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ORIGINAL ARTICLE

# Factors Associated With Fatigue in Early Arthritis: Results From a Multicenter National French Cohort Study

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***Objective.*** **Fatigue frequently occurs in patients with early arthritis (EA). Determinants of its severity are unknown. We aimed to identify the factors associated with fatigue in EA and changes in fatigue after 1 year of followup.**

***Methods.*** **The Evaluation et Suivi de Polyarthrites Indifférenciées Récentes (Assessment and Followup of Early Undifferentiated Arthritis) cohort study is a multicenter, prospective, national cohort of patients with EA. At baseline and every 6 months up to 1 year, we recorded sociodemographic, clinical, and treatment characteristics, Arthritis Impact Measurement Scales 2 Short Form (AIMS2-SF) and Short Form 36 (SF-36) scores for health-related quality of life (HRQOL), and fatigue severity by a visual analog scale (f-VAS) and the SF-36 vitality score (fatigue_SF36).**

***Results.*** **We included 813 patients (77% women, mean ± SD age 48 ± 13 years). At baseline, fatigue as assessed by the f-VAS or fatigue_SF36 was independently associated with young age, female sex, low education level, smoking, increased Disease Activity Score in 28 joints (DAS28), waking up at night, Sjögren's syndrome, and worse AIMS2-SF physical, affect, and symptom scores. At 1-year followup, a favorable change in fatigue scores was associated with increased baseline AIMS2-SF physical and affect scores (better quality of life), high baseline fatigue scores, and improved 1-year AIMS2-SF affect scores. Age, sex, and change in AIMS2-SF physical score, DAS28, and hemoglobin or C-reactive protein level were inconsistently associated with change in fatigue scores. The AIMS2-SF affect score explained most of the variance in baseline fatigue score and was an important factor in 1-year change in fatigue score.**

***Conclusion.*** **Fatigue in EA is multifactorial. Its level and its course are strongly associated with HRQOL, notably the affect dimension. These results should help professionals inform patients about fatigue, explore its causes, and develop tailored interventions.**

## INTRODUCTION

Fatigue has a major impact on patients living with rheumatoid arthritis (RA). Significant fatigue is reported by 40–80% of patients and is frequently their most disabling symptom (1–3). In qualitative studies, fatigue is described as different from normal tiredness in that it is overwhelming, uncontrollable, and ignored (4). Moreover, patients sometimes think nothing can be done for it and do not talk to their physician about it (5).

The Outcome Measures in Rheumatology group identified fatigue among important symptoms for RA patients (6,7) and highly recommended that it be measured. Identification of its determinants is a prerequisite to interpreting its measurement. Fatigue and its determinants have mainly been studied in patients with established RA (8–13). Fatigue is often multifactorial and could be worsened by disease-related factors (disease activity, pain, anemia, treatment, activity of proinflammatory cytokines), comor-

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## Significance & Innovations

- Fatigue in early arthritis is multifactorial at the start of the disease.
- Fatigue level and its course are strongly associated with heath-related quality of life, notably the affect dimension.
- A high level of fatigue but better health-related quality of life scores at baseline are associated with 1-year improvement in fatigue for patients with early arthritis.

bid conditions (depression, sleep disorders, dyspnea), and lifestyle factors (smoking or alcohol consumption). Fatigue can also worsen because of factors such as level of activity or social support (2,10–13).

In early arthritis (EA), variation in fatigue level is probably more noticeable during the first months of the disease than in established RA. Its determinants have rarely been explored. We used the national Evaluation et Suivi de Polyarthrites Indifférenciées Récentes (Assessment and Followup of Early Undifferentiated Arthritis; ESPOIR) cohort to study the baseline association of fatigue and sociodemographic characteristics, lifestyle factors, disease characteristics, and quality of life measures and to identify the factors associated with a change in fatigue at 1-year followup.

## PATIENTS AND METHODS

**Design.** The ESPOIR cohort study is a multicenter national cohort of patients with EA of a duration of <6 months at baseline. This cohort is a nationwide project of the French Society of Rheumatology and was established to create a database to investigate the diagnosis, prognosis, pathogenesis, medicoeconomics, and outcome measures of EA and RA. The cohort was established with the assistance of general practitioners and rheumatologists referring patients with EA to hospitals participating in the ESPOIR cohort project (14). All included patients were followed up by the same investigators in each of the 14 regional centers all over the country (16 university hospital rheumatology departments) every 6 months during the first 2 years and then every year thereafter. We used information collected at baseline and at 6 and 12 months because we expected to observe an important change in fatigue level at this early stage of the disease. Indeed, this is a critical time for patients because they must face a new diagnosis and adapt to a chronic disease, and because treatment usually improves symptoms greatly.

**Patients.** Patients were included between December 2002 and March 2005. Inclusion criteria were age 18–70 years, having ≥2 inflammatory joints for 6 weeks, and arthritis onset of <6 months. Patients with a definite diagnosis different from RA were excluded. Therefore, all included patients had inflammatory arthritis for which an RA diagnosis was considered or already confirmed. Patients were included if they did not receive disease-modifying antirheumatic drugs (DMARDs) or corticosteroids before inclusion, except for <2 weeks before inclusion.

The protocol of the ESPOIR cohort study was approved by the Ethics Committee of Montpellier. Before inclusion, all patients gave their written informed consent to participate in this prospective study.

**Data collected.** At baseline, the following data were collected: sociodemographic data (age, sex, marital status, education level, and professional activity), lifestyle factors (smoking), personal health data (menopause status, thyroid disease, and comorbidities), clinical data (presence of Sjögren's syndrome according to the physician and likelihood of RA according to the American College of Rheumatology [ACR]/European League Against Rheumatism [EULAR] criteria) (15), and delay between the first swollen joint and the first visit to the rheumatologist (16). The delay between the first symptom (first occurrence of a stable swollen joint) and DMARD initiation was determined to assess the quality of care. Data on rheumatoid factor and anti–cyclic citrullinated peptide 2 antibodies as well as joint radiography findings (modified Sharp/van der Heijde score) were also collected at baseline.

At baseline and at each followup visit, data for the following clinical and biologic variables were collected: disease characteristics (waking up at night and disease activity as measured by the Disease Activity Score in 28 joints [DAS28]) (17), treatment (opioids, nonsteroidal antiinflammatory drugs, corticosteroids, and DMARDs), and hemoglobin and C-reactive protein (CRP) levels. Functional ability and health-related quality of life (HRQOL) were assessed by the Health Assessment Questionnaire (HAQ) (18,19), the Short Form 36 (SF-36) Health Survey (20), and a disease-specific HRQOL instrument, the Arthritis Impact Measurement Scales 2 Short Form (AIMS2-SF) (21). The AIMS2-SF measures 5 domains of health: physical function divided into upper and lower body limitations, symptoms, affect, social isolation, and work. The affect dimension includes 5 items for tension or mood.

**Outcome measures.** Fatigue severity was assessed by a visual analog scale (f-VAS) and the vitality subscale of the SF-36 (20) at each visit.

The global assessment of fatigue severity with the f-VAS was assessed over the previous 48 hours by a 100-mm VAS, where 0 = no fatigue and 100 = worst fatigue. An f-VAS score ≤20 mm was considered low fatigue (8). The sensitivity to change of global fatigue assessed by a single VAS is as good as other multidimensional scales measuring fatigue (22).

The vitality subscale of the SF-36 contains 4 items (feel full of pep, worn out, lots of energy, or feel tired) exploring both fatigue and a related concept, energy level. Item responses were rated on a 6-point Likert scale, where 0 = all the time and 5 = none of the time. The sum score was

standardized from 0 (worst) to 100 (best). The psychometric properties of the SF-36 vitality subscale have been widely documented, and Cronbach's alpha for the French version is 0.82 (23). To simplify the reporting of the results, the vitality subscale of the SF-36 was renamed the fatigue_SF36, with scores ranging from 0 (no fatigue) to 100 (worst fatigue).

**Statistical analysis.** Dimension scores of the SF-36 and AIMS2-SF for HRQOL were standardized, where 0 = worst quality of life to 100 = best quality of life. Continuous data were summarized by the means and SDs and categorical data by the number (percentage). Changes in fatigue were also described as the percentage of patients with improved, unchanged, or worsened fatigue on the basis of the minimum clinically important difference (MCID) determined for RA: −11 and +12 for the fatigue_SF36 score and −9 and +15 for the f-VAS score for worsened and improved conditions, respectively (24).

Factors associated with fatigue at baseline were examined by analysis of variance or Pearson's correlation coefficient. A stepwise multiple linear regression model entered candidate variables ($P < 0.2$ on univariate analysis for all variables and correlation coefficient >0.2 for quantitative variables). The fatigue_SF36 and f-VAS variables were studied separately. Partial $R^2$ and $R^2$ were computed to measure the variance in fatigue scores explained by each variable and by the whole model.

To identify the factors associated with change in fatigue during the first year after inclusion, patients were divided into 3 categories according to MCID values for fatigue: improved, unchanged, or worsened. Variables collected at baseline and those with changed values between baseline and 1 year (e.g., variation in DAS28) were analyzed by polytomous logistic regression, with the 3 categories as dependent variables. The models provided regression coefficients for independent variables, the antilogs of which were odds ratios (ORs) expressing the effect, when changing 1 unit of the independent variable, on the odds of being in the group of patients with improved or worsened fatigue as compared with the group of patients with unchanged fatigue, holding other variables constant in the equation model. The scores for different instruments (SF-36, AIMS2-SF, and HAQ) measuring the same dimensions of HRQOL or functional ability were not entered in the same statistical model to avoid colinearity. The AIMS2-SF scores were preferred to the SF-36 scores to avoid expected correlations with the fatigue_SF36 score of the SF-36. Effects on the log-odds scale of possible factors associated with change in fatigue were checked for linearity. A stepwise regression model entered candidate variables ($P < 0.2$ on univariate analysis). The max-rescaled $R^2$ was used to assess the fit of the model.

Statistical significance was set at a $P$ value less than 0.05. All computations used SAS for Windows, version 9.1. To achieve a 10-point difference in fatigue scores between 2 groups on a scale of 0 to 100 with a significance level of a $P$ value less than 0.05, a power of 80%, and an SD of 25 for both instruments (24), a total of 198 patients were necessary for the cross-sectional analysis. For polytomous logistic regression, to achieve an increase of an OR of 1.5 with a significance level of a $P$ value less than 0.05 and a power of 80%, a sample size of 644 was required (25).

## RESULTS

A total of 814 patients with EA were included between December 2002 and March 2005. One patient withdrew consent, and data for 813 patients were analyzed. Data were collected at 6 months and at 1 year for 757 and 731 patients, respectively. The number of patients with complete data was 810 at baseline, 754 at 6 months, and 728 at 1 year.

The demographic and clinical characteristics of the patients are shown in Table 1. Of the 813 patients, 641 (79.1%; the ACR/EULAR criteria for RA could not be determined for 3 patients) fulfilled the ACR/EULAR criteria for RA, which confirmed that the EA patients enrolled in the ESPOIR cohort were at high risk of RA. The mean ± SD duration between onset of arthritis and inclusion in the ESPOIR cohort was 3 ± 2 months (median 3 months, interquartile range 2–4 months). The baseline demographic and clinical characteristics of the participants with and without data collected at 6 and 12 months were not different.

At baseline, according to the f-VAS data, only 21.5% of the patients (n = 174) reported having a low level of fatigue (≤20 mm); the f-VAS score was 20–40 mm for 18.5% of the patients (n = 150) and >40 mm (worst fatigue) for 60.0% (n = 487). Similarly, only 3.1% of the patients (n = 25) had a fatigue_SF36 score ≤20 (best); the fatigue_SF36 score was 20–40 for 14.4% of the patients (n = 117) and >40 (worst) for 82.5% (n = 669).

The mean level of fatigue decreased at 6 months and was stable up to 1 year. At 1 year, according to fatigue_SF36 score changes, 11.3% (n = 86), 43.5% (n = 317), and 45.2% (n = 329) of patients showed worsened, stable, or improved fatigue, respectively. These figures were 23.9% (n = 174), 34.3% (n = 250), and 41.8% (n = 304) by the f-VAS, respectively. The mean ± SD delay between the first symptom (first occurrence of a stable swollen joint) and DMARD initiation was 131.9 ± 69.0 days.

Results of the cross-sectional univariate analysis at baseline are shown in Table 2. Factors associated with a high baseline fatigue_SF36 score (high fatigue level) were low education level, smoking, comorbidity, waking up at night, Sjögren's syndrome, high DAS28 score, opioid use, low HRQOL scores (worse HRQOL), low hemoglobin level, and high CRP level.

The determinants of a high baseline f-VAS score (high fatigue level) were center, young age, female sex, low education level, smoking, waking up at night, Sjögren's syndrome, high DAS28 score, ACR/EULAR criteria for RA, opioid use, low HRQOL scores (worse HRQOL), low hemoglobin level, and high CRP level.

On multivariate analysis (Table 3), the factors independently associated with high baseline fatigue score were demographics (young age, female sex, and low education level), patient and disease characteristics (smoking, waking up at night, high DAS28 score, and Sjögren's syndrome), and HRQOL (low AIMS2-SF physical, affect, and

**Table 1. Demographic and clinical characteristics of the 813 patients at baseline***

| | Values |
|---|---|
| Age, mean ± SD years | 47.6 ± 12.6 |
| Sex, women | 624 (76.8) |
| Marital status, living as a couple | 594 (73.2) |
| Education level | |
| Primary | 101 (12.4) |
| Secondary | 457 (56.2) |
| University | 255 (31.4) |
| Professional activity | |
| Full time | 397 (48.9) |
| Part time | 84 (10.3) |
| None (housewife/husband, student, unemployed, retired) | 307 (37.8) |
| None (disability, pension) | 24 (3.0) |
| Smoking | 183 (47.2) |
| Menopausal | 284 (45.5) |
| Thyroid disease | 90 (11.1) |
| ≥1 comorbidity | 539 (66.8) |
| Times waking up at night, mean ± SD no. per night | 1.9 ± 2.4 |
| DAS28, mean ± SD | 5.1 ± 1.3 |
| Sjögren's syndrome | 235 (28.9) |
| ACR/EULAR criteria for RA at baseline | 641 (79.1) |
| Time since first arthritis, mean ± SD months† | 2.9 ± 1.8 |
| Time to consult a rheumatologist, mean ± SD days‡ | 74.9 ± 76.6 |
| Opioids | 322 (39.6) |
| NSAIDs | 736 (90.5) |
| Corticosteroids | 9 (1.1) |
| DMARDs | 59 (7.3) |
| f-VAS, mean ± SD | 47.8 ± 28.2 |
| Fatigue_SF36, mean ± SD | 60.9 ± 19.2 |
| HAQ (range 0–3), mean ± SD | 1.0 ± 0.7 |
| SF-36 PCS, mean ± SD | 37.4 ± 8.9 |
| SF-36 MCS, mean ± SD | 39.5 ± 11.0 |
| AIMS2-SF physical, mean ± SD | 74.1 ± 12.6 |
| AIMS2-SF symptoms, mean ± SD | 37.7 ± 25.4 |
| AIMS2-SF affect, mean ± SD | 58.3 ± 19.9 |
| AIMS2-SF social isolation, mean ± SD | 48.9 ± 15.7 |
| AIMS2-SF work, mean ± SD | 63.9 ± 29.9 |
| Hemoglobin level, mean ± SD gm/dl | 13.0 ± 1.3 |
| C-reactive protein level, mean ± SD mg/liter | 20.3 ± 32.4 |
| Rheumatoid factor | 376 (45.8) |
| Anti–CCP-2 antibodies | 315 (38.8) |
| Modified Sharp/van der Heijde score (range 0–314), mean ± SD | 6.0 ± 10.1 |

* The values are the number (percentage) unless otherwise indicated. The fatigue_SF36 and f-VAS scores range from 0 (no fatigue) to 100 (worst fatigue); the Short Form 36 (SF-36) and AIMS2-SF scores range from 0 (worst quality of life) to 100 (best quality of life). DAS28 = Disease Activity Score in 28 joints; ACR = American College of Rheumatology; EULAR = European League Against Rheumatism; RA = rheumatoid arthritis; NSAIDs = nonsteroidal antiinflammatory drugs; DMARDs = disease-modifying antirheumatic drugs; f-VAS = visual analog scale; fatigue_SF36 = SF-36 vitality subscale; HAQ = Health Assessment Questionnaire; PCS = physical component subscale; MCS = mental component subscale; AIMS2-SF = Arthritis Impact Measurement Scales 2 Short Form; anti–CCP-2 = anti–cyclic citrullinated peptide 2.
† Time since first arthritis is the delay between the first stable swollen joint and inclusion in the study.
‡ Time to consult a rheumatologist is the time from the first occurrence of a stable swollen joint needed to consult a rheumatologist.

symptom scores). The factors associated with fatigue were not identical for each fatigue outcome.

The factors associated with change in fatigue at 1 year, with the unchanged fatigue level as the reference category, are shown in Table 4. As assessed by the fatigue_SF36 score, 1-year improvement of fatigue was associated with high baseline AIMS2-SF physical and affect scores and high baseline fatigue_SF36 score and with improved 1-year AIMS2-SF physical and affect scores and hemoglobin level: for a 1-point increase in baseline AIMS2-SF physical and affect scores (better HRQOL) and a 1-point increase in baseline fatigue_SF36 score (high fatigue), the ORs for improvement in fatigue were 1.38, 1.75, and 2.39, respectively; for a 1-point improvement in 1-year AIMS2-SF physical and affect scores and a 1-point increase in 1-year hemoglobin level (gm/dl), the ORs for improvement in fatigue were 1.40, 1.87, and 1.41, respectively.

**Table 2. Determinants of fatigue at baseline for subjects with early arthritis in the ESPOIR cohort: univariate analysis***

| | | Baseline fatigue_SF36 (n = 811) | | Baseline f-VAS (n = 811) | |
|---|---|---|---|---|---|
| | No. | Value | *P* | Value | *P* |
| Age, R (95% CI) | 811 | −0.06 (−0.13, 0.01) | 0.11 | −0.08 (−0.14, −0.01) | 0.03 |
| Sex | | | 0.12 | | 0.0006 |
| Women | 623 | 61.4 ± 19.0 | | 49.6 ± 28.3 | |
| Men | 188 | 58.9 ± 19.7 | | 41.6 ± 27.2 | |
| Education | | | 0.002 | | < 0.0001 |
| Primary | 100 | 63.4 ± 17.7 | | 49.0 ± 28.4 | |
| Secondary | 456 | 62.3 ± 19.4 | | 51.3 ± 28.1 | |
| University | 255 | 57.3 ± 19.2 | | 41.0 ± 27.1 | |
| Smoking | | | 0.04 | | 0.0007 |
| Yes | 182 | 63.4 ± 18.8 | | 54.0 ± 27.4 | |
| No | 629 | 60.1 ± 19.3 | | 46.0 ± 28.2 | |
| Comorbidity | | | 0.03 | | 0.10 |
| Yes | 538 | 62.0 ± 19.1 | | 49.1 ± 28.5 | |
| No | 267 | 58.9 ± 19.2 | | 45.7 ± 27.3 | |
| Wake up at night | | | < 0.0001 | | < 0.0001 |
| Yes | 519 | 64.2 ± 17.9 | | 52.1 ± 26.5 | |
| No | 292 | 54.9 ± 20.0 | | 40.0 ± 29.5 | |
| DAS28, R (95% CI) | 798 | 0.34 (0.28, 0.40) | < 0.0001 | 0.29 (0.23, 0.36) | < 0.0001 |
| Sjögren's syndrome | | | < 0.0001 | | < 0.0001 |
| Yes | 234 | 66.4 ± 17.8 | | 57.6 ± 26.7 | |
| No | 577 | 58.6 ± 19.3 | | 43.8 ± 27.8 | |
| ACR/EULAR criteria for RA at baseline | | | 0.16 | | 0.03 |
| Yes | 640 | 61.4 ± 18.8 | | 49.0 ± 27.3 | |
| No | 169 | 59.1 ± 20.7 | | 43.2 ± 30.9 | |
| Opioids | | | < 0.0001 | | 0.001 |
| Yes | 320 | 64.3 ± 18.9 | | 51.8 ± 27.2 | |
| No | 491 | 58.6 ± 19.1 | | 45.1 ± 28.6 | |
| HAQ score (range 0–3), R (95% CI) | 811 | 0.51 (0.46, 0.56) | < 0.0001 | 0.37 (0.30, 0.42) | < 0.0001 |
| SF-36 PCS score, R (95% CI) | 804 | −0.44 (−0.50, −0.39) | < 0.0001 | −0.31 (−0.37, −0.25) | < 0.0001 |
| SF-36 MCS score, R (95% CI) | 804 | −0.70 (−0.73, −0.66) | < 0.0001 | −0.38 (−0.44, −0.32) | < 0.0001 |
| AIMS2-SF physical, R (95% CI) | 811 | −0.49 (−0.54, −0.43) | < 0.0001 | −0.33 (−0.39, −0.26) | < 0.0001 |
| AIMS2-SF symptoms, R (95% CI) | 810 | −0.40 (−0.45, −0.34) | < 0.0001 | −0.30 (−0.36, −0.24) | < 0.0001 |
| AIMS2-SF affect, R (95% CI) | 810 | −0.60 (−0.64, −0.56) | < 0.0001 | −0.36 (−0.42, −0.30) | < 0.0001 |
| AIMS2-SF social isolation, R (95% CI) | 810 | −0.24 (−0.30, −0.17) | < 0.0001 | −0.18 (−0.24, −0.11) | < 0.0001 |
| AIMS2-SF work, R (95% CI) | 699 | −0.39 (−0.45, −0.33) | < 0.0001 | −0.22 (−0.29, −0.15) | < 0.0001 |
| Hemoglobin level (gm/dl), R (95% CI) | 808 | −0.10 (−0.17, −0.03) | 0.005 | −0.02 (−0.09, 0.05) | 0.56 |
| C-reactive protein level (mg/liter), R (95% CI) | 810 | 0.20 (0.13, 0.26) | < 0.0001 | 0.08 (0.01, 0.15) | 0.02 |

* Values are the mean ± SD unless otherwise indicated. The Short Form 36 (SF-36) and AIMS2-SF scores range from 0 (worst quality of life) to 100 (best quality of life). The other factors (marital status, professional activity, menopause status, thyroid disease, nonsteroidal antiinflammatory drug use, corticosteroid use, disease-modifying antirheumatic drug use, time since early arthritis onset, time from first occurrence of a stable swollen joint needed to consult a rheumatologist, and modified Sharp/van der Heijde score) were not associated with fatigue scores. Two patients for each fatigue measure did not complete the patient-reported outcomes questionnaires. ESPOIR = Evaluation et Suivi de Polyarthrites Indifférenciées Récentes (Assessment and Followup of Early Undifferentiated Arthritis); fatigue_SF36 = SF-36 vitality subscale; f-VAS = visual analog scale; 95% CI = 95% confidence interval; DAS28 = Disease Activity Score in 28 joints; ACR = American College of Rheumatology; EULAR = European League Against Rheumatism; RA = rheumatoid arthritis; HAQ = Health Assessment Questionnaire; PCS = physical component subscale; MCS = mental component subscale; AIMS2-SF = Arthritis Impact Measurement Scales 2 Short Form.

Worsened fatigue between baseline and 1 year was associated with age, sex, baseline AIMS2-SF physical and affect scores, and baseline fatigue_SF36 score, as well as 1-year change in AIMS2-SF affect score and CRP level: for female sex, for a 1-point increase in age, baseline AIMS2-SF physical and affect scores, and baseline fatigue_SF36 score, the ORs were 3.16, 0.72, 0.72, 0.73, and 0.45, respectively; for a 1-point increase in 1-year AIMS2-SF affect score and a 1-point decrease in CRP level (mg/liter), the ORs were 0.57 and 0.81, respectively.

As assessed by the f-VAS, 1-year improvement in fatigue was associated with high baseline AIMS2-SF physical and affect scores and high baseline f-VAS score (high level of fatigue) and improved 1-year DAS28 and AIMS2-SF affect scores. Worsened fatigue at 1 year was associated with baseline AIMS2-SF affect and f-VAS scores, time to DMARD initiation, and 1-year change in DAS28 and AIMS2-SF affect scores.

## DISCUSSION

Fatigue has rarely been studied in EA, when important changes can be expected because patients must adapt to a

**Table 3. Factors associated with baseline fatigue for patients with early arthritis in the ESPOIR cohort: cross-sectional multivariate analyses***

| Factors | Fatigue_SF36 | | | f-VAS | | |
|---|---|---|---|---|---|---|
| | β (SE) | $R^2$ | *P* | β (SE) | $R^2$ | *P* |
| Age, years | −0.12 (0.04) | 0.003 | 0.008 | −0.24 (0.08) | 0.01 | 0.001 |
| Sex, female/male | † | † | † | 5.11 (2.13) | 0.01 | 0.02 |
| Education level, primary/secondary/university | −1.22 (0.59) | 0.004 | 0.04 | −3.67 (1.00) | 0.01 | 0.0002 |
| Smoking status, yes/no | † | † | † | 5.98 (2.19) | 0.01 | 0.006 |
| Comorbidity, yes/no | 2.09 (1.12) | 0.003 | 0.06 | NS‡ | NS‡ | NS‡ |
| Waking up at night, yes/no | 2.00 (1.23) | 0.002 | 0.10 | 4.85 (2.07) | 0.01 | 0.02 |
| DAS28 | 1.14 (0.53) | 0.002 | 0.03 | 2.08 (0.83) | 0.04 | 0.01 |
| Sjögren's syndrome, yes/no | † | | † | 7.95 (2.02) | 0.02 | < 0.0001 |
| ACR/EULAR criteria for RA at baseline | −2.44 (1.42) | 0.002 | 0.09 | † | † | † |
| AIMS2-SF physical | −0.20 (0.04) | 0.05 | < 0.0001 | −0.19 (0.07) | 0.01 | 0.01 |
| AIMS2-SF symptoms | −0.07 (0.03) | 0.01 | 0.007 | −0.09 (0.04) | 0.01 | 0.05 |
| AIMS2-SF affect | −0.41 (0.03) | 0.35 | < 0.0001 | −0.24 (0.05) | 0.13 | < 0.0001 |
| Center | NS‡ | NS‡ | NS‡ | 0.44 (0.22) | 0.004 | 0.05 |
| $R^2$ | | 0.43 | | | 0.25 | |

* The Short Form 36 (SF-36) and AIMS2-SF scores range from 0 (worst quality of life) to 100 (best quality of life). The fatigue_SF36 and f-VAS scores range from 0 (no fatigue) to 100 (worst fatigue). ESPOIR = Evaluation et Suivi de Polyarthrites Indifférenciées Récentes (Assessment and Followup of Early Undifferentiated Arthritis); fatigue_SF36 = SF-36 vitality subscale; f-VAS = visual analog scale; β = coefficient of the linear regression; NS = not significant; DAS28 = Disease Activity Score in 28 joints; ACR = American College of Rheumatology; EULAR = European League Against Rheumatism; RA = rheumatoid arthritis; AIMS2-SF = Arthritis Impact Measurement Scales 2 Short Form.
† Variables not entered in the stepwise regression analysis (NS at the $P < 0.2$ level on multivariate analysis).
‡ NS on univariate analysis.

chronic disorder and treatment produces symptom relief. Our study confirmed that fatigue is an important feature of EA. Only 21.5% of the patients in the ESPOIR cohort reported a low level of fatigue at baseline as assessed by the f-VAS. In addition, the mean ± SD fatigue_SF36 score for these patients was high (60.9 ± 19.2 on a scale where 0 = no fatigue and 100 = worst fatigue), as compared with the mean ± SD score for the French general population (42.6 ± 18.0) (26). One of the strengths of the ESPOIR cohort is its inclusion of a broad group of patients with EA. Moreover, the ESPOIR cohort included all patients with EA regardless of disease severity or activity, which allows for assessing the disease course in a real-life setting that may differ from clinical trials. These results are important for interpreting fatigue scores and their variations and should help professionals inform patients about fatigue, examine its causes, and develop tailored interventions.

At baseline, fatigue was independently associated with several demographic data (age, sex, and education level), patient and disease characteristics (smoking, DAS28 score, waking up at night, and Sjögren's syndrome), and HRQOL, but not professional activity. The high number of variables associated with fatigue highlights its multifactorial origin. However, the explained variance of the 2 scores of fatigue (the f-VAS and fatigue_SF36) was not high at baseline, which suggests that measuring fatigue may capture some elements missed by measures taking into account only symptoms, physical function, and mental health.

Demographic characteristics are inconsistently associated with fatigue for RA patients (1,3,9–12). The association between fatigue and smoking was previously found with systemic sclerosis (27) and fibromyalgia (28), but not EA or RA. Behaviors such as smoking may be linked to fatigue and pain. The results of different studies analyzing the association of fatigue and disease activity, including ours, are conflicting, and when an association is found, it seems marginal (1,9,11). The association we found between fatigue and pain measured with the AIMS2-SF symptoms score, sleep disorders, or mental health state confirmed results found in several studies of RA patients (1,3,8–11). As in established RA, psychological distress is highly correlated with fatigue in EA (27,29,30). Efforts to relieve fatigue such as resting, avoiding certain activities, or trying to think of something else (31) are often insufficient and can lead to an increased sense of helplessness and depression (32). Fatigue seems to be explained in large part by self-efficacy in coping with RA (3,12). Conversely, a history of an affective disorder independently predicts increased levels of fatigue in RA patients (13,33). To be in a poor mood is likely to increase somatic awareness and increase the tendency to focus on the sensations of pain and fatigue. As patients cope with their disease over time, factors associated with fatigue are probably modified.

We found that increased baseline AIMS2-SF physical and affect scores (better quality of life), high baseline fatigue scores, and improved 1-year AIMS2-SF affect scores were associated with a favorable change in fatigue scores (increased odds of improved condition and reduced odds of worsened condition as compared with patients with unchanged scores). Age and sex were inconsistently predictive of fatigue evolution at 1 year, as were changes in the AIMS2-SF physical score, DAS28, and hemoglobin or CRP level.

The affect score change had an important influence on fatigue change, which may suggest that affect and fatigue measures are closely related concepts. However, fatigue

**Table 4. Factors associated with a 1-year change in fatigue: multivariate polytomous regression analysis***

| Factors | Fatigue_SF36 change | | f-VAS change | |
|---|---|---|---|---|
| | OR (95% CI) | *P* | OR (95% CI) | *P* |
| Fatigue improvement† | | | | |
| Baseline factors | | | | |
| Age‡ | 1.15 (0.95, 1.39) | 0.15 | 1.21 (1.00, 1.47) | 0.05 |
| Sex | 0.85 (0.49, 1.48) | 0.57 | § | § |
| Sjögren's syndrome (yes/no) | NS¶ | NS¶ | § | § |
| Fatigue scores (fatigue_SF36 or f-VAS)‡ | 2.39 (1.95, 2.94) | < 0.0001 | 1.57 (1.40, 1.75) | < 0.0001 |
| AIMS2-SF physical‡ | 1.38 (1.11, 1.71) | 0.004 | 1.32 (1.07, 1.63) | 0.01 |
| AIMS2-SF affect‡ | 1.75 (1.45, 2.11) | < 0.0001 | 1.26 (1.07, 1.49) | 0.01 |
| Time to DMARD initiation# | § | § | 0.99 (0.96, 1.02) | 0.48 |
| Changed factors | | | | |
| ΔDAS28 (baseline to 1 year) | 1.12 (0.94, 1.35) | 0.21 | 1.25 (1.04, 1.50) | 0.02 |
| ΔAIMS2-SF physical (1 year to baseline)‡ | 1.40 (1.14, 1.72) | 0.001 | 1.20 (0.98, 1.47) | 0.08 |
| ΔAIMS2-SF affect (1 year to baseline)‡ | 1.87 (1.57, 2.24) | < 0.0001 | 1.43 (1.21, 1.68) | < 0.0001 |
| ΔHemoglobin level (1 year to baseline) | 1.41 (1.10, 1.80) | 0.01 | § | § |
| ΔC-reactive protein level (baseline to 1 year)‡ | 0.96 (0.89, 1.04) | 0.35 | 1.03 (0.95, 1.11) | 0.54 |
| Fatigue worsening† | | | | |
| Baseline factors | | | | |
| Age‡ | 0.72 (0.54, 0.95) | 0.02 | 0.91 (0.74, 1.13) | 0.39 |
| Sex | 3.16 (1.15, 8.67) | 0.03 | § | § |
| Sjögren's syndrome (yes/no) | NS¶ | NS¶ | § | § |
| Fatigue scores (fatigue_SF36 or f-VAS)‡ | 0.45 (0.35, 0.59) | < 0.0001 | 0.69 (0.61, 0.79) | < 0.0001 |
| AIMS2-SF physical‡ | 0.72 (0.54, 0.95) | 0.02 | 0.86 (0.69, 1.07) | 0.17 |
| AIMS2-SF affect‡ | 0.73 (0.55, 0.96) | 0.02 | 0.78 (0.64, 0.93) | 0.01 |
| Time to DMARD initiation# | § | § | 0.95 (0.91, 0.99) | 0.01 |
| Changed factors | | | | |
| ΔDAS28 (baseline to 1 year) | 0.80 (0.61, 1.04) | 0.09 | 0.81 (0.66, 0.99) | 0.03 |
| ΔAIMS2-SF physical (1 year to baseline)‡ | 1.03 (0.78, 1.36) | 0.84 | 0.87 (0.71, 1.07) | 0.19 |
| ΔAIMS2-SF affect (1 year to baseline)‡ | 0.57 (0.44, 0.73) | < 0.0001 | 0.79 (0.67, 0.94) | 0.01 |
| ΔHemoglobin level (1 year to baseline) | 0.97 (0.68, 1.39) | 0.88 | § | § |
| ΔC-reactive protein level (baseline to 1 year)‡ | 0.81 (0.65, 0.99) | 0.04 | 0.92 (0.83, 1.02) | 0.10 |
| Model $R^2$ | 0.56 | | 0.45 | |

* The fatigue_SF36 and f-VAS scores range from 0 (no fatigue) to 100 (worst fatigue). The model for fatigue_SF36 was adjusted for age, sex, baseline fatigue_SF36 score, and time to DMARD initiation and for DAS28, AIMS2-SF physical function, symptoms, and affect scores, hemoglobin level, and C-reactive protein (CRP) level (baseline and change scores). The model for f-VAS was adjusted for center, age, sex, smoking status, Sjögren's syndrome, baseline f-VAS score, and time to DMARD initiation and for DAS28, AIMS2-SF physical function, symptoms, and affect scores, hemoglobin level, and CRP level (baseline and change scores). For improvement, an OR >1 means that the odds of improved fatigue is increased. For worsening, an OR <1 means that the odds of worsened fatigue is decreased. An OR >1 for improvement and an OR <1 for worsening indicate a better outcome. The Short Form 36 (SF-36) and AIMS2-SF scores range from 0 (worst quality of life) to 100 (best quality of life). Fatigue_SF36 = SF-36 vitality subscale; f-VAS = visual analog scale; OR = odds ratio; 95% CI = 95% confidence interval; NS = not significant; AIMS2-SF = Arthritis Impact Measurement Scales 2 Short Form; DMARD = disease-modifying antirheumatic drug; DAS28 = Disease Activity Score in 28 joints; model $R^2$ = max-rescaled model $R^2$.
† The reference level is unchanged.
‡ Results for 10-unit changes.
§ Variables were not entered in the stepwise regression analysis (NS at the $P < 0.2$ level).
¶ NS in bivariate analysis.
# Results for 3-unit changes (in months).

was also influenced by baseline HRQOL scores, which can be explained by personality characteristics or by health status. An improved DAS28 score was also associated with an improved f-VAS score.

Therefore, fatigue may have multifactorial causes at disease onset. Identifying and treating factors contributing to fatigue is the first step in the management of this symptom (e.g., treating pain and sleep disturbance and modifying smoking habits). Because psychological health is a major determinant in fatigue change, targeted psychological care or cognitive–behavioral therapy to modify perceptions of fatigue and self-efficacy may improve the health status of people with EA (34).

The 2 different measures of fatigue we used did not provide exactly the same results. The fatigue_SF36 score was mainly associated with patient-reported outcomes, whereas the f-VAS score was influenced by individual characteristics, especially demographics, lifestyle factors, Sjögren's syndrome, and disease characteristics. These results are important for interpreting these scores and following them. These differences also confirm that an absence of fatigue does not necessarily mean the presence of energy (35–37).

Our study has several limitations. First, fatigue probably has several dimensions, including cognitive and physical dimensions. The 2 measures of fatigue we used did not take into account these different dimensions. Unfortunately, the RA-specific Multidimensional Assessment of Fatigue scale was not yet adapted in French and could not be used in this study (37–39). Second, the f-VAS was not

standardized in different studies (37). However, some differences in precision were observed in cross-sectional measurements of VAS, whereas in longitudinal analysis, precision appeared to be consistent, regardless of the characteristics of the scales (40). Third, we used no definite diagnostic criteria for Sjögren's syndrome, only the assertion of the rheumatologist. Finally, our results suggest that affect state and fatigue measures are closely related concepts and that when one improves, the other also improves. Nevertheless, we cannot conclude a causal relationship between HRQOL and fatigue. Causality can be interpreted in both directions: HRQOL had an impact on fatigue or fatigue had an impact on HRQOL. We chose to study factors associated with fatigue because in clinical practice, treating the psychological state or the perception of health state is probably easier than treating the fatigue itself.

Fatigue is an important phenomenon to measure in EA. It appears to be multifactorial at the beginning of the disease and cannot be considered the sole consequence of disease activity, whose role is marginal. The AIMS2-SF affect score explained most of the baseline variance in fatigue. The course of fatigue was strongly associated with modifications in HRQOL, notably the affect dimension, but also baseline HRQOL and level of fatigue. These results should help professionals caring for RA patients to communicate to patients about fatigue, explore its causes, and develop tailored interventions.

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### AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Rat 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.** Rat, Fautrel, Boumier, Guillemin.
**Acquisition of data.** Rat, Fautrel, Boumier, Goupille.
**Analysis and interpretation of data.** Rat, Pouchot, Boumier, Guillemin.

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Merck Sharp & Dohme, Abbott, Amgen, and Wyeth had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Merck Sharp & Dohme, Abbott, Amgen, and Wyeth.

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