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Clinical science

Patients with rheumatoid arthritis presenting with mono- or oligo-arthritis and high VAS-ratings remain the most fatigued during 5 years of follow-up

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Abstract

Objectives: The severity of fatigue in RA has improved very little in recent decades, leaving a large unmet need. Fortunately, not all RA patients suffer from persistent fatigue, but the subgroup of patients who suffer the most is insufficiently recognizable at diagnosis. As disease activity is partly coupled to fatigue, DAS components may associate with the course of fatigue. We aimed to identify those RA patients who remain fatigued by studying DAS components at diagnosis in relation to the course of fatigue over a 5-year follow-up period in two independent early RA cohorts.

Methods: In all, 1560 consecutive RA patients included in the Leiden Early Arthritis Cohort and 415 RA patients included in the tREACH trial were studied. Swollen joint count, tender joint count, ESR and Patient Global Assessment (PGA) [on a Visual Analogue Scale (VAS)] were studied in relation to fatigue (VAS, 0–100 mm) over a period of 5 years, using linear mixed models.

Results: Higher tender joint count and higher PGA at diagnosis were associated with a more severe course of fatigue. Furthermore, patients with mono- or oligo-arthritis at diagnosis remained more fatigued. The swollen joint count, in contrast, showed an inverse association. An investigation of combinations of the aforementioned characteristics revealed that patients presenting with mono- or oligo-arthritis and PGA ≥ 50 remained the most fatigued over time (+20 mm *vs* polyarthritis with PGA < 50), while the DAS course over time did not differ. This subgroup comprised 14% of the early RA population. Data from the tREACH trial showed similar findings.

Conclusion: The RA patients who remain the most fatigued were those characterized by mono- or oligo-arthritis and high PGA (VAS ≥ 50) at diagnosis. This understanding may enable early-intervention with non-pharmacological approaches in dedicated patient groups.

Keywords: early arthritis, fatigue, RA.

Rheumatology key messages

- RA patients presenting with mono-/oligo-arthritis are more fatigued during the disease course than patients presenting with polyarthritis.
- In particular, patients presenting with mono-/oligo-arthritis and high VAS scores remain the most fatigued.
- This allows identification of a subgroup (14%) in which non-pharmacological intervention for fatigue can be of added value.

Introduction

RA is the most prevalent auto-immune inflammatory disease and is characterized by not only joint inflammation and joint damage, but also symptoms such as pain and fatigue [1]. The fatigue is described by patients as overwhelming and debilitating, and it reduces the ability to carry out daily activities [2]. The prevalence is high, as up to 80% of RA patients experience fatigue to some degree [3]. Although advances in RA treatment in the last decennia have improved most long-term outcomes, including joint damage and physical functioning [4, 5], management of fatigue has improved little [6, 7]. Currently, RA patients consider fatigue as one of the most important disease-related outcomes, and persistence of fatigue remains a large unmet need [1, 8–10].

Fatigue in RA is known to be multifactorial in nature. The severity of fatigue is directly coupled to the severity of the inflammation, and obtaining a low DAS or early remission has been associated with rapid and sustained reduction of fatigue [11, 12]. However, fatigue is only partially explained by inflammation, and other factors such as mental health, pain, sleep, and physical functioning have also been associated [13–16]. Interestingly, a recent study investigated various

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trajectories of fatigue in early RA and reported relationships with pain, mental health, and sleep quality [12]. The well-known observation that fatigue can be persistent in patients despite reaching DAS remission may be connected to these findings [15, 17, 18]. However, not all RA patients suffer from persistent fatigue, and recognizing the subgroup who remains fatigued in an early disease stage remains difficult.

We therefore aimed to characterize patients with RA at the time of diagnosis who were likely to remain fatigued during the disease course. Because of the described associations of DAS with the course of fatigue, we hypothesized that evaluation of DAS components at diagnosis may be associated with the course of fatigue. This might help in early identification of those RA patients who are most likely to experience persistent fatigue. To this end, we investigated the course of fatigue over a 5-year follow-up period, and the mean difference in level of fatigue in relation to individual DAS components at diagnosis, in two large, independent, early RA cohorts.

Methods

Patients

Cohort 1 is the Early Arthritis Cohort (EAC) in Leiden, the Netherlands. This is an ongoing population-based inception cohort in the Netherlands that was started in 1993; it is described in detail elsewhere [19]. In short, consecutive patients with recent-onset clinical arthritis with symptom duration of <2 years were included. Only those patients with a clinical diagnosis of RA plus fulfilment of the 1987 or 2010 ACR criteria were included in this current study [20, 21]. Patients were treated in line with national and international guidelines, as described in detail by Matthijssen *et al.* [5] The initial treatment generally consisted of MTX, and a treat-to-target approach was used. Written informed consent was obtained from all patients. The study was approved by the local Medical Ethics Committee of the LUMC.

Data from the Treatment in the Rotterdam Early Arthritis Cohort (tREACH) were studied for validation (cohort 2). This multicentre stratified single-blinded randomized controlled clinical study included patients of ≥18 years and with recent-onset arthritis. Again, for this analysis, only patients with a clinical diagnosis of RA plus fulfilment of the 1987 or 2010 ACR criteria were included [20, 21]. The treatment protocol is described in detail elsewhere; also here treatment adjustments were DAS steered [22, 23]. Written informed consent was obtained from all patients. The study was approved by the local Medical Ethics Committee of the Erasmus MC (MEC-2006–252).

Patients' partners were involved in the design of EAC Leiden and the tREACH trial. EAC Leiden was approved by the Local Medical Ethics Committee, named 'Commissie Medische Ethiek'. Informed consent was obtained from all patients, and the study complies with the Declaration of Helsinki. tREACH Rotterdam was approved by the Local Medical Ethics Committee, named "Commissie Medische Ethiek". Informed consent was obtained from all patients, and the study complies with the Declaration of Helsinki.

Measurements

In cohort 1, DASs including the 44-swollen joint count (SJC) and 68-tender joint count (TJC) were obtained at baseline. Patients also filled out questionnaires: HAQs, 36-item Short Form Health Survey (SF-36) (from 2015 onwards), and Patient Global Assessment (PGA) [24, 25]. Blood samples were taken for routine laboratory screening, including determination of CRP, ESR, IgM RF and ACPA [26]. Follow-up visits were scheduled at 4 months and 12 months, and yearly thereafter. At every study visit, fatigue scores were obtained using a Visual Analogue Scale (VAS; 0–100 mm). Patients were asked to grade their fatigue during the last 24 hours: "Did you experience any fatigue during the last 24 hours?". Higher scores are equal to more severe fatigue.

The same measurements were undertaken in cohort 2 at baseline and during follow-up, except for the TJC, which included 53 joints. In addition, in cohort 2, the Hospital Anxiety and Depression Scale (HADS) and European Quality of Life with 5 dimensions (EQ-5D) questionnaires were filled in at baseline [27–30]. Follow-up visits occurred every 3 months [22].

Statistical analyses

The trajectory of fatigue during the first 5 years after diagnosis was explored, using a linear mixed model (LMM). Associations between individual DAS components (SJC, TJC, ESR and PGA) and fatigue over 5 years of follow-up time were assessed using a multivariable LMM, with fatigue scores as the dependent variable and the DAS components, or combinations of DAS components, as independent variables. Analyses were repeated with corrections for age and sex and were also stratified for ACPA status (anti-CCP2 positivity), because earlier literature has shown differences in fatigue levels for ACPA status [31, 32]. Analyses were performed in Stata 17.0, and two-sided *P*-values of <0.05 were considered statistically significant.

Results

Patient characteristics

In all, 1560 consecutive RA patients from the EAC (cohort 1) and 415 RA patients from tREACH (cohort 2) were studied. The baseline characteristics are reported in Table 1. Two-thirds of patients were female subjects, and 44% and 51% of the EAC and tREACH patients, respectively, were ACPA-positive, in line with earlier observations in these and other early arthritis cohorts [14, 15, 33].

Table 1. Baseline characteristics of RA patients included in both cohorts

Variable	Cohort 1 *n* = 1560	Cohort 2 *n* = 415
Age, mean (S.D.)	58 (15)	54 (14)
Female sex, *n* (%)	1018 (65)	279 (67)
Symptom duration in weeks, median (IQR)	16 (8–33)	21 (13–30)
DAS44, mean (S.D.)	3.6 (1.20)	3.3 (0.96)
SJC44, median (IQR)	6 (3–11)	7 (4–12)
TJC68/53, median (IQR)	10 (5–18)	10 (5–15)
ESR, median (IQR)	27 (11–43)	21 (12–38)
ACPA positivity, *n* (%)	683 (44)	213 (51)
RF positivity, *n* (%)	813 (52)	209 (50)
Fatigue (VAS), median (IQR)	50 (20–70)	52 (28–73)
Pain (VAS), median (IQR)	56 (37–71)	60 (30–80)
PGA (VAS) score, median (IQR)	40 (20–60)	52 (30–68)
HAQ, median (IQR)	1 (0.5–1.5)	1.0 (0.4–1.5)

IQR: interquartile range; PGA: Patient Global Assessment; SJC44: Swollen Joint Count (44 joints); TJC: Tender Joint Count (68 joints in cohort 1, 53 joints in cohort 2); VAS: Visual Analogue Scale.

Course of fatigue in the RA populations

The median fatigue score at diagnosis (VAS ranging 0–100) was 50 mm in cohort 1 and 52 mm in cohort 2. In cohort 1, the median fatigue score declined from 50 mm to 40 mm after 5 years. The trajectory of the fatigue is presented in Supplementary Fig. S1, available at *Rheumatology* online; the average fatigue decrease was 1.4 mm per year. In cohort 2, the median fatigue score declined from 52 mm to 41 mm and the average decrease was 1.8 mm per year (Supplementary Fig. S1, available at *Rheumatology* online). Thus, although there was a decrease in fatigue at the group level, the magnitude of this decline was small.

Fatigue severity was inversely associated with SJC and directly associated with PGA and TJC

Associations between the DAS components (SJC, TJC, ESR and PGA) at diagnosis and the severity of fatigue during the first 5 years of follow-up after diagnosis were assessed (Table 2). SJC at diagnosis was significantly and inversely associated with fatigue over time. The ESR also showed an inverse association (Table 2). The TJC and PGA, on the other hand, showed a direct (course in the same direction) relation with the severity of fatigue over time. Similar results were obtained after correction for age and sex (Supplementary Table S1, available at *Rheumatology* online). In addition, the results were similar after stratification for ACPA status (Supplementary Table S2, available at *Rheumatology* online). There was no significant interaction with time for each continuous individual DAS component at diagnosis. The associations for SJC, TJC and PGA were validated in cohort 2, except for the association with ESR at baseline (Table 2). The associations of SJC, TJC and PGA in relation to the course of fatigue were therefore further explored.

RA patients presenting with polyarthritis had less severe fatigue during the disease course

SJC was categorized into clinically relevant groups: mono-arthritis (SJC = 1), oligo-arthritis (SJC = 2–4) and polyarthritis (SJC ≥ 5). In cohort 1, RA patients presenting with oligo-arthritis were more fatigued over a 5-year follow-up period compared with RA patients with polyarthritis (Supplementary Table S3, available at *Rheumatology* online; Fig. 1A); RA patients with mono-arthritis at diagnosis also remained more fatigued. Similar results were found in cohort 2 (Supplementary Table S3, available at *Rheumatology* online, Fig. 1A). In other words, RA patients with polyarthritis at diagnosis were less fatigued over time.

Table 2. Mean differences in fatigue scores for individual DAS components

	Cohort 1		Cohort 2	
	β (95% CI)	*P*-value	β (95% CI)	*P*-value
SJC	−0.66 (−0.88, −0.44)	<0.001	−0.74 (−1.1, −0.40)	<0.001
TJC	+0.58 (+0.46, +0.70)	<0.001	+0.81 (+0.54, +1.1)	<0.001
ESR	−0.07 (−0.11, −0.03)	0.001	−0.04 (−0.14, +0.06)	0.40
PGA	+0.37 (+0.32, +0.41)	<0.001	+0.31 (0.22,+0.40)	<0.001

β is the mean difference in fatigue over the total follow-up time. A β of −0.66 means the average fatigue score over 5 years decreases by 0.66 mm for each +1 SJC. PGA: Patient Global Assessment; SJC: Swollen Joint Count (44 joints); TJC: Tender Joint Count (68 joints in cohort 1, 53 joints in cohort 2); VAS: Visual Analogue Scale.

High PGA and more tender joints at diagnosis were associated with more severe fatigue over time

PGA at diagnosis was categorized into quartiles. RA patients with PGA scores in the range of 75–100 mm experienced the most fatigue over the total follow-up period of time (in cohort 1 the VAS-score was 26 mm higher compared with the lowest quartile, data shown in Supplementary Table S3, available at *Rheumatology* online, Fig. 1B). For the other PGA quartiles there was a severity-dependent reduction, and less severe fatigue was associated with lower PGA scores at diagnosis.

In cohort 1, the median TJC was 10, and therefore TJC categorization could not be done in accordance with the SJC group classification (mono/oligo/poly). In addition, the TJC data were skewed. For these reasons, the median and interquartile range (IQR) were used for generating the TJC groups: 0, 1–5, 6–16 and ≥17 tender joints, respectively. As shown in Fig. 1C, there was a stepwise increase in fatigue severity for the these TJC groups (effect sizes in Supplementary Table S3, available at *Rheumatology* online). Again, similar findings were found in cohort 2.

RA patients with mono- or oligo-arthritis and high PGA at diagnosis remained the most fatigued over time

The findings were combined to identify the patient who remain the most fatigued. The PGA was chosen (rather than the TJC), because of the higher effect sizes of the association. Additionally, the two highest PGA quartiles were summed into 'high PGA'. Patients presenting with mono- or oligo-arthritis and high PGA were the most fatigued over time, followed by patients with polyarthritis and high PGA (Fig. 2, Table 3). The results were similar after correction for age and sex, and when ACPA-positive and ACPA-negative RA subgroups were considered separately (Supplementary Tables S4 and S5, available at *Rheumatology* online).

Splitting the high PGA group showed that, in the group presenting with a mono- or oligo-arthritis, patients with a PGA score of ≥75 mm had even more severe fatigue compared with those with a PGA of between 50 mm and 75 mm. However, the PGA ≥ 75 mm group was small (Supplementary Fig. S2, available at *Rheumatology* online).

Finally, in cohort 1, the TJC categories were incorporated into the grouping. This resulted in eight different categories for combinations of SJC, TJC and PGA. Patients with mono- or oligo-arthritis and high PGA and TJC had the most severe persistent fatigue (Supplementary Fig. S3, available at *Rheumatology* online). The differences between the other seven groups were smaller, and this additional categorization seemed less helpful in finding meaningful differences in fatigue between the groups.

Subsequently, the four groups, based on mono/oligo and polyarthritis and presence/absence of high PGA, were studied in the validation cohort, cohort 2 (Fig. 2, Table 3). Here, also, patients presenting with a mono- or oligo-arthritis and high PGA remained most fatigued over time. To estimate the size of this subgroup in the total RA population, cohort 1 was used, because it is a population-based inception cohort in which consecutive RA patients from the region have been included. This group is estimated to be 14% (216/1560) of the total RA population. When splitting between PGA of 50–75 mm and ≥75 mm, the groups were estimated to be 11% and 3% of the total RA population, respectively.

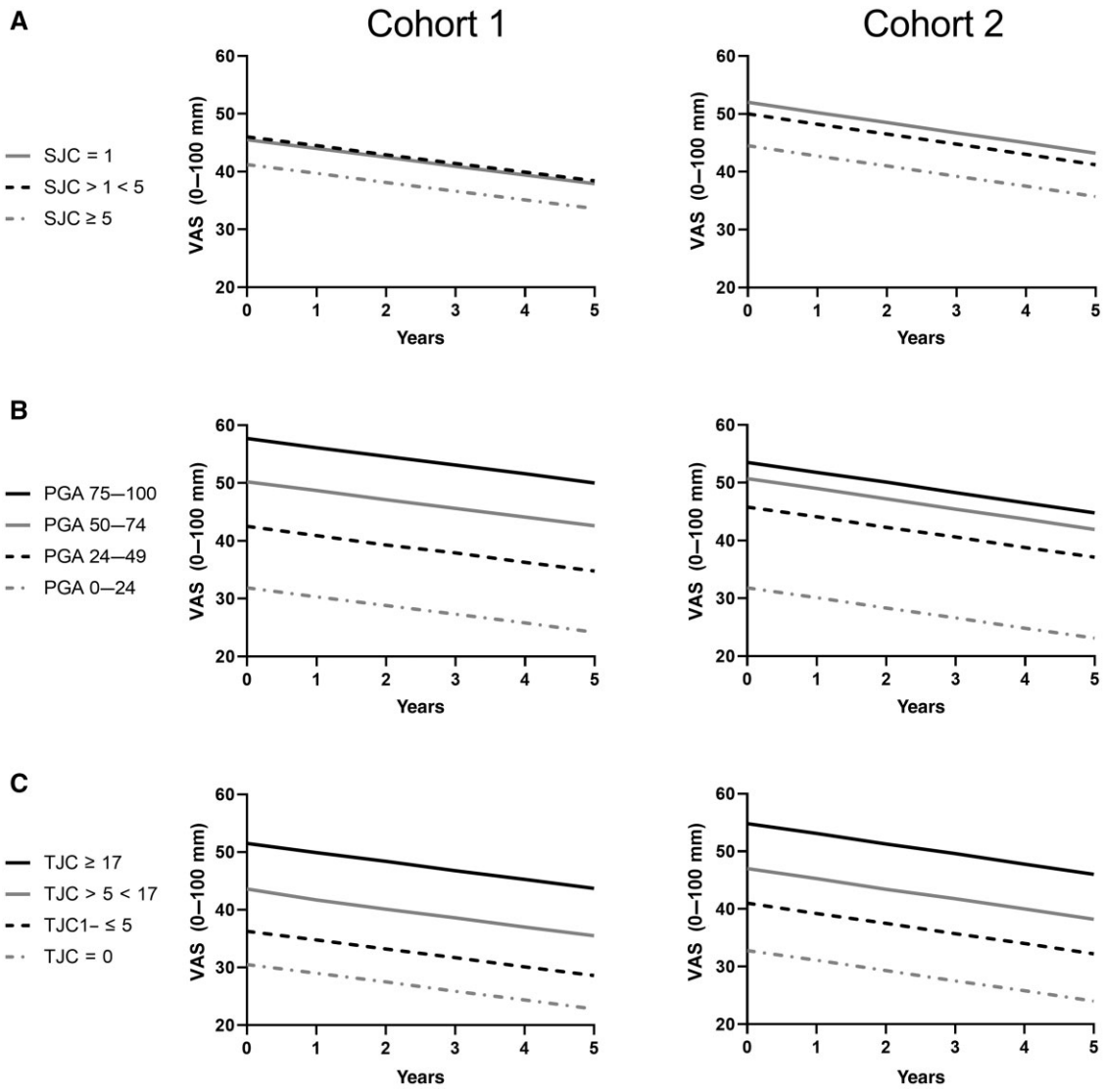

Figure 1. Fatigue trajectories stratified for individual DAS components at diagnosis. Depicted are mean effect sizes of fatigue scores stratified for different DAS components at diagnosis. (A) Stratification based on swollen joint count. (B) Stratification based on patient global assessment. (C) Stratification based on tender joint count. SJC: swollen joint count; PGA: patient global assessment; TJC: tender joint count

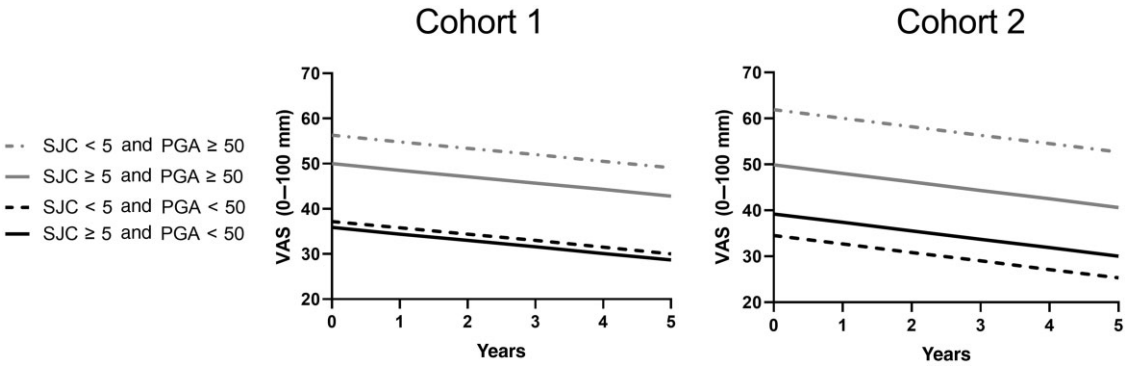

Figure 2. Fatigue trajectories stratified for combined DAS characteristics at diagnosis. Depicted are mean effect sizes of fatigue scores stratified for the various subgroups. The subgroups are based on combined DAS characteristics at diagnosis. SJC: swollen joint count; PGA: patient global assessment

Patient characteristics at diagnosis were comparable in the various subgroups

The patient characteristics of the four subgroups of cohort 1 and 2, as shown in Fig. 2, are provided in Supplementary Tables S6 and S7, available at *Rheumatology* online. Except for the differences that are related to the grouping, no obvious differences were present; although the group that presented with mono- or oligo-arthritis and high PGA had

Table 3. Mean differences in fatigue scores stratified for combined DAS characteristics at diagnosis

	Cohort 1		Cohort 2	
	β (95% CI)	*P*-value	β (95% CI)	*P*-value
SJC < 5 and PGA ≥ 50	Ref	Ref	Ref	Ref
SJC ≥ 5 and PGA ≥ 50	−6.3 (−13, +0.21)	0.058	−12 (−23, −0.61)	0.039
SJC < 5 and PGA < 50	−19 (−27, −11)	<0.001	−27 (−46, −8.4)	0.005
SJC ≥ 5 and PGA < 50	−20 (−27, −14)	<0.001	−23 (−34, −11)	<0.001

β is the mean difference in fatigue over the total follow-up time. A β of −6.3 means the average fatigue score decreases by 6.3 mm if patients have ≥5 swollen joints and a PGA of ≥50 mm, compared with patients with a SJC of <5 and a PGA of ≥50 mm at diagnosis. Corresponding fatigue trajectories for the subgroups are depicted in Fig. 2. PGA: Patient Global Assessment; SJC: Swollen Joint Count (44 joints).

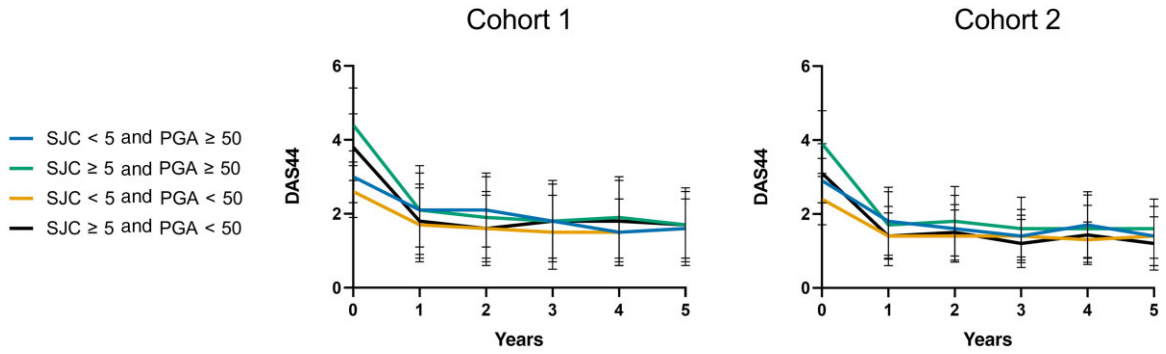

Figure 3. DASs over time for the various subgroups. Depicted are unmodelled means (and S.D.s) of DASs over time for the various subgroups (based on swollen joint count and patient global assessment at diagnosis) for both cohorts. SJC: swollen joint count; PGA: patient global assessment

slightly more female subjects (72% *vs* 61–66% in the other three groups).

Because fatigue and PGA evaluations may be related to other domains, and these may also differ between patient groups, we examined whether the four groups of cohort 1and 2 differed at baseline in health-related quality of life, and whether the four groups of cohort 2 differed at baseline in quality of life and HADS scores. As presented for the Physical Component Summary (PCS) and Mental Component Summary (MCS) from the SF-36 in Supplementary Fig. S4 (available at *Rheumatology* online), patients presenting with mono- or oligo-arthritis and high PGA had no relevant differences in scores for the PCS and MCS compared with the other three groups. Also, the anxiety and depression scores from the HADS and EQ-5D questionnaire did not show relevant differences at baseline in cohort 2 (represented in Supplementary Fig. S5, available at *Rheumatology* online). Thus, although patient-reported outcomes are often multifactorial, we did not see other factors or signs in the data, such as depression, that were strongly associated with having mono- or oligo-arthritis with a high PGA at the time of diagnosis.

Finally, total DAS over time was plotted for the four groups in both cohorts (Fig. 3). Despite the differences at baseline, there were no relevant differences in the course thereafter during the 5-year follow-up period. Thus, the group that remained most fatigued did not differ in DAS severity over time.

Discussion

Fatigue is one of the most important patient-reported outcomes and a large unmet need in RA. Nonetheless, not all RA patients experience fatigue to the same degree, and the group that will suffer more is not yet easily recognizable at the time of diagnosis. Since both DAS at diagnosis and its decline after treatment initiation have been related to decrease in fatigue, we further explored this relationship by investigating associations between DAS components and the course of fatigue over a 5-year follow-up period in two large early-RA cohorts. This study showed that RA patients presenting with mono- or oligo-arthritis in combination with high PGA scores had the most severe persistent fatigue over time. These findings were validated in the second cohort.

At first glance, the inverse relationship between the number of swollen joints and the severity of fatigue feels counterintuitive. Especially since the course of fatigue and DAS scores have shown a direct, positive relationship, and achieving remission is associated with a decrease in fatigue over time [11, 12, 16, 34, 35]. We studied the DAS components at the time of diagnosis, rather than over time. In addition, earlier research has also found inverse relationships between joint inflammation and fatigue. A recent study observed that a higher degree of joint inflammation at US at baseline was related to less severe fatigue [11]. This finding is in line with our findings for SJC. Thus, despite direct associations between DAS and fatigue at group levels, there is accumulating data that indicate that individuals with a higher number of inflamed joints have less severe fatigue.

Multiple studies have shown that fatigue is only partly coupled to inflammation, and that pain, mental health, sleep, and physical functioning also contribute to the variation in fatigue [35, 36]. Likewise, a recent mediation study in longitudinal data suggested that many factors, such as mental health and sleep, other than inflammation are important [12]. In our

data, the PGA was strongly related to a severe course of fatigue. Intuitively, the PGA is a proxy for general well-being and related factors [37].

For the aforementioned reasons, the subgroups of RA patients were studied in relation to health-related quality of life, anxiety, and depression. In these measures, RA patients with high PGA scores were roughly comparable with those in the other subgroups. This argued against another dominant factor, such as depression, explaining the differences in fatigue between the four groups.

One may wonder whether (some) patients presenting with few swollen joints and high PGA have (or may develop) secondary FM. In both cohorts together, only 5 patients officially received this diagnosis. However, there may be a grey area or continuum between unexplained fatigue and FM, and it must be noted that official criteria for diagnosing/classifying secondary FM are absent [38, 39]. However, while underreporting of secondary FM cannot be ruled out, the group of patients with few swollen joints and high PGA comprised 14% of the total RA population, a prevalence that may be higher than that expected for FM.

We studied the DAS components at baseline, because we wished to identify those RA patients who remained the most fatigued at baseline, using markers that are regularly assessed in clinical practice. In other words, and in contrast to previous studies, we did not wish to study the correlation between change in DAS with change in fatigue. Patients in both of our cohorts had a treat-to-target treatment approach, and in each the DAS course did not differ between the four PGA groups. Thus, the differences in fatigue were not explained by differences in DAS during the disease course.

The number of RA patients in the mono- or oligo-arthritis with high PGA group ($\geq$50 mm) represented 14% of the total RA population when using a PGA cut-off of 50 mm, and 3% when using a PGA cut-off of 75 mm at baseline. Recognizing that these patients will likely suffer the most from persistent fatigue, they could most probably benefit from the early start of non-pharmacological interventions in addition to starting DMARD therapy. Two recent randomized controlled trials evaluated the effect of (remote) cognitive behavioural therapy on fatigue experienced in patients with inflammatory rheumatic diseases and showed positive beneficial effects [40, 41]. Presuming that the effects from cognitive behavioural therapy might be enhanced if these interventions were started in an earlier disease phase, the present results might support a dedicated two-way tracked treatment for a small subgroup of RA patients. In these patients, treatment with DMARDs could be combined with psychological interventions aimed at reducing fatigue.

We studied the course of fatigue without using a cut-off, as we felt that any choice for categorizing or labelling fatigue as 'severe' vs 'non-severe' and 'persistent' vs 'non-persistent' may be arbitrary. By showing the VAS scores of fatigue over time, the actual data can be interpreted. However, we did use categories for combinations of the individual DAS components to identify subgroups. This may promote uptake in clinical practice.

A possible limitation of this study is that fatigue was measured with the VAS and not with more extensive questionnaires like the Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire (BRAF MDQ) or the Multidimensional Assessment of Fatigue (MAF). While these questionnaires would have yielded more information, the fatigue VAS scores in RA have good test–retest and sensitivity-to-change reliability [42].

A strength of this study is the presence of a validation cohort. In total, a 5-year disease course for 1975 early-RA patients was studied, and the replication of the findings shows the robustness of the current results.

Changes in a VAS of $\geq$10 mm are generally considered clinically relevant. Although the overall decline in the fatigue scores was small, as has been described before for both cohorts [6, 7], it is interesting to note that the reduction in severity of the fatigue in RA patients presenting with mono- or oligo-arthritis and a high PGA (>50) is well above this minimal clinically important difference.

In conclusion, we showed that RA patients presenting with mono- or oligo-arthritis and high PGA, defined as $\geq$50 mm, have a severe course of fatigue. These RA patients can be easily recognized at diagnosis, using day-to-day assessments from our outpatient clinics. Future studies on the efficacy of additional non-pharmacological treatments, such as cognitive behavioural therapy, preferentially within this subgroup of RA patients, are needed, because these patients have the highest unmet need.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Contribution statement

A.B., M.V., P.d.J. and A.H.M.v.d.H.-v.M. were involved in study conception and design. M.V., A.H.M.v.d.H.-v.M., A.L. and P.d.J. contributed to collection of data. A.B. and M.V. performed the data analysis. M.V., A.B. and A.H.M.v.d.H.-v.M. interpreted the results. A.B. and A.H.M.v.d.H.-v.M. wrote the first version of the manuscript. All authors critically revised the manuscript and approved the final version.

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