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Depression and anxiety in systemic lupus erythematosus
The crosstalk between immunological, clinical, and psychosocial factors

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Abstract

Depression and anxiety cause severe loss of quality of life for patients with systemic lupus erythematosus. The causes and factors that contribute to these psychological manifestations in lupus are difficult to disentangle. This study compared clinical, psychological, and demographic factors between lupus patients, depressed patients, and rheumatoid arthritis patients to discover lupus-specific contributors to depression. Lupus-specific manifestations of depression were also investigated.

Physiological, clinical, and psychosocial data were collected from 77 patients. ELISA was used to measure cytokine levels. Univariate and Multivariate analyses were used to compare the patient populations and identify correlations between key physical and psychological indicators.

The prevalence of depression in the SLE cohort was 6 times greater than the healthy control subjects. Pain, IL-6, and Pittsburgh Sleep Quality index values were all significantly higher in SLE patients compared with the healthy control group ($P < .001$, $P = .038$, and $P = .005$, respectively). Anxiety levels were significantly higher in SLE patients compared to healthy and RA control patients ($P = .020$ and .011, respectively). Serum IL-10 concentrations, relationship assessment scale, and fatigue severity scale values were found to be correlated with depression among the SLE patients ($P = .036$, $P = .007$, and $P = .001$, respectively). Relationship assessment and fatigue severity scale scores were found to be the best indicators of depression for the SLE patients ($P = .042$ and .028, respectively).

Fatigue Severity, relationship satisfaction, and IL-10 concentrations are indicators of depression in lupus patients. Despite also suffering from the pain and disability that accompanies chronic autoimmune disease, the rheumatoid arthritis patients had less anxiety and better relationship scores.

Abbreviations: CRP = C-reactive protein, EPE = Ethical Committee, ESR = erythrocyte sedimentation rate, FSS = Fatigue Severity Scale, HADS = Hospital Anxiety and Depression Scale, IL = interleukin, PSQI = Pittsburgh Sleep Quality Index, RA = rheumatoid arthritis, RAS = Relationship Assessment Scale, SF-36 = Medical Outcomes Study Questionnaire Short Form 36 Health Survey, SLE = systemic lupus erythematosus, Th = T-helper, TNF = tumor necrosis factor.

Keywords: depression, IL-10, lupus, rheumatoid arthritis

1. Introduction

Systemic lupus erythematosus (SLE) is a common autoimmune disease afflicting 1 to 12 people per 5000 worldwide.[1]

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Symptoms often include fever, arthritis, fatigue, weight loss, lymphadenopathy, a characteristic "butterfly rash," renal disease and cytopenia, in a pleomorphic clinical presentation. Psychological manifestations such as depression and anxiety are very common. Major depression is present in approximately 25% of lupus patients, and major anxiety in 37%.[2] These presentations are often among the earliest symptoms to manifest in lupus.[3,4] There are mixed results regarding the association between lupus disease activity and depression and anxiety, with some studies showing a connection and others finding no association.[5–9] Several factors have been linked to depression in lupus, including certain autoantibody specificities, neurological damage, presence of rashes, and the concentration of certain cytokines. Socioeconomic status, and factors associated with socioeconomic status, such as reserve capacity and psychological resilience, affect the relationship between depression and anxiety in lupus.[10,11] These diverse findings indicate the depression and anxiety in lupus is likely mediated through a complex mixture of biological, social, economical, and environmental contributors.

Fatigue and pain are frequently rated by SLE patients as having a strong negative effect on quality of life.[12,13] Clinical tests attempting to measure severity of disease fail to satisfactorily correlate with fatigue and pain in SLE patients, making it difficult

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to estimate patient discomfort and subsequently apply appropriate treatments in a timely manner.[7]

SLE is associated with depression, a finding that may result from both the physical effect of the autoimmunity on the nervous system and the suffering due to pain and disability. Many confounding variables exist in the lupus patient population, including age, disease activity, weight, fatigue, sleep, and physical activity. Therefore, it is no simple matter to identify both psychological and physical factors that contribute to the mood disorders in SLE patients.

Lupus is such a heterogeneous disease that even evaluating disease activity is difficult. Lupus patients also tend to have unexpected presentation of inflammatory markers. For example, the C-reactive protein (CRP) levels can be lower than expected with respect to the erythrocyte sedimentation rate (ESR) scores.[14] Both ESR and CRP appear to behave differently when opportunistic infection appears or in the presence of a flare, representing a valuable clinical tool. Inflammatory markers can give insight into clinical disease status, but need to be used in conjunction with other tests and patient history to be effective.[15] Very little is known about the relationship between inflammatory markers and depression in lupus.

Rheumatoid arthritis (RA) is a highly prevalent autoimmune disease, affecting 0.5 to 1% of the population worldwide[16] with an important contribution to global disability.[16] In RA, immune complexes cause local joint inflammation promoting an inflammatory response responsible for severe pain and fatigue.[17] This inflammation also provokes systemic responses, including greater risk for cardiovascular disease.[18] Rheumatoid arthritis is also associated with psychological manifestations, although not to the same extent as lupus. Multiple causes appear to be implicated in RA-associated depression.[19,20] For this work, rheumatoid arthritis patients were used as a control group to understand what aspects of lupus-associated depression and anxiety could be attributed to generalized pain, fatigue, and disability associated with chronic autoimmune disease. This allows us to separate these more general effects common to both diseases from lupus-specific manifestations of psychological distress.

We hypothesized that depression in lupus is not merely caused by the effects of pain and disability associated with autoimmune disease in general, but has aspects that are specific to lupus. To identify these lupus-specific aspects of lupus-associated depression, we compared depression in lupus patients with rheumatoid arthritis patients and with patients with primary depression. We further hypothesize that psychosocial factors, such as education level and marital status, are associated with depression and anxiety in lupus. By identifying the aspects of lupus-associated depression that are specific to lupus, we hope to better understand and potentially treat this quality of life-diminishing aspect of lupus.

2. Methods

2.1. Study patients

This cohort study included 77 total Caucasian patients, 15 patients with systemic lupus erythematosus (SLE), 21 rheumatoid arthritis (RA) patients, 20 healthy control subjects, and 21 otherwise healthy patients seeking treatment for depression (primary depression). All patients were recruited from the same geographic region (northern Portugal). All SLE and RA patients were previously diagnosed according to ACR criteria and followed at an outpatient unit. Diagnosis and stage of disease

activity was established according to the American Rheumatism Association Classification Criteria[21] for Rheumatoid Arthritis and the 1997 American college of Rheumatology criteria for diagnosing SLE. The duration of the disease was measured from the time when the patients first met at least 4 of the classification criteria. These patients were recruited from the Rheumatology service at the time of a clinic visit, and were being treated at the time of the study.

The primary depression subjects were recruited from a group of patients diagnosed with depression by a psychiatrist and undergoing treatment at a private psychiatric clinic.

To eliminate inter-interviewer variation, psychiatric evaluation and psychometric markers were tested by 1 psychiatrist and 1 psychologist to establish the severity of depression. A convenience age-matched sample of healthy women was also recruited. Exclusion criteria comprised history of substance abuse, personality disorders, and/or other major psychopathology than depression. Patients and controls were subsequently interviewed by phone by trained interviewers using the Hospital Anxiety and Depression Scale, as well as other psychosocial instruments described below. The literature corroborates phone interviews as valid and precise tools for psychological data collection.[22]

Participants' socio-demographic data included age, educational level, employment status (active/nonactive), and marital status (Table 1). Laboratory and SLE clinical evaluations were obtained for the SLE and rheumatoid arthritis patients through the clinical records (Table 2). Lab tests included leukocytes (10^9/L), lymphocytes (percentage), platelets (10^9/L), erythrocyte sedimentation rate (mm/h), anti-dsDNA antibody titer (IU/mL), and C-reactive protein level (mg/dL). Serum levels of IL-6 (pg/mL), IL-10 (pg/mL, and TNF-α (pg/mL) were measured using standardized ELISA assays, utilized per manufacturer's instructions (EBiosciences). The confounding variables of physical activity, smoking, and alcohol consumption were also recorded. Further, physical activity was assessed based on involvement in sporting activities.

The study was submitted and approved by the Ethical Committee of the São João Hospital IRB (EPE) in accordance with the Declaration of Helsinki. The nature and the purpose of the study were explained to all participants who signed the informed consent form before they entered the study.

2.2. Psychosocial evaluation

Socio-demographic characterization included age, education measured as years of school, marital status, and socio-economic class evaluation. Psychological evaluations were obtained through a battery of standardized instruments. The Chronbach's alpha for each of these scales is shown in Table 3.

2.2.1. Fatigue severity scale (FSS). The short form of the FSS allows evaluation of self-reported fatigue.[23] The Portuguese version includes 9 items and is recommended as the instrument of choice for research purposes in studies involving patients diagnosed with SLE.[24]

The FSS demonstrates good psychometric properties (Cronbach's α= 0.89 and test–retest reliability 0.84). A final score is obtained from the mean of all scored items, with higher scores revealing higher severity of fatigue. Presence of clinical levels of fatigue was defined by a FSS score >3. The scale has proved to be sensitive to change and reliable for telephone interviewing. The FSS has also been shown to be reliable across different patient populations.[25]

Table 1

Sociodemographic of the study cohort.

Characteristics	All subjects (N=77)	SLE subjects (N=15)	Healthy subjects (N=20)	t value	P value	Depressed subjects (N=21)	t value	P value	RA subjects (N=21)	t value	P value
Sex—no. (%)					.571†			.250†			.062†
Female	67 (87%)	15 (100%)	19 (95%)			18 (86%)			16 (73%)		
Male	10 (13%)	0 (0%)	1 (5%)			3 (14%)			5 (24%)		
Age, mean±SD	48.38±12.17	49±8.21	43.95±11.77	-1.420	.165*	47.81±14.8	−0.281	.780*	52.71±11.17	1.092	.282*
Education Lvl (yr)±SD	9.73±4.8	7.6±3.98	13.5±3.15	4.897	<.001*	9.76±4.36	1.521	.138*	7.62±5.08	0.012	.990*
Education Lvl—no. (%)					<.001†			.264†			.229†
Primary (<4 yrs)	17 (22%)	4 (27%)	0 (0%)			4 (19%)			9 (43%)		
Middle school (4 < 12 yrs)	17 (22%)	7 (47%)	1 (5%)			4 (19%)			5 (24%)		
High school (12<14 yrs)	10 (13%)	1 (7%)	2 (10%)			5 (24%)			2 (10%)		
College (14 ≤ 18 yrs)	33 (43%)	3 (2%)	17 (85%)			8 (38%)			5 (24%)		
Marital status—no. (%)					.123†			.495†			.818†
Unmarried	17 (22%)	2 (13%)	8 (40%)			5 (24%)			2 (10%)		
Married	50 (65%)	12 (80%)	8 (40%)			13 (62%)			16 (76%)		
Divorced	8 (10%)	1 (7%)	4 (20%)			1 (5%)			2 (10%)		
Widowed	3 (4%)	0 (0%)	0 (0%)			2 (10%)			1 (5%)		
Unemployed—no. (%)					.044†			.175†			.482†
Yes	38 (49%)	10 (67%)	6 (30%)			8 (38%)			14 (67%)		
No	39 (51%)	5 (33%)	14 (70%)			13 (62%)			7 (33%)		

SLE = systemic lupus erythematosus, RA = rheumatoid arthritis.

* Independent samples t test.

† Fisher exact χ^2 test.

2.2.2. Hospital anxiety and depression scale (HADS).

The Hospital Anxiety and Depression Scale (HADS) is a self-rating scale with good psychometric properties (Cronbach's alpha coefficients of 0.94), designed to measure anxiety and depression in physically ill individuals.[26] Translated and adapted for Portugal,[27] it is subdivided in 2 subscales of 7 items that independently measure anxiety and depression. The partial result of each scale varies between 0 and 21. Scores ranging from 8 to 10 are considered mild, from 11 to 14 moderate, and 15 to 21 severe[28] and the authors suggest 8 as the cutoff point, considering values below as indicating the absence of anxiety and depression.[26] It is important to note that the scale is indicative of depressive symptoms in the last week, and not necessarily clinical depression. As such, it is a measure that evaluates current symptoms that are commonly present during major depressive episodes; however, it does not delineate specifics for the diagnosis of a major depressive episode. The score can change over time even in depressed individuals.

2.2.3. Pittsburgh sleep quality index (PSQI).

This instrument presents good psychometric properties, with high reliability (Cronbach's alpha=0.83) and validity. The 7 components evaluated: sleep latency, sleep disturbances, sleep duration, sleep quality, sleep efficiency, use of sleep medications and daytime dysfunction allow the gathering of a global score varying from 0 to 21.[29] The PSQI is reliable for sleep quality assessment in telephone interviews and permits the identification of poor sleepers (score > 5).[30] A higher PSQI indicates a lower quality of sleep whereas a higher quality of sleep is indicated by lower scores. Normal PSQIs are reported being anywhere between 0 and 5. Any index above 5 indicates poor sleep quality for the patient.

2.2.4. Relationship assessment scale (RAS).

The RAS[31] (Portuguese experimental version from Mesquita, Barbosa, & Figueiredo-Braga, 2014) is a 7-item instrument, with a 5-point scale that measures general satisfaction with the relationship.

2.2.5. Medical Outcomes Study Questionnaire Short Form 36 Health Survey (SF-36).

The SF-36,[32] Portuguese version,[33] is a 36-item questionnaire that measures functional health and well-being in 8 domains: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health, and reported health transition. The instrument allows a score for each domain, as well as a global score. Higher scores indicate better health.

2.3. Statistical analysis

Significant differences in the demographical, clinical, and psychological variables between the SLE subjects, healthy controls, RA subjects, and primary depression subjects were determined using the independent t-test, Fisher exact χ^2, Mann–Whitney U, Wilcoxon rank sum, or Welch tests when considered appropriate. Fishers exact χ^2 was used in place of the standard χ^2 test, which would typically be utilized, due to the smaller sample size of the groups compared. The statistical test used for the comparisons is indicated in the table legends.

Univariate analysis was accomplished by using generalized linear regression with HADS depression scores as the dependent variable and the individual variable suspected of showing a correlation to depression as the independent variable.

2.4. Multivariate analysis

Multivariate analysis was performed using a generalized linear model on all variables examined in the study with the exception of socioeconomic status, age, and anxiety. The best fit model was determined using the model with the appropriate number of variables (less than or equal to 2 variables due to the small SLE

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Table 2

Univariate analysis of the study cohorts.

SLE subject cohort [SLE HADS depression ~ SLE characteristic]

Characteristics	Psuedo R²	AICc	Coefficient	Odds ratio (95% CI)	P value
Disease duration (yrs), mean ± SD	0.008	99.73	0.004	1.00 (0.98–1.03)	.736
Body mass index, mean ± SD	0.142	97.55	0.016	1.02 (1.00–1.04)	.116
Pain Score, median	0.128	97.79	0.044	1.04 (0.98–1.11)	.161
Sedimentation velocity (mm/h), mean ± SD	0.590	88.46	0.006	1.01 (1.00–1.01)	.197
C-reactive protein (mg/L), mean ± SD	0.603	88.03	0.600	1.82 (0.79–4.06)	.150
Leukocytes (10^9/L), mean ± SD	0.575	88.92	−0.051	0.95 (0.86–1.04)	.294
Lymphocytes (%), mean ± SD	0.588	88.50	−0.017	0.98 (0.96–1.01)	.203
Anti-dsDNA (IU/mL), mean ± SD	0.549	89.70	0.000	1.00 (1.00–1.00)	.565
IL-6 (pg/mL), mean ± SD	0.575	88.92	0.009	0.95 (0.86–1.04)	.680
IL-10 (pg/mL), mean ± SD	0.463	91.22	−0.057	0.94 (0.89–0.99)	.036
TNF-Alpha (pg/mL), mean ± SD	0.380	93.25	−0.002	1.00 (1.00–1.00)	.118
PSQI, mean ± SD	0.056	98.97	0.028	1.03 (0.97–1.09)	.352
Relationship Assessment Scale, mean ± SD	0.926	68.96	−0.064	0.94 (0.89–0.98)	.007
Fatigue Severity Scale, mean ± SD	0.565	87.35	0.273	1.31 (1.13–1.54)	.001

Depressed subject cohort [depressed HADS depression ~ depressed characteristic]

Characteristics	Psuedo R²	AICc	Coefficient	Odds ratio (95% CI)	P value
Body mass index, mean ± SD	0.010	148.14	0.008	1.01 (0.97–1.04)	.659
Pain Score, median	0.630	128.46	0.138	1.15 (1.08–1.22)	<.001
IL-6 (pg/mL), mean ± SD	0.207	143.68	0.064	1.07 (1.01–1.12)	.020
IL-10 (pg/mL), mean ± SD	0.325	140.48	0.014	1.01 (1.00–1.02)	.003
TNF-Alpha (pg/mL), mean ± SD	0.119	145.79	0.002	1.00 (1.00–1.00)	.093
PSQI, mean ± SD	0.249	142.60	0.051	1.05 (1.01–1.10)	.018
Relationship Assessment Scale, mean ± SD	0.999	45.97	−0.084	0.92 (0.87–0.97)	<.001
Fatigue Severity Scale, mean ± SD	0.734	123.24	0.191	1.21 (1.11–1.32)	<.001

RA subject cohort [RA HADS depression ~ RA characteristic]

Characteristics	Psuedo R²	AICc	Coefficent	Odds ratio (95% CI)	P value
Disease duration (yrs), mean ± SD	0.935	117.71	0.011	1.01 (0.99–1.03)	.190
Body mass index, mean ± SD	0.014	119.05	−0.011	0.99 (0.95–1.03)	.634
Pain Score, median	0.516	107.67	0.166	1.18 (1.07–1.31)	.001
Sedimentation velocity (mm/h), mean ± SD	0.452	109.64	0.016	1.02 (1.01–1.02)	<.001
C-reactive protein (mg/L), mean ± SD	0.317	113.18	0.017	1.02 (1.00–1.03)	.006
Leukocytes (10^9/L), mean ± SD	0.006	119.17	−0.008	0.99 (0.94–1.04)	.752
Lymphocytes (%), mean ± SD	0.392	111.33	−0.037	0.96 (0.94–0.99)	.004
Anti-dsDNA (IU/mL), mean ± SD	< 0.001	119.27	0.000	1.00 (1.00–1.00)	.922
IL-6 (pg/mL), mean ± SD	0.988	75.51	0.006	1.01 (0.98–1.03)	.597
IL-10 (pg/mL), mean ± SD	0.994	68.99	0.121	1.13 (1.03–1.23)	.005
TNF-Alpha (pg/mL), mean ± SD	0.988	75.19	0.001	1.00 (1.00–1.00)	.430
PSQI, mean ± SD	< 0.001	119.27	−0.002	1.00 (0.96–1.04)	.929
Relationship Assessment Scale, mean ± SD	0.966	82.71	−0.040	0.96 (0.92–1.01)	.073
Fatigue Severity Scale, mean ± SD	0.677	102.41	0.272	1.31 (1.12–1.56)	.001

SLE = systemic lupus erythematosus, RA = rheumatoid arthritis.

cohort) and the highest pseudo R² value with the lowest approximate AICc value. In the multivariate analysis, the HADS depression score for the SLE subjects was used as the dependent variable. Statistical analysis was performed using the statistical software R and SPSS (IBM). The generalized linear model was used because some of the independent variables used in the model did not have normal distributions, which is typical with the data we are working with. The parameter limits of the best fit model were determined using the model with the appropriate number of variables (less than or equal to 2 dependent variables due to the small SLE cohort) and the highest pseudo R2 value (less than or equal to 0.65) with the lowest approximate AICc value. This model allows for more flexibility when working with the type of distributions demonstrated by variables recorded from our

Table 3

Cronbach alpha for psychosocial assessment data sets.

	SLE	Healthy	Depressed	RA
Hospital Anxiety and Depression Scale	0.883	0.860	0.896	0.796
Pittsburgh Sleep Quality Index	0.745	0.441	0.726	0.872
Relationship Assessment Scale	0.714	0.864	0.789	0.770
Fatigue Severity Scale	0.946	0.897	0.960	0.921

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Table 4

Post hoc power analysis of study cohorts.

Characteristics	Linear regression				T test			
	SLE	Healthy	Depressed	RA	SLE	Healthy	Depressed	RA
Age	N/A	N/A	N/A	N/A	1.000	1.000	0.999	1.000
Education, y	N/A	N/A	N/A	N/A	0.670	1.000	0.975	0.351
Disease Duration	0.930	N/A	N/A	0.886	0.966	N/A	N/A	0.619
BMI	0.932	N/A	0.970	0.884	0.999	1.000	1.000	1.000
Pain	0.932	N/A	0.974	0.897	0.676	0.668	0.928	0.885
SV	0.890	N/A	N/A	0.896	0.030	N/A	N/A	0.069
CRP	0.891	N/A	N/A	0.891	0.069	N/A	N/A	0.090
Leukocytes	0.889	N/A	N/A	0.884	0.999	N/A	N/A	0.596
Lymphocytes	0.890	N/A	N/A	0.894	1.000	N/A	N/A	0.999
Anti-dsDNA Ig	0.888	N/A	N/A	0.884	N/A	N/A	N/A	N/A
IL-6	0.911	N/A	0.971	0.593	0.045	0.076	0.258	0.081
IL-10	0.894	N/A	0.972	0.616	0.393	0.083	0.257	0.232
TNF	0.891	N/A	0.970	0.595	0.151	0.201	0.295	0.139
HADS Depression	N/A	N/A	N/A	N/A	0.610	0.135	0.400	0.058
HADS Anxiety	N/A	N/A	N/A	N/A	0.941	0.922	0.971	0.297
Pittsburgh Sleep Quality Index	0.889	N/A	0.971	0.884	0.978	0.911	0.996	0.206
Relationship Assessment Scale	0.845	N/A	0.445	0.682	1.000	1.000	1.000	1.000
Fatigue Severity Scale	0.903	N/A	0.967	0.872	0.999	0.981	0.865	0.999
Multivariate Model = 0.655								

cohort. An alpha value less than or equal to 0.05 was considered significant in all analysis.

A post-hoc power analysis was performed to test for the likelihood of type 2 errors, in which true correlations are missed due to inadequate sample size. The advantage of a post-hoc power analysis is that it can consider the actual variation seen in the sample, as opposed to a projected variance, and thus provides a realistic analysis. The power analysis revealed a very low probability (nothing less than 0.84) for this type of error in all of the correlation analyses, which were the basis for all of the conclusions drawn in this study (Table 4).

3. Results

The study was comprised of 77 Caucasian men and women with a mean age of 48.38 ± 12.17 years. The sociodemographic information gathered about each cohort is displayed in Table 1. Of the 77 subjects, 15 were diagnosed systemic lupus erythematosus patients, 21 were diagnosed rheumatoid arthritis patients, 20 subjects were healthy controls, and 21 were individuals being treated for depression at a private psychiatric clinic. The lupus patients had an average age of 49 ± 8.21 years. The arthritis patients had an average age of 52.71 ± 11.17 years, while the healthy controls and depressed subjects had a mean of 43.95 ± 11.77 and 47.81 ± 14.8 years, respectively. There is some variability between the mean ages of the groups, but this difference was not found to be statistically significant (Table 1).

The level of education received based on years in school is similar for the SLE, depressed, and RA subjects. However, the healthy control group had a higher percentage of well-educated members ($P < .001$). The distribution of marital status was similar for all the study groups with the majority of subjects currently in a marital relationship. There were some slight differences in employment status between the groups. The distribution between the SLE and RA patients is similar, with 33% of patients from both groups currently employed, while the healthy control and depressed groups had 70% and 62% of the study subjects currently employed, respectively. The differences between the employment

status of the study cohorts were not considered significantly different (Table 1). Although the difference did not reach statistical significance, the finding that only half as many patients with either lupus or rheumatoid arthritis were employed is suggestive of the degree of disability that accompanies these diseases.

3.1. Clinical manifestations

The SLE cohort had a mean disease duration of 17.80 ± 7.32 years, which was similar to the mean duration of disease among the rheumatoid arthritis subjects, 17.57 ± 10.24 (Table 5). The mean body mass index scores were fairly similar for all groups. It is important to note that the potential confounding variables of smoking, drinking, and physical activity are similar between the groups being compared in the study (Table 5). The SLE patients demonstrated higher pain scores on average than all of the other groups, and significantly higher than the healthy control group ($P < .001$). Univariate regression analysis found that none of these characteristics showed direct correlation with depression (Table 2).

The SLE patients did not have elevated levels of sedimentation velocity (mm/h), leukocyte concentrations (10^9/L), or lymphocyte percentage. These measurements were similar between the SLE and RA subjects (Table 5). However, RA patients had elevated levels of CRP compared with the SLE patients ($P = .010$). This has been previously observed when comparing SLE and RA laboratory data.[34] The SLE patients exhibited increased levels of both IL-6 and IL-10 compared with the healthy subjects ($P = .038$ and $P = .016$, respectively) (Fig. 1). While there are some slight differences between the levels of IL-6, IL-10, and TNF-α between the other groups, these differences are not significantly different. Univariate regression analysis demonstrated an inverse correlation between IL-10 levels and depression in the SLE subjects ($P = .036$) (Table 2) (Fig. 2).

3.2. Psychosocial function

The SLE subjects had the highest proportion of individuals with moderate to severe depression of any group. Forty percent of the

Table 5

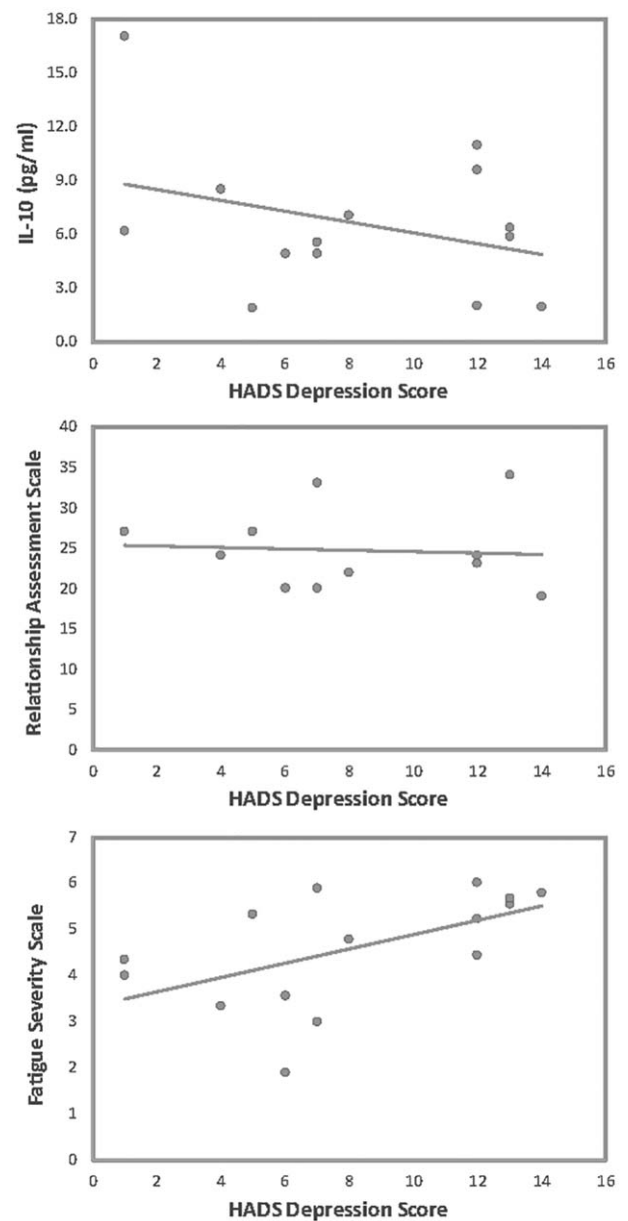### Clinical, laboratory, and psychological characteristics.

Characteristics	All subjects (N=77)	SLE subjects (N=15)	Healthy subjects (N=20)	Odds ratio (95% CI)	SLE and healthy t value	P value	Depressed subjects (N=21)	Odds ratio (95% CI)	SLE and depressed t value	P value	RA subjects (N=21)	Odds ratio (95% CI)	SLE and RA t value	P value
Disease duration (yrs), mean±SD	17.68±4.15	17.80±7.32	N/A			.304*	N/A			.221*	17.57±10.24		0.074	.942*
Body mass index, mean±SD	26.16±5.65	27.89±8.2	25.39±4.71		−1.055		24.94±4.44		−1.264		26.89±5.32		−0.444	.660*
Pain Score (0–10), median	5.0	7.0	0.0			.000‡	5.0			.783‡	5.0			.213‡
Smoking—no. (%) Yes	13 (18%)	1 (7%)	6 (30%)	0.17 (0.02–1.57)		.199†	2 (10%)	0.68 (0.06–8.25)		1.000†	5 (24%)	0.23 (0.02–2.20)		.367†
Drinking—no. (%) Yes	17 (22%)	2 (13%)	5 (25%)	0.46 (0.08–2.79)		.627†	6 (29%)	0.38 (0.07–2.25)		.424†	4 (19%)	0.65 (0.10–4.14)		1.000†
Physically active—no. (%) Yes	32 (42%)	7 (47%)	12 (60%)	0.58 (0.15–2.26)		.506†	8 (38%)	1.42 (0.37–5.45)		.736†	5 (24%)	2.80 (0.67–11.67)		.175†
Laboratory analysis														
Sedimentation velocity (mm/h), mean±SD	17.94±19.1	20.69±20.1	N/A				N/A				15.84±18.64		0.683	.500*
C-reactive protein (mg/L), mean±SD	3.74±10.11	0.27±0.23	N/A				N/A				3.42±4.25		−2.957	.010§
Leukocytes (10^9/L), mean±SD	7.25±3.84	6.3±2.13	N/A				N/A				7.97±4.7		−1.303	.205§
Lymphocytes (%), mean±SD	26.95±7.81	29.05±6.77	N/A				N/A				25.34±8.35		1.303	.203*
Anti-dsDNA (IU/mL), mean±SD	N/A	635.54±1504.14	N/A				N/A				N/A			
IL-6 (pg/mL), mean±SD	3.25±6.36	3.74±4.16	1.11±1.34			.038§	1.30±2.23			.060§	10.48±12.76			.137§
IL-10 (pg/mL), mean±SD	6.06±9.71	6.62±4.04	3.07±3.77			.016*	9.18±15.66			.482§	4.12±2.97			.112*
TNF-Alpha (pg/mL), mean±SD	56.25±95.73	73.52±113.25	33.77±53.08			.241§	38.44±69.75			.264*	109.92±151.85			.507*
Psychosocial assessments														
HADS Depression Score, mean±SD	6.32±4.70	8.07±4.37	4.15±3.25			.007‡	8.2±5.33			.947‡	5.06±4.51			.081†
Depression groups—no. (%)						.046†				.736†				.122†
low (HADS <8)	58 (75%)	9 (60%)	18 (90%)	0.17 (0.03–1.00)			14 (67%)	0.75 (0.19–2.97)			17 (81%)	0.35 (0.08–1.58)		
high (HADS ≥ 8)	19 (25%)	6 (40%)	2 (10%)	6.00 (1.00–35.90)			7 (33%)	1.33 (0.34–5.27)			4 (19%)	2.83 (0.63–12.71)		
HADS Anxiety Score, mean±SD	8.57±4.50	10.93±4.68	7.30±3.48			.020‡	9.58±4.44			.536‡	6.27±4.32			.011‡
Anxiety Groups—no. (%)						.020†				.736†				.025‡
low (HADS<8)	55 (71%)	8 (53%)	17 (85%)	0.20 (0.04–0.99)			12 (57%)	0.86 (0.23–3.25)			18 (86%)	0.19 (0.04–0.93)		
high (HADS ≥ 8)	22 (29%)	7 (47%)	3 (15%)	4.96 (1.01–24.37)			9 (43%)	1.17 (0.31–4.42)			3 (14%)	5.52 (1.07–25.70)		
Pittsburgh Sleep Quality Index, mean±SD	6.32±3.52	7.67±3.06	4.75±2.29			.005‡	6.43±2.60			.300‡	6.76±4.97			.233‡
Pittsburgh Sleep Quality Index, no. (%)						.920†				1.000†				.728†
normal (PSQI ≤ 5)	35 (45%)	5 (33%)	13 (65%)	0.27 (0.07–1.11)			7 (33%)	1.00 (0.25–4.08)			10 (48%)	0.55 (0.14–2.17)		
poor (PSQI ≥ 6)	42 (55%)	10 (67%)	7 (35%)	3.71 (0.90–15.26)			14 (67%)	1.00 (0.25–4.08)			11 (52%)	1.82 (0.46–7.18)		
Relationship Assessment Scale, mean±SD	27.56±5.38	24.75±4.81	28.07±4.62			.050‡	26.24±5.11			.610‡	30.82±5.69			.015‡
Fatigue Severity Scale, mean±SD	4.00±1.71	4.6±1.30	3.00±1.30			.002‡	3.84±1.95			.234‡	4.93±1.62			.497‡
Fatigue Severity Scale, no. (%)						.071†				.296†				1.000†
low (FSS ≤ 4)	50 (65%)	7 (47%)	16 (80%)	0.22 (0.05–0.97)			15 (71%)	0.35 (0.09–1.40)			12 (57%)	0.66 (0.17–2.49)		
high (FSS ≥ 5)	27 (35%)	8 (53%)	4 (20%)	4.57 (1.03–20.35)			6 (29%)	2.86 (0.71–11.44)			9 (43%)	1.52 (0.40–5.78)		

All variables are correlated with the HADS depression score.

SLE = Systemic Lupus Erythematosus, RA = rheumatoid arthritis.

* Independent samples t test.

† Fisher exact χ^2 test.

‡ Mann–Whitney U test.

§ Welch t test.
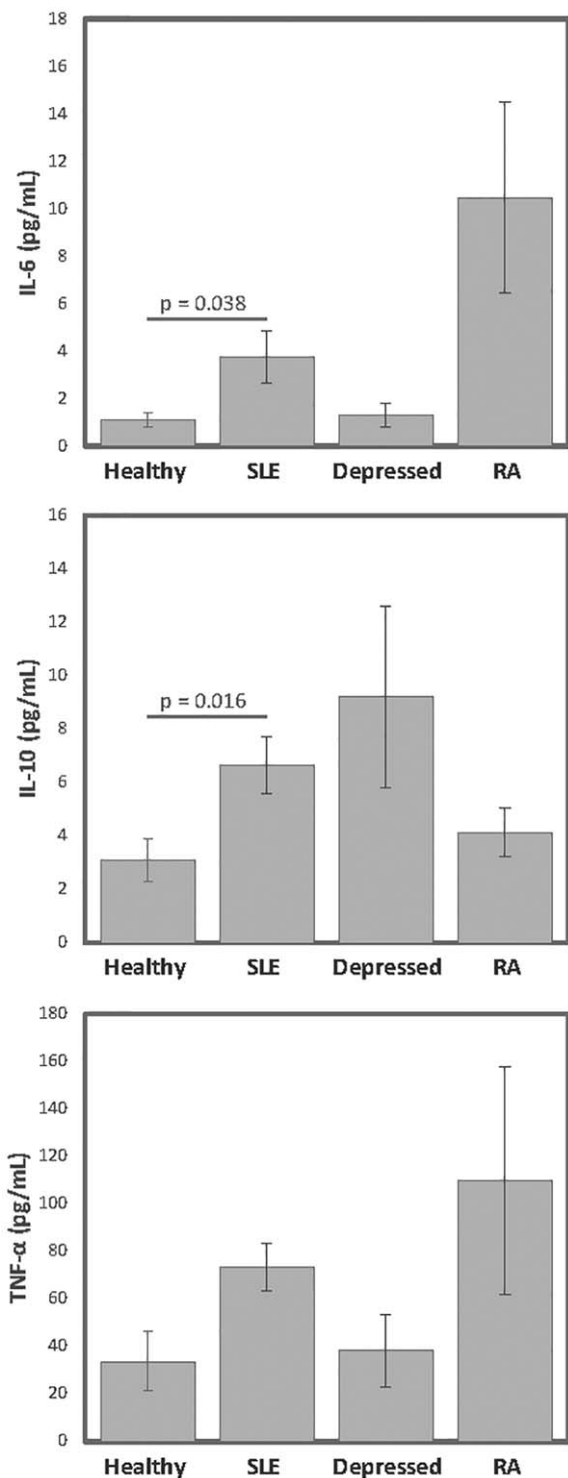
Figure 1. Cytokine serum concentrations differ between cohort subgroups. SLE IL-6 and IL-10 serum concentrations are statistically higher than healthy subjects. RA patients demonstrate slightly higher average serum levels of pro-inflammatory cytokines IL-6 and TNF-α. Depressed and SLE patients demonstrate slightly higher concentrations of IL-10 on average than other cohort subjects. IL = interleukin, RA = rheumatoid arthritis, SLE = systemic lupus erythematosus, TNF = tumor necrosis factor.

Figure 2. Linear regression identifies clinical and psychological assessments that are correlated with depression in SLE patients. Univariate analysis found IL-10, relationship assessment scale, and fatigue severity scale values to be correlated with depression in our SLE cohort. IL-10 and relationship satisfaction are negatively correlated with depression, while fatigue severity is positively correlated.

SLE patients demonstrated HADS depression scores above 10 (Table 5). The SLE patients showed a 6-fold greater likelihood than the healthy control group to have moderate or severe depression ($P = .007$, Mann–Whitney U test, Table 5). The SLE patients had significantly higher depression scores than the healthy control subjects ($P = .007$), but not higher than the depressed or RA subjects. The SLE subjects experienced higher levels of anxiety compared to both the healthy controls and the RA patients ($P = .020$ and $P = .011$, respectively). However, the depressed group had similar anxiety scores.

Upon examination of the quality of sleep that the study patients were experiencing, as recorded by the Pittsburgh Sleep Quality Index (PSQI) assessment, the SLE cohort had a mean index of 7.67 ± 3.06, which was higher than the healthy control subjects ($P = .005$). A higher PSQI indicates a lower quality of sleep, while a higher quality of sleep is indicated by lower scores. The SLE cohort had 67% report poor sleep quality based on the PSQI

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standard. This distribution of patients who experienced lower quality of sleep is similar in the SLE cohort compared with the depressed and RA subjects (Table 5).

All married and cohabiting cohort patients had their relationship satisfaction measured based on the relationship assessment scale criteria. Higher values indicate increased satisfaction with their significant other or spouse. Interestingly, the SLE patients record less satisfaction in their relationship than any of the other subgroups, with a mean scale score of 24.75 ± 4.81. This score was significantly lower than both the healthy control and RA patients ($P = .050$ and $P = .015$, respectively). The decrease in relationship satisfaction for SLE patients compared to primary depression patients did not reach statistical significance. The RA patients, albeit also suffering from a chronic and debilitating autoimmune disease, had a mean relationship assessment scale score of 30.82 ± 5.69. The reported scores for SLE patients from the relationship assessment scale showed a distinct negative correlation with HADS depression scores ($P = .007$) (Table 2) (Fig. 2).

To measure the combination of both physical and mental fatigue that the patients were experiencing, the fatigue severity scale was utilized. Higher scores indicate higher fatigue reported by the patient. The SLE patients reported a mean score of 4.6 ± 1.30, which was similar to the RA patients who reported a fatigue score of 4.93 ± 1.62 (Table 5). This was significantly more than the healthy control subjects ($P = .002$). Of interest is the fact that the depressed patients did not have significantly lower fatigue than the SLE subjects ($P = .234$) While depressed patients do not have fatigue scores that were as elevated as fatigue scores in patients with SLE, patients who are depressed on average report higher scores than those observed in "healthy" populations. This finding is unsurprising as individuals with depression commonly report fatigue as a common symptoms, and is often observed by physicians who treat depressed patients.[35] The SLE patients were nearly 4.57 times more likely to have heightened levels of fatigue compared to the healthy control patients. Further, a direct positive correlation was observed between fatigue severity scale scores and depression levels in the SLE patients ($P = .001$) (Table 2).

3.3. Multivariate analysis

Of the data collected from the clinical and psychosocial assessment of the SLE patients, we investigated which characteristics that correlated with depression could best indicate depression in our model.[35–37] Due to the relatively small SLE cohort of this study, the model could not compensate for age or socioeconomic status as would be appropriate for a larger cohort. However, it can still indicate which variables among those identified in the study show the closest correlation with depression among the patients. Anxiety was not included as a candidate for the multivariate model due to the co-relatedness with the HADS depression score and because it was derived from the same assessment as the depression score. Both the fatigue severity ($P = .028$) and relationship assessment ($P = .042$) scales were indicated as strong correlates and predictors of depression among the SLE cohort (Table 6).

4. Discussion

The study utilized the comparison of multiple groups to identify the factors that influence depression in patients with systemic lupus erythematosus. Comparing the RA and SLE patients shows

Table 6

Multivariant model for SLE Study Cohort 2.

Variables	Odds ratio (95% CI)	P value
Fatigue Severity Scale	1.21 (1.03–1.45)	.028
Relationship Assessment Scale	0.95 (0.91–1.00)	.042
Model Fit Summary	pseudo R^2	AICc
	0.952	67.400

what is likely the result of a chronic inflammatory disease. Comparison with the depression group indicates what factors are the result of psychological components. Taken together, the use of these groups offers a new perspective on factors that could be relevant to depression in the SLE patients. The strongest findings were that: first, levels of IL-10 show a correlation with HADS depression scores and appear to be a good indicator of depression in SLE patients. Second, relationship assessment scale scores were lower on average among our SLE patients compared with all other patient cohorts, and relationship assessment scale scores showed a correlation with HADS depression scores, implying that relationship assessment would be another indicator of depression for SLE patients. Lastly, the fatigue severity scale scores were strongly correlated with HADS depression scores in SLE patients in both univariate and multivariate analysis. This instrument was the most sensitive in relation to correlation with HADS depression scores, as evidenced by the heightened odds ratios, and appears to be a good predictor of depression in SLE patients.

The SLE cohort had increased pain levels compared to the healthy control cohort, but not to either the depressed or arthritis patients. Pain and depression are strongly interwoven in physical and psychiatric disorders[38] and SLE.[39]

Previous studies have shown that IL-6 and IL-10 can be associated with depression.[40] Several cross-sectional studies have found that those exhibiting depressive manifestations have increased levels of CRP, TNF-α, IL-1, IL-6, and IL-2 and that these are associated with depression in patients being treated for clinical depression.[41,42] We also observed that IL-6, IL-10, pain scores, Pittsburgh sleep quality index scores, relationship assessment scale scores, and fatigue severity scale scores were correlated with increased HADS depression scores in depressed patients (Table 2). We also observed elevated levels of IL-6 in the SLE cohort compared to the healthy patients. Increased levels of IL-6 in SLE and RA patients agree with the current literature, as patients being treated for depression often exhibit elevated levels of IL-6.[41,43,44] IL-6 could be a good indicator of depression in general; however, we did not find that IL-6 levels were significantly correlated with HADS depression scores among our SLE cohort. Since lupus patients have increased levels of IL-6 overall, this may mask an association between IL-6 and depression in lupus. It is likely that this is why we do not observe a correlation between our SLE cohort's IL-6 levels and HADS depression scores.

The SLE cohort displayed increased serum concentrations of IL-10 compared to the healthy control subjects. However, the IL-10 levels measured from our SLE patients were actually lower on average than those measured from our depressed subjects. The difference in IL-10 concentrations between these 2 groups was not significant.

IL-10 is responsible for helping drive the Th2 mediated response that results in increased B cell activation, IgG class switching, and increased antibody production. It is also strongly

associated with disease activity in patients with SLE.[45–47] Relatively lower levels of IL-10 were associated with more severe HADS depression scores in the lupus patients, a finding that was unexpected, especially since there was an association between higher IL-10 and more severe depression in the RA and depressed patients (Table 2). This type of relationship between IL-10 and depression is unexpected, as it may be expected that increased disease activity would cause increased IL-10 and depression, not the opposite. The negative trend between IL-10 and HADS depression scores in our SLE cohort could be due to the different pathophysiology of SLE when compared with other rheumatological and immunological diseases such as RA. Given that it contradicts other published studies, it is also possible that in this case it is a false positive result. However, these findings call for further investigation into the role of IL-10 in depression, especially depression in lupus.

It is still unclear if IL-10 is related to depression as there are conflicting reports in the literature with regard to human studies[48] and in animal models.[49] IL-10 imbalance does affect depressive behaviors.[50] In studies involving SLE patients it has been previously observed that heightened levels of IL-10 are likely correlated with depression and neuropsychiatric disorders.[51,52].

Investigation into a relationship between lupus disease activity and depression or anxiety has met with mixed results, with some studies indicating a correlation and others not finding evidence for correlation.[5–9] Although some studies have indicated that disease activity correlates with depression, there may be confounding factors that mask the effects. These could include such things as depressive symptoms lagging behind inflammatory indicators, socioeconomic factors masking or exacerbating depression, or personal psychological variables such as cognition, helplessness, or resilience that interfere with a straightforward analysis.

The SLE patients presented elevated anxiety scores, significantly more than the healthy and RA subjects. This supports observations of other studies.[53,54] Anxiety scores, although still higher in the lupus patients, were not significantly different from the depressed patients. The increased anxiety scores of the SLE patients compared to the RA patients suggest that increased levels of anxiety in lupus are not likely to be due only to the pain, disability, or fear that comes from the presence of a chronic inflammatory disease, as these are also present in rheumatoid arthritis. These factors likely still contribute to anxiety, but cannot completely explain the heightened anxiety in lupus patients.

Unique to this study was the correlation observed between relationship assessment scale (RAS) and HADS depression scores. The SLE patients have the lowest average RAS score between all the subgroups in the study, significantly lower than the healthy and arthritis patients. In addition, the RAS scores reported from the SLE patients were significantly correlated to depression in the univariate and multivariate analysis (Tables 2 and 6). While a large quantity of studies have observed that quality of life is negatively affected in SLE patients and is correlated with depression, none have utilized the relationship assessment scale to quantify relationship satisfaction. Relationship quality and adjustment is known to contribute to better or worse coping with illness, and bidirectionally influences depression.[55]

This study provides evidence that depression and relationship satisfaction show a correlation in the SLE patients. The finding that the RA patients have higher relationship satisfaction than lupus patients despite also having chronic autoimmune disease indicates that it is likely that specific biological or psychological manifestations of lupus affect the relationship in addition to the physical limitations of a chronic disease.

Many studies have noted the importance of social support, both familial and nonfamilial, with regards to depression.[56–60] We also observed a correlation between depression scores and relationship satisfaction in our depressed patient cohort (Table 2). Social support is a crucial environmental resource that is necessary for mental health. Good social support has been shown to provide protection from depression and elevate individual's emotional state.[61] It has also been established that depressive characteristics are associated with a decrease in peer-related social support.[56,62] While the data generated from our cohort study does not allow us to determine directionality of the relationship between relationship satisfaction and depression, it is clear that familial social support is important for mental health and that a decrease in relationship satisfaction is an indicator of depression.

In this study we found the SLE cohort to have higher PSQI values, indicating poor sleep compared to the healthy control group, but these values were not significantly different from the arthritic and depressed patients. These results suggest that the sleep quality of SLE patients, while not good, does not likely contribute directly to depression. For the time being, treatment of fatigue remains an obstacle for patients and health care professionals to surmount. Given that the depression in lupus is significantly related to fatigue (Table 6), it may be that the treatment of depression can lead to improvements in fatigue.

While this study provides some valuable insight into the factors associated with depression in patients suffering from systemic lupus erythematosus, it does exhibit several distinct limitations. First, the samples sizes of the SLE, RA, Healthy, and primary depression cohorts are all relatively small, with the patient cohorts not exceeding more than 21 at the most and the SLE patient cohort containing only 15 subjects. Another limitation to consider is the sociodemographic imbalance of the SLE cohort to the healthy subjects. While the SLE, RA, and depressed subjects tend to share similar sociodemographics, the healthy subjects tend to have more education and demonstrate lower levels of unemployment. This could be a confounding factor in depression. It likely also indicates the level to which lupus causes disability and interferes with productivity.

Depression and anxiety in lupus are influenced by a complicated mix of biological, social, and psychological factors. This study found that fatigue severity, relationship satisfaction, and IL-10 concentrations are indicators of depression in lupus patients, with fatigue and relationship satisfaction being the best predictors of depression. Interestingly, these 3 variables represent all 3 of the different influences: biological, social, and psychological. Continued study of these factors is necessary to fully understand the causes and potential treatments for these debilitating aspects of lupus.

Author contributions

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Data curation: Georgina Terrosa, Marta Figueiredo, Cristina Mesquita, Brian Poole.
Formal analysis: Caleb Cornaby, Alice Cortez, Cristina Mesquita, Brian Poole.

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