Lupus (2016) 25, 988–996
http://lup.sagepub.com

PAPER

Insomnia symptoms, perceived stress and coping strategies in patients with systemic lupus erythematosus

L Palagini[1], M Mauri[1], U Faraguna[2,3], L Carli[4], C Tani[4], L Dell'Osso[1], M Mosca[4] and D Riemann[5]
[1]Department of Clinical and Experimental Medicine, Psychiatric Unit, University of Pisa, Italy; [2]Department of Translational Research and of New Surgical and Medical Technologies, University of Pisa, Italy; [3]Department of Developmental Neuroscience, Stella Maris Scientific Institute, Pisa, Italy.; [4]Department of Clinical Experimental Medicine, Rheumatology Unit, University of Pisa, Italy; and [5]Department of Clinical Psychology and Psychophysiology/Sleep Medicine, Center for Mental Disorders, Freiburg University Medical Center, Germany

Objective: The aim of this study is to evaluate perceived stress and coping strategies in individuals with systemic lupus erythematosus (SLE) according to the presence of insomnia symptoms, using a set of variables that include anxiety and depressive symptoms evaluation. **Methods:** Ninety SLE women were evaluated in a cross-sectional study using the Perceived Stress Scale (PSS), Brief COPE, Pittsburgh Sleep Quality Index (PSQI), Insomnia Severity Index (ISI), Beck Depression Inventory (BDI) and Self-rating Anxiety Scale (SAS). **Results:** Individuals with insomnia symptoms ($n = 57$, 66%) presented higher PSS ($p < 0.001$), PSQI ($p < 0.0001$), BDI, ($p < 0.0001$) scores and showed less-effective coping strategies such as the use of behavioral disengagement ($p = 0.04$), self-blame ($p = 0.02$) and emotional-focused coping ($p = 0.001$). In a multi-regression model ISI was the independent determinant of high PSS and of behavioral disengagement; PSQI was the only determinant of self-blame ($p = 0.02$) and emotional-focused coping. **Conclusions:** SLE individuals with insomnia symptoms show high levels of perceived stress and more frequent use of disengaging and emotional-focused coping strategies. This body of evidence suggests that individuals with SLE and comorbid insomnia symptoms may therefore require additional interventions for insomnia. *Lupus* (2016) **25,** 988–996.

Key words: Neuropsychiatric lupus; systemic lupus erythematosus; nephritis

Introduction

Systemic lupus erythematosus (SLE) is a chronic multisystem, inflammatory, autoimmune disorder characterized by a variety of clinical manifestations and organ involvement.[1,2]

Neuropsychiatric manifestations such as depression[3] are frequently observed in SLE and significantly interfere with patients' quality of life, social relationships and productivity.[2–5]

Although earlier diagnosis and better treatment options have improved the survival of SLE patients in recent decades,[6] the course of SLE is characterized by recurrent flares that have been related to stress[7–11] and depression[3] and may lead to progressive disability.[12] Research for prevention and treatment of SLE should thus continue to receive high priority. Insomnia has emerged as a major determinant of psychic and somatic health including rheumatologic disorders[13–19] and SLE.[15–18]

Sleep disorders are an important part of the symptomatology of SLE: they occur in more than half of patients and are associated with disease activity, fatigue and depressive symptoms.[18,20–22] As a role for stress has been hypothesized in the development of flares in SLE,[7,8,10,11,23,24] overactivation of the stress system that has been described in insomnia known as ''hyperarousal''[25–27] may be interesting from an SLE point of view. In particular, evidence is accumulating for the hypothesis that conditions of sleep loss, including insomnia, might act as a neurobiologic stressor per se,[28] leading to sympathetic nervous system and hypothalamus-pituitary-adrenal axis over-activation, pro-inflammatory responses that in turn may be involved in the modulation of depression, pain and fatigue in SLE too.[3,20,29]

Despite this evidence, no prior research has examined the possible association between insomnia, stress and the potential impact on SLE individuals.

Correspondence to: Laura Palagini, Department of Clinical and Experimental Medicine, Psychiatric Unit, University of Pisa, School of Medicine, Via Roma 67, 56100, Pisa, Italy.
Email: lpalagini@tiscali.it; l.palagini@ao-pisa.toscana.it
Received 17 July 2015; accepted 7 January 2016

10.1177/0961203316631630

According to the appraisal theory, the physiological effects resulting from a stressful event are determined by the individual perception of an event.[30] Appraisal of stress has been related to flares in SLE.[10] Recommendations for lupus patients to reduce perceived stress are based on numerous studies establishing the association between daily stress and disease exacerbation.[7,8,10,11,23,24] Once the event has occurred and been appraised as a stressor, the second process relates to how the individual self-regulates and reduces stress, referred to as "coping."[31] Some of these coping strategies may prove beneficial, while others may instead prove to be "maladaptive" or less effective.[30–32]

A meta-analysis showed emotion-focused strategies, aimed at thinking or feeling in a different way about a stressful situation, to be less effective and to be related to poor mental health[33] with respect to problem-focused coping, aimed at performing something active to modify a stressful situation.[33] In addition, disengagement coping is considered a psychological risk factor or a disadaptive response to stressful events.[34] The course of the disease and the mental well-being of SLE patients have been shown to be influenced by coping strategies applied;[35–37] disengaging and emotional coping styles have been described to interfere with the course of the disease, with the mental well-being and the quality of life in SLE.[11,38]

In the attempt to clarify the relationship between insomnia symptoms and both appraisal and coping of stress in SLE, this study examined a clinical sample of SLE patients who were evaluated according to the presence or absence of insomnia symptoms. Participants were categorized into two groups: 1) SLE patients with insomnia symptoms, and 2) SLE patients without insomnia symptoms. The hypothesis of the study was that SLE participants with insomnia symptoms will show higher rates of stress-appraisal and more maladaptive coping strategies than SLE participants without insomnia symptoms. As insomnia is a risk factor for psychiatric disorders,[39] we also expected to see higher psychological problems in the SLE group with insomnia symptoms.

Methods

Participants

From January 2012 to December 2013, consecutive outpatients attending the Lupus Clinic of the Rheumatology Unit of the University of Pisa, Italy, were evaluated. Participants underwent a face-to-face evaluation conducted by a medical doctor with expertise in the sleep field (LP). Sleep disorders were assessed by clinical evaluation and the use of sleep-related questionnaires. All enrolled individuals fulfilled at least four of the American College of Rheumatology (ACR) revised criteria for SLE.[40] SLE patients underwent a complete medical evaluation, including a clinical interview to determine the patients' medical, neurologic and psychiatric disorders and pre-existing sleep disorders. Inclusion criteria were age >18 years and written informed consent; exclusion criteria were cognitive impairment that would preclude the completion of the questionnaires; severe medical diseases including end-stage renal disease and active neoplastic disease. Furthermore, patients who were suspected of suffering from another sleep disorder (for example: sleep apnea syndrome, snoring), based on clinical evaluation that was conducted by a medical doctor with expertise in the sleep field (LP) and according to the International Classification of Sleep Disorders, third edition (ICSD-3) criteria,[41] also were excluded. In addition, individuals with a score of 1 or more on item 10 of the Pittsburgh Sleep Quality Index (PSQI)[42] regarding self-reported symptoms or symptoms reported by the patient's roommate were excluded from the study.

Clinical evaluations

After enrollment, participants underwent a standard medical examination. For SLE patients, medical and pharmacological history, previous organ involvement as well as actual disease manifestations and ongoing therapies were recorded. Previous or ongoing neurological manifestations were defined according to the ACR nomenclature and case definitions.[43]

Cumulative glucocorticorticoid (GC) dosages until the assessment time were also computed. Disease activity was evaluated using the European Consensus Lupus Activity Measurement Index (ECLAM) in a range from 0 to 6; a score > 2 was considered as indicative of active disease.[44] Cumulative organ damage was measured using the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SLICC/ACR DI) (range 3–6).[45]

Questionnaires

Measurements of sleep

PSQI

Sleep quality was evaluated through the administration of the PSQI. The PSQI is a widely used,

self-rated, standardized questionnaire assessing sleep quality in the previous month. The 19 questions are grouped in seven component scores, each exploring a different sleep feature; the sum yields a global PSQI score[42] used to define poor sleep quality when >5. The following PSQI-derived data were also analyzed: sleep latency (component 2), sleep duration (component 3), habitual sleep efficiency (component 4), and use of medication (component 6).[42]

Insomnia Severity Index (ISI)

Insomnia severity was evaluated with the ISI. ISI is a self-reported, seven-item questionnaire that assesses insomnia in the previous two weeks. It is a reliable and valid instrument to index a diagnosis of and severity of insomnia. The sum yields a global score ranging from 0 to 28. Individuals were categorized as having no insomnia if the ISI score ranged from 0 to 7. The presence of insomnia symptoms was defined by an ISI score of 8 or higher.[46]

Measurements of stress

Appraisal of stress: Perceived Stress Scale (PSS)

Perception of stress was assessed using the PSS.[47] It measures the degree to which events are appraised as stressful. Items were designed to tap how unpredictable, uncontrollable, and overloaded respondents found their lives during the last month. The scale also includes a number of direct queries about current levels of experienced stress. Normative values[47] for 30- to 44-year-old women are >14.

Coping of stress: Brief COPE

Coping strategies were evaluated using the Brief COPE scale, which assesses for coping responses to stressors.[32] The Brief COPE specifically referenced coping strategies in which participants engaged in response to stressors. A shortened version of the original instrument, the Brief COPE is a 14 subscale and 28-item multifactorial questionnaire designed to assess levels of engagement in various coping techniques.[32] The 14 subscales are composed of two items each, with higher scores indicating greater use of the respective coping strategy. Coping strategies measured in the Brief COPE include Acceptance, Religion, Planning, Positive Reframing, Using Instrumental Support, Active Coping, Using Emotional Support, Humor, Self-Distraction, Venting of Emotions, Self-blame, Behavioral Disengagement, Denial and Substance Use. Participants were asked to respond to each item on a four-point Likert scale, indicating what they generally do and feel when they experience stressful events (1 = "I have not been doing this at all" – 4 = "I have been doing this a lot").[32] Problem-focused vs. emotion-focused coping strategies were considered. Composite scores for these two strategies of coping were obtained by summing their scales: Acceptance, Religion, Planning, Positive Reframing, Using Instrumental Support, Active Coping, Using Emotional Support and Humor comprised the Problem-focused coping score, while Self-Distraction, Venting of Emotions, Self-blame, Behavioral Disengagement, Denial and Substance Use comprised the Emotion-focused coping score.[48]

Measurements of psychiatric symptoms

Beck Depression Inventory (BDI)

Depressive symptoms were assessed using the BDI. The BDI is a 21-question inventory for self-assessment, one of the most widely used instruments for measuring the severity of depression. The total score ranges from 0–63. According to the BDI authors' recommendations, a BDI score greater than 9 is indicative of depressive symptoms.[49]

Self-rating Anxiety Scale (SAS)

Anxiety symptoms were assessed with the SAS. The SAS is a 20-item self-reported assessment scale based on scoring in four groups of manifestations: cognitive, autonomic, motor and central nervous system symptoms. Each question is scored on a Likert-type scale of 1–4. The total score ranges from 0–80. The presence of clinically relevant anxiety symptoms is defined[50] by SAS scores > 44.

Statistical analysis

Statistical analysis was performed using NCSS 2008.[51] Results were expressed as mean ± standard deviation (SD). Shapiro-Wilk test was used to check normality of the variables. Differences in means between individuals with or without insomnia symptoms were assessed using *t*-tests for normally distributed variables, or Mann-Whitney *U*/Wilcoxon test for non-normally distributed variables. The Box-Cox transformation was performed for non-normal distributed variables. Categorical variables were analyzed via the χ^2 test. An a priori power estimation analysis returned a sample size of $n = 20$ to reach a power of 0.8. A post hoc power analysis a posteriori was conducted on simple size; a power- > 0.8 was considered significant. Univariate linear regression analysis was performed in order to test the correlates of the PSS, expressed by PSS score,

and of coping strategies, using responses on the Brief COPE subscales. Then multiple linear regression models were built, with the PSS or Brief COPE subscales entered as dependent variables, and as independent variables those measures that were found to be significantly correlated with the dependent variables in the univariate analyses. All the multiple regression models were checked for multicollinearity: a variable was excluded from the model if it had a variance inflation factor greater than 10 and a condition number greater than 100 in the Eigenvalues of Centered Correlations.

Results

Descriptive statistics

Among the 100 individuals enrolled, all females, those with clinically evaluated or self-reported (or reported by roommate) sleep apneas, snoring, and leg restlessness ($n=6$) or with incomplete data ($n=4$) were excluded. The final analysis was performed on 90 patients. Clinical characteristics of the study population are listed in Table 1. Participants with insomnia symptoms showed significantly higher renal involvement (28 participants = 49.1%, past $p=0.03$) than patients with no insomnia symptoms. No differences in disease activity (ECLAM mean score) were found among the groups (Table 1). Post hoc power analysis a posteriori revealed a power of 0.99.

Sleep and psychological characteristics

Sleep and psychiatric characteristics of the study population are listed in Table 2. Participants with insomnia symptoms exhibited poorer sleep quality, and higher insomnia severity; 29.8% showed a sleep latency >30 minutes ($n=17$, $p=0.02$), 49.1% ($n=28$, $p<0.001$) a short sleep duration (<6 hours), and 64.9% a low sleep efficiency (<85%) ($n=37$, $p=0.01$) compared to SLE patients with no insomnia symptoms (respectively 11.4%, $n=4$; 14.2%, $n=4$; 25.7%, $n=13$). Despite the presence of these sleep problems, the use of sleep medications at least once or twice a week was very limited in the group of SLE patients with insomnia symptoms (15.7%, $n=9$ vs 2% $n=1$, $p=0.006$). Individuals with insomnia also showed higher rates of depressive symptoms than SLE patients with no insomnia symptoms ($p=0.003$); significantly, 40.3% ($n=23$) of the SLE patients with insomnia symptoms showed depressive symptoms.

Table 1 Clinical characteristics of the study population

	Overall (n = *90*)	*No insomnia symptoms* (n = *33*)	*With insomnia symptoms* (n = *57*)	p *value*
Age (years)	43 ± 11	42 ± 11	43 ± 11	0.23
Education (%)				
-Undergraduates	90.	91	92	0.61
-Graduated	10	9	8	0.55
Employment status (%)				
-Unemployed/household	52	52	53	0.52
-Employed	48	48	47	
SLE duration (years)	15 ± 8	14 ± 8	15 ± 8	0.19
Neurologic involvement (%)	12	10	13	0.19[a]
Renal involvement (%)	38	24.2	49.1	0.03[a,b]
ECLAM mean score	0.9 ± 1.2	0.9 ± 1.0	0.9 ± 1.4	0.64[a]
SLICC mean score	0.9 ± 1.3	0.6 ± 0.8	1.0 ± 1.5	0.78[a]
Glucocorticosteroids (%)	88	90	89	0.67[a]
Immunosuppressive drugs (%)	42.2	36	43	0.92[a]
Cyclophosphamide (%)	3	3	3	0.72[a]
Mycophenolate mofetil (%)	25	18	29	0.25[a]
Azathioprine (%)	7	3	7	0.69[a]
Cyclosporine (%)	5	6	5	0.84[a]
Methotrexate (%)	3	4	2	0.67[a]
Fibromyalgia (%)	15	11	13	0.25[a]

Results were expressed in mean ± standard deviation (SD). SLE: systemic lupus erythematosus; *ECLAM: European Consensus Lupus Activity Measurement; SLICC = System Lupus International Collaborating Clinics/ACR Damage Index for Systemic Lupus Erythematosus*, [a]*Mann-Whitney U*/Wilcoxon test for non-normally distributed variables, [b]$p<0.05$.

Perceived stress and coping strategies

PSS scores were significantly higher in SLE patients with insomnia symptoms in comparison to those without insomnia symptoms ($p=0.001$) (Table 3).

Participants with insomnia symptoms reported more use of behavioral disengagement (2.7 ± 1.2 vs 2.3 ± 0.7, $p=0.04$), self-blame (5.6 ± 1.8 vs 4.8 ± 1.6, $p=0.02$) and emotional-focused strategies (22.9 ± 2.8 vs 20.8 ± 2.8, $p=0.001$) than participants without insomnia symptoms (see Table 3).

Determinants of perceived stress

In the univariate analysis perceived stress (PSS score) was significantly related to insomnia severity ($p<0.001$), sleep quality ($p<0.001$) and depressive symptoms ($p<0.02$) (Table 4). It was not related to education level ($p=0.10$), employment status ($p=0.22$), SLE duration ($p=0.20$), neurologic involvement ($p=0.50$), renal involvement ($p=0.64$), ECLAM index ($p=0.49$) or SLICC index ($p=0.41$). In the multiple linear regression analysis, including renal involvement, according

Table 2 Sleep and psychological characteristics of the study population

	Overall	*No insomnia symptoms*	*With insomnia symptoms*	p *value*
ISI score	8.9 ± 5.0	5 (0–7)	10 (8–14)	0.001[a,c]
PSQI score	7.5 ± 3.9	4 (4–5)	8 (6–13)	0.001[a,c]
PSQI SL > 30 minutes		11.4%	29.8%	0.02[a,b]
PSQI SD < 6 hours		14.2%	49.1%	<0.001[a,c]
PSQI SE < 85%		25.7%	4.9%	0.01[a,b]
PSQI USM		2%	15.7%	0.006[a,c]
SAS score	31.6 ± 14	20 (20–32)	20 (20–20)	0.07[a]
BDI score	5.6 ± 7.3	1 (0–3)	5 (1–13)	0.001[a,c]

Results of the overall sample are expressed mean ± standard deviation, while values for subgroups based on the presence of insomnia symptoms are expressed as median (25%–75%). *ISI: Insomnia Severity Index; PSQI: Pittsburgh Sleep Quality Index; PSQI subscales: SL: Sleep Latency; SD: Sleep Duration; SE: Sleep Efficiency; USM: use of sleep medication; SAS: Self-Rating Anxiety Scale; BDI: Beck Depression Inventory*. [a]*Mann-Whitney U*/Wilcoxon test for non-normally distributed variables. Significance: [b]$p < 0.05$, [c]$p < 0.001$.

Table 3 Perceived stress scale and Brief COPE scores

	Overall	*No insomnia symptoms*	*With insomnia symptoms*	p *value*
Perceived Stress Scale score	17.4 ± 4.8	12 (10–17)	19 (17–22)	0.001[a,c]
Brief COPE subscales				
Positive reframing	5.2 ± 1.5	5.4 ± 2.1	5.4 ± 1	0.83
Self-distraction	4.5 ± 1.3	4.6 ± 1.2	4.0 ± 1.3	0.92
Venting	5.4 ± 2.3	5.2 ± 1.8	5.6 ± 1.7	0.43[a]
Use of instrumental support	5.4 ± 2.3	5.5 ± 2.1	5.4 ± 2.3	0.56
Active coping	7.2 ± 1.4	7.1 ± 1.5	7.4 ± 0.9	0.23
Denial	2.2 ± 0.7	2.2 ± 0.7	2.2 ± 0.8	0.24
Religion	4.6 ± 2.5	5. ± 2.1	4.3 ± 2.6	0.47
Humor	4.2 ± 1.7	4.2 ± 1.7	4.3 ± 1.8	0.82
Behavioral disengagement	2.5 ± 1.1	2.3 ± 0.7	2.7 ± 1.2	0.04[b]
Use of emotional support	5.3 ± 2.4	5.5 ± 2.4	5.0 ± 2.3	0.33
Substance use	2.0 ± 0.1	2.0 ± 0.1	2.0 ± 0.0	0.19[a]
Acceptance	7.2 ± 2.0	7.2 ± 1.4	7.2 ± 1.2	0.94
Planning	7.3 ± 1.1	7.3 ± 1.0	7.1 ± 1.4	0.29
Self-blame	5.3 ± 1.8	4.8 ± 1.6	5.6 ± 1.8	0.02[b]
Emotion-focused	22.1 ± 2.9	20.8 ± 2.8	22.9 ± 2.8	0.001[c]
Problem-focused	46.8 ± 8.7	45.8 ± 7.7	46.5 ± 9.1	0.25

Results were expressed in mean ± standard deviation-SD and as median (25%–75%). [a]*Mann-Whitney U*/Wilcoxon test for non-normally distributed variables. Significance: [b]$p < 0.05$, [c]$p < 0.001$.

to the ISI, PSQI, and BDI, only insomnia symptoms ($p = 0.008$) (Figure 1, Table 4) were significantly associated with higher perceived stress (Table 4).

Table 4 Determinants of perceived stress

	Univariate linear regression		*Multiple linear regression*	
PSS	*Coeff*	p *value*	*Coeff*	p *value*
Education	0.16	0.10	–	–
Employment status	0.09	0.22	–	–
SLE duration	0.07	0.20	–	–
Neurologic involvement	0.01	0.50	–	–
Renal involvement	0.40	0.64	–	–
ECLAM	0.20	0.49	–	–
SLICC	0.30	0.41	–	–
ISI	0.49	<0.0001[b]	0.34	0.008[b]
PSQI	0.62	<0.0001[b]	0.23	0.17
SAS	−0.04	0.16		
BDI	0.25	0.02[a]	0.08	0.38

Results of the univariate linear regression and of the multiple linear regression model with Perceived Stress Scale (PSS) *as a dependent variable and the other clinical, sleep and* psychological *variables as independent variables. SLE: systemic lupus erythematosus*; ECLAM: European Consensus Lupus Activity Measurement; SLICC: System Lupus International Collaborating Clinics/American College of Rheumatology (ACR) Damage Index for Systemic Lupus Erythematosus; *ISI: Insomnia Severity Index; PSQI: Pittsburgh Sleep Quality Index; SAS: Self-Rating Anxiety Scale; BDI: Beck Depression Inventory*. Significant correlations: [a]$p < 0.05$, [b]$p < 0.01$.

Determinants of coping strategies

In the univariate analysis behavioral disengagement was significantly related to insomnia severity ($p = 0.01$), sleep quality ($p = 0.003$) and depressive symptoms ($p = 0.01$). In the multiple linear regression analysis including ISI, PSQI, and BDI, the only independent determinant of behavioral disengagement was poor sleep quality ($p = 0.01$) (Table 5).

In the univariate analysis the use of self-blame was positively related to insomnia severity ($p = 0.006$) and poor sleep quality ($p = 0.05$) (Table 5). In the multiple linear regression analysis including ISI and PSQI, insomnia severity ($p = 0.04$) was the only determinant of the use of self-blame.

In the univariate analysis the use of emotional-focused coping strategies was related to insomnia severity ($p = 0.01$), poor sleep quality ($p = 0.002$) and perceived stress ($p = 0.03$). In the multiple linear regression analysis including ISI, PSQI and PSS, poor sleep quality ($p = 0.04$) was the only determinant of the use of self-blame (Table 5).

Discussion

The present study investigated the perceived stress and coping strategies in patients with SLE according to the presence or absence of insomnia

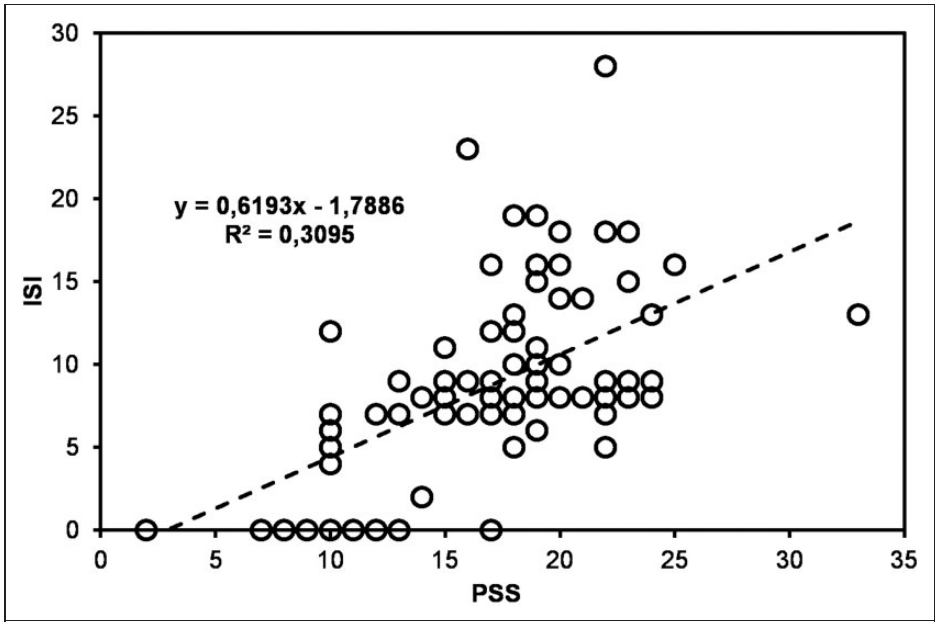

Figure 1 Scatter plot representing the correlation between Perceived Stress Score (PSS) and insomnia severity in SLE. SLE: systemic lupus erythematosus; ISI: Insomnia Severity Index.

symptoms. The main finding of the study was that SLE patients with insomnia symptoms showed increased perceived stress, less-effective coping strategies, and higher rates of psychiatric symptoms, especially depressive symptoms, compared to SLE patients with no insomnia symptoms. Although in the present study a cause-effect relationship cannot be established because of its cross-sectional nature, we may hypothesize insomnia symptoms play a role in the perception of stress in SLE and, indirectly, in coping strategies in SLE.

Insomnia symptoms were frequent in patients with SLE, afflicting 63% of the sample, thus confirming previous findings showing disturbed sleep to be common in SLE patients.[18,20–22]

Interestingly, these patients showed more frequently a renal involvement, compared to SLE patients with no insomnia symptoms. It is well established that chronic kidney disease is associated per se with a variety of sleep disorders.[52,53] However, renal damage could simply reflect a greater degree of disease severity in SLE patients with insomnia symptoms. We may hypothesize insomnia symptoms to play a role in disease severity as it was previously hypothesized or, conversely, we may hypothesize that patients with more severe disease could be at higher risk for insomnia.[18,20]

Longitudinal design studies may examine if SLE individuals with symptoms of insomnia who receive sleep interventions may require less medications or may improve disease severity compared to those who do not receive sleep interventions.

Individuals with insomnia symptoms showed higher levels of comorbid psychiatric symptoms especially depressive symptoms as seen previously in other studies.[20,21,29] The presence of insomnia symptoms may thus be associated with high levels of depressive symptoms in SLE patients: depression is a very common complaint and it is included in the SLE neuropsychiatric manifestations.[3,54] This finding was expected as insomnia is considered a risk factor for depression[39,55] and insomnia and depression have been shown to be in a causal bidirectional relationship.[56,57] Based on this point of view, sleep interventions may be required in SLE patients in order to favor depressive symptom prevention and treatment.

Patients with insomnia symptoms showed a higher level of perceived stress than non-insomniacs, which may be related to the presence of insomnia symptoms. This finding may suggest that SLE individuals with symptoms of insomnia are more likely to perceive challenging events as stressful. This is in line with previous studies regarding patients with insomnia showing high level of perceived stress.[58–60] This is an important issue as high perceived stress has been related to flares in SLE[10] and numerous studies have demonstrated the associations between daily stress and SLE disease exacerbation.[7,8,10,11,23,24]

Table 5 Determinants of coping strategies

	Univariate linear regression		*Multiple linear regression*	
Behavioral disengagement	*Coeff*	p *value*	*Coeff*	p *value*
ISI	*0.05*	0.01[a]	0.06	0.08
PSQI	0.08	0.003[b]	0.07	0.01[a]
SAS	0.04	0.08	–	
BDI	0.03	0.01[a]	0.02	0.06
PSS	0.04	0.09	–	
Self-Blame	Coeff.	p-value	Coeff.	p-value
ISI	*0.090*	0.006[b]	*0.11*	0.04[a]
PSQI	0.093	0.05[a]	0.20	0.77
SAS	−0.007	0.59	–	–
BDI	−0.003	0.91	–	–
PSS	−0.06	0.12	–	–
Emotional focused coping	Coeff	*p* value	Coeff	*p* value
ISI	0.18	0.01[a]	0.10	0.28
PSQI	*0.24*	0.002[b]	0.18	0.04[a]
SAS	*0.01*	0.57	–	
BDI	0.03	0.39	–	
PSS	0.16	0.03[a]	0.07	0.36

Results of the univariate linear regression analysis and the multiple linear regression with coping strategies considered as dependent variables *and the other sleep and* psychological *variables as independent variables*. *ISI: Insomnia Severity Index; PSQI: Pittsburgh Sleep Quality Index; SAS: Self-Rating Anxiety Scale; BDI: Beck Depression Inventory; PSS: Perceived Stress Scale*. Significant correlations: [a]$p < 0.05$, [b]$p < 0.01$.

Possible mechanisms accounting for such an association were beyond the aim of our study.

However, these results may be consistent with the hypothesis that the condition of sleep loss might act as a neurobiologic stressor leading to sympathetic nervous system and hypothalamus-pituitary-adrenal axis over-activation and pro-inflammatory responses.[28] Pathophysiological mechanisms such as the over-activation (or "hyperarousal") of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis described in insomnia[25–27] may be involved in modulating stress perception in SLE patients with insomnia. A longitudinal study design should establish in this kind of patients the cause-effect relationship among insomnia symptoms and appraisal of stress.

Another important aspect of the present study is that patients with comorbid insomnia symptoms and SLE also exhibited less-effective coping strategies, such as disengaging coping or emotional-focused coping. Particularly, SLE patients with insomnia symptoms showed a higher use of behavioral disengagement, which is a coping style that has previously been described in individuals with insomnia.[60] In this SLE sample the use of behavioral disengagement was related to poor sleep quality, thus confirming previous observations in insomnia patients.

Self-blame was another disengaging coping strategy observed in this group of SLE patients with insomnia symptoms, and was related to poor sleep related to insomnia severity. In previous research the use of self-blame has been related to poor psychosocial adjustment to the chronic illness and to poorer functional status in SLE, thus resulting in particularly maladaptive behavior in SLE.[61–63]

Individuals with insomnia symptoms also showed a higher use of emotional-focused coping strategies. Emotion-focused coping has also been associated with poor adjustment to the chronic illness and increased levels of depression in rheumatologic disorders[61,62] including SLE,[9] resulting thus in maladaptive behavior in SLE.

Although a cause-effect relationship cannot be established, we may hypothesize insomnia symptoms to play a role in the appraisal of stress and, in turn, to negatively influence coping strategies in SLE. As previously seen, the course of the disease and the mental well-being of SLE patients may be influenced by the kinds of coping strategy engaged, thus the main implication of these results reinforces the idea that insomnia symptoms should be an important target of treatment in SLE patients.

In conclusion, this study suggests that insomnia symptoms are frequent in SLE individuals. Insomnia symptoms may contribute to disease severity and to higher levels of neuropsychiatric manifestations, especially depression. SLE individuals with insomnia symptoms showed high levels of perceived stress in conjunction with more frequent use of disengaging and emotional-focused coping strategies that were related to insomnia severity and poor sleep quality. These data suggest that individuals with comorbid SLE and insomnia symptoms may be at higher risk for further negative health outcomes, and may therefore require additional interventions for insomnia. These results may confirm the hypothesis according to which conditions of sleep loss might act as a neurobiologic stressor per se, leading to sympathetic nervous system and hypothalamus-pituitary-adrenal axis overactivation and pro-inflammatory responses.[28] Prevention and treatment of insomnia symptoms should receive attention in patients with SLE, since insomnia treatments may be relevant for reducing SLE severity including neuropsychiatric manifestations, and may be involved in the perception of stress and in the coping strategies engage in by SLE patients.

We should acknowledge several limitations of the study. The study employed a cross-sectional

design, so the cause-effect relationship between variables cannot be established.

Future studies should employ a longitudinal design and should incorporate clinical methods designed to treat insomnia symptoms. Other limitations include the small sample size and the fact that patients were selected from a single SLE center: future studies should be designed to include multiple SLE centers in order to select greater samples of SLE patients. In addition the present study did not evaluate a control group: the inclusion of a control group of individuals with another chronic disorder may be useful in order to understand if the presence of insomnia symptoms may affect in the same way individuals with SLE or patients with other chronic disease. Further studies should also include patients with other sleep disorders, such as obstructive sleep apnea syndrome, in order to generalize these findings.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1 D'Cruz DP, Khamashta MA, Hughes GR. Systemic lupus erythematosus. *Lancet* 2007; 369: 587–596.
2 Agmon-Levin N, Mosca M, Petri M, Shoenfeld Y. Systemic lupus erythematosus one disease or many? *Autoimmun* 2012; 11: 593–595.
3 Palagini L, Mosca M, Tani C, Gemignani A, Mauri M, Bombardieri S. Depression and systemic lupus erythematosus: A systematic review. *Lupus* 2013; 22: 409–416.
4 Mosca M, Govoni M, Tomietto P, *et al*. The development of a simple questionnaire to screen patients with SLE for the presence of neuropsychiatric symptoms in routine clinical practice. *Lupus* 2011; 20: 485–492.
5 Turchetti G, Yazdany J, Palla I, Yelin E, Mosca M. Systemic lupus erythematosus and the economic perspective: A systematic literature review and points to consider. *Clin Exp Rheumatol* 2012; 30: 116–122.
6 Trager J, Ward MM. Mortality and causes of death in systemic lupus erythematosus. *Curr Opin Rheumatol* 2007; 13: 345–351.
7 Da Costa D, Dobkin PL, Pinard L, *et al*. The role of stress in functional disability among women with systemic lupus erythematosus: A prospective study. *Arthritis Care Res* 1999; 12: 112–119.
8 Pawlak CR, Witte T, Heiken H, *et al*. Flares in patients with systemic lupus erythematosus are associated with daily psychological stress. *Psychother Psychosom* 2003; 72: 159–165.
9 Kozora E, Ellison MC, Waxmonsky JA, Wamboldt FS, Patterson TL. Major life stress, coping styles, and social support in relation to psychological distress in patients with systemic lupus erythematosus. *Lupus* 2005; 14: 363–372.
10 Birmingham DJ, Nagaraja HN, Rovin BH, *et al*. Fluctuation in self-perceived stress and increased risk of flare in patients with lupus nephritis carrying the serotonin receptor 1A –1019 G allele. *Arthritis Rheum* 2006; 54: 3291–3299.
11 Bricou O, Taieb O, Baubet T, Gal B, Guillevin L, Moro MR. Stress and coping strategies in systemic lupus erythematosus: A review. *Neuroimmunomodulation* 2006; 13: 283–293.
12 Vos T, Flaxman AD, Naghavi M, *et al*. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: A systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; 380: 2163–2219.
13 Knutson KL. Does inadequate sleep play a role in vulnerability to obesity? *Am J Hum Biol* 2012; 24: 361–371.
14 Riemann D, Baglioni C, Spiegelhalder K. Lack of sleep and insomnia. Impact on somatic and mental health [article in German]. *Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz* 2011; 54: 1296–1302.
15 Abad VC, Sarinas PS, Guilleminault C. Sleep and rheumatologic disorders. *Sleep Med Rev* 2008; 12: 211–228.
16 Fernandez-Mendoza J, Vgontzas AN. Insomnia and its impact on physical and mental health. *Curr Psychiatry Rep* 2013; 15: 418.
17 Palagini L, Bruno RM, Gemignani A, Baglioni C, Ghiadoni L, Riemann D. Sleep loss and hypertension: A systematic review. *Curr Pharm Des* 2013; 19: 2409–2419.
18 Palagini L, Tani C, Mauri M, *et al*. Sleep disorders and systemic lupus erythematosus. *Lupus* 2014; 23: 115–123.
19 Riemann D, Nissen C, Palagini L, Otte A, Perlis ML, Spiegelhalder K. The neurobiology, investigation, and treatment of chronic insomnia. *Lancet Neurol* 2015; 14: 547–558.
20 Palagini L, Tani C, Bruno RM, *et al*. Poor sleep quality in systemic lupus erythematosus: Does it depend on depressive symptoms? *Lupus* 2014; 23: 1350–1357.
21 Costa DD, Bernatsky S, Dritsa M, *et al*. Determinants of sleep quality in women with systemic lupus erythematosus. *Arthritis Rheum* 2005; 53: 272–278.
22 Vina ER, Green SL, Trivedi T, Kwoh CK, Utset TO. Correlates of sleep abnormalities in systemic lupus: A cross-sectional survey in an urban, academic center. *J Clin Rheumatol* 2013; 19: 7–13.
23 Wekking EM, Vingerhoets AJ, van Dam AP, Nossent JC, Swaak AJ. Daily stressors and systemic lupus erythematosus: A longitudinal analysis—first findings. *Psychother Psychosom* 1991; 55: 108–113.
24 Peralta-Ramírez M, Jiménez-Alonso J, Godoy-García JF, Perez-García M Group Lupus Virgen de las Nieves. The effects of daily stress and stressful life events on the clinical symptomatology of patients with lupus erythematosus. *Psychosom Med* 2004; 66: 788–794.
25 Bonnet MH, Arand DL. Hyperarousal and insomnia: State of the science. *Sleep Med Rev* 2010; 14: 9–15.
26 Riemann D, Spiegelhalder K, Feige B, *et al*. The hyperarousal model of insomnia: A review of the concept and its evidence. *Sleep Med Rev* 2010; 14: 19–31.
27 Roehrs T, Gumenyuk V, Drake C, Roth T. Physiological correlates of insomnia. *Curr Top Behav Neurosci* 2014; 21: 277–290.
28 Meerlo P, Sgoifo A, Suchecki D. Restricted and disrupted sleep: Effects on autonomic function, neuroendocrine stress systems and stress responsivity. *Sleep Med Rev* 2008; 12: 197–210.
29 McKinley PS, Ouellette SC, Winkel GH. The contributions of disease activity, sleep patterns, and depression to fatigue in systemic lupus erythematosus. *Arthritis Rheum* 1995; 38: 826–834.
30 Lazarus RS. Toward better research on stress and coping. *Am Psychol* 2000; 55: 665–673.
31 Cummings EM, Greene AL, Karraker KH. (eds). *Life-span developmental psychology: Perspectives on stress and coping*. Hillsdale, NJ. Lawrence Erlbaum Associates, 1991.
32 Carver CS. You want to measure coping but your protocol's too long: Consider the Brief COPE. *Int J Behav Med* 1997; 4: 92–100.

33 Penley JA, Tomaka J, Wiebe JS. The association of coping to physical and psychological health outcomes: A meta-analytic review. *J Behav Med* 2002; 25: 551–603.
34 Holahan CJ, Moos RH. Risk, resistance, and psychological distress: A longitudinal analysis with adults and children. *J Abnorm Psychol* 1987; 96: 3–13.
35 Adams SG, Dammers PM, Saia TL, Brantley P, Gaydos GR. Stress, depression, and anxiety predict average symptom severity and daily symptom fluctuation in systemic lupus erythematosus. *J Behav Med* 1994; 17: 459–477.
36 McCracken LM, Semenchuk EM, Goetsch VL. Cross-sectional and longitudinal analyses of coping responses and health status in persons with systemic lupus erythematosus. *Behav Med* 1995; 20: 179–187.
37 Dobkin PL, Fortin PR, Joseph L, Esdaile JM, Danoff DS, Clarke AE. Psychosocial contributors to mental and physical health in patients with systemic lupus erythematosus. *Arthritis Care Res* 1998; 11: 23–31.
38 Herrmann M, Schölmerich J, Straub RH. Stress and rheumatic diseases. *Rheum Dis Clin North Am* 2000; 26: 737–763.
39 Baglioni C, Battagliese G, Feige B, *et al*. Insomnia as a predictor of depression: A meta-analytic evaluation of longitudinal epidemiological studies. *J Affect Disord* 2011; 135: 10–19.
40 Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; 40: 1725.
41 American Academy of Sleep Medicine. *International classification of sleep disorders—third edition*. (ICSD-3). Chicago: American Academy of Sleep Medicine, 2014.
42 Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Res* 1989; 28: 193–213.
43 The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. *Arthritis Rheum* 1999; 42: 599–608.
44 Mosca M, Bencivelli W, Vitali C, Carrai P, Neri R, Bombardieri S. The validity of the ECLAM index for the retrospective evaluation of disease activity in systemic lupus erythematosus. *Lupus* 2000; 9: 445–450.
45 Gladman DD, Urowitz MB, Goldsmith CH, *et al*. The reliability of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index in patients with systemic lupus erythematosus. *Arthritis Rheum* 1997; 40: 809–813.
46 Morin CM. *Insomnia: Psychological assessment and management*. New York: Guilford Press, 1993.
47 Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav* 1983; 24: 385–396.
48 Tuncay T, Musabak I, Gok DE, Kutlu M. The relationship between anxiety, coping strategies and characteristics of patients with diabetes. *Health Qual Life Outcomes* 2008; 6: 79.
49 Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* 1961; 4: 561–571.
50 Zung WW. A rating instrument for anxiety disorders. *Psychosomatics* 1971; 12: 371–379.
51 NCSS Statistical Software. Kaysville, Utah, USA, 2008.
52 Gusbeth-Tatomir P, Boisteanu D, Seica A, Buga C, Covic A. Sleep disorders: A systematic review of an emerging major clinical issue in renal patients. *Int Urol Nephrol* 2007; 39: 1217–1226.
53 Pierratos A, Hanly PJ. Sleep disorders over the full range of chronic kidney disease. *Blood Purif* 2011; 31: 146–150.
54 Mosca M, Govoni M, Tomietto P, *et al*. The development of a simple questionnaire to screen patients with SLE for the presence of neuropsychiatric symptoms in routine clinical practice. *Lupus* 2011; 20: 485–492.
55 Meerlo P, Havekes R, Steiger A. Chronically restricted or disrupted sleep as a causal factor in the development of depression. *Curr Top Behav Neurosci* 2015; 25: 459–481.
56 Harvey AG. Insomnia, psychiatric disorders, and the transdiagnostic perspective. *Curr Dir Psychol Sci* 2008; 17: 299–303.
57 Sivertsen B, Salo P, Mykletun A, *et al*. The bidirectional association between depression and insomnia: The HUNT study. *Psychosom Med* 2012; 74: 758–765.
58 Friedman L, Brooks JO 3rd, Bliwise DL, Yesavage JA, Wicks DS. Perceptions of life stress and chronic insomnia in older adults. *Psychol Aging* 1995; 10: 352–357.
59 Morin CM, Rodrigue S, Ivers H. Role of stress, arousal, and coping skills in primary insomnia. *Psychosom Med* 2003; 65: 259–267.
60 Pillai V, Roth T, Mullins HM, Drake CL. Moderators and mediators of the relationship between stress and insomnia: Stressor chronicity, cognitive intrusion, and coping behavior. *Sleep* 2014; 37: 1199–1208.
61 Felton BJ, Revenson TA, Hinrichesen GA. Stress and coping in the explanation of psychological adjustment among chronically ill adults. *Soc Sci Med* 1984; 18: 889–898.
62 Bombardier CH, D'Amico C, Jordan JS. The relationship of appraisal and coping to chronic illness adjustment. *Behav Res Ther* 1990; 28: 297–304.
63 Manne SL, Zautra AJ. Couples coping with chronic illness: Women with rheumatoid arthritis and their healthy husbands. *J Behav Med* 1990; 13: 327–342.