The Incidence and Prevalence of Systemic Lupus Erythematosus, 2002–2004

The Georgia Lupus Registry

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Objective. The Georgia Lupus Registry is a population-based registry designed to improve our ability to estimate the incidence and prevalence of systemic lupus erythematosus (SLE) in a large population.

Methods. Potential cases of SLE were identified from multiple sources during the years 2002 through 2004. Cases were defined according to the American College of Rheumatology (ACR) criteria for SLE or a combined definition. Age-standardized rates were determined and stratified by race and sex. With capture–recapture analyses, we estimated the underascertainment of cases.

Results. Using the ACR case definition, the overall crude and age-adjusted incidence rate was 5.6 per 100,000, with capture–recapture and combined definition rates being slightly higher. The age-adjusted incidence rate in women was >5 times higher than that for men (9.2 versus 1.8). Black women had an incidence rate nearly 3 times higher than that in white women, with a significantly higher rate in the group ages 30–59 years. The overall crude and age-adjusted prevalence rates were 74.4 and 73 per 100,000, respectively. The age-adjusted prevalence rate in women was nearly 9 times higher than that for men (127.6 versus 14.7). Black women had very high rates (196.2). A striking difference was seen in the proportion of prevalent cases with end-stage renal disease, with 7-fold greater involvement among black patients.

Conclusion. With the more complete case-finding methods we used, the incidence and prevalence rates of SLE are among the highest reported in the US. The results continue to underscore striking sex, age, and racial disparities between black patients and white patients with SLE.

In the 1950s, systemic lupus erythematosus (SLE) was thought to be rare, predominantly affecting women with light hair, fair skin, and an “inability to tan” (1). An epidemiologic study from 1956 through 1965 showed for the first time a higher burden of disease in black women compared to white women (2). We now recognize the disproportionate burden of SLE in women, particularly during their childbearing years, and in certain racial groups. These epidemiologic studies advanced our understanding of the burden of SLE but were limited in their ability to find all cases in the population and, thus, describe the full spectrum of diagnosed cases of SLE.

Given the recent significant increase in awareness of and research in SLE, along with the availability of innovative techniques (3), the purpose of this study by the Georgia Lupus Registry was to advance our epidemiologic understanding of SLE by doing more complete case finding in a targeted population, avoiding referral bias in a particular institution, using available case definitions to better define the incidence and prevalence of diagnosed SLE, and characterizing individuals with
this disease from a population perspective. The Georgia Lupus Registry is one of two recently completed Centers for Disease Control and Prevention (CDC)--funded population-based lupus registries designed to minimize many of the limitations of previous studies. An innovative tool in this approach is the use of the state public health surveillance exemption to the Health Insurance Portability and Accountability Act (HIPAA) to acquire greater access to protected health information without requiring individual patient consent, a limitation that can bias the findings. This novel and powerful approach allows for an unprecedented completeness of case finding from multiple sites of ascertainment throughout the targeted community. Coupled with detailed training of abstractors, strict quality control of data gathering and processing, multiple sources of case ascertainment that minimizes bias from a consent process or institution type, and the high number of cases, this study provides more reliable population-based estimates of incidence and prevalence of SLE than previously reported.

PATIENTS AND METHODS

The Georgia Lupus Registry. In 2002, the CDC Arthritis Program supplied funding for the Georgia Department of Public Health (GA DPH) to conduct surveillance of SLE in 2 Georgia counties with large black populations: Fulton and DeKalb (3). To avoid biased ascertainment and underreporting as a result of recruiting large numbers of community patients, the GA DPH, as a “public health authority,” used its public health surveillance exemption to the HIPAA Privacy Rule (45 Code of Federal Regulations [CFR], parts 160 and 164) to obtain protected health information without written consent of the patient (45 CFR, 164.512[b]). Protected health information was needed in order to determine if the diagnosed cases met the various case definition criteria and to provide enough information to prevent duplicate counting of patients when the same patient was encountered in multiple facilities. The GA DPH contracted with Emory University in Atlanta as its designated agent to provide lupus expertise and manage the project. The CDC considered this surveillance project to be “public health practice” (rather than research) that did not need CDC Institutional Review Board (IRB) review, but it was reviewed and approved by the IRBs at Emory University and the GA DPH.

Study population and period. The study population consisted of residents of Fulton and DeKalb counties, which include the city of Atlanta, in Georgia. Prevalence was estimated for 2002 and incidence for 2002–2004. The Bureau of the Census estimate of the population for the two counties in 2002 was 1,552,970, with 51.1% women, 49.3% black persons, and 46.4% white persons (4), and this population remained stable during 2003–2004. The registry captured diagnosed cases retrospectively. Case ascertainment efforts began in late 2004 in order for data elements to have had time to be captured in various records and data systems. Given the tremendous effort required to obtain and validate cases through multiple sources in the pluralistic US health care system, data collection was not completed until 2011.

Case definitions. SLE is a complex disease that is currently defined according to a variety of case definitions. The gold standard case definition is a diagnosis by expert clinical assessment, usually a rheumatologist, which is impractical for large population-based studies. We used 3 case definitions for this study: ≥4 American College of Rheumatology (ACR) criteria, the treating rheumatologist’s diagnosis, and <4 ACR criteria plus lupus-related kidney disease.

Meeting ≥4 ACR criteria. The most widely accepted standard for SLE diagnosis is meeting ≥4 of the 11 revised classification criteria as defined by the ACR in 1982 (5) and as updated in 1997 (6) (≥4 ACR criteria).

Diagnosis by the treating rheumatologist. Patients who met 3 of the ACR criteria were required to have in their medical record a documented statement of diagnosis of SLE by a board-certified rheumatologist. This acknowledges that a clinical diagnosis by the treating rheumatologist with direct access to the patient is important, particularly in prevalent cases in which the patients had longstanding disease, where certain records may have been inaccessible for our study or lost over time.

Meeting <4 ACR criteria plus having lupus-related kidney disease. In the absence of fulfilling ≥4 of the 11 ACR revised criteria, patients with SLE renal involvement were defined by either biopsy findings consistent with World Health Organization class II–VI lupus nephritis (7–9) or end-stage renal disease (ESRD) requiring dialysis or renal transplantation, with documentation of SLE in their medical record. Biopsy data were linked to SLE administrative coding or clinical documentation and were deemed a significant enough clinico-pathologic finding to suggest that a patient has SLE in the absence of meeting the full ACR criteria (10). The presence of ESRD for which dialysis or renal transplantation was required plus documentation of SLE in the medical record avoids missing patients who may have spent most of their time at dialysis centers for care and/or were busy dealing with other comorbid conditions. The likelihood of being able to locate or access medical records in which most of the ACR criteria are documented decreases for these patients. Incident and prevalent cases may have achieved ESRD status before 2004 or 2002, respectively.

For purposes of analysis, we report our results in 2 ways: according to the standard case definition (≥4 ACR criteria) alone and according to a “combined” case definition that includes all 3 case definitions.

Incident cases were defined as patients newly diagnosed as having SLE from January 1, 2002 through December 31, 2004. Prevalent cases were defined as those with a diagnosis of SLE of any duration during the year 2002. Both must also have met a case definition with a documented address in 1 of the 2 targeted counties during the time of interest.

Case ascertainment, screening, and validation. The primary sources of potential cases included hospitals, rheumatologists, nephrology groups, and dermatology groups in and around the catchment area (Figure 1). Administrative databases were queried retrospectively for the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic code 710.0 (SLE), as well as codes
**THE GEORGIA LUPUS REGISTRY**

**Figure 1.** Flow chart showing case-finding procedure for systemic lupus erythematosus (SLE), according to a case definition of ≥4 American College of Rheumatology (ACR) criteria, in Fulton and DeKalb Counties, Georgia, 2002–2004. Case-finding proceeded from primary and secondary data sources of potential cases to screening/abstracting of records to meeting case definitions. Validated SLE cases were those that met ≥4 ACR criteria. A total of 103 incident cases in 2002 were also counted as prevalent cases.

695.4 (discoid lupus), 710.8 (other specified connective tissue disease), and 710.9 (unspecified connective tissue disease). Antiphospholipid antibody syndrome, which lacks a specific ICD-9-CM code, was searched for if a consistent code was used at a particular facility.

Secondary sources included regional commercial and hospital-based laboratories, which were queried respectively for antinuclear antibodies (ANAs) at a titer ≥1:320, anti-DNA antibodies, and/or anti-Sm antibodies, depressed levels of complement, and anticardiolipin antibodies. Pathology laboratories were queried for cutaneous and renal biopsy findings consistent with lupus. Data were also obtained from the Veterans Administration, electronic medical record systems, and the US Renal Data System (USRDS), which captures all patients with ESRD receiving any kidney replacement therapy (e.g., dialysis or kidney transplantation).

After final screening for residency in the target counties during the target time period, available medical records were abstracted for over 200 data elements, each with detailed definitions in a data dictionary; elements were sought continuously from all sources (without stopping when a certain number of case definition criteria were met). Demographic information, such as race, was obtained from the medical record. Date of diagnosis was the earliest date assigned in the medical record by the patient’s treating physician because the date at which the patient met ≥4 ACR criteria, which is often used to define incidence in prospective studies, was difficult to accurately ascertain retrospectively.

Before entering the field, abstractors were thoroughly trained and tested by board-certified rheumatologists who were expert in lupus care (SSL and CD). Abstractors continued to undergo quality assessments every 100 records. This required a minimum interobserver agreement of 90% of all elements and 95% of ACR criteria using the abstraction by the principal investigators (SSL and CD) as the gold standard or remedial training until those criteria were met.

**Statistical analysis.** Crude SLE incidence rates and 95% confidence intervals (95% CIs) as well as race- and sex-stratified rates were estimated using methods based on the Poisson distribution (11). Denominator data for estimating rates in DeKalb and Fulton counties for the years 2002–2004 were obtained from the postcensal population estimates (4). Age-adjusted estimates and 95% CIs were calculated based on the standard 2000 projected age distribution by the direct method using the R software package (the ageadjust.direct routine) (12), which calculates age standardized (adjusted) rates and “exact” confidence intervals based on the gamma distribution (13). Similar methods were used to estimate the 2002 prevalence.

Capture–recapture (C-RC) methods estimate the completeness of case ascertainment when using multiple information sources. Log-linear models were used to estimate the true SLE population size by evaluating the degree of overlap among 3 data sources (hospitals, specialists, and health care systems), which were chosen by expert opinion of the investigators (SSL and CD) to be the primary sources of cases. Modeling was performed separately for incident and prevalent data based on patients who met the case definition of ≥4 ACR criteria. The log-linear model was used to estimate the number of persons who were missed in the population.

Seven hierarchical log-linear models were fit to the data: 1 model assuming independence among the 3 data sources, 3 models of pairwise interaction, and 3 models of 2 pairwise interactions. The best fitting model was determined by goodness-of-fit statistics and the parsimony principle. Based on the estimated undercount, revised (C-RC) estimates of incidence and prevalence were calculated. All (C-RC) analyses followed the methods described by Bishop et al (14) and McCarty et al (15) and were implemented using SAS Proc Genmod software (SAS Institute).

**RESULTS**

**Incidence.** Using the ≥4 ACR criteria definition. In 2002–2004, a total of 267 cases fulfilled ≥4 ACR criteria for SLE, including 196 black patients, 62 white patients, and 9 patients of other racial groups (Table 1). The overall crude and age-adjusted incidence rates were similar (5.6 per 100,000 person-years). Age-adjusted incidence rates were 5 times higher among women than men (9.2 [95% CI 8.1, 10.5] versus 1.8 [95% CI 1.3, 2.4]). Among women, the age-adjusted rates in black persons were nearly 3 times higher than those in white persons (13.4 versus 4.7); among men, the rates in black persons were >4 times higher than those in white persons (3.2 versus 0.7). C-RC analysis estimated that there were 31 (95% CI 18, 55) missed cases of SLE, resulting in a higher C-RC adjusted rate of 6.3 per 100,000 person-years.

Overall age-specific incidence rates were significantly different between black and white persons, both
in women and in men. Figure 2 shows age-specific rates by sex and race. Black women had significantly higher incidence rates compared to white women in the 30–59 age range, especially those in the 30–39 age stratum (Figure 2A). No age-specific differences between black and white men with SLE were found, although there were significantly fewer men in these strata (Figure 2B). No age-specific differences between black and white women in the 30–59 age range, especially those in the 30–39 age stratum (Figure 2A). No age-specific differences between black and white men with SLE were found, although there were significantly fewer men in these strata (Figure 2B).

The overall mean ± SD age at diagnosis was 40.5 ± 16.5 years, with no significant difference between women and men (40.7 ± 16.3 years versus 39.4 ± 17.9 years; P = 0.48). However, black patients were significantly younger at diagnosis than white patients were (39.4 ± 15.9 years versus 45.4 ± 17.7 years; P = 0.016). Among females, the only incident cases in those <12 years of age were in black children. In the 12–19 age stratum, black female and male cases predominated, with white cases occurring only in females.

Using the combined case definition. The combined case definition yielded an additional 78 cases and a total of 345 incident cases, increasing the crude and age-adjusted rates to 7.3 and 6.9 per 100,000 person-years, respectively (Table 1). Of these 78 additional cases, 72 met 3 of the ACR criteria, 13 had renal biopsy findings consistent with lupus nephritis (5 of these had documented ANA and/or anti-DNA antibody), and none had ESRD. All patients were identified as black or white, except for 11 who were Asian and 3 whose race was not known.

Using the combined case definition, the age-adjusted rate in women was 6 times higher than that in men (11.7 versus 1.9 per 100,000 person-years). The age-adjusted rate in black patients was 3.2 times higher than that in white patients (10.7 versus 3.3 per 100,000 person-years). The proportions were different when comparing sex by race. The rate in women was 2.9 times higher in black patients than in white patients (17.0 versus 5.8 per 100,000 person-years). Black men had a 4.3 times higher incidence rate compared with white men (3.4 versus 0.8 per 100,000 person-years).

**Prevalence.** Using the ≥4 ACR criteria definition. In 2002, a total of 1,156 persons fulfilled ≥4 ACR criteria for SLE, including 889 black patients, 251 white patients, and 16 patients of other races (Table 2). The overall crude prevalence rate was 74.4 (95% CI 70.3, 78.9) per 100,000 person-years. Age-adjusted prevalence rates were similar to the crude rates. The age-adjusted prevalence rate in women was nearly 9 times higher than that in men (127.6 versus 14.7). Among women, the prevalence rate in black patients was >3 times higher than that in white patients (196.2 versus 59.0); among men, the prevalence rate in black patients was >3 times higher than that in white patients (23.7 versus 7.5).

C-RC analysis was done only for the ≥4 ACR criteria case definition and yielded an estimated 133 (95% CI 98, 181) missing SLE cases, resulting in a
C-RC adjusted prevalence rate of 83 per 100,000 person-years.

Using the combined case definition. The “combined” case definition yielded an additional 290 cases, for a total of 1,446 prevalent cases, increasing the crude and adjusted prevalence rates to 93.1 and 92.1 per 100,000 person-years, respectively (Table 2). Of these 290 cases, 213 met 3 ACR criteria, 52 had renal biopsy findings consistent with lupus nephritis (27 of these had documented ANA and/or anti-DNA antibody), and 49 had ESRD. Of those with ESRD, 11 had a documented ANA and/or anti-DNA antibody, and all met ≥3 ACR criteria (8 had documented ANA and/or anti-DNA antibody).

The age-adjusted prevalence rate in women was >8 times higher than that in men (159.8 versus 19.6). The age-adjusted prevalence rate in black persons was >3 times higher than that in white persons (147.5 versus 43.1 per 100,000 person-years). When comparing the age-adjusted prevalence rates in women, the rates among black persons were >3 times higher than those among white persons (241.5 versus 77.7); in men, the rates among black persons were >3 times higher than those among white persons (32.2 versus 9.6). Overall rates were significantly different between black and white persons, both in women and in men. Black women had significantly higher prevalence rates as compared to white women across all age strata except for age groups 0–11 years and ≥70 years (Figure 2C). For men, prevalence rates were noticeably higher in black persons than in white persons between the ages of 20 and 49 years (Figure 2D).

Clinical manifestations. Among incident cases meeting ≥4 ACR criteria, arthritis, hematologic disor-

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**Figure 2.** Age-specific incidence and prevalence rates of systemic lupus erythematosus, according to a case definition of ≥4 American College of Rheumatology criteria, by sex and race, in Fulton and DeKalb Counties, Georgia, 2002–2004. Bars show the 95% confidence intervals.
Table 2. Prevalence of SLE in Fulton and DeKalb counties in Georgia, January 1, 2002 through December 31, 2002, according to 2 analytical case definitions, categorized by race and sex *

<table>
<thead>
<tr>
<th>Race/ethnicity, sex</th>
<th>Catchment area population (person-years)</th>
<th>No. of cases</th>
<th>Crude rate (95% CI)</th>
<th>Age-adjusted rate (95% CI)</th>
<th>No. of cases missed (95% CI)</th>
<th>Capture-recapture adjusted rate (95% CI)</th>
<th>No. of cases</th>
<th>Crude rate (95% CI)</th>
<th>Age-adjusted rate (95% CI)</th>
<th>No. of cases missed (95% CI)</th>
<th>Capture-recapture adjusted rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1,552,970</td>
<td>1,156</td>
<td>74.4 (70.3, 78.9)</td>
<td>73.0 (68.9, 77.4)</td>
<td>133 (98, 181)</td>
<td>83.0 (78.6, 87.7)</td>
<td>1,446</td>
<td>93.1 (88.4, 98)</td>
<td>92.1 (87.4, 97)</td>
<td>1,300</td>
<td>163.7 (155, 172.8)</td>
</tr>
<tr>
<td>Women</td>
<td>794,310</td>
<td>1,043</td>
<td>131.3 (123.6, 139.5)</td>
<td>127.6 (120, 135.7)</td>
<td>115 (83, 159)</td>
<td>145.8 (137.6, 154.4)</td>
<td>1,300</td>
<td>163.7 (155, 172.8)</td>
<td>159.8 (151.3, 168.8)</td>
<td>1,094</td>
<td>142.9 (134.7, 151.6)</td>
</tr>
<tr>
<td>Black</td>
<td>765,475</td>
<td>889</td>
<td>116.1 (108.8, 124.0)</td>
<td>118.5 (111.1, 126.5)</td>
<td>91 (64, 131)</td>
<td>128.0 (120.3, 136.3)</td>
<td>1,094</td>
<td>142.9 (134.7, 151.6)</td>
<td>147.5 (139.2, 156.4)</td>
<td>985</td>
<td>241.0 (226.5, 256.6)</td>
</tr>
<tr>
<td>White</td>
<td>720,292</td>
<td>251</td>
<td>34.8 (30.8, 39.4)</td>
<td>32.7 (28.8, 37.2)</td>
<td>36 (18, 73)</td>
<td>39.8 (35.5, 44.7)</td>
<td>328</td>
<td>45.5 (40.9, 50.7)</td>
<td>43.1 (38.5, 48.1)</td>
<td>36</td>
<td>9.8 (7.1, 13.6)</td>
</tr>
<tr>
<td>Men</td>
<td>367,378</td>
<td>29</td>
<td>7.9 (5.5, 11.3)</td>
<td>7.5 (5.2, 10.9)</td>
<td>4 (0.19)</td>
<td>9.0 (6.4, 12.6)</td>
<td>36</td>
<td>9.8 (7.1, 13.6)</td>
<td>9.6 (6.9, 13.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Rates are per 100,000 person-years (95% confidence intervals [95% CIs]). Age-adjusted rates used the 2000 projected US population.
† The combined case definition for systemic lupus erythematosus (SLE) consisted of the following 3 criteria: ≥4 American College of Rheumatology (ACR) criteria; 3 ACR criteria plus a final diagnosis of SLE rendered by a rheumatologist; or <4 ACR criteria and either biopsy findings consistent with World Health Organization class II–VI lupus nephritis or end-stage renal disease secondary to SLE that required dialysis/renal transplantation.
‡ Values are the estimated number of SLE cases that were missed and the capture-recapture–adjusted incidence rate.
Table 3. Clinical manifestations of SLE among the incident and prevalent cases, January 1, 2002 through December 31, 2004, categorized by race*

<table>
<thead>
<tr>
<th>Clinical manifestation</th>
<th>No. (%) of incident cases</th>
<th>Subgroup difference (95% CI)</th>
<th>No. (%) of prevalent cases</th>
<th>Subgroup difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall (n = 267)</td>
<td>Black patients (n = 196)</td>
<td>White patients (n = 62)</td>
<td></td>
</tr>
<tr>
<td>Malar rash</td>
<td>55 (20.6)</td>
<td>38 (19.4)</td>
<td>12 (19.4)</td>
<td>0.0 (−25.6, 25.7)</td>
</tr>
<tr>
<td>Discoid rash</td>
<td>40 (15.0)</td>
<td>32 (16.3)</td>
<td>7 (11.3)</td>
<td>5.0 (−21.7, 31.8)</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>43 (16.1)</td>
<td>25 (12.8)</td>
<td>17 (27.4)</td>
<td>−14.7 (−39.6, 10.2)</td>
</tr>
<tr>
<td>Oral ulcers</td>
<td>61 (22.8)</td>
<td>42 (21.4)</td>
<td>18 (29)</td>
<td>−7.6 (−32.0, 16.8)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>167 (62.5)</td>
<td>122 (62.2)</td>
<td>38 (61.3)</td>
<td>1.0 (−16.8, 18.7)</td>
</tr>
<tr>
<td>Serositis</td>
<td>91 (34.1)</td>
<td>74 (37.8)</td>
<td>15 (24.2)</td>
<td>13.6 (−10.8, 37.9)</td>
</tr>
<tr>
<td>Renal disorder</td>
<td>91 (34.1)</td>
<td>75 (38.3)</td>
<td>12 (19.4)</td>
<td>18.9 (−6.0, 43.8)</td>
</tr>
<tr>
<td>ESRD</td>
<td>5 (1.9)</td>
<td>4 (2)</td>
<td>1 (1.6)</td>
<td>0.4 (−27.9, 28.7)</td>
</tr>
<tr>
<td>Neurologic disorder</td>
<td>24 (9.0)</td>
<td>18 (9.2)</td>
<td>6 (9.7)</td>
<td>−0.5 (−27.7, 26.7)</td>
</tr>
<tr>
<td>Hematologic disorder</td>
<td>216 (80.9)</td>
<td>160 (81.6)</td>
<td>49 (79)</td>
<td>2.6 (−10.3, 15.5)</td>
</tr>
<tr>
<td>Immunologic disorder</td>
<td>187 (70.0)</td>
<td>143 (73)</td>
<td>38 (61.3)</td>
<td>11.7 (−5.4, 28.8)</td>
</tr>
<tr>
<td>Antinuclear antibody</td>
<td>244 (91.4)</td>
<td>180 (91.8)</td>
<td>56 (90.3)</td>
<td>1.5 (−7.2, 10.2)</td>
</tr>
</tbody>
</table>

* Clinical manifestations consisted of the 11 American College of Rheumatology (ACR) criteria for systemic lupus erythematosus (SLE) plus end-stage renal disease (ESRD; defined by abstraction and the US Renal Data System database). For incident cases, manifestations were counted through the first year after diagnosis. For prevalent cases, manifestations were counted through December 31, 2002. 95% CI = 95% confidence interval.

DISCUSSION

SLE is one of the most challenging conditions to study at the population level. Several studies throughout the world have attempted to advance our epidemiologic knowledge of SLE, and the results have varied widely. We limited our review in the present study to those in the North American region (Table 4). Discrepancies in occurrence rates are in part due to the inherent disparities of SLE (i.e., higher rates in certain ethnic groups). Other reasons include the use of different case definitions, biased sources for case ascertainment, small source populations, the different demographic groups targeted, the protean manifestations of the disease that make diagnosis difficult, the poor reliability of self-report, the lack of reliability in coding in health system databases, and poor access to health care for high-risk populations. These latter differences exist not only across countries and health care systems, but also within the same country. Although no one study can address these limitations completely, the methodologic advances in this study resulted in some of the most reliable population-based estimates of the incidence and prevalence of SLE.

Leveraging the state’s public health surveillance exemption to obtain and review patient information from medical records and various databases without the patients’ consent was a powerful tool for maximizing case ascertainment that had never been used before for SLE. This led to a better population-based assessment without compromising patient confidentiality. This also required significant effort in maximizing the quality of the data, which was enhanced through the collection of uniformly defined data elements, regular quality assessments of the abstractors and data, and sharing of best practices with a parallel registry in Michigan through monthly teleconferences facilitated by the CDC. Multiple sources of cases captured a wide spectrum of disease, both in terms of phenotype and in terms of the degree of disease severity. This included all major sources of pediatric cases. The large numbers of cases led to greater precision of the estimates and greater power to compare certain groups.

How cases are defined is essential to the interpretation of a study and its comparability to other studies. The “gold standard” for diagnosing SLE is by clinical assessment by an experienced clinician (i.e., a
<table>
<thead>
<tr>
<th>Study years, location and country (ref.)</th>
<th>Population at risk (race/ethnicity)</th>
<th>Case definition</th>
<th>Case ascertainment sources</th>
<th>No. of SLE cases</th>
<th>Incidence, per 100,000 per year</th>
<th>Prevalence, per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>1956–1965, New York, NY and Jefferson County, AL, US (2)</td>
<td>1,165,700 (white and black)</td>
<td>Clinical suspicion, characteristic serologic and pathologic findings ≥4 ACR 1971 criteria by chart review</td>
<td>Hospital files, selected clinics and rheumatologists, LE cell tests</td>
<td>193 total (124 white, 69 black)</td>
<td>2.0 overall†</td>
<td>19 overall†</td>
</tr>
<tr>
<td>1965–1973, San Francisco, CA, US (27)</td>
<td>121,444 Kaiser members (all races) 905,759 (1970)–786,775 (1980)</td>
<td>≥4 ACR 1971 criteria by chart review</td>
<td>Outpatient diagnoses from internists and dermatologists Hospital discharge records (SLE)</td>
<td>74 total</td>
<td>7.6 overall</td>
<td>51 overall</td>
</tr>
<tr>
<td>1970–1977, Baltimore, MD, US (28)</td>
<td>146,500 (~95% African Caribbean, &lt;5% white)</td>
<td>≥4 ACR 1982 criteria by chart review</td>
<td>Hospital discharge records, all internal medicine and dermatology specialists by physician report, death certificates in Public Health Department</td>
<td>302 total (79 white, 223 black)</td>
<td>4.6 overall†</td>
<td>ND</td>
</tr>
<tr>
<td>1980–1990, island of Curacao, The Netherlands Antilles (29)</td>
<td>1,336,449 (all races)</td>
<td>≥4 ACR criteria validated by chart review</td>
<td>Rheumatologists, hospitals, university database (SLE)</td>
<td>191 total (141 white, 48 black, 2 other)</td>
<td>2.4 overall</td>
<td>ND</td>
</tr>
<tr>
<td>1980–1996, province of Manitoba, Canada (31)</td>
<td>~1,100,000 (NAN and NANN)</td>
<td>≥4 ACR 1982 criteria validated by chart review</td>
<td>Regional arthritis center database and medical records of all rheumatologists, hematologists, nephrologists, and general internists</td>
<td>257 total (49 NAN, 208 NANN)</td>
<td>2.0–7.4 in NAN, 0.9–2.3 in NANN</td>
<td>42.3 in NAN, 20.6 in NANN</td>
</tr>
<tr>
<td>1997, Nogales, AZ, US (32)</td>
<td>19,489 (92% Mexican American)</td>
<td>≥4 ACR 1982 criteria (definite) or ≥3 ACR criteria (probable) by chart review and examination</td>
<td>Community referrals to lupus evaluation center, practice database search (SLE)</td>
<td>26 total (19 definite, 7 probable)</td>
<td>ND</td>
<td>94 overall</td>
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<tr>
<td>1990–1999, island of Martinique, French West Indies (33)</td>
<td>381,427 (mostly African Caribbean)</td>
<td>≥4 ACR 1982 criteria by investigator chart review</td>
<td>Hospital electronic records (university and community hospitals, practitioners, and software of specialists, independent practitioners, ANA and aPL recorded in files, social security files, mortality database)</td>
<td>286 total</td>
<td>4.7 overall</td>
<td>64.2 overall</td>
</tr>
<tr>
<td>2000, NHANES-III, US population sample (34)</td>
<td>20,050 (all races)</td>
<td>Self-reported physician diagnosis with/without SLE drugs</td>
<td>Self-reported physician diagnosis from NHANES-III</td>
<td>40 by self-report, 12 taking SLE drugs</td>
<td>ND</td>
<td>241 by self-report, 54 taking SLE drugs</td>
</tr>
<tr>
<td>Study years, location and country (ref.)</td>
<td>Population at risk (race/ethnicity)</td>
<td>Case definition</td>
<td>Case ascertainment sources</td>
<td>No. of SLE cases</td>
<td>Incidence, per 100,000 per year</td>
<td>Prevalence, per 100,000</td>
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<tr>
<td>1991–2001, rural North Central Wisconsin, US (35)</td>
<td>77,280 (97% white)</td>
<td>≥4 ACR 1982 criteria (definite) or 1–3 ACR criteria (incomplete) by chart review</td>
<td>Community clinic electronic records (SLE)</td>
<td>174 total (117 definite, 57 incomplete)</td>
<td>5.1 definite†, 8.2 definite in females†, 1.9 definite in males†</td>
<td>79 definite†, 132 definite in females†, 25 definite in males†</td>
</tr>
<tr>
<td>2003, Puerto Rico, US (36)</td>
<td>552,733 private insured people (race ND)</td>
<td>ICD-9 code 710.0</td>
<td>All insurance claims submitted by health care providers (physicians, dentists, laboratories, pharmacies, and hospitals)</td>
<td>877 total (812 female, 65 male)</td>
<td>ND</td>
<td>159 overall, 277 in females, 25 in males</td>
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<tr>
<td>1994–2003, province of Quebec, Canada (37)</td>
<td>~7.5 million (all races)</td>
<td>≥2 health care claims for SLE (&gt;2 months and &lt;2 years apart)</td>
<td>Administrative data (billing codes, hospitalization data, and procedure code data)</td>
<td>3,825 total (2003)</td>
<td>3.0 by PB, 2.8 by HDD</td>
<td>33 by PB, 33 by HDD, 51 composite, 45 Bayesian model</td>
</tr>
<tr>
<td>2008–2010 depending on region, Mexico City, Nuevo Leon, Yucatan, Sinaloa, Chihuahua, Mexico (38)</td>
<td>Sample of 19,213 people ≥18 years old (race/ethnicity ND)</td>
<td>≥4 ACR 1982 criteria by study rheumatologist assessment</td>
<td>COPCORD methodology (community-based survey-directed physician assessments)</td>
<td>NA</td>
<td>ND</td>
<td>60 overall†, 80 in females, 40 in males, 90 in Mexico City, 70 in Nuevo Leon, 70 in Yucatan, 40 in Sinaloa, 40 in Chihuahua</td>
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<tr>
<td>2000–2009, island of Barbados (39)</td>
<td>268,792 (93% of African origin)</td>
<td>≥4 ACR 1982 criteria</td>
<td>Clinic charts from public and private rheumatology services, letters and calls to physicians</td>
<td>183 total (172 female, 11 male)</td>
<td>6.59 total†, 12.1 in females†, 0.77 in males†</td>
<td>84.1 overall, 152.6 in females, 10.1 in males</td>
</tr>
<tr>
<td>2002–2004, Atlanta, GA, US (present study)</td>
<td>1,552,970 (49.3% black, 46.4% white)</td>
<td>≥4 ACR 1982 criteria or “combined” definition by review of charts and laboratory data</td>
<td>Hospital, rheumatologists, dermatologists, nephrologists, laboratories, pathology laboratories, VA, USRDS</td>
<td>1,446 total (1,300 female, 146 male)</td>
<td>6.9 total†, 11.7 in females†, 1.9 in males†</td>
<td>92.1 total†, 159.8 in females†, 19.6 in males†</td>
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</table>

* SLE = systemic lupus erythematosus; ACR = American College of Rheumatology; ND = not determined; ANA = antinuclear antibody; NANN = North American native; NANN = North American non-native; aPL = antiphospholipid antibody; NHANES-III = Third National Health and Nutrition Examination Survey; ICD-9 = International Classification of Diseases, Ninth Revision; PB = physician billing; HDD = hospital discharge data; COPCORD = Community-Oriented Program for the Control of Rheumatic Diseases; NA = not available; VA = Veterans Administration; USRDS = US Renal Data System.
† Age-adjusted to national or regional population.
‡ Age- and sex-adjusted.
rheumatologist), which is often impractical for population-based studies. Currently, the most commonly accepted definition is the ACR 1997 updated criteria for the classification of SLE (5,6). While the use of the ACR criteria enhances the comparability of research studies, the sensitivity of the 1982 criteria has been shown to be only 83% in an external population, as compared with 96% in the test population. The criteria also tend to be skewed toward limited detection of mild cases of SLE and incident cases at early stages of their prodrome. The population size would therefore be underestimated and biased toward those with longer disease duration and greater disease severity. Epidemiologic studies would benefit from alternative definitions for comparison.

Since the fulfillment of a single case definition in the field did not limit the extent of information that was obtained, this study used an alternative definition that improved sensitivity while minimizing the effect on specificity, which is acceptable for a large epidemiologic study. Previous studies often used one case definition. Alternative case definitions, if available, often were defined as those who met incomplete ACR criteria. Diagnoses validated with administrative data or by self-report have limitations and should be supplemented with additional data in situations when medical review is not feasible (16,17).

The burden of SLE in the Atlanta, Georgia, area is significant, with an overall age-adjusted prevalence rate among the highest reported in the US, at 73 per 100,000 person-years according to the ACR criteria, 83 according to C-RC modeling, and 92.1 according to the combined case definition. The overall age-adjusted incidence rate is similarly high, at 5.6 per 100,000 person-years by the ACR criteria, 6.3 by C-RC modeling, and 6.9 by the combined case definition. Use of the combined case definition yielded higher rates and underscores some limitations of the ACR classification criteria, which should be viewed as a minimal estimate in this retrospective study, given the potential for data to be missed or overlooked (18). High rates may be partly due to improved awareness of SLE leading to increased referrals and testing, as well as improved 5-year survival rates, which have gone from <50% to >90% because of earlier diagnosis and more aggressive treatment (19,20). Including undiagnosed or early cases, which were not addressed in this study, would raise these estimates.

Striking sex, age, and racial disparities in SLE have been confirmed. Women have an age-adjusted incidence rate >5 times higher and a prevalence rate >8 times higher than men, as identified by the ACR criteria. The relatively higher ratio of females to males that we found in prevalent cases (8:1) as compared to incidence cases (5:1) may be related to a greater awareness among physicians of SLE in general and, as a result, in men in particular. Likewise, mortality rates have been reported to be relatively higher in men than in women, particularly by studies from the 1980s and 1990s (21). As the diagnosis of SLE and the life expectancy of SLE patients improve, further studies of mortality rates will advance our understanding of potential differences in the burden of disease and its outcomes by sex. Black persons have an incidence and prevalence rate >3 times higher, and develop SLE earlier, than white persons. SLE particularly burdens the black female population, with some of the highest incidence and prevalence rates ever reported (15,22). Black women between the ages of 30 and 59 years were at particularly high risk of developing SLE (Figure 2A). In women <20 years old, there were only 4 incident cases in white persons, as compared to 20 in black persons. Only black females developed SLE during ages <12 years (n = 5). Although age-specific prevalence rates were significantly higher in black women than in white women across all age groups, the difference was more striking between the ages of 30 and 69 years (Figure 2C). In men, black persons also had higher prevalence rates than white persons, particularly between the ages of 20 and 50 years (Figure 2D). Our findings suggest that different age-related patterns of mortality rates by sex and race may occur in SLE patients, as indicated in previous studies (23).

The burden of ESRD continues to be high, affecting 6.7% and 1.9% of prevalent and incident cases (as defined by ≥4 ACR criteria), respectively. A striking difference was seen in the proportion with ESRD, where there was no racial difference among the incident cases, but a 7-fold greater involvement in black patients among the prevalent cases. Some of this can be explained by an inherently higher risk of developing nephritis in persons of African descent (24). However, it also indicates a strong potential for disparities in health care access and other socioeconomic factors (25). A total of 49 of the 127 prevalent ESRD cases did not meet at least 3 ACR criteria, indicating that up to one-third of ESRD cases occurring in patients with lupus nephritis may not meet the ACR criteria for SLE. Renal biopsy findings consistent with SLE, particularly in the setting of suggestive autoantibodies, are thought to be indisputable evidence of SLE and should be considered a sufficient “stand-alone” clinical criterion in prospective studies (26). In an epidemiologic study such as this, given that SLE patients with ESRD are seen less often by rheumatologists and nephrologists outside dialysis centers, documentation of
many of these serologic test results may have been lost with archived or destroyed records.

There are several limitations to this study. First, the US healthcare system is complex, heterogeneous, and fragmented, requiring that each practice and institution be approached separately to voluntarily participate in this study. Second, data were collected retrospectively from medical records designed for clinical use and varied tremendously with respect to organization, legibility, and accessibility. The result of these 2 limitations was a labor-intensive process that required work into 2011 to evaluate records for the study period of 2002–2004. Although trained abstractors were audited periodically to ensure consistency and accuracy, a degree of variability in clinical diagnosis by rheumatologists cannot be excluded. As a result of the retrospective nature of this registry, the degree to which the experience of treating physicians affected the definition of cases, particularly those who had milder disease or met fewer ACR criteria, cannot be determined. Third, there is underascertainment of serologic test results, particularly in prevalent cases in which diagnostic tests could have occurred many years ago and the results lost in the records, thus leading to lower rates of documented ANA and other autoantibodies than would have been expected in a prospective study (Table 3). Fourth, the catchment area was defined by artificial county boundaries. Fifth, the results of this study are best generalized to white and black persons in the Southeastern US and not to other racial/ethnic groups and not in other regions or countries. Sixth, race/ethnicity was assigned based primarily on the physician’s assessment as documented in the medical record. This may not reflect the patient’s true self-identity. Finally, this study was not able to estimate the rate of undiagnosed disease.

The Georgia Lupus Registry advances our epidemiologic understanding of SLE, a disease that is complicated and difficult to diagnose, and confirms the significant burden of SLE, particularly in younger black women, and ESRD in black patients as compared to white patients. It is part of a larger, coordinated effort to more accurately estimate the burden of SLE among other high-risk groups in the US, such as Hispanic, Asian, and North American native/Alaska native persons. Experience from this study could also inform efforts to develop ongoing surveillance of SLE and other medical conditions for which similar challenges exist.

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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. Lim 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. Lim, Helmick, Gordon, Drenkard.

Acquisition of data. Lim, Bayakly, Drenkard.

Analysis and interpretation of data. Lim, Helmick, Gordon, Easley, Drenkard.

REFERENCES