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14. ABSTRACT: **Objective**. To identify potential clusters of systemic lupus erythematosus (SLE) organ-specific flares and their relationship to fine particulate matter pollution (PM2.5), temperature, ozone concentration, resultant wind, relative humidity, and barometric pressure in the Hopkins Lupus Cohort, using spatiotemporal cluster analysis. **Methods**. A total of 1,628 patients who fulfilled the Systemic Lupus International Collaborating Clinics classification criteria for SLE and who had a home address recorded were included in the analysis. Disease activity was assessed using the Lupus Activity Index. Assessment of rash, joint involvement, serositis, and neurologic, pulmonary, renal, and hematologic activity was quantified on a 0–3 visual analog scale (VAS). An organ-specific flare was defined as an increase in VAS of ≥1 point compared to the previous visit. Spatiotemporal clusters were detected using SaTScan software. Regression models were used for cluster adjustment and included individual, county-level, and environmental variables. **Results**. Significant clusters unadjusted for environmental variables were identified for joint flares ($P < 0.05$; n = 3), rash flares ($P < 0.05$; n = 4), hematologic flares ($P < 0.05$; n = 3), neurologic flares ($P < 0.05$; n = 2), renal flares ($P < 0.001$; n = 4), serositis ($P < 0.001$; n = 2), and pulmonary flares ($P < 0.001$; n = 2). The majority of the clusters identified changed in significance, temporal extent, or spatial extent after adjustment for environmental variables. **Conclusion**. We describe the first spatiotemporal clusters of lupus organ-specific flares. Seasonal, as well as multi-year, cluster patterns were identified, differing in extent and location for the various organ-specific flare types. Further studies focusing on each individual organ-specific flare are needed to better understand the driving forces behind these observed changes.

15. SUBJECT TERMS

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INTRODUCTION:

We pursued the identification of potential clusters of systemic lupus erythematosus (SLE) organ-specific flares and their relationship to fine particulate matter pollution (PM2.5), temperature, ozone concentration, resultant wind, relative humidity, and barometric pressure in the Hopkins Lupus Cohort, using spatiotemporal cluster analysis.

KEYWORDS: Systemic lupus erythematosus, environmental factors, pollution, disease activity, spatiotemporal analysis

GOALS

What were the major goals of the project?

Specific Aim 1 Identify environmental, atmospheric and demographic determinants predictive of organ specific flares in lupus.

Specific Aim 2 Perform spatial temporal cluster detection analyses of organ specific flares in lupus (unadjusted cluster detection).

Specific Aim 3 Using the results from Aim 1, repeat the spatial temporal cluster detection analyses from Aim 2 to assess the degree to which environmental, atmospheric and other variables explain clusters of lupus flares (adjusted cluster detection).

ACCOMPLISHMENTS

What was accomplished under these goals?

Please see methodology for project in manuscript attached as appendix: Stojan G, Kvit A, Curriero FC, Petri M. A Spatiotemporal Analysis of Organ-Specific Lupus Flares in Relation to Atmospheric Variables and Fine Particulate Matter Pollution. Arthritis Rheumatol. 2020 Jul;72(7):1134-1142. doi: 10.1002/art.41217. Epub 2020 May 2. PMID: 32017464; PMCID: PMC7329611.

Results:

In a univariate regression analysis, rash flares (odds ratio [OR] 1.029) and joint flares (OR 1.026) were found to be positively associated with PM2.5 exposure ($P < 0.05$), while serositis (OR 1.028) was found to be marginally associated ($P = 0.053$). Rash flares (OR 1.065), joint flares (OR 1.047), and hematologic flares (OR 1.095) were found to be significantly positively associated with temperature, while renal flares (OR 0.960) were found to be marginally negatively associated with temperature ($P = 0.072$). Ozone concentration was associated with rash (OR 1.01, $P < 0.05$) and negatively associated with renal flares (OR 0.992). Resultant wind was positively associated ($P < 0.05$) with joint flares (OR 1.039), neurologic flares (OR 1.099), renal flares (OR 1.028), and pulmonary flares (OR 1.135). Relative humidity was associated with joint flares (OR 1.163, $P < 0.05$) and marginally associated with neurologic flares (OR 1.297, $P = 0.077$). No significant associations were found for barometric pressure. Furthermore, rash, serositis, and renal flares were found to be negatively associated with age ($P < 0.05$). Rash and serositis symptoms were found to be more likely in African American than white populations (marginally for serositis [$P = 0.092$]), and odds of joint flare were higher for African American patients than for patients of other nonwhite races. Rash flares were found to be more likely in smokers (OR 1.862) and to be negatively associated ($P < 0.05$) with years of education (OR 0.943). Renal flares were

also negatively associated with years of education (OR 0.943). Finally, joint flares (OR 0.969) and renal flares (OR 0.964) were found to be negatively associated with median county income ($P < 0.05$). These findings are summarized in Table 2 (see attached publication).

For most outcomes, the clusters identified changed spatially or temporally when environmental variables were considered in addition to county and individual ones. The general interpretation of cluster behavior after adjustment for environmental covariates can be classified into the following 3 categories:

1. Clusters that remain unchanged temporally or spatially after adjustment for environmental covariates indicate areas where no association between environmental covariates and flare occurrence was identified.

2. Clusters that disappear or decrease spatially or temporally after adjustment for environmental covariates indicate areas where there were high levels of covariates along with a general positive association of the covariates with the number of flares, or low levels of covariates with a general negative association. 3. Clusters that emerge or increase spatially or temporally after adjustment for environmental covariates indicate areas where there were low levels of covariates along with a general positive association of the covariates with the number of flares, or high levels of covariates with a general negative association.

Three statistically significant ($P < 0.05$) environmentally unadjusted clusters were identified for joint flares. One encompassed most of Maryland's Eastern Shore and Delaware and ranged from July 2001 to July 2005. A second cluster was located to the southwest, including Washington, DC and parts of Virginia and Maryland, and ranged from April 2001 to July 2009. The third cluster centered around the city of Baltimore and Baltimore County and ranged from January 2002 to September 2005. After adjustment for environmental variables, cluster 1 located on the Eastern Shore decreased temporally, cluster 2 in the west remained unchanged, and cluster 3 decreased spatially and shifted temporally. A new cluster (cluster 4) appeared in the northeast after adjustment (Figure 2: see attached publication). After adjustment for individual and county variables, 4 significant ($P < 0.05$) rash flare clusters were identified in eastern Maryland, southeastern Pennsylvania, and Delaware. Clusters 1 and 2 located on the Eastern Shore and north of the city of Baltimore, respectively, decreased spatially after adjustment, while clusters 3 and 4, located in the southwest and northeast, respectively, increased spatially after adjustment (Figure 3: see attached publication). Three significant environmentally unadjusted ($P < 0.05$) hematologic clusters were identified. Two were around New Jersey (from September 2000 to February 2002 and from February 2001 to February 2002), and one was located in western Maryland and Virginia (from December 2002 to December 2005). None of these clusters remained significant after adjustment for atmospheric variables and PM2.5 (Figure 4: see attached publicaton).

Two large significant neurologic flare clusters were identified, in the eastern and western halves of the study area ($P < 0.05$) (Supplementary Figure 1, available on the *Arthritis & Rheumatology* web site at http://onlin elibr ary.wiley.com/doi/10.1002/art.41217/ abstract). After adjustment for atmospheric variables and PM2.5, spatially and temporally smaller clusters during time periods different from the original clusters appeared. Two significant environmentally unadjusted serositis clusters were identified, and both remained temporally and spatially unchanged after adjustment for environmental variables ($P < 0.001$) (Supplementary Figure 2, available on the *Arthritis & Rheumatology* web site at http://onlin elibr ary.wiley.com/doi/10.1002/art.41217/ abstract). Four highly significant renal clusters were identified (*P*

< 0.001) (Supplementary Figure 3, available on the *Arthritis & Rheumatology* web site at http://onlin elibr ary.wiley.com/doi/10.1002/art.41217/ abstract), spanning from 2001, 2002, and 2004 to 2006, taking up much of the map except for some counties in the west and south. These clusters remained largely unchanged spatially after adjustment for atmospheric variables and PM2.5, while clusters 2 and 3 became slightly smaller temporally after adjustment. Two significant pulmonary flare clusters were identified in the northwest, spanning from January to July of 1999 ($P < 0.001$) (Supplementary Figure 4, available on the *Arthritis & Rheumatology* web site at http://onlin elibr ary.wiley.com/doi/10.1002/ art.41217/ abstract). Both clusters became spatially smaller after adjustment for atmospheric variables and PM2.5, and a third cluster appeared in the northeast after adjustment.

Discussion:

Cluster detection, the identification of spatial units adjacent in space that are associated with distinctive patterns of data of interest relative to background variation, is an important tool in disciplines such as spatial epidemiology and disease surveillance (16). Clusters have distinctive risks of an event of interest, typically elevated, but possibly reduced, relative to background variation (16). We performed a spatiotemporal cluster analysis of the Hopkins Lupus Cohort and detected the first spatiotemporal lupus flare clusters. Seasonal, as well as multi-year, cluster patterns were identified, differing in extent and location for the various organ-specific flare types. The large-scale, multi-year clusters we defined did not conform to any known pattern of infectious disease or environmental exposure. After adjustment for individual or environmental covariates, there were at least slight changes in the temporal or spatial extent, or significance, of nearly all of the identified clusters, with serositis clusters being the only ones that remained almost entirely unchanged. Generally, a decrease in temporal extent, as seen for some of the joint flare clusters (Figure 2: see attached publication) or renal flare clusters (Supplementary Figure 3: see attached publication), or spatial extent, as seen for the neurologic flare clusters and pulmonary flare clusters (Supplementary Figures 1 and 4: see attached publication), after adjustment for covariates indicates that the adjusted covariates were partially driving the occurrence of that cluster at that time and location. After adjustment for environmental variables, some clusters increased in spatial extent, such as rash flare cluster 3, or temporal extent, such as rash flare cluster 1 (Figure 3: see attached publication). An increase in cluster size, temporal extent, or significance after adjustment for covariates might suggest an area where flare activity is high, despite the presence of individual and environmental covariates that are associated with lower flare activity, and thus this is an area of particular interest for further research. GEE-based regression analysis was used to quantify the effects of individual, county, and environmental variables on the odds of flare outcomes. While these results were needed to properly adjust the cluster detection analysis, a more in-depth analysis was outside the scope of this study. An inference-based approach that not only identifies and quantifies these effects but also allows further investigation into effect modification, separating residual variability at the individual and county level (multilevel modeling) and deriving the most parsimonious models for each flare outcome, is of interest and will be the primary focus of our future work. The potential mechanisms underlying the effect of environmental factors on lupus flares is an interesting subject to speculate on. Elevated temperature has profound effects on the immune system, particularly by increasing T cell proliferation rates, interleukin-1 (IL-1)–driven secretion of IL-2, and primary antibody responses to T-dependent antigens (17,18), but whether changes in environmental temperature affect the immune response is unknown. Rodo et al described a causal relationship between large-scale wind currents originating in northeastern China and the major epidemics of Kawasaki disease in Japan, Hawaii, and San Diego (19).

Candida were the dominant fungal species (54% of all fungal DNA clones) isolated in the aerosol samples from these wind currents (20), underlining the potential of aerosols transported by wind currents over long distances to trigger human disease. PM2.5 has been shown to alter innate immunity by affecting Toll-like receptor signaling, inflammasome activation, and oxidative stress (21–23). One could speculate that similar mechanisms underlie the effect of these environmental factors on lupus flares. The shortcoming of cluster analysis as an epidemiologic method is the low likelihood of establishing a definitive cause-and- effect relationship between the health event and an exposure. Clusters are useful for generating hypotheses but may not be as useful for testing hypotheses. The issues raised by a cluster cannot be definitively answered by the investigation per se, since they require an alternative epidemiologic approach. This is also true regarding the interpretation of the cluster changes after adjustment. While a change in clusters after adjustment for individual or environmental covariates suggests that these covariates in part drive the formation, location, or temporal extent of these clusters, the exact interpretation of every change can be difficult and requires further study.

The difficulty in interpretation is partially driven by SaTScan software itself, which produces a ranked list of clusters based on significance. To make reporting and interpretability easier, by default SaTScan reports only clusters that do not spatially overlap, meaning that there can be multiple significant overlapping clusters identified in an area, but only the most significant of those would be reported. A slight change in the significance of the clusters could lead to a change in ranking order, and ultimately change what clusters are mapped and reported, even if the change in significance is minimal. By loosening the default restrictions and allowing SaTScan to report spatially overlaying clusters as long as they do not contain the centroids of more significant clusters, we allowed more significant clusters to be reported, without making the plots overwhelming. We describe the first spatiotemporal clusters of lupus organ-specific disease activity. Seasonal, as well as multi-year, cluster patterns were identified, differing in extent and location for the various organ-specific flare types. Many of the clusters identified changed in significance, temporal extent, or spatial extent after adjusting for environmental or individual covariates. Further study focusing on each individual lupus organ-specific flare is needed to better understand the driving forces behind these observed changes.

TRAINING OPPORTUNITIES

What opportunities for training and professional development has the project provided?

Nothing to report

How were the results disseminated to communities of interest?

Nothing to report

What do you plan to do during the next reporting period to accomplish the goals?

IMPACT

What was the impact on the development of the principal discipline(s) of the project?

This was the first study to employ spatial-temporal analysis in a well defined, longitudinal lupus cohort

which showed the presence of distinctive spatial-temporal clusters of organ specific lupus flares which changed in space and time with adjustment for atmospheric and environmental variables, indicating their likely role in the occurrence of the described clusters. These exciting findings could change the approach to the study of environmental factors in SLE and related autoimmune diseases

What was the impact on other disciplines?

Nothing to report

What was the impact on technology transfer?

Nothing to report

What was the impact on society beyond science and technology?

This study could hint to a connection between climate change and the changing frequency/severity of SLE over time. A better understanding of the relation between the immune system and environment, could lead to public health changes with the specific purpose of decreasing the incidence of autoimmune flares.

CHANGES/PROBLEMS

Actual or anticipated problems or delays and actions or plans to resolve them

Nothing to report

Changes with a significant inpact on expenditures;

Nothing to report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

Nothing to report

Significant changes in use of biohazards and/or select agents

Nothing to report

PRODUCTS

List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

Publications, conference papers, and presentations

Journal publications.

G Stojan, A Kvit, FC Curriero, M Petri. A Spatiotemporal Analysis of Organ-Specific Lupus Flares in Relation to Atmospheric Variables and Fine Particulate Matter Pollution. Arthritis Rheumatol. 2020 Jul;72(7):1134-1142. doi: 10.1002/art.41217

Books or other non-periodical, one-time publications.

1. G Stojan, A Kvit, F Curriero, M Petri. Outdoor Air Pollution and Systemic Lupus Erythematosus, Abstract nr 1019, ACR Convergence 2020
2. G Stojan, A Kvit, F Curriero, M Petri. Environmental and Atmospheric Factors in Systemic Lupus Erythematosus: A Regression Analysis. Abstract 695, ACR Annual Meeting 2019
3. G Stojan, A Kvit, F Curriero, M Petri. A Spatial-temporal Analysis of Organ- specific Lupus Flares in Relation to Fine Particulate Matter Pollution and Temperature. Abstract 895 ACR Annual Meeting 2019

Other publications, conference papers and presentations.

11/2019 Environmental and Atmospheric Factors in Systemic Lupus Erythematosus: A Regression Analysis, American College of Rheumatology Annual Meeting, Atlanta, GA

11/2019 A Spatial-temporal Analysis of Organ-specific Lupus Flares in Relation to Fine Particulate Matter Pollution and Temperature, Epidemiology & Public Health: SLE session, American College of Rheumatology Annual Meeting, Atlanta, GA

Website(s) or other Internet site(s

1. Why Rising Temperatures Could Make Life Harder for Lupus Patients, PBS, December 2019
2. Atmospheric & Environmental Changes Tied to Organ-Specific Lupus Flares. The Rheumatologist, November 2019
3. Atmospheric and environmental changes impact organ-specific lupus flares, EurekAlert AAAS, November 2019
4. Sudden weather changes may trigger organ-specific lupus flares, Healio Rheumatology, November 2019

Technologies or techniques

Spatiotemporal analysis is a well-established epidemiological method – no new techniques or

technologies were created

Inventions, patent applications, and/or licenses

Nothing to report

Other Products

Nothing to report

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

George Stojan, principal investigator: no change
Anton Kvit, research analyst: no change
Frank Curriero, co-investigator: no change
Michelle Petri, co-investigator: no change

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report

What other organizations were involved as partners?

Nothing to report

SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

Nothing to report

QUAD CHARTS: NA.

APPENDICES

Publication: G Stojan, A Kvit, FC Curriero, M Petri. A Spatiotemporal Analysis of Organ-Specific Lupus Flares in Relation to Atmospheric Variables and Fine Particulate Matter Pollution. Arthritis Rheumatol. 2020 Jul;72(7):1134-1142. doi: 10.1002/art.41217

American College of Rheumatology
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A Spatiotemporal Analysis of Organ-Specific Lupus Flares in Relation to Atmospheric Variables and Fine Particulate Matter Pollution

George Stojan, Anton Kvit, Frank C. Curriero, and Michelle Petri

Objective. To identify potential clusters of systemic lupus erythematosus (SLE) organ-specific flares and their relationship to fine particulate matter pollution (PM2.5), temperature, ozone concentration, resultant wind, relative humidity, and barometric pressure in the Hopkins Lupus Cohort, using spatiotemporal cluster analysis.

Methods. A total of 1,628 patients who fulfilled the Systemic Lupus International Collaborating Clinics classification criteria for SLE and who had a home address recorded were included in the analysis. Disease activity was assessed using the Lupus Activity Index. Assessment of rash, joint involvement, serositis, and neurologic, pulmonary, renal, and hematologic activity was quantified on a 0–3 visual analog scale (VAS). An organ-specific flare was defined as an increase in VAS of ≥1 point compared to the previous visit. Spatiotemporal clusters were detected using SaTScan software. Regression models were used for cluster adjustment and included individual, county-level, and environmental variables.

Results. Significant clusters unadjusted for environmental variables were identified for joint flares ($P < 0.05$; n = 3), rash flares ($P < 0.05$; n = 4), hematologic flares ($P < 0.05$; n = 3), neurologic flares ($P < 0.05$; n = 2), renal flares ($P < 0.001$; n = 4), serositis ($P < 0.001$; n = 2), and pulmonary flares ($P < 0.001$; n = 2). The majority of the clusters identified changed in significance, temporal extent, or spatial extent after adjustment for environmental variables.

Conclusion. We describe the first spatiotemporal clusters of lupus organ-specific flares. Seasonal, as well as multi-year, cluster patterns were identified, differing in extent and location for the various organ-specific flare types. Further studies focusing on each individual organ-specific flare are needed to better understand the driving forces behind these observed changes.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a complex multisystem autoimmune disease with strong epidemiologic evidence of association with several environmental factors, including crystalline silica exposure (1), cigarette smoking (2), and exogenous estrogens (oral contraceptives and postmenopausal hormones) (3), as well as potential associations between other exogenous factors such as mercury (4), ultraviolet radiation, solvents, and pesticides (5).

With regard to atmospheric impact, significant seasonal variation in SLE disease activity has been described, with more arthritis activity in the spring and summer months, an increase in renal activity in the winter months, significantly higher anti–double-stranded DNA (anti-dsDNA) antibody titers in the fall, and a significant variation in global disease activity, as measured by the Safety of Estrogens in Lupus Erythematosus National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), through the year (6). In a cohort of 2,802 SLE patients from China, the absolute number of patients with active SLE (SLEDAI >12) in a month was positively correlated with the amount of precipitation and wind speed (7). There was no significant correlation between average temperature, average humidity, or average percentage of sunshine hours and SLE activity.

Fine particulate matter pollution (PM2.5) averaged for up to 10 days prior to patient visit was associated with anti-dsDNA

Supported by the Office of the Assistant Secretary of Defense for Health Affairs and Lupus Research Program (award W81XWH19-1-0793), the National Center for Research Resources, NIH (grant UL1-RR-025005), and the NIH Roadmap for Medical Research. The Hopkins Lupus Cohort was supported by the NIH (grants AR-43727 and AR-69572). Dr. Stojan's work was supported by the Jerome L. Greene Foundation. Dr. Curriero's work was supported by the NIH (grant R01-AI-123931).

George Stojan, MD, Anton Kvit, MS, Frank C. Curriero, PhD, Michelle Petri, MD, MPH: Johns Hopkins University, Baltimore, Maryland.

Dr. Petri has received consulting fees, speaking fees, and/or honoraria from Amgen, EMD Serono, and Merck (less than $10,000 each) and research support from AstraZeneca, Exagen Diagnostics, and GlaxoSmithKline. No other disclosures relevant to this article were reported.

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antibodies and cellular casts, but not with global disease activity, in a Montreal lupus cohort (8). A population-based cohort study from Taiwan showed a positive association between a 10.2 μg/m^3 increase in fine particulate matter concentration and new diagnoses of SLE (9). Similarly, population-based studies from Alberta and Quebec showed that PM2.5 exposure may be associated with an increased risk of systemic autoimmune diseases, including SLE (10).

We pursued the development of spatiotemporal analytical models of lupus flares with the goal of identifying potential flare clusters and their relationship to PM2.5 and temperature changes. These spatiotemporal models serve as the foundation for a novel approach to the study of environmental factors in SLE.

PATIENTS AND METHODS

Patients and activity indices. As previously described (11), the Hopkins Lupus Cohort is a prospective cohort study of predictors of lupus flare, atherosclerosis, and health status in SLE. The study cohort includes all patients at the Hopkins Lupus Center who have a clinical diagnosis of SLE and meet classification criteria for SLE (12). All patients provided written informed consent to participate in the study. Patients enrolled in the cohort are followed up quarterly or more frequently if clinically necessary. Clinical features, laboratory findings, and damage accrual data are recorded at the time of entry into the cohort and are updated at subsequent visits. The Hopkins Lupus Cohort has been approved by the Johns Hopkins University School of Medicine Institutional Review Board and complies with the Health Insurance Portability and Accountability Act.

The Hopkins Lupus Cohort included 2,486 patients, with the vast majority of patients living in Maryland and the surrounding states. A 350-kilometer radial buffer around the Johns Hopkins Lupus Center was therefore considered as the study area, since it included a high and consistent density of patients necessary for cluster detection. This area included most of Maryland, Delaware, and Washington, DC, as well as parts of Pennsylvania, New Jersey, Virginia, and West Virginia (Figure 1).

Patients who had home addresses within the study area between 1999 and 2017 were included in the study. A 1999 cutoff was selected since consistent PM2.5 data were available beginning in that year. All address changes during study follow up were recorded and were considered. Disease activity was assessed by the Lupus Activity Index (13). Assessment of rash, joint involvement, serositis, and neurologic, pulmonary, renal, and hematologic activity was quantified on a 0–3 visual analog scale (VAS).

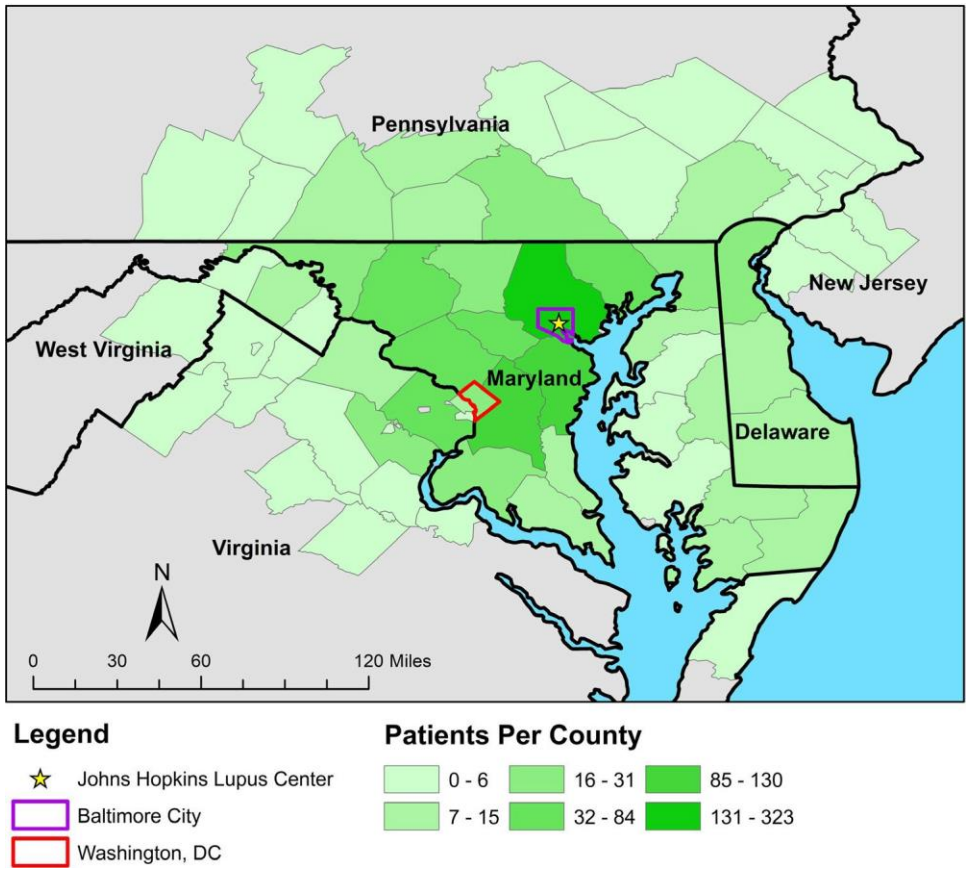


Figure 1. The Johns Hopkins Lupus Cohort study area. Patients with systemic lupus erythematosus in the Johns Hopkins Lupus Cohort who had home addresses within this study area during the period from 1999 to 2017 were included in the cluster analysis.

An organ-specific flare was defined as an increase in VAS of ≥1 point compared to the previous visit. For the increase to count as a flare, the previous visit must have been within 110 days of the current visit. Patients were generally asked to check in at least every 3 months; however, this time period varied, and 92 day, 100 day, and 110 day cutoffs were considered. A 110 day cutoff was considered the most appropriate, since it allowed retention of 70% of the records while still excluding patients who visited too rarely to determine whether a flare had occurred. After applying all of the criteria described above, 1,628 patients with a total of 29,677 visits were included in the study. Individual variables considered in the analysis included patient sex, age, race, smoking status, household income, years of education, and urban versus rural living environment. County-level variables included median income and the proportion of the population who were African American. Flare types included rash, joint, serositis, and neurologic, renal, pulmonary, and hematologic flares. Available data are further summarized in Table 1.

Daily PM2.5 data measured in micrograms per cubic meter, temperature measured in degrees Fahrenheit, ozone concentration measured in parts per million (ppm), resultant wind measured in miles per hour, relative humidity expressed as a percentage, and barometric pressure expressed as millimeters of mercury (mm Hg) were collected at various monitoring stations in the eastern US and obtained from the Environmental Protection Agency. Ordinary kriging was used via the "gstat" R package (14) to predict the 10-day average level of the environmental variables for each patient prior to each visit date. Ordinary kriging (15) is a widely used statistical interpolation method that allows the prediction of the value of a variable in any geographic location based on known variable measures at other locations, while taking into account the spatial dependence in the distribution of the measured variable. This method allowed us to predict environmental exposures for each patient based on appropriately weighted exposure measures at the surrounding monitoring stations.

Both univariate and multivariate generalized estimating equation (GEE) logistic regression models with an exchangeable correlation structure were built to study the association of individual variables (age, sex, race, smoking status, household income, years of education, and urban living status), county variables (county income and the proportion of the population who were African American), and environmental variables (PM2.5, temperature, ozone concentration, resultant wind, barometric pressure, and relative humidity) with the 7 different types of lupus disease activity listed above. GEE regression was used in order to account for the repeated measures each patient was subject to during their multiple clinic visits, thus violating the independence assumption necessary for ordinary regression.

Spatiotemporal cluster detection of flares was conducted using SaTScan software version 9.4.4. In order to detect such clusters, SaTScan utilizes a moving window of variable size, that centers at each data point location, and considers all possible time intervals, recording the number of observed and expected cases inside and outside the window. For each window location, size, and time, the observed and expected cases are compared, the likelihood function is maximized, identifying the window that is least likely to occur by chance, and this process is repeated 999 times through Monte Carlo hypothesis testing in order to obtain a *P* value, and identify the window as a statistically significant cluster. The method used to calculate expected cases depends

Table 1. Individual and county-level variables and lupus flare outcomes, by patient sex*

	Women (n = 1,504)	Men (n = 124)	Total (n = 1,628)
No. of clinic visits	27,376	2,301	29,677
Age, mean years	38.8	43.2	39.1
Race			
African American	618 (41.1)	41 (33.1)	659 (40.5)
White	761 (50.6)	74 (59.7)	835 (51.3)
Other	125 (8.3)	9 (7.3)	134 (8.2)
Years of education, mean	14.3	14.2	14.3
Annual household income, mean dollars	65,491.2	77,642.5	66,322.2
Ever smoker	157 (10.4)	9 (7.3)	166 (10.2)
Urban living environment	1,281 (85.2)	101 (81.5)	1,382 (84.9)
Annual county income, mean dollars	63,655.7	65,802.7	63,823.7
African American proportion of county population, mean %	29.9	27.0	29.7
Lupus flares†			
Rash flares	1,146 (4.2)	61 (2.7)	1,207 (4.1)
Joint flares	1,665 (6.1)	102 (4.4)	1,767 (6)
Serologic flares	470 (1.7)	25 (1.1)	495 (1.7)
Neurologic flares	292 (1.1)	22 (1.0)	314 (1.1)
Renal flares	1,696 (6.2)	188 (8.2)	1,884 (6.3)
Pulmonary flares	58 (0.2)	3 (0.1)	61 (0.2)
Hematologic flares	446 (1.6)	62 (2.7)	508 (1.7)

*** Except where indicated otherwise, values are the number (%).**
† Values are the number of flares (% of clinic visits).

Table 2. Associations between outcome variables and individual, county, and environmental covariates in univariate regression analysis*

Variable	Rash		Joints		Serositis		Neurologic		Renal		Pulmonary		Hematologic	
	OR	*P*	OR	*P*	OR	*P*	OR	*P*	OR	*P*	OR	*P*	OR	*P*
Age	0.989	0.021	1.000	>0.9	0.968	<0.001	0.997	>0.9	0.976	<0.001	0.993	>0.9	0.991	>0.9
Sex	0.620	0.5115	0.721	0.7095	0.683	>0.9	1.127	>0.9	1.341	0.3225	0.640	>0.9	1.822	0.3705
Race (other)	0.671	>0.9	0.571	0.0075	0.764	>0.9	0.448	0.6885	0.924	>0.9	1.450	>0.9	1.037	>0.9
Race (white)	0.668	<0.001	0.875	0.7965	0.658	0.0915	0.734	>0.9	0.536	<0.001	0.574	>0.9	0.986	>0.9
Ever smoker	1.862	<0.001	1.201	0.8745	0.499	0.8475	0.990	>0.9	0.957	>0.9	1.166	>0.9	1.023	>0.9
Household income†	0.993	>0.9	0.989	0.153	0.995	>0.9	0.998	>0.9	0.998	>0.9	1.009	>0.9	1.004	>0.9
Years of education	0.943	0.012	0.972	0.4605	0.943	0.498	1.007	>0.9	0.943	<0.001	0.980	>0.9	1.007	>0.9
Urban living environment	0.975	>0.9	0.929	>0.9	0.954	>0.9	0.812	>0.9	0.840	0.9225	0.936	>0.9	0.968	>0.9
Af of	1.044	0.438	1.006	>0.9	0.959	>0.9	1.005	>0.9	1.034	0.6795	0.989	>0.9	1.025	>0.9
Median county income†	0.980	>0.9	0.969	0.0015	0.994	>0.9	0.949	0.144	0.964	0.0015	0.908	0.153	0.985	>0.9
PM2.5	1.029	<0.001	1.026	<0.001	1.028	0.0525	1.026	0.399	1.004	>0.9	1.043	0.8625	1.025	0.138
Temperature (degrees F)‡	1.065	0.033	1.047	0.0285	1.061	0.6135	1.068	>0.9	0.960	0.072	1.108	>0.9	1.095	0.027
Ozone concentration (ppm)	1.013	<0.001	1.004	>0.9	1.011	0.3255	1.002	>0.9	0.992	0.0105	1.010	>0.9	1.005	>0.9
Resultant wind (miles/hour)‡	1.009	>0.9	1.039	<0.001	1.007	>0.9	1.099	<0.001	1.028	0.0165	1.135	0.0045	1.046	0.1
Barometric pressure (mm Hg)‡	0.993	0.5655	1.004	>0.9	1.006	>0.9	0.989	>0.9	0.998	>0.9	1.053	0.6585	1.007	>0.9
Relative humidity (%)‡	0.991	>0.9	1.163	<0.001	1.125	>0.9	1.297	0.0765	1.045	>0.9	1.293	>0.9	1.159	0.1365

*** *P* values less than 0.05 were considered significant; *P* values less than 0.1 were considered marginally significant. All *P* values were Bonferroni adjusted. PM2.5 = fine particulate matter pollution; ppm = parts per million.**
† Odds ratio (OR) per $5,000.
‡ OR per 10 units.

on the selected statistical model. Patient data were aggregated to 66 counties that spanned the study area and were considered the spatial units for the analysis. A discrete Poisson SaTScan model was utilized, where the total number of each type of lupus flares per day, in each county, is considered to be the case, and the total number of patient visits per day, in each county, is considered to be the population, if the cluster is unadjusted.

In order to determine whether individual, county, or environmental covariates help explain the identified clusters, the expected number of flares determined from the GEE logistic regressions described above can be used in place of the population within the SaTScan Poisson model. In this study, 2 adjusted spatiotemporal cluster analyses were conducted. In the first, only adjustments for individual and county level socioeconomic factors were made. In the second, in addition to the individual and county variables, adjustments based on environmental variables were included. One-month–long minimum time intervals were considered for this analysis, and spatially overlapping clusters were allowed as long as the overlapping cluster did not contain the centroid of the cluster that was already there.

Data availability

The data that support the findings of this study are available upon request from the corresponding author. The data are not publicly available since they contain information that could compromise research participant privacy.

RESULTS

In a univariate regression analysis, rash flares (odds ratio [OR] 1.029) and joint flares (OR 1.026) were found to be positively associated with PM2.5 exposure ($P < 0.05$), while serositis (OR 1.028) was found to be marginally associated ($P = 0.053$). Rash flares (OR 1.065), joint flares (OR 1.047), and hematologic flares (OR 1.095) were found to be significantly positively associated with temperature, while renal flares (OR 0.960) were found to be marginally negatively associated with temperature ($P = 0.072$). Ozone concentration was associated with rash (OR 1.01, $P < 0.05$) and negatively associated with renal flares (OR 0.992). Resultant wind was positively associated ($P < 0.05$) with joint flares (OR 1.039), neurologic flares (OR 1.099), renal flares (OR 1.028), and pulmonary flares (OR 1.135). Relative humidity was associated with joint flares (OR 1.163, $P < 0.05$) and marginally associated with neurologic flares (OR 1.297, $P = 0.077$). No significant associations were found for barometric pressure. Furthermore, rash, serositis, and renal flares were found to be negatively associated with age ($P < 0.05$). Rash and serositis symptoms were found to be more likely in African American than white populations (marginally for serositis [$P = 0.092$]), and odds of joint flare were higher for African American patients than for patients of other nonwhite races. Rash flares were found to be more likely in smokers (OR 1.862) and to be negatively associated ($P < 0.05$) with years of education (OR 0.943). Renal flares were also negatively associated with years of education (OR 0.943). Finally, joint flares (OR 0.969) and renal flares (OR 0.964) were found to be negatively associated with median county income ($P < 0.05$). These findings are summarized in Table 2.

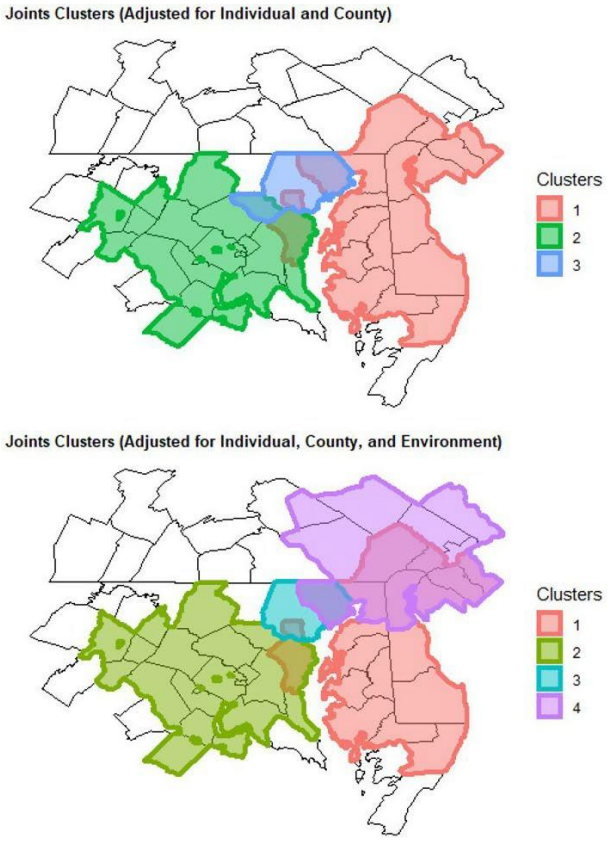
For most outcomes, the clusters identified changed spatially or temporally when environmental variables were considered in addition to county and individual ones. The general interpretation of cluster behavior after adjustment for environmental covariates can be classified into the following 3 categories:

1. Clusters that remain unchanged temporally or spatially after adjustment for environmental covariates indicate areas where no association between environmental covariates and flare occurrence was identified.
2. Clusters that disappear or decrease spatially or temporally after adjustment for environmental covariates indicate areas where there were high levels of covariates along with a general positive association of the covariates with the number of flares, or low levels of covariates with a general negative association.
3. Clusters that emerge or increase spatially or temporally after adjustment for environmental covariates indicate areas where there were low levels of covariates along with a general positive association of the covariates with the number of flares, or high levels of covariates with a general negative association.

Three statistically significant ($P < 0.05$) environmentally unadjusted clusters were identified for joint flares. One encompassed most of Maryland's Eastern Shore and Delaware and ranged from July 2001 to July 2005. A second cluster was located to the southwest, including Washington, DC and parts of Virginia and Maryland, and ranged from April 2001 to July 2009. The third cluster centered around the city of Baltimore and Baltimore County and ranged from January 2002 to September 2005. After adjustment for environmental variables, cluster 1 located on the Eastern Shore decreased temporally, cluster 2 in the west remained unchanged, and cluster 3 decreased spatially and shifted temporally. A new cluster (cluster 4) appeared in the northeast after adjustment (Figure 2).

After adjustment for individual and county variables, 4 significant ($P < 0.05$) rash flare clusters were identified in eastern Maryland, southeastern Pennsylvania, and Delaware. Clusters 1 and 2 located on the Eastern Shore and north of the city of Baltimore, respectively, decreased spatially after adjustment, while clusters 3 and 4, located in the southwest and northeast, respectively, increased spatially after adjustment (Figure 3).

Three significant environmentally unadjusted ($P < 0.05$) hematologic clusters were identified. Two were around New Jersey (from September 2000 to February 2002 and from February 2001 to February 2002), and one was located in western Maryland and Virginia (from December 2002 to December 2005). None



Cluster	Start Date	End Date	P-Value	Observed	Expected	Area
1	2001/7/28	2005/7/27	< 0.001	314	207	21403
2	2001/4/28	2009/7/27	< 0.001	423	315	18270
3	2002/1/28	2005/9/27	< 0.001	273	190	3726

Cluster	Start Date	End Date	P-Value	Observed	Expected	Area
1	2004/2/28	2005/6/27	< 0.001	126	64.0	21403
2	2001/4/28	2009/7/27	0.003	423	329.8	18270
3	2003/1/28	2007/4/27	0.004	262	187.2	3071
4	2004/4/28	2005/6/27	0.028	38	14.7	17141

Figure 2. Top, Clusters of joint flares in patients with systemic lupus erythematosus (SLE) after adjustment for individual variables (age, sex, race, smoking status, household income, years of education, and urban living status) and county variables (county income and the proportion of the population who were African American). Bottom, Clusters of joint flares in SLE patients after adjustment for individual variables, county variables, and environmental variables (fine particulate matter pollution, temperature, ozone concentration, resultant wind, barometric pressure, and relative humidity). After adjustment for environmental variables, cluster 1 decreased temporally, cluster 2 remained unchanged, and cluster 3 decreased spatially and shifted temporally. A new cluster (cluster 4) in the northeast was identified after adjustment. The beginning and end dates, *P* value, observed and expected values, and area in square kilometers are shown for each cluster.

of these clusters remained significant after adjustment for atmospheric variables and PM2.5 (Figure 4).

Two large significant neurologic flare clusters were identified, in the eastern and western halves of the study area ($P < 0.05$) (Supplementary Figure 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41217/abstract). After adjustment for atmospheric variables and PM2.5, spatially and temporally smaller clusters during time periods different from the original clusters appeared. Two significant environmentally unadjusted serositis clusters were identified, and both remained temporally and spatially unchanged after adjustment for environmental variables ($P < 0.001$) (Supplementary Figure 2, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41217/abstract).

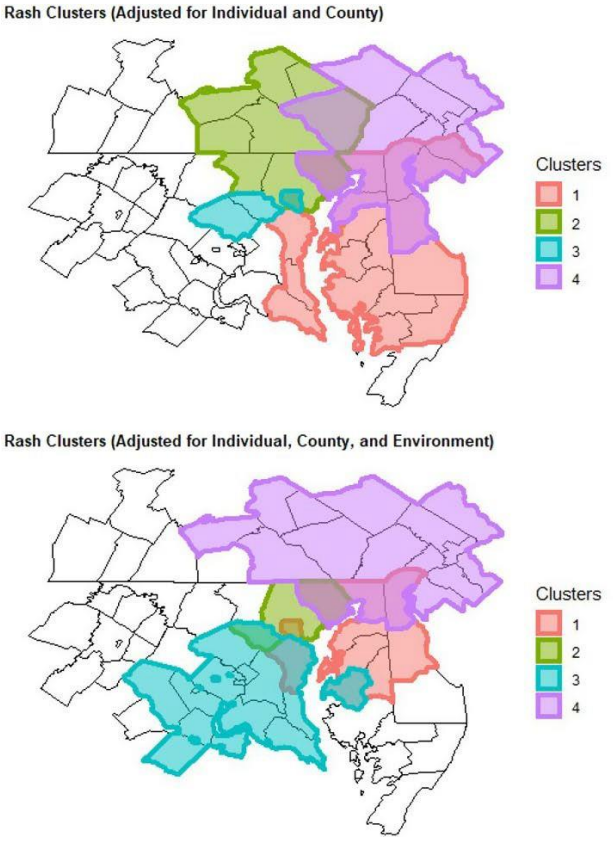
Four highly significant renal clusters were identified ($P < 0.001$) (Supplementary Figure 3, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41217/abstract), spanning from 2001, 2002, and 2004 to 2006, taking up much of the map except for some counties in the west and south. These clusters remained largely unchanged spatially after adjustment for atmospheric variables and PM2.5, while clusters 2 and 3 became slightly smaller temporally after adjustment.

Two significant pulmonary flare clusters were identified in the northwest, spanning from January to July of 1999 ($P < 0.001$) (Supplementary Figure 4, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41217/abstract). Both clusters became spatially smaller after adjustment for atmospheric variables and PM2.5, and a third cluster appeared in the northeast after adjustment.

DISCUSSION

Cluster detection, the identification of spatial units adjacent in space that are associated with distinctive patterns of data of interest relative to background variation, is an important tool in disciplines such as spatial epidemiology and disease surveillance (16). Clusters have distinctive risks of an event of interest, typically elevated, but possibly reduced, relative to background variation (16).

We performed a spatiotemporal cluster analysis of the Hopkins Lupus Cohort and detected the first spatiotemporal lupus flare



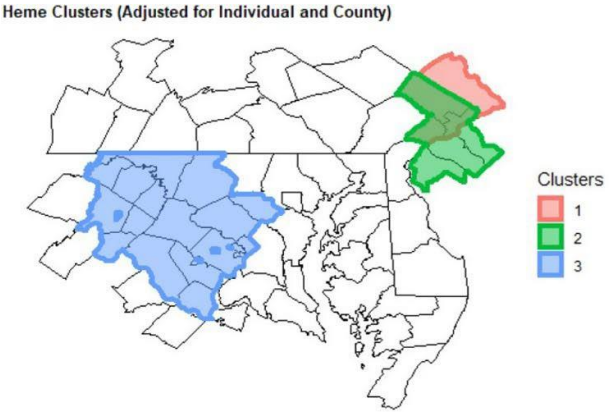
Cluster	Start Date	End Date	P-Value	Observed	Expected	Area
1	2003/6/28	2009/8/27	< 0.001	315	202	21009
2	2003/12/28	2007/9/27	< 0.001	194	117	14313
3	2003/1/28	2007/9/27	< 0.001	174	102	2207
4	2003/4/28	2007/5/27	0.012	67	32	18537

Cluster	Start Date	End Date	P-Value	Observed	Expected	Area
1	2002/11/28	2009/11/27	< 0.001	331	219.1	9816
2	2003/1/28	2009/7/27	< 0.001	312	219.7	3726
3	2003/3/28	2007/6/27	< 0.001	171	105.1	14467
4	2002/9/28	2007/9/27	0.001	89	44.8	22371

Figure 3. Top, Clusters of rash flares in patients with systemic lupus erythematosus (SLE) after adjustment for individual variables (age, sex, race, smoking status, household income, years of education, and urban living status) and county variables (county income and the proportion of the population who were African American). Bottom, Clusters of rash flares in SLE patients after adjustment for individual variables, county variables, and environmental variables (fine particulate matter pollution, temperature, ozone concentration, resultant wind, barometric pressure, and relative humidity). After adjustment for environmental variables, clusters 1 and 2 decreased spatially, while clusters 3 and 4 increased spatially. The beginning and end dates, *P* value, observed and expected values, and area in square kilometers are shown for each cluster.

clusters. Seasonal, as well as multi-year, cluster patterns were identified, differing in extent and location for the various organ-specific flare types. The large-scale, multi-year clusters we defined did not conform to any known pattern of infectious disease or environmental exposure.

After adjustment for individual or environmental covariates, there were at least slight changes in the temporal or spatial extent, or significance, of nearly all of the identified clusters, with serositis clusters being the only ones that remained almost entirely



Cluster	Start Date	End Date	P-Value	Observed	Expected	Area
1	2001/2/28	2002/2/27	0.038	6	0.292	3738
2	2000/9/28	2002/2/27	0.04	7	0.481	4491
3	2002/12/28	2005/12/27	0.043	45	20.064	14994

Figure 4. Clusters of hematologic (heme) flares in patients with systemic lupus erythematosus (SLE) after adjustment for individual variables (age, sex, race, smoking status, household income, years of education, and urban living status) and county variables (county income and the proportion of the population who were African American). No significant clusters ($P < 0.05$) were identified after adjustment for individual variables, county variables, and environmental variables (fine particulate matter pollution, temperature, ozone concentration, resultant wind, barometric pressure, and relative humidity). The beginning and end dates, *P* value, observed and expected values, and area in square kilometers are shown for each cluster.

unchanged. Generally, a decrease in temporal extent, as seen for some of the joint flare clusters (Figure 2) or renal flare clusters (Supplementary Figure 3), or spatial extent, as seen for the neurologic flare clusters and pulmonary flare clusters (Supplementary Figures 1 and 4), after adjustment for covariates indicates that the adjusted covariates were partially driving the occurrence of that cluster at that time and location. After adjustment for environmental variables, some clusters increased in spatial extent, such as rash flare cluster 3, or temporal extent, such as rash flare cluster 1 (Figure 3). An increase in cluster size, temporal extent, or significance after adjustment for covariates might suggest an area where flare activity is high, despite the presence of individual and environmental covariates that are associated with lower flare activity, and thus this is an area of particular interest for further research.

GEE-based regression analysis was used to quantify the effects of individual, county, and environmental variables on the odds of flare outcomes. While these results were needed to properly adjust the cluster detection analysis, a more in-depth analysis was outside the scope of this study. An inference-based approach that not only identifies and quantifies these effects but also allows further investigation into effect modification, separating residual variability at the individual and county level (multilevel modeling) and deriving the most parsimonious models for each flare outcome, is of interest and will be the primary focus of our future work.

The potential mechanisms underlying the effect of environmental factors on lupus flares is an interesting subject to speculate on. Elevated temperature has profound effects on the immune system, particularly by increasing T cell proliferation rates, interleukin-1 (IL-1)–driven secretion of IL-2, and primary antibody responses to T-dependent antigens (17,18), but whether changes in environmental temperature affect the immune response is unknown. Rodó et al described a causal relationship between large-scale wind currents originating in northeastern China and the major epidemics of Kawasaki disease in Japan, Hawaii, and San Diego (19). *Candida* were the dominant fungal species (54% of all fungal DNA clones) isolated in the aerosol samples from these wind currents (20), underlining the potential of aerosols transported by wind currents over long distances to trigger human disease. PM2.5 has been shown to alter innate immunity by affecting Toll-like receptor signaling, inflammasome activation, and oxidative stress (21–23). One could speculate that similar mechanisms underlie the effect of these environmental factors on lupus flares.

The shortcoming of cluster analysis as an epidemiologic method is the low likelihood of establishing a definitive cause-and-effect relationship between the health event and an exposure. Clusters are useful for generating hypotheses but may not be as useful for testing hypotheses. The issues raised by a cluster cannot be definitively answered by the investigation per se, since they require an alternative epidemiologic approach. This is also true regarding the interpretation of the cluster changes after adjustment. While a change in clusters after adjustment for individual or environmental covariates suggests that these covariates in part drive the formation, location, or temporal extent of these clusters, the exact interpretation of every change can be difficult and requires further study.

The difficulty in interpretation is partially driven by SaTScan software itself, which produces a ranked list of clusters based on significance. To make reporting and interpretability easier, by default SaTScan reports only clusters that do not spatially overlap, meaning that there can be multiple significant overlapping clusters identified in an area, but only the most significant of those would be reported. A slight change in the significance of the clusters could lead to a change in ranking order, and ultimately change what clusters are mapped and reported, even if the change in significance is minimal. By loosening the default restrictions and allowing SaTScan to report spatially overlaying clusters as long as they do not contain the centroids of more significant clusters, we allowed more significant clusters to be reported, without making the plots overwhelming.

We describe the first spatiotemporal clusters of lupus organ-specific disease activity. Seasonal, as well as multi-year, cluster patterns were identified, differing in extent and location for the various organ-specific flare types. Many of the clusters identified changed in significance, temporal extent, or spatial extent after adjusting for environmental or individual covariates. Further study focusing on each individual lupus organ-specific flare is needed to better understand the driving forces behind these observed changes.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Stojan had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Stojan.

Acquisition of data. Stojan, Petri.

Analysis and interpretation of data. Stojan, Kvit, Curriero, Petri.

REFERENCES

1. Parks CG, Cooper GS, Nylander-French LA, Sanderson WT, Dement JM, Cohen PL, et al. Occupational exposure to crystalline silica and risk of systemic lupus erythematosus: a population-based, case–control study in the Southeastern United States. Arthritis Rheum 2002;46:1840–50.
2. Costenbader KH, Kim DJ, Peerzada J, Lockman S, Nobles-Knight D, Petri M, et al. Cigarette smoking and the risk of systemic lupus erythematosus: a meta-analysis. Arthritis Rheum 2004;50:849–57.
3. Costenbader KH, Feskanich D, Stampfer MJ, Karlson EW. Reproductive and menopausal factors and risk of systemic lupus erythematosus in women. Arthritis Rheum 2007;56:1251–62.
4. Mok CC, Leung B, Fong B, Wong CK. THU0300 serum mercury level and disease activity of systemic lupus erythematosus (SLE): a case-control study [abstract]. Ann Rheum Dis 2013;72 Suppl 3:A267.
5. Parks CG, de Souza Espindola Santos A, Barbhaiya M, Costenbader KH. Understanding the role of environmental factors in the development of systemic lupus erythematosus. Best Pract Res Clin Rheumatol 2017;31:306–20.

6. Duarte-García A, Fang H, To CH, Magder LS, Petri M. Seasonal variation in the activity of systemic lupus erythematosus. J Rheumatol 2012;39:1392–8.
7. Yang J, Lu YW, Pan HF, Tao JH, Zou YF, Bao W, et al. Seasonal distribution of systemic lupus erythematosus activity and its correlation with climate factors. Rheumatol Int 2012;32:2393–9.
8. Bernatsky S, Fournier M, Pineau CA, Clarke AE, Vinet E, Smargiassi A. Associations between ambient fine particulate levels and disease activity in patients with systemic lupus erythematosus (SLE). Environ Health Perspect 2011;119:45–9.
9. Jung CR, Chung WT, Chen WT, Lee RY, Hwang BF. Long-term exposure to traffic-related air pollution and systemic lupus erythematosus in Taiwan: a cohort study. Sci Total Environ 2019;668:342–9.
10. Bernatsky S, Smargiassi A, Barnabe C, Svenson LW, Brand A, Martin RV, et al. Fine particulate air pollution and systemic autoimmune rheumatic disease in two Canadian provinces. Environ Res 2016;146:85–91.
11. Petri M. Hopkins Lupus Cohort: 1999 update. Rheum Dis Clin North Am 2000;26:199–213.
12. Petri M, Orbai AM, Alarcon GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012;64:2677–86.
13. Petri M, Genovese M, Engle E, Hochberg M. Definition, incidence, and clinical description of flare in systemic lupus erythematosus: a prospective cohort study. Arthritis Rheum 1991;34:937–44.
14. Pebesma EJ. Multivariable geostatistics in S: the gstat package. Comput Geosci 2004;30:683–91.
15. Cressie N. Spatial prediction and ordinary kriging. Math Geol 1988; 20:405–21.
16. Lee J, Gangnon RE, Zhu J. Cluster detection of spatial regression coefficients. Stat Med 2017;36:1118–33.
17. Lederman HM, Brill CR, Murphy PA. Interleukin 1-driven secretion of interleukin 2 is highly temperature-dependent. J Immunol 1987;138:3808–11.
18. Gern JE, Jayman JR, Goldberg LI, Murphy PA, Lederman HM. Temperature is a powerful promoter of interleukin 2 transcription. Cytokine 1991;3:389–97.
19. Rodó X, Ballester J, Cayan D, Melish ME, Nakamura Y, Uehara R, et al. Association of Kawasaki disease with tropospheric wind patterns. Sci Rep 2011;1:152.
20. Rodó X, Curcoll R, Robinson M, Ballester J, Burns JC, Cayan DR, et al. Tropospheric winds from northeastern China carry the etiologic agent of Kawasaki disease from its source to Japan. Proc Natl Acad Sci U S A 2014;111:7952–7.
21. Davis BK, Wen H, Ting JP. The inflammasome NLRs in immunity, inflammation, and associated diseases. Annu Rev Immunol 2011;29:707–35.
22. Bauer RN, Diaz-Sanchez D, Jaspers I. Effects of air pollutants on innate immunity: the role of Toll-like receptors and nucleotide-binding oligomerization domain–like receptors. J Allergy Clin Immunol 2012;129:14–24.
23. Miller RL, Peden DB. Environmental effects on immune responses in patients with atopy and asthma. J Allergy Clin Immunol 2014;134: 1001–8.