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Clinical science

The association of trauma with self-reported flares and disease activity in systemic lupus erythematosus (SLE)

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Abstract

Objectives: Trauma has been linked to incident SLE, but its relationship with SLE disease activity is unknown. This analysis examines associations between trauma exposures and patient-reported SLE disease activity and flares.

Methods: Data were from the California Lupus Epidemiology Study (CLUES). Flares were self-reported as any flare and, of those, flares accompanied by medical care (hospitalization or physician contact). The Systemic Lupus Activity Questionnaire (SLAQ) assessed disease activity. The Brief Trauma Questionnaire (BTQ) assessed all historical trauma exposures. The Adverse Childhood Experiences (ACEs) questionnaire was available for a subset. Multivariable regression analyses ($n = 252$) examined whether trauma exposure was associated with flares or SLAQ controlling for age, sex, poverty, race/ethnicity, comorbidities, perceived stress, disease duration and self-reported disease damage.

Results: Excluding exposure to serious illness, 63.4% reported ≥1 trauma exposure. Any traumatic event, excluding illness, doubled the odds of a flare [OR 2.27 (95% CI 1.24, 4.17)] and was associated with significantly higher SLAQ scores [β 2.31 (0.86, 3.76)]. Adjusted odds of any flare and flare with medical care were significantly elevated for those with both BTQ and ACE exposures [5.91 (2.21, 15.82) and 4.69 (1.56, 14.07), respectively]. SLAQ scores were also higher for those with both exposures [β 5.22 (3.00, 7.44)].

Conclusion: In this cohort, those with a history of trauma reported more flares and greater disease activity. Identifying mechanisms of associations between trauma and disease activity and flares, as well as interventions to mitigate the effects of trauma exposures is critical, given the high rates of trauma exposures.

Keywords: SLE, stress, trauma, self-reported flares, self-reported disease activity

Rheumatology key messages

- Trauma was frequently reported by individuals with systemic lupus erythematosus.
- Trauma exposures were significantly associated with self-reported flares and disease activity.
- Identifying mechanisms of these associations and interventions to reduce the impact of trauma is critical.

Introduction

The unpredictability of SLE flares is a source of frustration and decreased quality of life for patients. Flares can be frequent in SLE, and although estimates vary, physician-diagnosed flares are thought to occur at a rate of 0.1–0.4 flares per patient-year [1]. Each episode of flare can lead to the accrual of organ damage due to increased inflammation and subsequent fibrosis in affected organs, as well as toxicities from the medications (such as glucocorticoids) used to treat the flare [2]. The aetiology for most flares remains unknown [3].

Defining flares can be complex given the known differences in perceptions of disease activity between patients and health care professionals [4–6]. For example, physicians typically focus on objective signs such as organ dysfunction, rashes, arthritis or laboratory abnormalities. In contrast, individuals

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with SLE may focus more on pain, fatigue, functioning and daily activities [7]. These patient-reported flares may fall beneath clinical-assessed thresholds but nevertheless affect daily function and quality of life [8].

The role of stress and trauma exposures in SLE outcomes is being increasingly recognized. Several studies have linked trauma exposure and/or symptoms of post-traumatic stress disorder to the development of autoimmune conditions in general and to SLE specifically [9–14]. Daily psychological stress has been consistently linked to poorer patient-reported SLE outcomes [15], and some reports have shown associations with disease activity and flares [16–19]. The role of trauma exposures in disease activity is less well defined. Adverse events in childhood (ACEs) have been linked to worse patient-reported outcomes in SLE, but not to physician-assessed disease activity [20]. However, early life trauma exposures may sensitize people so that reactions to later traumatic or stressful experiences are magnified [21]. Whether trauma exposures are associated with future SLE disease flares is unknown.

In this study, we examined the question of whether prior traumatic exposures were associated with self-reported SLE disease flares.

Methods

Subjects

Subjects were participants in the California Lupus Epidemiology Study (CLUES), a multi-racial/ethnic cohort of individuals with physician-confirmed SLE. Some participants ($n = 171$) were recruited from the California Lupus Surveillance Project (CLSP), a population-based cohort of individuals with SLE living in San Francisco County from 2007 to 2009 [22]. Additional participants ($n = 260$) residing in the nine counties in the San Francisco Bay Area geographic region were recruited through local academic and community rheumatology clinics and through existing local research cohorts. There were no substantive differences between the two groups in distribution of socio-demographic or clinical characteristics. In addition to residence in the San Francisco Bay Area, other inclusion criteria were a confirmed SLE diagnosis; oral language fluency in English, Spanish, Cantonese, or Mandarin; age $\geq$18 years; and ability to provide informed consent.

Baseline study procedures involve an in-person research clinic visit, which includes collection and review of medical records prior to the visit; a history and physical examination conducted by a physician specializing in SLE; collection of biospecimens for clinical and research purposes; and completion of a structured interview administered by an experienced research assistant. All SLE diagnoses were confirmed by study physicians according to any of the following definitions: (i) the patient met $\geq$4 of the 11 ACR revised criteria for the classification SLE as defined in 1982 and updated in 1997 [23, 24]; (ii) the patient met $\geq$3 of the 11 ACR criteria plus a documented rheumatologist's diagnosis of SLE; or (iii) the patient had a confirmed diagnosis of lupus nephritis. These case definitions were used in the SLE surveillance studies supported by the Centers for Disease Control and Prevention recognition that all historical records may not have been accessible when surveillance activities were undertaken [22, 25–27].

CLUES specifically aimed to include a diverse patient sample, with representation from the four largest US racial/ethnic groups. Study visits and interviews were conducted in English, Spanish, Mandarin or Cantonese. All study procedures were reviewed and approved by the UCSF Institutional Review Board, and all participants provided consent. The study complies with the Declaration of Helsinki.

A subgroup of participants was unable to attend the baseline in-person visit [$n = 37$ (22%) from CLSP and $n = 62$ (24%) from additional Bay Area recruits]. For these individuals, medical records were collected, and the same structured interview was administered by telephone. Diagnoses were confirmed through medical record review.

Subsequent to baseline, follow-up interviews have been conducted annually, in addition to a follow-up in-person visit at Year 3 for a subset. Unless otherwise noted, all data for these analyses were drawn from the Year 5 interviews. Retention for annual follow-up interviews averaged 86%; however, between baseline and Year 5, 179 participants have been lost to follow-up (including 14 deaths), leaving a sample size of 252 for these analyses.

Variables

Self-reported SLE disease activity

The Systemic Lupus Activity Questionnaire (SLAQ), a self-report measure of SLE disease activity validated against the Systemic Lupus Activity Measure (SLAM), was used to capture self-reported disease activity [28, 29]. SLAQ scores range from 0 to 44, with higher scores reflecting more disease activity.

SLE flares

Individuals were first asked if they had experienced a lupus flare in the past 3 months, an item from the SLAQ. If they responded that they had not, they were then asked whether they had a flare in the past year. A positive response to either question was defined as having a self-reported flare. Those who reported flares were asked a follow-up question about whether they had contacted their doctor or had been hospitalized for the flare. Because very few hospitalizations were reported, physician contacts and hospitalizations were combined to define a flare that involved medical care.

Trauma

The 10-item Brief Trauma Questionnaire (BTQ) was administered to assess the experience of trauma [30]. The BTQ was designed to assess Criterion A traumatic experiences (life threat/serious injury). Items query trauma exposures by asking if (i) an event has happened to respondents; (ii) they felt their life was in danger or they would be seriously injured; and (iii) they were seriously injured because of the event. Fig. 1 shows the BTQ items and illustrates how individual items are scored. The total number of BTQ positive responses were calculated, as well as whether any positive response was reported (dichotomous).

One of the BTQ items (Item 4, Fig. 1) asks whether the individual has ever had a life-threatening illness. In alternate scoring of the BTQ (total score and dichotomous), this item was omitted, as SLE could be considered as a life-threatening illness.

Adverse Childhood Experiences (ACEs)

At the baseline CLUES in-person visit, participants completed the 10-item ACEs questionnaire which assesses events that happened before the age of 18 in three domains (household challenges, neglect and abuse) [31]. Scores range from 0 to 10. Based on a previous publication, we stratified ACE

	Has this ever happened to you?	Did you think your life was in danger or you might be seriously injured?	Were you seriously injured?
	Yes →	Yes	Yes
1. Have you ever served in a war zone, or have you ever served in a noncombat job that exposed you to war-related casualties	2% (5)	1.2% (3)	0
2. Have you ever been in a serious car accident or a serious accident at work or somewhere else?	25.5% (64)	17.9% (45)	10.0% (25)
3. Have you ever been in a major natural or technological disaster, such as a fire, earthquake, tornado, hurricane, explosion, or chemical spill?	40.6% (102)	22.7% (57)	0.8% (2)
4. Have you ever had a life-threatening illness such as cancer, a heart attack, leukemia, AIDS, multiple sclerosis, etc.?	47.8% (120)	37.5 (94)	
5. Before age 18, were you ever physically punished or beaten by a parent, caretaker, or teacher so that: you were very frightened or thought you would be injured; or you received bruises, cuts, welts, lumps, or other injuries?	25.9% (65)	12.4% (31)	6.0% (15)
6. Besides what you just told me about, have you ever been attacked, beaten, or mugged by anyone, including friends, family members of strangers?	27.5% (69)	19.1% (48)	8.8% (22)
7. Has anyone ever made or pressured you into having some type of unwanted sexual contact?	32.3% (81)	13.6% (34)	10.0% (25)
8. Have you ever been in any other situation in which you were seriously injured, or have you ever been in any other situation in which you feared you might be seriously injured or killed?	21.1% (53)	7.6% (19)	
9. Has a close family member or friend died violently, for example, in a serious car crash, mugging, or attack?	23.5% (59)		
10. Other than the events you already told me about, have you ever witnessed a situation in which someone was seriously injured or killed, or have you ever witnessed a situation in which you feared someone else would be seriously injured or killed?	27.5% (69)		

Items shaded in blue are scored as positive.
The total number of possible positive responses is 10, so BTQ scores can range from 0 to 10.
Actual BTQ scores ranged from 0 to 9.

Figure 1. Brief Trauma Questionnaire items, scoring and response frequencies

responses as 0 or 1 *vs* 2 or more [32]. ACEs questionnaires were not included until the baseline visits had been underway for several months, and they were administered only to individuals who participated in an in-person visit and to those who spoke English or Spanish (a validated Chinese version was not available). As a result, 183 of the 252 participants in the current cohort completed the ACEs questionnaire.

In analyses including both the ACEs questionnaire and the BTQ, the BTQ item specifically referring to events that happened before age 18 (Item 5, Fig. 1) was omitted from BTQ scoring because of content overlap.

Other variables

The Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) [33] and SLICC/ACR Damage Index (SLICC-DI) [34] were completed by physicians for participants who completed a research clinic visit at baseline and Year 3. However, because the most recent assessment was two years previously and because all participants did not have the in-person visit, the Brief Index of Lupus Damage (BILD), a validated patient-reported measure of disease damage, administered in the Year 4 interview was included in analyses [35, 36] to reflect accumulation of disease activity.

Table 1. Characteristics of sample

	Total $n = 252$	Flare in past year			Flare w/medical care		
		No $n = 146$ (57.9%)	Yes $n = 106$ (42.1%)	P[a]	No $n = 186$ (73.8%)	Yes $n = 65$ (26.2%)	P[a]
Sociodemographic							
Age, years	49.7 (13.4)	49.2 (14.0)	50.4 (12.4)	0.47	49.2 (14.0)	50.4 (12.4)	0.69
Female	90.5 (228)	89.7 (131)	91.5 (97)	0.67	89.3 (166)	93.9 (62)	0.33
Race/ethnicity group				0.28			0.17
White	33.3 (84)	33.6 (49)	33.0 (35)		35.0 (65)	28.8 (19)	
Black	9.9 (25)	8.2 (12)	12.3 (13)		9.1 (17)	12.1 (8)	
Asian	30.6 (77)	27.4 (40)	34.9 (37)		26.9 (50)	40.9 (27)	
Hispanic	23.4 (59)	27.4 (40)	17.9 (19)		25.8 (48)	16.7 (11)	
Other	2.8 (7)	3.4 (5)	1.9 (2)		3.2 (6)	1.5 (1)	
Income below poverty	12.3 (29)	12.7 (17)	11.9 (12)	0.99	12.9 (22)	10.9 (7)	0.83
General health							
Comorbid conditions							
Cardiovascular	47.2 (119)	47.3 (69)	47.2 (50)	0.99	46.2 (86)	50.0 (33)	0.67
Asthma, other pulmonary	21.8 (55)	18.3 (34)	31.8 (21)	0.03	16.4 (24)	29.3 (31)	0.02
Diabetes	5.2 (13)	4.1 (6)	6.6 (7)	0.40	5.4 (10)	4.6 (3)	0.99
Fibromyalgia	10.4 (26)	8.2 (12)	13.3 (14)	0.21	9.1 (17)	13.9 (9)	0.34
Smoking, ever	32.8 (82)	30.3 (44)	36.2 (38)	0.34	29.7 (55)	41.5 (27)	0.09
Smoking, now	2.8 (7)	3.4 (5)	1.9 (2)	0.70	2.7 (5)	3.0 (2)	0.99
High perceived stress[b]	23.4 (59)	18.5 (27)	30.2 (32)	0.04	19.9 (37)	33.3 (22)	0.04
Lupus-related							
Disease duration (years)	22.4 (10.7)	22.9 (11.5)	21.8 (9.4)	0.42	22.6 (10.9)	22.0 (10.0)	0.72
SLEDAI, Year 3 ($n = 186$)	3.1 (3.3)	2.8 (3.1)	3.4 (3.5)	0.20	2.9 (3.2)	3.5 (3.5)	0.28
SLICC-DI, Year 3 ($n = 186$)	2.1 (2.2)	2.0 (2.3)	2.2 (2.0)	0.59	2.1 (2.3)	2.2 (1.8)	0.66
BILD	2.5 (2.4)	2.4 (2.4)	2.6 (2.4)	0.42	2.5 (2.5)	2.5 (2.1)	0.89
Current glucocorticoid use	45.2 (114)	40.4 (59)	51.9 (55)	0.07	40.9 (76)	57.6 (38)	0.02
High dose glucocorticoids	13.9 (35)	8.2 (12)	21.7 (23)	0.003	9.7 (18)	25.8 (17)	0.003
Immunosuppressive use	51.2 (129)	45.9 (67)	58.5 (62)	0.056	46.8 (87)	63.6 (42)	0.02

[a] P-values from t-tests or χ^2 analyses comparing groups with and without flares.
[b] High stress defined as the top quartile of scores for the Perceived Stress Scale (PSS).
BILD: Brief Index of Lupus Damage; SLICC-DI: SLICC/ACR Damage Index.

Supplemental analyses included both SLEDAI and SLICC-DI from Year 3 as covariates.

Age at lupus diagnosis was obtained during the baseline physician examination or was self-reported for the interview-only group. Race, ethnicity, age, household income and education level were self-reported. Comorbid conditions were self-reported from a standard checklist. Current medications were recorded during interviews and confirmed during physician interviews. The following medications were classified as immunosuppressive agents: azathioprine, mycophenolate, methotrexate, ciclosporin, leflunomide, cyclophosphamide, rituximab, or other biologics. Dose of prednisone or other glucocorticoids was also collected. Glucocorticoids other than prednisone were converted to prednisone-equivalent dosages. Moderate-high-dose prednisone was defined as $\geq$7.5 mg per day for at least three months in the past year.

Perceived stress was assessed with the four-item Perceived Stress Scale (PSS), which queries perceptions of stress over the previous month [37]. Scores can range from 0 to 16. Because there is no standardized cut-off for the PSS, scores in the upper quartile were defined as high stress.

Statistical analysis

Characteristics of individuals who did and did not experience a flare were compared using t tests or χ^2 analyses. Unadjusted analyses examined whether trauma (number of events or any event) was associated with flares, using Wilcoxon–Mann–Whitney two-sample tests and χ^2 analyses. Multivariable logistic regression analyses examined whether trauma (number of events or any event) was associated with the occurrence of flares controlling for age; sex; poverty (defined as income below 125% of federal poverty level for household size); race/ethnicity; comorbid cardiovascular disease, asthma or other pulmonary conditions, or fibromyalgia; history of smoking; high perceived stress; disease duration; and BILD. Finally, analyses were repeated to examine whether ACEs were associated with flares in addition to trauma identified by the BTQ. For this analysis, the BTQ item on childhood trauma was excluded. As noted above, ACE responses were dichotomized as 0 (0 or 1 exposures) or 1 (2 or more exposures). Four groups were defined based on trauma exposure by each measure (no ACEs/no BTQ, no ACEs/yes BTQ, yes ACEs/no BTQ, yes ACEs/yes BTQ). Multivariable logistic regression analyses then estimated the odds of flare for each group, with no trauma by either measure as the reference group. These analyses controlled for the same covariates listed above. In a sensitivity analysis, all analyses were repeated including the Year 3 SLEDAI and SLICC-DI as covariates among the 186 individuals for whom these scores were available.

Results

Among the 252 individuals in this analysis, mean age was 50 (13) years, disease duration 22 (11) years, 90% were female,

Table 2. Trauma exposures (number of exposures or any exposure) by self-reported flare status

		Flare in past year			Flare w/medical care		
	Total ($n = 252$)	No ($n = 146$)	Yes ($n = 106$)	P[a]	No ($n = 186$)	Yes ($n = 66$)	P[a]
Number of trauma exposures mean ± SD							
Total	1.9 (1.9)	**1.4 (1.4)**	**2.6 (2.3)**	**<0.0001**	**1.6 (1.7)**	**2.6 (2.4)**	**0.003**
Total excluding illness	1.5 (1.7)	**1.1 (1.3)**	**2.1 (2.1)**	**<0.0001**	**1.3 (1.5)**	**2.2 (2.2)**	**0.006**
Any trauma exposure (dichotomous) % (n)							
Any	70.9 (178)	66.2 (96)	77.4 (82)	0.07	68.7 (127)	77.3 (51)	0.21
Any excluding illness	63.4 (159)	**56.6 (82)**	**72.6 (77)**	**0.01**	60.5 (112)	71.2 (47)	0.14

[a] P-values from χ^2 or Wilcoxon-Mann–Whitney two-sample test.
Bolded values are statistically significant, $P < 0.05$.

Table 3. Association of trauma exposures with self-reported flares and disease activity (adjusted)

	Flare in past year		Flare w/medical care		SLAQ	
	OR (95% CI)[a]	P	OR (95% CI)[a]	P	β (95% CI)[b]	P
Number of trauma exposures						
Total	**1.45 (1.22, 1.72)**	**<0.0001**	**1.32 (1.11, 1.56)**	**0.0013**	**1.05 (0.69, 1.41)**	**<0.0001**
Total excluding illness	**1.52 (1.24, 1.85)**	**<0.0001**	**1.35 (1.12 1.63)**	**0.0015**	**1.14 (0.74, 1.54)**	**<0.0001**
Any trauma exposure (dichotomous)						
Any	1.76 (0.93, 3.31)	0.08	1.27 (0.62, 2.60)	0.51	**2.30 (0.77, 3.84)**	**0.0034**
Any excluding illness	**2.27 (1.24, 4.17)**	**0.0082**	1.53 (0.77, 3.02)	0.12	**2.31 (0.86, 3.76)**	**0.0019**

[a] Odds ratios (95% confidence intervals) and P-values from multivariable logistic regression analysis controlling for age, female, poverty, race/ethnicity, high perceived stress, history of smoking, number of comorbidities (cardiovascular disease, asthma or other pulmonary disease, fibromyalgia), disease duration and BILD.
[b] Parameter estimates (95% confidence intervals) and P-values from multivariable linear regression analysis controlling for age, female, poverty, race/ethnicity, high perceived stress, history of smoking, number of comorbidities (cardiovascular disease, asthma or other pulmonary disease, fibromyalgia), disease duration and BILD.
BILD: Brief Index of Lupus Damage; SLAQ: Systemic Lupus Activity Questionnaire.
Bolded values are statistically significant, $P < 0.05$.

31% Asian, 23% Hispanic, 33% White non-Hispanic, and 10% African-American. A total of 106 (42%) reported any flare in the past year; 62% of these ($n = 66$) reported a flare that was accompanied by a doctor visit or hospitalization (Table 1). Members of the cohort in these analyses were significantly younger at baseline than those who dropped out prior to the Year 5 interview [48.2 (15.2) years *vs* 45.4 (13.4) years, $P = 0.054$] and a significantly larger portion had incomes below the poverty level at baseline (29.8% *vs* 14.2%, $P = 0.0024$) (Supplementary Table S1, available at *Rheumatology* online). There were no significant differences in either the number of ACEs reported or the proportion who had ≥2 ACES.

Individuals who reported any flare in the past year and a flare with associated medical care were more likely to have asthma or another pulmonary condition, a greater proportion had high perceived stress, and a greater proportion were taking high dose GCs (Table 1). There were no other significant differences between individuals with and without any reported flare. Among individuals who had a flare with medical care, a greater proportion were also taking GCs and immunosuppressive medications.

Almost three-quarters of the cohort (70.9%) reported at least one trauma exposure; excluding the BTQ serious illness item, 63.4% reported at least one exposure (Table 2). Thirty-eight percent reported exposure to an illness that they considered life-threatening (Fig. 1, Item 4). Fifteen percent of the cohort reported three or more trauma exposures.

The number of trauma exposures was significantly higher for those who reported a flare or a flare with medical care compared with those who did not (Table 2). When considering a dichotomous categorization of trauma (none *vs* any), individuals who reported any trauma exposure had significantly higher SLAQ scores than those without a trauma exposure [no trauma, 6.5 (5.3); at least one trauma exposure, 10.2 (7.1), $P < 0.0001$]. A significantly greater proportion of those with any trauma exposure excluding illness also reported a flare in the past year. Results were similar from sensitivity analyses including only the cohort participants with SLEDAI and SLICC-DI scores (Supplementary Table S2, available at *Rheumatology* online).

In adjusted analyses, a greater number of trauma exposures was associated with a significantly greater odds of flare and flare with medical care, as well as significantly higher SLAQ scores (Table 3). The odds of a flare were 45–52% higher for each trauma exposure; odds of a flare with medical care were 32–35% higher. Any traumatic event, excluding illness, more than doubled the odds of a flare [OR 2.27 (95% CI 1.24, 4.17)]. Odds of a flare with medical care were elevated for those who had experienced any trauma, but the confidence interval did not exclude 1 [1.53 (0.77, 3.02)]. The same patterns of associations were noted in sensitivity analyses including SLEDAI and SLICC-DI (Supplementary Table S3, available at *Rheumatology* online).

Over 50% of individuals who reported both BTQ-identified trauma exposures and ACEs reported any flare, compared with approximately one-quarter of those with neither exposure [adjusted OR 5.91 (2.21, 15.82)] (Table 4). Thirty-seven percent of those with both BTQ and ACE

Table 4. Association of trauma exposures with self-reported flares and disease activity, considering both ACEs[a] and BTQ[b] ($n = 173$)

	Flare in past year			Flare w/medical care			SLAQ		
	% (n)[c]	OR (95% CI)[d]	*P*	% (n)	OR (95% CI)[d]	*P*	Mean ± SD	β (95% CI)[e]	*P*
Any trauma exposure									
ACEs = 0, BTQ = 0 ($n = 44$)	27.3 (12)	Reference	—	15.9 (7)	Reference	—	6.4 (4.8)	Reference	—
ACEs = 0, BTQ = 1 ($n = 69$)	37.7 (26)	1.90 (0.74, 4.86)	0.18	21.7 (15)	1.29 (0.43, 3.91)	0.65	7.9 (6.0)	1.07 (-1.07, 3.21)	0.32
ACEs = 1 BTQ = 0 ($n = 12$)	33.3 (4)	1.92 (0.43, 8.49)	0.39	25.0 (3)	2.43 (0.47, 12.42)	0.29	5.8 (5.9)	0.45 (-3.06, 3.91)	0.80
ACEs = 1, BTQ = 1 ($n = 58$)	58.6 (34)	**5.14 (1.87, 14.10)**	**0.0015**	37.9 (22)	**4.04 (1.31, 12.42)**	**0.015**	13.1 (6.7)	**5.15 (2.87, 7.42)**	**<0.0001**
	$P = 0.0097$			$P = 0.06$			$P < 0.0001$		
Any trauma exposure, excluding illness									
ACEs = 0, BTQ = 0 ($n = 54$)	25.9 (14)	Reference	—	14.8 (8)	Reference	—	6.2 (4.7)	Reference	—
ACEs = 0, BTQ = 1 ($n = 59$)	40.7 (24)	2.25 (0.92, 5.52)	0.08	23.7 (14)	1.67 (0.58, 4.84)	0.34	8.4 (6.2)	1.18 (-0.87, 3.24)	0.26
ACEs = 1 BTQ = 0 ($n = 16$)	37.5 (6)	2.04 (0.56, 7.41)	0.28	31.3 (5)	3.07 (0.75, 12.51)	0.12	7.8 (5.8)	1.27 (-1.74, 4.29)	0.41
ACEs = 1, BTQ = 1 ($n = 54$)	59.3 (32)	**5.91 (2.21, 15.82)**	**0.0004**	37.0 (20)	**4.69 (1.56, 14.07)**	**0.0059**	13.2 (7.0)	**5.22 (3.00, 7.44)**	**<0.0001**
	$P = 0.0058$			$P = 0.06$			$P < 0.0001$		

[a] ACEs dichotomized so that ACEs = 0 corresponds to an ACE score of 0 or 1 and ACEs = 1 corresponds to ACE score of ≥2.
[b] The BTQ was scored excluding item 5, which refers to trauma exposures prior to age 18. BTQ = 0 corresponds to a score of 0; BTQ = 1 corresponds to a score of 1 or more.
[c] *P*-value from χ^2 analysis.
[d] Odds ratios (95% CIs) and *P*-values from multivariable logistic regression analysis controlling for age, female, poverty, race/ethnicity, high perceived stress, history of smoking, number of comorbidities (cardiovascular disease, asthma or other pulmonary disease, fibromyalgia), disease duration, and BILD.
[e] Parameter estimates (95% CIs) and *P*-values from multivariable linear regression analysis controlling for age, female, poverty, race/ethnicity, high perceived stress, history of smoking, number of comorbidities (cardiovascular disease, asthma or other pulmonary disease, fibromyalgia), disease duration, and BILD.
ACEs: Adverse Childhood Experiences; BILD: Brief Index of Lupus Damage; BTQ: Brief Trauma Questionnaire; SLAQ: Systemic Lupus Activity Questionnaire; SLICC-DI: SLICC/ACR Damage Index.
Bolded values are statistically significant, $P < 0.05$.

trauma exposures reported a flare with medical care compared with 15% of those with neither exposure [adjusted OR 4.69 (1.56, 14.07)]. SLAQ scores were also significantly higher for individuals who reported both BTQ and ACE trauma exposures [β 5.22 (3.00, 7.44)]. Sensitivity analyses yielded similar results (Supplementary Table S4, available at *Rheumatology* online).

Discussion

Our results showed that any traumatic exposure, excluding illness, doubled the odds of a flare and was associated with significantly higher SLAQ scores. The adjusted odds of any flare and flare with medical care were even greater for those with both BTQ and ACE exposures, increased five-fold compared with individuals with neither ACE nor BTQ trauma exposures. SLAQ scores were also highest for those with both BTQ and ACE exposures.

Self-reported flares were common in this cohort, with 42% reporting a flare in the past year. This frequency is lower than has been reported in other studies of patient-reported flares, although the method of ascertaining flares has varied among studies. For example, two previous cohort studies found that over 80% of the SLE patients studied reported at least one flare over the 12 months prior to interview [5, 8]. Flares requiring medical care were less common, but still reported by over a quarter of participants. Though the rate of self-reported flares in our cohort was lower than reported in prior studies, it was also substantially higher than rates of physician-identified flares.

Trauma appeared to be associated with participant-reported flares. A large portion of this cohort reported trauma exposures. Thirty-eight percent reported exposure to an illness they considered life-threating. Although participants were not queried about the specific illness, it is possible that a proportion of these respondents were referring to their SLE. Previous studies have also noted patient reports of the trauma they experience if they have difficulties or delays in diagnosis or their symptoms are not believed or understood [38]. Excluding the experience of a life-threatening illness, 63% reported at least one trauma exposure.

The association of trauma exposures with incident SLE has been reported [9–11, 13, 14]. An association between perceived stress and both patient- and physician-reported disease activity has also been reported [15]. Less studied is how prior trauma may affect current SLE disease activity and flares, over and above the effects of perceived stress. We found that the number of traumatic events, excluding illness, was associated with increased odds of both any flare and a flare associated with medical care even after adjusting for covariates including perceived stress. The experience of any traumatic event excluding illness was associated with a two-fold increase in the odds of any flare, but not increased odds of a flare with medical care.

Individuals who experienced trauma exposures during childhood (ACEs) as well as additional exposures later in life had the greatest odds of flares. It appears that trauma exposures during childhood may magnify the impact of other trauma exposures in terms of the association with flares. This supposition is consistent with previous research. Evidence shows that childhood maltreatment is associated with multiple physical, mental and emotional symptoms that persist into adulthood [39]. Childhood trauma can lead to neurological and psychological disruptions such as alterations in hormonal pathways that regulate stress [40]. Additional evidence has shown that prior trauma appears to prime the individual for greater reactions to new trauma [21].

Multiple hypotheses have been generated to explain how stress or trauma might affect either the onset of SLE or SLE disease activity. Stress exposures are known to affect the functioning of the hypothalamic-pituitary-adrenal (HPA) axis, which plays an important role in immune function [41]. HPA axis functioning appears to differ for individuals with SLE compared with those without SLE, which may explain the association between trauma exposures and SLE onset or disease

activity. DNA methylation changes, shorter telomere length, higher levels of inflammatory markers such as C-reactive protein, TNF alpha receptor II, and interleukin-6, and impaired endothelial function have also been observed in individuals with PTSD or who have experienced trauma [42–44]. These genomic and immunologic alternations may contribute to future increased SLE disease activity. Trauma exposures may also increase pain sensitization throughout life [45, 46]. Increased pain in adulthood may therefore have non-inflammatory mechanisms but be self-reported as disease activity or flares in SLE. There is some support for this hypothesis, given the association between ACEs and worse patient-reported outcomes including greater self-reported disease activity [20]. It is also possible that the relationship between trauma and SLE disease activity may be driven by behavioural changes such as sleep disruptions, which are known to occur following traumatic exposures [47].

This study does have limitations. All flares were self-reported. It is fairly well established that patient and physician assessments of disease activity are not always consistent; the same may hold true for flares. However, the association between trauma exposure and flares was maintained when the analysis was limited to flares that were accompanied by medical care, and trauma exposures were associated with self-reported disease activity. Nevertheless, it is possible that medical care could have been engaged without the physician agreeing that a flare was present. It would be useful in the future to examine whether self-reported flares were accompanied by changes in therapy, as well as whether medical care was sought. On the other hand, self- perceived flares are impactful to individuals with lupus even if they do not meet criteria for physician-assessed flare. Physician assessments of disease activity and damage (SLEDAI and SDI) were not available for the entire sample, but sensitivity analyses among the portion of the cohort for which these scores were available yielded similar results. Previous studies have noted the impact of post-traumatic stress disorder (PTSD) on SLE incidence; we did not perform an assessment of PTSD, which may have affected the associations noted. We did not have a sufficient number of individuals in all racial or ethnic groups to test whether these associations varied by race or ethnicity, although data exist that some groups experience a greater trauma burden [48]. While we controlled for additional sociodemographic and health variables in analyses, results may not be generalizable to all persons with SLE; for example, those who are younger. We also did not assess adherence to medications. It is possible that individuals with trauma exposures were less like to take their SLE medications as prescribed [49], which may have contributed to greater disease activity and more frequent flares. We do not have certainty on the temporal sequencing of trauma exposures and flares. Both flares and the BTQ were ascertained during the Year 5 interview. It is possible that a flare reported as occurring in the previous year actually happened prior to a trauma exposure reported on the BTQ that also happened in the prior year. It is also possible that recall bias influenced our these findings (i.e. that individuals with more active or more severe disease may be more likely to recall and report prior trauma). Given the wide range of symptoms and SLE manifestations, it may be difficult for patients to tease out the SLE-specific *vs* symptoms from other conditions, such as mood disorders or fibromyalgia. Therefore, an increase in symptoms, or flare, attributed to lupus may actually have other origins. Finally, the possibility that factors other than those we have accounted for in our analyses may explain the association between trauma exposures and self-reported flares or disease activity.

These limitations are mitigated by the strengths of the study. Few SLE cohorts have included comprehensive assessments of childhood and other traumatic experiences. This is the first study to examine the combined associations of perceived psychological stress and both childhood and adult trauma exposures with SLE outcomes. While we did not conduct separate analyses for racial or ethnic groups, our cohort is quite diverse. All participants have rheumatologist-confirmed SLE.

Conclusion

Individuals with SLE who have experienced trauma during adulthood may be at increased risk for more frequent self-reported flares over time, including flares for which they seek medical care, and the experience of childhood trauma may magnify that risk. Because trauma appears to amplify responses to new stressors, trauma history may contribute to disease activity and symptom experiences of individuals with SLE. A number of interventions have been proposed to counteract the effects of trauma, including mindfulness practices, cognitive behaviour therapy and physical activity [50]. While cognitive behavioural therapy has been demonstrated to improve pain, depressive symptoms and function, and to reduce perceived stress among women with lupus [51], few other non-pharmacologic programs have been tested among people with SLE. Identifying the mechanisms underlying the association between trauma and disease activity and flares is critical to inform targeted interventions to mitigate the long-term adverse sequelae of prior trauma in SLE.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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