Longitudinal trajectories of fatigue in early RA

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Longitudinal trajectories of fatigue in early RA: the role of inflammation, perceived disease impact, and early treatment response

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Abstract

Objectives. Fatigue is common in rheumatoid arthritis (RA). We aimed to explore its longitudinal course, predictors, and association with disease activity in early RA.
Methods. Data came from the 2-year treat-to-target trial Care in early RA (CareRA) and its 3-year extension. Fatigue was measured on visual analogue scale, Multidimensional Fatigue Inventory, and Short Form-36 (SF-36) Vitality. Longitudinal fatigue trajectories were identified with multivariate growth mixture modelling. Early predictors of fatigue, and the association of fatigue and its trajectories with disease activity and clinical/psychosocial outcomes, were studied with linear mixed models and multilevel mediation.
Results. We included 356 and 244 patients in 2-year and 5-year analyses, respectively. Four fatigue trajectories were identified: Rapid, Gradual, and Transient improvement, and Early Deterioration, including 10%, 14%, 56%, and 20% of patients. Worse pain, mental health and emotional functioning were seen in the Early Deterioration group. Higher pain, patient global assessment (PGA) and disability (HAQ), lower SF-36 mental components, and fewer swollen joints at baseline predicted higher fatigue over 5 years, while early disease remission strongly improved 5-year fatigue. The association between SDAI and fatigue was mediated by PGA, pain, mental health, and sleep quality.
Conclusions. Although fatigue evolves dynamically over time in early RA, most patients do not achieve sustained fatigue improvement despite intensive DMARD-therapy. Higher 5-year fatigue levels were seen in patients with more perceived disease impact and fewer swollen joints at baseline. Conversely, early inflammatory disease control strongly improved long-term fatigue, pointing towards an early window of opportunity to prevent persistent fatigue.

Keywords: rheumatoid arthritis - fatigue - patient-reported outcomes - longitudinal - predictors

Key messages:

- **What is already known on this topic**? Although patients with rheumatoid arthritis (RA) commonly experience fatigue as a complex unmet need, its long-term longitudinal evolution in early RA has rarely been described with multidimensional measures, and it remains unclear if disease activity directly affects this evolution.
- **What this study adds** – This study shows that fatigue is a persistent symptom in RA despite intensive DMARD-treatment, with only one-in-four patients making lasting improvements and 20% even experiencing worsening multidimensional fatigue. While more perceived disease impact and fewer swollen joints at baseline predicted higher fatigue over up to 5 years of follow-up, improved long-term fatigue was particularly seen when disease remission was achieved early, even when relapses of disease activity occurred later on.
- **How this study might affect research, practice or policy** – These findings support the existence of an early window of opportunity to prevent long-term fatigue in RA through prompt inflammatory disease control with pharmacological therapy. Nonetheless, pain, sleep and psychosocial determinants seem to play an important mediating role in the experience of fatigue, and clinicians should reserve specific attention for these factors to timely consider additional non-pharmacological approaches.

INTRODUCTION

Fatigue is common in rheumatoid arthritis (RA) and a major challenge in its management(1). Fatigue is an experience of severe tiredness or exhaustion not clearly caused by excessive energy expenditure(2). An estimated 10-20% of the general population regularly report significant fatigue, attributable to both physical and psychosocial causes(3–5). This burden is even more apparent in the rheumatic diseases, and 40-80% of patients with RA are affected by severe fatigue(6,7). Patients experience fatigue as overwhelming and unpredictable, inciting a vicious circle that strongly impacts quality of life(8). Moreover, people suffering from RA consider fatigue a crucial disease outcome and consistently rate it among the primary treatment goals in both established and early disease(9–11). Consequently, fatigue has long been recognized as an essential outcome to assess in RA-related trials(12,13).

Although complementary care strategies like nurse-led care(14,15), peer mentoring(16) and cognitive behavioural therapy(17) could be beneficial, assessing and managing RA-related fatigue remains challenging. Fatigue is a multidimensional symptom whose causes, experience and impact are unique for each individual(18). Therefore, it is ideally assessed with multidimensional instruments(19). However, most studies measure fatigue on a visual analogue scale (VAS), which, despite being a reliable alternative(20), might lack detail about underlying mechanisms. To comprehensively assess RA-related fatigue, understanding its root causes is crucial. Although inflammation could be involved by influencing neurotransmitters(21), the relationship between RA disease activity and fatigue is complex and confounded by cognitive and psychosocial aspects(18). For instance, while fatigue can improve with disease-modifying antirheumatic drugs (DMARDs)(22), many patients still experience fatigue despite inflammatory disease control(23–25). More insight into

contributors of persistent fatigue could highlight mechanisms other than inflammation and support management of this burden. Moreover, given its unpredictability, RA-related fatigue might evolve differently over time across specific patient subgroups(26–28).

Studies on contributors of RA-related fatigue should therefore include multidimensional fatigue measures, assessed longitudinally, starting in early disease and with multivariate methods that account for confounders(29). Moreover, contributors should be differentiated into either predisposing factors to support early identification of at-risk patients, or time-dependent associated factors, like inflammation, that could be modifiable with interventions(5). We aimed to identify predisposing and associated factors of RA-related fatigue by examining the longitudinal trajectory of multidimensional fatigue in early RA.

METHODS

Study design

Data were obtained from the Care in early RA (CareRA) trial and its extension CareRA-plus. CareRA was a 2-year, investigator-initiated, randomised controlled trial comparing several DMARD-regimens with/without glucocorticoid-bridging in DMARD-naïve patients with early RA. CareRA-plus was its 3-year observational extension. Details on the trial design have been published elsewhere (also see Supplement 1)(30,31). All participants completing CareRA were eligible for CareRA-plus. Protocols were approved by the participating centres' medical ethics committees, and all participants provided written informed consent.

Patient and public involvement

Although patients were not actively involved in designing the trial, patient-reported outcomes (PROs) to collect were selected based on daily contacts between the investigators and patients with RA, and these outcomes' relevance in early RA was confirmed in a qualitative study(9).

Outcomes

Assessment at screening included demographic characteristics, routine radiographs, rheumatoid factor and/or anti-citrullinated peptide antibodies, and comorbidities scored on the Rheumatic Diseases Comorbidity Index (RDCI). Clinical assessments during follow-up included tender/swollen joint counts (TJC28/SJC28), patient's/physician's global assessment of disease (PGA/PhGA), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). SDAI was derived as primary composite measure of disease activity(32). In addition, participants completed the Health Assessment Questionnaire (HAQ) and VAS for pain and fatigue at every visit, and the Short Form-36 (SF-36), Revised Illness Perception Questionnaire (IPQ-R) and Pittsburgh Sleep Quality Index (PSQI) at baseline and week 16, 52 and 104(33–35).

Starting from year 2, participants were assessed 6-monthly until year 5. Assessments during this phase were identical to the first 2 years, but PROs were limited to the HAQ and VAS for pain and fatigue.

Fatigue

Multiple measures of fatigue were collected, including a VAS (0-100) at every visit. Additionally, SF-36 Vitality (0-100, higher score implies less fatigue) and the Multidimensional Fatigue Inventory (MFI) were recorded at baseline and week 16, 52 and 104(36). The MFI is a

20-item questionnaire covering 5 dimensions of fatigue: General Fatigue (GF), Physical Fatigue (PF), Mental Fatigue (MF), Reduced Motivation (RM), and Reduced Activity (RA). Higher scores (4-20) indicate more fatigue.

Statistical analysis

Based on conceptual knowledge and data exploration, missingness (15% total) was assumed to be at random and handled with multiple imputation (m=20). Results were pooled using Rubin's rules wherever possible(37). Descriptive statistics were reported as means (SD) or proportions, and measures of fatigue at baseline were compared with Spearman correlation.

Before investigating distinct fatigue trajectories, we first studied the group-level evolution of fatigue (VAS) over time with linear mixed models (LMMs) including only participants with available 5-year data (Supplement 2A).

Based on these models, and because multidimensional fatigue measures were available during only this timeframe, the first 2 years were chosen to study longitudinal fatigue trajectories. We constructed a multivariate growth mixture model (GMM) following a three-step approach(38), with participant-specific random intercepts, and including as dependent variables the five dimensions of the MFI, SF-36 Vitality, and fatigue VAS. GMMs attempt to identify distinct classes of individuals with similar evolutions of one or more outcomes over time, while including random effects accounting for inter-individual, within-trajectory variance(39). Models were constructed for 2-5 trajectories with linear, quadratic, cubic and spline functions to model time. The optimal model was selected based on model fit statistics(40), and models deriving classes of <10% of participants were excluded to avoid overfitting (Supplement 3).

Second, after identifying trajectories, the longitudinal association of trajectory membership with clinical/psychosocial outcomes was studied with LMMs adjusted for age, gender, treatment type, autoantibodies, RDCI, and time-varying SDAI. Confidence intervals were derived through bootstrapping (5000 iterations of random sampling with replacement).

Third, baseline predictors of fatigue (VAS) over 2 and 5 years were studied with multivariable LMMs including participant-specific random intercepts and adjusted for age, gender, treatment type, and time. This method was chosen over predicting trajectory membership because it allowed to predict fatigue over the full 5-year follow-up. First, all candidate predictors were included simultaneously in an initial multivariable model and subsequently excluded through a backwards-stepwise procedure based on predictors' statistical significance, model fit statistics, and conceptual reasons. Baseline PGA, PhGA, pain and HAQ were studied in separate models because of collinearity (Spearman $r>0.60$). Additionally, early treatment response was studied as a candidate predictor, defined as "early remission with sustained control", "secondary relapse", "delayed remission", or "non-remission" based on whether remission (SDAI ≤3.3) was achieved by week 16 with/without relapse before year 2. Considering treat-to-target recommendations, relapse was defined for this purpose as loss of low-disease-activity (SDAI >11)(41). Finally, the time-varying association of fatigue with clinical/psychosocial variables was studied in similar LMMs, adjusting for age, gender, treatment type, and time. The time-varying association between SDAI and fatigue (VAS) was then studied in more detail with a multilevel mediation analysis, including these clinical/psychosocial variables as candidate mediators and clustering within participants.

P-values were adjusted for multiple comparisons with Bonferroni-Holm correction where applicable, and p-values <0.05 were considered statistically significant. All analyses were carried out in R 4.0.3 (packages: *mice*, *lcmm*, *lme4*, *lavaan*, and *lavaanPlot*).

RESULTS

In total, 379 patients were included in CareRA, of which 23 were excluded from this analysis because they did not complete the baseline MFI (Supplement 4). All remaining 356 participants were included in the 2-year analyses after imputation. Of these, 244 entered CareRA-plus and were included in the 5-year analyses. Baseline characteristics of the 2-year and 5-year study populations were similar (Table 1).

Table 1. Baseline characteristics of participants included in analyses.

	2-year data available (n = 356)	**5-year data available (n = 244)**
Age, years	52 (13)	53 (13)
Women, n (%)	243 (68)	164 (67)
BMI, kg/m^2	26 (4)	27 (4)
RF-positive, n (%)	241 (66)	169 (69)
ACPA-positive, n (%)	237 (65)	176 (72)
Erosive disease, n (%)	95 (27)	67 (27)
RDCI (0-9)	0.8 (1.1)	0.9 (1.1)
Symptom duration, months	8 (12)	8 (13)
Fatigue		
VAS, mm (0-100)	48 (24)	47 (24)
MFI General Fatigue (0-20)	14 (4)	14 (4)
MFI Physical Fatigue (0-20)	14 (4)	14 (4)
MFI Mental Fatigue (0-20)	10 (4)	10 (4)
MFI Reduced Activity (0-20)	13 (4)	13 (4)
MFI Reduced Motivation (0-20)	11 (4)	11 (4)
SF-36 Vitality (0-100)	48 (20)	48 (20)
Clinical variables		
SDAI	37 (32)	38 (33)
DAS28-CRP	4.5 (1.3)	4.5 (1.3)
TJC28 (0-28)	9 (6)	9 (6)
SJC28 (0-28)	7 (5)	7 (5)
PGA, mm (0-100)	55 (24)	55 (23)
Pain, mm (0-100)	56 (24)	55 (23)
PhGA, mm (0-100)	52 (19)	50 (18)
CRP, mg/L	10 (24)	12 (26)
ESR, mm/h	30 (23)	31 (24)
HAQ (0-3)	1.0 (0.7)	1.0 (0.7)
SF-36 PCS (0-100)	33 (10)	34 (10)
SF-36 MCS (0-100)	47 (12)	47 (12)

Results are reported as mean (SD) unless otherwise specified. *BMI = body mass index, RF = rheumatoid factor, ACPA = anti-citrullinated peptide antibody, RDCI = Rheumatic Diseases Comorbidity Index, VAS = Visual Analogue Scale, MFI = Multidimensional Fatigue Inventory, SF-36 = Short Form-36, SDAI = Simple Disease Activity Index, DAS28-CRP = Disease Activity Score in 28 joints with C-reactive protein, TJC28 = tender joint count in 28 joints, SJC28 = swollen joint count in 28 joints, PGA = patient's global assessment of disease activity, PhGA = physician's global assessment of disease activity, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, HAQ = Health Assessment Questionnaire, PCS = Physical Component Score, MCS = Mental Component Score*

Baseline fatigue

On average, participants reported moderate levels of fatigue at baseline, with a mean of 48/100 on both VAS and SF-36 Vitality, and scores of 10-14/20 on the different MFI-subscales. VAS fatigue was moderately to strongly correlated with more complex measures of fatigue (Supplement 5). However, it correlated less convincingly with measures of more cognitive fatigue, such as MFI-subscales Mental Fatigue (r=0.33), Reduced Motivation (r=0.36) and Reduced Activity (r=0.39).

Group-level fatigue evolution over 5 years

On average, fatigue (VAS) improved rapidly during the first 16 weeks, before reaching seemingly stable values (Supplement 2B). However, there continued to be significant changes over time at both the group and inter-individual level until year 2 (Supplement 2C). Between years 2 and 5, fatigue no longer changed significantly, implying that 5-year fatigue outcomes were mainly determined during the first 2 years of the trial.

Longitudinal fatigue trajectories and associated factors

Growth mixture analysis identified four latent trajectory classes for the evolution of multidimensional fatigue during the first 2 years (Figure 1). The Rapid Improvement group (n=37/356, 10%) showed a vast improvement in all fatigue measures over the first 16 weeks, before reaching stable values around week 52. In the Gradual Improvement trajectory

(n=50/356, 14%), all measures of fatigue improved more steadily until week 104. Most participants (n=198/356, 56%) were characterized by a Transient Improvement in fatigue, where fatigue decreased over the first months, but any net improvement was lost by week 52. Finally, 20% of participants showed an Early Deterioration (n=71/356) of fatigue over the first 16 weeks, before reaching stable scores at higher levels than baseline.

Compared to the Rapid Improvement group, participants with an Early Deterioration trajectory reported higher pain (VAS) over both 2 and 5 years of follow-up and had significantly lower scores on SF-36 Mental health and Emotional role functioning after adjusting for confounders like SDAI and comorbidities (Table 2). Similarly, the Gradual Improvement group scored worse than Rapid Improvers on SF-36 Mental health and Social functioning over 2 years. Similar trends suggested worse outcomes for Transient Improvers, although these differences were not significant after adjusting for multiple comparisons. No differences were found between trajectories for SDAI, HAQ, or PSQI.

Table 2. Association of fatigue trajectory with outcomes over 2 years (A) and 5 years (B).

A.	**Gradual improvement (n = 50/356, 14%)**		**Transient improvement (n = 198/356, 56%)**		**Early deterioration (n = 71/356, 20%)**	
Outcome	**ß (95% CI)**	**p-value (*)**	**ß (95% CI)**	**p-value (*)**	**ß (95% CI)**	**p-value (*)**
SDAI	0.66 (-2.61 to 3.93)	0.69 (0.96)	-0.10 (-0.07 to 0.04)	0.94 (0.94)	0.42 (-0.36 to 1.20)	0.79 (0.79)
Pain (VAS)	3.01 (-2.93 to 8.95)	0.32 (0.96)	6.57 (1.69 to 11.45)	***0.008 (0.06)***	9.82 (4.19 to 15.45)	**< 0.001 (0.004)**
HAQ	0.12 (-0.04 to 0.28)	0.14 (0.58)	0.08 (-0.06 to 0.22)	0.26 (0.53)	0.08 (-0.08 to 0.24)	0.27 (0.55)
SF-36 MH	-8.98 (-14.92 to -3.04)	**0.003 (0.018)**	-5.94 (-10.76 to -1.12)	***0.016 (0.10)***	-9.42 (-14.93 to -3.91)	**< 0.001 (0.005)**
SF-36 SF	-12.09 (-19.40 to -4.78)	**0.001 (0.007)**	-5.01 (-11.09 to 1.07)	0.11 (0.53)	-8.56 (-15.48 to -1.64)	***0.015 (0.06)***
SF-36 RE	-12.44 (-24.08 to -0.80)	0.04 (0.18)	-7.77 (-17.45 to 1.91)	0.12 (0.53)	-14.87 (-25.89 to -3.85)	**0.008 (0.04)**
PSQI global	0.66 (-0.69 to 2.01)	0.33 (0.96)	0.82 (-0.28 to 1.92)	0.15 (0.53)	1.10 (-0.15 to 2.35)	0.086 (0.26)
B.	**Gradual improvement (n = 40/244, 16%)**		**Transient improvement (n = 131/244, 54%)**		**Early deterioration (n = 52/244, 21%)**	
Outcome	**ß (95% CI)**	**p-value**	**ß (95% CI)**	**p-value**	**ß (95% CI)**	**p-value**
SDAI	-0.12 (-3.47 to 3.23)	0.95 (1.00)	-0.53 (-3.45 to 2.39)	0.72 (0.72)	0.64 (-2.61 to 3.89)	0.70 (0.70)
Pain (VAS)	1.87 (-5.48 to 9.22)	0.62 (1.00)	5.10 (-4.94 to 15.14)	0.12 (0.35)	9.77 (2.64 to 16.90)	**0.007 (0.021)**
HAQ	0.08 (-0.14 to 0.29)	0.47 (1.00)	0.11 (-0.09 to 0.31)	0.26 (0.52)	0.13 (-0.09 to 0.35)	0.25 (0.50)

Results were obtained from multivariate linear mixed models (LMM) with the reported outcome as the dependent variable and fatigue trajectory as the predictor (rapid improvement trajectory as the reference class). The SF-36 vitality dimension was not studied as an outcome since it was included as a determinant of the fatigue trajectories. All models were adjusted for age, gender, treatment arm, autoantibody status, SDAI, and RDCI as possible confounders. Confidence intervals were derived through bootstrapping (5000 iterations of random sampling with replacement).

* P-value adjusted for multiple comparisons with Bonferroni-Holm-correction. Since correction was applied separately for each trajectory and for 2 and 5-year outcomes, up to 7 p-values were considered in these adjustments.

SDAI = Simple Disease Activity Index, CRP = C-reactive protein, VAS = Visual Analogue Scale, HAQ = Health Assessment Questionnaire, SF-36 = Short Form-36, MH = mental health, SF = social functioning, RE = emotional role functioning, PSQI = Pittsburgh Sleep Quality Index

Predictors and associated factors of long-term fatigue

During variable selection, no predisposing effects on fatigue over both 2 and 5 years were found for autoantibodies, RDCI, symptom duration, erosive disease, or BMI (Supplement 6). Similarly, age, gender, and treatment type did not predict long-term fatigue but were kept in the final models as covariates.

In these final models, higher PGA, pain and HAQ, and lower SF-36 MCS at baseline were associated with more fatigue over both 2 and 5 years of follow-up (Table 3). Furthermore, higher 2-year and 5-year fatigue levels were seen in patients with a lower baseline SJC28 and in patients with delayed (n=98) or non-remission (n=121) rather than early remission with sustained control (n=85). Among patients with early remission, no difference in 2-year or 5-year fatigue was found with sustained control compared to secondary relapse (n=52).

Table 3. Baseline and early predictors of fatigue (VAS) levels over time.

	Baseline – year 2 (n = 356)		**Baseline – year 5 (n = 244)**	
Baseline predictors	**ß (95% CI)**	**p-value (*)**	**ß (95% CI)**	**p-value (*)**
BMI (kg/m^2)	0.43 (0.04 to 0.82)	***0.036 (0.14)***	-	-
PGA (0-100)	0.22 (0.14 to 0.30)	**< 0.001 (< 0.001)**	0.15 (0.05 to 0.25)	**0.002 (0.01)**
PhGA (0-100)	0.21 (0.09 to 0.33)	**0.001 (0.007)**	0.10 (-0.05 to 0.25)	0.20 (0.40)
SJC (0-28)	-0.64 (-1.13 to -0.15)	**0.010 (0.05)**	-0.91 (-1.56 to -0.26)	**0.006 (0.04)**
TJC (0-28)	0.18 (-0.25 to 0.61)	0.42 (0.84)	0.59 (0.04 to 1.14)	0.038 (0.15)
CRP (mg/dL)	0.02 (-0.06 to 0.10)	0.56 (0.84)	0.00 (-0.08 to 0.09)	0.92 (0.92)
Pain (0-100)	0.21 (0.13 to 0.29)	**< 0.001 (< 0.001)**	0.17 (0.08 to 0.26)	**< 0.001 (0.004)**
HAQ (0-3)	5.22 (2.18 to 8.26)	**0.001 (0.007)**	4.67 (1.08 to 8.26)	**0.011 (0.05)**
SF-36 MCS (0-100)	-0.36 (-0.52 to -0.20)	**< 0.001 (< 0.001)**	-0.42 (-0.60 to -0.24)	**< 0.001 (< 0.001)**
Treatment response$^{\perp}$				
Secondary relapse (n=52/356)	5.24 (-0.39 to 10.87)	0.07 (0.21)	5.37 (-1.04 to 11.78)	0.10 (0.30)
Delayed remission (n=98/356)	9.87 (4.91 to 14.83)	**< 0.001 (< 0.001)**	10.15 (4.39 to 15.91)	**< 0.001 (0.005)**
Non-remission (n=121/356)	21.66 (17.15 to 26.17)	**< 0.001 (< 0.001)**	20.89 (15.48 to 26.30)	**< 0.001 (< 0.001)**

Results were obtained from multivariable linear mixed models (LMMs) with fatigue (VAS) as the dependent variable and a participant-specific random intercept. Fatigue (VAS) and SF-36 Vitality were not studied as baseline predictors since these models were intended to study average fatigue levels over time rather than fatigue evolution relative to baseline. PGA, PhGA, pain, and HAQ were included in separate models because of collinearity (Spearman r>0.60). All models were adjusted for age, gender, treatment type, and time as confounders.

* P-value adjusted for multiple comparisons with Bonferroni-Holm-correction. Since correction was applied separately for 2 and 5-year outcomes, up to 12 p-values were considered in these adjustments.

$^{\perp}$ Early remission with sustained control as reference category (n=85/356). This model was adjusted for age, gender, treatment type, time, and baseline SDAI.

BMI = Body Mass Index, PGA = patient's global assessment, PhGA = physician's global assessment, SJC = swollen joint count, TJC = tender joint count, CRP = C-reactive protein, HAQ = Health Assessment Questionnaire, SF-36 MCS = Short Form-36 Mental Component Score, SDAI = Simple Disease Activity Index

In the time-varying LMMs, only pain, mental health and sleep quality were independently associated with fatigue over time (Supplement 7). Adjusted for other associated factors and multiple comparisons, SDAI, HAQ, IPQ-R, and the remaining SF-36 psychosocial dimensions were not associated with fatigue over time.

Moreover, the association between SDAI and fatigue (VAS) was fully mediated by PGA, pain, mental health, and sleep quality (Figure 2). Specifically, although there was a significant positive association between SDAI and VAS (standardized ß=0.39[0.31 to 0.46]), this association was fully explained by PGA (ß=0.19[0.10 to 0.28]) and pain (ß=0.18[0.11 to 0.26]), and to a lesser extent by SF-36 Mental health (ß=0.04[0.02 to 0.06]) and PSQI global score (ß=0.02[0.00 to 0.04]) (Supplement 8).

DISCUSSION

To our knowledge, this study is the first to describe in detail the longitudinal course of fatigue in early RA with rigorous, multivariate growth modelling methods and based on multidimensional measures of fatigue. Our results suggest that fatigue evolves dynamically during the first treatment months but often remains a persistent symptom, with less than 25% of patients experiencing lasting improvements despite intensive DMARD-treatment. Remarkably, one-in-five patients in our study even experienced worsening fatigue during early treatment, and these patients also reported more pain and impaired mental health over time. Moreover, higher scores on pain, disability, PGA, and impaired mental health at baseline were associated with persistently higher fatigue over 5 years of follow-up. However, the strongest predictor of long-term fatigue in our study was early achievement of disease remission, even when disease activity later relapsed. Despite this, mediation analysis suggested that the relationship between disease activity and fatigue is complex and fully

mediated by the PGA, pain, mental health, and sleep quality, implying a mainly indirect relation between fatigue and inflammation.

Several studies in early RA cohorts have suggested that the first treatment months are the most influential to determining long-term fatigue. Although long-term follow-up studies have identified improvements in group-level fatigue during the first year of treatment, fatigue remained largely unchanged during subsequent years(42,43). In a recent publication from the CATCH-cohort, the average improvement in fatigue was most pronounced during the first 3 months of treatment(44). Similarly, in our study, group-level fatigue improved predominantly during the first 4 months, whereas no significant changes were apparent between year 2 and year 5.

However, we found important inter-individual variation in fatigue evolution over time, characterized by either rapid, gradual, or transient improvement, or by early deterioration. These longitudinal trajectories depict fatigue as a persistent symptom, with most patients experiencing only temporary improvement. This is in line with previous longitudinal studies on RA-related fatigue, which have either reported stable trajectories over time(27,28) or found that only up to a third of patients experienced an improving trajectory(26,43). However, the trajectories we identified seem more dynamic, possibly because fatigue was assessed in detail during early disease, with both short assessment intervals and multidimensional instruments. For instance, 20% of our participants not only made no sustained improvement in fatigue, but even experienced worsening fatigue during the first treatment months. To our knowledge, only one study has reported a similar deterioration of fatigue during the early course of RA, although this did not result in a distinct trajectory(43). Our findings contribute to the awareness of a crucial unmet need for patients with RA,

particularly since worsening fatigue was associated with more pain and impaired mental health irrespective of disease activity. Furthermore, ample research has shown that fatigue often persists despite improved treatment, and even when achieving disease remission(23,25,42,45).

Stated differently, the association between disease activity and fatigue appears more complex than one might assume. We found that disease activity was indeed positively correlated with fatigue over time, but this association was fully mediated by the PGA and pain, and to a lesser extent by mental health and sleep quality. Conversely, joint counts and classical inflammatory markers played no apparent role in this association. These findings add to several studies reporting that fatigue is predominantly associated with pain, sleep, and psychological aspects like mood and self-efficacy, whereas inflammatory markers seem to contribute little to this association directly(46–48). Similarly, it has been suggested that improvements in fatigue with DMARDs are largely due to improved pain(7).

Because of these associations between fatigue and other PROs, it is unsurprising that most studies have identified PGA, pain, and mental health as baseline predictors of fatigue(26,43,49). Our findings confirm this, with higher baseline pain, PGA, and HAQ, and lower SF-36 MCS associated with consistently higher levels of fatigue over 5 years of follow-up. Strikingly though, a higher baseline swollen joint count predicted lower long-term fatigue. These findings add to recent results of the ARCTIC-trial, in which more swollen joints and higher ultrasound inflammation at baseline were associated with less fatigue at year 2, while a predisposing effect was seen for PGA(50). Together, results of both trials could indicate that RA-related fatigue is a composite of inflammation-driven fatigue and fatigue with a stronger

psychosocial background. Nevertheless, to improve long-term fatigue outcomes, it appears particularly important to achieve disease control early, likely through positive effects on both these pathways(51). For instance, both our study and the ARCTIC-trial identified early remission as the strongest predictor of long-term fatigue. In our study, this effect was evident from early on to even 5 years of follow-up. Moreover, our results add the crucial insight that these beneficial effects of early remission on long-term fatigue remain even when relapses of disease activity later occur, pointing towards an early window of opportunity to prevent long-term fatigue in RA.

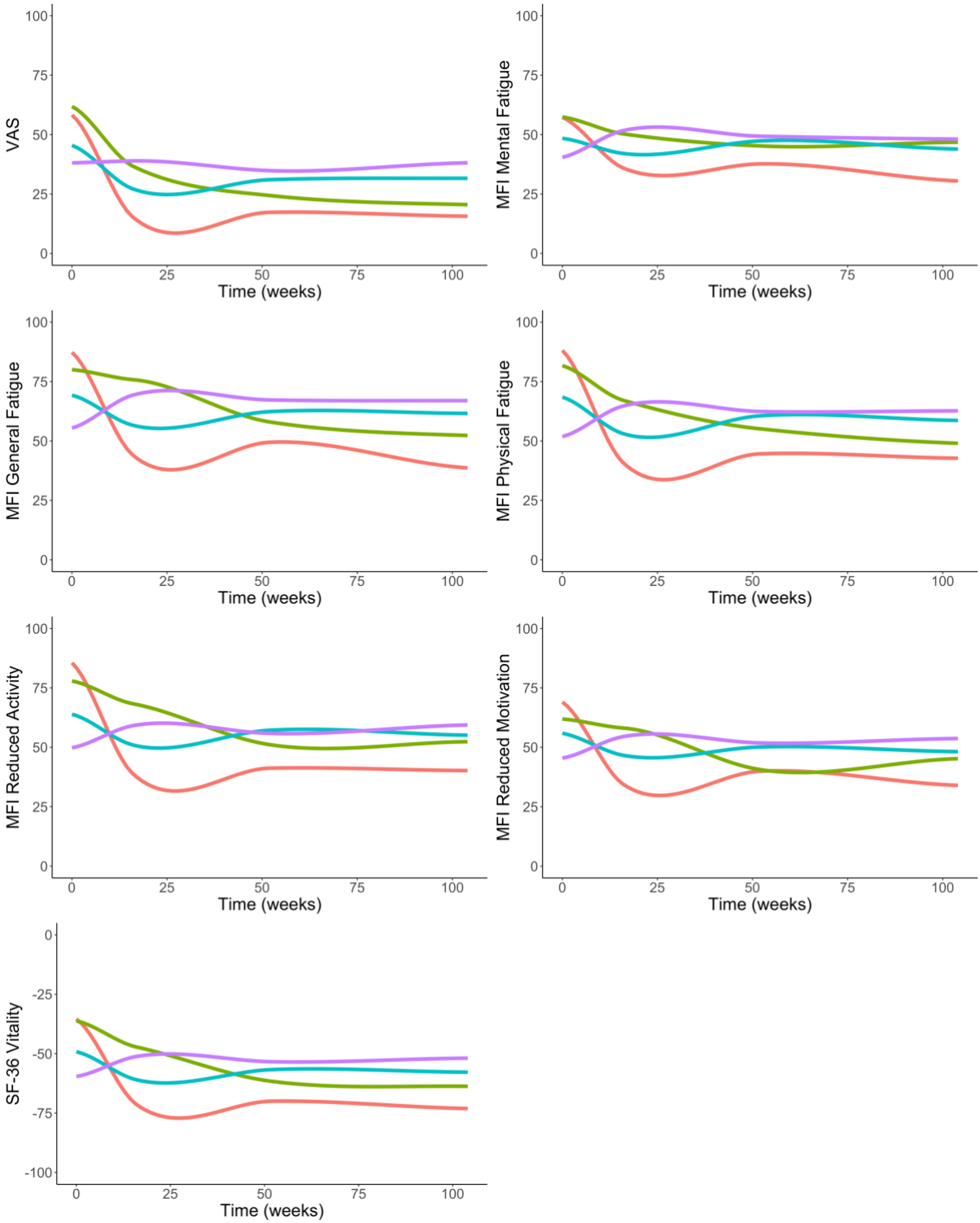
Our study has some limitations. Whereas during the first two trial years fatigue was measured frequently with multiple instruments, fatigue assessments during CareRA-plus were limited to a 6-monthly VAS. Consequently, our finding of a more stable fatigue course during this timeframe might be influenced by study design.

However, several strengths add credibility to our findings. Most studies assess fatigue on a VAS or numeric rating scale. While our results showed that a VAS correlates well with measures of general and physical fatigue, it seemed to capture aspects related to mental fatigue and motivation less convincingly. We assessed fatigue not only through several multidimensional instruments, but also longitudinally for up to 5 years in a pragmatic clinical trial representative for an early RA patient population. Moreover, fatigue was measured frequently during the first treatment months and studied with rigorous statistical methods, providing a uniquely detailed picture of its complexity in early RA.

Conclusion

We showed that fatigue is a dynamic but persistent symptom in early RA, with less than 25% of patients making lasting improvements despite intensive DMARD-treatment, and one-in-five patients even experiencing worsening fatigue during the first months. However, achieving early disease remission strongly improved fatigue over up to 5 years of follow-up, even when disease activity later relapsed. Thus, the first step to managing fatigue in early RA should be to seize this window of opportunity for prompt inflammatory disease control. Nonetheless, the association between disease activity and fatigue seems to be mainly explained by pain, mental health, and sleep quality. Moreover, higher fatigue over time was seen in patients who at baseline had more perceived disease impact and fewer swollen joints. Clinicians should thus reserve specific attention for the psychosocial determinants of fatigue and timely consider additional non-pharmacological approaches, particularly when no rapid improvement is made with pharmacotherapy.

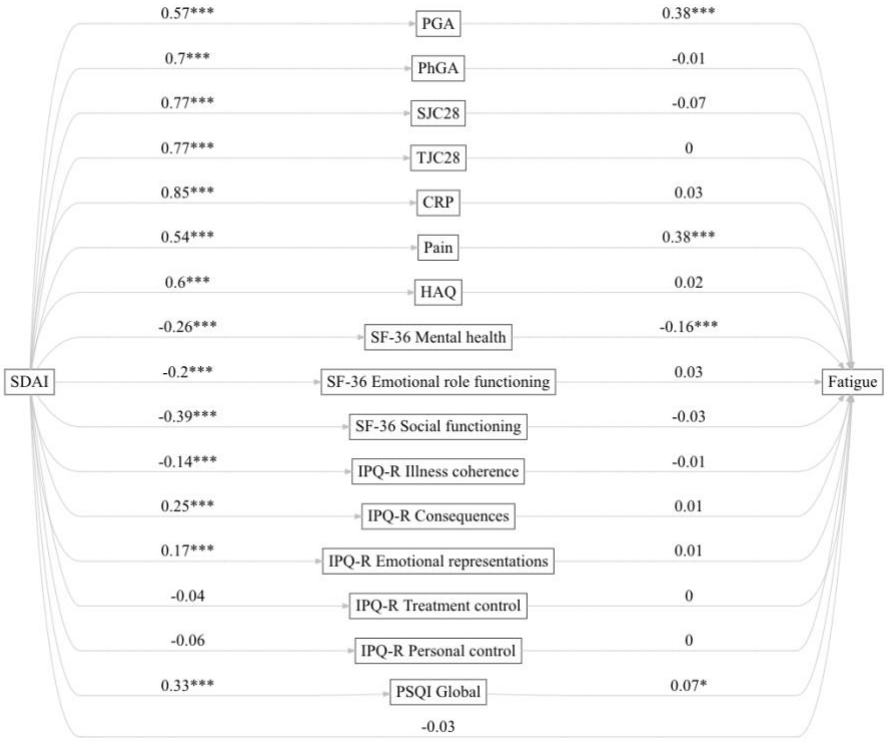
Figure 1. Latent trajectories of fatigue evolution over the first 2 years in CareRA (n = 356).



Red = Rapid Improvement (10%); Green = Gradual Improvement (14%); Blue = Transient Improvement (56%); Purple = Early Deterioration (20%). Trajectories were derived through multivariate growth mixture modelling with participant-specific random intercepts and including as dependent variables the five dimensions of the MFI, SF-36 Vitality, and fatigue VAS. All fatigue outcomes were standardised (0-100) for comparability.

VAS = Visual Analogue Scale, MFI = Multidimensional Fatigue Inventory, SF-36 = Short Form-36

Figure 2. Mediation analysis of the association between SDAI and fatigue (VAS) over time.



Results were obtained from multilevel mediation analysis studying the association between SDAI and fatigue (VAS) across baseline, week 16, 52 and 104, with participant-specific random intercepts (n = 356). Reported are the standardized regression coefficients with indicators of significance (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$).

VAS = Visual Analogue Scale, SDAI = Simple Disease Activity Index, PGA = patient's global assessment, PhGA = physician's global assessment, SJC28 = swollen joint count in 28 joints, TJC28 = tender joint counts in 28 joints, CRP = C-reactive protein, HAQ = Health Assessment Questionnaire, SF-36 = Short Form-36, IPQ-R = Revised Illness Perception Questionnaire, PSQI = Pittsburgh Sleep Quality Index

DECLARATIONS

Ethics approval and consent to participate: The study protocol (S51411; EudraCT number 2008-007225-39; S53336 for CareRA-plus) was approved by the University Hospitals Leuven Ethics Committee and all participants provided written informed consent before participation.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: PV, JJ and RW designed the study protocol in collaboration with the CareRA study group. Investigators of the CareRA study group, including PV and RW recruited and enrolled patients and were responsible for daily patient management. PV and JJ were responsible for coordination of the trial and collection of data. MD analyzed the data and drafted the article. DDC, PV, RW, SP, DB, and JJ revised the article critically for content. All authors gave final approval of the manuscript to be published.

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