scale. Hand and foot MRIs were performed at inclusion, after 12 and 24-months in 199 patients and were scored for inflammation (synovitis, tenosynovitis and osteitis combined). We studied whether RA-patients with more MRI-inflammation were more fatigued at diagnosis (linear regression), whether the 2-year course of MRI-inflammation associated with the course of fatigue (linear mixed models) and whether decrease in MRI-inflammation in year-1 associated with subsequent improvement in fatigue in year-2 (cross-lagged models). Similar analyses were done with DAS as inflammation measure.

Results

At diagnosis, higher DAS-scores were associated with more severe fatigue (p<0.001). However, patients with more MRI-inflammation were not more fatigued (p=0.94). During 2-year follow-up, DAS decrease associated with improvement in fatigue (p<0.001), but MRI-inflammation decrease did not (p=0.96). DAS decrease in year-1 associated with fatigue improvement in year-2 (p=0.012), as did MRI-inflammation decrease (p=0.039), with similar effect strength.

Conclusion

Sensitive measurements of joint inflammation did not explain fatigue in RA at diagnosis and follow-up. This supports the concept that fatigue in RA is partly uncoupled from inflammation.

KEY MESSAGES

What is already known about this subject?

- Fatigue in rheumatoid arthritis (RA) contributes majorly to the disease burden and is hypothesized to be caused by inflammation. However, ~50% of the variance of fatigue in RA cannot be explained by clinical measures of joint inflammation, and neither by other factors such as psychological factors or pain.
- Since MRI can detect joint inflammation more sensitively than the clinical joint counts as incorporated in the DAS, we hypothesized that joint inflammation of the hands and feet as detected by MRI could aid in explaining fatigue in RA

What does this study add?

- The association of fatigue and MRI-inflammation at baseline and during the disease course was studied in a consecutive cohort of >500 RA patients. In this large cohort, we observed that MRI-inflammation did not explain fatigue, both at baseline and during the disease course.

How might this impact on clinical practice or future developments?

- This suggests there is a ceiling effect for explaining fatigue by inflammation and supports the concept that fatigue in patients with classified RA is in part disconnected from inflammation.
- Consequently, this implies that aiming at imaging remission does not lower fatigue in RA

INTRODUCTION

Fatigue in rheumatoid arthritis (RA)-patients contributes majorly to the disease burden.[1] Despite the fact that treatment strategies have improved dramatically during the last decades, persistent fatigue is still a major issue and present in up to 80% of RA-patients.[2] Because of this, patient partners promote awareness of fatigue and stimulate research into fatigue, as an increased understanding of the underlying process may lead to novel ways to address fatigue in RA.[1]

Studies examining fatigue at diagnosis showed that it is associated with inflammation, expressed by the disease activity score (DAS) and by background factors such as young age, female sex, low education level, smoking, and mental health.[2,3] Studies on fatigue during the disease course have also shown that fatigue is associated with DAS, background factors and pain.[2,4,5] In addition, it has been shown that early intensive treatment and consequent early remission are associated with subsequent fatigue improvement.[6,7] However, only ~40% of the variance of fatigue in RA is explained by clinical inflammation.[4,8] Even when also considering other (possible) explanatory factors, such as mental health, disability and pain, ~50% of the variance of fatigue in RA remains unexplained.[4,5]

Imaging detects local joint inflammation more sensitively than the joint counts as incorporated in the DAS. Therefore we hypothesized that MRI-detected joint inflammation could aid in understanding fatigue in RA. To our knowledge, no studies have been performed so far to determine if part of fatigue is associated with imaging detected joint inflammation in the hands and feet, neither at the time of diagnosis, or during the course of the disease. Therefore, while fatigue causes a great burden of disease and is considered to be a consequence of inflammation, the contribution of imaging detected joint inflammation to fatigue in RA is undetermined; This prompted the current study. Our aim was to determine the contribution of MRI-inflammation to fatigue at diagnosis and during the disease course. We addressed three questions: 1) Are RA-patients with more MRI-inflammation at diagnosis more fatigued? 2) Is MRI-inflammation during the disease course associated with the course of fatigue? and 3) Is decrease in MRI-inflammation followed by decreasing fatigue? To confirm previous research on the association of DAS and fatigue and to allow for comparison of different forms of inflammation, these three analyses were repeated with DAS as an inflammatory measure.

METHODS

Patients

The Leiden early arthritis clinic (EAC) includes consecutive early arthritis patients (<2 years symptom duration) and has already been extensively described elsewhere.[9] In short, inclusion criteria were presence of synovitis determined at physical examination by rheumatologists and symptom duration of <2 years. After inclusion, patient-characteristics, disease activity and laboratory parameters were obtained at baseline, 4-months, 12-months and yearly thereafter by a trained research nurse. Fatigue was assessed yearly with a numeric rating scale (NRS) by a trained research nurse with the question "How tired were you today?" ranging from 0 (no fatigue) to 10 (extreme fatigue).[10] Patients were treated in routine care and in line with (inter-) national recommendations.[11,12] Treating physicians, patients and research nurses were blinded for any MRI data.

From August-2010 onwards MRIs were performed at baseline. RA-patients included in the EAC between August-2010 and March-2020 and fulfilling the 1987- or 2010 criteria within one year were evaluated in the present study (Flowchart in Supplementary 1). In some patients no baseline MRI was performed (mostly due to logistical reasons such as MRI-maintenance) and some baseline MRIs were of insufficient quality (e.g. no contrast enhanced sequences or insufficient fat suppression), implying missingness completely at random. Reassuringly, baseline characteristics were comparable in patients with and without baseline MRI, substantiating this assumption (Supplementary 2). Between 2010 and February-2015 MRIs of RA-patients were repeated at 12 and 24-months. Age, gender, MRI-inflammation and fatigue at baseline were not different between patients included in the periods with or without follow-up MRIs; patients with follow-up MRIs were slightly more often anti-citrullinated protein antibodies (ACPA)-positive (Supplementary 3). Consequently, we studied a representative consecutive sample of 526 early RA-patients that received an MRI at baseline and 199 patients that received follow-up MRIs.

MRI

Wrist, metacarpophalangeal (MCP(2-5)), and metatarsophalangeal (MTP(1-5))-joints on the most painful side at baseline (dominant side in case of symmetric symptoms) were imaged with 1.5TMRI (GE,Wisconsin,USA). Contrast-enhanced T1-weighted FSE fatsat sequences of the wrist and MCP were obtained in all patients. In June-2013, instead of axial T1 and T2-weighted FSE fatsat sequences in the axial plane, contrast-enhanced T1-weighted FSE fatsat sequences in both the coronal and axial plane of the MTPs were added to the protocol. Supplementary 4 provides a detailed scan- and scoring-protocol.

All MRIs were scored for synovitis, tenosynovitis and osteitis in line with RAMRIS and the method of Haavardsholm (Supplementary 4). Baseline MRIs were scored by two experienced readers, blinded to any clinical data. MRIs over time were scored by a single reader, with known time-order, blinded to any clinical data (including DAS and fatigue). Intraclass correlation coefficients were excellent (≥0.95 for total inflammation score; Supplementary 5&6).

Statistical analysis

To study the association of DAS and MRI-inflammation with fatigue at baseline, data was plotted for pairwise analysis and linear regression was used. Because of skewness, the total MRI-inflammation score was log-transformed. Analyses were performed both univariably and corrected for potential confounders: age, gender and ACPA-status. Analyses of MRI-inflammation were not corrected for DAS, because of the collider-effect. Because both MRI-inflammation and fatigue can (indirectly) cause a higher DAS, correction of the relationship of MRI-inflammation and fatigue by the DAS would cause invalid results. This is called a collider effect. The same would be true if we would study the relation between MRI-inflammation and fatigue in patients in DAS-remission. Therefore, these analyses were not performed. This is extensively explained in Supplementary 7.

To assess the association between the 2-year course of DAS and MRI-inflammation with fatigue, change during the first two years was plotted for pairwise analyses. Next, linear mixed models were used, univariably and corrected for the mentioned potential confounders. The mixed models studied the baseline, 1-year and 2-year visit and included a random effect for patient. To allow for robust estimation with few measurements per patient, the residuals and random effects were assumed to be independent. Here again the total MRI-inflammation score was log-transformed and analyses of MRI-inflammation were not corrected for DAS, because of a collider-effect (Supplementary 7).

To study whether decrease in DAS and MRI-inflammation preceded fatigue improvement, cross-lagged models were employed.[13] The influence of decrease in MRI-inflammation on (0-12months) on decrease of fatigue (12-24months) was evaluated corrected for baseline values of the parameters and simultaneous decrease. This was done to evaluate whether excess decrease (e.g. more change than the mean percentual decrease) in inflammation in the first year precedes and predicts excess fatigue decrease in the second year. This was done with the hypothesis that if MRI-inflammation decrease precedes fatigue decrease, MRI-inflammation decrease (0-12months) will associate with fatigue decrease (12-24months) but not the other way around.

The complex structure of the cross-lagged models results in estimates that are not easily interpreted. We therefore expressed them in standardized regression coefficients. Standardized regression coefficients allow for comparison of effect strength between predictors because they are independent of scale. They generally lie between -1 and 1 where a value of -1 (negative) or 1 (positive association) indicates full explanation of the dependent variable by the independent variable and a value of 0 indicates no association.

MRIs at 12-months and 24-months were missing in 20% and 43%, respectively (39 and 86 MRIs, respectively). We assumed that missingness was associated with a measured covariate (e.g. missing at random (MAR) in contrast to missingness completely at random (MCAR)). This was done because patients with less severe disease (as measured by ACPA-positivity) presumably had less follow-up with MRIs. This hypothesis was supported by higher ACPA-positivity (58%) in patients with 24-month MRIs than in patients without (42%;p=0.032) Therefore ACPA was included in the multivariable models, ACPA-stratification was performed and statistical methods appropriate for MAR were employed.

R3.6.3 was used. Two-sided p<0.05 were considered significant.

Sensitivity analyses

Because the associations of the individual DAS components with fatigue might differ, associations of the individual DAS components with fatigue at baseline and over time were assessed.

Because ACPA-positive and ACPA-negative RA are hypothesized to have a difference in underlying pathogenetic mechanisms, this could affect the relationship between inflammation and fatigue. Therefore, we repeated the analyses stratified for ACPA-status.

To ensure our results did not depend on the fatigue measure used and the period assessed, analyses were repeated with two fatigue questions (“Did you feel tired over the last 4 weeks?” and “Did you feel worn out over the last 4 weeks?”) of the short form (SF-)36 as outcome.[10]

Previous research did not show an effect of individual DMARDs on fatigue.[14] However, to ensure our findings over time were not confounded by treatment, we repeated analyses over time in patients receiving initial methotrexate therapy since this was the most frequently occurring initial treatment (69%).

RESULTS

Patient characteristics

526 consecutive RA-patients were studied: mean age was 59, 64% was female, 45% ACPA-positive and median (interquartile range) NRS fatigue was 6 (2-7; Supplementary 2). 199 patients received MRIs during follow-up and had similar baseline characteristics (Supplementary 3). In these patients, NRS fatigue was 6 (2-7) at baseline and decreased slightly to 5 (1-7) at 12-months and 4.5 (1-7) at 24-months.

Association of inflammation and fatigue at diagnosis

We assessed whether patients with more inflammation were more fatigued at diagnosis. RA-patients with more MRI-inflammation were not more fatigued at diagnosis in univariable and multivariable analyses (p=0.08 & p=0.94;Table 1;Figure 1). In contrast, patients with higher DAS were more fatigued at baseline (both p<0.001).

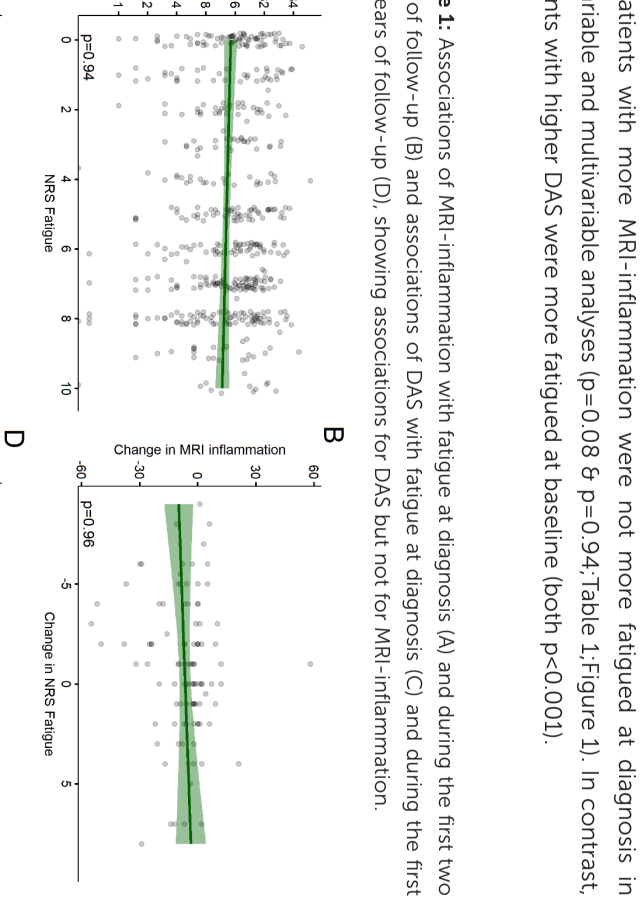

Figure 1: Associations of MRI-inflammation with fatigue at diagnosis (A) and during the first two years of follow-up (B) and associations of DAS with fatigue at diagnosis (C) and during the first two years of follow-up (D), showing associations for DAS but not for MRI-inflammation.

Table 1: Univariable and multivariable associations of MRI-inflammation and DAS at inclusion and fatigue at inclusion and associations of MRI-inflammation and DAS over time with fatigue course over time

Baseline	**Univariable**	**p-value**	**MRI-inflammation corrected for potential confounders**	**p-value**	**DAS corrected for potential confounders**	**p-value**
Total MRI-inflammation	-0.27 (-0.58;0.04)	0.08	-0.01 (-0.36;0.33)	0.94		
Disease activity score	**1.17 (0.80;1.53)**	**<0.001**			**1.22 (0.84;1.59)**	**<0.001**
ACPA	**-0.76 (-1.29;-0.22)**	**0.006**	**-0.80 (-1.33;-0.26)**	**0.004**	**-0.60 (-1.13;-0.09)**	**0.023**
Age in years	**-0.02 (-0.04;0.00)**	**0.031**	-0.01 (-0.04;0.01)	0.16	**-0.02 (-0.04;0.00)**	**0.021**
Female gender	**1.21 (0.67;1.75)**	**<0.001**	**1.21 (0.65;1.76)**	**<0.001**	**1.04 (0.50;1.58)**	**<0.001**
Over time	**Univariable**	**p-value**	**MRI-inflammation corrected for potential confounders**	**p-value**	**DAS corrected for potential confounders**	**p-value**
Total MRI-inflammation	-0.01 (-0.29;0.27)	0.95	-0.01 (-0.30;0.28)	0.96		
Disease activity score	**1.03 (0.78;1.28)**	**<0.001**			**1.01 (0.77;1.26)**	**<0.001**
ACPA	0.10 (-0.56;0.76)	0.77	0.09 (-0.58;0.76)	0.79	-0.06 (-0.66;0.55)	0.86
Age in years	-0.02 (-0.04;0.01)	0.16	0.00 (-0.03;0.03)	0.95	-0.02 (-0.04;0.00)	0.13
Female gender	**1.27 (0.59;1.94)**	**<0.001**	**1.49 (0.78;2.20)**	**<0.001**	**0.79 (0.15;1.43)**	**0.016**

Legend: ACPA: anti-citrullinated protein antibodies; DAS: disease activity score; bold results indicate p<0.05.

Legend: NRS, numeric rating scale. The y-axis in (A) log-transformed. NRS fatigue values in (A&C) were jittered along the x-axis with a width of 0.2 at either side

Association of course of inflammation and fatigue

The association between the time-courses of inflammation and fatigue during the first 2 years of the disease was assessed. The course of MRI-inflammation was not associated with that of fatigue (p=0.95&p=0.96; Table 1;Figure 1). However, DAS decrease was associated with simultaneous fatigue decrease (both p<0.001)

Time orders in decrease of inflammation and fatigue

We hypothesized that decrease in inflammation can precede fatigue improvement and therefore relatively more inflammation decrease would associate with relatively more subsequent fatigue decrease but not vice versa. In line with our hypothesis, MRI-inflammation decrease preceded fatigue decrease (p=0.039;Table 2), but fatigue decrease did not precede MRI-inflammation decrease (p=0.63).

In concordance with MRI-inflammation, DAS decrease 0-12 months preceded fatigue decrease 12-24 months (p=0.012) but fatigue decrease did not precede DAS decrease (p=0.23). The effect-strength of MRI-inflammation was similar, but not stronger, to than of DAS.

Table 2: Estimates of subsequent change of MRI-inflammation, DAS and fatigue

Subsequent change	Standardized regression coefficient	P-value
MRI-inflammation precedes fatigue	**0.17 (0.01;0.34)**	**0.039**
Fatigue precedes MRI-inflammation	0.04 (-0.12;0.20)	0.63
DAS precedes fatigue	**0.19 (0.04;0.34)**	**0.012**
Fatigue precedes DAS	0.10 (-0.07;0.27)	0.23

Legend: Analyses were performed with the hypothesis that if inflammation decrease precedes fatigue decrease, inflammation decrease (0-12m) will associate with fatigue decrease (12-24m) but not the other way around. Standardized regression coefficients of change of one inflammatory feature to subsequent change in another inflammatory feature, corrected for the simultaneous pattern and previous values of those inflammatory features, with 95% confidence intervals. bold: significant estimate (p<0.05). DAS: disease activity score.

Sensitivity analyses

The associations of the individual DAS components with fatigue were assessed (Supplementary 8). At baseline, the visual analogue scale for general health (VAS) and the tender joint count (TJC) associated with fatigue. Over time, also the swollen joint count (SJC) and erythrocyte sedimentation rate (ESR) associated with fatigue in univariable but not in multivariable analyses.

Analyses were repeated stratified for ACPA-status (Supplementary 9). Similar results were obtained, except that time-orders of fatigue and inflammation decrease did not attain statistical significance in ACPA-negative patients.

To ensure robustness of results, independent of the fatigue measure used and time period assessed, analyses with two questions of the SF-36 were performed (Supplementary 10). These yielded similar results except that time orders of decrease in MRI-inflammation and fatigue were not identified.

Sensitivity analyses over time in patients receiving initial methotrexate yielded similar results except that the association of MRI-inflammation decrease and subsequent fatigue decrease did not attain statistical significance (Supplementary 11).

DISCUSSION

Fatigue is an important contributor to disease burden in RA. It is considered a consequence of inflammation. Although the association of DAS with fatigue is extensively studied, the contribution of joint inflammation in the hands and feet, as detected by very sensitive imaging techniques, was unexplored. We observed that higher clinical disease activity was associated with more fatigue, both at the time of diagnosis and during the disease course. This confirms previous studies. In contrast, MRI-inflammation was not helpful in explaining fatigue. This supports the concept that fatigue in patients with classified RA is partly disconnected from inflammation and caused by other processes.

We observed that decrease of MRI-inflammation in year-1 preceded subsequent fatigue decrease in year-2. However it most likely did not aid in explaining fatigue on top of the DAS, because standardized regression coefficients were similar, indicating that these inflammation indicators explained similar variance in subsequent fatigue. Moreover, the observed association of MRI-inflammation decrease on subsequent improvement in fatigue was not observed in sensitivity analyses, indicating that this finding was less robust. Therefore, the results on the added value of imaging detected joint inflammation in the hands and feet in explaining fatigue in this study are rather negative.To further investigate which kind of inflammation best explains fatigue in RA, we assessed the association of the individual DAS components with fatigue. We found that the subjective markers of inflammation (VAS, TJC) better associated with fatigue and that the objective markers (SJC, ESR) did not associate with fatigue at baseline and in multivariable analyses. This might partly explain the absence of association of MRI-inflammation and fatigue as MRI-inflammation is a very objective measure of inflammation.

While MRI-inflammation is measured locally in small joints that are preferentially affected in RA, the DAS also includes more comprehensive joint counts as well as systemic measures of inflammation such as the ESR. Our aim was to investigate whether local joint inflammation as measured sensitively with MRI could aid in

explaining fatigue in RA. Despite this hypothesis, we found no association between MRI-detected joint inflammation and simultaneously present fatigue. Therefore we feel that the data suggest that fatigue is partly unexplained by inflammation, even when regular measures of inflammation and imaging detected inflammation are both considered. While clinical trials are needed to confirm this, the findings from the present observational study imply that treating MRI-inflammation does not result in lower fatigue. This is in contrast to treating clinical disease activity as measured by the DAS, which is associated with fatigue over time. This is also confirmed by a trial that failed to show an effect on fatigue when treatment was aimed at imaging remission instead of DAS remission.[15] Altogether, treatment strategies to lower fatigue should be aimed at the DAS or clinical remission and not at imaging detected inflammation.

We found that fatigue is partly unexplained by clinical inflammation and MRI-inflammation. This implies that it is partly disconnected from inflammation and might have become chronic by itself or might be caused by other processes such as depression and/or secondary fibromyalgia. Unfortunately, we were not able to assess these factors in the current study. Further research can help to elucidate into what extent fatigue in RA can be explained by these factors or has become chronic by itself. We reconfirmed the findings that showed that a decrease in DAS associated with a simultaneous decrease in fatigue and with subsequent decrease in fatigue.[6,7] Moreover, our study is the first to study time orders of MRI-inflammation decrease and fatigue decrease. In these analyses, time order of decrease implies the directionality of causality. Still, fatigue during disease course remains largely unexplained by inflammation, which implicates that fatigue has become chronic and possibly a separate disconnected process already very early in the disease-course. It remains to be studied whether MRI-inflammation in a pre-arthritis phase has a stronger connection with fatigue and whether intervention with DMARDs in the phase when disease processes are less mature is more effective in treating fatigue.

Our results were similar for RA-patients with and without ACPA. Both subsets of RA have differences in the underlying pathogenesis, with the adaptive immune response, and B-cells in particular, playing a more prominent role in the autoantibody positive RA. B-cell depletion has been proposed as a treatment for chronic fatigue.[16] If these cells would play an important role in fatigue in RA, it could be expected that ACPA-positive patients would have more severe fatigue at the time of diagnosis and that treatment could affect the response in fatigue differently in both ACPA-subsets. In contrast to this reasoning, in our data, ACPA-positive patients were less fatigued at baseline, similarly fatigued during the disease course and effects of inflammation on fatigue during disease course were also similar. This might argue against a major role for the B-cell response in fatigue in RA.

Unfortunately we could not study the effect of MRI-inflammation on fatigue in addition to the DAS due to a collider effect. However, since we found no effect of MRI-inflammation on simultaneous fatigue, it is unlikely that MRI-inflammation could explain simultaneous fatigue independent of the DAS. This is supported by previous finding that US remission in addition to DAS remission was not associated with lower fatigue.[17]

A limitation is that some MRIs were missing during follow-up. We assumed this missingness to be associated with disease severity (e.g. missingness at random/MAR) which was confirmed by more ACPA-positivity in patients completing 2-year MRIs. Statistical techniques appropriate for MAR were employed and correction for variables associated with disease severity (ACPA-status) was performed. This correction did not substantially alter our results, implying that missingness associated with disease severity did not substantially influence our univariable results. While, to our knowledge, this study was performed on the largest observational longitudinal database of MRI scans in RA, the number of missing MRIs during follow-up remains an important limitation.
In this study, we evaluated unilateral MRI-inflammation of the hands and feet of the most affected side. MRI-inflammation could also be present at other joint regions and in the preferential regions it is often bilaterally present. Reassuringly, previous literature showed that bilateral scanning conveyed little additional information compared to scanning of only the most affected side.[18,19] Although it is a limitation that not more joints were imaged, we think it is unlikely that it majorly affected our results.

We measured fatigue severity with a single item fatigue measure, the NRS: "How tired were you today?".[10] This measure is simple to administer and also has a good construct validity, sensitivity to change, and test-retest properties in RA. Many other multi-item or multidimensional fatigue measures are available and are able to explore various domains of fatigue.[10] Those multidomain scores can aid in understanding fatigue causality or the effect of fatigue-specific interventions. We repeated analyses with two items of the SF-36 that assesses a longer period of time (4 weeks) and obtained similar results.[10] Despite that separate items of the SF-36 have not been validated, this allowed us to associate MRI-inflammation with multiple reliable and easily interpretable measures of fatigue over a short and a long period. These analyses showed the robustness of our results.

In conclusion, in the first large observational study evaluating the relation between MRI detected joint inflammation and fatigue in RA, we showed that measuring inflammation with MRI does not aid in explaining fatigue in RA. The results imply that aiming at imaging remission does not lower fatigue in RA. Consequently treatment strategies to lower fatigue should be aimed at the DAS, as shown in previous studies. Fatigue

in RA is partly disconnected from inflammation and may have become chronic by itself. Other types of interventions may be explored to reduce the burden of fatigue in patients diagnosed with RA. However, it remains to be determined if imaging detected inflammation is more strongly connected to fatigue in phases that precede clinical arthritis, and if DMARD-treatment in this phase is more effective in reducing fatigue or preventing chronic fatigue.

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