Association of Childhood Abuse with Incident Systemic Lupus Erythematosus in Adulthood in a Longitudinal Cohort of Women

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ABSTRACT. ***Objective.*** Exposure to severe stressors may alter immune function and augment inflammation and cytokine release, increasing risk of autoimmune disease. We examined whether childhood abuse was associated with a heightened risk of incident systemic lupus erythematosus (SLE).

Methods. Data were drawn from the Nurses' Health Study II, a cohort of US female nurses enrolled in 1989, followed with biennial questionnaires. We measured childhood physical and emotional abuse with the Physical and Emotional Abuse Subscale of the Childhood Trauma Questionnaire and sexual abuse with the Sexual Maltreatment Scale of the Parent-Child Conflict Tactics Scale, both administered in 2001. We identified incident SLE (≥ 4 American College of Rheumatology 1997 classification criteria) through 2015. We used multivariable Cox regression models to evaluate the association between childhood abuse and SLE, accounting for potential confounders (e.g., parental education, occupation, home ownership) and mediators [e.g., depression, posttraumatic stress disorder (PTSD)].

Results. Among 67,516 women, there were 94 cases of incident SLE. In adjusted models, exposure to the highest versus lowest physical and emotional abuse was associated with 2.57 times greater risk of SLE (95% CI 1.30–5.12). We found that 17% ($p < 0.0001$) of SLE risk associated with abuse could be explained by depression and 23% ($p < 0.0001$) by PTSD. We did not observe a statistically significant association with sexual abuse (HR 0.84, 95% CI 0.40–1.77, highest vs lowest exposure).

Conclusion. We observed significantly increased risk of SLE among women who had experienced childhood physical and emotional abuse compared with women who had not. Exposure to childhood adversity may contribute to development of SLE. (First Release September 1 2019; J Rheumatol 2019;46:1589–96; doi:10.3899/jrheum.190009)

Key Indexing Terms:
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Systemic lupus erythematosus (SLE) is a prototypical autoimmune disease with the potential for multisystem organ involvement and significant morbidity. Exposures to stress-related disorders, including posttraumatic stress disorder (PTSD), have been associated with increased risk of subsequent autoimmune diseases[1,2]. In a longitudinal cohort of U.S. female nurses, women with high PTSD symptoms had nearly 3 times higher risk of incident SLE compared to women unexposed to trauma[3]. Hypothesized mechanisms include stress-driven alterations to the immune system through inflammatory cytokines and dysregulation of the hypothalamic-pituitary-adrenal axis and the autonomic nervous system, increasing susceptibility to autoimmune diseases and increased disease-related damage[4,5,6].

Adverse experiences during childhood, a particularly sensitive time period, have significant effects on longterm neuropsychiatric and physical functioning and health outcomes later in life[7,8,9]. Exposure to adverse childhood environments and experiences, including socioeconomic

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disadvantage and maltreatment, has been associated with higher levels of inflammatory markers and cytokines, including C-reactive protein and interleukin 6, as well as to alterations in cell-mediated immune function both later in childhood and in adulthood[9,10,11]. Childhood adversity has previously been linked to increased risk of chronic diseases and mental illness[9,12,13,14]. One study demonstrated that children exposed to 2 or more adverse childhood experiences were at 2-fold risk for hospitalization with a rheumatic disease compared with unexposed children[15]. Understanding the effects of this quite prevalent exposure on SLE incidence could inform interventions aimed at modifying risk among vulnerable individuals during potentially sensitive developmental periods.

We investigated this relationship in a large, longitudinal US-based cohort and hypothesized that exposure to childhood maltreatment would be associated with increased risk of developing SLE.

MATERIALS AND METHODS

We used data from the Nurses' Health Study II (NHSII), a longitudinal cohort of 116,429 female nurses, age 25–44 years at baseline in 1989, from 14 US states and followed with biennial questionnaires. In 2001, a questionnaire that assessed child abuse was sent to all NHSII participants who returned the most recent biennial questionnaire, with 75% response rate (68,376/91,279). We excluded participants with self-reported connective tissue disease at baseline, less than four 1997 American College of Rheumatology (ACR) revised classification criteria for SLE[16], or diagnosis prior to 1989 (n = 672). We also excluded individuals missing child abuse data.

This study was approved by the Partners Healthcare Institutional Review Board (no. 2015P001458); return of the questionnaires implied consent.

SLE case ascertainment. We identified incident SLE cases from June 1991 to June 2015. Women were asked to report new physician diagnoses of SLE on biennial questionnaires. Women indicating a new diagnosis were asked to complete the Connective Tissue Disease Screening Questionnaire[17] and to consent to release of their medical records. Medical records of all nurses who indicated SLE symptoms were independently reviewed by 2 board-certified rheumatologists. Cases were determined based on ≥ 4 1997 ACR criteria[16].

Childhood abuse exposure ascertainment. We assessed exposure to physical and emotional abuse using the Physical and Emotional Abuse Subscale of the Childhood Trauma Questionnaire (CTQ)[18]. This scale has been shown to have good internal consistency (Cronbach's alpha = 0.94) and test-retest reliability (intraclass correlation = 0.82)[18]. Participants were asked whether as a child (age < 11 yrs): "(1) people in my family hit me so hard that it left me with bruises and marks, (2) the punishments I received seemed cruel, (3) I was punished with a belt, a board, a cord, or some other hard object, (4) someone in my family yelled and screamed at me, (5) people in my family said hurtful or insulting things to me." We excluded 188 individuals with incomplete CTQ data. Item responses (0: never, 1: rarely, 2: sometimes, 3: often, or 4: very often true) were summed, the mean was determined, and then divided into quartiles to assess a dose-response relationship[19]. We also examined the CTQ score as a continuous variable.

We assessed sexual abuse using the 2-item Sexual Maltreatment Scale of the Parent-Child Conflict Tactics Scale (CTS)[20]. These questions were: "Were you ever touched in a sexual way by an adult or an older child or were you forced to touch an adult or an older child in a sexual way when you did not want to?" and "Did an adult or an older child ever force you or attempt to force you into any sexual activity by threatening you, holding you down or hurting you in some way when you did not want to?" Respondents were asked to indicate if this happened never, once, or more than once during childhood (up to age 11 yrs) and as a teenager (age 11–17 yrs). In keeping with prior work, 0 points was equivalent to no abuse, 1–2 points mild, 3–4 points moderate, and 5+ severe sexual abuse; responses were summed across questions[19]. These categories were examined separately and then moderate and severe categories were combined because of small sample sizes. We excluded 224 individuals with incomplete responses.

We conducted a secondary analysis examining physical assault using questions from the CTS[20]. We included this as a secondary analysis of physical abuse because the full CTS was not queried, and because our primary measure, the CTQ, identified both physical and emotional abuse. The CTS categorizes physical assault by type: "(1) spank you for discipline, (2) push, grab, or shove you, (3) kick, bite or punch you, (4) hit you with something that hurt your body, (5) choke or burn you, (6) physically attack you in some other way," and by frequency (never, once, a few times, more than a few times), during childhood (< 11 yrs) or during adolescence (11–17 yrs). Responses were summed and divided into none, mild, moderate, and severe. Moderate and severe categories were combined to maximize power and because the rate ratio estimates were nearly identical for the 2 categories. We combined childhood and adolescent abuse because the correlation was high ($R^2 = 0.80$, $p < 0.001$).

Covariate ascertainment. Covariates were ascertained from biennial surveys, 1989–2013. We calculated age based on birthdate, and categorized race as white and nonwhite. We examined parental occupation, home ownership, and education at the time of birth or infancy as different measures of childhood socioeconomic status, which may be a prior common cause of both childhood abuse and SLE risk. We categorized parental occupation for the parent with the highest occupation level as farmers, laborers, blue and lower white-collar workers (service, craftsmen, sales, clerical, military), and upper white-collar workers (managerial, professional)[21,22]. A separate variable indicated whether the mother worked outside the home. We dichotomized parental home ownership at the time of birth or infancy (yes/no) and categorized the highest level of education attained by either parent as ≤ high school, some college, and college graduate and above. We included self-reported birthweight [< 5.5 lbs, 5.5 to < 10 lbs (ref), ≥ 10 lbs], which has been validated in the NHSII and shown to be strongly correlated with birth records[23]. Higher birthweight has been associated with increased SLE risk and we hypothesized a relationship with child abuse as well[24]. We measured childhood obesity, given evidence suggesting it is associated with SLE risk and with childhood maltreatment[25,26], using a childhood somatogram score; participants chose a diagram that represented their body type at age 5 [very thin (1) to extremely obese (9), grouped as 1-4 (reference) and ≥ 5][27]. We also assessed age at menarche (age ≤ 10 yrs vs > 10) because this has also been associated with SLE risk and with childhood abuse[28,29].

We assessed additional covariates measured during adulthood and updated biennially that may be associated both with prior experiences of childhood abuse and with subsequent SLE risk. Smoking status was categorized as never, past, and current and body mass index (BMI) as 18.5 to < 25, 25 to < 30, and 30+. We also included measures of depression and of PTSD, because both are associated with prior child abuse exposure and with increased SLE risk[3,30,31,32]. We assessed depression (yes/no) as self-reported clinician diagnosis (queried biennially from 2003 to 2011), self-reported use of antidepressants (queried biennially beginning in 1993) or score < 60 on the Mental Health Inventory (measured in 1993, 1997, and 2001)[33]. We assessed history of trauma or PTSD in a subsample of participants who responded in 2008 to the Brief Trauma Questionnaire[34] and the 7-item Short Screening Scale for DSM-4 PTSD[35], categorized as no trauma, trauma and no PTSD, subclinical PTSD (1–3 symptoms), or probable PTSD (4–7 symptoms)[3]. We assessed postal code median household income (in 1989), as well as alcohol consumption (none, 0–5 g/day, and ≥ 5 g/day), updated biennially[36].

Statistical analysis. We examined the distribution of covariates by physical

and emotional abuse (CTQ) and sexual abuse exposure categories. We used Cox proportional hazards regression models to calculate the risk (HR) of incident SLE associated with physical and emotional abuse, with the lowest quartile of exposure as the reference. We also considered the CTQ score as a continuous variable to examine SLE risk in association with a 1-standard deviation increase in CTQ score. We first fit models that were age- and race-adjusted and then adjusted for childhood socioeconomic factors (parental occupation, education, home ownership), as well as childhood factors (birthweight, somatogram score at age 5 yrs, age at menarche), which may confound the association between abuse and SLE risk. We fit the same models with sexual abuse and physical assault measured by the CTS as the independent variables. We tested the proportional hazards assumption for our primary exposures and found no violations.

Adult BMI, alcohol consumption, area-level median household income, smoking, depression, and PTSD may lie on the causal pathway between abuse exposure and SLE incidence. We therefore used the SAS MEDIATE Macro method to estimate the proportion of the effect of childhood physical and emotional abuse on SLE risk that may be explained by each of these potential mediators in separate age- and race-adjusted, and childhood/parental-factor-adjusted models[37]. To assess mediation, we used Cox models as described above, additionally adjusted for these pathway variables. In sensitivity analyses, we also conducted a prospective analysis that included only SLE cases occurring after women returned the 2001 violence questionnaire, to minimize the possibility of recall bias.

RESULTS

Of the 67,516 women with CTQ data (70% with 26 years of followup data), 36,224 (54%) reported moderate or high levels of exposure to physical or emotional abuse, and among 67,480 women with sexual abuse data, 6732 (9.9%) reported moderate or high levels of sexual abuse (Table 1). A slightly higher percentage of nonwhite versus white women reported abuse. Individuals who were older at the time of report described modestly higher levels of childhood abuse. We found a higher prevalence of abuse among women with parents who had less education, were laborers or blue or lower white-collar workers, and who did not own homes. We also observed higher levels of physical and emotional abuse among women with lower birthweight and who were ≤ 10 years old at menarche. In adulthood, women who experienced childhood abuse had higher mean BMI data and were more likely to have smoked compared with women who did not. Depression and PTSD reported during adulthood were positively associated with abuse.

We confirmed 94 cases of SLE (Table 2). Nearly all were antinuclear antibody–positive, with mean ± SD ACR criteria of 5 ± 1. More than half were anti-dsDNA–positive, suggesting the potential for more active and severe disease, and the dominant manifestations were arthritis (73%) and hematologic involvement (64%). Of these SLE cases, 36 occurred after 2001, when the child abuse questionnaire was administered.

Considering the relationship between childhood physical and emotional abuse (measured by the CTQ) and SLE risk, we observed a nearly 3 times higher risk of SLE comparing the highest level of abuse to no abuse (HR 2.81, 95% CI 1.42–5.56) in age- and race-adjusted models. This was slightly attenuated after adjustment for parental and childhood factors (HR 2.57, 95% CI 1.30–5.12; Table 3). Each SD increase in CTQ score as a continuous measure was associated with a 28% higher risk of SLE (HR 1.28, 95% CI 1.08–1.53).

With mediation analyses in adjusted models, 5% (95% CI 2.0–11.9, p = 0.0003) of the effect of the highest level of abuse on SLE risk could be statistically explained by smoking status, and 2.9% (95% CI 1.2–6.7, p < 0.0001) by BMI. Additionally, we found that 16.7% (95% CI 8–31.7, p < 0.0001) of the risk of SLE associated with the highest level of abuse could be explained by depression and 23.3% (95% CI 7.2–54.4, p < 0.0001) by PTSD exposure. We included these mediators in our multivariable models adjusted for age, race, and childhood/parental factors, and found that in models additionally adjusted for smoking and BMI (Table 3, Model C) and depression (Table 4, Model D2), the risk of SLE comparing women who experienced the highest level of abuse versus the lowest was modestly attenuated but statistically significant. Adjustment for PTSD (Table 4, Model E2) significantly attenuated the association (HR 1.84, 95% CI 0.83–4.07). Alcohol consumption and postal code median household income were not statistically significant mediators of the association between childhood abuse and SLE risk.

In prospective analyses, the association between the highest degree of childhood physical and emotional abuse (vs no abuse) and SLE risk remained statistically significant, with a larger effect size (HR 3.14, 95% CI 1.03–9.56) in age- and race-adjusted models, and was only slightly attenuated after adjustment for childhood and parental factors (HR 3.11, 95% CI 1.01–9.57; Table 5). In adjusted models, we found a 41% increased risk of SLE for each SD increase in CTQ score (HR 1.41, 95% CI 1.07–1.86).

We separately examined the association between sexual abuse and SLE risk (Table 6). We did not observe an increased risk of SLE associated with any degree of sexual abuse in either age- and race-adjusted models or in models additionally adjusted for parental and childhood factors.

Secondary analysis. We examined the risk of SLE associated with the alternative measure of physical assault (CTS). The correlation between CTQ and CTS responses was high (R^2 = 0.77, p < 0.0001). Consistent with our findings with the CTQ, we observed higher SLE risk among women who experienced medium to high levels of physical abuse during childhood or adolescence compared to those who experienced none (HR 1.74, 95% CI 1.11–2.73; Appendix 1).

DISCUSSION

In this longitudinal cohort followed for more than 24 years, we observed nearly tripled risk of incident SLE among women who had experienced high levels of childhood physical and emotional abuse compared to women who had not. Adjustment for potential parental and childhood confounders attenuated this association only slightly. In

Table 1. Age-standardized characteristics in 1989 of Nurses' Health Study II participants in current analysis according to Childhood Trauma Questionnaire (CTQ) response categories (n = 67,516) and sexual abuse categories (n = 67,480).

Characteristic	CTQ Response Category, n = 67,516				Sexual Abuse Response Category, n = 67,480		
	None/Very Low, n = 14,703	Low, n = 16,589	Moderate, n = 20,153	High, n = 16,071	None, n = 44,841	Low, n = 15,907	Moderate/High, n = 6732
Age in 1989, mean yrs ± SD	34.8 ± 4.8	34.5 ± 4.7	34.4 ± 4.6	34.8 ± 4.5	34.5 ± 4.7	34.8 ± 4.6	34.8 ± 4.6
Nonwhite race, %	4.6	4.9	6.4	8.3	5.3	7.2	8.7
Parental education, %							
≤ High school	43.3	44.9	47.0	49.8	45.2	48.0	50.0
Some college	32.1	32.8	32.4	33.6	32.7	32.4	33.2
College and above	24.6	22.4	20.6	16.6	22.1	19.5	16.8
Parental occupation, %							
Mother works in home	62.9	62.5	61.8	58.7	62.8	60.4	55.5
Farmer	7.1	6.1	5.5	4.3	5.6	5.9	6.0
Laborer	7.8	8.3	9.3	11.1	8.7	9.8	10.8
Blue/lower white collar	46.4	49.3	50.9	52.8	49.4	51.2	51.1
White collar	27.6	25.3	22.9	18.3	25.0	21.4	17.6
Parental home ownership, %	52.3	48.9	47.9	44.0	49.2	47.0	44.6
Birthweight, %							
< 5.5 lbs	6.3	6.1	6.6	7.7	80.6	79.3	76.4
5.5–9.9 lbs	81.2	81.5	79.8	77.1	6.6	6.6	7.5
≥ 10 lbs	1.1	1.0	1.0	1.1	1.0	1.1	1.2
Age 5 yrs somatogram ≥ 5*, %	7.8	8.2	8.6	10.0	8.4	8.6	10.8
Menarche at age ≤ 10 yrs, %	7.0	7.2	7.6	8.6	7.1	7.8	10.8
Alcohol intake, %							
None	38.2	36.5	37.0	38.6	37.0	37.3	40.9
0–5 g/day	42.2	42.7	42.7	41.2	42.9	41.6	39.0
≥ 5 g/day	19.6	20.9	20.4	20.3	20.1	21.1	20.0
Postal code median household income in 1989, median US$ (IQR)	56,907 (45,516, 71,151)	56,890 (45,417, 71,795)	56,935 (45,545, 71,743)	56,450 (45,162, 71,082)	58,085 (46,434, 72,520)	56,479 (45,250, 71,250)	55,135 (44,150, 69,389)
Smoking status, %							
Never	71.3	68.6	65.7	59.8	68.6	62.8	58.0
Past	19.0	20.1	22.1	25.8	20.4	23.9	26.3
Current	9.8	11.3	12.2	14.5	11.1	13.3	15.8
BMI, %							
18.5 to < 25	70.5	69.1	67.7	64.0	69.4	66.1	61.4
25 to < 30	16.5	17.5	17.9	19.0	16.9	19.3	20.0
30+	8.6	9.5	10.6	13.2	9.6	11.1	15.4
Depression**, %							
None	76.2	72.5	66.6	56.0	70.9	64.9	53.4
Depression	23.8	27.5	33.4	44.0	29.1	35.1	46.6
Trauma and PTSD***, %							
No trauma, no PTSD	41.1	35.1	28.7	14.7	36.5	19.9	6.4
Trauma, no PTSD	37.8	39.8	40.5	37.4	38.8	42.5	31.8
PTSD low score	15.1	17.0	19.4	23.9	16.2	22.8	28.1
PTSD moderate + high score	6.0	8.2	11.5	24.1	8.4	14.8	33.7

Values except for age are age-standardized to the age distribution of the study population. * Age 5 yrs somatogram score represents the diagram that the participant chose that best represents her body type ranging from 1 (very thin) to 9 (very obese). ** Measured by self-reported physician diagnosis, Mental Health Inventory-5 score < 60, or use of antidepressant medication for subset of subjects with data available (n = 67,469 for CTQ and n = 66,904 for sexual abuse). *** PTSD data available for subset of subjects (n = 50,093 for CTQ and n = 50,082 for sexual abuse). IQR: interquartile range; BMI: body mass index; PTSD: posttraumatic stress disorder.

prospective analyses the association persisted, with more than 3 times higher risk among women who were exposed to childhood abuse compared to women who were not.

Our findings are in accord with studies that similarly demonstrated higher risk of autoimmune diseases among individuals exposed to trauma and extreme stress[1,3]. It is biologically plausible that adversity during childhood plays an important role in the development of autoimmune inflammatory conditions during adulthood. Children who experienced maltreatment have been shown to have elevated markers of inflammation into adulthood[11,38]. While the precise mechanism for this is unknown, one model suggests

Table 2. Characteristics of incident SLE cases (n = 94) in Nurses' Health Study II cohort with ≥ 4 American College of Rheumatology (ACR) classification criteria for SLE.

Characteristic	
ACR criteria, mean ± SD	5.0 ± 1.0
Age at SLE diagnosis, mean yrs ± SD	44.9 ± 8.7
ANA-positive	93 (98.9)
Anti-dsDNA–positive	49 (52.1)
Anti-Ro or Anti-La–positive	17 (18.1)
Anti-Sm–positive	6 (6.4)
Anti-RNP–positive	6 (6.4)
Arthritis	69 (73.4)
Hematologic involvement	60 (63.8)
Renal involvement	11 (11.7)
Seen by an ACR member rheumatologist	82 (87.2)

Values are n (%) unless otherwise indicated. SLE: systemic lupus erythematosus; ANA: antinuclear antibody.

that individuals who experienced significant early life adversity may have enhanced psychological and physiological stress sensitivity. When this sensitivity is compounded by fewer social and psychological resources to buffer stress, both psychological and physiological dysregulation may lead to immune dysregulation and inflammation[39]. At the biological level, the concept of "embedding" has been proposed, whereby childhood stress results in epigenetic changes, in particular in the DNA of immune system cells, which then have heightened inflammatory tendencies[40]. This results in heightened cytokine and chemokine responses to stress and reduced sensitivity to inhibitory hormonal signals[40]. When combined with other exposures, including higher risk for unhealthy life choices and genetic risk factors, the increased inflammation may lower the threshold for the development of autoimmune diseases such as SLE.

Studies have demonstrated associations between perinatal and early life exposures and risk of SLE. Childhood farm residence, for example, as well as childhood exposure to agricultural pesticides have been associated with increased SLE risk[41]. Both preterm birth and birthweight ≥ 10 lbs have similarly been linked to increased rates of SLE compared to at-term birth and normal birthweight, respectively[24,41]. While childhood adversity has not previously been studied in the context of SLE incidence, in a cohort of 166 patients, having 4 or more adverse childhood experiences was associated with more severe SLE-related damage in adulthood[42]. Although we were unable to examine cumulative lifetime exposure to trauma, studies suggest the unique effect of adverse childhood exposures on subsequent inflammatory and autoimmune disease risk[11,15].

The percentage of women reporting experiences of childhood abuse in NHSII is comparable with other large US-based studies. Among > 17,000 health maintenance organization members, 64% reported at least 1 of 8 categories of adverse childhood experiences, including emotional, physical, or sexual abuse[43]. We found a significant association between high levels of childhood physical and emotional abuse and risk of SLE that persisted after adjustment for childhood confounders. Adult BMI, smoking, and depression were modest mediators; however, the association persisted after adjustment for these factors. PTSD explained the largest percentage (23%) of the association between the highest level of abuse and SLE risk. While we do not know the etiology of the women's PTSD, studies demonstrate that childhood abuse increases vulnerability to PTSD in adulthood[44]. In a study also within the NHSII cohort, the highest number of PTSD symptoms was associated with nearly 3 times the risk of SLE[3]. It is plausible that individuals who do not develop PTSD related to this childhood trauma may not have as great a risk of SLE compared to those who do. There are no studies that examine the role of resilience and other protective factors that may mitigate the risk of autoimmune disease among individuals exposed to severe stressors.

We did not find a significant association between sexual abuse and SLE risk. The lack of association may be a result of underreporting of sexual abuse[45]. In our population, 10% of women reported exposure to moderate or high levels of sexual abuse. In a sample with more individuals exposed to higher levels of sexual abuse, an association might have been observed. It is also plausible that there are more established resources in place to detect and mitigate the effects of sexual abuse, but emotional abuse during childhood may remain hidden and have longer-term psychological and physical effects[46,47]. It may also be possible that sexual abuse does not contribute to SLE risk. A study that demonstrated an association between childhood adverse experiences and

Table 3. Association of childhood physical and emotional abuse as measured by the Childhood Trauma Questionnaire (CTQ) with risk of incident SLE in the Nurses' Health Study II cohort (n = 67,516).

CTQ Response	SLE Cases/person-yrs	Model A, HR (95% CI)	Model B, HR (95% CI)	Model C, HR (95% CI)
None/very low	11/361,724	Ref	Ref	Ref
Low	24/407,066	1.92 (0.94–3.92)	1.89 (0.92–3.87)	1.85 (0.90–3.79)
Moderate	25/493,200	1.66 (0.81–3.38)	1.58 (0.78–3.23)	1.52 (0.74–3.09)
High	34/386,815	2.81 (1.42–5.56)	2.57 (1.30–5.12)	2.38 (1.19–4.74)
p for trend		0.004	0.01	0.03

SLE: systemic lupus erythematosus.

Table 4. Association of childhood physical and emotional abuse as measured by the Childhood Trauma Questionnaire (CTQ) with risk of incident SLE in the Nurses' Health Study II cohort for subsets with depression (n = 67,469) and posttraumatic stress disorder (PTSD) data (n = 50,093).

CTQ Response	SLE Cases/ person-yrs	Model D1, HR (95% CI)	Model D2, HR (95% CI)	SLE Cases/ person-yrs	Model E1, HR (95% CI)	Model E2, HR (95% CI)
None/very low	8/306,527	Ref	Ref	9/271,790	Ref	Ref
Low	17/344,728	1.86 (0.80–4.31)	1.77 (0.76–4.11)	23/308,528	2.25 (1.04–4.88)	2.12 (0.97–4.61)
Moderate	21/417,376	1.85 (0.82–4.19)	1.68 (0.74–3.81)	19/370,845	1.46 (0.66–3.25)	1.33 (0.60–2.96)
High	32/325,999	3.31 (1.51–7.22)	2.71 (1.23–5.95)	24/291,448	2.22 (1.02–4.82)	1.84 (0.83–4.07)
p for trend		0.001	0.01		0.18	0.44

Model D1: For subset with depression data available, adjusted for age, race, and parental and childhood factor (maternal and paternal occupation, parental education, parental home ownership, birthweight, age at menarche, somatogram score at age 5 yrs). Model D2: For subset with depression data available, adjusted for age, race, parental and childhood factor, and adult history of depression. Model E1: For subset with PTSD data available, adjusted for age, race, and parental and childhood factor. Model E2: For subset with PTSD data available, adjusted for age, race, paternal and childhood factor, and adult history of PTSD. SLE: systemic lupus erythematosus.

Table 5. Association of childhood physical and emotional abuse as measured by the Childhood Trauma Questionnaire (CTQ) with risk of incident SLE occurring after assessment of CTQ (2001) in the Nurses' Health Study II cohort (n = 67,516).

CTQ Response	SLE Cases/ person-yrs	Age and Race-adjusted Model, HR (95% CI)	Parental and Childhood Factor–adjusted Model*, HR (95% CI)
None/very low	4/190,651	Ref	Ref
Low	5/213,847	1.09 (0.29–4.07)	1.12 (0.30–4.20)
Moderate	13/258,615	2.38 (0.77–7.33)	2.33 (0.75–7.17)
High	14/200,449	3.14 (1.03–9.56)	3.11 (1.01–9.57)
p for trend		0.01	0.01

* Model adjusted for age, race, maternal and paternal occupation, parental education, parental home ownership, birthweight, age at menarche, and somatogram score at age 5 yrs. SLE: systemic lupus erythematosus.

Table 6. Association of childhood sexual abuse with risk of incident SLE in the Nurses' Health Study II cohort (n = 67,480).

Sexual Abuse Response Categories	SLE Cases/ person-yrs	Age and Race-adjusted Model, HR (95% CI)	Parental and Childhood Factor–adjusted Model*, HR (95% CI)
None	61/1,098,429	Ref	Ref
Low	25/388,919	1.14 (0.71–1.81)	1.13 (0.71–1.80)
Moderate/high	8/160,650	0.87 (0.42–1.83)	0.84 (0.40–1.77)
p for trend		0.81	0.68

* Model adjusted for age, race, maternal and paternal occupation, parental education, parental home ownership, birthweight, age at menarche, and somatogram score at age 5 yrs. SLE: systemic lupus erythematosus.

autoimmune disease used a composite measure and did not separate sexual abuse from physical and emotional abuse[15]. In our cohort, while we observed a strong correlation, as expected, between the CTQ and the CTS, physical and emotional abuse was not strongly correlated with sexual abuse ($R^2 = 0.29$, $p < 0.0001$).

There are limitations to this work. This was a predominately white cohort of female nurse professionals and our findings may not be broadly generalizable (e.g., to men, other racial/ethnic groups, nonprofessionals). SLE disproportionately affects nonwhite racial/ethnic groups and lower socioeconomic status individuals and further studies are needed in diverse cohorts to determine whether these findings can be replicated. Experiences of childhood abuse were self-reported in adulthood and may be subject to recall bias, particularly among adults with chronic illnesses. However, in prospective analyses restricted to individuals who developed SLE after the report of childhood abuse, the association persisted. There may be misclassification of exposure because women may underreport experiences of both physical and sexual abuse[45,48]. Individuals may not report abuse for a number of reasons, including embarrassment, symptoms of victimization, a conscious desire to forget, or a lack of trust in the study[48,49]. While we were able to consider some markers of parental socioeconomic status, and perinatal and childhood exposures, residual or unmeasured confounding is possible.

We did not have information regarding other childhood stressors (e.g., food insecurity, housing instability, parental income) that may confound the observed association, or have an additive effect.

Our study also has several strengths. To our knowledge, this is the first longitudinal cohort study to specifically examine the relationship between childhood physical, emotional, and sexual abuse and risk of incident SLE. We used a large, richly characterized cohort with more than 24 years of followup data including information on parental sociodemographic factors and childhood and adulthood exposures. In addition, we confirmed our SLE cases by chart review and all met ACR criteria. We examined potential confounders and mediators, and we restricted our cases to those occurring after report of SLE to minimize recall bias.

In this cohort of US-based women, we observed a significant association between experiences of childhood physical and emotional abuse and incident SLE. Our study adds further evidence that exposure to severe childhood stressors, even after adjustment for parental socioeconomic factors, increases the risk of autoimmune disease. With findings that suggest that experiences of significant childhood abuse are likely more prevalent than previously appreciated, programs are needed to develop effective prevention strategies and to mitigate the far-reaching effects among those previously exposed. In addition, our study provides motivation for providers to actively screen patients for experiences of childhood abuse, as well as for onset of depression and PTSD, given their association with autoimmune disease risk.

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APPENDIX 1. Association of physical abuse measured by the Parent-Child Conflict Tactics Scale (CTS) with risk of incident SLE in the Nurses' Health Study II (n = 67,480).

CTS Response	SLE Cases/ person-yrs	Age and Race-adjusted Model, HR (95% CI)	Parental and Childhood Factor–adjusted Model*, HR (95% CI)
None	34/769,805	Ref	Ref
Low	17/333,488	1.13 (0.63–2.03)	1.12 (0.63–2.02)
Moderate/high	43/546,000	1.74 (1.11–2.73)	1.64 (1.04–2.59)
p for trend		0.01	0.03

* Model adjusted for age, race, maternal and paternal occupation, parental education, parental home ownership, birthweight, age at menarche, and somatogram score at age 5 yrs. SLE: systemic lupus erythematosus.