



LETTER TO THE EDITOR

Depression and Anxiety Associated With Systemic Lupus Erythematosus: A Nested, Case–Control Study in the *All of Us* Database

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1 | Background

Systemic lupus erythematosus (SLE) is a chronic illness, in which the immune system attacks healthy cells and tissues in the body in the majority of cases [1]. Although the increased risk of depression and anxiety in patients with SLE is known [2], studies investigating this association in diverse populations is limited. We examined the association of clinically diagnosed SLE and depression and anxiety using the All of Us (AoU) database, which is a National Health Institute initiative that focuses on biomedical research in historically underrepresented groups in the United States (US) with a cohort of 410 361 participants and growing [3]. This study's use of a diverse national cohort provides new insights into the mental health burden of SLE across populations with varying sociodemographic characteristics.

2 | Methods

Our matched case–control study included participants aged 18 years and older that were recruited to the AoU cohort from May 6, 2018 to December 20, 2024. We followed the STROBE reporting guideline.

Categorical variables such as sex, race, and ethnicity were analyzed using chi-squared tests or the Fisher exact test. For continuous variables like age, we used means and standard deviations

for distribution. To estimate the association between SLE and depression and anxiety, logistic regression was employed.

The identification of SLE and depression and anxiety were achieved through the use of electronic health record (EHR) data within the AoU database, specifically using SNOMED codes (detailed in the eMethods section of the Data S1). Each patient in our study was matched with four control individuals based on age, race and ethnicity, sex, smoking status, and hypothyroidism. Statistical significance was determined with a two-sided *p*-value of less than 0.05. All statistical analyses in this study were conducted using Python and utilizing libraries such as Pandas, NumPy, SciPy, Statsmodels, and Seaborn.

3 | Results

We identified 3799 individuals (both women and men) with SLE (mean [SD] age: 56.9 [14.5] years) and 15 180 matched controls (mean [SD] age: 56.9 [14.5] years). Age, sex, race and ethnicity, and smoking status were matched between SLE cases and controls. Individuals with SLE had higher diagnoses of depression and anxiety when compared to the control group (1933 [50.9%] vs. 3332 [22.0%]; *p* < 0.001 and 1940 [51.1%] vs. 3413 [22.5%]; *p* < 0.001), respectively (Table 1).

We observed a significant association between depression and anxiety with SLE in both univariable and multivariable models.

Abbreviations: AoU, all of us; EHR, electronic health record; SLE, systemic lupus erythematosus; UCSD, University of California, San Diego; US, United States.

TABLE 1 | Clinical characteristics of patients with SLE and control individuals matched by age, sex, and race and ethnicity.

Characteristic	Participants, no. (%) ^a		<i>p</i>
	Patients with SLE, (<i>n</i> = 3799)	Matched controls, (<i>n</i> = 15180)	
Age, mean (SD), years	56.9 (14.5)	56.9 (14.5)	1.00
Sex			
Female	3307 (87.1)	13 224 (87.1)	0.99
Male	404 (10.6)	1616 (10.7)	
Other ^b	88 (2.3)	340 (2.2)	
Race and ethnicity			
Not Hispanic or Latino			
Asian	90 (2.4)	360 (2.4)	1.00
Black	1020 (26.9)	4077 (26.9)	
White	1560 (41.1)	6240 (41.1)	
Hispanic or Latino			
Asian	< 20	< 20	
Black	20 (0.5)	80 (0.5)	
White	72 (1.9)	286 (1.9)	
Other ^c	1033 (27.2)	3032 (20.0)	
Ever smoker			
No	145 (3.8)	544 (3.6)	1.00
Yes	1229 (32.4)	4938 (32.5)	
NA	2425 (63.8)	9698 (64.0)	
Hypothyroidism	1091 (28.7)	1621 (10.7)	< 0.001
Depression	1933 (50.9)	3332 (22.0)	< 0.001
Anxiety	1940 (51.1)	3413 (22.5)	< 0.001

^aIn line with the data and statistics dissemination policy of the NIH All of Us Research Program, any values involving fewer than 20 individuals are presented in this manner to ensure participant privacy.

^bIncludes participants who either had no matching concept or who did not identify as male or female, preferred not to answer, or skipped the question.

^cIncludes participants who did not indicate Hispanic or Latino, skipped PMI, identified with multiple populations, chose not to answer, or belonged to single non-specified or Hispanic populations.

TABLE 2 | Association of SLE with depression and anxiety.

	Univariable analysis odds ratio (95% CI)	<i>p</i>	Multivariable analysis odds ratio (95% CI)	<i>p</i>
Depression	3.68 (3.42–3.97)	< 0.001	3.21 (2.97–3.47)	< 0.001
Anxiety	3.60 (3.34–3.87)	< 0.001	3.14 (2.90–3.39)	< 0.001

The univariable and multivariable analysis indicated that individuals with depression were more likely to have SLE (OR, 3.68; 95% CI, 3.42–3.97; $p < 0.001$) and (OR, 3.21; 95% CI, 2.97–3.47, $p < 0.001$), respectively. The univariable and multivariable analysis also indicated that individuals with anxiety were more likely to have SLE (OR, 3.60; 95% CI, 3.34–3.87; $p < 0.001$) and (OR, 3.14; 95% CI, 2.90–3.39, $p < 0.001$), respectively (Table 2). Our multivariate analysis was adjusted for hypothyroidism and

showed SLE was significantly associated with depression and anxiety.

4 | Discussion

SLE was significantly associated with depression and anxiety in our study in our multivariable analysis. Participants with SLE

had a 3.21- and 3.14-fold increase in odds of being diagnosed with depression and anxiety, respectively. Although our study does not confirm a causal relationship between SLE and depression and anxiety, it adds to the increasing body of literature suggesting a potential link. Hypothyroidism is known to be independently associated with depression and anxiety [4, 5].

Bachen, Chesney, and Criswell [6] investigated the prevalence of anxiety and depression in women with SLE and found that mood disorders and anxiety were more prevalent in the SLE population than the control group. Our results are aligned with these findings showing a higher rate of depression and anxiety in our SLE group than the control group. Our study builds on existing literature by utilizing a unique diverse national cohort, helping to address gaps in generalizability and representation identified in previous research.

The limitations of our study include lack of data on duration of diagnosis, severity, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria, treatment of SLE, and date of diagnosis. This study may not represent the entire population of the US. There may be confounding variables, such as socioeconomic status, access to healthcare [7], and a family history of mental disorders [8] which were not controlled for in our analysis that could be associated with increased depression and anxiety. Organ involvement related to treatment and damage, as well as cardiovascular disorders such as stroke, myocardial infarction, pulmonary embolism, and deep vein thrombosis were not accounted for in our analysis. These limitations may prevent us from fully exploring the nuances of SLE progression and its broader impact on not only mental but also physical health outcomes as well.

Given the chronic and multifaceted nature of SLE, it is important for healthcare providers to consider a multidisciplinary approach that not only addresses the physical manifestations of the disease but also prioritizes mental health. Routine screening for depression and anxiety should be integrated into the clinical management of SLE patients to ensure timely identification and intervention.

Author Contributions

N.A.A.F.: Conceptualization, methodology, validation, data curation, writing – original draft, writing – review and editing, project administration, prepared figures, supervision. F.D.: methodology, software, validation, formal analysis, data curation, writing – review and editing, prepared figures. R.O.: Conceptualization, methodology, validation, writing – review and editing, project administration, supervision. All authors have approved the final version for submission.

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Ethics Statement

The University of California, San Diego (UCSD) Institutional Review Board has been deemed our study (809009) exempt human subjects research.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data available on reasonable request from the authors.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.