Population-Based Incidence and Prevalence of Systemic Lupus Erythematosus: The Michigan Lupus Epidemiology and Surveillance Program

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The Michigan Lupus Epidemiology and Surveillance Program

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Objective. To estimate the incidence and prevalence of systemic lupus erythematosus (SLE) in a sociodemographically diverse southeastern Michigan source population of 2.4 million people.

Methods. SLE cases fulfilling the American College of Rheumatology classification criteria (primary case definition) or meeting rheumatologist-judged SLE criteria (secondary definition) and residing in Wayne or Washtenaw Counties during 2002–2004 were included. Case finding was performed from 6 source types, including hospitals and private specialists. Age-standardized rates were computed, and capture–recapture was performed to estimate underascertainment of cases.

Results. The overall age-adjusted incidence and prevalence (ACR definition) per 100,000 persons were 5.5 (95% confidence interval [95% CI] 5.0–6.1) and 72.8 (95% CI 70.8–74.8). Among females, the incidence was 9.3 per 100,000 persons and the prevalence was 128.7 per 100,000 persons. Only 7 cases were estimated to have been missed by capture–recapture, adjustment for which did not materially affect the rates. SLE prevalence was 2.3-fold higher in black persons than in white persons, and 10-fold higher in females than in males. Among incident cases, the mean ± SD age at diagnosis was 39.3 ± 16.6 years. Black SLE patients had a higher proportion of renal disease and end-stage renal disease (ESRD) (40.5% and 15.3%, respectively) as compared to white SLE patients (18.8% and 4.5%, respectively). Black patients with renal disease were diagnosed as having SLE at younger age than white patients with renal disease (mean ± SD 34.4 ± 14.9 years versus 41.9 ± 21.3 years; P = 0.05).

Conclusion. SLE prevalence was higher than has been described in most other population-based studies and reached 1 in 537 among black female persons. There were substantial racial disparities in the burden of SLE, with black patients experiencing earlier age at diagnosis, >2-fold increases in SLE incidence and prevalence, and increased proportions of renal disease and progression to ESRD as compared to white patients.

Estimating the incidence and prevalence of systemic lupus erythematosus (SLE) in the general popu-
dition is challenging and resource-intensive to perform. In part, this is due to the protean and systemic nature of the disease and the attendant diagnostic complexity that requires the synthesis of a multitude of clinical and laboratory findings, often obtained from a variety of health care settings. In the US, the fragmented health care system and lack of existing infrastructure suitable for the surveillance of autoimmune diseases such as SLE further complicates the implementation of population-based efforts to ascertain and validate cases. As a result, existing estimates of the incidence and prevalence of SLE vary widely, with close to 10-fold differences in published incidence estimates from the US (1,2). In response to the need for accurate and contemporary statistics related to the risk and burden of SLE, we developed the Michigan Lupus Epidemiology and Surveillance (MILES) program, which covers a sociodemographically diverse population in southeastern Michigan, consisting of ~2.4 million persons or ~25% of the population of Michigan (3).

In partnership with the Centers for Disease Control and Prevention (CDC) and the Michigan Department of Community Health (MDCH), we implemented the MILES program with the primary goal of ascertaining and validating all diagnosed cases of SLE in persons residing in the geographic region of the source population, in order to derive population-based incidence and prevalence estimates for SLE during 2002–2004. Given the large scope and diversity of the underlying population, the MILES program has enabled the characterization of disease patterns in population subsets with a high level of detail and precision.

PATIENTS AND METHODS

Regulatory approvals. As described elsewhere (4), this lupus surveillance project was conducted under a grant of authority from the MDCH as a public health surveillance activity, with Institutional Review Board exemptions and waiver for informed consent from the CDC, the MDCH, and the University of Michigan (UM).

Source population, catchment area, and surveillance period. The source population consisted of 2.4 million residents of the counties of Wayne (includes Detroit) and Washtenaw (includes Ann Arbor) in southeastern Michigan, comprising a mixed urban/rural population (57.7% white, 38.7% black, 3.7% other racial/ethnic groups according to 2003 US Census estimates) (3). Location of “usual residence” was determined according to the 2000 Census rules (5). To capture SLE cases receiving health care outside their residential county, the catchment area for case ascertainment also included neighboring Oakland County, as determined by a pilot analysis of data on health care utilization patterns (6).

SLE definitions and verification of diagnosis. Primary analyses were based on classification of SLE according to fulfillment of the current research standard: ≥4 of 11 American College of Rheumatology (ACR) criteria for SLE (7,8) (or, ACR definition). Secondary analyses used our rheumatologist definition, which was based on the consensus judgment of our team of 6 board-certified rheumatologist-investigators representing the major academic medical centers in southeastern Michigan. As detailed further in the data collection section below, in addition to data elements comprising the ACR classification criteria, we systematically ascertained data elements from other case definitions, including the Boston weighted criteria (9), as well as from validated SLE activity measures and components of the new Systemic Lupus International Collaborating Clinics (SLICC) criteria for the classification of SLE (10). In addition, free-text note fields were available for each organ system and included data on confounding diagnoses or other salient points substantiating the record. Thus, the judgment of the rheumatologists was based on the synthesis of medical history details beyond the ACR or other classification criteria. Based on the rheumatologist definition, some patients who satisfied fewer than 4 ACR criteria and had biopsy-proven lupus nephritis and/or additional objective features of SLE were considered to have SLE. The rheumatologist definition also excluded some patients who satisfied ≥4 ACR criteria but who had met subcriteria that could more likely be attributed to a comorbid illness, such as hepatitis C virus infection. If there was disagreement between the ACR and rheumatologist classifications, the record was reviewed independently by at least 2 physician-investigators to assure consensus on the rheumatologist definition that was recorded.

Case ascertainment. Multiple case-finding sources were used, including hospitals/health systems, private practice specialists (rheumatologists, nephrologists, and dermatologists), Medicaid claims, the US Renal Data System for end-stage renal disease (ESRD) patients with a diagnosis of SLE, and commercial laboratories. In addition, a random sample of primary care practices was taken in order to explore the utility of primary care practices for case finding, though this source did not yield adequate data for analysis. Case finding was customized to be compatible and as comprehensive as possible for each source/facility; queries were based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, Systematized Nomenclature of Medicine (SNOMED) codes for pathology reports, keyword/text searching of medical records, and/or other patient logs, as applicable (codes and keywords are listed in Supplementary Table 1, available on the Arthritis & Rheumatology web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38238/abstract).

Case ascertainment and abstraction in the source population was completed at 27 of 28 hospitals (96.4%), 59 of 67 rheumatologists (88.1%), 74 of 84 nephrologists (88.1%), and 50 of 86 dermatologists (58.1%). Of the 18 rheumatologists and nephrologists that were not included, ~20% had retired/closed practices since the surveillance period, 39% declined to participate, and the remainder were affiliated with larger health systems that we accessed. Of the dermatologists who were not included, the majority were not directly relevant...
to our surveillance program because of their area of subspecialization (e.g., cosmetic dermatology or Mohs surgery). In neighboring Oakland County, case ascertainment and abstraction were completed at an additional 10 hospitals and 20 private practices.

**Data collection.** Detailed sociodemographic and clinical data were collected (see Supplementary Table 2, available on the *Arthritis & Rheumatology* web site at http://online library.wiley.com/doi/10.1002/art.38238/abstract). Relevant clinical data included the ACR (7,8) and SLICC (10) classification criteria for SLE, components of validated SLE disease activity instruments (e.g., the SLE Disease Activity Index [SLEDAI] [11], the British Isles Lupus Assessment Group Index [BILAG] [12], and the Systemic Lupus Activity Measure [SLAM] [13,14]), and ACR consensus definitions (neuropsychiatric lupus) (15). Data elements were selected based on an iterative process among a working group of >10 rheumatology/public health faculty members. Clinical data included dates of SLE diagnosis and, for the major features of SLE (e.g., ACR criteria), both the date of onset and the source of the data (physician observation, medical document, or patient report), potentially confounding diagnoses (e.g., hepatitis C virus infection), common SLE medications, and the diagnosis recorded in the patient’s medical chart. For some data elements (e.g., antiphospholipid antibodies), the results of multiple assessments were recorded.

Data were collected by abstractors who had completed standardized, rigorous training, which included completion of pilot abstractions that were reviewed in detail by the rheumatologist-investigators against the source documentation. Continual quality assurance of data abstraction included reabstraction of 5% of the records, as well as physician review of all abstractions and provision of feedback. For each potential case, abstractors manually reviewed all available records. A medical record search engine (the Universal Medical Record Search Engine [UMERSE]) (16) was used when available to screen electronic records for keywords. Data were entered into a secure electronic data-capture system. Completed abstractions, representing the synthesis of data from all available sources, were reviewed in detail by at least one rheumatologist-investigator, who requested further information if necessary.

**Statistical analysis.** All cases contributed person-years to the prevalence numerators for each year (from diagnosis onward) of residence in the source population during 2002–2004 and to the incidence numerators for the year of diagnosis (if during 2002–2004). Age-, sex-, and race-specific denominators for 2002–2004, by county in Michigan, were based on US Census data (the vintage 2009 bridged-race population files

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**Figure 1.** Flow diagram of the ascertainment and verification of cases of systemic lupus erythematosus (SLE) in the Michigan Lupus Epidemiology and Surveillance program. For the category of not incident (inc) or prevalent (prev) during surveillance period, the prevalent cases included both newly diagnosed (incident) and existing cases (i.e., the incident cases are a subset of the prevalent cases). Dx = diagnosis; ACR = American College of Rheumatology; Rheum = rheumatologist.
produced by the National Center for Health Statistics and the US Census Bureau (3,17). The race-bridging methodology is used to create comparability between multiple-race (31 race categories) and single-race (4 race categories) data collection systems (1). Crude and stratum-specific mean annual incidence and prevalence rates were computed per 100,000 person-years. Rates were estimated as the number of incident or prevalent cases divided by the relevant number of person-years, and exact 95% confidence intervals (95% CIs) were computed. Age-standardized rates were calculated using the direct method (using 5-year age bands), with weights based on the 2000 US Standard Population (18).

To estimate underascertainment of cases, capture-recapture analysis (19) was used to take account for the degree of overlap among multiple case-finding sources. Specifically, we fit log-linear models (20) assuming there was no “3-way” interaction of sources. Contingency tables were set up with count data for the number of cases uniquely identified for each source and for pairs of sources. Each of these cells represented a potential predictor in the models, which included each of the sources and interaction terms, and then nonsignificant interactions were removed from the final model (up to 9 pairs of 2-way interactions for the 5-source models, and up to 5 pairs of 2-way interactions for the 4-source models). Goodness-of-fit statistics were used to identify the best models based on Pearson’s chi-square and the Bayesian information criterion (BIC) (21,22). The BIC includes 2 terms, the first corresponds to the number of estimated parameters and the second to the likelihood of the data, given the model. Thus, the BIC reflects the trade-off between model complexity and goodness-of-fit. Analyses were performed using SAS 9.2 (SAS Institute), R (R Foundation), and Stata (StataCorp) software packages.

RESULTS

Characteristics of the study population. As depicted by the flow diagram in Figure 1, among the 13,170 potential cases screened, a total of 2,278 prevalent cases, with a subset of 426 incident cases, were confirmed as meeting eligibility criteria (residency and time period)
and either the ACR or the rheumatologist definitions of SLE. A larger number of cases fulfilled the ACR definition as compared to the rheumatologist definition (2,139 versus 1,909) (Figure 1). The demographic features of the cases meeting the ACR definition were as follows: 1,957 (91.5%) female; 1,219 (57.0%) black, 820 (38.3%) white, 100 (4.7%) other/unknown race (Table 1). The vast majority of cases (2,124 of 2,278 [93.2%]) that were included in the Registry were ascertained by just 4 of the 6 case-finding source categories (Figure 2).

Incidence rates. According to the ACR definition, 399 cases were newly diagnosed during 2002–2004 (average of 133 new cases annually). Crude and age-standardized rates according to both SLE definitions, stratified by sex and race, are detailed in Table 1 and Figure 3A. By the ACR definition, the age-standardized incidence rates were as follows: for the overall population, 5.5 per 100,000 person-years (95% CI 5.0–6.1); for the female population, 9.3 (95% CI 8.3–10.3); and for the male population, 1.5 (95% CI 1.1–2.0) (incidence ratio of females to males 6:1). The age-standardized incidence rate among black patients was 7.9 (95% CI 6.9–9.1) and among white patients was 3.7 (95% CI 3.1–4.3). The incidence for black females (12.8 [95% CI 11.1–14.8]) was higher than for white females (6.3 [95%

Figure 2. Venn diagram depicting the overlap of cases identified by the 4 categories of case-finding sources used in the primary capture–recapture models. This diagram corresponds to unique prevalent cases classified as systemic lupus erythematosus (SLE) according to the American College of Rheumatology (ACR) definition. Capture–recapture modeling was performed using both 4-source and 5-source models; the models that used the 4 case-finding sources presented in this Venn diagram were determined to fit the data best and, thus, represent our primary capture–recapture modeling. The majority of cases in the registry (2,124 of 2,278 [93.2%]) meeting the ACR or rheumatologist definitions were ascertained from these 4 case-finding source categories. (The 2 case-finding sources that were not retained in the primary models were Medicaid and laboratory.) Based on the capture–recapture analysis of prevalent SLE cases meeting the ACR criteria, we estimated that an additional 7 prevalent SLE cases were in the source population (Wayne and Washtenaw Counties, Michigan, 2002–2004) but were not ascertained in the Registry. ESRD = end-stage renal disease (data from US Renal Data System).

Figure 3. A and B, Forest plots of the age-standardized incidence (A) and prevalence (B) rates of systemic lupus erythematosus (SLE), according to the American College of Rheumatology (ACR) and rheumatologist (Rheum) case definitions, categorized by sex and race/ethnicity. Values are the point estimates with 95% confidence intervals (95% CIs). Vertical dotted lines indicate the point estimates for the overall male and female rates according to the ACR definition. Numbers shown on the right y-axis are the average annual number of SLE cases during 2002–2004, with the age-standardized rate (ASR) per 100,000 persons and 95% CI. Pacif = Pacific.
Incidence rates were higher among black male patients as compared to white male patients, although they did not reach statistical significance (likely due to the small number of male patients). The numbers of incident cases for other racial/ethnic groups (7 Asian/Pacific Islander, 1 American Indian/Alaska Native, and 9 Hispanic patients) were small; thus, the incidence rates for these groups are not presented due to statistical imprecision. Incidence patterns by race and sex were similar according to the secondary rheumatologist definition, although the rates were slightly lower.

Capture–recapture modeling (applied to the ACR definition) using 4- and 5-source models was performed to assess the extent of underascertainment of cases by our surveillance program. Based on goodness-of-fit statistics, our primary capture–recapture models incorporated the following 4 case-finding sources: hospitals, rheumatology practices, nephrology/dermatology practices, and US Renal Data System/ESRD database. From this 4-source model, we estimated that we were unable to identify 2 (95% CI 1–4) incident SLE cases in the source population. Adjustment for this low level of underascertainment did not materially affect the incidence rates.

The mean ± SD age at diagnosis in the ACR-defined incident cases was 39.3 ± 16.6 years and was significantly younger in black female patients (37.1 ± 14.5 years) as compared to white female patients (43.9 ± 16.9 years; \( P < 0.001 \)), but was similar in black male patients (36.4 ± 18.6 years) as compared to white male patients (41.0 ± 19.9 years). Age-specific incidence rates (Figure 4A) in black female patients rose from early childhood and peaked in the twenties, while the rates for white female patients increased more gradually and plateaued from the thirties through fifties. Among males, the incidence rates appeared more constant across age groups.

**Prevalence rates.** From a total of 2,139 ACR-defined prevalent cases, the annual average number of person-years contributed during 2002–2004 was 1,708. The prevalence rates, including sex- and race-specific rates for both case definitions, are detailed in Table 1 and Figure 3B. The age-standardized prevalence was 72.8 per 100,000 person-years (95% CI 70.8–74.8) overall, 128.7 (95% CI 125.1–132.4) for females, and 12.8 (95% CI 11.7–14.1) for males. The age-standardized prevalence among black persons was more than double that for white persons, including among black females (186.3 [95% CI 179.4–193.4]) as compared to white females (86.7 [95% CI 82.8–90.8]). The estimated prevalence rates for Asians/Pacific Islander and Hispanic persons were lower than for black persons, although the small number of cases in these groups limits further comparisons.

While the age-specific prevalence for both black and white females peaked in the fourth decade of life, from ages 10–69 years, black females had a significantly higher prevalence than did white females or males of either racial/ethnic group (Figure 4B), demonstrating that the disproportionate disease burden among black females pertained across the majority of the lifespan. Based on our primary 4-source capture–recapture analyses (described above), we estimated that 7 (95% CI 5–10) prevalent SLE cases in the source population were
Table 2. Clinical manifestations among the prevalent cases of SLE, according to the ACR and rheumatologist case definitionsa

<table>
<thead>
<tr>
<th>Clinical manifestation</th>
<th>ACR definition</th>
<th>Rheumatologist definition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%) of overall group</td>
<td>No. (%) of black cases</td>
</tr>
<tr>
<td>Malar rash</td>
<td>1,055 (49.3)</td>
<td>520 (42.7)</td>
</tr>
<tr>
<td>Discoid rash</td>
<td>520 (24.3)</td>
<td>392 (32.2)†</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>1,036 (48.4)</td>
<td>505 (41.4)</td>
</tr>
<tr>
<td>Oral ulcers</td>
<td>892 (41.7)</td>
<td>462 (37.9)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>1,514 (70.8)</td>
<td>875 (71.8)</td>
</tr>
<tr>
<td>Serositis</td>
<td>938 (43.9)</td>
<td>559 (45.9)</td>
</tr>
<tr>
<td>Renal disorder</td>
<td>682 (31.9)</td>
<td>494 (40.5)†</td>
</tr>
<tr>
<td>ESRD</td>
<td>231 (10.8)</td>
<td>187 (15.3)†</td>
</tr>
<tr>
<td>Neurologic disorder</td>
<td>394 (18.4)</td>
<td>265 (21.7)†</td>
</tr>
<tr>
<td>Hematologic disorder</td>
<td>1,411 (66.0)</td>
<td>814 (66.8)</td>
</tr>
<tr>
<td>Immunologic disorder</td>
<td>1,436 (67.1)</td>
<td>864 (71.0)†</td>
</tr>
<tr>
<td>Antinuclear antibody</td>
<td>2,012 (94.1)</td>
<td>1,172 (96.1)†</td>
</tr>
</tbody>
</table>

*Prevalent cases consisted of both new (incident) and existing cases of systemic lupus erythematosus (SLE) during the years 2002–2004. Clinical manifestations consisted of the 11 American College of Rheumatology (ACR) criteria for SLE plus end-stage renal disease (ESRD). The overall group represents the entire population, including persons whose race/ethnicity was not known. The numerator for this category is larger than the sum of the individual subsets, since it includes persons of other racial/ethnic classifications.
†Significantly higher proportion of cases with the clinical manifestation between the black and white subgroups.
This study has several limitations. First, it was based on review of medical records, rather than direct patient examination, as most population-based epidemiologic studies must. Second, race and ethnicity were ascertainment from records, not self-reports, which would be the gold standard. Misclassification may be a particular concern for persons of Hispanic/Latino ethnicity, since many medical records systems do not assess Hispanic ethnicity as a separate variable from race, which in theory, could lead to underestimation. Third, although we tried to reach all targeted health care sources, a few (see the case ascertainment section above) did not permit access, and the slow cooperation of others necessitated active record reviews through 2011, requiring increased allocation of resources in order to complete the planned surveillance activities. The nonparticipating sites did not appear to differ systematically from the participating sites in terms of the demographics of the populations served or other discernible features. Fourth, we have likely underestimated incident and prevalent cases, as there may be undiagnosed cases in the community that have not reached the health care system for screening and diagnosis, and other cases may have received care outside the catchment area. However, the capture–recapture analyses estimated that our surveillance program missed only 7 cases in the source population, pointing to highly effective methods of defining catchment areas (based on a pilot analysis of health care utilization patterns) and case ascertainment. Fifth, we were unable to enlist the systematic cooperation of primary care providers for even more comprehensive findings, but the interactions we did have suggested that primary care practices are likely to refer SLE patients and are therefore unlikely to represent a large source of additional cases.

This study also has several strengths. First, it included multiple case-finding sources, including health care facilities in a county contiguous to the source population, which helped to ensure complete ascertainment in a mobile population. Other researchers have previously noted a substantial lack of overlap between administrative case-finding sources, particularly for prevalent SLE cases (31). Second, for each patient, there was comprehensive abstraction and synthesis of detailed clinical and laboratory data from multiple sources. With the public health authority from the MDCH enabling our access to all relevant records, a thorough profile could be constructed for the majority of patients. In some cases, the diagnosis of lupus could be confirmed only after combining data from several hospitals or physicians. Third, as noted above, the use of 2 analytical
case definitions (ACR and rheumatologist definitions) independently confirmed the diagnoses in the majority of patients and accommodated the clinical uncertainty of classifying SLE. The rheumatologist rates may be considered to yield conservative estimates and, thus, serve as a validated “lower bound” for the estimation of SLE. Fourth, the collaboration with colleagues from the CDC, the Georgia Lupus Registry, and the respective state health departments for the methods and infrastructure development can serve as a prototype for the implementation of other SLE registries, which will enhance opportunities for comparison of SLE statistics across sites. Indeed, new registries based on this framework have been initiated in regions with greater representation of other minority groups (Asian/Pacific Islander, Hispanic/Latino, and American Indian/Alaska Native groups).

Based on this comprehensive, population-based surveillance program, our data underscore substantial levels of confirmed SLE cases and considerable racial disparities in the epidemiology of SLE. Black persons had the highest risk and burden of SLE, the earliest age at diagnosis, and an increased proportion of renal disease and progression to ESRD. Such data support a focus of medical resources on early diagnosis and improved treatment of lupus nephritis in young black Americans.

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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. Somers 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. Somers, Marder, DeGuire, Gordon, Helmick, Dhar, Leisen, McCune.

Acquisition of data. Somers, Marder, Lewis, DeGuire, Dhar, Leisen, Shaltis, McCune.

Analysis and interpretation of data. Somers, Marder, Cagnoli, DeGuire, Gordon, Helmick, Wang, Wing, McCune.

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