Impact of cognitive impairment, depression, disease activity, and disease damage on quality of life in women with systemic lupus erythematosus

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Objectives: To define the relative role of cognitive impairment, depression, disease activity, and disease damage in the decreased health-related quality of life (HRQoL) frequently observed in systemic lupus erythematosus (SLE) patients.

Method: We studied 101 Chilean female SLE patients and applied the 12-item Medical Outcomes Study (MOS) Short Form Health Survey version 2 (SF-12v2) to assess HRQoL and the Cambridge Neuropsychological Test Automated Battery (CANTAB) to assess cognitive function. Analysis of covariance (ANCOVA) models included demographic and disease-related factors and cognitive function tests of sustained attention, memory, and executive function.

Results: All measures of HRQoL were lower in the 101 female SLE patients compared to the women from the Chilean general population. HRQoL was associated with the following factors: (i) depression symptoms, which were detrimental to all components of the physical and mental HRQoL scores; (ii) executive dysfunction (spatial planning), which was associated with lower scores on role limitations due to physical health problems and emotional problems, and general health perceptions; (iii) higher activity and organ damage were deleterious to role physical, bodily pain, and physical summary scores; and (iv) higher damage also impacted physical function. Impairments in sustained attention and memory did not decrease the HRQoL.

Conclusions: Our results highlight the relevance of executive dysfunction to poor physical and mental health components of HRQoL in SLE together with depression, while disease activity and disease damage are associated with lower HRQoL physical components. The need for cognitive function evaluation and rehabilitation in SLE is indicated.

Systemic lupus erythematosus (SLE) is a complex inflammatory autoimmune disease characterized by multisystem involvement that mostly affects young and middle-aged women. The focus on disease management is presently changing to include the decreased health-related quality of life (HRQoL) of lupus patients as the main outcome (1). Diffuse compromise of the central nervous system can be found in up to 80% of patients and entails manifestations such as depression and cognitive impairment (2). Depression is a well-established detrimental factor in the HRQoL of SLE patients (3–7). However, the role played by cognitive impairment in physical and mental states remains relatively unknown.

HRQoL can be defined as the extent to which a person’s expected physical, emotional, and social well-being are affected by a medical condition or its treatment. It incorporates concepts of subjectivity and multidimensionality, including physical and mental components (8). HRQoL is a particularly relevant outcome in chronic diseases such as SLE, in which a cure may not be available and health goals involve living with and managing the condition (5). Studies carried out over the past 10 years have demonstrated that the HRQoL of SLE patients is worse than that of the general population and comparable to other chronic diseases (9, 10). Nevertheless, the factors contributing to these problems remain to be characterized.

In our previous studies, approximately 20% of SLE patients had major depression (11) and 20% had cognitive deficits (12). Depression had a limited impact on cognitive impairment, affecting only one measure of executive function, whereas higher lupus disease activity impaired sustained attention and spatial working memory test...
performed an additional role in HRQoL to that widely reported for depression (3–7). At present, one study has shown an association between cognitive impairment and mental components of HRQoL, although executive function was assessed (7). Several other studies have associated cognitive impairment with a negative impact on employment (13–16), leaving HRQoL without direct assessment. Other factors currently under investigation in SLE, such as the contribution of disease activity or damage to HRQoL, remain controversial (4, 5, 9, 17–21). All these potentially detrimental factors should be included in a study aimed at better defining the relative contribution of cognitive impairment.

In the current study, we hypothesized that cognitive impairment as well as depression, higher disease activity, and higher damage scores may have a negative impact on the HRQoL physical or mental components, or both, in SLE.

**Method**

In this study, 101 women with SLE attending the facilities of the Health Network, the Pontifical Catholic University of Chile, were examined between July 2008 and August 2010. All participants voluntarily signed an informed consent approved by the Ethical Committee of our Institution. Inclusion criteria were women, Chilean, older than 16 years, and fulfilling four or more of the American College of Rheumatology (ACR) revised criteria for the classification of SLE (22). Exclusion criteria was severe renal failure, severe infections, mental disability that precluded performing the evaluation, history of severe mental illness, an estimated pre-morbid Intelligence Quotient of < 80, and glucocorticoid-induced mania. Patients were not excluded for memory complaints.

A 2- to 3-hour structured protocol assessment with breaks was performed on patients over 1 day. This included the assessment of sociodemographic data: age (years), years of education, employment status (with or without a paid job), marital status (being currently married/divorced/widowed), and disease duration since diagnosis. Global disease activity was evaluated with the SLE Disease Activity Index 2000 or SLEDAI-2K (23) and cumulative damage was ascertained with the Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index or SDI (24). Total doses of corticosteroids, antimalarials, and immunosuppressant medications currently been taken were registered. Healthy female controls of similar age were invited to participate through e-mail advertising within the hospital and university personnel. All controls were given a medical examination by LM and a current medical and/or psychiatric condition was discarded. No control was under psychotropic medication. Twenty-two healthy female controls of similar age were recruited between December 2009 and June 2010. Exclusion criteria were the presence of neurological or rheumatic diseases, past or present complaints of memory or attentional deficit, as described previously (12).

Clinical and self-rating scales were administered in the corresponding validated Spanish version. We administered the Confusion Assessment Method (CAM) test to assess delirium (25) and the Hospital Anxiety and Depression Scale (HADS) (26) to assess self-reported symptoms of depression or anxiety (score range 0–21). The Mini International Neuropsychiatric Interview (MINI-Plus) (27), a brief structured interview for major axis I psychiatric disorders in the Diagnostic and Statistical Manual of Mental Disorders IV, Spanish version (28), was applied for diagnosis of the presence of major depressive episode and anxiety disorders. Patients completed a brief cognitive test battery for dementia screening, the Addenbrooke’s Cognitive Examination – Revised (ACE-R) (29). The ACE-R maximum score is 100, with a cut-off score ≥ 82 to rule out dementia. We also applied the Cambridge Neuropsychological Test Automated Battery (CANTAB) (30, 31).

We used the CANTAB Eclipse™ version 2006 that runs on a Windows-based PC system. This is a touch screen computerized system specifically designed to evaluate cognitive impairments (30). CANTAB is a reliable tool for measuring subtle cognitive impairments, as expected in these patients, and has normative data that allow interpretation of the results (31). Two screening tests were applied to evaluate psychomotor function followed by cognitive tests chosen to cover a wide range of domains (30), such as attention, spatial memory and learning and executive function, thus obtaining a detailed examination of cognition functional networks. The CANTAB was applied by trained clinical psychologists. A broad description and the purpose of each test is given below. Further descriptions on outcome measures, time of administration, and screening tests can be found at CANTAB (www.camcog.com).

The Rapid Visual Information Processing (RVP) test was used to assess visual sustained attention, a cognitive function sensitive to dysfunction in the parietal and frontal lobe areas of the brain, and also a sensitive measure of general performance (32). Participants were asked to detect infrequent three-digit sequences from serially presented digits. A’ was defined as the outcome measure. This is a measure that reveals the sensitivity to the target sequence. This test has very little working memory loading, as the sequence of three digits remains on the screen during the performance of the test.

The Paired Associates Learning (PAL) test was used to assess episodic memory and learning. It tests the ability to form visuospatial associations and is primarily sensitive to changes in medial temporal lobe functioning and hippocampal dysfunction (33). PAL Total errors
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The Stockings of Cambridge (SOC) test was used to assess spatial planning and motor control. It is a measure of the dorsolateral prefrontal cortex function (34). SOC Mean initial thinking time (five moves), SOC Mean subsequent thinking time (five moves), and SOC Problems solved in minimum moves were analysed.

Standardized values in relation to the CANTAB standard deviation (sd) international normative data and raw scores were obtained for six outcome measures. Response times/latencies are reported in milliseconds and other responses are reported as numbers. Higher scores or numbers represent worse performance in tests, except for RVP A’ tests and SOC Problems solved in minimum moves.

Cognitive deficit was defined by a cut-off for definite impairment for a score below –2 sd in at least one outcome measure in two or three domains, following the ACR committee criteria (35) as described by Calderón et al (12).

To measure HRQoL we used the 12-item Medical Outcomes Study (MOS) Short Form Health Survey version 2 (SF-12v2), a generic instrument already validated in SLE (36), allowing a comparison with the Chilean general population. SF-12 is brief enough to be administered in less than 2 minutes (8). SF-12v2 consists of eight domains reflecting eight dimensions of life: physical functioning (PF), role limitations due to physical health problems (RP), bodily pain (BP), general health perceptions (GH), vitality, energy, or fatigue (VT), social functioning (SF), role limitations due to emotional problems (RE), and general mental health (MH). The survey provides psychometrically based physical component summary (PCS-12) and mental component summary (MCS-12) scores. The results were converted into a scale from 0 to 100, where 0 indicates the lowest quality of life and 100 the highest. All results were transformed according to the norm-based scoring that allows comparison among surveys. Additionally, this allowed a comparison with data from the Chilean National Survey on Quality of Life and Health ‘Encuesta Nacional de Calidad de Vida y Salud’ (ENCAVI) 2006 (http://epi.minsal.cl/estudios-y-encuestas-poblacionales/encuestas-poblacionales/descarga-encavi-2006/), which used the SF-12v2. This survey gave us permission to use data from 2536 women of similar age from the Chilean general population (GP).

Statistics

Descriptive data are shown as medians with interquartile range (IQR) percentiles 25th and 75th in parentheses. The Mann–Whitney U test and Fisher’s exact probability test two-tailed were applied for comparisons between SLE and healthy controls. The T-test was used for comparisons between SLE and the GP for HRQoL. Significance was set at an alpha level of 0.05. There were no missing data. We applied analysis of covariance (ANCOVA) models for each domain (rather than obtaining multivariate ANCOVA models, which included many unimportant variables), taking into consideration the decrease in statistical power with dependent variables that are highly correlated. Thus, we excluded one measure of the PAL (Total errors adjusted) that had high levels of correlations (0.76) with PAL Total errors (six shapes adjusted), and we only included the last in the analysis. The ANCOVA was performed with a selection of variables following the Akaike information criteria. These variables included working and marital status (nominal), disease duration (continuous), age in years (continuous), years of education (continuous), HADS depression score (continuous), SLEDAI-2K (continuous), SDI (continuous), prednisone dose (continuous), RVP, PAL, and SOC raw scores to examine their impact on SF-12v2 HRQoL eight measures and two summary components norm-based scores. To compare the SF-12v2 scores measured from the SLE sample with data from the ENCAVI Chilean GP, scores were age normalized through the QualityMetric Health Outcomes™ Scoring Software 4.0, based on a proposed standard population provided by this software (US 1990 GP). Statistics were performed using SPSS version 17.0 (2008; SPSS Inc, Chicago, IL, USA). ANCOVA was

Table 1. Description of SLE patients and healthy subjects.

|                          | SLE patients  | Healthy subjects | Mann–Whitney U test |
|--------------------------|--------------|------------------|---------------------|
|                          | Median       | (IQR)            | Median              | (IQR)              | p-value |
| Age (years)              | 35.0         | (26.5–43.5)      | 37.0                | (30.5–54.5)        | 0.165   |
| Education (years)        | 14           | (12–16)          | 16                  | (14–17)            | 0.004   |
| Disease duration (months) | 32           | (4–126)          | –                   | –                  | –       |
| SLEDAI-2K score          | 6            | (4–12)           | –                   | –                  | –       |
| SDI score                | 0            | (0–1)            | –                   | –                  | –       |
| Prednisone dose (mg/day) in 85 patients using prednisone | 10 | (5–25) | – | – | – |

SLE, Systemic lupus erythematosus; SLEDAI-2K, SLE Disease Activity Index 2000; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index. All participants were female. Data are median and interquartile range (IQR) percentiles 25th–75th.
also performed with patients with/without a major depressive episode instead of using the HADS depression score.

Results

A total of 101 female patients with SLE participated in this study. Their demographic and clinical characteristics are shown in Table 1. There was a statistical difference in education between patients and healthy controls (Mann–Whitney U test p-value = 0.004). Sixty-nine patients were working and 40 were married or in a stable relationship. Eighty-three patients were using antimalarials and 48 were receiving concurrent immunosuppressive therapy: 21 were on azathioprine, 16 on mycophenolate mofetil, five on methotrexate, three on rituximab, and three on cyclophosphamide. Seven patients had antiphospholipid syndrome. Supplementary Tables S1 and S2 show the involved items in the 92 patients with SLEDAI-2K > 0 and in 34 patients with an SDI score > 0, respectively.

In SLE patients the HADS test showed a median score of 6 (P25th–P75th: 3–10) for depression and 9 (5–13) for anxiety. Diagnosis of a major depressive episode was determined in 25 patients using the MINI-Plus. The ACE-R score was: median 94 (90–97). Three patients had an ACE-R score < 82 but were still able to continue with the protocol.

Table 2 shows CANTAB performances in each sub-test. Differences between the 101 SLE patients and 22 healthy controls are seen in RVP A’ (Mann–Whitney U test, statistical power 91.5%; p-value < 0.001) and SOC Problems solved in minimum moves (Mann–Whitney U test, statistical power 65.7%; p-value = 0.021). Table 2 also shows the number of subjects with a score below −2 sd. The cognitive domain most frequently involved was executive function in 32 patients and one control (Fisher’s exact test p-value = 0.014). In total, 18 patients and no control fulfilled the definition criteria for cognitive deficit of a score below −2 sd in at least one outcome measure in two or three domains (Fisher’s exact test p-value = 0.040; data not shown).

HRQoL results are shown in Table 3. The eight components and the PCS and MCS scores were significantly lower than those for a sample of females obtained from the Chilean general population (T-test, p-value < 0.002).

**Table 2. Comparisons of SLE patients and healthy subjects on CANTAB.**

| CANTAB test responses | SLE (n = 101) | Healthy subjects (n = 22) | Mann–Whitney U test | p-value |
|-----------------------|--------------|--------------------------|---------------------|---------|
| Sustained attention RVP A’ (ms) | Median (IQR) 0.88 (0.69–0.96) | Median (IQR) 0.92 (0.90–0.95) | 0.021 | < 0.001 |
| Spatial memory and learning Total errors (adjusted) (n) | Median (IQR) 6 (5–9) | Median (IQR) 8 (5–12) | 0.555 | 0.612 |
| Executive function SOC Mean initial thinking time (five moves) (ms) | Median (IQR) 688 (435–12 941) | Median (IQR) 942 (491–12 201) | 0.014 | 0.612 |
| Problems solved in minimum moves (n) | Median (IQR) 7 (6–9) | Median (IQR) 16 (7–9) | 0.021 | < 0.001 |

CANTAB, Cambridge Neuropsychological Test Automated Battery; RVP, Rapid Visual Information Processing; SOC, Stockings of Cambridge; sd, standard deviation.

HRQoL results are shown in Table 3. The eight components and the PCS and MCS scores were significantly lower than those for a sample of females obtained from the Chilean general population (T-test, p-value < 0.002).

**ANOVA results**

Ageing and higher depression symptoms scores were associated with worse physical components: PF, RP, BP, GH, and PCS-12 scores. Younger patients were associated with a lower GH score. In addition, the following factors were associated with physical components of SF-12v2, as shown in Table 4: (i) shorter disease duration and a higher SDI score were associated with lower physical function (ANOVA model R² = 0.40); (ii) shorter disease duration, a higher SLEDAI-2K score, and worse performance in the executive function domain SOC Problems solved in minimum...
Table 3. HRQoL SF-12 v2 scores in SLE patients and the Chilean general population, women only.

|                   | SLE n = 101 | General population * n = 2536 | T-test |
|-------------------|-------------|--------------------------------|--------|
|                   | Median  | (IQR)  | Median  | (IQR)  | p-value |
| Physical Functioning | 39.29   | (30.70–47.88) | 56.47   | (47.88–56.47) | < 0.001 |
| Role Physical      | 38.75   | (29.54–47.96) | 52.27   | (43.36–57.18) | < 0.001 |
| Bodily Pain        | 37.06   | (26.87–47.25) | 47.25   | (37.06–57.44) | < 0.001 |
| General Health     | 29.65   | (29.65–44.74) | 44.74   | (29.65–44.74) | < 0.002 |
| Physical Component Summary score | 39.22 | (32.28–49.53) | 48.67   | (41.18–52.99) | < 0.001 |
| Social Functioning | 36.37   | (26.27–46.47) | 46.47   | (36.37–56.57) | < 0.001 |
| Vitality           | 37.69   | (37.69–44.75) | 57.81   | (47.75–67.88) | < 0.001 |
| Role Emotional     | 33.71   | (14.15–39.30) | 50.49   | (39.30–56.08) | < 0.001 |
| Mental Health      | 40.16   | (27.97–49.30) | 52.35   | (40.16–58.45) | < 0.001 |
| Mental Component Summary score | 35.20 | (25.80–40.07) | 48.94   | (40.63–55.74) | < 0.001 |

HRQoL, Health-related quality of life; SF-12 v2, 12-item Medical Outcomes Study (MOS) Short Form Health Survey version 2; SLE, systemic lupus erythematosus.

SF-12v2 components norm-based scores. Median and interquartile range (IQR) percentiles 25th–75th are shown.

* Data obtained from the 2006 Chilean National Survey on Quality of Life and Health (http://epi.minsal.cl/estudios-y-encuestas-poblacionales/encuestas-poblacionales/descarga-encavi-2006/).

† Direct age-adjusted HRQoL performed according to a 1990 US population provided by SF-12v2.

Table 4. ANCOVA models showing coefficients and $R^2$ between demographic, disease-related, depression, and cognitive factors and physical components and physical component summary (PCS) scores of the SF-12v2.

|                   | Physical Functioning | Role Physical | Bodily Pain | General Health | PCS score |
|-------------------|----------------------|---------------|-------------|----------------|-----------|
| Age               | $-0.30^{**}$         | $-0.34^{**}$  | $-0.29^{**}$ | $0.19^{*}$     | $-0.34^{**}$ |
| Years of education| –                    | –             | –           | $-0.90^{*}$    | –         |
| Marital status: married/relationship | –                  | –             | –           | $-2.57^{*}$    | –         |
| Working status    | –                    | $-4.44^{*}$   | –           | –              | $-3.93^{*}$|
| SLE duration      | $0.03^{*}$           | $0.03^{*}$    | $0.02^{c}$  | $0.03^{*}$     | $0.04^{***}$|
| SLEDAI-2K         | $-0.24^{a}$          | $-0.40^{*}$   | $-0.67^{***}$ | –              | $-0.48^{***}$ |
| SDI               | $-3.78^{***}$        | $-2.33^{*}$   | $-2.07^{*}$ | $-1.46^{d}$    | $-3.54^{***}$|
| Prednisone dose   | –                    | –             | –           | $0.01^{*}$     | –         |
| Depression score  | $-1.00^{***}$        | $-1.28^{***}$ | $-1.28^{***}$ | $-1.07^{***}$  | $-0.82^{***}$ |
| SOC Mean subsequent thinking time (five moves) | –                  | –             | –           | $0.0001^{e}$   | –         |
| SOC Problems solved in minimum moves | –                  | $1.47^{*}$    | –           | $1.41^{**}$    | $0.83^{e}$ |
| Intercept         | $56.88^{***}$        | $49.96^{***}$ | $60.51^{***}$ | $12.79^{e}$    | $54.99^{***}$ |
| ANCOVA models $R^2$ | 0.40           | 0.42         | 0.47        | 0.44          | 0.43      |

ANCOVA, Analysis of covariance; SF-12 v2, 12-item Medical Outcomes Study (MOS) Short Form Health Survey version 2; SLE, systemic lupus erythematosus; SLEDAI-2K, SLE Disease Activity Index 2000; SDI, Systemic Lupus International Collaborating Clinics/ American College of Rheumatology (SLICC/ACR) Damage Index; SOC, Stockings of Cambridge.

Data shown are ANCOVA model coefficients.

P-values according to: $^{***} \leq 0.001$, $^{**} \leq 0.01$, $^{*} \leq 0.05$, and $R^2$.

$^a$ P-value = 0.095; $^b$ p-value = 0.051; $^c$ p-value = 0.068; $^d$ p-value = 0.08; $^e$ although these variables are not significant, they contribute to the fitting of the model.

Higher depression symptoms scores were associated with worse scores in all HRQoL mental components (SF, VT, RE, MH, and MCS-12) score, as shown in Table 5. Other factors included the following: (i) being married or in a stable relationship and shorter disease duration had a negative impact on social functioning (ANCOVA model $R^2 = 0.36$); (ii) worse performance in executive function SOC Problems solved in minimum moves negatively impacted on Role emotional ($R^2 = 0.29$); (iii) higher depression symptoms score was the only factor that

movements test were associated with lower Role physical ($R^2 = 0.42$); (iii) a higher SLEDAI-2K score and a higher SDI score were associated with lower scores on Bodily pain; (iv) fewer years of education, lower prednisone dose, and worse performance in executive function SOC Problems solved in minimum moves impacted on a lower GH component ($R^2 = 0.44$); and (v) working status, shorter disease duration, a higher SLEDAI-2K score, and a higher SDI score significantly impacted on a lower PCS-12 score ($R^2 = 0.43$).
Table 5. ANCOVA models showing coefficients and $R^2$ between demographic, disease-related, depression, and cognitive factors and mental components and mental component summary (MCS) score of the SF-12v2.

|                                | Social Functioning | Vitality | Role Emotional | Mental Health | MCS score |
|--------------------------------|--------------------|----------|----------------|---------------|-----------|
| Marital status: married/relationship | -4.39*             | -        | -              | -             | -         |
| SLE duration                   | 0.03*              | -        | -              | -             | -         |
| SDI                            | -                  | -        | -              | -             | 1.38b     |
| Prednisone dose                | 0.01*              | -        | -              | -             | -         |
| Depression score               | -1.42****          | -1.32****| -1.77****      | -2.04****     | -1.89***  |
| SOC Problems solved in minimum moves | -                  | 1.48*    | -              | -             | -         |
| Intercept                      | 47.27****          | 51.67****| 29.42****      | 50.94****     | 47.87**** |
| ANCOVA models $R^2$            | 0.35               | 0.41     | 0.29           | 0.81          | 0.45      |

ANOVA, Analysis of covariance; SF-12 v2, 12-item Medical Outcomes Study (MOS) Short Form Health Survey version 2; SLE, systemic lupus erythematosus; SLEDAI-2K, SLE Disease Activity Index 2000; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index; SOC, Stockings of Cambridge.

Data shown are ANCOVA models coefficients. P-values according to: *** ≤ 0.001, ** ≤ 0.01, * ≤ 0.05, and $R^2$.

* P-value = 0.068; b Although this variable is not significant it contributes to the fitting of the model.

negatively impacted Vitality ($R^2 = 0.41$), Mental health component ($R^2 = 0.62$), and Mental component summary score ($R^2 = 0.45$).

Attention and visuospatial memory and learning deficits were not associated with lower HRQoL. Similar results were obtained when patients with/without a major depressive episode (instead of the HADS depression score) were included in the ANCOVA (data not shown).

Discussion

In the present study we demonstrate the role of cognitive impairment, particularly of executive dysfunction, on physical and mental components of HRQoL. We assessed cognitive performance thoroughly and according to a strict criteria for which 18% of patients were described as having a cognitive deficit (12). Cognitive assessment included attention, memory and learning, and in particular executive functions. Of note, our results reveal an impact of planning impairment (SOC Problems solved in minimum moves) on role limitations due to physical health problems, general health perceptions, and role limitations due to emotional problems. Therefore, executive dysfunction contributes to worse mental and physical HRQoL. At odds with our hypothesis that visual memory and sustained attention impairments could be reflected in a lower HRQoL, no such association was found. However, few patients had attention or visuospatial memory impairments, making it difficult to rule out an impact on HRQoL. In the study by Tam et al (7) performed on 291 SLE patients, executive dysfunction related to poorer mental health subscale of the SF-36. This study had not included the analysis of other cognitive domains and did not report any association with the physical components of HRQoL. Our results are also in line with the detrimental role of depression on HRQoL (4, 7). In congruency with many previous studies, we found depression negatively impacting HRQoL (4, 7).

Additionally, we provide new evidence on the controversy regarding the relationship between HRQoL and disease activity and disease damage (4, 5, 9, 17–21). In the current study, ANCOVA results show that higher disease activity and higher disease damage scores had a negative impact on most of the physical functions of HRQoL. Previous studies reported either weak (9, 20) or absent (4, 5, 17, 19) associations of disease activity or disease damage with HRQoL. However, one study described a direct impact of higher disease activity in lower physical and mental components of the HRQoL (18). Moreover, another study showed that both higher disease activity and higher damage were associated with a worsening on HRQoL (21). HRQoL takes into account the patient’s perspective, whereas the clinician evaluates disease activity and damage (1). Therefore, differences in findings may be due to the spectrum bias phenomenon, where the sensitivity and/or specificity of a test might vary in gender ratio, age, or severity of disease and diverse statistical approaches including different methods to evaluate disease activity or severity. Whatever the case, our results favour the possibility that, when assessed with SLEDAI-2K and SDI scales, higher disease activity and damage contribute to worsening HRQoL physical functions. As described previously (37), we found that shorter disease duration was associated with worse scores in physical functioning, role physical, physical component summary score, and social functioning, perhaps revealing the impact of the recent diagnoses of a severe chronic disease in lupus patients.

With regard to sociodemographic factors influencing HRQoL, ageing was a negative predictor of quality of life, especially in the physical components, as described previously (7, 38). Married SLE patients reportedly had difficulties in intimate relationships even though marital status might be expected to be associated with better health outcomes (20). The multiethnic lupus cohort LUMINA study reported that love relationships, poverty, and fewer years of education were associated with worse quality of life (39). We also found that married lupus patients or those in a stable relationship had worse
social functioning, perhaps due to difficulties in fulfilling family life expectations. Regarding working status, Yazdany and Yelin reported that SLE profoundly affected HRQoL across a variety of domains, resulting in significant employment reductions (40). Of note, our patients who were working had lower physical component summary measures scores. Therefore, our results are in agreement with the notion that sociodemographic factors distinctly impact on HRQoL in SLE.

Our study was performed with a statistically robust model and thoroughly explored different domains of cognitive function with a well-validated neuropsychological battery. We also performed an ANCOVA with a factor cognitive deficit as present/absent obtaining similar results (data not shown). It is common practice to use a number of controls within a range of 20 to 40 for neurocognitive measures. In our specific case, considering that control performance was within CANTAB normative ranges, this gave us confidence in the comparison made between SLE patients’ data and the available normative data from CANTAB. We acknowledge that a weakness of the study is the low number of controls in addition to the low statistical power when comparing SLE patients’ test responses with healthy controls. However, the statistical power was sufficient to allow us to study RVP A’ and SOC Problems solved in minimum moves tests (statistical power: 91.5% and 67.5%; p-values < 0.001 and 0.021, respectively). A much higher number of healthy controls (between 100 and 500) would be needed to study PAL (statistical power: PAL Total errors: 41% and PAL Total errors six shapes: 15.2%), SOC Mean initial thinking time and SOC Mean subsequent thinking time tests (statistical power: 4% and 36.4%, respectively). Additionally, only one neuropsychological test was selected to assess a specific cognitive domain to control for the number of variables for statistical analysis and to avoid patient exhaustion. Even though the study protocol took 2 to 3 hours, this was carried out considering healthy breaks and assistance for patient completion of forms where needed. All assessments were carried out on the same day, precluding dropouts. We also acknowledge that other methods to assess disease activity in SLE may produce a different impact on results; nevertheless, the SLEDAI is perhaps the easiest assessment tool used in clinical practice (41), and future research should address which items relate the most to HRQoL. Our results only apply to females with SLE as the study was designed for women. Separation by gender in SLE in clinical research has been suggested to identify better approaches to each gender, as lupus predominantly affects women of childbearing age while male patients with SLE have more severe disease (42, 43). We also took into consideration that depression is more frequent in women than men (44, 45). The stigma of being diagnosed with lupus and changes in body image are essential factors not taken into account by SF-12v2 as a generic instrument. However, there are no validated disease-specific instruments including body image, sleep disturbances, planning and family life issues (46) available for Chilean patients.

Cognitive rehabilitation, particularly in executive function, may be necessary for a subgroup of SLE patients presenting planning deficits. Better treatments for SLE aimed at diminishing lupus activity and organ damage are also required to attenuate the negative impact on physical components of HRQoL. Treating depression in lupus patients might also improve mental and physical HRQoL. The present study constitutes an important advance towards understanding the relevance of executive dysfunction in the HRQoL of patients with SLE and highlights the need for cognitive function evaluation and rehabilitation.

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Supplementary Table S1. Involved items in the SLEDAI-2K.
Supplementary Table S2. Involved items in the SLE Damage Index.

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