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Anxiety Symptoms Among Patients With Systemic Lupus Erythematosus Persist Over Time and Are Independent of SLE Disease Activity

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Objective. The objectives of this study are to identify patterns of anxiety symptomology over time among patients with systemic lupus erythematosus (SLE) and to assess the longitudinal relationship between SLE disease activity and anxiety symptomology.

Methods. Longitudinal data from 139 patients with American College of Rheumatology or Systemic Lupus International Collborating Clinic (SLICC)-classified SLE were analyzed. Anxiety symptomology was assessed using the Patient-Reported Outcomes Measurement Information System (PROMIS) Emotional Distress: Anxiety Short Form 8a. SLE disease activity was measured using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)-2000 (S2K) and S2K Responder Index 50 (S2K RI-50). Group-based trajectory modeling (GBTM) identified longitudinal trajectories of anxiety symptomology. The relationship between disease activity and anxiety over time was assessed using multilevel linear regressions.

Results. The mean patient age was 40.2 years (standard deviation [SD], 12.7); 90.6% were female, and 56.1% were of Black race. All patients had at least three PROMIS anxiety scores over an average of 30.9 months (SD, 13.0). GBTM identified four trajectories of anxiety symptomology, labeled as the following: low (LA), average (AA), moderate (MA), and high anxiety (HA). Black patients were 2.47 (95% confidence interval: 1.19-5.12) times as likely as White patients to be classified into the MA or HA groups compared with the LA or AA groups. On multivariable analysis, active SLE disease was not significantly associated with anxiety over time ($P = 0.19$).

Conclusion. Anxiety trajectories remained stable over time, and racial differences in anxiety severity were observed. SLE disease activity was not longitudinally associated with anxiety after controlling for depression and other factors. Further understanding of the factors that contribute to the persistence of anxiety among individuals with SLE is necessary.

INTRODUCTION

Mood disorders are a common comorbidity in patients with systemic lupus erythematosus (SLE), and it is estimated that 40% of patients with SLE have comorbid mental health conditions (1). For example, anxiety has a prevalence rate of 35%-37% among patients with SLE (2,3), which is nearly double the national prevalence estimate of 18.1% (4). In 1999, the American College of Rheumatology revised its criteria for recognizing neuropsychiatric manifestations of SLE (NPSLE) (5). Mood disorders, including depression and anxiety disorders, were included in these updated NPSLE criteria. This implies that SLE disease activity may be a root cause of mood disorders (6) and that successful treatment of SLE could also alleviate the severity of mood disorders.

Several studies have examined the relationship between SLE disease activity and behavioral health, although with conflicting results. For example, two different studies showed both an association and a lack of association between SLE disease activity scores and the presence of a psychiatric diagnosis

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SIGNIFICANCE & INNOVATIONS

- This study identifies four unique longitudinal trajectories of anxiety symptomology in a cohort of patients with systemic lupus erythematosus (SLE).
- Anxiety symptoms in all trajectory groups remained stable over time.
- Black patients, compared with White patients, had higher odds of membership in trajectory groups with elevated anxiety and had higher anxiety scores over time, on average.
- After controlling for race and depression severity, active SLE disease was not significantly associated with anxiety scores over time.

(7,8). A large, international cohort study concluded that there was no association between SLE disease activity and mood disorders over time (9). In a systematic review, authors concluded that the relationship between disease activity and depression in patients with SLE is unresolved and requires further clarification (10).

One challenge with studies that relate disease activity with mood disorder lies in the known discordance of provider-reported versus patient-reported outcomes (11,12). For example, patient-reported global measures of disease activity were found to be associated with both current and future depression and anxiety symptoms (13). However, in this same study, only one of four physician-reported disease activity measures (the Systemic Lupus Activity Measure) was directly associated with depression scores, and two measures were inversely associated with anxiety scores (13). Another small study reported that levels of overall psychological distress and anxiety symptomology declined over a 1-year period following study entry, during which all patients had active disease at study entry and inactive disease at the 1-year follow-up (14). A larger cohort study of patients with SLE found no significant associations between two physician-reported measures of disease activity and risk of incident depression over time (15).

Another important consideration is the cross-sectional design of many existing studies, which limits interpretation because hypotheses beyond simple associations between SLE and mental health cannot be tested. SLE has a paroxysmal disease course, with alternating and unpredictable cycles of disease flares and relative inactivity. This provides an opportunity to further understand the link between mood disorders and SLE using longitudinal study designs. Monitoring patients over time permits examining whether the association between mental health and SLE disease activity that has been observed in some cross-sectional designs persists longitudinally and whether interactions between mental health and SLE vary among patients. Nevertheless, existing longitudinal studies on this topic are limited by small sample sizes and short duration of follow-up (13,14,16,17).

With these considerations in mind, we recently reported that depressed affect is both persistent and largely severe for up to 4 years in a Washington University cohort of patients with SLE (18). We were further curious to determine whether similar findings may be present for anxiety in this cohort. By specifically characterizing the course of anxiety over time, we can begin to understand whether such symptoms are periodic and in direct alignment with periods of active disease or persistent and independent of disease activity. As such, the goals of the study are the following: 1) to identify patterns of anxiety symptomology over time among patients with SLE and 2) to determine whether SLE disease activity is longitudinally associated with anxiety symptomology.

PATIENTS AND METHODS

Participants

Individuals eligible for participation in this study were the 256 unique patients with American College of Rheumatology or Systemic Lupus International Collaborating Clinics (SLICC)-classified SLE treated in the Washington University Lupus Clinic between February 2015 and January 2020. Several clinical measures were routinely collected at each clinic visit. Individuals with anxiety symptomology recorded during at least three visits, over a maximum of 48 months and 19 total visits, were included in the final analytic sample. This study was approved by the Institutional Review Board at Washington University in St. Louis (#201412100; initially approved February 17, 2015, last approved in perpetuity April 21, 2021).

Measures

SLE disease activity. SLE disease activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)-2000 (S2K) instrument at the patients' first clinic visit and the SLEDAI-2K Responder Index-50 (S2K RI-50) at follow-up visits (19,20). The S2K and S2K RI-50 are validated measures that allow providers to assess overall SLE disease activity (19). All providers passed standardized S2K RI-50 training (Kellahan and Kim). S2K and S2K-RI50 scores above 4 reflect active SLE (21). Erythrocyte sedimentation rate, anti-double-stranded DNA antibody titers, and C3 and C4 complement component levels were collected as additional surrogates of SLE disease activity (22).

Anxiety symptomology. Anxiety symptomology was assessed at each visit using the Patient-Reported Outcomes Measurement Information System (PROMIS) Emotional Distress: Anxiety Short Form 8a (23). PROMIS comprises a library of validated questionnaires that assess different patient-reported outcomes. The PROMIS anxiety scale assesses both cognitive and somatic symptoms associated with generalized

anxiety. Scores on this scale are converted to *t* scores that have a mean of 50, reflecting average levels of anxiety compared with the general adult population, and standard deviation (SD) of 10. Moderate symptomology is interpreted as *t* scores of 60-70 and severe symptomology as *t* scores above 70 (24).

Baseline characteristics. Baseline characteristics obtained at the patients' first clinic visit included age, biological sex, race, educational attainment, marital status, employment status, and obesity. The Center for Epidemiologic Studies Depression Scale Revised (CESD-R) was collected as an indicator of depressive symptomology, because depression and anxiety are highly correlated (25). The CESD-R has a range of 0-60, with higher scores indicating higher depression severity (26). The patient's comorbid health conditions and medication regimen were also recorded. When information was incomplete, the electronic health record immediately preceding and following the baseline visit was reviewed, and relevant data were extracted.

Statistical methods

Descriptive characteristics of the overall sample were reported as mean and SD for continuous variables and frequency and percentage for categorical variables. To identify unique trajectories of anxiety symptomology over time, group-based trajectory modeling was used (27). This method allowed for the identification of groups of individuals who followed similar anxiety symptomology patterns using a statistical approach, as opposed to a theoretical approach. The method then classified individuals into their most likely trajectory, based on the predicted probability of membership in each identified trajectory group. Analyses were performed using the add-on trajectory (TRAJ) procedure in SAS version 9.4 (SAS Institute) (28). The final model was selected based on the Bayesian Information Criteria (BIC), in which smaller values indicate better model fit and theoretical understanding of the data. Baseline characteristics of individuals in each identified anxiety trajectory group were compared using χ^2 tests, Fisher's exact tests, or analysis of variance (ANOVA).

To further understand the relationship between SLE disease activity and anxiety over time, multilevel linear regression models were used. The anxiety *t* score was the continuous outcome, and a categorical indicator of active versus inactive disease based on S2K or S2K RI-50 was the primary predictor. The multilevel model accounted for the multiple measurements of anxiety and disease activity from individuals over time. Univariable and multivariable logistic regressions were used to determine the relationship between baseline characteristics and classification in trajectory groups reflecting either elevated or normal anxiety symptomology. All analyses were conducted in SAS version 9.4 (SAS Institute), and $\alpha = 0.05$ was used to determine statistical significance.

RESULTS

Baseline characteristics. The final sample contained 139 patients with a minimum of 3 PROMIS anxiety scores over an average of 30.9 months (SD, 13.0; range, 2.6-48). Among all patients, the total number of assessments included was 920, and the average number of assessments per patient was 7.2 (SD, 3.2; range, 3-16). The average length of time between one assessment and the next was 150.7 days (SD, 101.5; range, 21-1036). The mean patient age was 40.2 years (SD, 12.7; range, 19-74; Table 1), 90.6% of the patients were female patients, and 56.1% were Black patients. Although complete baseline data were available for patient age, race, depression and anxiety scores, and medication use, we did not have complete data for several additional sociodemographic characteristics, namely education, marital status, and employment status. Nevertheless, the information that is available for these characteristics is reported in Table 1. For this subset of patients with information available, just over half had at least a college degree (55.4%) and were unmarried (55.4%), and approximately one third were employed (36.0%).

Regarding the clinical characteristics of patients at baseline (Table 1), 73.1% of participants had overweight or obesity (29.1% and 44.0%, respectively), and the average CESD-R score was 19.9 (SD, 14.9), corresponding to symptomology indicative of depressed affect. The mean PROMIS anxiety score in the population at baseline was 55.0 (SD, 12.7), corresponding to anxiety symptomology slightly above the average for a general adult population. Just over one third of subjects (35.9%) had active disease (S2K RI-50 score >4) at baseline, and the average baseline SLEDAI score in the full population was 4.3 (SD, 4.5). The prevalence of comorbid diseases among patients was 42.8% for hypertension, 16.5% for hyperlipidemia, 13.4% for hypothyroidism, and just under 10% for type 2 diabetes mellitus (9.0%) and antiphospholipid syndrome (9.4%). The average prednisone dose was 5.5 mg/d (SD, 10.5), and just under one quarter of patients (23.7%) were on a prednisone dose greater than 7.5 mg/d. One in five subjects (21.6%) were on either a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor, and 28.1% were prescribed a narcotic. Smaller proportions of the sample were on benzodiazepines, tricyclic antidepressants, or hypnotics (8.6%, 5.0%, and 7.9%, respectively). Most characteristics of individuals included in the final sample did not meaningfully differ from those of individuals excluded from the final sample (Supplemental Table S1). The only meaningful difference observed was with respect to the racial distribution, which indicated that a larger proportion of Black individuals were included in the final sample.

Table 1. Demographic and clinical characteristics of subjects included in the sample, overall and by identified anxiety trajectory group

Variable	Total (N = 139)	LA (n = 27)	AA (n = 37)	MA (n = 57)	HA (n = 18)	*P* value
Demographic characteristics						
Age at baseline, mean (SD), yr	40.2 (12.7)	37.8 (15.4)	40.2 (12.0)	41.2 (12.3)	40.9 (11.4)	0.716
Sex, n (% female)	126 (90.6)	24 (88.9)	34 (91.9)	53 (93.0)	15 (83.3)	0.579
Race, n (%)						0.008*
White	54 (38.8)	12 (44.4)	19 (51.4)	21 (36.8)	2 (11.1)	
Black	78 (56.1)	12 (44.4)	15 (40.5)	35 (61.4)	16 (88.9)	
Other	7 (5.0)	3 (11.1)	3 (8.1)	1 (1.75)	0 (0)	
Highest education attainment, n (%)						0.511
Unknown	39 (28.1)	5 (18.5)	10 (27.0)	17 (29.8)	7 (38.9)	
Less than 12th grade	3 (2.2)	0 (0.0)	0 (0.0)	2 (3.5)	1 (5.6)	
GED/high school/some college	68 (48.9)	15 (55.6)	17 (46.0)	27 (47.4)	9 (50.0)	
College/over college	29 (20.9)	7 (25.9)	10 (27.0)	11 (19.3)	1 (5.6)	
Marital status						0.848
Unknown	19 (13.7)	3 (11.1)	4 (10.8)	8 (14.0)	4 (22.2)	
Not married	77 (55.4)	17 (63.0)	19 (51.4)	32 (56.1)	9 (50.0)	
Married	43 (30.9)	7 (25.9)	14 (37.8)	17 (29.8)	5 (27.8)	
Employment status						0.239
Unknown	44 (31.7)	8 (29.6)	12 (32.4)	18 (31.6)	6 (33.3)	
Employed	50 (36.0)	14 (51.9)	14 (37.8)	20 (35.1)	2 (11.1)	
Unemployed	7 (5.0)	0 (0.0)	2 (5.4)	4 (7.0)	1 (5.6)	
Other[a]	38 (27.3)	5 (18.5)	9 (24.3)	15 (26.3)	9 (50.0)	
Clinical characteristics						
Obesity (n = 134)						0.726
Normal BMI (<25.0 kg/m^2)	36 (26.9)	7 (25.9)	11 (30.6)	13 (23.6)	5 (31.3)	
Overweight (25.0-29.9 kg/m^2)	39 (29.1)	7 (25.9)	11 (30.6)	19 (34.6)	2 (12.5)	
Obesity (≥30.0 kg/m^2)	59 (44.0)	13 (48.2)	14 (38.9)	23 (41.8)	9 (56.3)	
SLEDAI score (n = 132; SD)	4.3 (4.5)	2.5 (2.4)	4.3 (3.8)	4.5 (4.5)	5.9 (6.9)	0.097
SLEDAI at baseline (n = 131)						0.469
Active (>4)	47 (35.9)	6 (24.0)	14 (41.2)	19 (35.2)	8 (44.4)	
Inactive (<4)	84 (64.1)	19 (76.0)	20 (58.8)	35 (64.8)	10 (55.6)	
C3 complement (n = 128; SD)	114.0 (36.8)	115.6 (34.9)	105.7 (29.1)	116.5 (42.7)	119.6 (32.6)	0.519
C4 complement (n = 127; SD)	22.7 (10.0)	21.0 (6.8)	20.4 (8.6)	24.8 (12.0)	22.9 (9.0)	0.189
dsDNA (n = 63; SD)	134.9 (169.3)	138.4 (192.7)	141.0 (177.1)	143.3 (171.9)	56.9 (42.1)	0.771
dsDNA % positive (n = 129)	72 (55.8)	14 (56.0)	18 (54.6)	33 (60.0)	7 (43.8)	0.861
ESR (n = 123; SD)	28.7 (24.6)	25.2 (21.8)	31.7 (27.6)	30.5 (24.4)	23.4 (24.8)	0.583
CESD-R score at baseline (SD)	19.9 (14.9)	5.0 (5.2)	13.9 (9.9)	25.6 (12.7)	36.4 (13.4)	<0.001*
PROMIS anxiety score at baseline (SD)	55.0 (12.7)	38.9 (4.1)	48.7 (8.6)	62.0 (6.9)	70.2 (7.8)	<0.001*
Hypertension (n = 138)	59 (42.8)	10 (37.0)	16 (43.2)	23 (40.4)	10 (58.8)	0.514
Hyperlipidemia	23 (16.5)	4 (14.8)	5 (13.5)	10 (17.5)	4 (22.2)	0.858
Diabetes mellitus type 2 (n = 134)	12 (9.0)	3 (11.1)	3 (8.3)	6 (10.9)	0 (0.0)	0.644
Hypothyroidism (n = 134)	18 (13.4)	3 (11.1)	6 (16.7)	7 (12.7)	2 (12.5)	0.948
APLS	13 (9.4)	2 (7.4)	2 (5.4)	5 (8.8)	4 (23.5)	0.221
Baseline medication use						
Prednisone dose (mg/d)	5.5 (10.5)	2.0 (4.7)	3.3 (8.7)	7.8 (13.0)	7.9 (9.9)	0.040*
Prednisone dose >7.5 mg/d (%)	33 (23.7)	3 (11.1)	4 (10.8)	19 (33.3)	7 (38.9)	0.012*
SSRI or SNRI (%)	30 (21.6)	3 (11.1)	8 (21.6)	15 (26.3)	4 (22.2)	0.474
Benzodiazepines (%)	12 (8.6)	1 (3.7)	3 (8.1)	5 (8.8)	3 (16.7)	0.537
TCA (%)	7 (5.0)	3 (11.1)	1 (2.7)	2 (3.5)	1 (5.6)	0.449
Hypnotics (%)	11 (7.9)	0 (0.0)	4 (10.8)	6 (10.5)	1 (5.6)	0.319
Narcotics (%)	39 (28.1)	5 (18.5)	11 (29.7)	13 (22.8)	10 (55.6)	0.032*
Use of at least one psychotropic medication (%)[b]	49 (35.3)	6 (22.2)	12 (32.4)	25 (43.9)	6 (33.3)	0.260

Abbreviations: AA, average anxiety; APLS, antiphospholipid syndrome; BMI, body mass index; CESD-R, Center for Epidemiologic Studies Depression Scale Revised; dsDNA, anti-double-stranded DNA antibody titers; ESR, erythrocyte sedimentation rate; GED, general educational development; HA, high anxiety; LA, low anxiety; MA, moderate anxiety; PROMIS, Patient-Reported Outcomes Measurement Information System; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.
* Indicates statistically significant at $P < 0.05$.
[a] Other category includes individuals who are students, have a disability, or are retired.
[b] Psychotropic medication includes SSRIs, SNRI, benzodiazepines, hypnotics, or TCAs.

Anxiety trajectory group identification. Group-based trajectory models with three, four, and five anxiety trajectory groups were assessed. The three-group model was simplest, but the difference in BIC between the three- and four-group models was relatively large (Δ BIC = –60.76). Moreover, the four-group model identified two unique groups of patients with

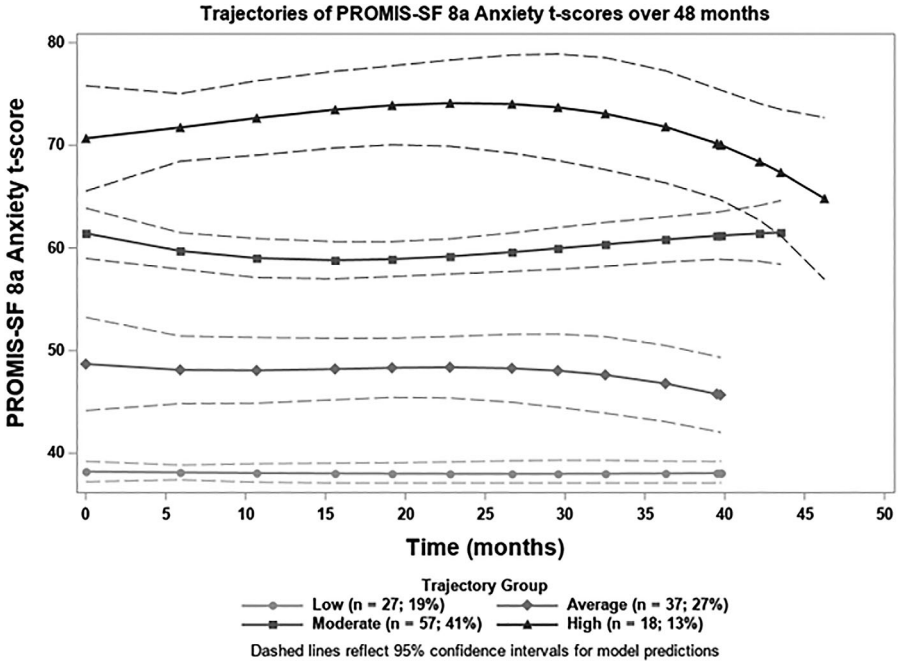

Figure 1. Identified trajectories of anxiety scores over time. PROMIS-SF, Patient-Reported Outcomes Measurement Information System Short Form.

moderate levels of anxiety symptomology over time, which provided a much more nuanced understanding of the trajectories than the three-group model. When comparing the four-group model with the five-group model, the change in BIC was smaller (Δ BIC = −19.28), and the additional trajectory was formed entirely from a very small subset of individuals with the highest anxiety symptomology. Thus, the four-group model was selected as the final model because it was both parsimonious and provided clinically meaningful insights (Figure 1).

The model-predicted PROMIS anxiety *t* scores over time for each identified trajectory are shown in Figure 1. The four trajectory groups were labeled as follows: low anxiety (LA; n = 27 [19%]), average anxiety (AA; n = 37 [27%]), moderate anxiety (MA; n = 57 [41%]), and high anxiety (HA; n = 18 [13%]). Figure 1 demonstrates that anxiety scores generally remained largely stable over time, with only the HA group showing a slight decrease toward the end of the time period.

Baseline characteristics of anxiety trajectory groups. Baseline demographic and clinical characteristics across anxiety trajectory groups are presented and compared in Table 1. Significant differences in race, CESD-R score, prednisone dose, and narcotic use were identified. The HA group had the highest proportion of Black (88.9%) and lowest proportion of White individuals (11.1%), whereas the AA group had the lowest proportion of Black (40.5%) and highest proportion of White individuals (51.4%; $P = 0.008$). CESD-R scores also varied significantly across anxiety trajectory groups ($P < 0.001$), with individuals in the HA group having the highest CESD-R scores. Prednisone dose at baseline was highest among individuals in the MA or HA groups ($P = 0.040$), and more than half of subjects in the HA group (55.6%) reported narcotic use ($P = 0.032$).

Table 2. Results from separate logistic regression models using baseline characteristics to predict membership in elevated anxiety symptomology groups (MA or HA) compared with normal or low symptomology groups (AA or LA)

Baseline characteristic	Odds ratio (95% CI)	*P* value
Age at baseline (y)	1.01 (0.99-1.04)	0.367
Gender		0.932
Female	0.95 (0.30-3.00)	
Male	Reference	
Race		0.041*
Black	2.47 (1.19-5.12)	
Other	<0.01 (<0.01 to >999.99)	
White	Reference	
BMI category		0.729
Overweight	1.25 (0.50-3.12)	
Obesity	1.38 (0.60-3.14)	
Normal	Reference	
Narcotics	1.56 (0.70-3.44)	0.275
SSRI/SNRI	1.68 (0.73-3.86)	0.224
Benzodiazepines	1.72 (0.49-6.02)	0.397
TCA	0.60 (0.13-2.78)	0.512
Hypnotics	1.48 (0.41-5.33)	0.548
CESD-R score	1.16 (1.10-1.22)	<0.001*
SLEDAI active	1.24 (0.61-2.54)	0.556

Abbreviations: AA, average anxiety; BMI, body mass index; CESD-R, Center for Epidemiologic Studies Depression Scale Revised; CI, confidence interval; HA, high anxiety; LA, low anxiety; MA, moderate anxiety; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.
* Indicates statistically significant at $P < 0.05$.

Baseline predictors of anxiety trajectory group membership. To determine the association between subjects' baseline characteristics and anxiety trajectory, several logistic regressions were performed (Table 2). The outcome variable was individuals' membership in elevated anxiety symptomology trajectory groups (MA or HA) compared with membership in average or low symptomology trajectory groups (LA or AA). When each baseline characteristic was assessed individually in a univariable model, only baseline CESD-R score and race were significantly associated with membership in an elevated anxiety trajectory. A one-unit increase in baseline CESD-R score was associated with a 16% increase in odds of being in an elevated anxiety group (odd ratio, 1.16; 95% confidence interval [CI]: 1.10-1.22; $P < 0.001$), and Black individuals were 2.47 times as likely (95% CI: 1.19-5.12; $P = 0.041$) as White individuals to be classified into an elevated anxiety group. Multivariable results are not included because after stepwise removal of nonsignificant variables, only CESD-R score remained statistically significant.

Relationship between SLE disease activity and anxiety over time. Multilevel linear regression models were used to examine the relationship between SLE disease activity and anxiety *t* scores over time (Table 3). Race, active SLE, and CESD-R scores were all significantly associated with anxiety *t* scores over time on univariate analysis. Multivariable analysis indicated that Black race—compared with White race—and higher CESD-R scores remained significantly associated with higher anxiety symptomology over time ($P = 0.006$ and $P < 0.001$, respectively), whereas active SLE was no longer associated (β = 0.71; 95% CI: −0.36 to 1.79; $P = 0.194$).

DISCUSSION

The present analysis used longitudinal data from patients at the Washington University Lupus Clinic and identified four patterns of anxiety symptomology, which were characterized by low, average, moderate, or high anxiety. More than 50% of individuals included in the sample were classified into the MA or HA groups. These distinct levels of anxiety symptomology were stable over time regardless of symptom severity. Differences in race, baseline depression scores, prednisone use, and narcotic use were identified across the four groups of anxiety symptomology. Importantly, active SLE disease was not associated with anxiety scores over time, after controlling for other factors.

The patient's race was found to be associated with anxiety symptoms consistently throughout our results. In particular, Black patients had increased odds of classification in the MA or HA group compared with White patients. Similarly, Black patients had higher anxiety scores than White patients over time. These findings are particularly interesting given that non-White patients have also been shown to have higher levels of disease activity and overall damage (1). Studies have shown that patients with SLE have higher levels of perceived stress and more exposure to life-threatening events or major adversity than individuals without SLE (29,30). Unsurprisingly, individuals of minority race are also known to have higher levels of stress and adverse event

Table 3. Univariate and multivariate results from linear mixed model predicting PROMIS Anxiety SF 8a *t* scores over time

Variable	Crude parameter estimate	*P* value	Adjusted parameter estimate	*P* value
Age at baseline (y)	0.06 (−0.09 to 0.20)	0.454	—	—
Gender		0.703		
Female	1.23 (−5.10 to 7.56)		—	—
Male	Reference			
Race		0.001*		0.006*
Black	5.84 (2.16, 9.52)		3.06 (0.91, 5.22)	
Other	−4.97 (−13.35 to 3.40)		−2.08 (−6.98 to 2.81)	
White	Reference		Reference	
S2K/S2K RI-50[a]		0.039*		0.194
Active[b]	1.28 (0.06 to 2.51)		0.71 (−0.36 to 1.79)	
Inactive	Reference		Reference	
Month[c]	−0.02 (−0.05 to 0.02)	0.278	—	—
Prednisone dose	0.03 (−0.03 to 0.08)	0.348	—	—
CESD-R score	0.49 (0.44 to 0.53)	<0.001*	0.515 (0.47 to 0.56)	<0.001*

Abbreviations: —, no data; CESD-R, Center for Epidemiologic Studies Depression Scale Revised; PROMIS, Patient-Reported Outcomes Measurement Information System; SF, Short Form.
* Indicates statistically significant at $P < 0.05$.
[a] S2K: Systemic Lupus Erythematosus Disease Activity Index-2000; S2K RI-50: S2K Responder Index-50.
[b] S2K or S2K RI-50 score greater than 4 is defined as active.
[c] The linear mixed model examines the overall relationship between the variables of interest and the PROMIS Anxiety *t* scores over multiple points in time. The month variable reflects the time in months from baseline at which each PROMIS Anxiety *t* score was collected. Disease activity, prednisone dose, and CESD-R score are also time-varying variables that have the potential to change at each measurement of the PROMIS Anxiety score.

exposures than White individuals (31,32). An important strength of the present study is that over half of the study participants are of Black race, enabling racial comparisons in the analysis. Interestingly, our data contrast with observations that Black individuals have lower rates of anxiety than White individuals (33). As such, the underlying factors driving the significant associations between race and anxiety symptomology in this population of patients with SLE should be further examined.

Patients' depression severity was also found to be consistently associated with anxiety symptoms over time. We previously reported that severity of depressed affect can also be classified into distinct trajectory groups that were similarly durable over time (18). When we examined baseline depression scores across the four anxiety trajectory groups, a dose–response relationship was observed. Depression severity was also significantly associated with anxiety symptomology over time. These findings are not particularly surprising given the high level of comorbidity between depression and anxiety disorders (25). A longitudinal study in a population of older adults has also shown significant relationships between depression and anxiety symptoms over time (34). A meta-analysis examining longitudinal studies of anxiety and depression also found bidirectional effects between all types of anxiety and depression symptoms and diagnosed disorders (35). In addition to being highly correlated, anxiety and depression are known to be more resistant to traditional treatments when they are comorbid, and individuals with both may require a more complex care plan (36). Moreover, in a rheumatologic setting, depression and anxiety have been shown to be associated with lower odds of sustained minimal disease activity in patients with psoriatic arthritis (37). Balancing high levels of anxiety with the complex care associated with SLE treatment in our cohort makes for a particularly challenging clinical encounter. Better understanding the degree of comorbid depression and anxiety in lupus patients and the ways in which these conditions impact each other are important avenues for future work.

Longitudinal studies of anxiety in patients with SLE are limited, but research examining patterns of this mental health condition among other unique populations does exist. A study of patients with type 2 diabetes also identified four trajectories of anxiety symptomology characterized by high, moderate-high, moderate-low, and low anxiety scores over time, all of which remained stable over the follow-up period (38). In individuals with stable coronary artery disease, similar trajectories with stable high, moderate, and low anxiety symptomology over a 15-year period were found, but an additional trajectory with increasing anxiety symptoms over time was also identified (39). This unique pattern of individuals with increasing anxiety symptoms over time was also shown in a study examining trajectories of anxiety and depression scores among mothers over a 13-year period (40). It is possible that an increase in anxiety symptoms among our cohort of patients with SLE would have been observed with a longer follow-up period or, alternatively, that this trajectory is not characteristic of patients with SLE.

To our knowledge, this is the first study to specifically examine patterns of anxiety symptomology over time among patients with SLE. Many studies have noted the high prevalence of anxiety among this unique group of patients (3,41–43) but have not evaluated anxiety patterns longitudinally. Those studies that have incorporated some sort of longitudinal context have been more exploratory in nature, such as a study by Gao et al that examined anxiety symptoms in patients with and without SLE at an initial visit and 1-year follow-up (44). This study found that patients with SLE had significantly higher anxiety symptom scores at both time points but did not evaluate the change in symptoms over time. Another study looked at the relationship between anxiety and both patient-reported and physician-reported SLE disease activity over time, but it did not evaluate unique patterns of anxiety symptomology over time (13). Additionally, one cohort study of patients newly diagnosed with rheumatoid arthritis found that anxiety prevalence and symptomology did significantly decrease at 6 and 12 months following their initial diagnosis, but the analyses did not characterize this trend beyond simple pairwise comparisons at the two time points (45). Thus, our work extends the body of evidence surrounding anxiety symptoms among patients with SLE by showing distinct, stable trajectories over time.

The present study's finding that active SLE was associated with anxiety over time in a univariate model, but not independently associated after controlling for race and depression scores, also warrants further discussion. This finding is in direct contrast to a study by Tay et al that found that SLE disease activity was independently associated with anxiety scores after controlling for depression scores (46). However, the study by Tay et al was a cross-sectional analysis of patients attending an adult lupus clinic in Singapore with no prior history of anxiety, depression, or other psychiatric condition and no psychotropic medication use (46). The findings herein are more aligned with the work of Ward et al, who found that several measures of disease activity were not correlated with current or future anxiety scores (13). Huang et al found that global SLE disease activity was associated with increased risk of depression in a univariable model but was not independently associated with depression risk after controlling for other covariates, similar to our findings (15). A key distinguishing factor of the present analysis is the use of longitudinal data to examine the relationship between SLE disease activity and anxiety symptomology over a period of up to 4 years. As such, these findings should be confirmed in other longitudinal studies of patients with SLE.

It is important to note that, although anxiety symptomology was reported directly by the patients, the S2K and S2K RI-50 were recorded by the physician. This distinction is important, as it alludes to the differences between patient-reported and physician-reported manifestations of SLE. This directly aligns with the new clinical distinctions between Type 1 and Type 2 SLE, in which Type 1 manifestations are captured by clinical disease activity measures whereas Type 2 manifestations are not (47). In

particular, Type 1 manifestations are the more classic clinical presentations of SLE, such as nephritis, arthritis, or cutaneous rash, whereas Type 2 manifestations include fatigue, body pain, depression, and anxiety (48). Existing studies of these distinct types of SLE have often shown that Type 2 SLE is not necessarily associated with periods of disease activity and does not change substantially over time (48). The present findings lend support to this distinction of a unique Type 2 clinical phenotype of SLE, particularly given the persistent levels of anxiety symptomology seen in the MA and HA groups and the lack of association with active SLE disease. Moreover, the proportion of patients with active SLE disease at baseline did not meaningfully differ across the identified anxiety trajectory groups. The proportion of patients in these MA and HA groups who were taking psychotropic medications at baseline is also much lower than would be expected, given the high and persistent anxiety symptomology experienced by these individuals. This emphasizes the importance of clinicians not only treating Type 1 manifestations of SLE but also recognizing and connecting patients with resources to manage anxiety symptomology and other mental health conditions, whether they are manifestations consistent with Type 2 SLE or simply comorbid mental health conditions.

Several limitations of this study must be noted. First, the sample includes patients from one specific clinic and geographic region, so the results may not be generalizable. Moreover, the sample was limited to patients with at least three clinic visits in which PROMIS anxiety scores were recorded. However, the demographic and clinical characteristics of individuals who were included versus those who were excluded were not meaningfully different (Supplemental Table S1). Several demographic variables of interest, such as employment or marital status, had high levels of missingness, so it was not possible to examine the relationship between these important psychosocial factors and anxiety trajectories. Similarly, several factors that are known to be associated with anxiety, SLE disease activity, and race—such as socioeconomic status, smoking status, or other substance use—were not consistently collected among the patients in the sample and could not be examined. Finally, anxiety symptomology was all self-reported by the patients and not necessarily reflective of a diagnosed mental health condition.

Our study used a sophisticated analytical method to identify four distinct longitudinal trajectories of anxiety symptomology that remained stable over time among a diverse sample of patients with SLE. The results are an important addition to the body of research surrounding longitudinal patterns of mental health among patients with SLE, which currently remains scarce. More than half of the patients exhibited moderate or high levels of anxiety over time, and SLE disease activity was not found to be independently associated with anxiety scores in a multivariable analysis. These findings help further characterize the longitudinal course of mental health in patients with SLE and are consistent with the notion that Type 2 manifestations of SLE remain chronic. Thus, future work should examine the efficacy of medication treatment in patients with SLE and the ways in which behavioral interventions aimed at mitigating adverse mental health for patients with SLE can be integrated into or linked with the clinical care setting. Additionally, it will be crucial to further understand the ways in which other social determinants of health—beyond just the patient's race—impact the persistence of adverse mental health among patients with lupus patients. Addressing both unmet mental health care needs and social determinants of health that impact the clinical course of patients with SLE will be crucial to improving their overall health outcomes.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. AHJK had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES

1. Seawell AH, Danoff-Burg S. Psychosocial research on systemic lupus erythematosus: a literature review. Lupus 2004;13:8–9.
2. Moustafa AT, Moazzami M, Engel L, Bangert E, Hassanein M, Marzouk S, et al. Prevalence and metric of depression and anxiety in systemic lupus erythematosus: a systematic review and meta-analysis. Semin Arthritis Rheum 2020;50:84–94.
3. Zhang L, Fu T, Yin R, Zhang Q, Shen B. Prevalence of depression and anxiety in systemic lupus erythematosus: a systematic review and meta-analysis. BMC Psychiatry 2017;17:70.
4. Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:617–27.
5. Ainiala H, Hietaharju A, Loukkola J, Peltola J, Korpela M, Metsänoja R, et al. Validity of the new American College of Rheumatology criteria for neuropsychiatric lupus syndromes: a population-based evaluation. Arthritis Rheum 2001;45:419–23.
6. Watson P, Storbeck J, Mattis P, Mackay M. Cognitive and emotional abnormalities in systemic lupus erythematosus: evidence for amygdala dysfunction. Neuropsychol Rev 2012;22:252–70.
7. Uguz F, Kucuk A, Cicek E, Kayhan F, Tunc R. Mood, anxiety and personality disorders in patients with systemic lupus erythematosus. Compr Psychiatry 2013;54:341–5.
8. Jarpa E, Babul M, Calderón J, González M, Martínez ME, Bravo-Zehnder M, et al. Common mental disorders and psychological distress in systemic lupus erythematosus are not associated with disease activity. Lupus 2011;20:58–66.
9. Hanly JG, Su L, Urowitz MB, Romero-Diaz J, Gordon C, Bae SC, et al. Mood disorders in systemic lupus erythematosus: results from an

international inception cohort study. Arthritis Rheumatol 2015;67:1837–47.
10. Palagini L, Mosca M, Tani C, Gemignani A, Mauri M, Bombardieri S. Depression and systemic lupus erythematosus: a systematic review. Lupus 2013;22:409–16.
11. Golder V, Ooi JJY, Antony AS, Ko T, Morton S, Kandane-Rathnayake R, et al. Discordance of patient and physician health status concerns in systemic lupus erythematosus. Lupus 2018;27:501–6.
12. Yen JC, Abrahamowicz M, Dobkin PL, Clarke AE, Battista RN, Fortin PR. Determinants of discordance between patients and physicians in their assessment of lupus disease activity. J Rheumatol 2003;30:1967–76.
13. Ward MM, Marx AS, Barry NN. Psychological distress and changes in the activity of systemic lupus erythematosus. Rheumatology (Oxford) 2002;41:184–8.
14. Segui J, Ramos-Casals M, Garcia-Carrasco M, Flores T de, Cervera R, Valdes M, et al. Psychiatric and psychosocial disorders in patients with systematic lupus erythematosus: a longitudinal study of active and inactive stages of the disease. Lupus 2000;9:584–8.
15. Huang X, Magder LS, Petri M. Predictors of incident depression in systemic lupus erythematosus. J Rheumatol 2014;41:1823–33.
16. Ayache DCG, Costa IP da. Personality traits and associated changes in women with lupus. Bras J Rheumatol 2009;49:643–57.
17. Walker SE, Smarr KL, Parker JC, Weidensaul DN, Nelson W, McMurray RW. Mood states and disease activity in patients with systemic lupus erythematosus treated with bromocriptine. Lupus 2000;9:527–33.
18. Kellahan SR, Huang X, Lew D, Xian H, Eisen S, Kim AHJ. Depressed symptomatology persists over time in systemic lupus erythematosus patients. Arthritis Care Res (Hoboken) 2021. E-pub ahead of print.
19. Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol 2002;29:288–91.
20. Touma Z, Gladman DD, Ibañez D, Urowitz MB. Development and initial validation of the systemic lupus erythematosus disease activity index 2000 responder index 50. J Rheumatol 2011;38:275–84.
21. Yee CS, Farewell VT, Isenberg DA, Griffiths B, Teh LS, Bruce IN, et al. The use of systemic lupus erythematosus disease activity index-2000 to define active disease and minimal clinically meaningful change based on data from a large cohort of systemic lupus erythematosus patients. Rheumatology (Oxford) 2011;50:982–8.
22. Tsokos GC. Systemic lupus erythematosus. N Engl J Med 2011;365:2110–21.
23. Pilkonis PA, Choi SW, Reise SP, Stover AM, Riley WT, Cella D. Item banks for measuring emotional distress from the patient-reported outcomes measurement information system (PROMIS): depression, anxiety, and anger. Assessment 2011;18:263–83.
24. HealthMeasures. PROMIS score cut points. 2021. URL: https://www.healthmeasures.net/score-and-interpret/interpret-scores/promis/promis-score-cut-points.
25. Pollack MH. Comorbid anxiety and depression. J Clin Psychiatry 2005;66 Suppl 8:22–9.
26. Radloff LS. The CES-D Scale: a self-report depression scale for research in the general population. Applied Psychological Medicine 1977;1:385–401.
27. Nagin DS. Analyzing developmental trajectories: a semiparametric, group-based approach. Psychol Methods 1999;4:139–57.
28. Jones BL, Nagin DS, Roeder K. A SAS procedure based on mixture models for estimating developmental trajectories. Sociol Methods Res 2001;29:374–93.
29. Peralta-Ramírez MI, Pérez-Mármol JM, Castañeda-Cabestany M, Santos-Ruiz AM, Montero-López E, Callejas-Rubio JL, et al. Association between perceived level of stress, clinical characteristics and psychopathological symptoms in women with systemic lupus erythematosus. Clin Exp Rheumatol 2018;36:434–41.
30. 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;14:363–72.
31. Schilling EA, Aseltine RH, Gore S. Adverse childhood experiences and mental health in young adults: a longitudinal survey. BMC Public Health 2007;7:1–10.
32. Williams DR, Yu Y, Jackson JS, Anderson NB. Racial differences in physical and mental health. Socio-economic status, stress and discrimination. J Health Psychol 1997;2:335–51.
33. Hunter LR, Schmidt NB. Anxiety psychopathology in African American adults: literature review and development of an empirically informed sociocultural model. Psychol Bull 2010;136:211–35.
34. Wetherell JL, Gatz M, Pedersen NL. A longitudinal analysis of anxiety and depressive symptoms. Psychol Aging 2001;16:187–95.
35. Jacobson NC, Newman MG. Anxiety and depression as bidirectional risk factors for one another: a meta-analysis of longitudinal studies. Psychol Bull 2017;143:1155–200.
36. Coplan JD, Aaronson CJ, Panthangi V, Kim Y. Treating comorbid anxiety and depression: psychosocial and pharmacological approaches. World J Psychiatry 2015;5:366–78.
37. Wong A, Ye JY, Cook RJ, Gladman DD, Chandran V. Depression and anxiety reduce the probability of achieving a state of sustained minimal disease activity in patients with psoriatic arthritis. Arthritis Care Res (Hoboken) 2021. E-pub ahead of print.
38. Deschênes SS, Burns RJ, Schmitz N. Trajectories of anxiety symptoms and associations with incident cardiovascular disease in adults with type 2 diabetes. J Psychosom Res 2018;104:95–100.
39. Peter RS, Meyer ML, Mons U, Schöttker B, Keller F, Schmucker R, et al. Long-term trajectories of anxiety and depression in patients with stable coronary heart disease and risk of subsequent cardiovascular events. Depress Anxiety 2020;37:784–92.
40. Skipstein A, Janson H, Stoolmiller M, Mathiesen KS. Trajectories of maternal symptoms of anxiety and depression. A 13-year longitudinal study of a population-based sample. BMC Public Health 2010;10:589.
41. Bachen EA, Chesney MA, Criswell LA. Prevalence of mood and anxiety disorders in women with systemic lupus erythematosus. Arthritis Rheum 2009;61:822–9.
42. Yoon S, Kang DH, Choi TY. Psychiatric symptoms in systemic lupus erythematosus: diagnosis and treatment. J Rheum Dis 2019;26:93–103.
43. Hawro T, Krupińska-Kun M, Rabe-Jabłońska J, Sysa-Jędrzejowska A, Robak E, Bogaczewicz J, et al. Psychiatric disorders in patients with systemic lupus erythematosus: association of anxiety disorder with shorter disease duration. Rheumatol Int 2011;31:1387–91.
44. Gao Y, Lau EYY, Wan JHY, Lau CS, Mok MY. Systemic lupus erythematosus patients with past neuropsychiatric involvement are associated with worse cognitive impairment: a longitudinal study. Lupus 2016;25:637–44.
45. Fragoulis GE, Cavanagh J, Tindell A, Derakhshan M, Paterson C, Porter D, et al. Depression and anxiety in an early rheumatoid arthritis inception cohort. Associations with demographic, socioeconomic and disease features. RMD Open 2020;6:e001376.
46. Tay SH, Cheung PPM, Mak A. Active disease is independently associated with more severe anxiety rather than depressive symptoms in patients with systemic lupus erythematosus. Lupus 2015;24:1392–9.
47. Rogers JL, Eudy AM, Pisetsky D, Criscione-Schreiber LG, Sun K, Doss J, et al. Utilizing clinical characteristics and patient-reported outcome measures to categorize lupus subtypes. Arthritis Care Res (Hoboken) 2020;73:386–93.
48. Pisetsky DS, Clowse MEB, Criscione-Schreiber LG, Rogers JL. A novel system to categorize the symptoms of systemic lupus erythematosus. Arthritis Care Res (Hoboken) 2019;71:735–41.