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Abstract

Objectives: To analyze the factors associated with fatigue focusing on comorbidities in a large cohort of rheumatoid arthritis (RA).

Methods: Cross-sectional analyses were performed on RA patients from the French COMEDRA cohort study, a nurse-led program for comorbidities management. Fatigue was assessed using Question 3 of the Rheumatoid Arthritis Impact of Disease (RAID) score on a 0-10 numerical rating scale (NRS). Fatigue was defined as acceptable if ≤2, moderate if 3 or 4, or severe if ≥5 out of 10. Using univariate and multivariate models, the relationship between fatigue and demographics, social, disease characteristics, comorbidities (cardiovascular, infections, cancer, pulmonary, osteoporosis, and psychiatric disorders), physical activity, quality of life, and treatments was investigated.

Results: 962 patients were analyzed. The mean fatigue score was 3.8±2.7, 40% of patients reported severe fatigue. Patients had an average of 1.8 additional morbid conditions, with anxiety/depression the most common (52%). In univariate analysis, severe fatigue was more frequent in women, in patients not working, and in those with less physical activity. It was associated with disease duration and activity, mHAQ, pain, sleeping and emotional difficulties. Severe fatigue correlated with Multimorbidity index assessing the number of morbid conditions and was associated with obesity, hypertension, COPD, and anxiety/depression. In multivariate models, the risk of severe fatigue was associated with female gender, disease activity, mHAQ, current treatment with NSAIDs and biologics, multimorbidity, obesity and anxiety/depression.

Conclusions: Assessment of comorbidities, psychological health and physical activity should be taken into account in order to address frequent RA-related severe fatigue.

Key words: rheumatoid arthritis, fatigue, comorbidities

Fatigue, along with pain, is the most frequent symptom in patients with rheumatoid arthritis (RA), affecting more than 80% of them (1,2). In half of patients, fatigue is severe (1,3) and persists in almost 30-40% of cases despite conventional or biologic disease-modifying antirheumatic drugs (DMARDs) (2,4–6). Mechanisms are complex and multidimensional, including factors that are disease-associated (inflammation, pain, or disability), patient-related, environment-related and medication-related (3). The majority of studies conducted to date were cross-sectional and analyzed fatigue's predictive factors. Among the main factors, associations have been demonstrated with disease activity, pain, disability, sleep, and depression, but the causal link in longitudinal studies has not been clearly established (3). Several studies have analyzed the impact of comorbidities on quality of life and disability (7–11), but few have focused on fatigue (12). The COMorbidities, EDucation in Rheumatoid Arthritis (COMEDRA) trial is a large multicenter French cohort study providing additional data on disease-related factors, including fatigue, cognitive/emotional functioning, social aspects, comorbidities, and treatments (13). It offered the opportunity to explore factors associated with fatigue in a large RA cohort focusing on social aspects, comorbidities, and treatment intake.

Patients and Methods

Study population and data collection

COMEDRA is a multicenter randomized controlled trial evaluating the impact of a nurse-led program on the management of comorbidities in a French cohort of RA patients (13). The study comprised the recording of pre-existing comorbidities, presence of risk factors, and implementation of the recommendation for detection and management of such

comorbidities. Patients with RA as defined by the 1987 American College of Rheumatology criteria, between 18 and 80 years of age, and with disease considered by the treating rheumatologist to have been stable for at least 3 months, were recruited from March 2011 to December 2011. Each patient gave his/her free, informed consent to participate, and French authorities approved the study protocol (Ethics approval: Ile-de-France III Ethics Committee, file #4-11 (B110057-30).

COMEDRA investigators collected data on socioeconomic characteristics (age, gender, employment status, and education level) and health-related risk factors (smoking status, BMI, physical activity, and alcohol consumption). Physical activity and alcohol consumption were self-reported as categorical variables 'physical activity ≥ 30 minutes by day' (yes/no) and 'alcohol consumption > 2 glasses by day' (yes/no). Furthermore, RA-related characteristics were recorded, including disease duration, tender 28-joint count, swollen 28-joint count, patient and physician global assessment, ESR, CRP, presence of rheumatoid factor or anti-citrullinated protein antibodies (ACPA), erosive disease, functional impairment using the modified Health Assessment Questionnaire (mHAQ), disease impact using the Rheumatoid Arthritis Impact of Disease (RAID) score, as well as health outcome using the EQ-5D. The following data on comorbidities was recorded by the nurse: coronary heart disease, stroke, peripheral vessel disease, hypertension, diabetes, obesity, chronic kidney disease, inflammatory bowel disease, thyroid disorders, alcohol problems, depression, anxiety, fracture, bronchiectasis, chronic obstructive pulmonary disease (COPD), cancer, and history of RA-related surgeries. This was employed to calculate the Multimorbidity Index (MMI) assessing the number of morbid conditions for a patient (14). Two types of MMI were computed, namely one enumerating comorbidities (MMI.count) and the other weighting comorbidities (MMI.weight) based on their association with health-related quality of life (14). This index was validated on two different cohorts, and showed good performance as

compared to the Charlson comorbidity index (14). Information on treatments comprised current and past use of synthetic and biologic DMARDs, glucocorticoids, and NSAIDs. Intake of glucocorticoids was assessed using the mean prednisone dose in milligram per day during the last 3 months. Intake of NSAIDs was assessed during the last 3 months.

Assessment of fatigue

Fatigue was assessed using Question 3 of the RAID score on a 0-10 numerical rating scale (NRS) (15). Respondents answered the question 'select the number that best describes how much fatigue you felt due to your rheumatoid arthritis during the last 7 days' with responses ranging from 0 (No fatigue) to 10 (Totally exhausted). Fatigue was defined as acceptable if ≤ 2, moderate if 3 or 4, or severe if ≥ 5 out of 10 (16–18).

Statistical analysis

By means of univariate analysis and multivariate models, we investigated the relationship between fatigue and demographics, social features, disease characteristics, comorbidities (cardiovascular, infections, cancer, pulmonary, osteoporosis, and psychiatric disorders), physical activity, quality of life, and treatments. All analyses were performed using Stata software (Version 13, StataCorp, College Station, TX) for a two-sided Type I error of α=5%. Patient characteristics were expressed as mean± standard-deviation (SD) or median (interquartile range) for continuous data (assumption of normality assessed by using the Shapiro-Wilk test) and as numbers and associated percentages for categorical parameters. The fatigue was categorized according to the predefined clinical threshold (acceptable ≤2; moderate 3-4; severe ≥ 5 out of 10) and analyzed as a categorical variable in bivariate and multivariable analyses. Because dichotomizing implies loss of information and hence loss of statistical power (19), continuous variables were analyzed without categorizing them unless

predefined clinical thresholds have been reported in the literature. Quantitative variables were compared between independent groups by ANOVA, or Kruskal-Wallis test if ANOVA conditions were not met (normality and homoscedasticity analyzed using the Bartlett test). When appropriate, post-hoc tests were performed taking into account multiple comparisons (Tukey-Kramer post ANOVA and Dunn after Kruskal-Wallis). Comparisons between independent groups were carried out using the Chi-squared or Fischer's exact test for categorical variables. When appropriate, a post-hoc test was used (Marascuillo procedure).

In order to determine factors associated to fatigue considered as a 3 classes variable, a multivariable polynomial ordinal regression model was carried out using the stepwise approach (backward and forward) on covariates fixed according to univariate results ($p<0.05$) and clinical relevance. A particular attention has been paid to the study of multicollinearity and interactions between covariates by studying the relationships between the covariables and by evaluating the impact to add or delete variables on multivariable model. More precisely, due to this collinearity with mHAQ, pain and sleeping difficulty could not be conserved in the multivariable model including MMI count. Because mHAQ and anxiety were strongly correlated, mHAQ was not conserved in multivariable analysis including anxiety/depression but was conserved in the model with MMI count. Results were expressed as relative-risk ratios and 95% confidence intervals (95%CI) and forest plots were employed to present the results. A sensitivity analysis in patients with low disease activity (DAS28≤3.2) was performed for multivariable analyses (data not shown).

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Results

Baseline characteristics

The COMEDRA cohort included a total of 970 patients, with RAID data available for 962, which were analyzed. The mean patient age was 57.7±11.1 years, and 763 (79%) were female. The median disease duration was 11.1 years [6.2-19.1], mean DAS28 CRP 3.1±1.3 with 62 % of patients having low disease activity as defined by a DAS28 below 3.2., RAID 3±2, and mHAQ 0.40±0.45. Overall, 84% of patients were positive for RF or ACPA and 73% had erosive RA, while 673 (70%) received methotrexate, 249 (26%) NSAIDs, and 364 (38%) glucocorticoids. In total, 672 (70%) were treated with a biologic, 355 (37%) of which with TNF inhibitors, 143 (15%) with tocilizumab, 92 (9.6%) with rituximab, and 78 (8%) with abatacept.

The median MMI.count was 2 [1-3], and MMI.weight was 8 [1-10.5]. The mean MMI.count was 1.8±1.4. The most common comorbidities were anxiety/depression (52%), fracture (32%), hypertension (30%), and obesity (16%). The mean and median fatigue scores were respectively 3.8±2.7 and 4 [1; 6]. Among this stable RA population, 387 patients (40%) had severe fatigue as defined by a fatigue NRS ≥5/10 out of 10.

Relationship between fatigue, socio-demographic aspects, comorbidities, and treatment

Severe fatigue was more frequent in women, in patients not working, and in those with less physical activity (Table 1). It was associated with disease duration, disease activity, mHAQ, pain, and sleeping difficulties (Table 1). Among comorbidities, severe fatigue was associated with obesity, hypertension, COPD and anxiety/depression. In addition to data shown in table 1, no significant association was observed with cancer (n=49, p=0.15), diabetes (n=56, p=0.17) or inflammatory bowel disease (n=10, p=0.14). The Multimorbidity score (MMI count) was correlated with fatigue NRS (r=0.28, p<0.001) and patients with severe fatigue

had an increased number of comorbidities (Table 1). Current treatments with NSAIDs, glucocorticoids, or biologics were associated with severe fatigue. In contrast, methotrexate use and the biologic type used did not impact the severity of fatigue.

Factors associated with fatigue level in multivariate models

The risk of being severely fatigued was associated with female gender, disease activity and mHAQ, current treatment with NSAIDs and biologics and multimorbidity (Figure 1A). Obesity and anxiety/depression were the comorbidities independently associated with severe fatigue (Figure 2A). Low physical activity, anxiety/depression and MMI count were also associated with moderate fatigue and but not female gender, obesity nor biotherapy (Figures 1, 2). Results in the 2 multivariable models were similar in the subgroup of patients with low disease activity (DAS28≤3.2).

Discussion

Our results confirmed that a significant proportion of RA patients (40%) suffered from persistent severe fatigue, though the disease was considered stable and in low disease activity. Anxiety/depression, reported by more than half of patients, was strongly associated with severe fatigue. Low physical activity, others comorbidities, such as obesity, hypertension or COPD, and multimorbidity contributed to this chronic fatigue. This study confirms that RA patients are typically affected by more than one disease (12). In this large RA cohort, patients had an average of 1.8 additional morbid conditions, with 50% having at least two additional conditions. MMI developed and validated in RA based on health-related quality of life (14) correlated with the intensity of fatigue. Fatigue levels were associated with female gender, disease activity, mHAQ, pain, and sleeping difficulties, in accordance with previous studies (1,3,6,18).

Severe fatigue was more common in patients receiving glucocorticoids, NSAIDs, and biotherapies, with similar fatigue regardless of biologic type used. Contrasting with common patient-reported side-effects (20), methotrexate use was not correlated with fatigue intensity in our study. While several recent studies on biological agent use in RA reported that these drugs had a beneficial effect on fatigue (2,4,5,21), our findings indicated that current NSAIDs and biological treatments were associated with severe fatigue, which may be due to the severity of the disease even the association persisted after adjusting for disease activity. In randomized controlled trials, anti-TNF and non-anti-TNF biologic agents had similar small to moderate effects on fatigue improvement whether this was a direct or indirect effect (21,22). Anti-inflammatory drugs, such as NSAIDs, glucocorticoids, and cytokine inhibitors, may directly act on pro-inflammatory cytokines involved in fatigue's biological mechanisms, in particular IL1 and IL6 (23). This may impact fatigue's inflammatory mechanism, operating early in the cascade. However, other non-inflammatory pathways of fatigue may be involved at a later time point in the chronic disease process and may explain the persistent fatigue despite well-controlled disease. Disturbance of the hypothalamus-pituitary-adrenal axis, cortisol production, and complex interactions with the immune system may influence fatigue (23). Muscle fatigue and dysfunction during recovery induced by the production of reactive oxygen/nitrogen species due to mitochondrial dysfunction may also be involved in peripheral or physical fatigue (24). In addition, fatigue's dimensions may vary over time, and the pathogenesis of fatigue's physical and cognitive dimensions may differ, as demonstrated in cancer-related fatigue, where fatigue can persist up to 10 years after remission (23,25).

This study displays several limitations. Because of its cross-sectional study design, the causal relationship between fatigue and associated factors could not be established. Fatigue NRS are unidimensional measures that capture only one aspect of fatigue, typically either the

severity or intensity. This study can thus not analyze all dimensions of fatigue. High acceptability, completion rates, and good validity support fatigue NRS usability, although it does not allow for assessing fatigue's multidimensional aspect (17,26). There is no standardized VAS or NRS cutoff for distinguishing high and low levels of fatigue. The selected cutoff of NRS>2/10 for moderate fatigue and ≥5/10 for severe fatigue were supported by a mean VAS fatigue score in healthy controls of 20.5 ± 0.02 mm and corresponded to what is described in previous studies in RA (16–18).

Fatigue NRS measurement was obtained using the RAID score, which was developed in an effort to combine easily, in only one questionnaire, the seven most important domains of RA impact (pain, functional capacity, fatigue, physical and emotional wellbeing, quality of sleep, and coping) without missing relevant information. The RAID questionnaire considering fatigue a core domain is very simple (seven NRS). Content and construct validity, comprehensibility, reliability, and sensitivity to change were well-documented (15,27).

This study has strengths as well involving a large cohort of patients followed up in real-life, with stable and low disease activity, and treated with various conventional and biologic DMARDs. Above all, this study allowed us to collect psychosocial and environmental variables, as well as data on comorbidities.

In conclusion, severe fatigue is a common symptom, even in patients with stable and well-controlled disease. In addition to anti-inflammatory medications, the possibilities of improving RA-related chronic fatigue in these patients should take into account non-pharmacological interventions, such as management of comorbidities (13), physical activity (28,29), as well as educational programs including self-management strategies and cognitive behavioral therapy (30).

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Patient consent Obtained.

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Références

1. van Dartel S a. A, Repping-Wuts JWJ, van Hoogmoed D, Bleijenberg G, van Riel PLCM, Fransen J. Association between fatigue and pain in rheumatoid arthritis: does pain precede fatigue or does fatigue precede pain? Arthritis Care Res 2013;65:862-9.

2. Genty M, Combe B, Kostine M, Ardouin E, Morel J, Lukas C. Improvement of fatigue in patients with rheumatoid arthritis treated with biologics: relationship with sleep disorders, depression and clinical efficacy. A prospective, multicentre study. Clin Exp Rheumatol 2017;35:85-92.

3. Nikolaus S, Bode C, Taal E, van de Laar MAFJ. Fatigue and factors related to fatigue in rheumatoid arthritis: a systematic review. Arthritis Care Res 2013;65:1128-46.

4. Druce KL, Jones GT, Macfarlane GJ, Basu N. Patients receiving anti-TNF therapies experience clinically important improvements in RA-related fatigue: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Rheumatology 2015;54:964-71.

5. Gossec L, Steinberg G, Rouanet S, Combe B. Fatigue in rheumatoid arthritis: quantitative findings on the efficacy of tocilizumab and on factors associated with fatigue. The French multicentre prospective PEPS Study. Clin Exp Rheumatol 2015;33:664–670.

6. Olsen CL, Lie E, Kvien TK, Zangi HA. Predictors of Fatigue in Rheumatoid Arthritis Patients in Remission or in a Low Disease Activity State. Arthritis Care Res 2016;68:1043-8.

7. Radner H, Smolen JS, Aletaha D. Impact of comorbidity on physical function in patients with rheumatoid arthritis. Ann Rheum Dis 2010;69:536-41.

8. Crilly MA, Johnston MC, Black C. Relationship of EQ-5D quality of life with the presence of co-morbidity and extra-articular features in patients with rheumatoid arthritis. Qual Life Res Int J Qual Life Asp Treat Care Rehabil 2014;23:1435-43.

9. Geryk LL, Carpenter DM, Blalock SJ, DeVellis RF, Jordan JM. The impact of co-morbidity on health-related quality of life in rheumatoid arthritis and osteoarthritis patients. Clin Exp Rheumatol 2015;33:366-74.

10. Mondor L, Maxwell CJ, Bronskill SE, Gruneir A, Wodchis WP. The relative impact of chronic conditions and multimorbidity on health-related quality of life in Ontario long-stay home care clients. Qual Life Res Int J Qual Life Asp Treat Care Rehabil 2016;25:2619-32.

11. van den Hoek J, Roorda LD, Boshuizen HC, Tijhuis GJ, van den Bos GA, Dekker J. Physical and Mental Functioning in Patients with Established Rheumatoid Arthritis over an 11-year Followup Period: The Role of Specific Comorbidities. J Rheumatol 2016;43:307-14.

12. Grøn KL, Ornbjerg LM, Hetland ML, Aslam F, Khan NA, Jacobs JWG, et al. The association of fatigue, comorbidity burden, disease activity, disability and gross domestic product in patients with rheumatoid arthritis. Results from 34 countries participating in the Quest-RA program. Clin Exp Rheumatol 2014;32:869-77.

13. Dougados M, Soubrier M, Perrodeau E, Gossec L, Fayet F, Gilson M, et al. Impact of a nurse-led programme on comorbidity management and impact of a patient self-assessment of disease activity on the management of rheumatoid arthritis: results of a prospective, multicentre, randomised, controlled trial (COMEDRA). Ann Rheum Dis 2015;74:1725-33.

14. Radner H, Yoshida K, Mjaavatten MD, Aletaha D, Frits M, Lu B, et al. Development of a multimorbidity index: Impact on quality of life using a rheumatoid arthritis cohort. Semin Arthritis Rheum 2015;45:167-73.

15. Gossec L, Paternotte S, Aanerud GJ, Balanescu A, Boumpas DT, Carmona L, et al. Finalisation and validation of the rheumatoid arthritis impact of disease score, a patient-derived composite measure of impact of rheumatoid arthritis: a EULAR initiative. Ann Rheum Dis 2011;70:935-42.

16. Pollard LC, Choy EH, Gonzalez J, Khoshaba B, Scott DL. Fatigue in rheumatoid arthritis reflects pain, not disease activity. Rheumatology 2006;45:885-9.

17. Hewlett S, Dures E, Almeida C. Measures of fatigue: Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire (BRAF MDQ), Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scales (BRAF NRS) for Severity, Effect, and Coping, Chalder Fatigue Questionnaire (CFQ), Checklist. Arthritis Care Res 2011;63:S263-86.

18. Hifinger M, Putrik P, Ramiro S, Keszei AP, Hmamouchi I, Dougados M, et al. In rheumatoid arthritis, country of residence has an important influence on fatigue: results from the multinational COMORA study. Rheumatology 2016;55:735-44.

19. Altman DG, Royston P. The cost of dichotomising continuous variables. BMJ 2006;332:1080.

20. Curtis JR, Xie F, Mackey D, Gerber N, Bharat A, Beukelman T, et al. Patient's experience with subcutaneous and oral methotrexate for the treatment of rheumatoid arthritis. BMC Musculoskelet Disord 2016;17:405.

21. Chauffier K, Salliot C, Berenbaum F, Sellam J. Effect of biotherapies on fatigue in rheumatoid arthritis: a systematic review of the literature and meta-analysis. Rheumatol Oxf Engl 2012;51:60-8.

22. Almeida C, Choy EH, Hewlett S, Kirwan JR, Cramp F, Chalder T, et al. Biologic interventions for fatigue in rheumatoid arthritis. In: The Cochrane Collaboration, editor. Cochrane Database of Systematic Reviews [Internet] Chichester, UK: John Wiley & Sons, Ltd; 2016 [cited 2017 Jul 29]. Available from: http://doi.wiley.com/10.1002/14651858.CD008334.pub2

23. Norheim KB, Jonsson G, Omdal R. Biological mechanisms of chronic fatigue. Rheumatology 2011;50:1009-18.

24. Cheng AJ, Yamada T, Rassier D, Andersson DC, Westerblad H, Lanner JT. ROS/RNS and contractile function in skeletal muscle during fatigue and recovery. J Physiol 2016;n/a-n/a.

25. de Raaf PJ, Sleijfer S, Lamers CHJ, Jager A, Gratama JW, van der Rijt CCD. Inflammation and fatigue dimensions in advanced cancer patients and cancer survivors: An explorative study. Cancer 2012;118:6005-11.

26. Wolfe F. Fatigue assessments in rheumatoid arthritis: comparative performance of visual analog scales and longer fatigue questionnaires in 7760 patients. J Rheumatol 2004;31:1896–1902.

27. Ter Wee MM, van Tuyl LH, Blomjous BS, Lems WF, Boers M, Terwee CB. Content validity of the Dutch Rheumatoid Arthritis Impact of Disease (RAID) score: results of focus group discussions in established rheumatoid arthritis patients and comparison with the International Classification of Functioning, Disability and Health core set for rheumatoid arthritis. Arthritis Res Ther 2016;18:22.

28. Rongen-van Dartel S a. A, Repping-Wuts H, Flendrie M, Bleijenberg G, Metsios GS, van den Hout WB, et al. Effect of Aerobic Exercise Training on Fatigue in Rheumatoid Arthritis: A Meta-Analysis. Arthritis Care Res 2015;67:1054-62.

29. Durcan L, Wilson F, Cunnane G. The Effect of Exercise on Sleep and Fatigue in Rheumatoid Arthritis: A Randomized Controlled Study. J Rheumatol 2014;41:1966-73.

30. Hewlett S, Ambler N, Almeida C, Cliss A, Hammond A, Kitchen K, et al. Self-management of fatigue in rheumatoid arthritis: a randomised controlled trial of group cognitive-behavioural therapy. Ann Rheum Dis 2011;70:1060-7.

Table1. Relationships between fatigue and socio-demographic aspects, comorbidities, and treatments.

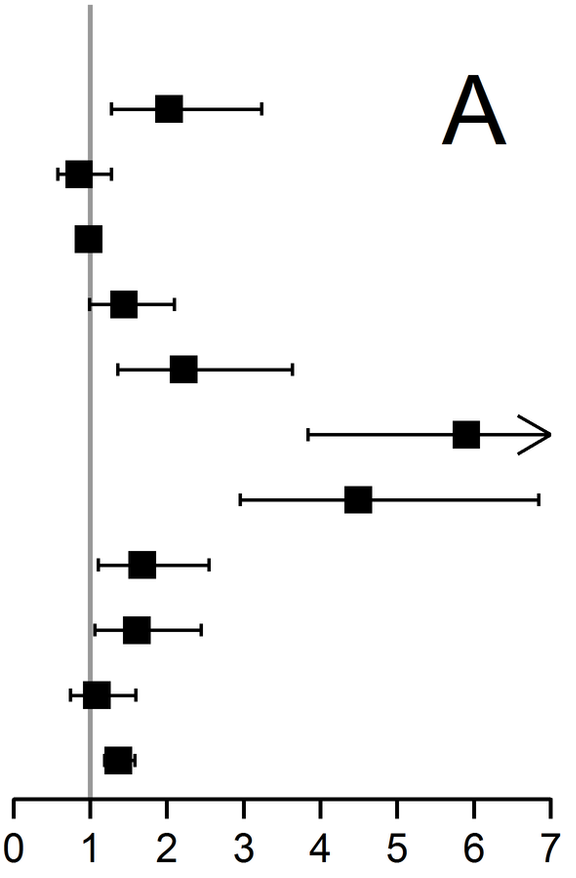
	Fatigue by class (n, %) Acceptable 0-1-2	Moderate 3-4	Severe ≥5	*p-value*	**Risk Ratio [95% CI]** Moderate fatigue Severe fatigue
Gender					
- Female(n=763)	254 (33.3)	178 (23.3)	331 (43.4)	*< 0.001*	1.16 [0.78;1.70]
- vs. Male (n=199)	89 (44.7)	54 (27.2)	56 (28.1)		2.07 [1.43;3.01] ***
Educational level					
- High school (n=680)	236 (34.7)	157 (23.1)	287 (42.2)	*0.14*	0.95 [0.66;1.36]
- vs University (n=282)	107 (37.9)	75 (26.6)	100 (35.5)		1.33 [0.94;1.80]
Professional status					
- Not working (n=628)	211 (33.6)	148 (23.6)	269 (42.8)	*0.07*	1.10 [0.78;1.56]
- vs Working (n=334)	132 (39.5)	84 (25.2)	118 (35.3)		1.43 [1.05;1.94] *
Physical activity					
- <30 min/day (n=353)	100 (28.3)	97 (27.5)	156 (44.2)	*0.001*	1.80 [1.26;2.55] ***
- vs ≥30 min/day (n=581)	237 (40.8)	128 (22.0)	216 (37.2)		1.71 [1.25;2.34]***
Disease duration (years); med [IQR]	10.3 [5.9 – 17.7]	10.9 [5.7 – 18.5]	12.1 [6.6 – 20.4]	*0.05*	1.01 [0.98;1.03] 1.02 [1.01;1.03] *
Disease activity (DAS28CRP)					
> 3.2 (n=361)	55 (15.2)	88 (24.4)	218 (60.4)	*< 0.001*	3.89 [2.58;5.87] *** 9.35 [6.41;13.64] ***
2.6-3.2 (n=164)	50 (30.5)	46 (28)	68 (41.5)		2.20 [1.39;3.48] *** 3.13 [2.04;4.81] ***
< 2.6 (n=437)	238 (54.5)	98 (22.4)	101 (23.1)		1
mHAQ					
- ≥ *0.5* (n=356)	54 (15.2)	78 (21.9)	224 (62.9)	*< 0.001*	6.58 [3.69;11.73] ***
- vs < 0.5 (n=593)	285 (48.0)	151 (25.5)	157 (26.5)		28.88 [16.67;50.01] ***
Pain (Question 1 RAID NRS); med [IQR]	1 [0 – 2]	3 [2 – 4]	4 [3 – 6]	*< 0.001*	1.64 [1.47;1.84] *** 2.44 [2.16;2.74] ***
Sleeping difficulties (Question 4 RAID NRS) med [IQR]	0 [0 – 1]	2 [1 – 3]	5 [2 – 7]	*< 0.001*	1.58 [1.42;1.75] *** 2.20 [1.97;2.44] ***
BMI					
- < 25 (n=531)	207 (39.0)	128 (24.1)	196 (36.9)	*0.001*	1
- 25-30 (n=276)	98 (35.5)	73 (26.5)	105 (38.0)		1.20 [0.83;1.75] 1.13 [0.81;1.59]
- ≥ 30 (n=155)	38 (24.5)	31 (20.0)	86 (55.5)		1.32 [0.78;2.23] 2.39 [1.56;3.67] ***
Hypertension					
- Yes (n=281)	83 (29.5)	63 (22.4)	135 (48.1)	*0.002*	1.19 [0.82;1.75]
- vs No (n=654)	255 (39.0)	162 (24.8)	237 (36.2)		1.75 [1.26;2.42] ***
COPD					
- Yes (n=63)	15 (23.8)	15 (23.8)	33 (52.4)	*0.06*	1.53 [0.73;3.20]
- vs No (n=870)	322 (37.0)	210 (24.1)	338 (38.9)		2.10 [1.12;3.93] *
Fracture history					
- Yes (n=296)	92 (31.1)	78 (26.3)	126 (42.6)	*0.08*	1.42 [0.99;2.04]
- vs No (n=638)	246 (38.6)	147 (23.0)	245 (38.4)		1.38 [0.99;1.90]
RA-related surgery					
- Yes (n=287)	95 (33.1)	65 (22.6)	127 (44.3)	*0.24*	0.99 [0.68;1.45]
- vs No (n=674)	248 (36.8)	167 (24.8)	259 (38.4)		1.27 [0.92;1.75]
Anxious or depressed (EQ5D-3L)					
- Moderately/extremely n=500	99 (19.8)	133 (26.7)	267 (53.5)	*< 0.001*	3.41 [2.4;4.85] ***
- vs Not n=455	241(53.2)	95 (21)	117(25.8)		5.56 [4;7.65] ***
MMI count score (mean ± SD)	1.4 ± 1.3	1.8 ± 1.4	2.25 ± 1.4	*< 0.001*	1.27 [1.11; 1.17]*** 1.60 [1.42; 1.82]***
Current NSAIDs					
- Yes (n=249)	64 (25.7)	65 (26.1)	120 (48.2)	*0.001*	1.70 [1.14;2.52] **
- vs No (n=713)	279 (39.1)	167 (23.4)	267 (37.5)		1.96 [1.39;2.77] ***
Current glucocorticoids					
- Yes (n=364)	105 (28.8)	92 (25.3)	167 (45.9)	*0.002*	1.49 [1.05;2.11] **
- vs No (n=598)	238 (39.8)	140 (23.4)	220 (36.8)		1.72 [1.27;2.33] ***
Current DMARD					
- biotherapy *(n=672)*	232 (34.5)	155 (23.1)	285 (42.4)	*0.03*	0.96 [0.67;1.38]
- vs conventional (n=270)	106 (39.3)	74 (27.4)	90 (33.3)		1.45 [1.04;2.01] **
Current Methotrexate					
- Yes (n=673)	251 (37.3)	158 (23.5)	264 (39.2)	*0.27*	1.28 [0.89; 1.84]
- No (n=289)	92 (31.8)	74 (25.6)	123 (42.6)		1.27 [0.92; 1.75]
Type of biotherapy					
- TNF inhibitors (n=355)	126 (35.5)	88 (24.8)	141 (39.7)	*NS*	1
- Tocilizumab (n=143)	49 (34.3)	30 (21.0)	64 (44.8)		0.88 [0.52; 1.49] 1.17 [0.75; 1.82]
- Rituximab (n=92)	28 (30.4)	24 (26.1)	40 (43.5)		1.23 [0.67; 2.26] 1.28 [0.74; 2.19]
- Abatacept (n=78)	29 (37.2)	13 (16.7)	36 (46.1)		0.65 [0.32; 1.30] 1.11 [0.64; 1.91]

*** p <0.001; ** p <0.01; * p <0.05.

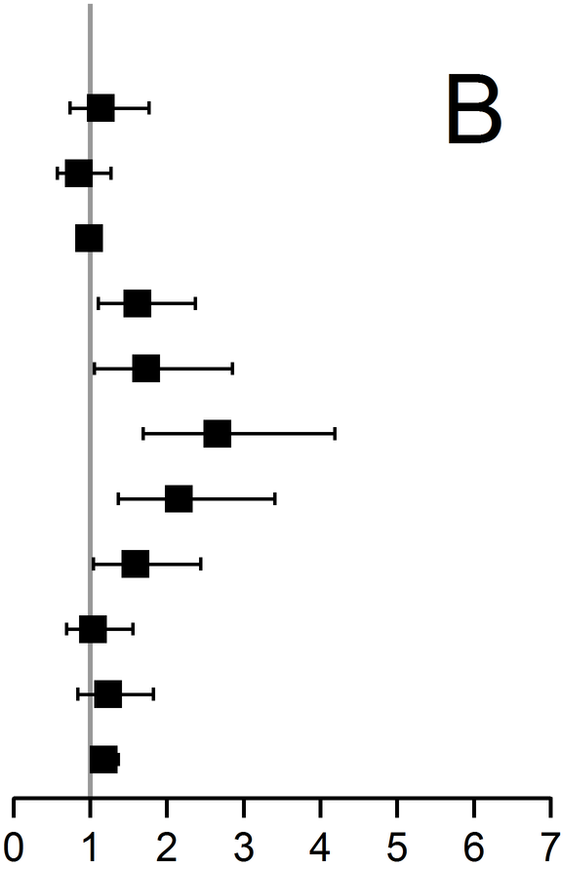
Figure 1. Forest plot showing the overall Risk ratio in multiple regression model including multimorbidity score (MMI.count) for severe fatigue (A) and moderate fatigue (B).

Figure 2. Forest plot showing the overall Risk ratio in multiple regression model including each comorbidity for severe fatigue (A) or moderate fatigue (B).

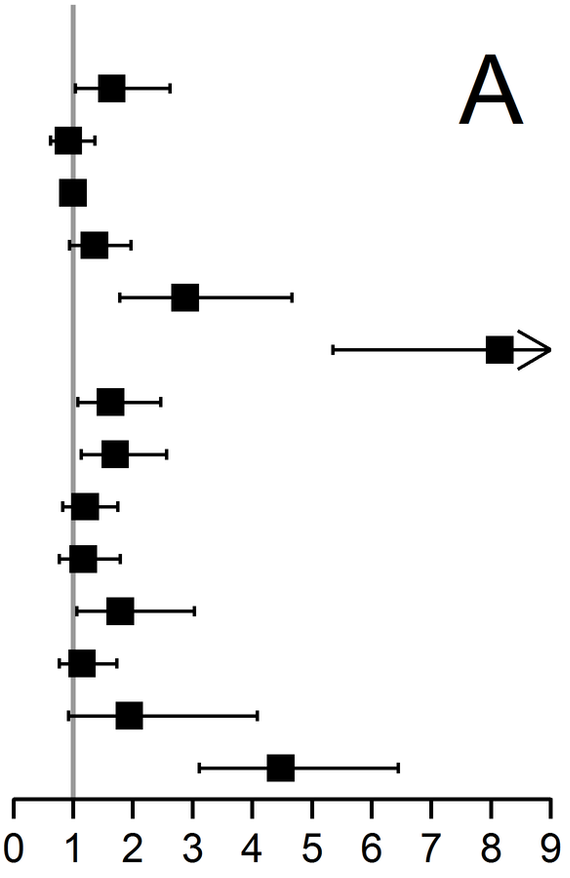
	RR	95% CI	p-value
Female gender	2.027	[1.273 ; 3.228]	0.003
Not working	0.854	[0.573 ; 1.272]	0.438
RA duration	0.978	[0.958 ; 0.998]	0.029
Low physical activity	1.439	[0.989 ; 2.094]	0.057
DAS 2.6-3.2	2.218	[1.354 ; 3.633]	0.002
DAS >3.2	5.900	[3.837 ; 9.072]	<0.001
mHAQ	4.492	[2.950 ; 6.840]	<0.001
Current NSAIDs	1.676	[1.103 ; 2.547]	0.016
Biotherapy	1.607	[1.058 ; 2.442]	0.026
Current steroïds	1.088	[0.743 ; 1.594]	0.665
MMI score (count)	1.366	[1.184 ; 1.577]	<0.001



	RR	95% CI	p-value
Female gender	1.135	[0.732 ; 1.761]	0.571
Not working	0.850	[0.570 ; 1.270]	0.428
RA duration	0.983	[0.962 ; 1.004]	0.114
Low physical activity	1.613	[1.100 ; 2.365]	0.014
DAS 2.6-3.2	1.729	[1.049 ; 2.850]	0.032
DAS >3.2	2.655	[1.685 ; 4.183]	<0.001
mHAQ	2.155	[1.366 ; 3.402]	0.001
Current NSAIDs	1.589	[1.036 ; 2.436]	0.034
Biotherapy	1.034	[0.688 ; 1.554]	0.873
Current steroïds	1.232	[0.834 ; 1.818]	0.295
MMI score (count)	1.175	[1.012 ; 1.364]	0.035



	RR	95% CI	p-value
Female gender	1.646	[1.035 ; 2.618]	0.035
Not working	0.919	[0.620 ; 1.361]	0.673
RA duration	0.994	[0.975 ; 1.013]	0.526
Low physical activity	1.354	[0.933 ; 1.965]	0.110
DAS 2.6-3.2	2.874	[1.772 ; 4.662]	<0.001
DAS >3.2	8.147	[5.343 ; 12.421]	<0.001
Current NSAIDs	1.623	[1.070 ; 2.461]	0.023
Biotherapy	1.703	[1.132 ; 2.563]	0.011
Current steroïds	1.198	[0.824 ; 1.741]	0.344
BMI 25-30	1.169	[0.766 ; 1.786]	0.469
BMI >30	1.786	[1.055 ; 3.023]	0.031
Hypertension	1.148	[0.763 ; 1.727]	0.509
COPD	1.939	[0.921 ; 4.084]	0.081
Anxiety/depression	4.476	[3.111 ; 6.439]	<0.001



	RR	95% CI	p-value
Female gender	0.910	[0.580 ; 1.427]	0.680
Not working	0.890	[0.595 ; 1.334]	0.573
RA duration	0.990	[0.970 ; 1.011]	0.348
Low physical activity	1.627	[1.108 ; 2.391]	0.013
DAS 2.6-3.2	1.946	[1.181 ; 3.208]	0.009
DAS >3.2	3.247	[2.079 ; 5.070]	<0.001
Current NSAIDs	1.445	[0.937 ; 2.229]	0.096
Biotherapy	1.072	[0.713 ; 1.613]	0.738
Current steroïds	1.337	[0.907 ; 1.971]	0.142
BMI 25-30	1.141	[0.742 ; 1.756]	0.547
BMI >30	0.831	[0.455 ; 1.519]	0.547
Hypertension	0.983	[0.635 ; 1.520]	0.937
COPD	1.576	[0.718 ; 3.460]	0.256
Anxiety/depression	3.169	[2.172 ; 4.624]	<0.001

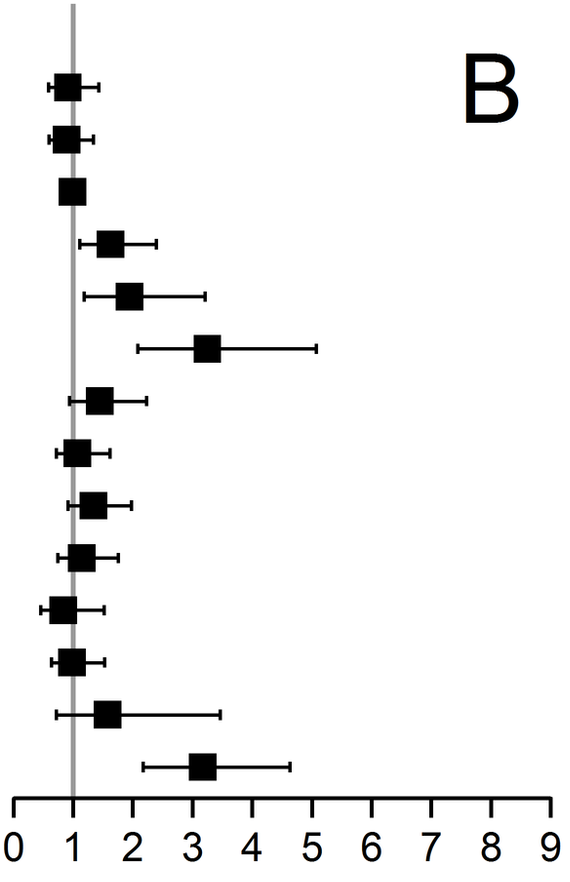


Table1. Relationships between fatigue and socio-demographic aspects, comorbidities, and treatments.

	Fatigue by class (n, %) Acceptable 0-1-2	 Moderate 3-4	 Severe ≥5	*p-value*	**Risk Ratio [95% CI]** Moderate fatigue Severe fatigue
Gender - Female(n=763) - vs. Male (n=199)	 254 (33.3) 89 (44.7)	 178 (23.3) 54 (27.2)	 331 (43.4) 56 (28.1)	*< 0.001*	1.16 [0.78;1.70] 2.07 [1.43;3.01] ***
Educational level - High school (n=680) - vs University (n=282)	 236 (34.7) 107 (37.9)	 157 (23.1) 75 (26.6)	 287 (42.2) 100 (35.5)	*0.14*	0.95 [0.66;1.36] 1.33 [0.94;1.80]
Professional status - Not working (n=628) - vs Working (n=334)	 211 (33.6) 132 (39.5)	 148 (23.6) 84 (25.2)	 269 (42.8) 118 (35.3)	*0.07*	1.10 [0.78;1.56] 1.43 [1.05;1.94] *
Physical activity - <30 min/day (n=353) - vs ≥30 min/day (n=581)	 100 (28.3) 237 (40.8)	 97 (27.5) 128 (22.0)	 156 (44.2) 216 (37.2)	*0.001*	1.80 [1.26;2.55] *** 1.71 [1.25;2.34]***
Disease duration (years); med [IQR]	10.3 [5.9 – 17.7]	10.9 [5.7 – 18.5]	12.1 [6.6 – 20.4]	*0.05*	1.01 [0.98;1.03] 1.02 [1.01;1.03] *
Disease activity (DAS28CRP) > 3.2 (n=361) 2.6-3.2 (n=164) < 2.6 (n=437)	 55 (15.2) 50 (30.5) 238 (54.5)	 88 (24.4) 46 (28) 98 (22.4)	 218 (60.4) 68 (41.5) 101 (23.1)	*< 0.001*	3.89 [2.58;5.87] *** 9.35 [6.41;13.64] *** 2.20 [1.39;3.48] *** 3.13 [2.04;4.81] *** 1
mHAQ - ≥ *0.5* (n=356) - vs < 0.5 (n=593)	 54 (15.2) 285 (48.0)	 78 (21.9) 151 (25.5)	 224 (62.9) 157 (26.5)	*< 0.001*	6.58 [3.69;11.73] *** 28.88 [16.67;50.01] ***
Pain (Question 1 RAID NRS); med [IQR]	1 [0 – 2]	3 [2 – 4]	4 [3 – 6]	*< 0.001*	1.64 [1.47;1.84] *** 2.44 [2.16;2.74] ***
Sleeping difficulties (Question 4 RAID NRS) med [IQR]	0 [0 – 1]	2 [1 – 3]	5 [2 – 7]	*< 0.001*	1.58 [1.42;1.75] *** 2.20 [1.97;2.44] ***
BMI - < 25 (n=531) - 25-30 (n=276) - ≥ 30 (n=155)	 207 (39.0) 98 (35.5) 38 (24.5)	 128 (24.1) 73 (26.5) 31 (20.0)	 196 (36.9) 105 (38.0) 86 (55.5)	*0.001*	1 1.20 [0.83;1.75] 1.13 [0.81;1.59] 1.32 [0.78;2.23] 2.39 [1.56;3.67] ***
Hypertension - Yes (n=281) - vs No (n=654)	 83 (29.5) 255 (39.0)	 63 (22.4) 162 (24.8)	 135 (48.1) 237 (36.2)	*0.002*	1.19 [0.82;1.75] 1.75 [1.26;2.42] ***
COPD - Yes (n=63) - vs No (n=870)	 15 (23.8) 322 (37.0)	 15 (23.8) 210 (24.1)	 33 (52.4) 338 (38.9)	*0.06*	1.53 [0.73;3.20] 2.10 [1.12;3.93] *
Fracture history - Yes (n=296) - vs No (n=638)	 92 (31.1) 246 (38.6)	 78 (26.3) 147 (23.0)	 126 (42.6) 245 (38.4)	*0.08*	1.42 [0.99;2.04] 1.38 [0.99;1.90]
RA-related surgery - Yes (n=287) - vs No (n=674)	 95 (33.1) 248 (36.8)	 65 (22.6) 167 (24.8)	 127 (44.3) 259 (38.4)	*0.24*	0.99 [0.68;1.45] 1.27 [0.92;1.75]
Anxious or depressed (EQ5D-3L) - Moderately/extremely n=500 - vs Not n=455	 99 (19.8) 241(53.2)	 133 (26.7) 95 (21)	 267 (53.5) 117(25.8)	*< 0.001*	3.41 [2.4;4.85] *** 5.56 [4;7.65] ***
MMI count score (mean ± SD)	1.4 ± 1.3	1.8 ± 1.4	2.25 ± 1.4	*< 0.001*	1.27 [1.11; 1.17]*** 1.60 [1.42; 1.82]***
Current NSAIDs - Yes (n=249) - vs No (n=713)	 64 (25.7) 279 (39.1)	 65 (26.1) 167 (23.4)	 120 (48.2) 267 (37.5)	*0.001*	1.70 [1.14;2.52] ** 1.96 [1.39;2.77] ***
Current glucocorticoids - Yes (n=364) - vs No (n=598)	 105 (28.8) 238 (39.8)	 92 (25.3) 140 (23.4)	 167 (45.9) 220 (36.8)	*0.002*	1.49 [1.05;2.11] ** 1.72 [1.27;2.33] ***
Current DMARD - biotherapy *(n=672)* - vs conventional (n=270)	 232 (34.5) 106 (39.3)	 155 (23.1) 74 (27.4)	 285 (42.4) 90 (33.3)	*0.03*	0.96 [0.67;1.38] 1.45 [1.04;2.01] **
Current Methotrexate - Yes (n=673) - No (n=289)	 251 (37.3) 92 (31.8)	 158 (23.5) 74 (25.6)	 264 (39.2) 123 (42.6)	*0.27*	1.28 [0.89; 1.84] 1.27 [0.92; 1.75]
Type of biotherapy - TNF inhibitors (n=355) - Tocilizumab (n=143) - Rituximab (n=92) - Abatacept (n=78)	 126 (35.5) 49 (34.3) 28 (30.4) 29 (37.2)	 88 (24.8) 30 (21.0) 24 (26.1) 13 (16.7)	 141 (39.7) 64 (44.8) 40 (43.5) 36 (46.1)	*NS*	1 0.88 [0.52; 1.49] 1.17 [0.75; 1.82] 1.23 [0.67; 2.26] 1.28 [0.74; 2.19] 0.65 [0.32; 1.30] 1.11 [0.64; 1.91]

*** p <0.001; ** p <0.01; * p <0.05.