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Post-Traumatic Stress Disorder (PTSD) and Risk of Systemic Lupus Erythematosus (SLE) among Medicaid Recipients

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Abstract

Objective: We studied post-traumatic stress disorder (PTSD), a severe trauma-related mental disorder, and systemic lupus erythematosus (SLE) risk in a large, diverse population enrolled in Medicaid, a U.S. government-sponsored health insurance program for low-income individuals.

Methods: We identified SLE cases and controls among patients 18–65 years old enrolled in Medicaid for ≥ 12 months in the 29 most populated US states from 2007 to 2010. SLE and PTSD case status were defined based on validated patterns of ICD-9 codes. Index date was the date of the first SLE code. Controls had no SLE codes but had another inpatient or outpatient code on the index date, and were matched 1:10 to cases by age, sex and race. Conditional logistic regressions calculated odds ratios (OR) and 95% confidence intervals (CI) for the association of PTSD with incident SLE, adjusting for smoking, obesity, oral contraceptive use, and other covariates.

Results: 10,942 incident SLE cases were matched to 109,420 controls. Prevalence of PTSD was higher in SLE cases at 10.74 cases of PTSD per 1,000 (95% CI 9.37–12.31) versus 7.83 (95% CI 7.42–8.27) in controls. The multivariable-adjusted OR for SLE among those with PTSD was 2.00 (95% CI 1.64–2.46).

Conclusion: In this large, racially and sociodemographic diverse US population, we found patients with prior PTSD diagnosis had twice the odds of a subsequent diagnosis of SLE. Studies are necessary to clarify the mechanisms driving the observed association and to inform possible interventions.

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Introduction

Systemic lupus erythematosus (SLE) is a complex, chronic autoimmune disease characterized by widespread dysfunction of the innate and adaptive immune systems and autoantibody formation. It can lead to significant clinical morbidity, including kidney failure, heart disease, and premature death.[1,2] Prevalence of lupus and lupus nephritis are much higher amongst women than men, people who identify with racial minority groups versus non-Hispanic Whites, and those with lower socioeconomic status.[1,3] Given these disparities in SLE, efforts to reduce incidence and identify potential pathways for treatment interventions need to consider individual and structural risk factors that account for such differences. One such risk factor is posttraumatic stress disorder.

Traumatic events, such as combat and sexual assault, have been linked to changes in the immune system,[4] and cohort studies have found higher rates of a variety of autoimmune diseases in persons with post-traumatic stress disorder (PTSD).[5,6] The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines PTSD as having exposure to a traumatic stressor, including violent assault, severe accident, abuse or life-threatening illness, which leads to a range of debilitating and intrusive symptoms.[7] These include a pervasive sense of imminent threat, avoidance of trauma-related stimuli, altered mood and cognition, hypervigilance, and subsequent negative impacts on daily functioning. PTSD is a common medical condition with past-year prevalence in the U.S. estimated at 3.5%, and more often affects women with a lifetime prevalence of 9.7% for women versus 3.6% for men.[8] Prevalence of PTSD is also higher among Black Americans than other racial and ethnic groups, partly due to differences in exposure to violence.[9]

It has been hypothesized that exposure to extreme stress, and the subsequent development of PTSD, may be causally related to SLE incidence. PTSD has been associated with a wide range of metabolic[10] and hormonal effects that could plausibly impact development of autoimmune disease. These include chronically lower glucocorticoid and higher catecholamine levels in the hypothalamic pituitary axis.[10] These alterations can in turn affect the immune system and inflammatory responses through many potential pathways, such as cytokine production, immune cell signaling, endocannabinoids, and epigenetic modifications, such as DNA methylation.[10–12]

Studies have shown potentially higher risks of a variety of different autoimmune diseases among people with PTSD, including in American military populations and in people exposed to the September 11th terrorist attack, and the civilian population in Sweden.[5,6,13,14] For SLE, data from the Nurses' Health Study II showed that trauma exposure and PTSD symptoms were associated with increased SLE risk, with a hazard ratio of 2.94 (95% CI 1.19–7.26).[15] However, this association has not been investigated in diverse population including males and females of a variety of socioeconomic, racial/ethnic and cultural backgrounds.

We aimed to examine the relationship between PTSD and incident SLE in a large, diverse group of Medicaid enrollees. We hypothesized that patients with incident SLE would be more likely to have a prior diagnosis of PTSD than those without SLE. Cases and controls

were matched for sex and race/ethnicity, and covariates included sociodemographic and health factors associated with increased risk of developing SLE. Research focused on Medicaid recipients is important given the substantial burden of SLE amongst Medicaid recipients and the higher rate of serious complications they face, especially among people identifying with racial or ethnic minority groups or who have low income.[1,3]

Methods

Study Population

We designed a case-control study using data from the Medicaid Analytic eXtract (MAX) database for patients ages 18 to 65 years old, living in the 29 most populated states in the US between January 1st, 2007 and December 31st, 2010. Medicaid is a health insurance program for low-income Americans. It is jointly run by federal and state governments, and is enriched for women with dependent children and unemployed people.

SLE Cases and Controls: Incident SLE cases were defined as having ≥3 ICD-9 codes for SLE from hospital discharge diagnoses or physician visit claims, occurring at least 30 days apart, which has previously yielded a positive predictive value of 92%.[16] The index date was the date of the first code for SLE after 12 or more months of enrollment. Controls were patients who did not have any codes for SLE, but who had another inpatient or outpatient claim on the index date. Controls were matched 1:10 to cases for age at index date, sex, and race/ethnicity. Patients with less than 12 months of continuous enrollment in Medicaid prior to the index or matched control date were excluded in order to increase the likelihood of SLE codes representing a new diagnosis.

Exposure: The exposure was PTSD, defined as having ≥2 ICD-9 codes for PTSD on different dates within 4 months, occurring prior to the index date for SLE.[17] This administrative algorithm for PTSD has been validated in a Veteran administration population with a positive predictive value (PPV) of 82%.[17] To further assess its validity in a non-military population, we administered the PTSD Checklist for DSM-5 (PCL-5) to 67 civilian subjects enrolled in our hospital system, who met the administrative algorithm definition (≥2 ICD-9 codes for PTSD on different dates within 4 months).[17] Patients were contacted via text and invited to fill out the survey on the hospital's online health portal. The 20-item self-administered PCL-5, scored from 1–80 points with a cut-off for probable PTSD of >30, has been extensively studied and validated.[18] These patients were 87% female, 83% White, 13% Black, and had a mean age of 52 years [Standard Deviation (SD) 14]. The PPV of this ICD-9 based algorithm was 96% compared to the PCL-5 score > 30.

Covariates: Matching factors included age at index date, sex, and race/ethnicity. Race/ethnicity in MAX is self-reported in mutually exclusive categories of Black/African American, American Indian/Alaska Native, Asian, Hispanic or Latino, and White. We also assessed variables that have been associated with increased risk of developing SLE including lower socioeconomic status (SES), obesity, tobacco use, and oral contraceptive use.[19–21] Several of these factors have also been associated with PTSD, including lower SES, obesity and tobacco use.[10,22,23] We used zip code level median household income as a measure

of area-level SES based on US Census data, divided into quartiles.[1] Obesity and tobacco use were defined based on ICD-9 codes.[24,25] Oral contraceptive use was defined based on national drug codes. Finally, we adjusted for US region of residence since this was significantly different between cases and controls.

Statistical Analyses

Conditional logistic regression was used to calculate the odds ratio (OR) and 95% confidence interval (CI) for PTSD present prior to the index date in SLE cases versus controls. We used multivariable analysis to adjust for additional variables collected prior to the SLE index date including SES, obesity, tobacco use, oral contraceptive use, US region of residence, and time enrolled in Medicaid.

We conducted two sensitivity analyses. In the first, we excluded SLE cases with less than 24 months of enrollment without a code for SLE prior to the index date to increase the likelihood of incident SLE. In the second sensitivity analysis, we excluded all patients with less than 6 months between the first code for PTSD and the first code for SLE or matched index date to increase the likelihood that PTSD occurred before the index date.

We also conducted a stratified analysis comparing the association of PTSD with SLE among individuals living in zip codes in the bottom half versus those in the top half of median household income. We tested for a formal multiplicative interaction between area-level SES and PTSD in the risk of SLE using an interaction term for continuous zip code level SES and PTSD in our main multivariable model.

Analyses were conducted using SAS 9.4 software. Institutional review board approval was obtained from the Mass General Brigham IRB for all aspects of this study. The data were obtained through a data use agreement with the Centers for Medicare and Medicaid Studies.

Results

We identified and included 10,942 cases of incident SLE. These were matched to 109,420 controls by age, sex and race. The sample was 94% female and included patients from diverse racial and ethnic backgrounds (Table 1). There were low recorded rates of smoking, obesity, and oral contraceptive use in both groups at the index date, but these did differ significantly in cases and controls. Additionally, there were significant differences in SES and US region of residence according to case status.

The prevalence of PTSD prior to the index date in the matched general population controls was 7.83 cases per 1,000 (95% CI 7.42–8.27), whereas it was 10.74 (95% CI 9.37–12.31) among those who later developed SLE (Table 2). The incidence rate of new cases of PTSD prior to the index date was 5.51 (95% CI 5.16–5.88) in the matched general population controls and 6.32 (95% CI 5.29–7.55) in those who later were diagnosed with SLE (Table 2). The median number of days between the first PTSD code and the first SLE code was 432 days, with a range of 1–1,356 days.

The OR for SLE among those with vs. without PTSD was 1.96 (95% CI 1.66–2.33, $p < 0.001$) in the matched but unadjusted conditional logistic regression, and 2.00 (95% CI

1.64–2.46, p<0.001) after further multivariable adjustment for area-level median household income, US region of residence, smoking, obesity, oral contraceptive use, and days enrolled in Medicaid prior to index date (Table 3). Further adjustment for the matching factors did not alter risk estimates (data not shown).

In the first sensitivity analysis including only patients with at least 24 months of enrollment without a code for SLE prior to the index date, there were 4,504 cases of SLE and 45,040 matched controls. Within this sample, the prevalence of PTSD was 15.74 (95% CI 12.71–19.49) among cases of SLE versus 9.97 (95% CI 9.09–10.93) for controls (Table 2). The incidence of PTSD among cases of SLE was 7.95 (95% CI 5.88–10.76), compared to 6.51 (95% CI 5.81–7.30) among controls (Table 2). The conditional logistic regression model estimated an OR for SLE of 2.64 (95% CI 2.07–3.4) (Table 3).

In the second sensitivity analysis, we excluded 35 patients whose SLE index date was less than 6 months from the first PTSD codes, as well as their matched controls. This yielded a sample of 10,907 cases and 109,193 controls. The OR for SLE in conditional logistic regression was 2.11 (95% CI 1.74–2.57) (Table 3).

In the analysis stratified by dichotomized median household income, those living in zip codes with the bottom half had an OR for SLE of 1.45 (95% CI 1.04–2.03) associated with PTSD, compared to 2.17 (95% CI 1.58–2.99) for those in the top half. This model adjusted for smoking, obesity, oral contraceptive use, US region of residence, and days enrolled in Medicaid prior to index date. We did not find a statistically significant multiplicative interaction between PTSD and continuous area-level SES (p interaction=0.09).

Conclusions

In this study of > 10,000 Medicaid enrollees from diverse socioeconomic and racial backgrounds, we find a doubling of risk of incident SLE among patients with pre-existing PTSD. This relationship was significant after adjusting for sociodemographic variables and other factors associated with development of SLE, and in two sensitivity analyses to test the robustness of our findings.

Our study builds on previous research into the risk of incident SLE among people with PTSD. A cohort study in active US military members noted a 58% higher risk of a long list of autoimmune disease in people with a history of PTSD, although the risk of SLE was not statistically significant with a hazard ratio of 1.4 (95% CI 0.7–2.8).[5] Similarly, a retrospective cohort study of American veterans noted significantly higher adjusted relative risk of several different autoimmune diseases in those with PTSD compared to veterans with psychiatric illnesses other than PTSD, but the risk of SLE was not statistically elevated with an adjusted relative risk of 1.18 (95% CI 0.85–1.51).[14] Both these past studies were likely influenced by samples that were 70 to 90% male, and therefore had relatively few cases of SLE, which strikes 9 times more females than males. In contrast, a study using the Nurses' Health Study II cohort uncovered a significantly higher risk of incident SLE among those with prior trauma exposure and PTSD, with a hazard ratio of 2.94 (95% CI 1.19–7.26) for those with a high number of PTSD symptoms.[15] A limitation of that study, however, was

the homogenous population of approximately 95% White, female nurses. Importantly, in the present study, the relationship between PTSD and SLE is found in a broader, racially-, ethnically-, and sociodemographically-diverse population in the U.S. posited to have a high baseline prevalence and incidence of PTSD.

Prior studies have demonstrated biologic changes in patients with PTSD that may explain its relationship to development of autoimmune disease. Widespread DNA methylation epigenetic changes[26,27] and shorter telomere length[28] have both been identified in patients with PTSD. Inflammatory markers such as C-reactive protein and interleukin-6 are also increased in populations of patients with PTSD compared to those without,[12] which could lead to downstream effects in inflammation and immune cell function. It is not yet clear which of these pathways or their combinations may be involved increased susceptibility to loss of self-tolerance, autoantibody formation, and development of autoimmune disease. Further research is needed to characterize the relationship between PTSD and development of SLE. Additionally, more work is needed to identify potential interventions that could modify the risk of developing autoimmune disease once PTSD is diagnosed. As noted in a retrospective cohort study in Sweden, there was a lower risk of developing any autoimmune disease amongst people with PTSD who were treated with selective serotonin reuptake inhibitors.[6] Likewise, characterizing the ongoing interplay between PTSD symptoms and the later disease course of SLE could illuminate common pathways to target for treatment of both conditions.

Limitations of this study include the case-control design, which precluded assessment of absolute risk, and the four-year time frame, restricting the interval between PTSD and SLE diagnoses. Studies with longer follow-up time are needed to further clarify this association. Patients with PTSD may develop SLE years later and would be missed given the follow-up time available for this study. We did not have granular data to examine prodromal symptoms or labs in the period around SLE diagnosis, and the first SLE code may not accurately reflect disease onset. We tried to address this in the first sensitivity analysis limited to cases of SLE with at least 2 years of enrollment without a SLE code. Diagnosis of SLE may also be delayed because of poor access to care or fragmented care, which disproportionately affect those living in areas with higher neighborhood deprivation indices.[29] We did use zip-code level median household income as a proxy for socioeconomic status and adjusted for this in our models. DMS-IV criteria and ICD-9 for PTSD were used during the study period, but have since been updated to DSM-V in 2013 and ICD-11 in 2018. The matches between the two DSM criteria and ICD codes are imperfect.[30] However, the administrative algorithm we employed had a high PPV of 96% when comparing to the current gold standard for population studies, the PCL-5. PTSD is underdiagnosed and many patients do not seek care, so our analysis is likely an underestimate of the true prevalence. Changes since 2010 with increasing healthcare access and recognition of mental health disorders, including the expansion of Medicaid in the Affordable Care Act, could mean that the prevalence of PTSD might be higher if measured now. PTSD often overlaps with other mental health and substance use disorders that could mediate a causal relationship between PTSD on development of SLE and other autoimmune diseases.[10] It is possible that patient developing SLE may present with neuropsychiatric manifestations that could be mistakenly diagnosed as PTSD. Rates of tobacco use and obesity were low in both case and control populations,

which is not surprising as these health behaviors often are not coded.[31,32] Since these covariates may be involved in the pathway from PTSD to development of SLE, the effect we found may be conservative. Finally, we found a potentially higher odds ratio of developing SLE for those with prior PTSD in people living in zip codes with higher median income as compared to lower, although was not a statistically significant interaction. Past studies have reported that people living in lower SES areas have higher rates of developing PTSD,[22] but our results suggest that the additional effect of PTSD among those living in poorer neighborhoods, who perhaps have many other sources of life stress, may be, somewhat paradoxically, less. It is also possible that other factors of living in lower SES areas may lead to delayed diagnoses as discussed above.

We uncovered a doubling of odds of SLE associated with a prior diagnosis of PTSD among this large, racially and sociodemographically diverse, US civilian patient population. It is still not clear which individuals with PTSD are at highest risk of SLE, and whether the onset of SLE is potentially preventable among those suffering from PTSD. Future studies are needed to better delineate the complex relationship between PTSD and autoimmune diseases such as SLE and to identify modifying influences and means for prevention.

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Significance and Innovations:

- We found a two-fold higher odds of SLE among patients with versus without a prior diagnosis of PTSD in a large diverse US population of adults enrolled in Medicaid.
- This study contributes to prior evidence of increased risks of SLE among those with PTSD in military populations and in cohorts of older and mainly White women, here uncovering a strong relationship between PTSD and incident SLE in a sociodemographically and racially diverse population.

Table 1.

Characteristics of US Medicaid Patients with SLE vs. Matched US Medicaid Patients without SLE (2007–2010), matched at the Index Date for SLE

Characteristic	SLE Cases (n=10,942)	Matched General Medicaid Population Controls (n= 109,420)
Mean age, years (SD) *	40.8 (12.4)	40.8 (12.4)
Female, % *	93.5	93.5
Race, % *		
Black or African American	39.8	39.9
White	37.5	37.5
Asian	2.3	2.3
Hispanic	16.9	16.9
American Indian/Alaska Native	0.95	0.87
Other	2.5	2.5
Median zip code level income, %		
1st Quartile	25.9	24.8
2nd Quartile	25.8	24.9
3rd Quartile	23.8	25.4
4th Quartile	24.6	25.0
US Region of Residence, %		
South	37.4	38.9
Northeast	21.8	19.4
Midwest	20.4	23.1
West	20.3	18.6
Smoking, %	11.3	7.3
Obesity, %	7.1	4.2
Oral contraceptive use (among women only), %	8.8	10.5

* Matching factor

IQR: interquartile range, SD: Standard deviation

Table 2:

Incidence and prevalence of PTSD in cases of SLE and controls

		Prevalence of PTSD per 1,000 person years		Incidence of PTSD per 1,000 person years	
		Prevalence	**CI**	**Incidence**	**CI**
All cases and controls	Cases of SLE	10.74	9.37–12.31	6.32	5.29–7.55
	Controls	7.83	7.42–8.27	5.51	5.16–5.88
Sensitivity analysis 1[1]	Cases of SLE	15.74	12.71–19.49	7.95	5.88–10.76
	Controls	9.97	9.09–10.93	6.51	5.81–7.30

[1] Excluded patients with <24 months of enrollment before the index date

Table 3.

Conditional logistic regression models for PTSD in relation to incident SLE, comparing PTSD to no PTSD

		Conditional logistic regression			Multivariable-adjusted conditional logistic regression[1]		
		OR	**CI**	**p-value**	**OR**	**CI**	**p-value**
All cases and controls	No PTSD	1.00	Ref		1.00	Ref	
	PTSD	1.96	1.66–2.33	**<0.0001**	2.00	1.64, 2.46	**<0.0001**
Sensitivity analysis 1[2]	No PTSD	1.00	Ref		1.00	Ref	
	PTSD	2.64	2.07–3.37	**<0.0001**	3.62	2.35–5.56	**<0.0001**
Sensitivity analysis 2[3]	No PTSD	1.00	Ref		1.00	Ref	
	PTSD	2.11	1.74–2.57	**<0.0001**	1.90	1.51–2.39	**<0.0001**

[1]Conditioned on matching factors, age, sex and race/ethnicity. Multivariable conditional logistic regression additionally adjusted for area-level median household income, US region of residence, smoking, obesity, oral contraceptive use, and days enrolled in Medicaid prior to index date.

[2]Excluded patients with <24 months of enrollment before the index date

[3]Excluded patients with <6 months between the first PTSD and SLE codes