

Seasonal Variation in the Activity of Systemic Lupus Erythematosus

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ABSTRACT. *Objective.* To determine whether there is any seasonal variation in the activity of systemic lupus erythematosus (SLE) overall and by individual organs.

Methods. The study group comprised 2102 patients with SLE who were followed in a prospective longitudinal cohort study. In this cohort, 92.3% of the patients were women. The mean \pm SD age of the patients was 47.9 ± 13.9 years, 56.3% were white, 37.1% were African American, and 3.1% were Asian. Global disease activity was recorded by the Safety of Estrogens in Lupus Erythematosus National Assessment – Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) and the physician's global assessment. Activity of each organ was also recorded using SLEDAI terms and a visual analog scale (VAS; 0 to 3).

Results. There was significant seasonal variation in photosensitive rash ($p < 0.0001$), which was more frequent in the spring and summer months ($p < 0.0001$). There was significantly more arthritis activity in spring and summer, as measured by both SELENA-SLEDAI ($p = 0.0057$) and the joint VAS ($p = 0.0047$). A decrease in renal activity was found in the summer months compared to the rest of the year ($p = 0.0397$). Serositis recorded by VAS had higher activity from August to October ($p = 0.0392$). Anti-dsDNA levels were significantly higher during October and November ($p < 0.0001$). There was significant seasonal variation in antiphospholipid antibody levels ($p < 0.0001$) and lupus anticoagulant ($p = 0.0003$). We found a significant variation in activity through the year in global disease activity as measured by SELENA-SLEDAI ($p = 0.048$).

Conclusion. In the Hopkins Lupus Cohort, skin and joint activity is increased during the spring and summer, but other organs have different patterns. These seasonal variations likely reflect environmental factors that influence disease activity, including ultraviolet light and infections. (First Release June 1 2012; J Rheumatol 2012;39:1392–8; doi:10.3899/jrheum.111196)

Key Indexing Terms:

SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE ACTIVITY SEASONAL VARIATION

There is evidence that several rheumatic diseases have seasonal variation. A seasonal pattern has been reported regarding the onset of weakness in inflammatory myopathy¹. Acute gout attacks are more common in the spring^{2,3}, and the onset of rheumatoid arthritis⁴ and granulomatosis with polyangiitis (Wegener's)⁵ is more common in the winter.

Previous studies of a seasonal influence on SLE activity

have yielded conflicting results, some suggesting that there was only an increased incidence of photosensitive rashes in the summer months^{6,7}, whereas others found more joint pain in the winter and spring^{8,9}. In addition, a study of renal biopsies¹⁰ found that the prevalence of class V lupus nephritis was significantly higher in winter and spring. Steup-Beekman, *et al*¹¹ did not observe a seasonal variation in flares or first occurrence of neuropsychiatric SLE. In a study of seasonal variation in the titers of antiphospholipid antibodies, there was no variation among patients who had strokes, but there was seasonal variability in the apparently normal population¹². Previous studies in SLE have had a small sample size or were retrospective. Our hypothesis, based on a preliminary study done in Hong Kong by To, *et al*, was that there would be seasonal variation in organ systems other than cutaneous lupus.

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The Hopkins Lupus Cohort is supported by the National Institutes of Health R01AR043727 grant and by the National Center for Research Resources, ULI RR 025005.

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Accepted for publication April 20, 2012.

MATERIALS AND METHODS

The study included all patients with SLE who were members of the Hopkins Lupus Cohort from 1986 through 2010. The Hopkins Lupus Cohort was approved by the Johns Hopkins University School of Medicine Institutional Review Board. All patients gave written informed consent. Patient inclusion in the prospective longitudinal cohort was based on the clinical diagnosis of SLE by 1 author (MP). Ninety-eight percent of the patients fulfilled at least 4 of the 1982 American College of Rheumatology revised criteria for the classification of SLE^{13,14}. Basic demographic characteristics, presenting and

cumulative clinical manifestations, and immunologic markers were recorded since cohort entry. The patients were seen quarterly or more frequently if medically indicated. At each patient visit, a complete history, examination, and routine laboratory testing were performed in a systematic and prospective fashion by protocol. The Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) revision of the SLE Disease Activity Index (SLEDAI)¹⁵ and the physician's global assessment (PGA) on a 0–3 visual analog scale (VAS)¹⁶ were calculated at each visit by 1 investigator (MP). The VAS, which comprise the Lupus Activity Index, have been validated¹⁷. Activity of each organ system was also recorded on a 0 to 3 VAS. Data were taken at each visit for anti-dsDNA, immunoglobulin M (IgM), IgG, IgA anti-cardiolipin, lupus anticoagulant (LAC) tested by dilute Russell's viper venom time (dRVVT), and complement levels. Viral and bacterial infections were registered at each visit. Results were plotted against the month during which they were reported.

Mean levels of disease activity scores for each organ system were calculated by month. General estimating equations (SAS Institute, Cary, NC, USA) were used to calculate p values accounting for the repeated observations from the same patients. For each organ system, we first calculated a "global" p value to assess the degree of evidence against the null hypothesis that the mean activity level is the same in all months. If there was strong evidence against the global null hypothesis (i.e., $p < 0.01$), we calculated post hoc p values to assess hypotheses about specific months or seasons. Linear regression models with interactions were used to assess whether the changes in seasonal variation varied by ethnicity or calendar year.

RESULTS

Included in our study were 2102 patients with SLE, of whom 1940 (92.3%) were women. The mean \pm SD age was 47.9 \pm 13.9 years. The mean number of cohort visits per patient was 22. A total of 1183 (56.3%) were white, 780 (37.1%) were African American, and 65 (3.1%) were Asian (Table 1).

Photosensitive rash. Photosensitive rash was identified by both the SELENA-SLEDAI and the rash VAS. There was strong evidence of seasonal variation (global $p < 0.0001$ and $p = 0.0015$ for the SLEDAI and VAS results, respectively; Figures 1A, 1B). There were significantly higher scores from April to September compared to the rest of the year ($p < 0.0001$). The results of the subanalysis by ethnicity showed seasonal variation of lupus rash by the VAS in whites ($p < 0.0001$), but not in African Americans ($p = 0.1356$). Similarly, the photosensitive rash by SELENA-SLEDAI showed significant seasonal variation for whites ($p < 0.0001$), but was not significant in African Americans ($p = 0.1148$).

Musculoskeletal activity. Arthritis was identified by both the SELENA-SLEDAI (≥ 2 joints with pain and signs of inflammation) and the joint VAS (which identified both arthralgias and arthritis). We observed significant seasonal variation through SELENA-SLEDAI (global $p = 0.0057$) and the VAS (global $p = 0.0047$; Figures 1C and 1D). There was significantly more arthritis activity in May through October, measured by both SELENA-SLEDAI ($p = 0.0002$) and the joint VAS ($p = 0.0002$; Figures 1C and 1D).

Central nervous system (CNS) activity. CNS activity was measured by both SELENA-SLEDAI and the neurologic VAS. Significant seasonal differences in CNS activity were not found (global $p = 0.0638$ for the SLEDAI and $p = 0.2118$ for VAS results). However, the highest amount of CNS activity shown by the SELENA-SLEDAI (Figure 2A) was in August, September, October, and November, compared to the

Table 1. Demographic characteristics of patients in the Hopkins Lupus Cohort (n = 2102). Data are n (%) unless otherwise indicated.

Characteristics	Total Cohort, n = 2102	White, n = 1183	African American, n = 780	Other Ethnicities, n = 139
Age at SLE onset, yrs, mean (SD)	29.4 (12.7)	29.6 (13.3)	29.6 (11.8)	26.4 (11.8)
Age at SLE diagnosis, yrs, mean (SD)	32.6 (12.9)	33.7 (13.4)	31.7 (12.0)	28.7 (12.4)
Age at last assessment, yrs, mean (SD)	42.9 (13.5)	43.7 (13.7)	42.8 (13.2)	36.9 (12.2)
Disease duration from SLE diagnosis to last visit, yrs, mean (SD)	10.8 (8.2)	10.5 (7.9)	11.5 (8.9)	8.9 (6.2)
Sex				
Women	1940 (92.3)	1082 (91.5)	727 (93.2)	131 (94.2)
Men	162 (7.7)	101 (8.5)	53 (6.8)	8 (5.8)
Ethnicity				
White	1183 (56.3)	—	—	—
African American	780 (37.1)	—	—	—
Other	139 (6.6)	—	—	—
Photosensitivity	1129 (53.9)	740 (62.9)	323 (41.5)	66 (47.5)
Arthritis	1540 (73.8)	840 (71.6)	605 (78.1)	95 (68.8)
Neurologic	78 (3.8)	35 (3.0)	40 (5.2)	3 (2.2)
Serositis	1034 (49.2)	548 (46.4)	422 (54.1)	64 (46.0)
Renal	879 (42.1)	370 (31.5)	434 (56.0)	75 (54.0)
Anti-dsDNA	1322 (63.1)	702 (59.6)	517 (66.3)	103 (74.6)
Low complement	1298 (57.5)	680 (57.5)	501 (64.3)	117 (84.2)
Anticardiolipin antibodies	966 (47.6)	551 (48.3)	351 (46.8)	64 (46.4)
Lupus anticoagulant	537 (26.5)	326 (28.5)	177 (23.6)	34 (25.2)
Raynaud's phenomenon	1094 (52.2)	654 (55.5)	377 (48.4)	63 (45.7)

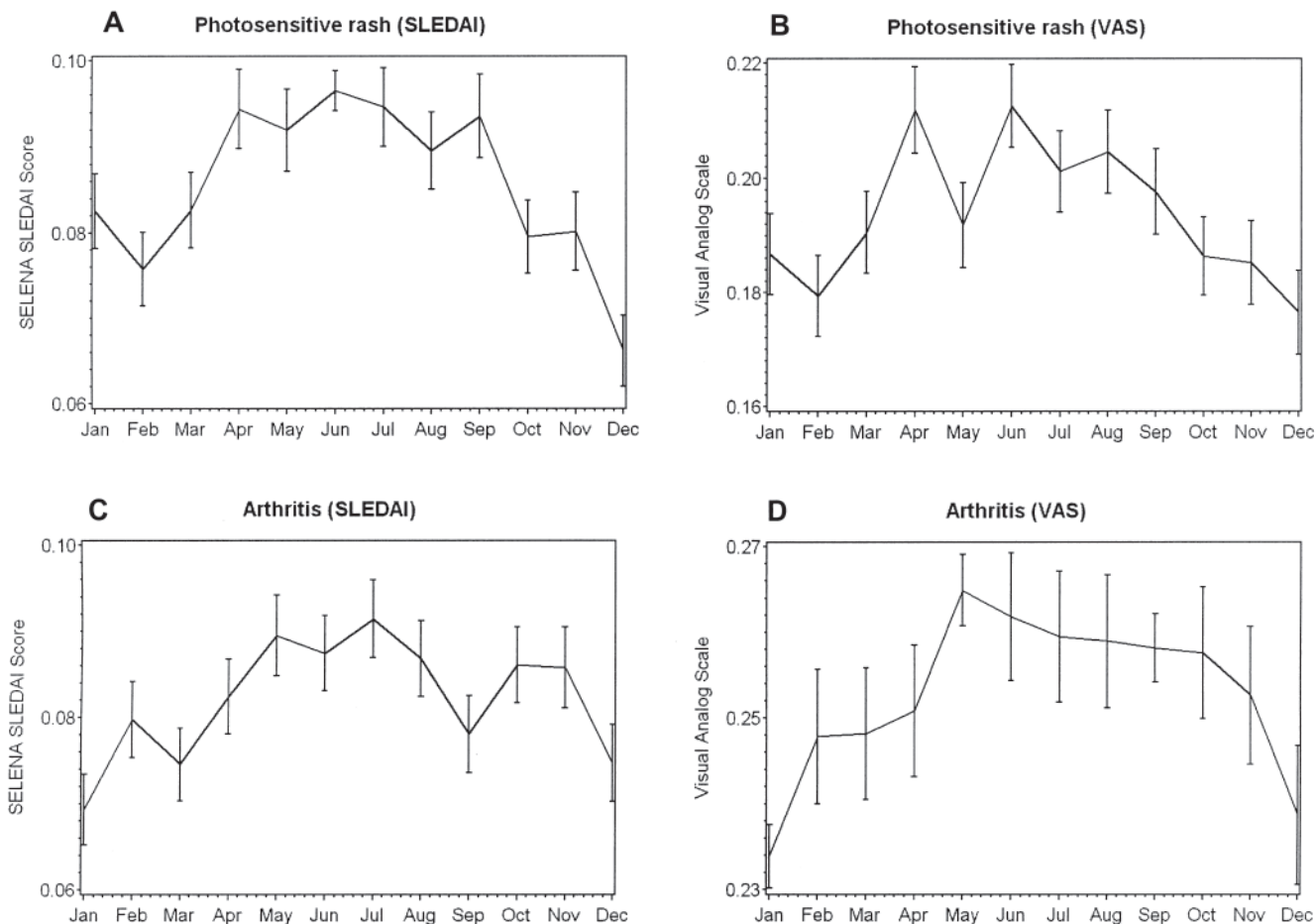


Figure 1. Lupus activity within various organ systems. A. Photosensitive rash identified by SELENA-SLEDAI. B. Photosensitive rash measured by visual analog scale (VAS). C. Arthritis identified by SELENA-SLEDAI. D. Arthritis measured by VAS. Values in the Y axis refer to the means of all observations at that month. Error bars represent mean \pm 1 standard error.

rest of the year. CNS activity revealed by the neurologic VAS was higher in August, October, and November (Figure 2B). The CNS activity pattern on the neurologic VAS appeared to be bimodal.

Serositis. Serositis was identified by combining the SELENA-SLEDAI terms of pericarditis and pleurisy and by the serositis VAS. We found some evidence of seasonal variation in serositis activity, measured by SELENA-SLEDAI (global $p = 0.0545$) and by the VAS (global $p = 0.0392$). We observed higher activity in August, September, and October, compared to the rest of the year, through both SELENA-SLEDAI (Figure 2C) and the serositis VAS ($p = 0.0019$; Figure 2D).

Renal. The renal VAS recorded renal activity. There was evidence of seasonal variation (global $p = 0.0397$). We observed a decrease from June through October ($p = 0.0005$; Figure 3A).

Anti-dsDNA levels. Anti-dsDNA levels, measured by *Crithidia*, were assessed at each visit. We observed significant variation through the year (global $p < 0.0001$). There was an elevation in anti-dsDNA levels from September through November, compared to other months ($p = 0.0138$). There was

also a striking elevation in October and November compared to the rest of the year ($p < 0.0001$; Figure 3B).

Low complement. C3 and C4 levels were assessed at each visit. We observed seasonal variation in the presence of low complement (global $p < 0.0001$; Figure 3C), with lowest levels in July.

Antiphospholipid antibodies. IgM, IgG, and IgA anticardiolipin antibodies and LAC (dRVVT) were assessed at each visit. We observed a seasonal variation in anticardiolipin IgM titer ($p < 0.0001$), anticardiolipin IgG ($p < 0.0001$), and anticardiolipin IgA (global $p = 0.0101$). We also observed significant variation of the LAC through the year (global $p = 0.0003$). Although there appeared to be a peak of LAC in September and October, the difference did not reach statistical significance ($p = 0.125$; Figure 3D).

Raynaud's phenomenon (RP). RP was identified by the RP VAS. As expected, we observed a clear pattern in RP. It was evidently more frequent in cold months than in summer months ($p < 0.0001$; Figure 3E).

Global disease activity of SLE. Global disease activity was

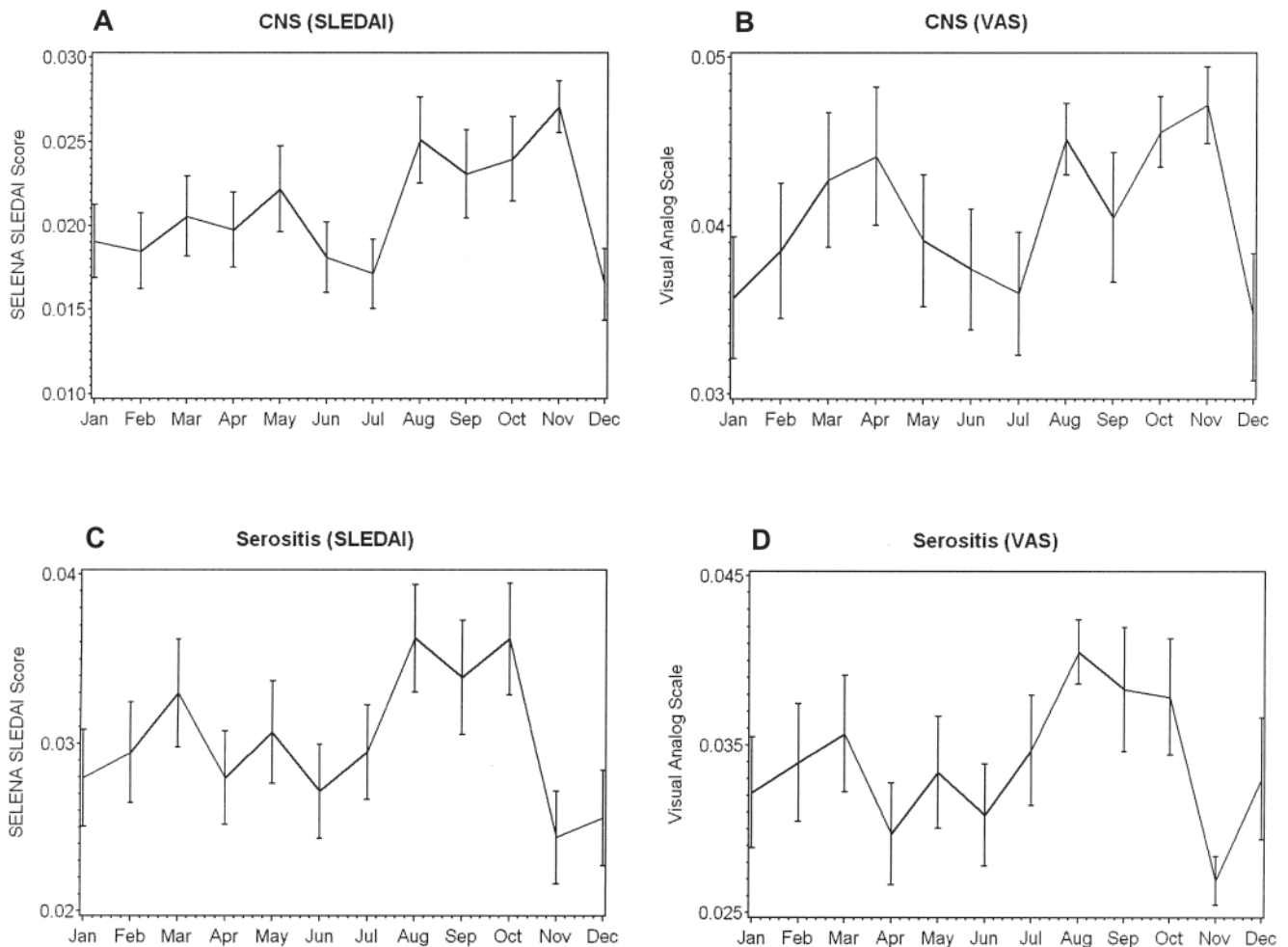


Figure 2. Lupus activity within various organ systems. A. Central nervous system (CNS) activity shown by SELENA-SLEDAI. B. CNS activity by visual analog scale (VAS). C. Serositis measured by SELENA-SLEDAI. D. Serositis shown by VAS. Values in the Y axis refer to the means of all observations at that month. Error bars represent mean \pm 1 standard error.

found by both the SELENA-SLEDAI total score and the PGA VAS. There were significant differences in SELENA-SLEDAI scores during the various months of the year (global $p = 0.0484$; Figure 4A). In contrast, we did not find an association with the PGA score (global $p = 0.4863$; Figure 4B).

Infections. Viral and bacterial infections were recorded at each visit. We observed a U-shaped curve, with increased prevalence of infections in colder months, with the lowest prevalence for bacterial infections in August (Figures 4C and 4D).

Seasonal variation by year or ethnicity. We divided the calendar years into 2 groups: before and after 2000. The results showed that for most of the clinical manifestations, there was no significant difference between the 2 time periods in seasonal variation in the activity of the disease. Two exceptions were found: arthritis identified by the VAS ($p = 0.035$) showed more seasonality in the period after 2000, and RP by VAS ($p = 0.001$) showed more seasonality in the period before 2000.

There was no strong evidence that seasonality of disease

activity differed between whites and African Americans. The exception to this was photosensitive rash, which exhibited seasonality for whites but not for African Americans ($p = 0.020$ for the VAS, $p = 0.007$ for SELENA-SLEDAI).

DISCUSSION

Our study found a significant seasonal variation in SLE disease activity in many different organ systems. These observations suggest the possibility of seasonally related environmental factors that might affect SLE activity levels. There has been a consensus that photosensitive rashes in SLE have a clear seasonality and occur predominantly in the summer. Our results clearly confirm this, but indicate that the pattern begins in spring. This reflects the influence of ultraviolet light on photosensitive rashes^{6,7,8}. Our results showed that photosensitive rash has a seasonal variation in whites, but not in African Americans.

Ultraviolet light exposure may exacerbate local and sys-

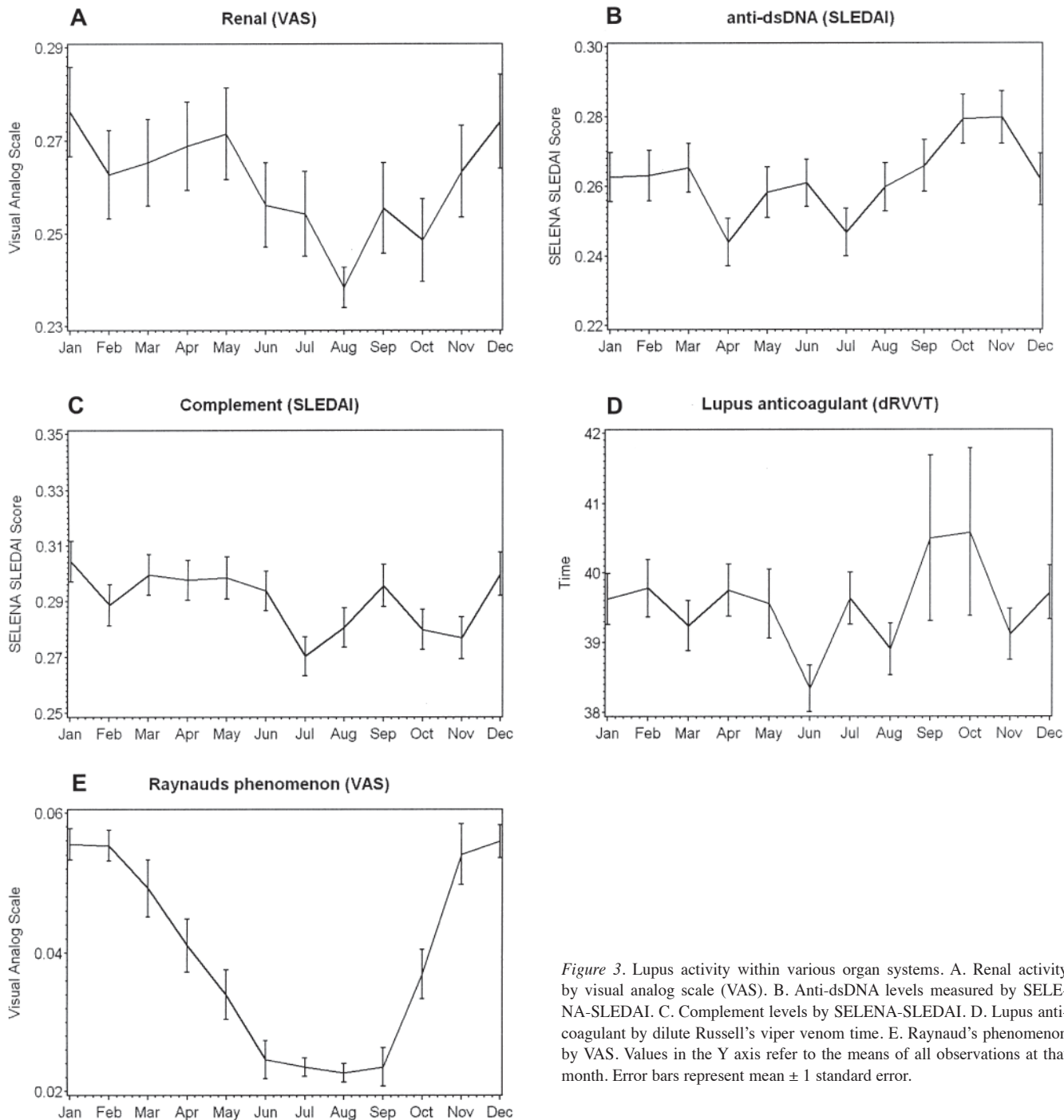


Figure 3. Lupus activity within various organ systems. A. Renal activity by visual analog scale (VAS). B. Anti-dsDNA levels measured by SELENA-SLEDAI. C. Complement levels by SELENA-SLEDAI. D. Lupus anticoagulant by dilute Russell's viper venom time. E. Raynaud's phenomenon by VAS. Values in the Y axis refer to the means of all observations at that month. Error bars represent mean \pm 1 standard error.

temic autoimmunity by inducing changes in the expression and binding of keratinocyte autoantigens. Autoantigens cluster on the cell surface of cultured keratinocytes because of apoptotic changes from ultraviolet irradiation. The translocation of usually cell-sequestered autoantigens to the cell surface of apoptotic blebs allows circulating autoantibodies to gain access to the autoantigens. Antibody binding to the exposed antigens may lead to tissue injury by complement or

inflammatory cells^{18,19}. This is more likely to be an issue in lightly pigmented people. Melanosomes are transferred to keratinocytes and accumulate atop the cell nucleus. They protect the nuclear DNA from ionizing radiation rays. Vilá, *et al* reported that patients who regularly used sunscreen had significantly less renal involvement, thrombocytopenia, hospitalization, and need for cyclophosphamide than patients who did not use it²⁰.

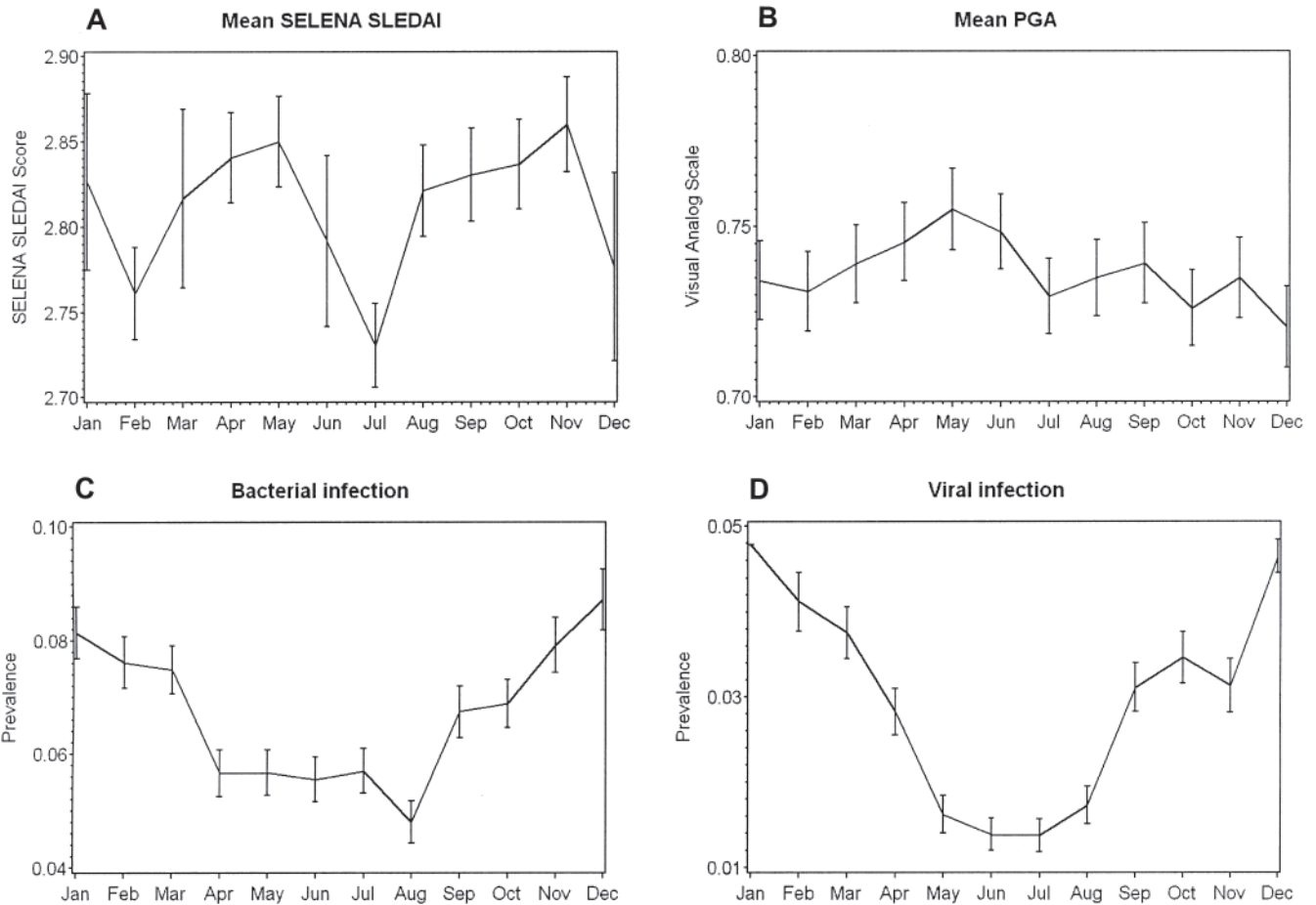


Figure 4. A. Mean SELENA-SLEDAI. B. Mean physicians' global assessment score by visual analog scale. C. Prevalence of bacterial infections. D. Prevalence of viral infections. Values in the Y axis for A and B refer to the means of all observations at that month. Error bars represent mean \pm 1 standard error. Values in the Y axis for C and D refer to the prevalence of infections at that month.

Joint activity has been reported to be increased in colder months^{8,9}. In contrast, we found increased joint activity in the summer months, measured by either the SELENA-SLEDAI or the joints VAS, showing a similar trend to skin activity. This raises the hypothesis that joint activity may also be triggered by ultraviolet light exposure. This observation does not concur with previous reports^{6,21}, which did not find high levels of activity in any other organ during the photosensitive rash months. It is interesting that joint activity, measured by both the SELENA-SLEDAI and the VAS, peaks 1 month after the skin activity.

Steup-Beekman, *et al* found no seasonal variation in first occurrence or in flares of CNS SLE¹¹. We observed higher CNS activity in the fall months. This observation raises the hypothesis of an association of neuropsychiatric manifestations and infections. Similar to the observations in the neuropsychiatric manifestations, serositis activity also showed an increase in the fall.

Previous publications report an increased incidence of class V lupus nephropathy during the winter and spring^{9,10}.

Szeto, *et al*⁹ observed increased renal activity in December and January, with another peak in July and August. We observed increased renal activity from November to May.

Anticardiolipin titer levels in healthy patients have a trend similar to seasonal respiratory tract infections¹². We did not observe this in our study. However, we found an increase in the LAC measured by the dRVVT in September and October. Interestingly, it peaks during the same months as infections.

There was not strong evidence of seasonality of global SLE activity shown by PGA. However, we did observe the highest global activity in April, May, and June. Hasan, *et al* also reported an increase in overall activity in the sunny season²². Global activity, revealed by the SELENA-SLEDAI, showed a statistically significant variation through the year, with peaks in spring and fall. The difference in global disease activity between SELENA-SLEDAI and PGA may be explained by the weighting of the SLEDAI and the inclusion of anti-dsDNA levels.

SLE is a disease with a wide range of clinical manifestations. Environmental stimuli, viral infections, genetic factors,

and immunologic abnormalities have all been associated with the pathophysiology of the disease. Previous studies have shown that the number of circulating lymphocytes undergoes seasonal changes, reaching a peak in winter months²³. A seasonal variation in adrenocortical function has been described, with an increase in corticosteroid secretion during the winter months²⁴. Previous studies found seasonal variations in several autoantibodies^{1,25}. Collier and Levin reported a seasonal variation in anti-dsDNA antibody levels, with higher levels during the winter months²⁶. A French study also showed higher levels of anti-dsDNA and lower complement levels after July, in agreement with our results²⁷.

We observed a similar trend in infections and renal activity. Both had a similar U-shape. Infections may be one of the triggers of renal activity, as suggested by Schlesinger, *et al*¹⁰.

It is important to consider that some of the inconsistencies between our study and others might be due to our large number of patients, followed for many years, yielding a very high power. It is also important to note that because of our large sample size, relatively small degrees of seasonality were statistically significant. The degree of seasonality for many of the conditions (even those with statistically significant seasonality) was relatively low, as is evident from the scales of Figures 1–4.

In the Hopkins Lupus Cohort, skin and joint activity are increased during the warmer months, most likely because of ultraviolet radiation exposure. Renal, serositis, and anti-dsDNA levels are increased during the colder months, possibly related to infections. This seasonality is important not just in clinical practice; it could also profoundly affect clinical trial results.

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