Stressful life events are associated with the diagnosis of systemic autoimmune rheumatic diseases among adults

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Abstract

Objective

To assess the association between life events and subsequent diagnosis of systemic autoimmune rheumatic diseases (SARDs) by comparing siblings discordant for SARDs and unrelated controls.

Methods

Life events 12 months prior to SARD diagnosis/reference date were queried using the Interview for Recent Life Events in 227 adults (96 probands with SARDs, 78 siblings, 53 controls). Probands were matched by age, sex, and race with their unaffected siblings or with unrelated controls. Logistic regression was used to calculate the relative odds of SARDs in relation to life events scores, adjusting for age, sex, race/ethnicity, education, and ever smoking.

Results

The study identified consistent trends of probands reporting greater numbers of total and highly stressful events, and higher stress ratings than their unaffected siblings. Probands reported greater numbers and higher stress ratings of total, uncontrollable, and undesirable events compared to unrelated controls (p<0.001–0.024). The number of highly stressful events and the scores of weighted major events were also greater in probands and siblings compared to unrelated controls (p<0.001–0.046). The number of total, major, uncontrollable, undesirable, and highly stressful life events (OR range 1.31-1.64, p-value range 0.001–0.049), along with their corresponding stress ratings (OR range 1.22-1.51, p-value range <0.001–0.016), were associated with higher odds of SARD diagnosis, based on probands compared to controls.

Conclusion

This case-control study of life events preceding SARDs diagnosis using a validated life events questionnaire provides support for an aetiologic role of negative life events and psychological stress in SARDs among adults.

Key words

psychosocial stress, autoimmune diseases, risk factors

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Introduction

The systemic autoimmune rheumatic diseases (SARDs) are multi-organ immune-mediated disorders thought to arise from the interaction of specific environmental exposures in genetically predisposed individuals (1). Growing evidence supports the role of psychosocial stress in the initial development of SARDs. Psychiatric comorbidities, including post-traumatic stress disorder (PTSD), have been linked to SARD diagnosis (2). Adverse childhood experiences (ACEs), which include potentially traumatic events occurring during childhood, such as abuse and neglect, have also been associated with the development of SARDs in adulthood, including systemic lupus erythematosus (SLE) (3, 4). The relationship between more ordinary life events, such as experiencing a divorce and a job promotion, with SARDs has been less explored.

Life events have been defined as social experiences that have a psychological impact on the individual (5). These occurrences and the individual appraisal of their magnitude and meaning can be associated with stress. Stress can be described as a mental state that triggers a cascade of physiological changes to meet environmental demands, promoting growth and adaptation, while contributing to illness and other disturbances.

Limited literature suggests that negative stressful life events may be risk factors for the onset of rheumatoid arthritis (RA) and SLE within 1–5 years after their occurrence (6). However, the data in other SARDs remains scarce (7). Some of the limitations in these studies have included the application of abbreviated or non-validated life events assessment tools, small samples sizes, and the investigation of few SARDs, which are individually rare (8).

Despite the phenotypic heterogeneity among SARDs, these diseases share many clinical manifestations, as well as genetic and environmental risk factors, whose interactions modulate disease expression and severity (9). Support for this concept includes the common occurrence of overlapping SARDs syndromes in the same patient, the intersection of autoantibodies and other laboratory features, common pathogenic molecular pathways, and familial aggregation of individuals with distinct SARDs (10). Viewing SARDs as a constellation of discrete elemental disorders with shared symptomatology, laboratory findings, and pathogenesis may be an effective approach for investigating their aetiopathogenesis, rather than studying each SARD individually (9). Shared genetic risk factors among close relatives, such as siblings, makes it possible to better investigate the contribution of environmental factors, such as the impact of stress, on their development. Discordant sibling studies can potentially help tease apart genetic and environmental components in the study of disease etiopathogenesis.

This study explored the association between psychosocial stress and SARDs by investigating life events within the year prior to diagnosis in adult siblings discordant for one of four SARDs and unrelated controls. We hypothesised that the diagnosis of SARDs may be associated with negative life events that preceded diagnosis. This study also examined how different categories of life events and their accompanying stress ratings are linked to a SARD diagnosis.

Patients and methods

Participants. This study examines life event data from the NIEHS Study of Twins or Siblings Discordant for Systemic Autoimmune Rheumatic Diseases (SARDs) (NCT00055055), an observational case-control study enrolling families from 2003 to 2021 in which one sibling was diagnosed with a SARD within 5 years of enrolment (proband) and a same-gender closest-in-age biologic sibling, within 5 years of the proband's age, with no documented autoimmune disease also enrolled. Probands were adults who met probable or definite criteria for a SARD, including RA, SLE, systemic sclerosis (SSc), or idiopathic inflammatory myopathies (IIM), and lived within the United States or Canada at diagnosis. Controls unrelated to probands and without documented autoimmune diseases were recruited from the National Institutes of Health (NIH) healthy volunteer programme. Controls were

Table I. Life events questionnaire used in this study, with scoring system and stress ratings*.

Categories of events‡	Example questions	Number of questions/score range†	Stress ratings	Weighted event score range††
Major events	Did you experience the birth of a child?	16 / 0–16	0 = not at all 1 = a little stressful 2 = somewhat stressful 3 = very stressful	0–48
Controllable events	Did you begin full or part-time education?	12 / 0–12		0–36
Uncontrollable events	Did you experience a serious accident?	27 / 0–27		0–81
Desirable events	Did you have a promotion?	6 / 0–6		0–18
Undesirable events	Did you fail an important exam or course?	40 / 0–40		0–120
Total number of events	N/A	65 / 0–65		0–105
Highly stressful events	Any question that was rated "very stressful"	65 / 0–65	3 = very stressful	N/A

*Paykel ES. Suicide attempts and recent life events (12).
‡Categories are not mutually exclusive.
†Number of events endorsed by categories within the year of the proband's diagnosis of systemic autoimmune rheumatic disease (SARD), which was also used as the reference date for unaffected siblings and unrelated control participants.
††Sum of event ratings endorsed, by categories, within the year of SARD diagnosis or reference date.

matched to probands within 10 years of age, and by sex and race/ethnicity. All participants underwent standardised medical assessment and medical record review that included the year prior to the matched proband's SARD diagnosis date. In compliance with the Helsinki Declaration of 1975/83, the study was approved by the NIH Institutional Review Board; written informed consent was obtained from all participants.

Life events questionnaire

Each participant reported life events that occurred within 12 months of the matched proband's date of a SARD diagnosis. Life events were captured by a questionnaire adapted from the Interview for Recent Life Events, comprised of 64 events, with an opportunity for recording one additional major occurrence (Table I). We followed several recommendations aimed at facilitating reliable recollection of life events, such as grouping events in sections by area of life (such as family, work), and using key religious or other holidays as reference points that could help in dating the events (11). The questions were categorised into total, major, controllable, uncontrollable, desirable, undesirable, which were not mutually exclusive categories (12). Life events were rated on a 4-point Likert scale according to the participants perceived level of stress (0, not at all stressful to 3, very stressful). Weighted event scores were then created by summing the stress ratings of all endorsed items for each event category. The highly stressful event score was calculated by summing the number of events that were rated as very stressful (Table I).

Statistical analyses

Analyses were performed using Stata (release 15; StataCorp, College Station, TX) and GraphPad Prism (v. 9.3.1; GraphPad, San Diego, CA). Continuous variables are presented as mean ± standard deviation and compared using a two-tailed Student's t-test, Wilcoxon signed-rank and rank-sum tests, and one-way ANOVA. Categorical variables are presented as counts (%) and compared using Chi-square, Fisher's exact, or McNamar's tests. *p*-values were adjusted by Bonferroni correction for multiple comparisons, with adjusted $p<0.05$ considered statistically significant.

Paired analyses were performed when comparing probands and unaffected siblings, whereas unpaired analyses were used when comparing probands and unrelated controls, or siblings and unrelated controls, because 16% of the participants were not matched.

Unadjusted and adjusted conditional logistic regression models were used to compare paired probands and siblings, while unconditional logistic regression models were performed to compare probands and unrelated controls to examine association with SARDs. The missing-indicator method was also used to incorporate all matched and unmatched controls in the same model (13). Adjusted logistic regression models were used to examine the association between life events and a SARD diagnosis included the following covariates: age at a SARD diagnosis or reference date, time from a SARD diagnosis or reference date to completion of the questionnaire, sex, self-reported race/ethnicity, education, and history of ever smoking. A sensitivity analysis was performed incorporating a history of depression or anxiety, based on medical record review and physician evaluation, as a covariate.

Results

The study included 227 adults (96 probands with SARDs, 78 unaffected siblings, and 53 unaffected, unrelated controls). Among the siblings, 14 pairs of monozygotic twins and 2 pairs of dizygotic twins participated (Table II). Unrelated controls tended to be younger than probands and unaffected siblings, but were within 10 years of proband's age, per eligibility requirements. Time between a SARD diagnosis or reference date and questionnaire completion date was shorter for probands (1.9±1.6 years) and their siblings (2.0±1.7 years) than for unrelated controls (2.8±1.8 years). A history of ever smoking was more frequently reported among probands than unrelated controls (40% *vs*. 17%, $p=0.027$), but was similar to smoking histories reported by siblings. IIM was the most frequent SARD diagnosis. Probands, unaffected siblings, and unrelated controls were similarly distributed with respect to race/ethnicity and highest educational level.

Table II. Demographic characteristics and systemic autoimmune rheumatic disease diagnoses, by study role*.

Characteristic	Probands (n=96) n (%)	Unaffected siblings (n=78) n (%)	Healthy controls (n=53) n (%)
Diagnosis age (mean ± SD)†	46.0 ± 16.2§	46.8 ± 17.1§	34.5 ± 17.6§
Time to study enrolment ‡ (mean ± SD)	1.9 ± 1.6‖	2.0 ± 1.7¶	2.8 ± 1.8‖ ¶
Twins			
Monozygotic	14 (15)	14 (18)	0 (0)
Dizygotic	2 (2)	2 (3)	0 (0)
Sex, Female	73 (76)	63 (81)	37 (70)
Race/Ethnicity:			
Non-Latino White	72 (75)	59 (76)	40 (76)
Other	24 (25)	19 (24)	13 (24)
Black or African American	12 (13)	10 (13)	7 (13)
Hispanic or Latino/a	5 (5)	4 (5)	5 (9)
Asian	3 (3)	2 (3)	0 (0)
American Indian or Alaska Native	0 (0)	0 (0)	0 (0)
Multiracial	4 (4)	3 (4)	1 (2)
Proband SARD diagnosis:			
Myositis (DM, PM, IBM)**	55 (57)§	NA	NA
Rheumatoid arthritis	14 (15)	NA	NA
Systemic lupus erythematosus	15 (16)	NA	NA
Systemic sclerosis	12 (13)	NA	NA
Highest education level:			
Less than College degree	34 (35)	33 (42)	16 (30)
College or Graduate degree	62 (65)	45 (58)	37 (70)
Ever smoking††	38 (40)‖	25 (32)	9 (17)‖
Dx of anxiety or depression	13 (14)	12 (15)	7 (13)

*Data includes both matched and unmatched subjects.
†Age at diagnosis for unaffected siblings and unrelated controls is their age on the reference date, the date of the matched proband's diagnosis.
‡Time in years, from date of systemic rheumatic disease diagnosis in probands (or reference date in siblings and unrelated controls) and date of questionnaire completion.
**Among probands with myositis: DM n=24 (43.6%), PM n=20 (36.4%), IBM n=11 (20.0%).
††Self-reported cigarette smoking ever.
Significant differences: § $p \leq 0.001$, ‖ $p \leq 0.005$, ¶ $p \leq 0.05$
SD: standard deviation; Dx: diagnosis; NA: not available; SARD: systemic autoimmune rheumatic disease; DM: dermatomyositis; PM: polymyositis; IBM: inclusion body myositis.

Life events and ratings

There was a trend towards a greater number of total and highly stressful life events, as well as greater stress ratings among probands compared to their unaffected siblings (Table III, Fig. 1A-B). Probands reported a greater number of life events in the 12 months prior to a SARD diagnosis than did the unrelated controls. They reported greater numbers of events in several categories, including total, uncontrollable, undesirable, and highly stressful events (p-value range <0.001–0.022) (Table III). The weighted scores, which included ratings of how stressful the events were, were also higher among probands compared to unrelated controls in the categories of total, major, uncontrollable, and undesirable events (p-value range <0.001–0.024). The number of highly stressful events and the weighted major events score were also greater among unaffected siblings compared to unrelated controls in the year prior to the reference date (p=0.019 and p=0.046) (Table III). Adjusted logistic regression analysis that compared probands and unrelated controls (Table IV) estimated an increased odds of SARD diagnosis among participants with more total (OR 1.31, 95% CI 1.11, 1.53), major (OR 2.03, 95% CI 1.00, 4.10), uncontrollable (OR 1.64, 95% CI 1.14, 2.35), and undesirable life events (OR 1.58, 95% CI 1.17, 2.11). The number of reported highly stressful events was associated with the greatest magnitude of effect on a SARD diagnosis, wherein one additional highly stressful event in the year prior to diagnosis was associated with an estimated 110% increase in the odds of SARD diagnosis (OR 2.10, 95% CI 1.35, 3.26). The odds of a SARD diagnosis also increased with higher reported perceived levels of stress in the same categories (OR range 1.22–1.51, p value range <0.001–0.016), and with higher weighted controllable events scores (OR 1.62, 95% CI 1.13, 2.33). Models that included the diagnosis of depression or anxiety as a covariate were similar in direction and magnitude to the adjusted logistic regression models reported above (data not shown).

Similar odds ratios trends to those identified in the regression analysis between probands and unaffected controls were found when modelling probands, their unaffected siblings, and controls all together, but associations were not statistically significant (Table V). There was no significant association in the comparison between probands and their unaffected siblings by adjusted conditional logistic regression modelling (Table VI).

Discussion

This study examined the relationship between the development of SARDs and reported life events within the year before diagnosis using a retrospective case-control investigation of adult siblings discordant for one of four SARDs and unrelated controls with an in-depth, previously validated life event questionnaire. Participants diagnosed with SARDs reported a higher frequency of life events in the year prior to diagnosis compared to the unrelated controls, including events categorised as negative life occurrences, such as uncontrollable, undesirable, and highly stressful events. Additionally, an increased odds of a SARD diagnosis was associated with higher perceived levels of stress corresponding to these events.

Our study identified consistent trends of probands reporting greater numbers of total life events and highly stressful events, as well as greater stressfulness associated with negative life events than in their unaffected siblings, but these differences were not statistically significant based on a paired analysis. Life events may correlate substantially between siblings, which likely reflects the increased probability of experiencing certain types of events due to shared familial environmental effects, heritability of personality traits, similar response pathways to stress, and the possibility that one person's negative experience could precipitate stress

Table III. Frequencies of life events and perceived stress ratings within the year of proband's diagnosis with systemic autoimmune rheumatic disease.

Life events/scores by category:	Paired analysis*		Unpaired analysis*		
	Probands (n=76) (mean ± SD)†	Unaffected siblings (n=76) (mean ± SD)†	Probands (n=96) (mean ± SD)	Unaffected siblings (n=78) (mean ± SD)	Healthy controls (n=53) (mean ± SD)
Number of life events by category					
Total events	3.5 ± 2.9	2.9 ± 3.4	3.5 ± 2.9‖	2.8 ± 3.4	2.3 ± 2.5‖
Major events	0.4 ± 0.7	0.4 ± 0.8	0.4 ± 0.8	0.4 ± 0.7	0.2 ± 0.5
Controllable events	0.5 ± 0.8	0.5 ± 0.9	0.5 ± 0.8	0.5 ± 0.9	0.5 ± 0.7
Uncontrollable events	1.4 ± 1.5	1.0 ± 1.2	1.4 ± 1.5§	1.0 ± 1.2	0.7 ± 0.9§
Desirable events	0.2 ± 0.5	0.2 ± 0.5	0.2 ± 0.5	0.2 ± 0.5	0.2 ± 0.5
Undesirable events	1.7 ± 1.9	1.4 ± 2.0	1.8 ± 2.1¶	1.4 ± 2.0	1.0 ± 1.2¶
Highly stressful events	1.5 ± 2.1	1.1 ± 2.3	1.5 ± 2.1‡	1.1 ± 2.3¶	0.3 ± 0.8‡
Weighted event scores by category**					
Weighted total events	7.0 ± 7.2	5.5 ± 7.8	7.1 ± 7.0‡	5.4 ± 7.7	2.7 ± 3.7‡
Weighted major events	1.0 ± 1.7	1.0 ± 2.0	1.1 ± 1.8¶	1.0 ± 2.0¶	0.3 ± 1.0¶
Weighted controllable events	0.9 ± 1.5	0.7 ± 1.4	0.9 ± 1.6	0.7 ± 1.4	0.5 ± 1.0
Weighted uncontrollable events	2.8 ± 3.4	2.1 ± 3.0	2.8 ± 3.4‡	2.0 ± 3.0	1.0 ± 1.8‡
Weighted desirable events	0.3 ± 0.9	0.2 ± 0.8	0.3 ± 0.9	0.2 ± 0.8	0.04 ± 0.2
Weighted undesirable events	3.8 ± 4.8	3.0 ± 4.7	3.9 ± 4.9§	2.9 ± 4.7	1.4 ± 2.0§

*Paired analysis was performed to compare probands and unaffected siblings, where all subjects were matched, whereas unpaired analysis was performed when comparing probands or unaffected siblings with unrelated controls.
**Life event scores were calculated by multiplying the number of events by their stress ratings in each category.
†No significant differences for paired probands *vs*. siblings.
Significant differences after Bonferroni correction: ‡ $p \leq 0.001$, § $p \leq 0.005$, ‖ $p \leq 0.01$, ¶ $p \leq 0.05$. SD: standard deviation.

Table IV. Association of stressful life events with systemic autoimmune rheumatic disease diagnosis between probands and unrelated controls*.

Life events/scores by category	Odds ratio	95% CI	*p*-value
Number of life events by category:			
Total number of events	1.31	1.11–1.53	0.001
Major events	2.03	1.00–4.10	0.049
Controllable events	1.47	0.82–2.64	0.198
Uncontrollable events	1.64	1.14–2.35	0.007
Desirable events	1.05	0.46–2.35	0.914
Undesirable events	1.58	1.17–2.11	0.002
Highly stressful events	2.10	1.35–3.26	0.001
Weighted event scores by category:			
Weighted total event score	1.22	1.11–1.36	<0.001
Weighted major event score	1.51	1.08–2.12	0.016
Weighted controllable event score	1.62	1.13–2.33	0.008
Weighted uncontrollable event score	1.30	1.09–1.57	0.004
Weighted desirable event score	2.43	0.70–8.48	0.163
Weighted undesirable event score	1.31	1.12–1.54	0.001

*Adjusted unconditional logistic regression modelling between probands and unrelated controls. Models were adjusted for age, sex, race/ethnicity, educational, ever cigarette smoking, and time from systemic autoimmune rheumatic disease diagnosis in probands (or from reference date in unrelated controls) to questionnaire completion. CI: confidence interval.

in their sibling (14). Our study may have been underpowered to detect additional differences in the number of life events and their perceived stressfulness between siblings due to overmatching.

Stressful life events have been described as life experiences that may result in change in individuals' lives, both facilitating growth and adaptation, as well as potentially contributing to illness. One of the key issues in studying the correlation between health outcomes and prior life events has been the individual differences in the perception of events, which is supported by this study's findings revealing greater stress ratings among probands. It is hypothesised that maladaptive psychosocial stress responses can trigger exaggerated reactivity of the stress-response systems, including the autonomic nervous system, the hypothalamic-pituitary-adrenal axis, and the immune system (15). These activations may lead to accelerated immune cell aging, altered immune cell gene expression, chronic amplification of pro-inflammatory cytokine production, and ultimately loss of normal self-tolerance, all common immunologic changes that occur in the development of SARDs (16).

Evidence supports that stress is involved in the pathogenesis of SARDs through interaction of the neuroendocrine and immune systems, which are fundamental to the maintenance of homeostasis (6, 17). Low levels of cortisol and norepinephrine in individuals with altered stress responses, as well as diminished glucocorticoid negative feedback of the hypothalamus-pituitary axis due to glucocorticoid resistance, have been linked to increased production of and augmented responses to proinflammatory cytokines. This leads to a heightened immune response, alterations in immune cell mobilisation, increase in lymphocyte proliferation and activation, and disruption in the gut epithelium and blood-brain barrier (17-19). These mechanisms have been hypothesised as mediators of development and flares of SARDs, among other poor health outcomes, and have been linked to early and stressful life events (20-22).

This investigation identified a gradient in the number of life events and corresponding stressfulness between probands, siblings, and unrelated controls. Such differences might reflect the

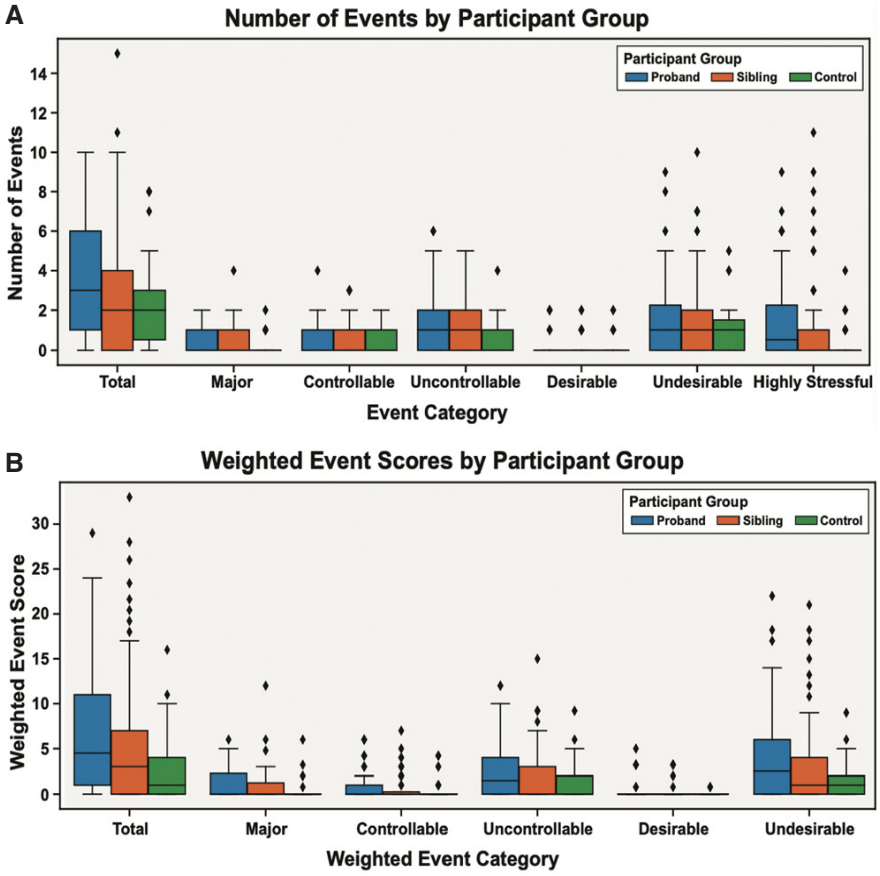

Fig. 1. A. Distribution of number of life events per category by participant group. **B.** Distribution of weighted event scores per category by participant group.

Table V. Adjusted conditional logistic regression modelling of life events scores with systemic autoimmune rheumatic disease diagnosis among probands, unaffected siblings, and unrelated controls*.

Life event/scores by category†	Odds ratio	95% CI	*p*-value
Number of life events by category:			
Total number of events	1.11	0.97–1.26	0.118
Major events	1.14	0.64–2.03	0.656
Controllable events	1.17	0.71–1.96	0.537
Uncontrollable events	1.30	0.98–1.72	0.075
Undesirable events	1.20	0.96–1.50	0.120
Highly stressful events	1.18	0.98–1.43	0.078
Weighted event scores by category:			
Weighted total event score	1.06	1.00–1.12	0.061
Weighted major event score	1.11	0.90–1.38	0.317
Weighted controllable event score	1.24	0.91–1.70	0.175
Weighted uncontrollable event score	1.12	0.99–1.27	0.069
Weighted undesirable event score	1.08	0.99–1.18	0.100

* Models were adjusted for age, sex, race/ethnicity, educational, cigarette smoking ever, and time from date of systemic rheumatic disease diagnosis in probands (or reference date in unaffected siblings and unrelated controls) to date of questionnaire completion.
†The missing indicator method was used for logistic regression modeling to combine matched and unmatched subjects (13). CI: confidence interval.

presence of stressful experience thresholds necessary to achieve dysregulation of stress-response systems in genetically predisposed individuals, ultimately leading to the onset of SARDs. Moreover, we hypothesise that life events and their associated stressfulness in the year prior to SARD diagnosis may serve as indicators of long-term patterns of cumulative stressful events and poor stress coping mechanisms, contributing to a potentially disproportional allostatic load among probands and worse health outcomes (23). The growing evidence suggesting common genetic variants and shared molecular pathways among different SARDs provided the framework of this study, which encompassed a combination of four SARDs as the outcome of interest and allowed a larger study sample size (10). Moreover, the discordant case-control sibling study design allowed the controlling of unmeasured genetic similarities between siblings, a potential challenge in the investigation of the impact of environmental factors in the development of SARDs.

This study also controlled for smoking and for education, a surrogate for socioeconomic status, both of which have been shown to correlate with a SARD diagnosis and exposure to stressors (24). Stressful life events were queried based on the Interview for Recent Life Events, which had been previously validated in a homogeneous population of predominantly White, highly educated, urban/suburban individuals (25). Although these demographic characteristics applied to our study population, we acknowledge that the findings may not apply to a broader range of potential life events and corresponding psychologic stressors that may affect individuals from other demographic and socioeconomic backgrounds. The retrospective nature of this study and its intrinsic vulnerability to recall bias is an additional limitation, moreover, the instrument used to query life events also does not discriminate between acute episodes of stress or chronic stress before disease onset. Another potential source of bias is our current lack of understanding of the temporal unfolding of SARDs: prediagnosis symptoms of a SARD could have contributed to the stress response related to life events, reflecting reverse causality. The inclusion of unrelated controls also adds additional considerations. Their reference date was not linked to an event of personal meaning, and this date was slightly longer than the recall time for probands and siblings. The use of controls could have introduced a bias toward volunteers who may have been less likely to have experienced stressful events proximal to their enrolment in the study. Finally, no

Table VI. Adjusted conditional logistic regression modelling of life events scores with systemic autoimmune rheumatic disease diagnosis among probands and their unaffected siblings*.

Life event/scores by category	Odds ratio	95% CI	*p*-value
Number of life events by category:			
Total number of events	1.07	0.94–1.23	0.309
Major events	0.96	0.52–1.78	0.899
Controllable events	1.02	0.59–1.76	0.956
Uncontrollable events	1.23	0.92–1.65	0.165
Desirable events	0.77	0.36–1.64	0.500
Undesirable events	1.12	0.88–1.42	0.369
Highly stressful events	1.12	0.92–1.36	0.270
Weighted event scores by category:			
Weighted total event score	1.04	0.98–1.10	0.211
Weighted major event score	1.05	0.84–1.31	0.678
Weighted controllable event score	1.10	0.78–1.54	0.595
Weighted uncontrollable event score	1.10	0.97–1.24	0.158
Weighted desirable event score	1.02	0.67–1.56	0.911
Weighted undesirable event score	1.05	0.96–1.16	0.304

* Models were adjusted for age, sex, race/ethnicity, educational, cigarette smoking ever, and time from date of systemic rheumatic disease diagnosis in probands (or reference date in unaffected siblings) to date of questionnaire completion. CI: confidence interval.

information on stress hormone levels, including salivary cortisol, was available for the participants to link to the life event questionnaire data.

Despite these limitations, the findings of this retrospective sibling- and control-matched analysis extend prior literature, here showing associations between stressful life events and the development of four different SARDs, including IIM, RA, SLE, and SSc among adults. Altogether, these findings should prompt the acknowledgement of the long-supported patient perception that stressful life events are prevalent in the pre-morbid period of SARDs (8, 26). Moreover, these results call for additional investigations on the impact of new contemporary stressors, such as social media and climate change, on SARDs, as well as prospective longitudinal and mechanistic studies to better understand the role of stress in the development of SARDs.

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References

1. KLARESKOG L, RONNELID J, SAEVARSDOTTIR S, PADYUKOV L, ALFREDSSON L: The importance of differences; On environment and its interactions with genes and immunity in the causation of rheumatoid arthritis. *J Intern Med* 2020; 287(5): 514-33. https://doi.org/10.1111/joim.13058
2. CASE SM, FELDMAN C, GUAN H *et al*.: Posttraumatic stress disorder and risk of systemic lupus erythematosus among medicaid recipients. *Arthritis Care Res* (Hoboken) 2023; 75(1): 174-79. https://doi.org/10.1002/acr.24758
3. COZIER YC, BARBHAIYA M, CASTRO-WEBB N *et al*.: Association of child abuse and systemic lupus erythematosus in black women during adulthood. *Arthritis Care Res* (Hoboken) 2021; 73(6): 833-40. https://doi.org/10.1002/acr.24188
4. PATTERSON SL, SAGUI-HENSON S, PRATHER AA: Measures of psychosocial stress and stressful exposures. *Arthritis Care Res* (Hoboken) 2020; 72(S10): 676-85. https://dx.doi.org/10.1002/acr.24228
5. PAYKEL ES: The interview for recent life events. *Psychol Med* 1997; 27(2): 301-10. https://doi.org/10.1017/S0033291796004424
6. PARKS CG, PETTINGER M, DE ROOS AJ, TINDLE HA, WALITT BT, HOWARD BV: Life events, caregiving, and risk of autoimmune rheumatic diseases in the Women's Health Initiative Observational Study. *Arthritis Care Res* (Hoboken) 2023; 75(12): 2519-28. https://doi.org/10.1002/acr.25164
7. CHEN Y, HUANG JZ, QIANG Y, WANG J, HAN MM: Investigation of stressful life events in patients with systemic sclerosis. *J Zhejiang Univ Sci B* 2008; 9(11): 853-56. https://doi.org/10.1631/jzus.b0820069
8. SCHWETLIK SN, BALDOCK K, HILL CL, FERRAR K: Chronic stress and arthritis: a scoping review. *Arthritis Care Res* (Hoboken) 2022; 74(6): 982-96. https://doi.org/10.1002/acr.24528
9. GOURLEY M, MILLER FW: Mechanisms of disease: environmental factors in the pathogenesis of rheumatic disease. *Nat Clin Pract Rheumatol* 2007; 3(3): 172-80. https://dx.doi.org/10.1038/ncprheum0435
10. YAMAMOTO K, OKADA Y: Shared genetic factors and their causality in autoimmune diseases. *Ann Rheum Dis* 2019; 78(11): 1449-51. https://doi.org/10.1136/annrheumdis-2019-215099
11. TURNER RJ, WHEATON B: Checklist measurement of stressful life events. *In*: COHEN S, KESSLER RC, GORDON LU (Eds.): Measuring stress: a guide for health and social scientists. *Oxford University Press* 1995: 29-58. https://psycnet.apa.org/record/1998-07054-001
12. PAYKEL ES, PRUSOFF BA, MYERS JK: Suicide attempts and recent life events. A controlled comparison. *Arch Gen Psychiatry* 1975; 32(3): 327-333. https://doi.org/10.1001/archpsyc.1975.01760210061003
13. HUBERMAN M, LANGHOLZ B: Application of the missing-indicator method in matched case-control studies with incomplete data. *Am J Epidemiol* 1999; 150(12): 1340-45. https://doi.org/10.1093/oxfordjournals.aje.a009966
14. BEMMELS HR, BURT SA, LEGRAND LN, IACONO WG, MCGUE M: The heritability of life events: an adolescent twin and adoption study. *Twin Res Hum Genet* 2008; 11(3): 257-65. https://doi.org/10.1375/twin.11.3.257
15. SEGERSTROM SC, MILLER GE: Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. *Psychol Bull* 2004: 130(4): 601-30. https://doi.org/10.1037/0033-2909.130.4.601
16. STOJANOVICH L: Stress and autoimmunity. *Autoimmun Rev* 2010; 9(5): A271-76. https://doi.org/10.1016/j.autrev.2009.11.014
17. CUTOLO M, STRAUB RH: Insights into endocrine-immunological disturbances in autoimmunity and their impact on treatment. *Arthritis Res Ther* 2009; 11(2): 218-24. https://doi.org/10.1186/ar2630.
18. CHAN KL, POLLER WC, SWIRSKI FK, RUSSO SJ: Central regulation of stress-evoked peripheral immune responses. *Nat Rev Neurosci* 2023; 24(10) 591-604. https://doi.org/10.1038/s41583-023-00729-2
19. DHABHAR FS: Effects of stress on immune function: the good, the bad, and the beautiful. *Immunol Res* 2014; 58(2-3). https://doi.org/10.1007/s12026-014-8517-0
20. FOGELMAN N, CANLI T: Early life stress, physiology, and genetics: a review. *Front Psychol* 2019; 10 (1668). https://doi.org/10.3389/fpsyg.2019.01668
21. DICH N, ROZING MP, KIVIMAKI M, DOAN SN: Life events, emotions, and immune function: evidence from Whitehall II Cohort Study. *Behav Med* 2020; 46(2): 153-160. https://doi.org/10.1080/08964289.2019.1570072
22. DUBE SR, FAIRWEATHER D, PEARSON W, FELITTI VJ, ANDA RF, CROFT JB: Cumulative childhood stress and autoimmune diseases in adults. *Psychosom Med* 2009; 71(2): 243-50. https://doi.org/10.1097/psy.0b013e3181907888
23. GUIDI J, LUCENTE M, SONINO N, FAVA GA: Allostatic load and its impact on health: a systematic review. *Psychother Psychosom* 2021; 90(1): 11-27. https://doi.org/10.1159/000510696
24. CONRAD N, MISRA S, VERBAKEL JY *et al*.: Incidence, prevalence, and co-occurrence of autoimmune disorders over time and by age, sex, and socioeconomic status: a population-based cohort study of 22 million individuals in the UK. *Lancet* 2023; 401(10391): 1878-90. https://doi.org/10.1016/S0140-6736(23)00457-9
25. PAYKEL ES: Methodological aspects of life events research. *J Psychosom Res* 1983; 27(5): 341-52. https://doi.org/10.1016/0022-3999(83)90065-x.
26. MCCRAY C. J, AGARWAL SK: Stress and autoimmunity. *Immunol Allergy Clin North Am* 2011; 31(1): 1-18. https://doi.org/10.1016/j.iac.2010.09.004