Impact of fatigue on health-related quality of life and illness perception in a monocentric cohort of patients with systemic lupus erythematosus

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ABSTRACT

Background Fatigue is a very common and debilitating symptom in patients with systemic lupus erythematosus (SLE), even among those with a mild or inactive disease. The objective of this study is to define fatigue determinants and describe the impact of fatigue on health-related quality of life (HRQoL) and illness perception in a monocentric cohort of patients with SLE.

Methods This is a cross-sectional study. Adult patients with SLE were included. For each patient, demographics, medications, comorbidities, organ damage (Systemic Lupus International Collaborating Clinics Damage Index), active disease manifestations and Systemic Lupus Disease Activity Index scores were collected. It was evaluated if each patient met the definitions of remission and low disease activity. At enrolment, each patient completed the Short Form-36 (SF-36), Functional Assessment Chronic Illness Therapy-Fatigue (FACIT-F), Lupus Impact Tracker (LIT), Systemic Lupus Activity Questionnaire (SLAQ) and Brief Index of Lupus Damage (BILD). The FACIT-F questionnaire was also administered to a group of healthy controls.

Results 223 patients were included (mean age 44.9±13.2 years, median disease duration 13 years). 18.2% had an active disease, 43.5% met the definition of remission and low disease activity. At enrolment, each patient completed the Short Form-36 (SF-36), Functional Assessment Chronic Illness Therapy-Fatigue (FACIT-F), Lupus Impact Tracker (LIT), Systemic Lupus Activity Questionnaire (SLAQ) and Brief Index of Lupus Damage (BILD). The FACIT-F questionnaire was also administered to a group of healthy controls.

Conclusions Fatigue in patients with SLE has a strong negative impact on HRQoL and patient perception of the disease burden. Fatigue seems irrespective of disease activity but significantly influenced by the presence of fibromyalgia.

INTRODUCTION

Despite great improvements in the prognosis of patients with systemic lupus erythematosus (SLE) in recent decades, health-related quality of life (HRQoL) remains compromised in such patients, both compared with healthy controls and with patients affected by other chronic diseases. EULAR recommendations for monitoring patients with SLE and ‘treat-to-target’ recommendations in SLE include HRQoL as an important variable which should be regularly monitored in routine clinical practice.

Many factors can influence HRQoL in patients with SLE, for example, musculoskeletal manifestations, organ damage, as well as demographic and socioeconomic factors, comorbidities, fibromyalgia, fatigue,
and mood disorders. Of these, fatigue undoubtedly deserves further consideration not least because it is an extremely common symptom of SLE, reported by over 50% of patients at some time during their disease history. In addition, patients may consider fatigue to be a symptom that is more severe than pain, depression or anxiety. Crucially, literature reports that fatigue is one of the major determinants of work loss and impairment of work productivity in patients with SLE. In a recent UK-specific online survey addressed to patients with SLE, fatigue, invisibility and the fluctuating nature of the disease emerged as the main barriers to maintaining employment for patients.

Psychosocial and behavioural factors, as well as mood and sleep disorders, may all play a major role in the aetiology of fatigue. The complexity of this symptom may explain why fatigue remains both an unmet need for patients with SLE and a challenge for their physicians. There are some new drugs which seem to be effective for fatigue: the available studies concerning the impact of belimumab on quality of life showed a significant effect of belimumab on fatigue: the available studies concerning the impact of belimumab on quality of life showed a significant effect.

The following data were collected for each patient at enrolment: epidemiological and demographic characteristics, disease duration, cumulative organ involvement, comorbidities, and concomitant medications. In addition, active disease manifestations and laboratory tests were evaluated at enrolment; disease activity was assessed using the Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Disease Activity Index (SELENA-SLEDAI) and the Physician Global Assessment (PGA); and organ damage was evaluated by the Systemic Lupus International Collaborating Clinics Damage Index (SLICC-DI). For patients with fibromyalgia, the diagnosis was pre-existing at enrolment in this study and was based on the ACR 1990 classification criteria.

At enrolment, the percentage of patients fulfilling the definitions of remission and low disease activity was also evaluated. The Definition Of Remission In SLE (DORIS) definition was adopted for remission: a durable state characterised by clinical SLEDAI=0 and PGA ≤0.5 (0–3). A distinction was made between 'on treatment' remission (which allowed stable maintenance antimalarials; low-dose corticosteroids (prednisone ≤5 mg/day); maintenance immunosuppressives and/or maintenance biologics) and 'off treatment' remission (which allowed only antimalarials). The Asian Pacific Lupus Consortium definition of 'low disease activity state' was used to define low disease activity.

At enrolment, each patient completed the following PROs to assess HRQoL, fatigue, impact of SLE on daily living, disease activity and organ damage:

- The Short Form-36 (SF-36) assesses HRQoL. This questionnaire addresses eight domains exploring different aspects of HRQoL (physical function, role physical, role emotional, bodily pain, general health, vitality, social functioning and mental health); domain scores can be summarised into two global scores: the physical component summary and the mental component summary. Each score ranges from 0 to 100, with higher values representing better self-perceived HRQoL.
- The Functional Assessment Chronic Illness Therapy-Fatigue (FACIT-Fatigue) (V4) was used to assess fatigue. FACIT-Fatigue assesses fatigue in the physical, emotional, functional, social and daily living domains, and has been validated for use in SLE and proved to be the most effective questionnaire in identifying symptom variations in patients with SLE. The score ranges from 0 to 52, with lower scores indicating worse fatigue.
- The Lupus Impact Tracker (LIT) is an SLE-specific questionnaire and was derived from LupusPRO in 2014 as a short-form instrument. LIT includes 10...
questions about cognition, lupus medications, physical health, pain/fatigue impact, emotional health, body image and planning.desires/goals. The final score of the LIT questionnaire ranges from 0 to 100, with lower scores indicating a lower impact of SLE on patients' life.

- The Systemic Lupus Activity Questionnaire (SLAQ) was used by patients to self-evaluate disease activity.
- The Brief Index of Lupus Damage (BILD) was used for patient self-evaluation of disease damage. BILD is derived from SLICC-DI and includes 26 items.
The FACIT-Fatigue questionnaire was also administered to a group of 65 healthy controls, matched in age and sex.

### Statistical analysis

Continuous data were reported as median and IQR or as mean and SD as appropriate. Categorical data were reported as percentage. The Student’s t-test, Mann-Whitney and \( \chi^2 \) tests were conducted for univariate analysis. The Spearman test was used for linear correlation between continuous data. Multivariate analysis was also performed by multiple linear and logistic regression for variables which were significantly associated within the univariate analysis. Analysis of variance with Bonferroni method was used for multiple comparison analysis. All \( p \) values less than 0.05 were considered statistically significant. Statistical analysis was performed using STATA V.13 software.

### RESULTS

The analysis included 223 consecutive patients with a diagnosis of SLE (1997 ACR classification criteria); patients were predominantly female (91.9%) and of Caucasian ethnicity (97.2%). Their mean age was 44.9±13.2 years, and the median disease duration was 13 years (IQR 5–20). Cumulative organ involvement of enrolled patients is reported in table 1.

The median SLEDAI score at baseline was 2 (IQR 0–4). Patients with SLEDAI score >4 were considered to have an active disease and represented 18.2% of the cohort; of these patients the median SLEDAI score was 8 (IQR 6–10), indicating a moderate disease activity. Of the patients, 49.3% had SLICC-DI score >0, with a median SLICC-DI score of 2 (IQR 1–3). Of the patients enrolled, 11.8% had a diagnosis of comitant fibromyalgia, according to the ACR 1990 classification criteria. The baseline characteristics of the cohort are summarised in table 2.

At enrolment, the most frequent active disease manifestations were articular (16.1%) and/or haematological (14.8%), followed by cutaneous manifestations (12.1%), while only a minority of patients manifested an active renal disease (6.7%) (table 1).

Most patients at enrolment were being treated with hydroxychloroquine (HCQ) (77.6%) and low-dose steroids (54.3%), with a median daily dose of 5 mg (IQR 5–5) of prednisone equivalent. Of the cohort, 45.3% were on immunosuppressive therapy with conventional disease-modifying antirheumatic drugs, while only a small percentage of patients (7.2%) were treated with biologic disease-modifying antirheumatic drugs, mainly belimumab, in combination with HCQ and/or an immunosuppressive drug (table 2).

At baseline, patients were divided into four groups, according to the following definitions: LLDAS; complete or clinical remission ‘on treatment’ (ROFT); complete or clinical remission ‘off treatment’ (ROFT); and active disease (for patients who did not meet any of the previous definitions). Of the patients in our cohort, 175/223 (78.5%) were at least in LLDAS. In particular, the majority of our patients also met the RONT definition (97/223; 43.5%); 45/223 (20.2%) were in ROFT condition, while 33/223 (14.8%) met only the definition of LLDAS. Finally, the remaining 48 patients (21.5%) manifested an active disease.

The median score of the FACIT-Fatigue questionnaire in our cohort was 40 (IQR 32–46, minimum 7, maximum 52), which was significantly lower compared with the FACIT-Fatigue score of 47 (IQR 44–50) of a group of matched healthy controls (p<0001).

Interestingly, similar FACIT-Fatigue scores were irrespective of age at enrolment and disease duration; no

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**Table 1** Cumulative and active organ involvement of the entire cohort

| Organ involvement | Cumulative, n (%) | Active, n (%) |
|-------------------|------------------|--------------|
| Joint             | 150 (67.6)       | 36 (16.1)    |
| Skin              | 120 (54.1)       | 27 (12.1)    |
| Haematological    | 114 (51.4)       | 33 (14.8)    |
| Renal             | 100 (45.1)       | 15 (6.7)     |
| Serositis         | 41 (18.5)        | 1 (0.4)      |
| Neuropsychiatric  | 28 (12.7)        | 0            |

**Table 2** Disease activity, damage, comorbidities and treatment at the time of enrolment

| Characteristic | n (%)       |
|---------------|-------------|
| Median SLEDAI | 2 (IQR 0–4) |
| Patients with active disease (SLEDAI >4) | 18.2% |
| Median SLEDAI of active patients | 8 (IQR 6–10) |
| Patients with SLICC-DI >0 | 49.3% |
| Median SLICC-DI (among patients with SLICC-DI >0) | 2 (IQR 1–3) |
| Patients with fibromyalgia | 11.8% |
| Patients on glucocorticoid | 54.3% |
| Median daily prednisone dose (IQR) | 5 mg (5–5) |
| Patients on hydroxychloroquine | 77.6% |
| Patients on cDMARDs | 45.3% |
| Patients on biologics | 7.2% |

cDMARDs, conventional disease-modifying antirheumatic drugs; SLEDAI, Systemic Lupus Disease Activity Index; SLICC-DI, Systemic Lupus International Collaborating Clinics-Damage Index.
correlation was observed between ongoing treatment and FACIT-Fatigue scores. On the contrary, FACIT-Fatigue scores were significantly lower (indicating greater fatigue) in patients with fibromyalgia (p<0.01).

As may be expected, FACIT-Fatigue demonstrated a strong correlation with all other PROs. In particular, FACIT-Fatigue scores showed a significant positive correlation with all the domains of SF-36 (p<0.001; r=0.53–0.77), suggesting that a lower level of fatigue was associated with a better HRQoL; the strongest correlation was between FACIT-Fatigue and the vitality domain (r=0.77), which both report patient tiredness. Moreover, a strong negative correlation was apparent between FACIT-Fatigue and LIT scores (r=−0.78; p<0.001), suggesting that fatigue is an important determinant in the perception of SLE impact on patients daily living, irrespective of disease activity and fibromyalgia.

FACIT-Fatigue scores also showed a strong negative correlation with the self-evaluation of disease activity questionnaire (SLAQ) (r=−0.72; p<0.001), as patients with more severe fatigue perceived their disease as being more active. FACIT-Fatigue also presented a significant negative correlation with the BILD questionnaire, which reports patient self-evaluation of disease damage (p<0.01; r=−0.28).

On the other hand, in comparison with the physician’s assessment, FACIT-Fatigue scores did not vary significantly among the four groups of disease activity (LLDAS, RONT, ROFT and active disease) (table 3), and no correlations were observed between FACIT-Fatigue and specific active organ involvement.

Similarly, there was no identifiable correlation between FACIT-Fatigue and the physician’s assessment of organ damage, as reported by the SLICC-DI.

### DISCUSSION

In this cross-sectional study we analysed the role of fatigue on patient HRQoL, as well as the relationship between the physician’s clinical evaluation of the disease and the patient’s perception of health status.

We enrolled consecutive patients with SLE regularly followed at the Rheumatology Unit of the University of Pisa. Our cohort consisted principally of outpatients with mild-moderate disease activity; 18.2% of participants had an SLEDAI score >4 (active disease), with a median SLEDAI score of 8. The most frequent active disease manifestations at enrolment were articular, haematological and cutaneous.

In terms of the particular aspect of fatigue, the median FACIT-Fatigue score of the participants was 40. Despite the fact that this score was higher compared with that of other SLE cohorts (eg, the EXPLORER trial), patient FACIT-Fatigue scores were significantly lower (more severe fatigue) compared with those of a group of matched healthy controls (47 vs 40; p<0.001). This underlines that, even in a group of outpatients with SLE who are predominantly in remission or in LLDAS, fatigue continues to be an important symptom characterising this chronic condition. This has also been confirmed in a recent work done in the framework of the European Reference Network on Rare and Complex Connective Tissue and Musculoskeletal Diseases (ERN ReCONNET), in which existing clinical practice guidelines on SLE have been reviewed with the aim of outlining the state of the art and identifying current unmet needs. In this context, the persistence of symptoms such as pain and fatigue, even when remission of SLE disease activity has been achieved, has emerged as an unmet need from the patient’s perspective.

In our study, FACIT-Fatigue scores did not present any correlation with age at enrolment and/or disease duration.

Fatigue in SLE has a multifactorial origin and disease activity may play a role in its pathogenesis. Some studies seem to demonstrate a correlation between fatigue and disease status, but this correlation appears rather controversial.

In our study, there was no correlation between FACIT-Fatigue and disease activity and damage accrual evaluated by the physician. Indeed, patients in LLDAS or remission did not report significantly higher FACIT-Fatigue scores, indicating lower fatigue, compared with active patients. Patient perception of health status therefore appeared to be independent of a physician’s assessment of the condition. Moreover, in our cohort, even with the limitation of a low number of active patients, none of the single active organ manifestations demonstrated a significant impact on fatigue severity. It is interesting to note that even patients who presented the most severe disease manifestations at baseline, such as active renal involvement, did not report higher levels of fatigue compared with inactive patients.

Our findings are consistent with some data in the literature that show that disease activity and damage are poor indicators of fatigue in patients with SLE. For example, in the LUMINA cohort, the analysis over time of factors associated with fatigue showed that pain, abnormal illness-related behaviours, helplessness and constitutional manifestations were associated with increased levels of fatigue, while SLE activity and damage were not.
Yilmaz-Oner et al.15 in a group of Turkish patients with SLE, found no significant association between fatigue and SLEDAI scores, but multidimensional assessment of fatigue scores were positively correlated with age, anxiety and depression and negatively correlated with the SF-36 domains.

Other factors may therefore influence the presence of fatigue, anxiety and depression disorders, for example, seem to be important independent predictors of fatigue in patients with SLE.2 47 In a recent work by Aziuddin et al.48 stress, depression and pain appeared to be the largest independent contributors to fatigue among 116 multiethnic patients with SLE, without a known concurrent fibromyalgia. On the contrary, disease activity, sleep and physical health were not associated with fatigue.

Of the comorbidities, fibromyalgia seems to significantly influence the severity of reported fatigue.15 In our cohort, fibromyalgia was seen to have a considerable impact on patient HRQoL. Indeed, in the multivariate analysis, FACIT-Fatigue scores were significantly lower (suggesting a higher level of fatigue) in patients with fibromyalgia compared with patients without (p<0.01), irrespective of disease activity, organ damage, age and disease duration. So this suggests that fibromyalgia may account for fatigue in our cohort more than inflammatory disease.

It is therefore crucial to assess and manage fatigue in the care of patients with SLE as it is one of the most common factors affecting all aspects of patient HRQoL,14 as is evident from our study. In fact, we observed a strong positive correlation not only between FACIT-Fatigue and the vitality domain (which also describes tiredness), but also with all other SF-36 domains (r=0.53–0.77), with a similar impact of fatigue both on physical and mental health. The correlation between fatigue and a lower HRQoL is already well documented in literature. For example, in the EXPLORER trial,36 FACIT-Fatigue scores showed a similar strong correlation with the SF-36 domain scores (r=0.520.68), irrespective of disease activity. Similarly, in a previous work, Bruce et al.15 observed a strong correlation between fatigue, measured by the Fatigue Severity Score, and the SF-36 domains in a cohort of 81 patients with SLE (from r=0.5 to r=0.82). Petri et al.39 analysed pooled treatment and placebo data from a phase Ib clinical trial of adults with moderate/severe SLE and found that improvements in patient-reported pain or fatigue correlated with improvements in overall health, measured by SF-36 and by Patient Global Health Assessment Numeric Rating Scale.

The strong, inverse correlation we observed between FACIT-Fatigue and LIT scores (r=0.78), irrespective of disease activity and fibromyalgia, is of particular interest. Patients with higher levels of fatigue manifested a greater perception of SLE impact. This underlines the fact that fatigue contributes significantly to the determination of disease burden in a patient’s daily living. In a recent work by Nowicka-Sauer et al.,50 fatigue together with anxiety, depression, sleep quality and pain has proved to have a significant relationship with negative illness perception.

As a final point, we found that higher levels of fatigue in our patients significantly correlated with higher SLAQ scores (r=−0.72), irrespective of fibromyalgia and disease activity or damage. This suggests that fatigue represents a puzzling factor in the complex clinical picture of patients with SLE, which leads them to overestimate SLE activity and severity and therefore become dissatisfied with the care process and health status.

We acknowledge that this study has some limitations, notably the fact that we have not evaluated certain factors which may be associated with fatigue and poor HRQoL, such as mood disorders, education level and socioeconomic conditions. Another limitation is the cross-sectional design of the study: it would be interesting to prospectively monitor patients to evaluate if, in each single patient, fatigue severity changes over time in response to different phases of the disease and/or to therapeutic interventions. Moreover, we evaluated the state of remission/LLDAS at last visit, but we did not consider, in our analysis, the duration of such conditions. Finally, being our patients were mainly Caucasians, we cannot generalise our results to all ethnic groups. Despite such limitations, we think that our study has certain strengths: namely, the large number of patients enrolled, all of which regularly followed at the same centre, and the availability of complete clinical data and PROs. In particular, we compared clinical parameters with the results of both generic and SLE-specific PROs, which give complementary information on patient health status.

Moreover, we do not believe that the outpatient origin of the majority of patients enrolled in this study should be considered a limitation. In fact, we think that it is more difficult for physicians to identify which factors have a negative impact on daily living for patients in remission or with a mild disease. Therefore, it is primarily in this context that the discrepancy between patient and physician perception becomes more evident and may negatively influence disease management.

CONCLUSIONS

In conclusion, fatigue appears as an extremely frequent and pervasive symptom in patients with SLE, even for those in remission or in LLDAS, and therefore deserves greater consideration in routine clinical care. The relationship between fatigue and disease activity and severity is controversial, and this makes it necessary to carry out a more comprehensive assessment of comorbidities such as fibromyalgia which play an undoubtedly important role in the genesis of fatigue. The persistence of such a debilitating symptom over time may lead the patient to overestimate disease activity, which in turn leads to dissatisfaction with the care process and could potentially impact adherence to treatment or care.

Finding effective intervention programmes to improve fatigue in patients with SLE is of utmost importance, if we...
consider the burden of this symptom on patients’ quality of life and its influence in determining patient-perceived SLE impact.

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REFERENCES
1 Urowitz MB, Gladman DD, TOM BDM, et al. Changing patterns in mortality and disease outcomes for patients with systemic lupus erythematosus. J Rheumatol 2008;35:2152–8.
2 Schmeding A, Schneider M, Fatigue SM. Fatigue, health-related quality of life and other patient-reported outcomes in systemic lupus erythematosus. Best Pract Res Clin Rheumatol 2010;24:363–75.
3 Rinaldi Set al. Health-Related quality of life in Italian patients with systemic lupus erythematosus. I. Relationship between physical and mental dimension and impact of age. Rheumatology 2004;43:1574–9.
4 Jolly M. How does quality of life of patients with systemic lupus erythematosus compare with that of other common chronic illnesses? J Rheumatol 2005;32:1706–8.
5 Chaigne B, Finchak A, Alpizar-Rodriguez D, et al. Differential impact of systemic lupus erythematosus and rheumatoid arthritis on health-related quality of life. Qual Life Res 2017;26:1767–75.
6 Wolfe F, Michaud K, Li T, et al. EQ-5D and SF-36 quality of life measures in systemic lupus erythematosus: comparisons with rheumatoid arthritis, noninflammatory rheumatic disorders, and the general population. Arthritis Care Res 2004;50:1585–93.
7 Pascual-Ramos V, Contreas-Yáñez I, Valencia-Quírones KR, et al. Rheumatoid arthritis patients achieved better quality of life than systemic lupus erythematosus patients at sustained remission. Clin Exp Rheumatol 2018;36:619–25.
8 Mosca M, Tani C, Aringer M, et al. European League against rheumatism recommendations for monitoring patients with systemic lupus erythematosus in clinical practice and in observational studies. Ann Rheum Dis 2010;69:1269–74.
9 van Vollenhoven RF, Mosca M, Bertias G, et al. Treat-to-target in systemic lupus erythematosus: recommendations from an international Task force. Ann Rheum Dis 2014;73:958–67.
10 Chaigne B, Chizzolini C, Perneger T, et al. Impact of disease activity on health-related quality of life in systemic lupus erythematosus – a cross-sectional analysis of the Swiss systemic lupus erythematosus cohort study (SSCS). BMC Immunol 2017;18:17.
11 Zhu YY, Tam LAL-S, LEE WWY, et al. Relationship between flare and health-related quality of life in patients with systemic lupus erythematosus. J Rheumatol 2010;37:568–73.
12 Piga M, Congia M, Gabba A, et al. Musculoskeletal manifestations as determinants of quality of life impairment in patients with systemic lupus erythematosus. Lupus 2018;27:190–8.
13 Mok CC, Ho LY, Cheung MY, et al. Effect of disease activity and damage on quality of life in patients with systemic lupus erythematosus: a 2-year prospective study. Scand J Rheumatol 2009;38:121–7.
14 Kiani AN, Petri M. Quality-Of-Life measurements versus disease activity in systemic lupus erythematosus. Curr Rheumatol Rep 2010;12:250–8.
15 Bruce IN, Mak VC, Hallett DG, et al. Factors associated with fatigue in patients with systemic lupus erythematosus. Ann Rheum Dis 1999;58:379–84.
16 Jump RL, Robinson ME, Armstrong AE, et al. Fatigue in systemic lupus erythematosus: contributions of disease activity, pain, depression, and perceived social support. J Rheumatol 2005;32:1699–705.
17 Basta F, Margiotta DPE, Vadacca M, et al. Is fatigue a cause of work disability in systemic lupus erythematosus? results from a systematic literature review. Eur Rev Med Pharmacol Sci 2018;22:4589–97.
18 Drenkard C, Bao G, Dennis G, et al. Burden of systemic lupus erythematosus on employment and work productivity: data from a large cohort in the southeastern United States. Arthritis Care Res 2014;66:878–87.
19 Booth S, Price E, Walker F. Fluctuation, invisibility, fatigue – the barriers to maintaining employment with systemic lupus erythematosus: results of an online survey. Lupus 2018;27:2284–91.
20 Da Costa D, Dritsa A, Bernatsky S, et al. Dimensions of fatigue in systemic lupus erythematosus: relationship to disease status and behavioral and psychosocial factors. J Rheumatol 2006;33:1282–8.
21 Moses N, Wiggers J, Nicholas C, et al. Prevalence and correlates of perceived unmet needs of people with systemic lupus erythematosus. Patient Educ Couns 2005;57:30–8.
22 Specchia ML, de Waure C, Gualano MR, et al. Health technology assessment of belimumab: a new monoclonal antibody for the treatment of systemic lupus erythematosus. Biomed Res Int 2014;2014:1–8.
23 Strand V, Levy RA, Cervera R, et al. Improvements in health-related quality of life with belimumab, a B-lymphocyte stimulator-specific inhibitor, in patients with autoantibody-positive systemic lupus erythematosus from the randomised controlled bliss trials. Ann Rheum Dis 2014;73:384–8.
24 Howard Tripp N, Tarn J, Natasari A, et al. Fatigue in primary Sjögren’s syndrome is associated with lower levels of proinflammatory cytokines. RMD Open 2016;2:e000282.
25 van Steenbergen HW, Tsonaka R, Huizinga TWJ, et al. Fatigue in rheumatoid arthritis: a persistent problem: a large longitudinal study. RMD Open 2015;1:e000041.
26 O’Dwyer T,_durcan L, Wilson F. Exercise and physical activity in systemic lupus erythematosus: a systematic review with meta-analyses. Semin Arthritis Rheum 2017;47:204–19.
27 Mahieu MA, Ahn GE, Chmiel JS, et al. Fatigue, patient reported outcomes, and objective measurement of physical activity in systemic lupus erythematosus. Lupus 2016;25:1190–9.
28 Griffiths B, Mosca M, Gordon C. Assessment of patients with systemic lupus erythematosus and the use of lupus disease activity indices. Best Pract Res Clin Rheumatol 2005;19:685–708.
29 Gladman DD, Goldsmith CH, Urowitz MB, et al. The systemic lupus international collaborating Clinics/American College of rheumatology (SLICC/ACR) damage index for systemic lupus erythematosus international comparison. J Rheumatol 2002;27:373–8.
30 Wolfe F, Smythe HA, Yunus MB, et al. The American College of rheumatology 1990 criteria for the classification of fibromyalgia. Report of the multicenter criteria Committee. Arthritis Rheum 1990;33:160–72.
31 van Vollenhoven R, Voskuyl A, Bertsias G, et al. A framework for remission in SLE: consensus findings from a large international Task force on definitions of remission in SLE (DORIS). Ann Rheum Dis 2017;76:554–61.
32 Franklin K, Lau CS, Navarra SV, et al. Definition and initial validation of a lupus low disease activity state (LLDAS). Ann Rheum Dis 2016;75:1615–21.
Stoll T, Gordon C, Seifert B, et al. Consistency and validity of patient administered assessment of quality of life by the mos SF-36; its association with disease activity and damage in patients with systemic lupus erythematosus. J Rheumatol 1997;24:1608–14.

Gladman D, Urowitz M, Fortin P, et al. Systemic lupus international collaborating clinics conference on assessment of lupus flare and quality of life measures in SLE. systemic lupus international collaborating clinics group. J Rheumatol 1996;23:1953–5.

Yellen SB, Cella DF, Webster K, et al. Measuring fatigue and other anemia-related symptoms with the functional assessment of cancer therapy (fatigue) measurement system. J Pain Symptom Manage 1997;13:63–74.

Lai JIN-S, Beaumont JL, Ogale S, et al. Validation of the functional assessment of chronic illness therapy-fatigue scale in patients with moderately to severely active systemic lupus erythematosus, participating in a clinical trial. J Rheumatol 2011;38:672–9.

Goligher EC, Pouchot J, Brant R, et al. Minimal clinically important difference for 7 measures of fatigue in patients with systemic lupus erythematosus. J Rheumatol 2008;35:635–42.

Jolly M, Garris CP, Mikolaitis RA, et al. Development and validation of the lupus impact Tracker: a patient-completed tool for clinical practice to assess and monitor the impact of systemic lupus erythematosus. Arthritis Care Res 2014;66:1542–50.

Karlson EW, Daltroy LH, Rivest C, et al. Validation of a systemic lupus activity questionnaire (SLAQ) for population studies. Lupus 2003;12:280–6.

Yazdany J, Trupin L, Gansky SA, et al. Brief index of lupus damage: a patient-reported measure of damage in systemic lupus erythematosus. Arthritis Care Res 2011;63:1170–7.

Petri M, Kawata AK, Fernandes AW, et al. Impaired health status and the effect of pain and fatigue on functioning in clinical trial patients with systemic lupus erythematosus. J Rheumatol 2013;40:1865–74.

Nowicka-Sauer K, Hajduk A, Kujawska-Danecka H, et al. Illness perception is significantly determined by depression and anxiety in systemic lupus erythematosus. Lupus 2018;27:454–60.