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The Problem of Pain in Systemic Lupus Erythematosus: An Explication of the Role of Biopsychosocial Mechanisms

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ABSTRACT. **Objective.** To define biopsychosocial mechanisms of pain that go above and beyond disease activity and organ damage in systemic lupus erythematosus (SLE).

Methods. We conducted a cross-sectional analysis of patient-reported data in a population-based registry of 766 people with SLE. Predictors of pain intensity and interference were examined using hierarchical linear regression. We built 2 main hierarchical regression models with pain intensity and interference as outcomes, both regressed on disease activity and organ damage. For each model, we sought to establish the relationship between pain outcomes and the primary exposures using sequential steps comprising the inclusion of each construct in 6 stages: demographic, socioeconomic, physical, psychological, behavioral, and social factors. We also conducted sensitivity analyses eliminating all overt aspects of pain in the disease activity measure and reestimated the models.

Results. Disease activity and organ damage explained 32–33% of the variance in pain intensity and interference. Sociodemographic factors accounted for an additional 4–9% of variance in pain outcomes, whereas psychosocial/behavioral factors accounted for the final 4% of variance. In the sensitivity analyses, we found that disease activity and organ damage explained 25% of the variance in pain outcomes.

Conclusion. Disease activity only explained 33% of the variance in pain outcomes. However, there was an attenuation in these associations after accounting for psychosocial/behavioral factors, highlighting their roles in modifying the relationship between disease activity and pain. These findings suggest that multilevel interventions may be needed to tackle the negative effect of pain in SLE.

Key Indexing Terms: biopsychosocial, disease activity, pain, social determinants of health, systemic lupus erythematosus

Roughly 50–100 million Americans are living with ongoing pain, resulting in healthcare costs of $635 billion annually.[1] An estimated 20 million people live with high-impact chronic pain with substantially restricted work, social, and self-care activities.[1] Pain is the most frequently reported symptom in rheumatology, with the etiology ascribed to inflammation, joint degeneration, and central sensitization.[2] Patients with systemic lupus erythematosus (SLE) rank pain as the most distressing symptom, above other symptoms such as fatigue, depression, sleep disturbance,

weight gain, rashes, and forgetfulness.[3] A previous survey revealed that 32% of patients with SLE listed joint and muscle pain and/or swelling as the symptom associated with the most negative impact on their lives.[3] Despite treatment advances, pain remains the most prominent, underaddressed patient complaint. In a study of persistently frequent (≥ 3 visits per year) emergency department visits among patients with SLE, pain was coded as the chief concern for 50% of these visits.[4]

Chronic pain has lasting personal costs to patients, including poor quality of life, disability, social isolation, stress, and other psychosocial problems. The prevalence of chronic pain (defined as persistent pain that occurs on at least half the days for ≥ 6 months) and increased pain intensity (defined as the magnitude of experienced pain) vary by age, race/ethnicity, sex, educational attainment, and income.[1,5,6] Pain interference (defined as pain that hinders major life activities) is also patterned by sociodemographic determinants.[1,5] Lifestyle-related factors such as smoking and obesity, as well as comorbidities, are implicated in more severe pain manifestations.[1,5] Despite the substantial effect of pain and extensive explorations of the determinants of health in SLE, the mechanisms of pain intensity and interference in SLE are not completely understood. We present a biopsychosocial approach (Supplementary Figure 1, available with the online version of this article) to explain pain intensity and interference as multidimensional, dynamic integration among disease-related, demographic, socioeconomic, physical, psychological, behavioral, and

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social constructs that reciprocally influence one another.[7,8] We hypothesized that disease activity and organ damage would be associated with increasing pain intensity and interference in a cross-sectional sample of predominantly Black patients with SLE, along with other determinants. Quantifying the potential effect of modifiable behavioral, psychosocial, and SLE-related factors is important for the development of appropriate interventions to address the problem of pain in SLE.

METHODS

Study setting. The Georgians Organized Against Lupus (GOAL) cohort is a population-based cohort of individuals with a validated diagnosis of SLE supported by the Centers for Disease Control and Prevention. The overall aim is to examine the effect of sociodemographic and healthcare factors on outcomes that are relevant to patients, healthcare providers, and policy makers. Recruitment and data collection methods have been previously described.[9] Consecutive annual sets of surveys have been administered to the GOAL cohort participants since 2012. All participants completed a self-report questionnaire to return by mail or to be completed online or by phone.

The Emory University Institutional Review Board, Grady Health System Research Oversight Committee, and Georgia Department of Public Health Institutional Review Board approved the GOAL study protocol. All participants provided informed consent.

Main exposures. Patient-reported responses from surveys through October 2015 to August 2017 were analyzed. The primary exposures of interest were disease activity and organ damage. Disease activity was measured using the Systemic Lupus Activity Questionnaire (SLAQ), a validated tool designed to be used in population-based studies outside the clinical setting, when physician assessment is not feasible.[10,11] The SLAQ includes 24 questions to assess disease activity symptoms and signs (e.g., fatigue, fever, skin rashes, arthritis) in the past 3 months. Items are endorsed as "no problem," "mild," "moderate," or "severe" and scored from 0 to 3. SLAQ scoring ranges from 0 to 44, with higher scores indicating greater SLE-related disease activity.

Organ damage accrual was measured using a validated self-administered version of the Brief Index of Lupus Damage.[12] This tool measures cumulative organ damage in 12 organ systems that has been present for at least 6 months since SLE onset. Items are coded as present or absent, with scores ranging from 0 to 30 and higher scores indicating greater organ damage. This has been used in epidemiological studies and has shown to predict or correlate with important outcomes such as death, work loss, and depression.[13,14,15]

Main outcomes. The primary outcomes of interest were pain interference and pain intensity as reported at baseline and measured by the Patient Reported Outcomes Measurement System (PROMIS) adult short forms (SF).[16]

Pain intensity was measured using the following question from the PROMIS Global Health SF v1.0 (PROMIS Global-10): "In the past 7 days, how would you rate your pain on average?" An 11-item ordinal scale from 0 to 10 is provided to answer the question, with a higher score indicating more pain intensity.

Pain interference was measured using the PROMIS-SF Pain Interference 4a. This 4-item questionnaire uses a 5-item Likert scale rated from 1 (not at all) to 5 (very much) to quantify the effect of pain on daily activities, working around the house, participation in social activities, and completing household chores in the past 7 days. Raw scores were calculated by the PROMIS HealthMeasures Scoring Service and converted to *t*-scores. A *t*-score of 50 represents the reference population (mean 50, SD 10). A higher PROMIS *t*-score represents a greater presence of the concept being measured.

Covariates. We broadly defined 6 main constructs, as shown in Supplementary Figure 1 (available with the online version of this article).

1.   Demographic factors included age at baseline, sex (female vs male), ethnicity (Black vs non-Black), and marital status (single vs married/ living with a partner).

2.   Socioeconomic factors included annual income in $10,000 increments, and educational attainment (high school or less, some college, and college and above).

3.   Physical factors included quality of sleep, which was assessed with the PROMIS-SF Sleep Disturbance 8a. This is an 8-item measure of self-reported perceptions of sleep quality, depth, and restoration within the past 7 days. Patient-reported data were collected to measure BMI in kg/m². Physical health was measured using a 5-point Likert scale question from the PROMIS Global-10: "In the past 7 days, how would you rate your physical health?" Answers were scored from 1 = poor to 5 = excellent.

4.   Psychological factors included anxiety, depression, and anger. These domains were measured using PROMIS-SFs (Depression 8a, Anxiety 4a, and Anger 5a). These 3 measures have demonstrated clinical validity across a range of chronic health conditions.[17]

5.   Behavioral factors included smoking, which was categorized as current vs not current. In addition, we used 3 scales from the Brief Coping Orientation to Problems Experienced (COPE) tool to measure negative mechanisms of coping (substance/alcohol use, self-blame, and denial) along with 1 scale to measure coping with religion. The tool has good psychometric properties to measure coping strategies used in everyday life or in distressing situations.[18,19]

6.   Social factors included emotional support and social isolation, which were measured with the following PROMIS-SFs: Social Isolation 6a assessed perceptions of being avoided, excluded, detached, or disconnected from, or unknown by others; and Emotional Support 4a measured feelings of being cared for and valued as a person and having confidant relationships.[20] In addition, a modified version of the Everyday Discrimination Scale was used to measure various forms of interpersonal mistreatment in participants' day-to-day lives over the previous 12 months. Examples include being "treated with less respect than other people" and "treated as if you are not smart." The 10 items on the scale are framed in the context of general mistreatment, without reference to race/ethnicity and other demographics. Responses were assessed with a 4-point scale (1 = never, 2 = rarely, 3 = sometimes, 4 = often), which was summed and averaged for a final score. The everyday discrimination scale has been widely used across samples of Black, White, and Chinese participants,[21,22,23,24] and has shown high levels of internal consistency as well as convergent and divergent validity.[21,25] We also measured unmet financial needs using the analogous 4-item scale included in the Conger Financial Strain measure.[26] The scale assesses specific needs that cannot be met due to financial hardship (e.g., not enough money to buy the [home/clothing/food/medical resources] we need).

Statistical analysis. The data were analyzed using SAS version 9.4 (SAS Institute). Baseline characteristics were obtained using summary statistics. Continuous variables were summarized using means, SDs, and medians. The unadjusted associations between covariates and the exposures and outcomes were estimated using linear regression. We used G*Power to conduct a posthoc calculation of required sample size for a linear multiple regression to test the increase in R^2 with a power of 95% and a model with 23 predictors, with small-to-medium effect size (0.05).[27] The required sample size was 664. We used all of the available data of 766 patients, making this study more than adequately powered.

Predictors of pain intensity and interference were examined using hierarchical linear regression. We built 2 main regression models: both pain intensity and pain interference regressed on disease activity and organ damage. Each regression model sought to establish the relationship between pain outcomes and the primary exposures using hierarchical steps comprising the inclusion of each construct in 6 stages: demographic (sex, age, marital status, and race/ethnicity), socioeconomic (annual household income and educational attainment), physical (sleep disturbance, BMI, and global health–physical), psychological (anxiety, depression, and anger), behavioral (smoking, coping with religion, coping with substance/alcohol abuse, and

coping with denial), and social (emotional support, social isolation, financial strain, and discrimination). In advance of the analyses, we specified an *a priori* framework (Supplementary Figure 1, available with the online version of this article) and a logically determined priority of each construct based on clinical expertise on how pain would be evaluated in a clinical scenario. Thus, entered into the first stage were biological or disease-related constructs: disease activity and organ damage. At Stage 2, demographic characteristics were entered, followed by socioeconomic factors at Stage 3, physical factors at Stage 4, psychological factors at Stage 5, behavioral factors at Stage 6, and social factors at Stage 7. Our goal was to determine whether newly added constructs showed significant improvement in the proportion of explained variance in pain intensity and interference by the models (R^2) over disease-related constructs.

Sensitivity analyses. To account for possible collinearity between disease activity and pain outcomes, we examined the effect of a modified SLAQ score without 6 pain-related measures: stomach pain, chest pain, muscle pain, headache, joint swelling, and joint pain. We modeled the 2 pain outcomes on the modified SLAQ score with the other variables to determine if there were changes in the inferences from the original SLAQ score. We also examined the individual contributions of constitutional, mucocutaneous, organ system, and musculoskeletal symptoms in SLAQ on pain outcomes. We replaced the full SLAQ with the scores for each of the individual contributions in Models 1 and 7.

RESULTS

Baseline characteristics. There were 766 participants, of which 93% were female (Table 1). The mean age was 48 years. A majority were Black (82%), nonsmokers (87%), single (62%), and had a reported annual income of < $40,000 (67%). The mean disease activity score was 16.2 and the mean organ damage score was 2.5. The means and SDs were 5.3 ± 2.9 for pain intensity and 54.8 ± 10.2 for pain interference. Means and SDs of PROMIS measures were 55.7 ± 9.9 for sleep disturbance, 51.3 ± 9.3 for emotional support, 51.8 ± 10.4 for depression, 5.8 ± 10.2 for anxiety, 49.0 ± 10.9 for social isolation, 2.5 ± 0.9 for physical health, and 52.8 ± 12.3 for anger. Other means and SDs were 1.8 ± 0.6 for everyday discrimination and 9.2 ± 3.3 for financial strain.

Bivariate analyses. The unadjusted associations between predictors, main exposures, and outcomes are shown in Table 2. The following characteristics were significantly associated with higher pain intensity: single marital status, Black ethnicity, lower household income, and lower educational attainment. Age and sex did not have a significant association with pain intensity. Higher levels of sleep disturbance and BMI were associated with higher pain intensity. Better self-reported physical health was associated with lower pain intensity. Participants who reported higher levels of anxiety, depression, and anger were also more likely to report higher pain intensity. Smokers were more likely to report higher pain intensity in comparison to nonsmokers. Higher reported levels of coping with religion or spirituality were associated with increased pain intensity. Increased negative coping characteristics (substance/alcohol use, self-blame, and denial) were associated with higher pain intensity. However, the association between coping and substance/alcohol use was not significant. Higher levels of emotional support were associated with decreased pain intensity; conversely, higher levels of social isolation, financial strain, and discrimination were associated

with increased pain intensity. These bivariate associations were similar for pain interference and disease activity (except for age). The following were significantly associated with organ damage: age, household income, sleep disturbance, physical health, anxiety, depression, as well as coping with self-blame, social isolation, and financial strain.

Hierarchical regression modeling. The association between pain intensity and disease activity and organ damage adjusted for all the constructs in the full model explained up to 53% of the variance in pain intensity (Table 3, Table 4, Figure 1). Disease activity and organ damage explained 31% of the variance in pain intensity, with increased disease activity correlating with increased pain intensity. However, the association between organ damage and pain intensity was not significant in the 7 models. The magnitude of the association between disease activity and pain intensity was attenuated going from the unadjusted model (β 0.179, 95% CI 0.159–0.199) to the full adjusted model (β 0.106, 95% CI 0.081–0.130). Demographic and socioeconomic factors accounted for an additional 9% of variance in pain intensity, with older age, male sex, Black ethnicity, lower income, and lower educational attainment showing significant association with increased pain intensity in the fully adjusted model. Sleep disturbance, BMI, and physical health explained an additional 9% of the variance in pain intensity; all 3 measures remained significant in the fully adjusted model. Increased sleep disturbance and increased BMI were associated with increased pain intensity, while better self-reported physical health was associated with lower pain intensity. Psychological, behavioral, and social factors accounted for the final 4% of the variance in pain intensity. Only anger and coping with denial remained significant in the fully adjusted model.

The findings of the hierarchical regression analyses of pain interference on disease activity and organ damage adjusted for the other constructs are shown in Table 5. Approximately 54% of the variance in pain interference was explained by the constructs. Disease activity and organ damage explained 33% of the variance in pain interference; however, only disease activity remained significantly predictive of pain interference in the fully adjusted model (Table 3, Figure 1). The effect size of the association between disease activity and pain interference was attenuated going from the unadjusted (β 0.593, 95% CI 0.528–0.659) to the fully adjusted model (β 0.261, 95% CI 0.180–0.341). Demographic and socioeconomic factors explained an additional 4% of the variance in pain interference. Only older age and lower educational attainment remained significant in the final model. BMI, sleep disturbance, and physical health explained a further 12% of the variance in pain interference, with all 3 measures remaining significant in the final model. Psychological, behavioral, and social factors accounted for the final 4% of the variance in pain interference; however, only anger and coping with self-blame remained significant in the fully adjusted model.

Sensitivity analyses. Supplementary Tables 1 and 2 (available with the online version of this article) show the findings of the sensitivity analyses using the modified disease activity measure in which all of the pain-related items in the disease activity score were removed. While the inferences from Tables 4 and 5 hold, the

Table 1. Baseline characteristics of patients in the Georgians Organized Against Lupus cohort.

		Overall, n = 766			Overall, n = 766
Pain outcomes			**Physical factors**		
Pain intensity, 1-item score	Mean ± SD	5.3 ± 2.9	PROMIS sleep disturbance, *t*-score	Mean ± SD	55.7 ± 9.9
	Median (IQR)	6.0 (3.0–8.0)		Median (IQR)	56.1 (51–63)
	Range	0–10		Range	32–73
PROMIS pain interference, *t*-score	Mean ± SD	58.3 ± 9.7	BMI, kg/m², n (%)	Mean ± SD	29.4 ± 8.0
	Median (IQR)	60.3 (53.9–65.5)		Median (IQR)	28.3 (24–34)
	Range	41.6–75.6		Range	13–66
Disease-related factors			PROMIS physical health 1-item score	Mean ± SD	2.5 ± 0.9
Disease activity (SLAQ score)	Mean ± SD	16.2 ± 9.1		Median (IQR)	2.0 (2–3)
	Median (IQR)	15.0 (9–22)		Range	1–5
	Range	0–44	**Psychological factors**		
Organ damage (BILD score)	Mean ± SD	2.5 ± 2.4	PROMIS anxiety, *t*-score	Mean ± SD	54.8 ± 10.2
	Median (IQR)	2.0 (1–4)		Median (IQR)	55.6 (47.9–61.7)
	Range	0–15		Range	40.3–81.4
Mild-to-severe pain manifestations in past 3 months, n (%)			PROMIS depression, *t*-score	Mean ± SD	51.8 ± 10.4
	Chest pain	367 (47.9)		Median (IQR)	52.3 (44.4–58.9)
	Stomach pain	421 (55.0)		Range	38.0–82.4
	Headache	452 (58.9)	PROMIS anger, *t*-score	Mean ± SD	52.8 ± 12.3
	Joint pain	658 (85.9)		Median (IQR)	52.8 (44–61)
	Muscle pain	573 (74.8)		Range	33–83
Current medications, n (%)	Steroids	395 (51.6)	**Behavioral health**		
	HCQ	539 (70.4)	Cigarette smoking[d], n (%)	Current	100 (13.1)
	Immunosuppressive drugs	280 (36.6)		Not current	663 (86.9)
	Biologics	44 (5.7)	Coping with spirituality and religion	Mean ± SD	6.2 ± 2.0
	CYC	15 (2.1)		Median (IQR)	7.0 (5.0–8.0)
Renal damage, n (%)[a]	Yes	53 (6.9)		Range	2–8
	No	713 (93.1)	Coping with substance and alcohol use	Mean ± SD	2.4 ± 1.1
Demographic factors				Median (IQR)	2.0 (2.0–2.0)
Age, yrs	Mean ± SD	48.4 ± 13.6		Range	2.0–8.0
	Median (IQR)	48.6 (38.3–58.4)	Coping with self-blame	Mean ± SD	3.5 ± 1.8
	Range	17.1–89.5		Median (IQR)	3.0 (2.0–5.0)
Sex, n (%)	Male	52 (6.8)		Range	2–8
	Female	714 (93.2)	Coping with denial	Mean ± SD	3.1 ± 1.6
Marital status[b], n (%)	Single	478 (62.4)		Median (IQR)	2.0 (2.0–4.0)
	Not single	288 (37.6)		Range	2–8
Ethnicity[c], n (%)	Non-Black	138 (18.0)	**Social factors**		
	Black	628 (82.0)	PROMIS emotional support	Mean ± SD	51.3 ± 9.3
Socioeconomic factors				Median (IQR)	49.9 (43.8–62.0)
Annual income level, n (%)	< $40,000	511 (66.7)		Range	25.8–62.0
	$40,000–69,000	120 (15.7)	PROMIS social isolation, *t*-score	Mean ± SD	49.0 ± 10.9
	≥ $70,000	135 (17.6)		Median (IQR)	49.0 (40.0–57.4)
Education level, n (%)	(1) High school or less	251 (32.8)		Range	34.4–76.2
	(2) Some college	253 (33.0)	Financial strain, unmet needs	Mean ± SD	9.2 ± 3.3
	(3) College or above	262 (34.2)		Median (IQR)	9.0 (8.0–11.0)
				Range	4–16
			Everyday discrimination scale	Mean ± SD	1.8 ± 0.6
				Median (IQR)	1.7 (1.2–2.1)
				Range	1.0–4.0

[a] Renal disease was defined as either receiving a kidney transplant or dialysis for more than 6 months. [b] Marital status was defined as (1) single = never married, divorced, or widowed or (2) not single = married or living with a partner. [c] This analysis was limited to non-Black and Black individuals. The original GOAL data set is multiethnic but the numbers of non-White and non-Black individuals were few. [d] Smoking status is defined as (1) current = smokes every day or some days or (2) not current = does not smoke. BILD: Brief Index of Lupus Damage; CYC: cyclophosphamide; HCQ: hydroxychloroquine; PROMIS: Patient Reported Outcomes Measurement Information System; SLAQ: Systemic Lupus Activity Questionnaire.

modified disease activity measure combined with organ damage explained 25% of the variance in pain intensity and interference, which is less than the 32–33% of the variance in the original models using the full disease activity scores. After combining the other constructs, the full models explained 51–52% of the variance in both outcomes. Table 3 and Figure 1 show that the

Table 2. Factors associated with pain outcomes and disease-related measures in individuals with SLE in the unadjusted linear regression.

	Pain Intensity	Pain Interference	Disease Activity	Organ Damage
Demographic factors				
Age at survey	0.006 (−0.009 to 0.022)	0.024 (−0.027 to 0.075)	**−0.072 (−0.119 to −0.025)**	**0.034 (0.021 to 0.046)**
Sex				
Male	Ref	Ref	Ref	Ref
Female	0.396 (−0.433 to 1.226)	−0.483 (−3.232 to 2.265)	−2.382 (−4.965 to 0.201)	0.316 (−0.368 to 1.000)
Marital status				
Not single	Ref	Ref	Ref	Ref
Single	**0.770 (0.342 to 1.199)**	**2.059 (0.635 to 3.483)**	**2.496 (1.169 to 3.823)**	0.261 (−0.094 to 0.617)
Ethnicity				
Non-Black	Ref	Ref	Ref	Ref
Black	**1.650 (1.117 to 2.182)**	**3.035 (1.243 to 4.827)**	**1.863 (0.172 to 3.553)**	0.151 (−0.299 to 0.600)
Socioeconomic factors				
Household income	**−0.439 (−0.514 to −0.365)**	**−1.262 (−1.515 to −1.008)**	**−1.139 (−1.376 to −0.902)**	**−0.147 (−0.213 to −0.082)**
Education				
High school or less	Ref	Ref	Ref	Ref
Some college	−0.465 (−0.956 to 0.026)	−0.776 (−2.422 to 0.870)	1.441 (−0.120 to 3.002)	0.134 (−0.293 to 0.560)
College or above	**−2.133 (−2.619 to −1.647)**	**−6.128 (−7.755 to −4.501)**	**−3.593 (−5.132 to −2.054)**	−0.087 (−0.508 to 0.335)
Physical factors				
PROMIS sleep disturbance	**0.142 (0.123 to 0.160)**	**0.518 (0.459 to 0.579)**	**0.455 (0.397 to 0.512)**	**0.036 (0.018 to 0.053)**
BMI	**0.083 (0.057 to 0.108)**	**0.237 (0.152 to 0.322)**	**0.112 (0.031 to 0.193)**	0.010 (−0.011 to 0.033)
PROMIS physical health	**−1.476 (−1.677 to −1.275)**	**−5.602 (−6.237 to −4.967)**	**−4.494 (−5.116 to −3.871)**	**−0.625 (−0.806 to −0.444)**
Psychological factors				
PROMIS anxiety	**0.089 (0.069 to 0.108)**	**0.379 (0.316 to 0.441)**	**0.388 (0.331 to 0.446)**	**0.018 (0.001 to 0.035)**
PROMIS depression	**0.089 (0.070 to 0.108)**	**0.348 (0.287 to 0.410)**	**0.451 (0.398 to 0.505)**	**0.027 (0.010 to 0.043)**
PROMIS anger	**0.092 (0.076 to 0.108)**	**0.360 (0.310 to 0.410)**	**0.338 (0.291 to 0.385)**	0.011 (−0.000 to 0.024)
Behavioral factors				
Smoking				
Not current	Ref	Ref	Ref	Ref
Current	**1.091 (0.476 to 1.707)**	**3.469 (1.431 to 5.507)**	**4.241 (2.340 to 6.142)**	0.331 (−0.179 to 0.842)
Coping with religion	**0.133 (0.028 to 0.237)**	**0.443 (0.096 to 0.790)**	0.182 (−0.145 to 0.510)	0.109 (0.027 to 0.196)
Coping with substance and alcohol use	0.177 (−0.015 to 0.369)	0.634 (−0.001 to 1.270)	**1.027 (0.434 to 1.620)**	0.009 (−0.149 to 0.167)
Coping with self-blame	**0.256 (0.138 to 0.374)**	**1.281 (0.895 to 1.667)**	**1.475 (1.123 to 1.828)**	**0.109 (0.011 to 0.208)**
Coping with denial	**0.474 (0.251 to 0.597)**	**1.387 (0.970 to 1.803)**	**1.467 (1.080 to 1.854)**	0.083 (−0.024 to 0.190)
Social factors				
PROMIS emotional support	**−0.044 (−0.067 to −0.022)**	**−0.231 (−0.304 to −0.156)**	**−0.242 (−0.310 to −0.175)**	−0.018 (−0.037 to 0.000)
PROMIS social isolation	**0.079 (0.061 to 0.097)**	**0.342 (0.283 to 0.401)**	**0.354 (0.300 to 0.408)**	**0.031 (0.015 to 0.047)**
Financial strain	**0.354 (0.294 to 0.415)**	**1.139 (0.934 to 1.344)**	**1.114 (0.925 to 1.304)**	**0.102 (0.047 to 0.157)**
Discrimination score	**0.640 (0.311 to 0.970)**	**2.401 (1.312 to 3.490)**	**3.658 (2.663 to 4.653)**	0.249 (−0.025 to 0.524)

Values indicate β coefficients (95% CI). Bolded values are statistically significant. PROMIS: Patient Reported Outcomes Measurement Information System; SLE: systemic lupus erythematosus.

other constructs (physical, psychological, behavioral, and social) explain more of the variance in pain outcomes after accounting for the pain items in disease activity.

In addition, individual contributions of SLAQ symptoms to the variance in pain outcomes varied (Supplementary Tables 3 and 4, available with the online version of this article). Consistent with Supplementary Tables 1 and 2, we found that the models with constitutional, mucocutaneous, and organ system symptoms explained 17–27% of the variance in pain outcomes, while the models with musculoskeletal symptoms contributed 38–39% of the variance in pain outcomes.

DISCUSSION
Our findings highlight the complex and dynamic interactions of 7 constructs in the perceptions of pain among patients with SLE. We found that individuals reporting increased disease activity also reported higher pain intensity and interference. There was an attenuation in these associations after accounting for other constructs, highlighting their roles in modifying the relationship between disease activity and pain intensity. The biopsychosocial model has been used in understanding the correlates of pain and fatigue in rheumatoid arthritis, multiple sclerosis, osteoarthritis, and sickle cell disease.[28,29,30,31,32] These studies found significant roles of disease activity/inflammation and psychosocial factors, similar to our findings. Our findings are consistent with a cohort of patients with SLE in which disease activity measured by the Systemic Lupus Activity Measure (SLAM) and Systemic Lupus Erythematosus Disease Activity Index was more than twice as

Table 3. Summary of the hierarchical linear regression models.

Outcome	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
Pain intensity							
R^2	0.312	0.362	0.405	0.489	0.496	0.514	0.531
ΔR^2	–	0.046	0.043	0.085	0.007	0.018	0.017
Pain interference							
R^2	0.330	0.343	0.374	0.498	0.512	0.520	0.540
ΔR^2	–	0.013	0.031	0.124	0.013	0.008	0.020
Pain intensity*							
R^2	0.245	0.288	0.348	0.463	0.471	0.493	0.510
ΔR^2	–	0.042	0.060	0.116	0.008	0.022	0.017
Pain interference*							
R^2	0.254	0.264	0.307	0.479	0.500	0.509	0.524
ΔR^2	–	0.010	0.043	0.172	0.018	0.012	0.015

Model 1: disease-related factors; Model 2: Model 1 + demographic factors; Model 3: Model 2 + socioeconomic factors; Model 4: Model 3 + physical factors; Model 5: Model 4 + psychological factors; Model 6: Model 5 + behavioral factors; Model 7: Model 6 + social factors. * These models comprise the sensitivity analyses that include the modified Systemic Lupus Activity Questionnaire (SLAQ), which removes overt mentions of pain including stomach pain, chest pain, headache, joint swelling, joint pain, and muscle pain.

high in a group of patients reporting high levels of pain compared with those reporting low levels of pain.[33]

Our understanding of the mechanisms of inflammation that affect pain in SLE (and in general) is evolving. However, we confidently used SLAQ as a surrogate for inflammation because higher disease activity is correlated with higher levels of serum biomarkers of inflammation.[34] When we omitted pain-related items from the SLAQ score, the association between disease activity and pain intensity persisted. Further, we examined the individual contributions of constitutional, mucocutaneous, organ system, and musculoskeletal symptoms in SLAQ and found that mucocutaneous and constitutional symptoms contributed to pain to a lesser extent than musculoskeletal symptoms. Greco, et al[35] showed similar findings in their study investigating chronic pain clustering in SLE. The pain clusters did not change significantly when pain symptoms were omitted from the revised SLAM.[35] All these findings suggest that individual, behavioral, and social factors can potentially exacerbate or attenuate the intensity of pain caused by inflammatory mediators in patients with SLE with active disease.

We found that demographic and lifestyle constructs play crucial roles in pain severity. Our finding that older age was independently associated with increased pain intensity and interference is consistent with other epidemiological studies that have found an age-related increase in the prevalence of chronic pain.[1] We found that Black patients reported higher pain intensity than non-Black patients. These findings run parallel with sex and racial/ethnic differences in the development and outcomes of SLE.[36,37] Males also seem to have more severe disease compared with females.[38] However, these findings are contrary to what is known in the general population, in which females and White individuals have higher prevalence of chronic pain, suggesting that pain in SLE has a different epidemiological profile.[1] We found that higher socioeconomic status was protective for pain outcomes. In patients with SLE, socioeconomic status is associated with lower disease activity and damage accrual.[39] In the general population, socioeconomic disadvantage is associated

with almost every aspect of poorer health, including increased morbidity and decreased life expectancy. Not surprisingly, it is also consistently associated with increased risk for pain.[40]

A growing body of research suggests that obesity and poor sleep quality, which have been associated with pain outcomes, may play important roles in SLE outcomes. Several studies have linked obesity with disease activity, increased risk of renal disease, cardiovascular complications, fibromyalgia, depression, poorer functional capacity, and decreased quality of life in patients with SLE.[41,42,43,44] Obesity is hypothesized to cause pain through excess mechanical stresses. Due to its proinflammatory state, obesity is also a marker of increased functional and psychological complications in chronic pain.[45] Moreover, recent reports along with our findings suggest that complex pathways may link sleep disturbance and pain along with depression and cognitive symptoms.[46] Thus, further research is needed to determine whether interventions specifically developed to tackle those factors may effectively improve pain outcomes in SLE populations.

In addition, we found that psychological, behavioral, and social factors were associated with pain intensity and interference in the unadjusted models. In the fully adjusted models, these associations were no longer significant. When we omitted overt manifestations of pain from the disease activity measure (as seen in the sensitivity analyses), we found that psychosocial and demographic factors accounted for more variance in pain intensity and interference, highlighting their importance in pain outcomes. The psychosocial burden of SLE is immense. Compared to the general population, patients with SLE report impaired quality of life and more fatigue, fibromyalgia, anxiety, and depression.[47] These psychosocial factors also disproportionately increased with disease activity and organ damage. Future studies elucidating the role of psychosocial factors in pain are needed for the appropriate design of targeted interventions for patients with SLE.

Our study has some limitations. First, we cannot rule out residual and unmeasured confounding due to variables not capturing the complete essence of constructs such as

Table 4. Hierarchical linear regression analyses of 7 constructs with pain intensity as outcome.

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
R^2	0.312	0.362	0.405	0.489	0.496	0.514	0.531
ΔR^2	–	0.046	0.043	0.085	0.007	0.018	0.017
Disease-related factors							
Disease activity	**0.179 (0.159 to 0.199)**	**0.182 (0.163 to 0.202)**	**0.165 (0.144 to 0.185)**	**0.114 (0.092 to 0.136)**	**0.114 (0.091 to 0.137)**	**0.112 (0.088 to 0.135)**	**0.106 (0.081 to 0.130)**
Organ damage	0.018 (–0.057 to 0.092)	–0.021 (–0.096 to 0.053)	–0.027 (–0.101 to 0.046)	–0.044 (–0.114 to 0.025)	–0.042 (–0.111 to 0.028)	–0.043 (–0.114 to 0.028)	–0.026 (–0.098 to 0.046)
Demographic factors							
Age at survey		**0.024 (0.011 to 0.036)**	**0.024 (0.011 to 0.036)**	**0.021 (0.009 to 0.033)**	**0.023 (0.011 to 0.035)**	**0.021 (0.009 to 0.034)**	**0.021 (0.008 to 0.034)**
Sex							
Male		Ref	Ref	Ref	Ref	Ref	Ref
Female		**–0.851 (–1.528 to –0.174)**	**–0.676 (–1.333 to –0.019)**	**–0.809 (–1.443 to –0.175)**	**–0.817 (–1.449 to –0.185)**	**–0.841 (–1.502 to –0.181)**	**–0.932 (–1.607 to –0.257)**
Marital status							
Not single		Ref	Ref	Ref	Ref	Ref	Ref
Single		0.072 (–0.293 to 0.437)	–0.387 (–0.777 to 0.003)	–0.310 (–0.679 to 0.06)	–0.248 (–0.619 to 0.123)	–0.208 (–0.591 to 0.174)	–0.186 (–0.577 to 0.205)
Ethnicity							
Non-Black		Ref	Ref	Ref	Ref	Ref	Ref
Black		**1.334 (0.874 to 1.794)**	**0.905 (0.44 to 1.37)**	**0.792 (0.353 to 1.232)**	**0.766 (0.325 to 1.207)**	**0.668 (0.212 to 1.125)**	**0.726 (0.251 to 1.201)**
Socioeconomic factors							
Household income			**–0.181 (–0.274 to –0.088)**	**–0.139 (–0.227 to –0.052)**	**–0.143 (–0.231 to –0.056)**	**–0.148 (–0.238 to –0.058)**	**–0.121 (–0.218 to –0.024)**
Education							
High school or less			Ref	Ref	Ref	Ref	Ref
Some college			**–0.457 (–0.876 to –0.038)**	**–0.472 (–0.866 to –0.078)**	**–0.452 (–0.848 to –0.056)**	–0.337 (–0.747 to 0.074)	–0.356 (–0.786 to 0.073)
College or above			**–0.853 (–1.338 to –0.369)**	**–0.829 (–1.284 to –0.374)**	**–0.792 (–1.248 to –0.336)**	**–0.574 (–1.048 to –0.101)**	**–0.630 (–1.119 to –0.142)**
Physical factors							
PROMIS sleep disturbance				**0.060 (0.041 to 0.079)**	**0.056 (0.037 to 0.076)**	**0.057 (0.037 to 0.077)**	**0.051 (0.030 to 0.071)**
BMI				**0.041 (0.021 to 0.061)**	**0.04 (0.020 to 0.060)**	**0.037 (0.017 to 0.058)**	**0.041 (0.019 to 0.063)**
PROMIS physical health				**–0.455 (–0.655 to –0.256)**	**–0.456 (–0.659 to –0.253)**	**–0.538 (–0.748 to –0.329)**	**–0.637 (–0.855 to –0.419)**
Psychological factors							
PROMIS anxiety					–0.015 (–0.038 to 0.008)	–0.01 (–0.034 to 0.015)	–0.006 (–0.032 to 0.019)
PROMIS depression					–0.016 (–0.036 to 0.005)	–0.012 (–0.034 to 0.009)	–0.010 (–0.032 to 0.012)
PROMIS anger					**0.028 (0.010 to 0.047)**	**0.028 (0.009 to 0.047)**	**0.026 (0.005 to 0.046)**
Behavioral factors							
Smoking							
Not current						Ref	Ref
Current						–0.024 (–0.516 to 0.469)	0.041 (–0.474 to 0.557)
Coping with religion						0.015 (–0.068 to 0.098)	0.021 (–0.065 to 0.108)
Coping with substance and alcohol use						0.002 (–0.151 to 0.155)	0.004 (–0.15 to 0.158)
Coping with self-blame						**–0.178 (–0.294 to –0.063)**	**–0.197 (–0.317 to –0.076)**
Coping with denial						**0.152 (0.040 to 0.264)**	**0.159 (0.045 to 0.274)**
Social factors							
PROMIS emotional support							0.007 (–0.014 to 0.029)
PROMIS social isolation							0.001 (–0.022 to 0.025)
Financial strain							0.030 (–0.034 to 0.094)
Discrimination score							–0.196 (–0.494 to 0.102)

Model 1: Disease-related factors; Model 2: Model 1 + demographic factors; Model 3: Model 2 + socioeconomic factors; Model 4: Model 3 + physical factors; Model 5: Model 4 + psychological factors; Model 6: Model 5 + behavioral factors; Model 7: Model 6 + social factors. Statistically significant variables in the final model are bolded. PROMIS: Patient Reported Outcomes Measurement Information System.
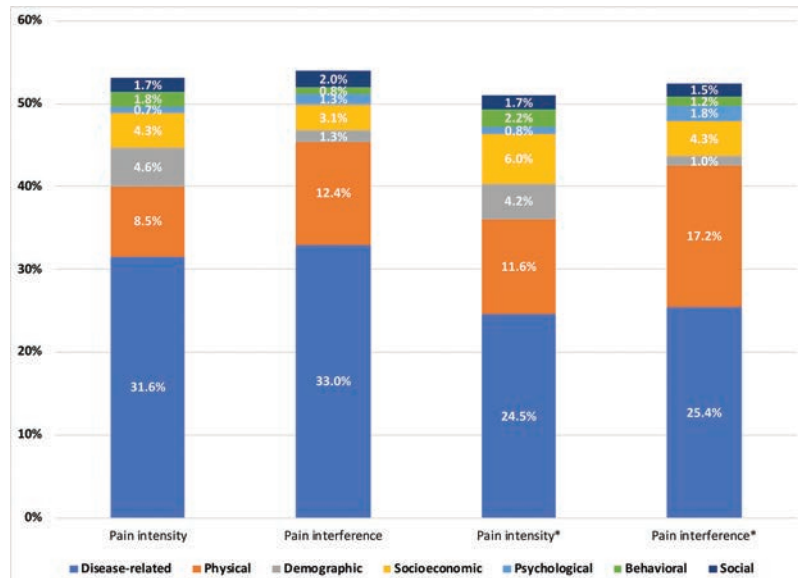
Figure 1. A representation of the proportion of variance in pain intensity and pain interference explained by 7 constructs in the biopsychosocial framework. * Corresponds to results of the sensitivity analysis that tested the model using the modified SLAQ. The modified SLAQ score removes stomach pain, chest pain, headache, joint swelling, joint pain, and muscle pain. SLAQ: Systemic Lupus Activity Questionnaire.

socioeconomic and psychological factors. Second, the survey did not capture information on fibromyalgia. Third, the cohort may not be generalizable to the US population of patients with SLE. However, as SLE affects predominantly Black women—comprising 43% of SLE cases in the US according to prevalence estimates—our findings are generalizable to a large US population, particularly the southeastern region of the country. Fourth, given the different assessment periods for the patient-reported outcomes and the cross-sectional nature of the design, we were unable to investigate the temporal relation between pain and associated factors, which in turn may affect the interpretation of our results. Finally, our findings may be confounded by the ordering of the constructs in the regression models. The choice of the order of the constructs was made prior to model building, based on the assumption that the main predictors of pain in SLE are disease activity and organ damage. Our findings suggest that a range of multidimensional interventions to reduce pain should continue to be directed to disease-related factors, as clinically indicated. This is the single construct that explained the largest proportion of variation in pain. However, this proportion never exceeded 33% in our models, with significant remaining proportions explained by demographic, socioeconomic, physical, psychological, behavioral, and social factors. These are constructs that are not modified directly by immunologic interventions but speak to other mechanisms that should be considered when aiming to improve the lives of those with SLE. This may include programs focusing on reducing obesity and improving sleep hygiene, as well as psychological interventions addressing anxiety, depression, and anger. Behavioral interventions, such as smoking cessation and improving coping skills, should be considered. Social programs to improve emotional support and decrease isolation may be helpful. Validated and

culturally appropriate self-management programs will be an important tool in this space.

Our study has several strengths. To our knowledge, this was the first study to present a biopsychosocial model for pain intensity and interference in SLE. We leveraged a large sample of patients to make these inferences. However, this was a cross-sectional study and we were unable to answer questions about causality. Therefore, future studies of longitudinal design are needed to ascertain causality. In addition, while our models elucidate a proportion of factors, there is also a significant proportion of variance that remains undefined. Further research is needed to confirm these observations as well as to identify other factors that continue to remain undefined in our models.

ONLINE SUPPLEMENT
Supplementary material accompanies the online version of this article.

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Table 5. Hierarchical linear regression analyses of 7 constructs with pain interference as outcome.

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
R^2	0.330	0.343	0.374	0.498	0.512	0.520	0.540
ΔR^2	–	0.013	0.031	0.124	0.013	0.008	0.020
Disease-related factors							
Disease activity	0.593 (0.528 to 0.659)	0.606 (0.539 to 0.672)	0.552 (0.483 to 0.620)	0.323 (0.252 to 0.394)	0.292 (0.217 to 0.368)	0.282 (0.205 to 0.360)	**0.261 (0.180 to 0.341)**
Organ damage	0.248 (0.002 to 0.494)	0.15 (–0.102 to 0.402)	0.144 (–0.107 to 0.395)	0.042 (–0.187 to 0.271)	0.081 (–0.146 to 0.309)	0.094 (–0.142 to 0.330)	0.138 (–0.101 to 0.377)
Demographic factors							
Age at survey		0.065 (0.022 to 0.109)	0.065 (0.022 to 0.107)	0.065 (0.026 to 0.104)	0.073 (0.034 to 0.112)	0.060 (0.018 to 0.101)	**0.051 (0.008 to 0.095)**
Sex							
Male		Ref	Ref	Ref	Ref	Ref	Ref
Female		–1.111 (–3.388 to 1.166)	–0.650 (–2.882 to 1.583)	–1.541 (–3.618 to 0.536)	–1.587 (–3.642 to 0.468)	–1.439 (–3.613 to 0.735)	–1.659 (–3.900 to 0.582)
Marital status							
Not single		Ref	Ref	Ref	Ref	Ref	Ref
Single		0.173 (–1.059 to 1.406)	–1.104 (–2.432 to 0.225)	–0.471 (–1.687 to 0.746)	–0.182 (–1.395 to 1.03)	–0.153 (–1.419 to 1.113)	–0.286 (–1.579 to 1.007)
Ethnicity							
Non-Black		Ref	Ref	Ref	Ref	Ref	Ref
Black		1.864 (0.316 to 3.412)	0.630 (–0.954 to 2.214)	0.311 (–1.136 to 1.757)	0.304 (–1.136 to 1.744)	–0.003 (–1.516 to 1.510)	0.184 (–1.394 to 1.762)
Socioeconomic factors							
Household income			–0.494 (–0.810 to –0.178)	–0.257 (–0.546 to 0.032)	–0.254 (–0.539 to 0.032)	–0.301 (–0.599 to –0.004)	–0.264 (–0.585 to 0.056)
Education							
High school or less			Ref	Ref	Ref	Ref	Ref
Some college			–1.003 (–2.427 to 0.422)	–0.879 (–2.173 to 0.415)	–0.703 (–1.995 to 0.588)	–0.472 (–1.828 to 0.884)	–0.388 (–1.808 to 1.031)
College or above			–2.508 (–4.156 to –0.861)	–2.195 (–3.692 to –0.698)	–2.082 (–3.569 to –0.595)	–1.717 (–3.285 to –0.150)	**–1.687 (–3.306 to –0.067)**
Physical factors							
PROMIS sleep disturbance				0.254 (0.193 to 0.315)	0.216 (0.153 to 0.279)	0.216 (0.150 to 0.282)	**0.200 (0.131 to 0.269)**
BMI				0.093 (0.028 to 0.159)	0.089 (0.023 to 0.154)	0.08 (0.011 to 0.148)	**0.092 (0.021 to 0.164)**
PROMIS physical health				–2.415 (–3.067 to –1.762)	–2.226 (–2.885 to –1.566)	–2.379 (–3.067 to –1.692)	**–2.647 (–3.369 to –1.925)**
Psychological factors							
PROMIS anxiety					0.012 (–0.063 to 0.087)	0.037 (–0.044 to 0.117)	0.016 (–0.069 to 0.101)
PROMIS depression					–0.047 (–0.115 to 0.021)	–0.026 (–0.096 to 0.045)	–0.017 (–0.091 to 0.057)
PROMIS anger					**0.125 (0.065–0.186)**	**0.125 (0.061–0.189)**	**0.137 (0.069–0.204)**
Behavioral factors							
Smoking							
Not current						Ref	Ref
Current						0.179 (–1.441 to 1.798)	0.297 (–1.397 to 1.991)
Coping with religion						0.087 (–0.186 to 0.360)	0.185 (–0.101 to 0.471)
Coping with substance and alcohol use						–0.305 (–0.804 to 0.194)	–0.317 (–0.824 to 0.190)
Coping with self-blame						–0.307 (–0.689 to 0.075)	**–0.424 (–0.823 to –0.026)**
Coping with denial						0.046 (–0.325 to 0.418)	0.047 (–0.333 to 0.427)
Social factors							
PROMIS emotional support							–0.016 (–0.086 to 0.054)
PROMIS social isolation							0.043 (–0.034 to 0.120)
Financial strain							–0.013 (–0.226 to 0.199)
Discrimination score							–0.595 (–1.581 to 0.392)

Model 1: Disease-related factors; Model 2: Model 1 + demographic factors; Model 3: Model 2 + socioeconomic factors; Model 4: Model 3 + physical factors; Model 5: Model 4 + psychological factors; Model 6: Model 5 + behavioral factors; Model 7: Model 6 + social factors. Statistically significant variables in the final model are bolded. PROMIS: Patient Reported Outcomes Measurement Information System.

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