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Identification and Prediction of Fatigue Trajectories in People With Rheumatoid Arthritis

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Objective. We aimed to identify groups demonstrating different long-term trajectories of fatigue among people with rheumatoid arthritis and determine baseline predictors for these trajectories.

Methods. Our study included 2741 people aged 18 to 75 years who were independent in daily living. Data were collected from the Swedish Rheumatology Quality Register and questionnaires at baseline, 14 months, and 26 months. Fatigue was rated on a 100-mm visual analog scale. K-means cluster analysis was used to identify fatigue trajectories. Multinomial logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals for potential predictors of trajectory membership.

Results. The mean age was 60 years, 73% of participants were female, and the mean baseline fatigue level was 39. Three distinct fatigue trajectories were identified, representing mild (mean 15, n = 1024), moderate (mean 41, n = 986), and severe (mean 71, n = 731) fatigue. Consistent patterns indicated that poorer health perception (ORs 1.68-18.40), more pain (ORs 1.38-5.04), anxiety/depression (ORs 0.85-6.19), and activity limitation (ORs 1.43-7.39) were associated with more severe fatigue. Those in the severe fatigue group, compared with those in the mild fatigue group, were more likely to be college educated than university educated (OR 1.56) and less likely to maintain physical activity (OR 0.54). Those in the severe fatigue group, compared with those in both the moderate (OR 0.67) and mild (OR 0.59) fatigue groups, were less likely to have one additional adult in the household.

Conclusion. This study identified stable fatigue trajectories, predicted by health perception, pain, anxiety/depression, activity limitation, educational level, maintained physical activity, and household composition. Interventions aimed at reducing these disabilities and supporting physical activity behaviors may help reduce fatigue.

INTRODUCTION

Fatigue is frequently reported among people with rheumatoid arthritis (RA), with considerable impact on their daily lives (1–3). The inconsistent relationship between fatigue and disease activity in RA (4–6) and unclear effects of medical interventions (7–9) have inspired researchers to include other illness-related aspects to further understand fatigue (10). Physical activity interventions and studies on psychosocial counseling, including cognitive behavioral therapy, mindfulness training, and lifestyle management and education, have been undertaken in people with RA and seem to result in small reductions of fatigue that indicate potential mechanisms deserving further exploration (11).

Cross-sectional studies indicate that fatigue has strong and consistent associations with pain, anxiety, depression, sleep disturbance, and activity limitation (6,12,13). No clear and consistent association between persistent fatigue levels and sex has been found (12). Younger age does not seem to be related to fatigue in univariate analysis, but it tends to contribute significantly in multivariate models (12).

Although fatigue has been described in cohorts of people with RA in numerous studies and its correlates have been explored in cross-sectional studies (12), there have been few studies

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SIGNIFICANCE & INNOVATIONS

- Three distinct trajectories of fatigue over 2 years could be identified in a large cohort of people with rheumatoid arthritis selected irrespective of levels of fatigue.
- Poor health perception and more pain, anxiety/depression, and activity limitation increased the likelihood of severe fatigue.
- Physical activity and having other adults in the household decreased the likelihood of severe fatigue.

on natural patterns of fatigue over time in large cohorts. Rather, longitudinal studies often focus on fatigue in relation to drug effects (9,14,15) or in groups selected on the basis of predefined levels of fatigue, ie, those with clinically relevant fatigue (16,17) or those with severe fatigue (18). Furthermore, a recent systematic review indicates that longitudinal analyses more consistently identify associations between fatigue and other variables in univariate analyses than in predictions of fatigue change with multivariate analyses applied. It was therefore suggested that future research should longitudinally monitor multiple variables and use multivariate statistical analyses to obtain insight into causal network models that influence fatigue in individual patients (12).

To our knowledge, in large cohorts of people with RA selected irrespective of fatigue level, longitudinal studies using multivariate analyses to explore patterns of change and their predictors are scarce. Such studies would contribute to the identification of individuals at risk for long-term fatigue and enhance its prevention.

The objectives of the present study were to identify and describe groups demonstrating different trajectories of fatigue over 2 years among people with RA and to determine baseline predictors of each trajectory.

MATERIALS AND METHODS

Design and participants. This longitudinal study used data from six rheumatology clinics that report to the Swedish Rheumatology Quality Register (SRQ): two university hospitals and four county hospitals in different parts of Sweden (19). All participants included in the register had been diagnosed with RA according to the American College of Rheumatology criteria (20). Participants in the present study were 18 to 75 years of age and independent in their daily living activities (Stanford Health Assessment Questionnaire Disability Index [HAQ-DI] score ≤ 2) (21). A total of 5391 eligible individuals were sent a postal questionnaire, of whom 3152 responded. Differences between responders and nonresponders to the questionnaire have been reported in our previous article (19). The same questionnaire was mailed again at 14 and 26 months. The current study includes data from 2741 individuals who completed the questionnaire at least twice. Data on the sampling process were presented in a previous article (22).

Assessment methods. The dependent variable was fatigue, rated on a 100-mm visual analog scale (VAS) from 0 ("no fatigue") to 100 ("maximal fatigue"). The VAS is sensitive to changes of fatigue in people with RA and has good face validity (23).

The below variables were used for descriptive purposes and/or included as independent variables in the analyses. Data were collected as follows:

- Information on age, sex, and disease duration (time since first visit to rheumatologist) was retrieved from the SRQ, whereas data on education (university = post college; college = 10th-12th grade; other = polytechnic school, for example; basic = first to ninth grade), income (above or below average), number of adults and children in the household, and Swedish language skills were collected by study-specific questionnaires.
- The number of respiratory, cardiovascular, neurological, or psychiatric diseases; diabetes mellitus; or other comorbidities were reported in the study-specific questionnaire.
- Perceived health and pain were rated by using a 100-mm VAS; health ranged from 0 ("totally fine") to 100 ("worst imaginable"), and pain ranged from 0 ("none") to 100 ("maximal") (24). Both variables were categorized into three groups for analysis; health was divided according to tertiles in the current sample, and pain was divided according to Collins et al (25) as <30, <55, and ≥ 55.
- Anxiety/depression was assessed with one item from the EuroQol five dimensions and ranged from 1 to 3, with 1 indicating "no problems" and 3 indicating "extreme problems" (26).
- Activity limitation was assessed by using the HAQ-DI, which asks about the ability to perform 20 daily activities; scores ranged from 0 ("without difficulty") to 3 ("unable to perform") (21).
- Current (past week) and maintained (past 6 months) health-enhancing physical activity (HEPA) wase assessed with two different questionnaires. The short version of the International Physical Activity Questionnaire (IPAQ) assesses overall physical activity during the past week (27), and "current HEPA" was considered obtained if aerobic physical activity of at least moderate intensity was performed for a minimum of 30 minutes on most days of the week. The Exercise Stage Assessment Instrument (ESAI) (28) was slightly modified for the present study to include two questions: one on a minimum of 30 minutes of aerobic exercise of at least moderate intensity on most days of the week and one on strength training at least twice a week (19). "Maintained HEPA" was considered obtained if both types of exercise had been performed accordingly for at least 6 months (22).

Data management and statistical analyses. Descriptive statistics (means and SDs or proportions, as appropriate) were calculated for the total sample and stratified by the identified trajectories of fatigue. Multiple imputation (MICE

package in R) was used to impute missing data among the potential predictors of fatigue trajectories (29).

Using the kml package in the R software program (30,31), K-means cluster analysis was used to identify trajectories of fatigue. The cluster analysis was performed four times, varying the number of clusters from two to five. The Calinski and Harabasz criterion (32), along with consideration of clinical importance and interpretability, was used to select the number of clusters that best fit the data. After selecting the number of clusters, univariate multinomial logistic regression was used to compare baseline characteristics of the sample between the identified trajectories of fatigue. We then used multivariable multinomial logistic regression to calculate odds ratios (OR) and 95% confidence intervals for the association between potential predictors of trajectory membership and each trajectory, with a variable identifying trajectory membership as the outcome. Every predictor significantly ($P < 0.1$) associated with trajectory membership in the univariate model was then included in the multivariable model. All analyses were run by using the imputed and complete case data sets. There were no major differences between the results of the two analyses; therefore, the imputed results are presented.

Ethics. Ethical approval for the study was obtained from the Stockholm Regional Ethical Review Board (2010/1232-31/1 and 2011/1241-32) and conducted in compliance with the Helsinki Declaration. The participants were informed about the study by letter, and they consented by returning their questionnaires.

RESULTS

In our sample of 2741 participants, the average age was 60 years (SD = 11.0), 73% of participants were female, and the average level of fatigue at baseline was 39 (SD = 26.7). The 411 excluded individuals reported higher fatigue levels (mean = 45, SD = 27.2, $P < 0.001$) and were younger (mean = 58 years, SD = 12.7, $P < 0.001$) but the proportion of women was similar (76%, $P > 0.05$). They also had a shorter disease duration and rated their health perception, pain, and activity limitation as worse (data not shown) compared with the 2741 participants.

K-means cluster analysis identified three distinct trajectories of fatigue that were considered both clinically and statistically relevant (Figure 1). Baseline characteristics of the total sample and each of the three fatigue trajectory groups are described in Table 1. Two groups, representing mild (n = 1024, 37%) and moderate (n = 986, 36%) levels of fatigue, were similar in size, whereas the group with severe (n = 731, 27%) fatigue was smaller but still represented approximately a quarter of the sample. The mean (SD) fatigue levels for the mild, moderate, and severe groups were 15 (26.7), 41 (12.7), and 71 (14.4), respectively.

The results from the multivariate multinomial logistic regression analysis are presented in Table 2 as ORs and 95% confidence intervals for all potential predictors of being in the moderate versus mild, severe versus mild, and severe versus moderate group. Age and sex were not associated with any of the fatigue trajectory groups. However, the likelihood of being in a more severe fatigue group was consistently associated with poorer health perception and more pain, anxiety/depression, and activity limitation. Participants who reported having one additional adult in the household were less likely to be in the severe fatigue group compared with both the moderate and mild groups. Furthermore, those with a college-level education, compared with those with university-level studies, were more likely to have severe fatigue versus mild fatigue; those who maintained HEPA were less likely to have severe fatigue versus mild fatigue; and those with

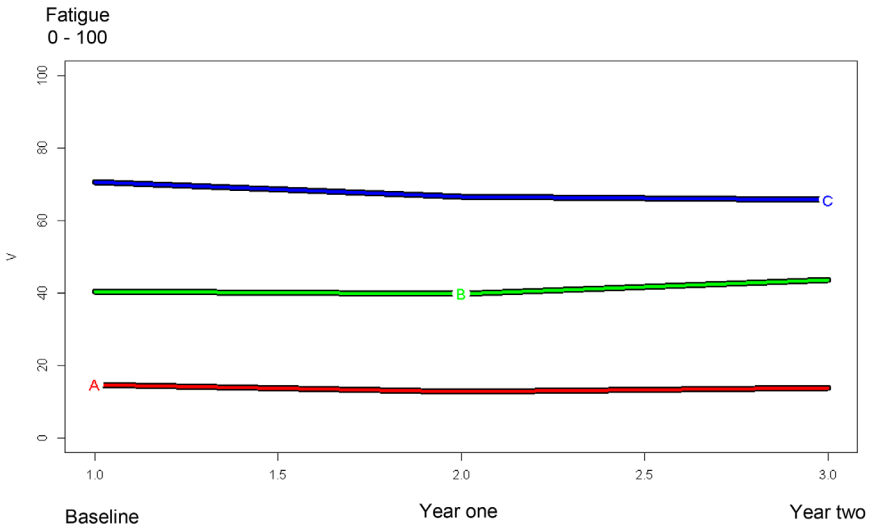

FIGURE 1. Trajectories illustrating the three groups of fatigue identified by K-means cluster analysis: mild (A: n = 1024, 37.4%), moderate (B: n = 986, 36.0%), and severe (C: n = 731, 26.7%) levels of fatigue.

TABLE 1. Baseline characteristics of the total study sample and comparison of three groups of fatigue (mild, moderate, and severe)

	Total sample, N = 2741	Mild, n = 1024	Moderate, n = 986	Severe, n = 731	*P* value between groups
Fatigue (VAS, 0-100), mean (SD)					
All	39 (26.7)	15 (12.7)	41 (17.3)	71 (14.4)	<0.0001
Age, years					
All, mean (SD)	60 (11.0)	59 (11.6)	60 (10.8)	60 (10.1)	0.057
18-34, n (%)	93 (3)	41 (4)	33 (3)	19 (3)	0.081
35-54, n (%)	635 (23)	253 (25)	205 (21)	177 (24)	
≥55, n (%)	2013 (73)	730 (71)	748 (76)	535 (73)	
Sex, n (%)					
Women	1995 (73)	723 (71)	720 (73)	552 (76)	0.074
Men	746 (27)	301 (29)	266 (27)	179 (25)	
Disease duration, months					
All, mean (SD)	141 (118.9)	130 (111.1)	143 (121.5)	154 (124.7)	<0.001
0-24, n (%)	210 (8)	84 (9)	79 (8)	47 (7)	0.270
25-55, n (%)	469 (18)	186 (19)	162 (17)	121 (17)	
≥56, n (%)	1968 (74)	723 (73)	713 (75)	532 (76)	
Education, n (%)					
University	909 (34)	404 (40)	304 (31)	201 (28)	0.002
College	702 (26)	229 (23)	255 (26)	218 (30)	
Other	319 (12)	110 (11)	117 (12)	92 (13)	
Basic	786 (29)	276 (27)	299 (31)	211 (29)	
Income, n (%)					
Below average	1393 (52)	424 (42)	538 (56)	431 (61)	<0.001
Above average	1277 (48)	583 (58)	422 (44)	272 (39)	
Other adults in household, n (%)					
0	633 (23)	202 (20)	223 (23)	208 (29)	0.011
1	1765 (65)	701 (69)	636 (66)	428 (59)	
2-3	287 (11)	105 (10)	104 (11)	78 (11)	
>3	24 (1)	10 (1)	8 (1)	6 (1)	
Children at home, n (%)					
0	2303 (85)	833 (82)	857 (88)	613 (84)	0.005
1	189 (7)	81 (8)	46 (5)	62 (9)	
≥2	229 (8)	104 (10)	74 (8)	51 (7)	
Swedish language literacy, n (%)					
Yes	2662 (98)	1011 (99)	959 (99)	692 (97)	<0.0001
No	47 (2)	8 (1)	15 (2)	24 (3)	
Comorbidities, n (%)					
0	1191 (44)	531 (52)	405 (41)	255 (35)	<0.0001
1	473 (17)	179 (18)	188 (19)	106 (15)	
≥2	1077 (39)	314 (31)	393 (40)	370 (51)	
Health perception (VAS, 0-100)					
All, mean (SD)	34 (25.3)	17 (15.1)	35 (23.0)	57 (21.3)	<0.0001
0-18 (lowest tertile), n (%)	924 (35)	652 (65)	237 (25)	35 (5)	<0.0001
19-45 (middle tertile), n (%)	873 (33)	287 (29)	417 (44)	169 (24)	
46-100 (highest tertile), n (%)	876 (33)	61 (6)	303 (32)	512 (72)	
Pain (VAS, 0-100)					
All, mean (SD)	33 (25.3)	16 (15.9)	33 (21.5)	55 (23.2)	<0.0001
0-29, n (%)	1459 (53)	846 (83)	492 (50)	121 (17)	<0.0001
30-54, n (%)	641 (24)	133 (13)	296 (30)	212 (29)	
≥55, n (%)	631 (23)	41 (4)	194 (20)	396 (54)	
Anxiety/depression (EQ-5D-3L), n (%)					
None	1783 (66)	864 (85)	631 (64)	288 (40)	<0.0001
Moderate	890 (33)	149 (15)	345 (35)	396 (55)	
Extreme	50 (2)	4 (0)	7 (1)	39 (5)	
Activity limitation (HAQ-DI, 0-3)					
All, mean (SD)	0.62 (0.59)	0.30 (0.41)	0.65 (0.54)	1.05 (0.59)	<0.0001
0, n (%)	681 (25)	466 (46)	176 (18)	39 (5)	<0.0001
0.1-1.0, n (%)	1429 (52)	493 (49)	596 (61)	340 (47)	
1.1-3.0, n (%)	619 (23)	58 (6)	211 (22)	350 (48)	

(Continued)

TABLE 1. (*Cont'd*)

	Total sample, N = 2741	Mild, n = 1024	Moderate, n = 986	Severe, n = 731	*P* value between groups
Current HEPA (IPAQ), n (%)					
Yes	1909 (70)	791 (78)	678 (69)	440 (60)	<0.0001
No	822 (30)	229 (23)	305 (31)	288 (40)	
Maintained HEPA (ESAI)					
Yes	292 (12)	150 (16)	93 (10)	49 (8)	<0.0001
No	2259 (89)	811 (84)	840 (90)	608 (93)	

Abbreviations: EQ-5D-3L, EuroQol five dimensions; ESAI, Exercise Stage Assessment Index; HAQ-DI, Stanford Health Assessment Questionnaire Disability Index; HEPA, health-enhancing physical activity; IPAQ, International Physical Activity Questionnaire; VAS, visual analog scale.

TABLE 2. Comparisons, using ORs and 95% CIs, of baseline predictors between the three groups of severely (n = 731), moderately (n = 986), and mildly (n = 1024) fatigued groups based on the multinominal logistic regression analysis using multiple imputation

	Moderate vs mild			Severe vs mild			Severe vs moderate		
	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
Age, years									
35-54 vs 18-34	0.73	0.42-1.27	0.267	0.72	0.33-1.58	0.413	0.99	0.49-2.01	0.974
≥55 vs 18-34	0.59	0.34-1.03	0.064	0.52	0.24-1.14	0.104	0.88	0.43-1.79	0.725
Sex									
Women vs men	0.87	0.69-1.10	0.245	0.78	0.57-1.06	0.115	0.90	0.69-1.17	0.418
Disease duration, months									
25-55 vs 0-24	0.95	0.62-1.45	0.817	1.07	0.61-1.88	0.807	1.13	0.69-1.83	0.630
≥56 vs 0-24	0.95	0.66-1.37	0.772	0.97	0.59-1.59	0.914	1.03	0.67-1.58	0.901
Education									
College vs university	1.27	0.97-1.66	0.085	**1.56**	**1.10-2.21**	**0.013**	1.23	0.91-1.66	0.172
Other vs university	1.07	0.76-1.53	0.690	1.12	0.71-1.77	0.632	1.04	0.71-1.53	0.836
Basic vs university	0.87	0.65-1.15	0.331	0.75	0.52-1.09	0.136	0.87	0.63-1.19	0.383
Income									
Above vs below average	0.83	0.67-1.05	0.119	0.92	0.69-1.24	0.601	1.11	0.86-1.43	0.435
Additional adults in household									
1 vs 0	0.88	0.69-1.14	0.335	**0.59**	**0.43-0.81**	**0.001**	**0.67**	**0.51-0.86**	**0.002**
2-3 vs 0	1.18	0.80-1.74	0.396	0.79	0.48-1.29	0.350	**0.67**	**0.44-1.01**	**0.055**
>3 vs 0	0.67	0.23-1.91	0.449	0.48	0.13-1.79	0.273	0.72	0.22-2.35	0.584
Children at home									
1 vs 0	0.76	0.49-1.17	0.213	1.50	0.87-2.58	0.149	**1.98**	**1.22-3.20**	**0.005**
≥2 vs 0	0.88	0.57-1.34	0.548	1.06	0.60-1.87	0.838	1.21	0.74-1.98	0.452
Comorbidities									
1 vs 0	1.27	0.97-1.68	0.088	1.16	0.80-1.69	0.435	0.91	0.66-1.27	0.587
≥2 vs 0	1.16	0.92-1.46	0.211	1.30	0.97-1.75	0.083	1.12	0.87-1.44	0.373
Health perception (VAS, 0-100), tertiles									
19-45 vs 0-18	**2.44**	**1.9-3.14**	**<0.0001**	**4.10**	**2.61-6.45**	**<0.0001**	**1.68**	**1.07-2.63**	**0.024**
46-100 vs 0-18	**5.20**	**3.45-7.83**	**<0.0001**	**18.40**	**10.59-32.00**	**<0.0001**	**3.54**	**2.16-5.81**	**<0.0001**
Pain (VAS, 0-100)									
30-54 vs 0-29	**1.38**	**1.03-1.84**	**0.031**	**2.08**	**1.44-3.02**	**<0.0001**	**1.51**	**1.09-2.09**	**0.012**
≥55 vs 0-29	**1.83**	**1.17-2.88**	**0.009**	**5.04**	**3.06-8.30**	**<0.0001**	**2.75**	**1.90-3.97**	**<0.0001**
Anxiety/depression (EQ-5D-3L)									
Moderate vs none	**1.96**	**1.54-2.51**	**<0.0001**	**3.53**	**2.65-4.71**	**<0.0001**	**1.80**	**1.43-2.26**	**<0.0001**
Extreme vs none	0.85	0.24-3.06	0.807	**5.28**	**1.61-17.35**	**0.006**	**6.19**	**2.60-14.7**	**<0.0001**
Activity limitation (HAQ-DI, 0-3)									
0.1-1.0 vs 0	**1.87**	**1.47-2.38**	**<0.0001**	**2.66**	**1.75-4.05**	**<0.0001**	1.43	0.94-2.16	0.093
1.1-3.0 vs 0	**3.00**	**2.00-4.50**	**<0.0001**	**7.39**	**4.33-12.64**	**<0.0001**	**2.46**	**1.55-3.93**	**<0.0001**
Current HEPA (IPAQ)									
Yes vs no	0.98	0.78-1.24	0.883	0.99	0.74-1.32	0.957	1.01	0.80-1.28	0.936
Maintained HEPA (ESAI)									
Yes vs no	0.72	0.53-0.99	0.045	**0.54**	**0.34-0.85**	**0.008**	0.74	0.49-1.12	0.159

Note: ORs from multivariable models are adjusted for all other variables in the model. The bold values are indicates significants of *p*-values.
Abbreviations: CI, confidence interval; EQ-5D-3L, EuroQol five dimensions; ESAI, Exercise Stage Assessment Index; HAQ-DI, Stanford Health Assessment Questionnaire Disability Index; HEPA, health-enhancing physical activity; IPAQ, International Physical Activity Questionnaire; OR, odds ratio; VAS, visual analog scale.

one child, compared with those with no children, were more likely to have severe fatigue versus moderate fatigue.

DISCUSSION

To our knowledge, the present study included the largest sample and the longest follow-up time among longitudinal studies investigating predictors of fatigue in RA using multivariate analyses. We identified, in a sample selected irrespective of fatigue severity and medical state, three stable fatigue trajectory groups that were predicted by not only previously identified factors, such as anxiety and depression, pain, and activity limitation, but also health perception, educational level, household composition, and maintained HEPA.

We identified three groups, which we defined by fatigue levels as mild, moderate, and severe. Participants in the severe fatigue group reported fatigue levels in the higher area of the typical high fatigue range (≥50 mm) (15,33). The fatigue level reported by participants in the mild group was below the often-used cutoff for clinically relevant fatigue (≥20 mm) (34), and those in the moderate group reported fatigue levels within the range previously used for moderate levels of fatigue (>2 but <5, using a scale 0-10) (15,33). This consistency strengthens the credibility and clinical relevance of our identification of severe fatigue. Furthermore, although we identified stable patterns of fatigue over time in our sample of people with all stages of RA, previous studies on patients with early RA have found either reduced reports of fatigue over 5 years (16) or a decrease of fatigue during the first year after diagnosis followed by a stable course (8). It has also been found that initial low levels of fatigue 3 months after diagnosis was a good predictor of subsequent low levels of fatigue (15). It is thus worth noting that development of fatigue over time differs between samples despite the use of the same assessment method (ie, the fatigue VAS).

Certain factors (anxiety, depression, pain, and activity limitation) were identified as robust predictors of the three fatigue trajectories identified in our study. This is not surprising because they have previously been identified in cross-sectional studies. Our findings also partly support findings in previous studies using a longitudinal design and multivariate analyses, although their results are somewhat conflicting (5,35,36). Anxiety was identified as a predictor of fatigue in one previous study (36), whereas depression was identified as a fatigue predictor in one study (35) but not in another (36). Pain predicted fatigue in two studies (5,35), and activity limitation predicted fatigue in one study (36) but not in another (5). These disparate findings could possibly be attributed to different sample characteristics and variations in predictors included. To our knowledge, no previous study with a similar design to ours has either used or identified general health perception as a consistent predictor of fatigue severity. However, it is not surprising because general health perception includes many disabilities already known to be associated with fatigue.

Educational level was identified as a predictor of fatigue in our study, but the findings were not clear-cut, and furthermore they contrast with those in a previous longitudinal study (5). Thus, educational level, known to influence many symptoms, disabilities, and behaviors, should be explored further regarding its long-term prediction of fatigue. We also found that severe fatigue was less likely if one additional adult was included in the household. This may be attributed to the potential for shared responsibilities and more time for rest and activities to reduce fatigue. This assumption is supported by findings of a previous long-term study that identified less help at home as an independent predictor of more severe fatigue (36). However, this is not clear-cut because having other adults in the household may also represent barriers for daily activities (37). Similarly, our finding that having one child, but not more, in the home predicted severe fatigue versus moderate, but not mild, fatigue is hard to interpret. Further research is thus needed to better understand household composition as a predictor of fatigue.

Associations between physical (in)activity and fatigue have previously been reported in studies with cross-sectional designs (38–40). One previous longitudinal study found that physical activity was not a predictor of fatigue (36). This finding was partly supported by those of a recent longitudinal study reporting associations between changes in fatigue and changes in sedentary time and standing time but not between changed fatigue and changed stepping time (41). To the best of our knowledge, our study is the first to clearly identify HEPA as an independent predictor of less likelihood of severe fatigue in a large study with a longitudinal design. It is worth noting, though, that this association was found only in those who maintained HEPA for the past 6 months, which implies that attention should be paid not only to symptoms but also to lifestyle factors, such as physical activity, in relation to severe fatigue.

Age, sex, disease duration, income, and comorbidities did not predict fatigue severity in our study. This indicates that in our register-based sample, disease-related symptoms, disabilities, and behaviors are more important in the prediction of fatigue than demographic factors.

The main strengths of our study are the large well-defined sample, the longitudinal design, and the comprehensive set of potential predictors. In addition, our inclusion of people with different fatigue severities from mild to moderate and severe is also important for a better understanding of fatigue prediction over time. Like many other studies, whether described or not, our study includes a sample of individuals with better health and a better psychosocial situation than those not included, which should be taken in account when extrapolating the present results. The main limitation of our study is that disease activity data were not available for this sample recruited from the SRQ, including many individuals without a recent clinical assessment. The relationship between disease activity and fatigue is, however, not clear-cut (6), and our previous cross-sectional study, which included a subsample of the present cohort, did not find any

relationship between fatigue and disease activity (42). Another limitation is our use of a single rating scale to assess fatigue, which is known to be a multidimensional and multifaced condition (10,43). Despite previous frequent use of the fatigue VAS (16,23,43), we acknowledge that although it clearly eased the questionnaire burden on the participants, it might not have fully captured the complexity and impact of fatigue (44,45). Furthermore, our findings cannot fully explain the prediction of fatigue trajectories in people with RA that may well be associated with psychological and molecular mechanisms or other factors not included in our study. However, the large number of variables included and the powerful longitudinal trajectory analysis identified several clinically relevant predictors for health professionals to use in daily practice. It should also be acknowledged that although we use the term "predictor," it may not be possible to differentiate between predictors and effects of fatigue, eg, depression and physical activity.

All participants were included in a national quality register and treated in accordance with current guidelines on RA medication. We must hence assume that this treatment was optimal for most patients included. Our findings thus confirm that evidence-based pharmacological treatment is not enough to reduce severe fatigue and support previous longitudinal studies suggesting that fatigue in RA remains an "unmet need" (8). Unfortunately, the SRQ did not include data on nonpharmacological interventions at the time of our data collection. However, because no substantial resources have been dedicated to implement evidence-based nonpharmacological care in Swedish rheumatology, we have reason to believe that the quality varies across clinical sites and is not optimal on a national level. On the basis of our results, inclusion of evidence-based programs for pain management, daily activity pacing, psychosocial counseling, and physical activity support may be valuable and should be considered to optimize the nonpharmacological treatment of fatigue.

In conclusion, our findings suggest that stable fatigue trajectories, predicted by health perception, pain, anxiety/depression, activity limitation, educational level, maintained physical activity, and household composition, can be identified. Interventions aimed at reducing these disabilities and supporting healthy physical activity behaviors might help reduce fatigue.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual contact, and all authors approved the final version to be published. Dr. Opava had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Demmelmaier, Opava.
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