The Longitudinal Course of Fatigue in Rheumatoid Arthritis: Results from the Norfolk Arthritis Register

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ABSTRACT. ***Objective.*** Fatigue is common and burdensome in rheumatoid arthritis (RA). Despite RA fatigue progression varying significantly between individuals in practice, existing longitudinal analyses only examine symptom advancement on a population level. This study aimed to determine fatigue trajectories at an individual level and to characterize those patients with the poorest prognosis, with a view to enabling earlier interventions.

Methods. Patients with RA reporting clinically relevant baseline fatigue (≥ 20 mm on a 0–100 mm visual analog scale) were identified from a longterm inflammatory polyarthritis cohort (the Norfolk Arthritis Register). Fatigue changes from baseline to 1- and 4-year followups were calculated, and sex-stratified group-based trajectory modeling (GBTM) determined trajectories of the symptom between which baseline characteristics were compared.

Results. Among 338 patients, only minimal average changes were observed between recruitment to 1 year (6.0 mm, SD 26.9) and 4 years (5.5 mm, SD 29.3). This was despite 45.6% and 40.7% of participants reporting clinically significant improvements (≥ 10 mm) at these respective followups. GBTM revealed varied trajectories of fatigue, which for both sexes consisted of Improved (men, n = 48 and women, n = 81) or persistent Moderate-high paths (n = 54, n = 105), and further included a persistent High trajectory in women (n = 50). Participants who followed persistent trajectories were best distinguished from improvers by patient-reported rather than demographic or clinical variables.

Conclusion. Among patients with RA presenting with clinically relevant fatigue, distinct longitudinal symptom trajectories were identified on an individual level despite nominal average changes in fatigue on a group level. It is possible to identify and characterize subgroups of participants who report persistent fatigue and should therefore be targeted to receive future fatigue-alleviating interventions.
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FATIGUE RHEUMATOID ARTHRITIS TRAJECTORY

Fatigue is a dominant and burdensome symptom in patients with rheumatoid arthritis (RA). It affects up to 80% of patients[1,2] and is strongly associated with longterm disability and difficulties with maintaining employment[3,4,5,6,7,8]. However, little is known about the longitudinal course of this symptom that is considered to be a principal determinant of poor quality of life[9,10,11].

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To date, few longitudinal studies exist, but those that do have focused on examining average changes in fatigue across 1 year either in the population as a whole or in researcher-defined subgroups[12,13,14]. Our analysis has assumed a "1 size fits all" advancement of fatigue that, given its multifactorial origin and varied progression reported in clinic, is unlikely to comprehensively account for the variable characteristic of the symptom[12]. Instead, we hypothesize that there are likely subgroups of patients between whom the course of fatigue differs and that interventions could be better targeted to address those in greatest need, particularly if they can be identified early by their baseline characteristics.

Our novel study aimed to describe the longitudinal course of fatigue in an inception cohort of early RA. Patients reporting fatigue at baseline were considered most clinically relevant because they were most likely to require and benefit from future stratified and early interventions. It sought to compare the results of average change analysis with those of more complex analysis that evaluated individual variation in symptom trajectory. In doing so, it aimed to determine whether latent fatigue subgroups existed, and if so, to characterize groups that had the worst fatigue prognosis by using baseline characteristics.

MATERIALS AND METHODS

Data from 2326 participants were obtained from the Norfolk Arthritis Register (NOAR). NOAR's data collection methods have been described elsewhere[15,16,17]. It was a large primary care-based cohort study that was established in 1989 and recruited adult patients who meet the criteria for inflammatory arthritis (≥ 2 swollen joints lasting for ≥ 4 weeks) and who were registered with a general practitioner based in the former Norwich Health Authority, Norfolk, UK. At baseline, and annually for up to 5 years, NOAR identified a comprehensive set of demographic, clinical, and psychosocial variables and cumulatively applied the 1987 American College of Rheumatology (ACR) classification criteria[18].

Participants were eligible for inclusion in our analysis if they cumulatively met the ACR RA classification criteria by Year 5 and were recruited < 24 months since symptom onset. Additionally, eligible patients were required to have reported fatigue, and reported using a visual analog scale (VAS; validated for use in RA populations[19]) anchored as 0 mm (no problem) to 100 mm (major problem) at baseline and at least at 1-year followup assessment.

Our study sought to determine the longterm progression of fatigue in participants for whom fatigue was present at an early stage of the disease. Thus, eligibility was further restricted to those participants who reported clinically relevant fatigue at baseline (defined as 0–100 mm VAS ≥ 20 mm)[1,2]. The minimum clinically important difference (MCID) in fatigue of 10 mm was selected with reference to previous literature[20]. Data from baseline to the fourth anniversary assessment were used.

Data. In addition to the fatigue data, a selection of other variables was used in our current analysis:

(1) Participant characteristics and self-reported health state: Age at registration, sex, ethnicity, and work status were identified by self-reported questionnaires. Like fatigue, 0–100 mm VAS were also used to identify baseline pain (0 mm = "no pain" to 100 mm = "severe pain"), and sleep problems and stomach problems (both 0 mm = "no problem" to 100 mm = "major problem"). The MCID for all VAS scales was 10 mm to ensure consistency of interpretation with the fatigue VAS.

(2) Clinical status: At baseline serological status, symptom duration and disease activity were reported. Disease activity was reported using the 28-joint Disease Activity Score with C-reactive protein (MCID 1.2 units[21]). History of comorbidities — including chronic obstructive pulmonary disorder, depression, and hypertension — were recorded using the International Classification of Diseases, 10th edition classification codes and a checkbox table. The use of medications of interest — β blockers, thyroxine, antidepressants, analgesics, and nonsteroidal antiinflammatory drugs (NSAID) — at the time of baseline assessment was also identified using the National Health Service read codes. Whether the participant had ever received steroids and were currently receiving disease-modifying antirheumatic drugs (DMARD) were separately recorded using checkbox tables, with a dichotomous variable pertaining to DMARD use at the baseline assessment used in our analysis.

(3) Disability: Participants rated their ability to complete given tasks — dressing, rising, eating, walking, hygiene, grip, reach, and usual activities — using the British version of the Health Assessment Questionnaire (HAQ) Disability Index. The scale, which was developed and validated with patients with RA[22], is scored on a scale of 0 (no disability) to 3 (completely disabled), with the MCID in HAQ considered to be 0.22 units[23].

Analysis. Descriptive statistics were used to characterize the mean fatigue scores reported at baseline and at each followup, as well as mean change in fatigue scores between baseline and the 1- and 4-year followups. Data from the 5-year followup were not used because few of the eligible participants had completed the assessment at the time of the data release (n = 79).

Differing fatigue trajectories were determined using group-based trajectory modeling (GBTM), which has previously been used to determine trajectories of disability and psychological distress in patients with RA[24,25]. A full technical overview of this method is available elsewhere[26,27]. GBTM is an empirical procedure that uses multinomial modeling with maximum likelihood to determine clusters of individuals who follow similar symptom trajectories. The analysis provides a formal way to determine the best-fit number of trajectories and a precision estimate of group membership allocation.

The groups identified by GBTM can be used to predict differences in the likelihood of a particular outcome across groups[28] and to characterize the groups of individuals at baseline that experience different outcomes over the course of followup.

GBTM for censored normal data (i.e., a continuous scale with minimum and maximum values) was used to determine fatigue trajectories over the course of 4 years from enrollment. Initially, 4 plausible fatigue trajectories — improved, worsened, chronic high, and chronic low fatigue — were proposed with cubic order polynomials. Trajectories were added or removed as per model fit statistics, with the best fitting number of trajectories determined as the one with the lowest Bayesian information criterion, if strong support (i.e., value ≥ 6[27]) was provided by the log Bayes factor [$2\log_e(B_{10})$]. Model fit was further improved by the specification of the correct order polynomial (e.g., linear, cubic, etc.). Importantly, although the GBTM analysis was originally conducted for all participants, issues of determining best-model fit led to the adoption of a sex-stratified approach.

To characterize patients whom it would be clinically important to identify (i.e., those who may require interventions), between group differences were examined using chi-squared tests and independent Student t tests. Groupings were conducted to compare those who improved in fatigue (i.e., would not require additional interventions) with all those who did not improve and may require additional interventions.

All analysis was conducted using Stata 12.1.

RESULTS

In total, 338 participants were eligible for our analysis. Briefly, baseline characteristics showed that participants tended to be white (98.8%) and female (69.8%) with a mean age at registration of 56 years (SD 14.6) and median symptom duration of 6.3 months (interquartile range 4.2–11.0). Both disease activity and disability were moderate (mean 4.42, SD 1.23 and mean 1.22, SD 0.71, respectively), and VAS pain was high (mean 49, SD 25.9). Finally, 10.2% were not working because of illness (Table 1).

Of the 338 eligible participants, 108 (32%) provided fatigue data at the 4-year followup. There were no clinically or statistically significant differences between those who

Table 1. Baseline characteristics of participants eligible for the study (n = 338). Values are mean (SD) or % unless otherwise specified.

Characteristics	Values
Age, yrs	56 (14.6)
Female	69.8
White	98.8
Not working because of illness	10.2
RF+	61
Disease duration, mos, median (IQR)	6.3 (4.2–11.0)
DAS28	4.42 (1.23)
VAS pain	49 (25.9)
VAS fatigue	57.8 (22.0)
Disability, HAQ	1.22 (0.71)

RF: rheumatoid factor; IQR: interquartile range; DAS28: Disease Activity Score at 28 joints; VAS: visual analog scale; HAQ: Health Assessment Questionnaire.

provided data until the 4-year followup and those who did not for ethnicity, rheumatoid factor-positive status, disease activity, disability, pain, and fatigue (data not shown). However, a greater proportion of those who provided data were women than among those lost to followup (77.8% vs 66.1%, p = 0.03). They were significantly younger (mean 50.3, SD 9.6 vs mean 58.7, SD 15.8, p < 0.001), and accordingly, a smaller proportion were retired (data not shown).

Fatigue at baseline and changes within 1 and 4 years. The mean fatigue level reported at baseline was 57.8 mm (SD 22.0), and with an average reduction of 6.0 mm (26.95), the mean fatigue score reported at the first anniversary followup was 51.7 mm (26.0). In the longterm, the mean score at the fourth anniversary was 52.3 mm (26.4), representing an average improvement of 5.5 mm (29.3). Figure 1 displays the mean fatigue scores reported at each assessment, indicating little variation in symptom reporting occurred.

In spite of the minimal average changes in fatigue, important proportions of the sample experienced clinically significant improvements in fatigue by the first (45.6%) and fourth (40.7%) anniversary assessments when compared with baseline scores. Further, compared with the baseline scores, at the first and fourth anniversary assessments, 33.4% and 33.3% of participants reported a clinically significant worsening of fatigue, respectively. Thus, there was more variation in fatigue progression than indicated by average change analysis.

GBTM. The issues of model fit that lead to a sex-stratified approach arose because the best-fit number of trajectories differed between the sexes. Therefore, while 2 trajectories labeled as "Improved" and "Moderate-high fatigue" best represented the course of fatigue in men, for women the course of fatigue was best identified by 3 trajectories: "Improved," "Moderate-high fatigue," and "High fatigue" (Figure 2). Importantly, in both sexes, there were no significant differences between the trajectory groups for the proportion of people who were lost to followup by the 4-year followup (data not shown).

Group characteristics. Group characterization sought to examine whether those with the poorest prognostic outcome, who may be in need of fatigue-specific interventions, could be distinguished at baseline from those who improved. Therefore, for men, those in the Moderate-high trajectory were compared with those with Improved fatigue, where for women, Improved participants were compared with "Nonimproved" participants, consisting of Moderate-high and High fatigue trajectories.

Male participants. Of the demographic variables examined (Table 2), it was only baseline employment status that significantly differed between male trajectory groups (p = 0.01), with a greater proportion of those in the Moderate-high fatigue group not working because of illness compared with those in the Improved group (20.7% vs 0.0%). Of the clinical variables examined, only the proportion of participants who had ever received steroids (38.9% vs 14.6%, p = 0.01) and those reporting analgesic use at recruitment differed significantly between the groups (53.7% vs 20.8%, p = 0.001), and importantly, there was no clinically or statistically significant difference between the groups for baseline disease activity (mean 4.05, SD 1.31 vs mean 4.31, SD 1.47, p = 0.43).

Patient-reported variables better distinguished the fatigue groups (Table 2) because those in the Moderate-high fatigue group reported a statistically and clinically significantly poorer baseline health state than those in the Improved group for disability (mean 1.52, SD 0.73 vs mean 0.93, SD 0.70, p < 0.001), pain (62.3, 24.0 vs 34.5, 22.2, p < 0.001), fatigue (65.1, 20.6 vs 43.2, 20.4, p < 0.001), sleep problems (51.9, 29.8 vs 33.5, 29.0, p = 0.002), and stomach problems (25.1, 29.9 vs 14.1, 22.9, p = 0.04).

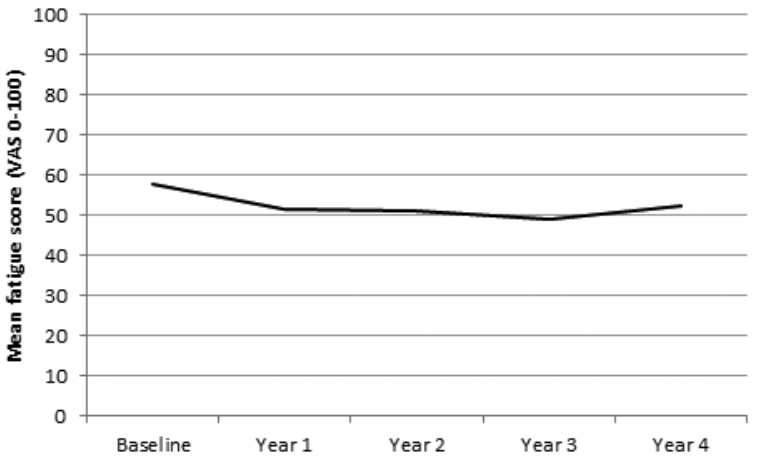

Figure 1. Mean fatigue scores (VAS 1–100 mm) across the followup period. VAS: visual analog scale.

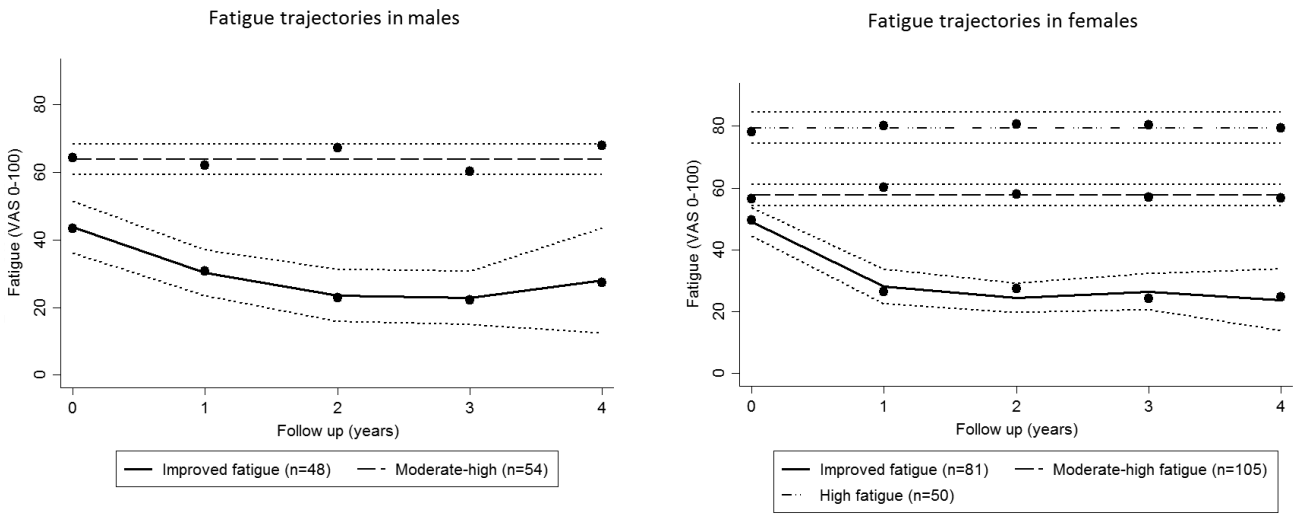

Figure 2. Trajectories of fatigue in men (left) and women (right) with 95% CI. VAS: visual analog scale.

Female participants. In the female participants, for the purposes of clinical interpretation and use, between-group comparisons (Table 2) were conducted between those who followed an improved course (i.e., Improved group) and those who did not (i.e., Moderate-high fatigue and High fatigue groups). It was the latter group that was considered to have prolonged fatigue burden and therefore to represent those most in need of fatigue interventions.

Few demographic or clinical variables characterized female nonimprovers, though they were significantly younger than improvers (mean 51.7, SD 14.5 vs mean 59.2, SD 14.2, $p < 0.001$), with statistically, but not clinically, significant higher baseline disease activity (4.67, 1.15 vs 4.16, 1.08, $p = 0.003$). More nonimprovers were receiving antidepressants (12.9% vs 1.2%, $p = 0.003$) and NSAID (49.7% vs 32.1%, $p = 0.01$) at baseline and a higher proportion had a history of depression than improvers (44.5% vs 16.25%, $p < 0.001$).

As in the male participants, patient-reported variables were more consistently informative as to the existence of between-group differences because those following Non-improved trajectories reported a clinically and statistically significantly poorer baseline health state. This was evidenced by the reporting of more disability (mean 1.30, SD 0.69 vs mean 1.06, SD 0.66, $p = 0.01$), pain (53.0, 23.8 vs 40.8, 35.6, $p < 0.001$), fatigue (63.8, 20.8 vs 49.9, 19.6, $p < 0.001$), sleep (54.3, 29.2 vs 41.2, 27.3, $p < 0.001$), and stomach problems (26.5, 27.1 vs 16.0, 25.0, $p = 0.004$) than those who followed an Improved trajectory.

DISCUSSION

Our analysis has demonstrated that in patients with RA, the longitudinal course of fatigue is better characterized by the adoption of discreet symptom trajectories rather than examining average changes. In particular, the longitudinal course of fatigue differs between the sexes, with an additional chronic trajectory observed in women. We identified differences in the baseline characteristics of those patients who follow these different trajectories and note that few of the differences pertained to clinical factors.

There are a number of limitations within our current study that should be addressed. First, because of our eligibility criteria requiring data at a minimum of baseline and 1 year, there is a concern of sample bias if those who did not meet this criterion were systematically different from those who did. However, no such bias was identified because comparisons between those who were included and those excluded revealed no clinically meaningful differences for core variables such as age, sex, fatigue, and disease activity (data not shown).

Second, although this represents one of the largest studies to have examined RA-related fatigue, the sample size still compromises some aspects of statistical power. For example, in spite of one-third of the sample reporting a clinically relevant worsening of fatigue between baseline and either the 1-year or 4-year followup, no "worsened fatigue" trajectory was identified.

GBTM and related approaches allow for the examination of individual differences in symptom progression and associated disease outcomes[26,28], which seems particularly important for patient-reported outcomes such as fatigue. The disease-course approach to symptom analysis may be especially pertinent here because fatigue has been identified as a significant predictor of medical costs, employment loss and disability, poor quality of life, and reduced well-being[3,4,5,6,7,8,29]; to our knowledge, ours is the first known study to apply this technique to RA fatigue. It is clear that our results emphasize the need for fatigue to be more explicitly and rapidly targeted in RA populations to relieve both patient and economic burden.

Although ours is the first known study applying this technique to fatigue, trajectory modeling studies have been

Table 2. Baseline characteristics for fatigue trajectory groups. Values are mean (SD) or % unless otherwise specified.

Characteristics	Male Participants				Female Participants			
	Improved, n = 48	n	Moderate-high, n = 54	n	Improved, n = 81	n	Nonimproved‡, n = 155	n
Age at registration, yrs	62.4 (12.1)	48	58.0 (14.23)	54	59.2 (14.2)	81	51.7 (14.5)**	155
Employment status								
Working now	43.7	48	32.0	53	36.2	80	44.1	152
Retired	52.1		41.5		45.0		24.3	
Not working because of illness	0.0		20.7*		6.2		11.8	
Other	4.2		5.8		12.6		19.8	
Disease duration, mos, median (IQR)	6.2 (3.0–8.2)	48	6.1 (4.6–11.0)	54	6.3 (4.2–9.2)	81	6.3 (4.4–11.7)	155
1987 RA classification criteria	75.0	48	63.0	54	74.1	81	67.1	155
RF+	62.5	48	53.2	47	54.5	77	56.4	149
DAS28	4.05 (1.31)	38	4.31 (1.47)	40	4.16 (1.08)	63	4.67 (1.15)**	132
Disability, HAQ	0.93 (0.70)	48	1.52 (0.73) **†	54	1.06 (0.66)	81	1.30 (0.69)*†	155
Pain, VAS 0–100	34.5 (22.2)	48	62.3 (24.0) **†	54	40.8 (35.6)	81	53.0 (23.8)**†	155
Fatigue, VAS 0–100	43.2 (20.4)	48	65.1 (20.6) **†	54	49.9 (19.6)	81	63.8 (20.8)**†	155
Sleep problems, VAS 0–100	33.5 (29.0)	48	51.9 (29.8)**†	54	41.2 (27.3)	81	54.3 (29.2)**†	155
Stomach problems, VAS 0–100	14.1 (22.9)	48	25.1 (29.9) *†	54	16.0 (25.0)	80	26.5 (27.1)**†	153
Steroids	14.6	48	38.9**	54	17.3	81	23.2	155
β blockers	8.3	48	9.3	54	8.6	81	3.9	155
Thyroxine	4.2	48	1.8	54	8.6	81	11.6	155
Antidepressants	0.0	48	3.7	54	1.2	81	12.9**	155
DMARD	62.5	48	74.1	54	65.4	81	52.3	155
Analgesics	20.8	48	53.7**	54	29.6	81	36.8	155
NSAID	41.7	48	38.9	54	32.1	81	49.7*	155
History of renal disease	0	47	0	54	0	80	1.3	155
History of COPD	10.6	47	22.2	54	21.2	80	29.0	155
History of stroke	0	47	3.7	54	2.5	80	0.6	155
History of depression	14.9	48	20.4	54	16.25	80	44.5**	155
History of HTN	34.0	48	35.2	54	21.2	80	22.6	155

‡ Nonimproved fatigue, Moderate-high, and High fatigue participants.* $p < 0.05$. ** $p < 0.01$. † Clinically significant. IQR: interquartile range; RA: rheumatoid arthritis; RF: rheumatoid factor; DAS28: Disease Activity Score at 28 joints; HAQ: Health Assessment Questionnaire; VAS: visual analog scale; DMARD: disease-modifying antirheumatic drugs; NSAID: nonsteroidal antiinflammatory drugs; COPD: chronic obstructive pulmonary disease; HTN: hypertension.

conducted in RA samples to examine psychological distress[25] or disability[24,30,31]. Across these studies, there is a consistency in the emerging results that patient-reported variables better characterize trajectory members than disease factors[30], and these differences may have important implications for the future management of fatigue by informing a stratified approach to treatment. For example, our analysis identified a High fatigue trajectory in female participants that was not found to exist in the male participants. It is possible that the smaller sample size of men compared with women prohibited the delineation of a male High fatigue group from the Moderate-high fatigue participants. However, it is known that women report higher (more severe) values of fatigue than men[32,33,34] and thus the existence of the High fatigue trajectory in only women may reflect this difference in severity. On the other hand, we propose that the existence of the additional High fatigue trajectory may reflect the effect of depression/mental health on fatigue reports.

Previous work has shown that those with a history of depression are predisposed to greater fatigue-reporting in the future and that this is heightened by current poor mental health[35,36]. In our study, not only did higher proportions of nonimprovers have a history of depression and current use of antidepressants, but the prevalence of depression and antidepressant use was 2- and 3-fold higher in women than males, respectively. We suggest the increased prevalence of poor mental health markers may indicate that a specific subgroup of mental health-driven fatigue exists in female participants, but not in male participants.

It has previously been contended that fatigue is not driven by inflammatory disease factors[1,37,38], and that stronger associations exist between fatigue and other self-report variables rather than measures of disease activity[33,37,39,40]. Our work appears to support this, though it is noted that statistically, but not clinically, significant differences in disease activity were observed between female improvers and nonimprovers. Unfortunately, disease activity scores were not longitudinally collected over the specific time frame of our study and so it was not possible to examine any longterm relationship between fatigue and disease activity or inflammation, though this would be of interest for future studies.

Nevertheless, few clinical variables served to distinguish

those on different trajectories and instead, patient-reported variables appeared to be more informative regarding between-group differences. Clearly it is important to target fatigue for treatment.

However, as yet there are no recommended fatigue-specific interventions, and though the symptom has been shown to respond to pharmacological[41] and nonpharmacological therapies[42], it is not clear how best to manage the symptom. Further, while we propose that interventions will be particularly important for those who will report a chronic fatigue course, it is not yet clear whether those with Moderate-high and High fatigue should receive different management strategies.

We suggest that future validation studies should focus on the development of fatigue-specific interventions and clinical prediction tools to inform the inclusion criteria of future trials of the interventions designed. Ultimately, these studies would also benefit from the use of sophisticated disease-course analysis to identify predictors and mediators of fatigue outcome. In doing so, such studies should be well positioned to best identify those who should be targeted to receive certain treatments in place of other options (e.g., cognitive behavioral therapy and/or exercise).

Fatigue is a principal determinant of employment loss and disability, and of poor quality of life and reduced well-being more generally[3,4,5,6,7,8,43]. Our novel approach to analysis of RA fatigue indicates fatigue to be a chronic complaint for many patients from the time of onset. Consequently, our work contributes to the growing body of evidence[4,44,45] that highlights the importance of fatigue, the need to examine the symptom in its own right, and the need to specifically target the symptom from an early stage of disease.

Our study examined the progression of fatigue over 4 years from an early disease onset. We have demonstrated that average changes in fatigue are poorly informative of the variable characteristic of symptom progression. In addition, we have characterized patients who followed different trajectories and have shown that few clinical factors distinguished group members. Ultimately, these results provide support for the importance of future treatment stratification strategies that will be crucial in providing solutions for this complex, disabling patient priority.

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