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Predictors of fatigue and persistent fatigue in early rheumatoid arthritis: a longitudinal observational study, data from the ESPOIR cohort

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Objective: To determine, in a cohort of patients with early rheumatoid arthritis (RA), factors associated with fatigue at baseline, describe its evolution over 5 years of follow-up, and determine baseline predictors of persistent fatigue.
Method: We selected patients fulfilling the 2010 American College of Rheumatology/European League Against Rheumatism criteria for RA included in the ESPOIR cohort. Using bivariable and multivariable logistic regression models, we examined baseline variables associated with baseline fatigue (defined by visual analogue scale fatigue > 20) and baseline predictors of persistent fatigue (if the patient experienced fatigue at all visits during the 5 year follow-up period).
Results: We analysed 673 patients; 80.7% reported fatigue at baseline. At baseline, fatigue was associated with female gender, younger age, greater severity of morning stiffness, sleep problems, higher Health Assessment Questionnaire levels, presence of sicca symptoms, history of thyroid problems, and presence of psychological distress (depressive or anxiety symptoms). At 5 years of follow-up, the percentage of fatigued patients who reported fatigue at all time-points since baseline was 24.6% (referred to as 'persistent fatigue'). Independent baseline predictors were presence of sicca symptoms, greater severity of morning stiffness, and psychological distress.
Conclusions: Fatigue is a frequent symptom in RA. The presence of sicca symptoms, greater severity of morning stiffness, and presence of psychological distress at baseline were associated with baseline fatigue and persistent fatigue at 5 years. We did not observe any association between baseline fatigue or persistent fatigue and the Disease Activity Score based on 28-joint count–erythrocyte sedimentation rate.

Fatigue is a common and important symptom in many chronic inflammatory diseases, including rheumatoid arthritis (RA) (1–8). About 40–80% (5–9) of RA patients have identified fatigue as one of their main concerns. It is recognized as a symptom that is as severe as, if not worse than, pain (6, 10). It is considered one of the most frustrating, uncontrollable, and overwhelming symptoms (11, 12). Patients often report fatigue as an abnormal tiredness, which first occurred prior to the onset of RA (11). Fatigue in RA is poorly understood and appears to be multifactorial (7, 12–15). Hewlett et al (14) proposed a conceptual model for RA fatigue, suggesting interactions between three factors: 'personal' (personal issues in the life of a patient), 'disease processes' (RA), and 'cognitive, behavioural' (thoughts, feelings, and behaviour).

As recommended by the Outcome Measures in Rheumatology group in 2007 and a European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) task force in 2008, fatigue should be measured in all RA clinical trials whenever possible (16). Despite these recommendations, it is largely ignored and rarely assessed in clinical practice (13).

Fatigue in patients with established RA has been related to female gender, young age, disease activity, pain, poor sleep quality, anaemia, mental health problems, depression, and activity limitation (2, 5–7, 10, 17–40).

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Most studies that evaluate fatigue were conducted in patients with established disease. For early RA only a limited number of studies are available, most of which are cross-sectional rather than longitudinal and often have limited sample sizes (17, 18, 22). Considering that little is known about the course of fatigue in early RA, we conducted an analysis of prospectively collected repeated measurements over 5 years. The objectives of this study were to identify factors associated with fatigue at baseline, to describe its course over 5 years, and to determine predictors of persistent fatigue.

Method

Study population

We used data from the Étude et Suivi des Polyarthrites Indifférenciées Récentes (ESPOIR) cohort. ESPOIR is a prospective observational cohort of patients with early arthritis promoted by the French Society of Rheumatology. In total, 813 patients (aged 18–70 years) with early inflammatory arthritis (disease duration < 6 months) and a probable clinical diagnosis of RA or undifferentiated arthritis were enrolled between December 2002 and March 2005 in 14 French academic regional centres. Patients were naïve to disease-modifying anti-rheumatic drugs (DMARDs). Corticosteroids were permitted only if prescribed for < 2 weeks and with a maximum mean dose of 20 mg/week (37, 38).

For the current study, we selected among the ESPOIR cohort only those patients fulfilling the 2010 ACR/EULAR criteria for RA at the 12 month visit (M12).

Follow-up

Patients were followed with clinical and laboratory examinations at baseline (M0) and after 6, 12, 18, 24, 36, 48, and 60 months (M6, 12, 18, 24, 36, 48, and 60).

Data collection

Collected variables included:

- Demographic variables: age (years), gender (male/female), smoking status (yes/no), educational level (university/primary or secondary school), professional graduate (yes/no), and marital status (couple/single).
- Clinical history: initial pattern of joint involvement (acute/chronic), joint symptoms (symmetric/asymmetric), oligopolyarticular at onset of symptoms (yes/no), presence of fever at onset of symptoms (yes/no), menopausal status (yes/no), pain at the time of assessment [range 0–100 mm visual analogue scale (VAS)], sleep problems at the time of assessment (yes/no), history of thyroid problems (yes/no), and presence of sicca symptoms at the time of assessment (as indicated by the rheumatologist) (yes/no).
- Clinical examination and disease-related data: functional capacity assessed by the Health Assessment Questionnaire (HAQ) value (0–3 scale), Disease Activity Score in 28 joints (DAS28) value, morning stiffness severity (range 0–100 VAS) and duration (min), and body mass index (BMI) (kg/m^2).
- Biological data: included erythrocyte sedimentation rate (ESR) (positivity cut-off 28 mm/h) and C-reactive protein (CRP) levels (positivity cut-off 5 mg/L), positivity or negativity of anti-cyclic citrullinated peptide (anti-CCP) antibody [enzyme-linked immunosorbent assay (ELISA), DiaSorin, positive 50 units/mL] or rheumatoid factor (RF) (ELISA, Menarini, positive 9 IU/mL), and anaemia (haemoglobin cut-off 12 mg/dL for females, 13 mg/dL for males).
- Radiological characteristics: presence or absence of erosions.

Fatigue assessment

Fatigue was measured using a VAS; it was assessed at baseline, and at M6, 12, 18, 24, 36, 48, and 60. VAS fatigue involves the severity of the fatigue over the past week, with the anchors: no fatigue (0 mm) and extreme fatigue (100 mm). The scale is sensitive to change, valid, and feasible, but no cut-off level has been determined (39–42).

In the present study, VAS fatigue score was dichotomized: patients with a score < 20 (no fatigue) and patients with a score ≥ 20 (fatigue). We used the cut-off of 20 in accordance with previous studies (6, 17, 24). We defined 'persistent fatigue' as reported fatigue at all visits over 5 years of follow-up.

Other assessments

Psychological distress was measured using the five-item Mental Health Inventory questionnaire (MHI-5). It is a screening tool for identifying depressive or anxiety symptoms. It is part of the mental health subscale of the Medical Outcomes Study 36-item Short Form Health Survey. An MHI-5 score ≥ 52 indicated minimal psychological distress and < 52 major psychological distress (anxiety or depression) (43–46).

Statistical analysis

Descriptive statistics. Descriptive data are presented as mean ± sd or number and percentage.

Factors associated with fatigue at baseline. The sample was subdivided into two groups for comparative purposes: patients with and without baseline fatigue. We examined the association of variables and fatigue at inclusion using logistic regression analysis. Odds ratios (ORs) and 95%

confidence intervals (CIs) were calculated for possible associated factors. To determine which variables were independently associated with baseline fatigue, baseline variables associated with baseline fatigue in the bivariable analysis (selection criterion: $p < 0.15$) were entered into a multivariable model. Non-significant ($p > 0.05$) covariates were removed via backward stepwise elimination until significant variables ($p < 0.05$) remained in the final model (backward method).

Baseline factors predicting persistent fatigue. We examined the association of variables with persistent fatigue using logistic regression analysis. Baseline variables associated with persistent fatigue in the bivariable analysis (selection criterion: $p < 0.15$) were entered into the multivariable model. Non-significant ($p > 0.05$) covariates were removed via backward stepwise elimination until significant variables ($p < 0.05$) remained in the final model (backward method).

Data were analysed using Stata, version 12 (StataCorp, College Station, TX, USA).

Results

Patient characteristics

Characteristics of the patients at baseline are shown in Table 1.

Of the 813 ESPOIR patients, 677 (83.3%) fulfilled the 2010 ACR/EULAR criteria for RA at M12. The number of patients with complete data regarding fatigue assessments was 673 at M0, 633 at M6, 615 M12, 593 at M18, 586 M24, 537 at M36, 517 at M48, and 441 at M60 (34% of the initial number of patients).

No large differences were seen in the 5 year course of fatigue when using available data only and after imputation of missing values.

After a statistical analysis we found that there were no significant differences between the patients who had complete data and those who did not.

We analysed the 673 patients with early RA at M0: 77.3% women, mean ± sd age 48.6 ± 12 years, with a disease duration of 26.2 ± 40.9 days. In total, 46.7% of patients were positive for anti-CCP and 49.9% for RF. As expected, at baseline, mean levels of disease activity (5.3 ± 1.2) and disability (1.0 ± 0.7) were high. High CRP and ESR levels were present in 451 (67.8%) and 280 (42.1%) patients, respectively.

Baseline level and course of fatigue over 5 years. Among the patients fulfilling the 2010 ACR/EULAR criteria for RA at the first year of follow-up visit with full data available, the mean ± VAS fatigue score was 48.8 ± 27.3 at M0, 39.87 ± 28.51 at M6, 38.53 ± 28.95 at M12, 35.96 ± 27.17 at M18, 35.42 ± 28.74 at M24, 34.76 ± 28.44 at M36, 44.33 ± 28.33 at M48, and 33.51 ± 27.73 at M60.

Table 1. Demographic and clinical characteristics at baseline of the 673 patients with early rheumatoid arthritis (RA).

Baseline characteristic†	Value
Female gender	522 (77.3)
Age at disease onset (years)	48.6 ± 12.3
Marital status	
Couple	491 (72.7)
Single	184 (27.3)
Educational level	
Primary/secondary school	470 (69.6)
University	205 (30.4)
Professional graduates	195 (28.9)
Menopausal‡	247 (47.3)
Smoking status	322 (47.7)
Initial pattern of joint involvement	
Acute	153 (22.7)
Subacute/chronic	522 (77.3)
Joint symptoms	
Symmetric	407 (60.3)
Asymmetric	268 (39.7)
Oligopolyarticular at the beginning	554 (82.1)
Fever at RA onset	63 (9.3)
Anaemia	140 (20.8)
Anti-CCP antibody positive	315 (46.7)
Rheumatoid factor positive	337 (49.9)
Elevated level of ESR (cut-off > 28 mm/h)	280 (42.1)
Elevated level of CRP (cut-off > 5 mg/L)	451 (67.8)
Pain	662 (98.1)
Morning stiffness (range 0–100 VAS)	53.1 ± 26.4
Morning stiffness duration > 60 min	374 (55.4)
Sleep problems	524 (77.5)
HAQ score (0–3 scale)	1.0 ± 0.7
DAS28 score	5.3 ± 1.2
Sicca syndrome	198 (29.3)
Body mass index (kg/m^2)	24.9 ± 4.5
> 3 comorbidities	284 (42.1)
History of diabetes	26 (3.9)
History of thyroid problems	79 (11.7)
Depression or anxiety symptoms	313 (46.4)
Radiographic changes	102 (15.1)

Data are shown as number (percentage) or mean ± sd.
†Anaemia was missing in three patients, sleep problems in one patient, abnormal ESR in 10 patients, abnormal CRP in 10 patients, morning stiffness range in two patients, DAS28 in 13, and body mass index in five patients.
‡For menopausal patients: total females N = 522.
Anti-CCP, anti-cyclic citrullinated peptide; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; VAS, visual analogue scale; HAQ, Health Assessment Questionnaire; DAS28, Disease Activity Score in 28 joints.

At baseline, fatigue (VAS fatigue score > 20) was reported in 80.7% (543 patients) of 673 patients with available data. The percentage of fatigued patients who reported fatigue at all time-points since baseline was 74.7% at M6 (308 of 509 fatigued patients with complete data), 57.7% at M12 (285 of 494 fatigued patients with complete data), 46% at M18 (217 of 472 fatigued patients with complete data), 39.1% at M24 (182 of 465 fatigued patients with complete data), 32.3% at M36 (139 of 431 fatigued patients with complete data), 28.7% at M48 (119 of 414 fatigued patients with complete data), and 24.6% at M60 (97 of 394 fatigued patients with complete data) (Figure 1).

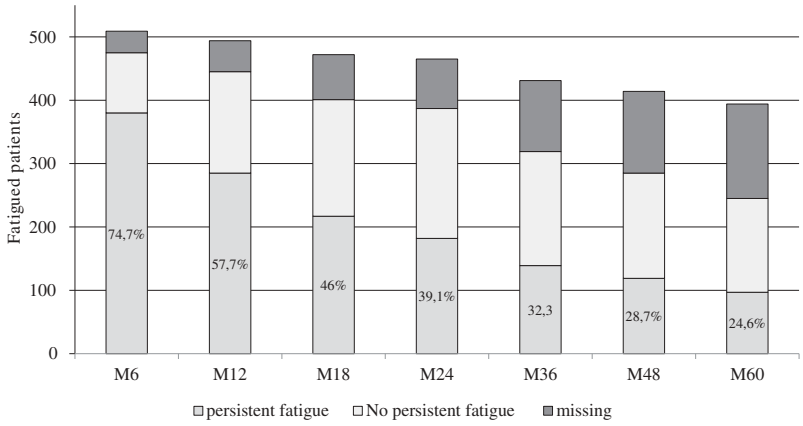

Figure 1. Patients who reported fatigue at all time-points of follow-up.

Factors associated with fatigue at baseline (defined as VAS fatigue > 20). Multivariable logistic regression analysis (Table 2) indicated that female gender (OR = 1.69, 95% CI 1.03–2.77, p = 0.037), younger age (OR = 1.03, 95% CI 1.01–1.04, p = 0.030), greater severity of morning stiffness (OR = 1.01, 95% CI 1.00–1.02, p < 0.001), presence of sleep problems (OR = 1.71, 95% CI 1.06–2.76, p = 0.026), higher HAQ levels (OR = 2.01,

Table 2. Bivariable and multivariable logistic regression analysis of the variables associated with fatigue at baseline (N = 673).

	Bivariable		Multivariable	
Variable†	OR (95% CI)	p	OR (95% CI)	p
Female gender	1.79 (1.17–2.74)	0.007*	1.69 (1.03–2.77)	0.037*
Age at disease onset (years)‡	1.02 (1.01–1.04)	0.031*	1.03 (1.01–1.04)	0.030*
Married	1.23 (0.81–1.87)	0.329		
Superior educational level	0.63 (0.42–0.94)	0.025*		
Professional graduate	0.62 (0.41–0.94)	0.024*		
Menopausal status	0.84 (0.53–1.34)	0.481		
Smoking status	0.93 (0.63–1.36)	0.723		
Initial pattern of the joint involvement: acute	0.81 (0.66–1.01)	0.064*		
Joint symptoms: symmetric	1.06 (0.71–1.57)	0.753		
Oligopolyarticular at the beginning	0.78 (0.48–1.27)	0.331		
Fever at RA onset	0.58 (0.27–1.25)	0.167		
Anaemia	1.11 (0.68–1.80)	0.670		
Anti-CCP antibodies	0.90 (0.61–1.33)	0.619		
Rheumatoid factor	1.32 (0.89–1.94)	0.155		
Elevated level of ESR (cut-off > 28 mm/h)	1.10 (0.74–1.63)	0.622		
Elevated level of CRP (cut-off > 5 mg/L)	1.06 (0.70–1.60)	0.769		
Presence of pain	3.70 (1.22–11.21)	0.020*		
Morning stiffness (range 0–100 VAS)‡	1.02 (1.02–1.03)	< 0.001*	1.01 (1.00–1.02)	< 0.001*
Morning stiffness duration (min)‡	1.71 (1.16–2.52)	0.006*		
Sleep problems	2.76 (1.82–4.18)	< 0.001*	1.71 (1.06–2.76)	0.026*
HAQ score (0–3 scale)‡	3.57 (2.50–5.09)	< 0.001*	2.01 (1.34–3.02)	0.001*
DAS28‡	1.54 (1.30–1.83)	< 0.001*		
Sicca syndrome	2.33 (1.42–3.82)	0.001*	2.04 (1.18–3.54)	0.011*
Body mass index (kg/m^2)‡	0.99 (0.95–1.04)	0.930		
> 3 comorbidities	1.26 (0.85–1.86)	0.247		
History of diabetes	1.56 (0.64–3.81)	0.320	2.29 (1.21–4.34)	0.011*
History of thyroid problems	1.73 (1.01–2.96)	0.043*		
History of depression/anxiety	3.42 (2.21–5.30)	< 0.001*	2.06 (1.27–3.33)	0.003*
Radiographic changes	1.26 (0.75–2.10)	0.370		

†Time to consult a rheumatologist was missing in 12 patients, anaemia in three patients, abnormal ESR in 10 patients, abnormal CRP in 10 patients, morning stiffness range in two patients, sleep problems in 207 patients, DAS28 in 13 patients, sicca syndrome in five patients, and body mass index in five patients.
‡Quantitative variable.
*Significant variable (p < 0.05).
RA, rheumatoid arthritis; anti-CCP, anti-cyclic citrullinated peptide; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; VAS, visual analogue scale; HAQ, Health Assessment Questionnaire; DAS28, Disease Activity Score in 28 joints; OR, odds ratio; CI, confidence interval.

95% CI 1.34–3.02, p < 0.001), presence of sicca symptoms (OR = 2.04, 95% CI 1.34–3.02, p < 0.001), history of thyroid problems (OR = 2.29, 95% CI 1.21–4.34, p < 0.001), and psychological distress (depressive or anxiety symptoms) (OR = 2.06, 95% CI 1.27–3.33, p = 0.003) were associated with fatigue at baseline.

Factors predicting persistent fatigue at 5 years of follow-up. Multivariable modelling showed that greater severity of morning stiffness (OR = 1.01, 95% CI 1.00–1.02, p = 0.019), presence of sicca symptoms at baseline (OR = 2.53, 95% CI 1.55–4.11, p < 0.001), and psychological distress (depressive or anxiety symptoms) (OR = 2.60, 95% CI 1.60–4.22, p < 0.001) were independently associated with persistent fatigue (Table 3). In multivariable analysis, baseline disease activity measured by DAS28 was not a predictor of persistent fatigue (OR = 1.15, 95% CI 0.96–1.38, p = 0.125).

Discussion

In this large cohort of patients with early RA, we observed that fatigue is a highly prevalent symptom. The prevalence of fatigue varies in the literature depending on the definition and assessment tools used (5–9).

At baseline, we reported fatigue in 80.6% of the total study population.

At 5 years of follow-up, the percentage of fatigued patients who reported fatigue at all time-points since baseline was 24.6%, which we refer to as 'persistent fatigue'.

To measure fatigue, we used the VAS fatigue score. This score has been shown to be a valid and reliable measure (39–42). In our cohort, the mean ± sd VAS fatigue baseline value was 48.8 ± 27.3 (the higher the score the more severe the fatigue). Similar values were reported in previous studies with similar populations (17, 18). This outcome might be regarded a limitation: we used a single item (VAS score)

Table 3. Bivariable and multivariable logistic regression analysis of the variables associated with persistent fatigue at 5 years of follow-up (N = 441).

	Bivariable		Multivariable	
Variable†	OR (95% CI)	p	OR (95% CI)	p
Female gender	2.12 (1.12–3.99)	0.020*		
Age at disease onset (years)‡	1.01 (0.99–1.03)	0.493		
Married	0.99 (0.59–1.68)	0.995		
Superior educational level	0.47 (0.27–0.82)	0.009*		
Professional graduate	0.50 (0.28–0.88)	0.017*		
Menopausal status	1.07 (0.65–1.75)	0.774		
Smoking status	0.80 (0.51–1.26)	0.342		
Initial pattern of the joint involvement: acute	0.99 (0.78–1.25)	0.949		
Joint symptoms: symmetric	0.67 (0.42–1.08)	0.105		
Oligopolyarticular at the beginning	1.19 (0.88–1.61)	0.256		
Fever at RA onset	0.63 (0.30–1.34)	0.239		
Anaemia	0.77 (0.43–1.38)	0.386		
Anti-CCP antibody negative	0.65 (0.41–1.03)	0.069		
Rheumatoid factor	1.12 (0.72–1.79)	0.553		
Elevated level of ESR (cut-off > 28 mm/h)	0.78 (0.49–1.25)	0.310		
Elevated level of CRP (cut-off > 5 mg/L)	0.79 (0.49–1.2)	0.345		
Presence of pain	1.3 (0.23–0.36)	< 0.107		
Morning stiffness (range 0–100 VAS)‡	1.01 (1.00–1.02)	0.001*	1.01 (1.00–1.02)	0.019*
Morning stiffness duration (min)‡	1.57 (0.98–2.51)	0.060*		
Sleep problems	1.79 (0.99–3.22)	0.051*		
HAQ score (0–3 scale)‡	1.68 (1.22–2.33)	0.001*		
DAS28‡	1.15 (0.96–1.38)	0.125		
Sicca syndrome‡	2.90 (1.82–4.64)	< 0.001*	2.53 (1.55–4.11)	< 0.001*
Body mass index (kg/m^2)‡	0.99 (0.94–1.04)	0.939		
> 3 comorbidities	1.21 (0.77–1.91)	0.397		
History of diabetes	0.76 (0.23–2.46)	0.658		
History of thyroid problems	1.34 (0.65–2.77)	0.425		
History of depression/anxiety	2.98 (1.87–4.77)	< 0.001*	2.60 (1.60–4.22)	< 0.001*
Radiographic changes	1.40 (0.72–2.74)	0.317		

†Anaemia was missing in one patient, ESR and CRP values in seven patients, morning stiffness in one patient, and sleep problems in 143 patients.
‡Quantitative variable.
*Significant variable (p < 0.05).
RA, rheumatoid arthritis; anti-CCP, anti-cyclic citrullinated peptide; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; VAS, visual analogue scale; HAQ, Health Assessment Questionnaire; DAS28, Disease Activity Score in 28 joints; OR, odds ratio; CI, confidence interval.

to measure fatigue, and a single scale may not take into account the multidimensional and fluctuating nature of fatigue. However, the VAS fatigue score has been found to be more sensitive to change than other scales and suitable for measuring global fatigue (38, 40–42). There are no standardized VAS cut-offs for distinguishing the presence or absence of fatigue. However, the cut-off used corresponds to what is described in previous studies (6, 17, 24).

Only a few studies have evaluated fatigue in early RA or early arthritis cohorts (17, 18, 22). In line with results obtained in other studies in early RA patients, we found that female gender (17, 18), younger patients (17, 18), greater severity of morning stiffness (18), higher HAQ values (17, 18, 22), presence of sicca symptoms (18), sleep disturbances (17, 22), and psychological distress (depressive or anxiety symptoms) (18, 19, 22) are associated with fatigue at baseline. The wide conceptual spectrum of associated variables clearly highlights the multifactorial origin of this symptom.

A history of thyroid disorders was related to baseline fatigue in our cohort. This association was not previously found in rheumatic conditions. This may be because fatigue is one of the most frequent complaints in thyroid diseases (47, 48). We found also that sicca symptoms are associated with baseline fatigue as well as being a predictor of persistent fatigue at 5 years of follow-up. This may be related to the association of RA with a secondary Sjögren's syndrome, as fatigue is a major aspect of the disease.

As previously reported, the results of the current study failed to provide evidence that pain is significantly related to fatigue in early RA (26).

Different cross-sectional epidemiological studies reveal an inconsistent association between fatigue and disease activity (5–8, 10, 20, 26, 33, 36). In our study, at the early stage of disease, DAS-28 was found to have a statistically significant relationship with fatigue, but only in bivariable analysis. Neither DAS-28 nor ESR was a predictor of fatigue or persistent fatigue over 5 years of follow-up. In contrast to common subjectively based perceptions, RA-related fatigue does not appear to be related to inflammatory disease activity in this cohort of early RA patients. This could be explained by the apparently prominent impact of psychological factors on perceived and reported fatigue over disease activity. It should also be noted that a surrogate of disease activity, namely duration of morning stiffness, remained an independent significant predictive factor of persistent fatigue.

Chronic medical illnesses are associated with increased prevalence of depressive symptoms and disorders. Studies conducted in established RA have reported that the prevalence of depression ranges between 13% and 20%, a two- to three-fold higher rate than in the general population (27). Depression seems to be one of the leading factors of fatigue in RA (5, 6, 18–24, 27, 29–31, 33–35).

To measure psychological distress we used a short screening questionnaire for mental health (MHI-5). The MHI-5 is a brief self-administered questionnaire and includes scales for anxiety and depression. It is a screening tool for identifying depressive and anxiety symptoms (43) but not an instrument for formal diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for depression and anxiety (44). In our cohort, up to 46% of patients reported psychological distress (symptoms of depression or anxiety), which is consistent with the report by Overman et al (9). It is therefore crucial that these aspects are monitored in early arthritis patients, and specific management offered to all patients. In established RA, Walter et al (32) demonstrated that depression was a predictor of fatigue at 1 year of follow-up. Another longitudinal study reports that worse values in VAS for general health and disability were predictors of fatigue (32). Feldthusen et al (23) found that pain and depressive mood were the strongest predictors of later fatigue.

As indicated previously (29), there has been a limited number of longitudinal analyses of fatigue in RA (17–19, 23–25, 49). Nikolaus et al (36) addressed the need to conduct longitudinal studies with representative samples and multivariable analysis in the examination of fatigue, which was the approach used in this study.

In an early RA population, Van Steenbergen et al (18) identified that, despite improved treatment strategies and decreased inflammation levels during disease course, fatigue severity in RA remained unchanged. Moreover, they found that the female gender, younger age, and higher inflammatory markers (higher swollen and tender joint counts and CRP) were predictors of fatigue at 8 years. Rat et al (17), in a longitudinal study over 1 year, showed that the course of fatigue was strongly associated with modifications in health-related quality of life (HRQoL), notably the affect dimension, but also baseline HRQoL and level of fatigue. Contrary to expectations, Treharne et al (19) showed that patients who had lower inflammation at baseline reported higher fatigue 1 year later.

The longitudinal design and recruitment of a large number of patients with very early RA are the major strengths of our study. The ESPOIR cohort included all patients with early arthritis regardless of disease severity or activity, which allows the disease course to be assessed in a real-life setting.

The results illustrate the multidimensional origin of fatigue and suggest that many patients may need non-pharmacological interventions to manage and reduce fatigue, even if inflammatory activity is controlled. The determining factors associated with persistent fatigue can be considered clinically relevant, since daily practice could be improved by identifying these factors, designing measures to develop potential interventions and modifying them through specific management.

Conclusion

Our results confirm that fatigue is a common phenomenon in early RA. Fatigue cannot be considered only a consequence of disease activity; rather, it appears to be multifactorial at the beginning of the disease. Fatigue should be addressed and explored systematically in clinical practice because, if overlooked, psychological disorders requiring specific management can lead to persistently altered perceived health status.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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