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Physical Inactivity and Incident Depression in a Multiracial, Multiethnic Systemic Lupus Erythematosus Cohort

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Abstract

Objective.—Physical activity is known to improve depressive symptoms. The present study was undertaken to examine physical inactivity as a predictor of incident depression in systemic lupus erythematosus (SLE).

Methods.—Data derive from the California Lupus Epidemiology Study (CLUES), a longitudinal cohort with confirmed SLE diagnoses. Physical inactivity was assessed from a single item, "I rarely or never do any physical activities," and depressive symptoms by the 8-item Patient Health Questionnaire (PHQ-8). Analysis included those not depressed at baseline (PHQ-8 score <10) who completed an in-person baseline assessment and at least 1 follow-up visit (n = 225). Incident depression was defined as a PHQ-8 score of ≥10 at follow-up. Cox proportional hazards regression modeled incident depression over 2 years as a function of baseline physical inactivity, controlling for age, sex, race, income, comorbidities, disease activity, and disease damage.

Results.—At baseline, the mean ± SD age of the participants was 45 ± 15 years, 88% were female, and 70% identified as non-White. Mean PHQ scores for those without depression at

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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 submitted for publication. Dr. Katz 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.

Study conception and design. Yazdany, Dall'Era, Katz.

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No potential conflicts of interest relevant to this article were reported.

baseline did not differ by activity status, but those who were inactive at baseline were significantly more likely to develop depression over the next 2 years (hazard ratio [HR] 2.89 [95% confidence interval (95% Cl) 1.46–5.71]). After adjusting for covariates, the association remained strong, including a >3-fold increased risk of incident depression among the sedentary group (HR 3.88 [95% Cl 1.67–9.03]).

Conclusion.—In this diverse SLE cohort, a simple question about physical inactivity was highly predictive of incident depression over the subsequent 2 years. Results suggest an urgent need for approaches to reduce sedentary behavior in this high-risk population.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune condition characterized by autoantibody formation, multisystem organ involvement, and increased mortality. It also confers an increased risk of comorbid depression, and prior research has shown that the lifetime prevalence of major depressive disorder is 40–50% in the setting of SLE relative to 17% in the general population of US adults (1–3). The greater burden of depression experienced in this patient group is important due to the deleterious effects on quality of life, as well as associations with greater disability, interference with medication compliance, and worse patient-reported outcomes (4–6).

Although the higher prevalence of depression in lupus relative to the general population is well demonstrated, the psychosocial, biological, and lifestyle factors responsible (and measures that can be taken to mitigate them) are not yet well defined. Prior studies to better understand risk factors for depression in lupus suggest that disease activity (7) and treatment with glucocorticoids (8) may play a role, but the link between depression and disease activity has been inconsistent across studies. Moreover, indices of disease severity do not fully account for the relative burden of depression in this patient group (7–9). Physical Inactivity confers an increased risk of incident depression in the general population (10–13) and may contribute to a higher incidence of mood disorders in SLE, but the link between inactivity and incident depression in this high-risk group has not been explored.

In order to address this knowledge gap, we sought to determine whether physical inactivity predicts subsequent new onset depression among individuals with SLE, and if so, the magnitude of the associated risk. We used data from a racially and ethnically diverse lupus cohort to assess whether patients who were not depressed at baseline but reported low physical activity were at increased risk for developing depression over time.

PATIENTS AND METHODS

Study design and participants.

Subjects were participants in the California Lupus Epidemiology Study (CLUES), a prospective longitudinal sample of individuals with SLE. Briefly, starting in 2015, participants in CLUES were recruited through the California Lupus Surveillance Project, which used outpatient, hospital, and laboratory records to identify all SLE patients residing in San Francisco County from 2007 to 2009 (14). Additional participants in the geographic region were identified through academic and community rheumatology clinics and from

earlier studies of genetic risk factors for SLE outcomes (15,16). SLE diagnoses were confirmed by study physicians based on the following: 1) >4 of the 11 American College of Rheumatology (ACR) revised criteria for the classification of SLE (17,18); 2) meeting 3 of the 11 ACR criteria with a rheumatologist's documented diagnosis of SLE; or 3) a confirmed diagnosis of lupus nephritis. This combined definition of SLE has been used in prior population-based studies (16).

Participants were assessed annually either by telephone or in person. For the baseline assessment, the majority of participants (332 of 431) completed an in-person research clinic visit, whereas annual follow-up visits were conducted either in-person or by telephone. The in-person visits included collection and review of medical records prior to the visit; a history and physical examination conducted by a physician specializing in lupus; collection of biospecimens for clinical and research purposes; and completion of a structured interview administered by an experienced research assistant. CLUES specifically aimed to include a diverse patient sample, with representation from multiple racial and ethnic groups speaking multiple languages. Therefore, research clinic visits and interviews were conducted in 4 languages: English, Spanish, Mandarin, or Cantonese. The study was approved by the University of California, San Francisco Institutional Review Board, and all participants provided informed consent.

Given our objective to assess independent predictors of incident depression, participants were included in these analyses If they completed an in-person baseline assessment, at least 1 follow-up visit, and did not meet criteria for depression at baseline (see definition of depression below). There were 306 participants who completed an in-person assessment at baseline and had at least 1 follow-up assessment, of whom 81 met criteria for depression at baseline; the remaining 225 participants without depression at baseline were eligible for inclusion in this analysis.

Measures.

Sedentary behavior.—The primary predictor of interest was physical inactivity at the baseline assessment period. Inactivity was assessed using a single item from the Rapid Assessment of Physical Activity instrument; participants who agreed to the statement, "I rarely or never do any physical activities" were classified as inactive. We focused the analysis on endorsement of sedentary behavior rather than self-report of time spent exercising, as prior exercise studies indicate that self-report physical activity is frequently over-reported (19).

Incident depression.—The primary outcome was incident depression, assessed by the 8-item Patient Health Questionnaire depression scale (PHQ-8), a validated screening measure for which scores of ≥10 have a high correspondence with clinical diagnoses of depressive disorders in large clinical studies (20). We use the term "depression," although we recognize that meeting the ≥10 cut point is not the equivalent of a clinical diagnosis of depression. Incident depression was defined as a change in PHQ-8 score from <10 at baseline to ≥10 during follow-up.

SLE-specific disease factors.—Age of diagnosis was obtained by self-report. Disease damage was measured with the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI), a physician-completed assessment that provides a composite score for cumulative organ damage (21). Disease activity was measured with the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), a validated physician-completed instrument that consists of data from 24 weighted clinical and laboratory variables from 9 organ systems (22,23). Participants were also queried regarding current treatment with glucocorticoids (including dosage and frequency) as well as other immunomodulatory medications.

Other variables.

Participants were asked about sociodemographic characteristics, including sex, age, race, educational attainment (categorized as high-school graduate or less, versus those with additional education), and income (categorized for analysis as household income < or >125% of the federal poverty level). Height and weight were measured during the baseline in-person visit or self-reported by telephone-only participants, and body mass Index (BMI) was calculated as weight (kg) divided by height (m^2). Participants were also queried regarding smoking status and major comorbidities such as cardiovascular disease, diabetes mellitus, asthma, and cancer.

Statistical analysis.

Differences In characteristics of participants who were inactive versus active at baseline were tested using *t*-tests and chi-square analyses. For the analysis of risk of onset depression, we defined follow-up time as the number of months from the baseline interview to the first interview with a PHQ-8 score of ≥10, or until the most recent interview date, for those whose PHQ-8 scores remained <10. Kaplan-Meier life table analysis was used to compare incident depression by physical activity level over time, and differences were tested using a log rank test. In bivarlate analyses, we compared risk of depression onset based on physical activity status, sociodemographic factors, lupus disease characteristics such as disease activity (SLEDAI), and comorbidities using unadjusted Cox proportional hazards regression models. We also assessed for interaction, including for an interaction effect between physical inactivity and income, and physical inactivity and history of depression, to determine If the association between physical inactivity and incident depression differed by poverty status or prior depressive episodes. We fit a multivariable Cox model to evaluate the independent association of physical inactivity with risk of depression onset, adjusting for race, sex, age, poverty-level income, comorbidities (cardiovascular disease, diabetes mellitus, asthma, malignancy), disease activity (SLEDAI), and disease damage (SDI). The proportional hazards assumption was investigated by testing the constancy of the log hazard ratio (HR) over time by means of the log-minus-log survival plots and interaction with time (log transformed); these tests revealed no violations of the proportional hazards assumption. All analyses were performed using Stata, version 14.

RESULTS

Sample characteristics.

Table 1 shows the baseline characteristics of the study participants for the overall sample and according to physical activity status (physically inactive versus active). The cohort participants were racially and ethnically diverse; they were 35% Asian, 30% White, 22% Hispanic, 10% African American, and 2% percent other. Eighteen percent of participants reported doing no physical activity (sedentary), and people in the sedentary group were more likely to be Hispanic or African American, live on or below poverty income, and have less education. The participants in the inactive group were more likely to have a history of lupus nephritis and a higher BMI, but there was no significant association for physical inactivity with lupus disease activity or disease damage.

Bivariate associations of inactivity with incident depression.

We Included patients with a history of depression, which represented 26.1 % of the cohort (Table 1), but no participants were depressed at baseline because participants meeting criteria for depression were excluded In order to assess for new-onset depression during follow-up. The inactive behavior was stable over the first year of the study; only 5% of participants provided a different response to the question regarding inactivity between the baseline assessment and study visit performed 1 year later. Importantly, the mean ± SD PHQ-8 score at baseline did not differ by activity status (3.96 ± 2.78 among Inactive, 3.43 ± 3.13 among active; $P = 0.23$, data not shown). In other words, scores of the participants in the inactive group were not hovering just below the PHQ-8 score threshold for depression during the baseline assessment.

There were 37 incident cases of depression (16% of the cohort) over a mean of 26 months of follow-up. Among participants who were inactive at baseline, the percent with incident depression was 38%, compared to 14% among the nonsedentary participants. In bivariate Cox proportional hazards regression analyses, several sociodemographic, behavior/lifestyle, and health factors were significantly associated with greater risk of incident depression. Physical inactivity showed a strong unadjusted association with incident depression (HR 2.89 [95% confidence interval (95% Cl) 1.46–5.71]) (Table 2). Among the sociodemographic factors, poverty-level income was the only variable to significantly associate with depression (HR 2.27 [95% Cl 1.08–4.77]). The factors related to health status that were significantly associated with incident depression Included cardiovascular disease (HR 3.46 [95% Cl 1.70–7.04]) and physician-assessed disease damage (SDI) (HR 1.23 [95% Cl 1.08–1.40]). Kaplan-Meier analysis showed a significantly increased risk of depression onset among the inactive group in comparison to the active group (log-rank chi square = 12.4, $P < 0.001$) (Figure 1). There was no interaction between inactivity and poverty on risk of depression.

Multivariable analysis.

In the multivariable Cox proportional hazards regression model, inactivity at baseline associated with more than a 3-fold increased risk of Incident depression (HR 3.88 [95% Cl 1.67–9.03]) during the follow-up period, adjusted for age, sex, race, income, self-report

disease activity, self-report disease damage, and comorbidities (Table 3). The other variables In the multivariable model that significantly associated with elevated depression risk included male sex, White race, and higher lupus disease damage, but physical inactivity conferred the greatest and most statistically significant risk (data not shown).

DISCUSSION

This study is the first to Investigate whether physical Inactivity impacts new-onset depression In individuals with SLE. We found that low levels of physical activity were highly predictive of incident depression in this group. Among this cohort of individuals with lupus who were sedentary, there was a >3-fold increased risk of new-onset depression over the subsequent 2 years, even after adjusting for comorbidities, sociodemographic risk factors, and indices of disease severity and damage. Furthermore, physical inactivity was the strongest independent predictor of new-onset depression, even more than poverty-level income, racial and ethnic minority status, SLE disease activity, coexisting cardiovascular disease, or other comorbidities. Given the high burden of depression experienced by lupus patients relative to the general population (even among those with low disease activity and less severe disease), this finding is an important step toward understanding the contribution of lifestyle factors to mood symptoms in a uniquely vulnerable patient group.

Prior studies have demonstrated that exercise reduces the risk of incident depression in the general population, but this is the first study to our knowledge to investigate the relationship of physical inactivity to incident depression in patients with systemic lupus, a uniquely vulnerable group. Factors known to contribute to the higher burden of depression in SLE relative to the general population include reaction to chronic illness, fatigue, treatment side effects, and socioeconomic factors (4,8,9,24,25). In a minority of SLE patients, depression is immune mediated and associated with anti-ribosomal P antibodies and antibodies to *N*-methyl-D-aspartate receptors (26,27). This study builds on existing literature by establishing inactivity as a strong independent predictor of depression In SLE. Furthermore, we show that an affirmative response to the simple statement, “I rarely or never do any physical activities” was the most predictive variable for subsequent depression, suggesting an important opportunity to reduce the burden of depression among lupus patients by screening and intervening on sedentary behavior as part of routine health care maintenance. For example, this question could be integrated during ambulatory rheumatology check-in procedures, and an affirmative response could trigger treating physicians to provide education, instruction, and prescription of exercise.

Even patients who did not meet public health guidelines for physical activity but participated in some amount of regular light activity were at significantly lower risk of incident depression relative to the sedentary group in our study. This finding is in keeping with the US Office of Disease Prevention and Health Promotion 2018 Physical Activity Guidelines Update, which asserts that people incur health benefits even with small increases in activity (28). Moore et al showed that there is no lower threshold for the amount of leisure time in physical activity that confers a benefit for all-cause mortality (any amount is helpful with an increasing magnitude of benefit up to 20 hours per week) (29), and our data suggest a similar relationship between any amount of physical activity and risk reduction for

incident depression in SLE. The understanding that “any physical activity counts” toward reducing risk of worse health outcomes should be shared with people living with SLE who face physical, psychological, social, or environmental barriers to achieving recommended physical activity targets but can safely reduce sedentary behavior.

One limitation of this study is the use of pat lent-reported instruments to adjudicate the predictor and outcome variables. For example, incident depression was assessed using a depression screening measure as opposed to clinician-confirmed diagnosis, and therefore, depression may have been missed among participants who either did not feel comfortable, or who did not understand, all of the items included in the PHQ-8. However, multiple steps were taken to mitigate this limitation, including the use of a validated instrument with favorable psychometric properties (20), use of questionnaires in multiple languages administered by research staff with language concordance, and a script for study interviewers to increase participant comfort while answering sensitive questions. In addition, since we used a depression score cut point, there was a risk that the inactive participants were hovering just under the cutoff for depression during the baseline assessment. Given this concern, we examined the distribution of PHQ-8 scores among the study sample at baseline and found that they did not differ by physical activity status, indicating a meaningful change over time in PHQ-8 scores for the inactive group relative to the nonsedentary patients. Physical inactivity was also assessed by self-report, and some participants may not have responded accurately, but single-item self-report measures of physical inactivity have demonstrated similar accuracy compared to objectively measured inactivity (30). We intentionally evaluated self-reported absence of activity rather than self-reported levels of activity to mitigate the risk of activity overestimation.

We found a strong independent association between inactivity and Incident depression, but as with all observational studies, there is a risk of unmeasured confounding, and we cannot definitively infer causation. However, we were able to leverage longitudinal data to exclude participants with depression at baseline and to prospectively assess whether physical activity relates to subsequent depressive symptoms. Additionally, we used detailed clinical and sociodemographic data provided by study participants, as well as physician-assessed measures of disease activity and damage completed by rheumatologists specializing in SLE, to build a comprehensive multivariable model that included covariates for each major factor with the potential to impact both physical activity and depression.

In conclusion, we found that physical inactivity, a modifiable lifestyle behavior, is common in SLE and confers a significant independent risk of incident depression among this patient group. Our findings have important clinical implications, as roughly 40% of people with lupus will experience depression during their lifetime (1), and strategies to prevent depression represent a major unmet need for those with this disease. Results support the importance of even low levels of physical activity and suggest an urgent need for approaches (such as health care providers’ physical activity prescriptions and referrals to appropriate community-based exercise programs) to increase physical activity in this high-risk patient population. In addition to reducing the risk of important physical comorbidities such as cardiovascular disease, our data suggest that a small Increase in physical activity may also reduce the risk of major mental health challenges experienced disproportionally in SLE.

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SIGNIFICANCE & INNOVATIONS

- This is the first study examining the association between physical inactivity and risk of incident depression in systemic lupus erythematosus (SLE).
- After adjusting for potential confounding factors, physical inactivity conferred a >3-fold increased risk of developing depression over 2 years of follow-up among a diverse lupus cohort.
- Physical inactivity was the strongest independent predictor of new onset depression, even more than poverty-level income, racial-ethnic minority status, SLE disease activity, coexisting cardiovascular disease, or other comorbidities.
- Interventions to reduce sedentary behavior among SLE patients may reduce the disproportionate burden of depression experienced by this high-risk group.

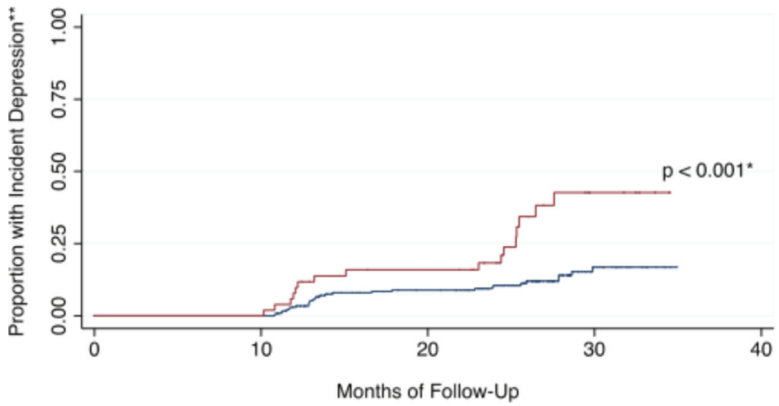

Figure 1.

Cumulative proportion of systemic lupus erythematosus patients with depression by physical activity for the sedentary (red) and not sedentary (blue) groups. * = *P* by Kaplan-Meier life table analysis log rank test; ** = incident depression defined as a change in the 8-item Patient Health Questionnaire depression scale from <10 at baseline to ≥10 during follow-up.

Table 1.

Characteristics of patients with systemic lupus erythematosus (SLE) according to physical activity category *

Characteristic	Overall (n = 225)	Active (n = 184)	Inactive (n = 41)	*P*
Sociodemographlc factors				
Age, mean ± SD years	45.0 ± 14.2	44.5 ± 13.8	47.0 ± 15.4	0.306
Female	88.4	87.5	92.7	0.348
Race				0.031 †
White	30.2	33.7	14.6	
Hispanic	22.2	19.6	34.2	
African American	10.2	8.7	17.1	
Asian	35.1	35.3	34.2	
Unspecified or other	2.2	2.7	0.0	
Poverty income ‡	16.3	13.0	32.4	0.005 †
High school education or less	18.7	13.6	41.5	<0.001 †
Marital status				0.013 †
Never married	35.4	36.8	29.3	
Married or living with partner	56.1	56.0	56.1	
Divorced	7.2	6.0	9.8	
Widowed	1.4	0.6	4.9	
Lupus-specific characteristics				
SLE disease duration, mean ± SD years	16.8 ± 10.5	16.9 ± 10.4	16.2 ± 11.0	0.696
Disease activity by SLEDAI, mean ± SD	2.9 ± 2.9	2.9 ± 3.0	2.6 ± 2.7	0.572
Disease damage by SDI, mean ± SD	1.8 ± 2.0	1.7 ±1.9	2.2 ± 2.1	0.138
Lupus Severity Index, mean ± SD	6.9 ± 1.6	6.8 ± 1.6	7.1 ± 1.6	0.415
History of lupus nephritis	56.5	55.0	63.4	0.323
Prednisone ≥7.5 mg/day	21.8	21.7	22.0	0.976
Any glucocorticoid use over prior year	64.7	61.9	77.8	0.071
Current hydroxychloroquine use	95.7	96.2	93.6	0.523
Comorbidities and health status				
Cardiovascular dlsease §	12.0	9.2	24.4	0.007 †

Characteristic	Overall (n = 225)	Active (n = 184)	Inactive (n = 41)	*P*
Diabetes mellitus	7.1	6.0	12.2	0.165
Asthma	9.3	8.2	14.6	0.197
History of malignancy	8.0	7.6	9.8	0.647
Body mass index, mean ± SD kg/m^2	25.6 ± 6.2	25.2 ± 5.2	27.8 ± 9.3	0.013[†]
Current smoker	3.6	3.9	2.5	0.679
History of depression	26.1	26.2	25.6	0.939

[*] Values are the percentage unless indicated otherwise. *P* values were calculated using chi-square tests for categorical measures and *t*-tests for continuous measures. SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index.

[†] Significant.

[‡] Poverty income defined as ≤125% of the federal poverty level.

[§] Cardiovascular disease: history of stroke, coronary artery disease, and/or myocardial infarction.

Table 2.

Bivariate associations of physical inactivity and covariates with incident depression*

Characteristic	No depression (n = 188)	Incident depression (n = 37)	Unadjusted HR (95% CI)
Physical activity status			
Inactive†	14.4	37.8	2.89 (1.46–5.71)‡
At least minimal physical activity	85.6	62.2	Ref.
Sociodemographic factors			
Age, mean ± SD years	44.3 ±14.1	48.2 ± 13.8	1.01 (0.99–1.04)
Female	89.4	83.8	0.64 (0.27 1.55)
Race/ethnicity			0.79 (0.61–1.03)
White	28.7	37.8	
Hispanic	21.3	27.0	
African American	10.6	8.1	
Asian	36.7	27.0	
Other	2.7	0.0	
Poverty income§	13.6	29.4	2.27 (1.08–4.77)‡
Education less than a bachelor's degree	43.6	59.5	1.56 (0.80–3.02)
Marital status			0.99 (0.61–1.61)
Never married	35.5	35.1	
Married or living with partner	55.9	56.8	
Divorced or separated	7.0	8.1	
Widowed	1.6	0.0	
Lupus-specific characteristics			
SLE disease duration, mean ± SD years	16.2 ±10.1	19.7 ± 12.0	1.02 (0.99–1.05)
Age of diagnosis, mean ± SD years	28.2 ±12.1	28.5 ± 12.2	1.00 (0.98–1.03)
Disease activity by SLEDAI, mean ± SD	2.9 ± 3.0	2.6 ± 2.8	0.97 (0.87–1.09)
Disease damage by SDI, mean ± SD	1.6 ± 1.8	2.8 ± 2.5	1.23 (1.08 1.40)‡
History of lupus nephritis	55.4	62.2	1.22 (0.63–2.40)
Prednisone ≥7.5 mg/day	22.3	18.9	0.77 (0.34–1.76)
Comorbidities			

Characteristic	No depression (n = 188)	Incident depression (n = 37)	Unadjusted HR (95% Cl)
Cardiovascular disease	8.5	29.7	3.46 (1.70–7.04)‡
Diabetes mellitus	5.3	16.7	2.27 (0.92–5.60)
Asthma	7.5	18.9	2.21 (0.95 5.12)
Obesity (BMI ≥30 kg/m^2)	18.1	24.3	1.36 (0.64–2.90)
History of malignancy	8.5	5.5	0.73 (0.17–3.02)
History of depression	24.7	33.3	0.73 (0.17–3.02)

*Values are the percentage unless indicated otherwise. “No depression” was defined as depressive symptoms by the 8-item Patient Health Questionnaire (PHQ-8) below the cutoff for depression (PHQ-8 score <10) throughout the study period. 95% Cl = 95% confidence interval; BMI = body mass index; HR = hazard ratio; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; Ref. = reference.

†Inactive was defined as rare participation in physical activities by self-report.

‡Significant.

§Poverty income was defined as ≤125% of the federal poverty level.

Table 3.

Adjusted risk of incident depression according to physical activity status among systemic lupus erythematosus patients *

	HR_{adj} (95% CI)†
Physically active	1 (−)
Physically inactive	3.88 (1.67–9.03)

*Among the 225 patients eligible for inclusion in the multivariable analysis, 22 had missing data for ≥1 of the covariates (e.g., income), resulting in n = 201 for the adjusted model. 95% Cl = 95% confidence interval; HR_{adj} = adjusted hazard ratio.

†HR_{adj} obtained from the Cox proportional hazards model adjusted for age, sex, race, income, comorbidities (cardiovascular disease, diabetes mellitus, asthma, malignancy), disease activity by the Systemic Lupus Erythematosus Disease Activity Index, and disease damage by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.