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ORIGINAL ARTICLE

Incidence of Systemic Lupus Erythematosus in the United Kingdom, 1990–1999

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Objective. **To estimate the annual incidence of systemic lupus erythematosus (SLE) over a 10-year period in the UK, and to examine age-, sex-, and region-specific rates.**

Methods. **The study was based on the UK General Practice Research Database (GPRD), which covers ~5% of the UK population. We estimated SLE incidence rates, during the period 1990–1999, among persons registered with practices contributing to the GPRD, representing >33 million person-years of observation.**

Results. **A total of 1,638 patients with incident SLE (1,374 females, 264 males) were identified. The age-standardized SLE incidence in the UK during the 1990s was 7.89 per 100,000 (95% confidence interval [95% CI] 7.46, 8.31) for females and 1.53 per 100,000 (95% CI 1.34, 1.71) for males (overall female-to-male ratio 5.2:1). Peak incidence occurred at age 50–54 years for females and 70–74 years for males. There was a small but insignificant increase of SLE incidence over the 10 years among females but not males. No clear association between latitude and SLE incidence was found, but regional variations existed, with age-standardized rates ranging from 3.56 per 100,000 (95% CI 3.00, 4.13) for the West Midlands to 7.62 per 100,000 (95% CI 5.59, 9.65) for Northern Ireland.**

Conclusion. **This study provides updated estimates of SLE incidence in the UK. Standard methodology throughout the study period and target population allowed for comparison of rates over time and across regions.**

KEY WORDS. Systemic lupus erythematosus; Epidemiology; General Practice Research Database; United Kingdom.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disorder with significant morbidity and mortality for which there is a paucity of epidemiologic information. Previous active surveillance studies of SLE incidence have been confined to relatively small geographic areas (1–3), and the most recent of these studies from the UK dates back to 1991 (1). Due to the diagnostic complexity of SLE and its relative rarity, active surveillance studies require considerable time and expense. For example, an ongoing Centers for Disease Control and Prevention–sponsored SLE surveillance study in southeastern Michigan, which covers a base population of 2.3 million people, is operating on direct costs of over 1 million US dollars for 3 years (McCune WJ: personal communication). In contrast, existing research databases afford the opportunity to perform studies of rare diseases at low cost. The UK General Practice Research Database (GPRD) is a population-based database covering a representative sample (5%) of the UK population of ~60 million people. Internationally, this is the largest research database of anonymized longitudinal medical records from primary care. The present study utilized the GPRD to study the incidence of SLE in England, Scotland, Wales, and Northern Ireland over a 10-year period (1990–1999) with detailed analysis of geographic variation and time trends.

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PATIENTS AND METHODS

Database and study population. More than 98% of the UK population is registered with a general practitioner

working in the National Health Service (NHS). The GPRD covers 5% of NHS patients, and consists of anonymized electronic clinical records of patients registered with contributing general practices. At any given time, there are ~3 million active patients in the GPRD. The practices included in the GPRD are broadly representative of practices in the UK in terms of geographic distribution, practice sizes, and the age and sex distributions of registered patients (4). These practices are under contract to register all active patients and to record all significant morbid events, including all hospitalizations or specialist referrals and outcomes, prescriptions, significant test results, and dates of onset for chronic or recurrent conditions (4).

Contributing practices must meet a range of data quality criteria before they are included in the GPRD, and ongoing quality control is conducted for practices to remain up to standard (5). The quality of the information in the database, including the completeness of recording of diagnoses made in medical facilities outside the practice, has been validated in a number of independent studies and has been found to be high (5). There is excellent agreement between prescribing data from the GPRD and national data from the UK Prescription Pricing Authority (6).

The period for this study was January 1, 1990 to December 31, 1999. Ethics approval for this research was obtained from the Scientific and Ethical Advisory Group, which reviews all GPRD proposals.

Identification of SLE cases. The Oxford Medical Information Systems (OXMIS) (7) and Read (8) coding systems are used to record clinical data in the GPRD. OXMIS and Read codes for SLE were identified from a coding dictionary by 4 investigators (3 physician epidemiologists and 1 rheumatic disease epidemiologist) and were verified by a rheumatologist whose subspecialty is SLE (list of codes available upon request). Patients with at least 1 SLE code in their medical history were identified. The date corresponding to the first SLE record represented the date of diagnosis. With the exception of subacute cutaneous lupus erythematosus (SCLE), codes for cutaneous variants of lupus were not considered to represent SLE. SCLE was retained because a high proportion of patients with SCLE develop SLE.

SLE cases were considered to be potentially incident if the date of diagnosis occurred during the study period and while the patient was registered with a practice contributing data to the GPRD. Incidence rates have been shown to be overestimated during the initial months after patients first register with a contributing practice because prevalent disease is recorded but may not be correctly dated as a past diagnosis. The relevant period during which this overestimation occurs varies by disease (9). We used a modification of the method described by Lewis et al (9) to determine the correct period. We considered all SLE cases with a date of diagnosis occurring after the first day of followup in the GPRD. Hazard function estimates were computed by the classic life table method, using the first date within the analysis time window (i.e., the later of the patient registration date or the date the practice started contributing data) as the time origin and the time of the first SLE-related medical code per patient as the event date. The analysis was stratified according to whether patients registered with a general practice before or after the practice began contributing data to the GPRD. Evaluation of the hazard function demonstrated that the hazard of diagnosis became constant ~12 months after patients had registered with a contributing general practice, and was constant from the beginning of followup for patients already registered with a practice when the practice started contributing data to the GPRD. Therefore, for our study, at least 12 months of followup after patient registration were necessary before the patient was eligible to be an incident SLE case.

Statistical analysis. Crude and stratum-specific incidence rates were computed per 100,000 person-years. Rates were estimated by dividing the number of incident cases by the GPRD population denominator. Denominators for the entire GPRD population were available by sex, age, and NHS region (a geographic proxy) for each calendar year at its midpoint (July 1). Age-standardized rates were calculated using the direct method, with weights based on the European Standard Population (10), and 95% confidence intervals (95% CIs) for age-standardized rates were calculated based on the Poisson approximation. Age-standardized annual incidence rates were calculated during the 1990s to determine whether rates changed over the study period. Linear regression was used to assess trends over time. Standardized rate ratios and 95% CIs were used for the comparison of age-standardized rates by region. Data management and analysis were performed using SAS software, version 8 (SAS Institute, Cary, NC) and Stata software, version 8 (StataCorp, College Station, TX).

RESULTS

SLE cases. There were a total of 33,666,320 person-years of observation in the GPRD over the study period of 1990–1999, and 2,116 potential patients with SLE were identified as having diagnosis dates during this time. Of these patients, 22 were excluded due to having exclusively cutaneous lupus codes. A further 456 patients were prevalent (i.e., identified as having been diagnosed prior to inclusion in the GPRD), leaving 1,638 incident SLE cases for this analysis. A total of 1,374 (83.9%) patients with incident SLE were female. The mean ± SD age at diagnosis for all patients was 47.3 ± 16.4 years. On average, females were diagnosed at an earlier age than males (mean ± SD age 46.3 ± 16.3 versus 52.2 ± 16.3 years; $P < 0.0001$).

Incidence. *Age and sex.* Crude and age-standardized incidence estimates for the decade of study are presented in Table 1. The overall age-standardized incidence was 4.71 per 100,000 (95% CI 4.48, 4.94), 7.89 per 100,000 (95% CI 7.46, 8.31) for females and 1.53 per 100,000 (95% CI 1.34, 1.71) for males. Age-specific rates for each sex are displayed in Figure 1. Rates were similar for ages 0–14 years, but started to diverge sharply thereafter, with females having significantly higher rates of SLE incidence

Table 1. Crude and age-standardized systemic lupus erythematosus incidence rates (per 100,000) during 1990–1999*

	No.	Crude incidence	Age-standardized Incidence	Age-standardized 95% CI
Overall	1,638	4.87	4.71	4.48, 4.94
Female	1,374	8.01	7.89	7.46, 8.31
Male	264	1.60	1.53	1.34, 1.71

* 95% CI = 95% confidence interval.

until approximately age 70. The peak incidence among females occurred in the 50–54 year age group (13.38 per 100,000; 95% CI 11.13, 15.63), whereas males experienced the highest incidence in the 70–74 year age group (4.36 per 100,000; 95% CI 2.71, 6.00).

Temporality. Sex-specific and overall incidence rates by year are depicted in Figure 2. Among males, the incidence appeared stable over the entire decade. Based on linear regression, there appeared to be a modest trend of increasing incidence among females, equivalent to an additional 1 case per 100,000 females over the 10 years (95% CI −0.1, 2.2), but this did not reach significance (P = 0.073).

Geography. Regions were classified according to the 8 NHS administrative regions in England and by country for Wales, Northern Ireland, and Scotland (11). Age-standardized incidence rates are displayed by region of the UK in Figure 3. There was lack of a clear association between SLE incidence and latitude (P = 0.135). However, regional variations of SLE incidence are noted. Age-standardized rates ranged from a low of 3.56 per 100,000 (95% CI 3.00, 4.13) for the West Midlands to a high of 7.62 per 100,000 (95% CI 5.59, 9.65) for Northern Ireland. Standardized rate ratios, comparing the age-standardized incidence for each region with that overall for the UK, are displayed in Table 2. The West Midlands and South West of England had significantly lower rates than the overall UK, whereas the North West and Northern Ireland had significantly higher incidence.

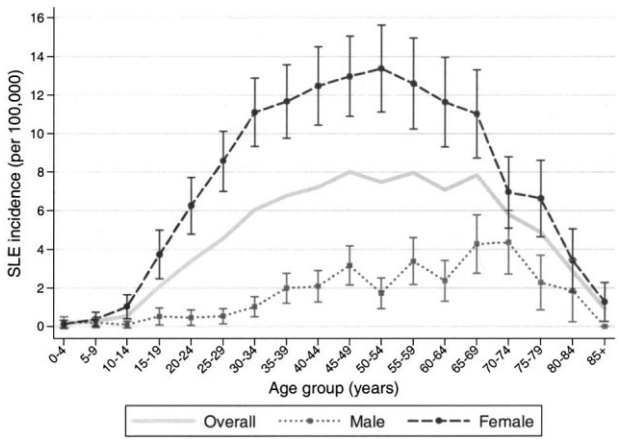

Figure 1. Age- and sex-specific systemic lupus erythematosus (SLE) incidence rates (per 100,000) with 95% confidence intervals.

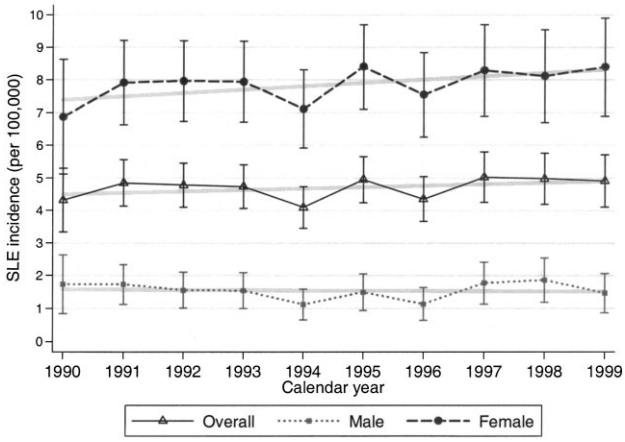

Figure 2. Overall and sex-specific age-standardized systemic lupus erythematosus (SLE) incidence rates (per 100,000) with 95% confidence intervals, by calendar year. The linear best fit lines are also displayed.

Treatment. Prescription drug data were collated for the study population. The proportions of patients treated with certain drugs are reported in Table 3. We looked at drugs separately and also formed 2 composite categories. The first was antimalarials and immunosuppressive agents, which included the following drugs traditionally used for

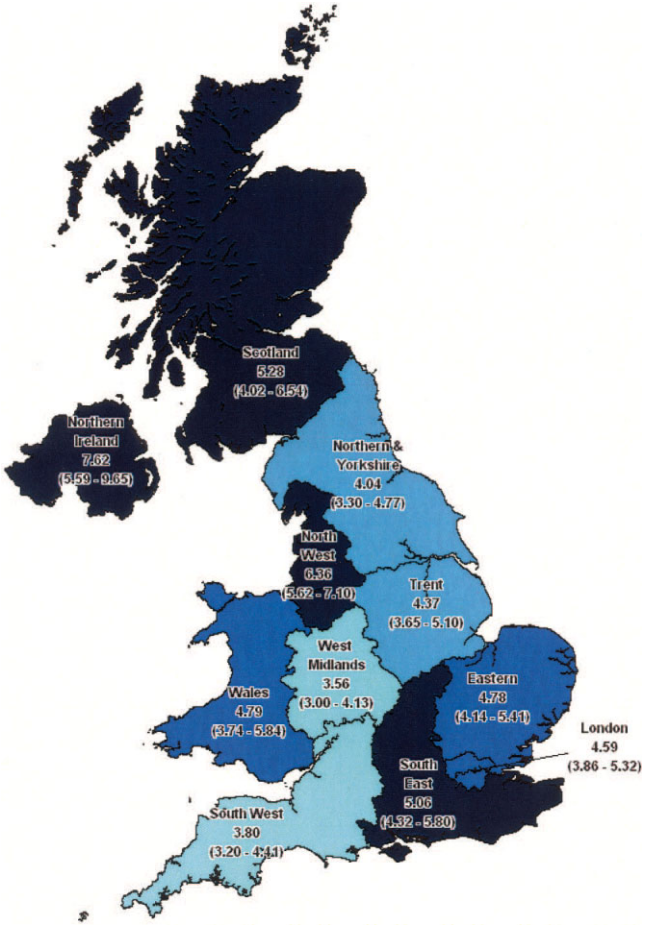

Figure 3. Age-standardized systemic lupus erythematosus incidence rates (per 100,000) by region.

Table 2. Standardized rate ratios and 95% confidence intervals (95% CIs) comparing region-specific age-standardized incidence rates with the overall systemic lupus erythematosus incidence for the UK

Region	Standardized rate ratio	95% CI
West Midlands	0.76	0.65, 0.88
South West	0.81	0.69, 0.94
Northern and Yorkshire	0.86	0.72, 1.02
Trent	0.93	0.79, 1.1
London	0.98	0.83, 1.15
Eastern	1.01	0.88, 1.17
Wales	1.02	0.81, 1.28
South East	1.07	0.92, 1.26
Scotland	1.12	0.87, 1.45
North West	1.35	1.17, 1.55
Northern Ireland	1.62	1.16, 2.27

the treatment of SLE or other rheumatic diseases: antimalarials (hydroxychloroquine, chloroquine, or quinacrine), azathioprine, cyclophosphamide, chlorambucil, cyclosporin, methotrexate, and leflunomide. The other category was rheumatoid arthritis (RA) disease-modifying antirheumatic drugs, which included 3 drugs used in rheumatology almost exclusively for the treatment of RA: penicillamine, gold, and sulfasalazine. This second category was used to indicate the degree of potential overlap or misclassification between patients with SLE and those with RA.

DISCUSSION

This large, population-based study included 1,638 patients with incident SLE and >33 million person-years of observation over a 10-year period. The overall age-standardized SLE incidence estimate for the UK was 4.71 (95% CI 4.48, 4.94). Sex-specific estimates were 7.89 per 100,000 (95% CI 7.46, 8.31) for females and 1.53 per 100,000 (95% CI 1.34, 1.71) for males. Unfortunately, data on race, ethnicity, and birth location are not available in the GPRD, although racial and ethnic differences in SLE incidence have been well described (1,12). However, the size of this study and uniformity of methodology throughout the study period and catchment area enable more precise characterization of sex- and age-specific incidence rates than previously available, as well as exploration of temporal and geographic trends.

Table 3. Prescription drugs used by systemic lupus erythematosus population (n = 1,638)*

Drug	Values†
NSAID	1,293 (78.9)
Corticosteroids	831 (50.7)
Antimalarials/immunosuppressive agents	793 (48.4)
Antimalarials	628 (38.3)
Azathioprine	226 (13.8)
Mycophenolate mofetil	6 (0.37)
Cyclophosphamide	30 (1.83)
Chlorambucil	4 (0.24)
Cyclosporin	20 (1.22)
Methotrexate	77 (4.70)
Leflunomide	2 (0.12)
DMARDs: RA	96 (5.86)
Penicillamine	18 (1.10)
Gold	13 (0.79)
Sulfasalazine	84 (5.13)

* Values are the number (percentage). NSAID = nonsteroidal anti-inflammatory drug; DMARDs = disease-modifying antirheumatic drugs; RA = rheumatoid arthritis.
† Percentages do not equal 100% because individuals could have had >1 drug.

The GPRD is well suited to the performance of disease incidence studies because it provides a representative sample of the UK population, and because general practitioners in the UK serve as the gatekeepers for clinical care for >98% of the population. The database systematically includes diagnostic codes, but not all signs, symptoms, or laboratory findings leading to a diagnosis, so there were insufficient data to determine whether all cases fulfilled the American College of Rheumatology (ACR) criteria (13,14). However, when patients are referred for specialty or tertiary care, the general practitioner electronically enters salient findings from the consultant visits into the GPRD. Therefore, even though the database is based in general practice, the diagnosis of SLE was typically established by a rheumatologist. Given access to universal health coverage in the UK, and given that only a very small segment of the population remains unregistered with the NHS, the GPRD is an efficient means for capturing a cross-section of patients with SLE covering the spectrum of disease severity, not just those requiring the most aggressive disease management. The major limitation of secondary data analysis studies, such as those based on the GPRD, is that detailed data relevant to the disease of interest may not be uniformly available (e.g., autoantibody profiles). In contrast, active surveillance studies must expend a great deal of resources identifying patients who have not reached tertiary care centers. However, many active surveillance studies have the advantage of being customized for disease-specific investigations, which enables a more thorough characterization of the study population.

Our SLE incidence data correspond to other published estimates, although they are not directly comparable because we were unable to utilize the ACR criteria as our case definition. However, the confidence intervals from the current study are tighter given the large sample size. As reviewed by Hochberg, international SLE incidence estimates have been reported (during the last half of the 1900s) to range from 1.8 to 7.6 per 100,000 (12). A systematic review published in 1997 reported a weighted mean SLE incidence, based on 10 studies, of 7.3 per 100,000 (15).

Two SLE surveillance studies from the UK were published in the 1990s. Johnson et al performed an active surveillance study based on the Metropolitan Districts of Birmingham and Solihull, England (1). They identified 33 new cases of SLE and estimated incidence among adults (ages ≥18 years) during calendar year 1991 to be 3.8 per 100,000 (95% CI 2.5, 5.1); sex-specific estimates were 6.8 per 100,000 (95% CI 4.4, 9.2) for females and 0.5 per 100,000 (95% CI 0.1, 1.7) for males. In the other UK study, Hopkinson et al calculated the SLE incidence for the Greater Nottingham metropolitan community for the pe-

riod of January 1989 through April 1990 (2). Based on 23 incident cases, the age-standardized annual incidence estimates (adjusted to the European Standard Population, which we also used) were 4.0 per 100,000 (95% CI 2.3, 5.6) overall, 6.5 per 100,000 (95% CI 3.5, 9.4) for females, and 1.5 per 100,000 (95% CI 0.02, 2.9) for males. Both of these studies used the ACR classification scheme (≥4 ACR criteria) for their case definitions (13). Our regional estimates are remarkably similar to the Birmingham and Nottingham estimates cited above. We calculated the age-adjusted incidence of SLE in the West Midlands (which encompasses Birmingham) to be 3.56 per 100,000 (95% CI 3.00, 4.13) and in Trent (which encompasses Nottingham) to be 4.37 per 100,000 (95% CI 3.65, 5.10).

The close comparability of our results with those of the active surveillance studies described above serves as external validation for our methodology and as evidence that the GPRD can be utilized for the study of SLE. Another recent study endeavored to estimate SLE incidence during the mid-1990s using the GPRD (16). However, this study used a highly exclusive requirement that patients have at least 3 years of available data to be eligible for the study population. This requirement potentially led to a biased estimate of SLE incidence: the overall estimated crude incidence of SLE in this previous study was 3.02 per 100,000 compared with 4.87 per 100,000 in our study. As Lewis et al (9) demonstrated, it is important to use a disease-specific empirical approach for the delineation of the time intervals used to distinguish prevalent from incident cases in the GPRD. We conducted such an analysis, modifying the approach of Lewis et al (9) (as described in the methods section). We therefore believe it is unlikely that existing cases of SLE were misclassified as new cases for the purposes of our study. Furthermore, the scope of the prior GPRD-based SLE incidence study was limited in that it did not include age-standardization, narrow age categories, or data on annual or region-specific rates.

We were able to classify age in 5-year bands, whereas many other studies are confined to using broader age categories due to smaller sample sizes. We found that peak incidence of SLE occurred in the 50–54 year age category for females and the 70–74 year category for males. Although SLE is often considered to be a disease affecting women in their reproductive years, other groups have likewise reported peak incidence among women to occur around or after menopause. Hopkinson et al reported a peak incidence of 18.4 per 100,000 women in the 50–59 year age group in the Nottingham population (2), and Jonsson et al reported a peak incidence of ~12.5 per 100,000 women ages 55–64 years in a southern Sweden population (17). We also included pediatric patients, whereas some other studies have been restricted to adult populations. Corresponding to the concept that autoimmune diseases tend to occur at a higher rate among females beginning around puberty, we documented that the sex-specific incidence rates became divergent with the 15–19 year age group, and that the ratio of female to male incidence started to equalize again around age 70–74 years.

Annual incidence rates from 1990 to 1999 were examined to discern whether there was a temporal trend. There was a small but insignificant increase of SLE incidence over the 10 years among females, but not males. Based on the linear trend among females in our study, the increase we observed equates to ~1 additional new case of SLE per 100,000 females over 10 years. Few studies have previously examined SLE incidence over time. Uramoto et al described a roughly 3.5-fold increase in SLE incidence in Rochester, Minnesota from 1950–1979 (1.51 per 100,000) to 1980–1992 (5.56 per 100,000) (18). The magnitude of increase was similar in both sexes, although slightly higher among females. The authors stated that improved recognition of mild disease over the 4 decades may have contributed to the observed increase in incidence. Unfortunately, an annualized rate of increase cannot be directly calculated based on their data. However, the level of increase that we detected among females appears to be substantially lower (approximately a 1.5-fold increase if extrapolating our data over 40 years). In a study based in Allegheny County, Pennsylvania from January 1985 through December 1990, McCarty et al reported stable incidence of disease over the 6-year period (average 2.4 per 100,000) (3). Considering these studies together, it appears that earlier indications of the increase in SLE incidence may have been partially an artifact of changing diagnostic capabilities, and that in more recent years data do not support substantial changes in SLE incidence.

If SLE incidence is indeed relatively stable, it would indicate that there have not been appreciable changes in exposure to potential etiologic agents over time. However, the slight suggestion that SLE incidence may be increasing at a higher rate among females versus males raises the question of whether there are risk factors for SLE with differential patterns of exposure between the sexes. It will be extremely useful to replicate incidence studies, using the same methodologies and population bases originally used, to determine how incidence measurements in the future compare with those that can be extrapolated from current data. Large databases, such as the GPRD, should be utilized to the extent possible, because a high level of statistical precision is necessary to detect small changes in rates.

Although temporal trends were not striking, geographic variations in SLE incidence were evident in our study. The region with the lowest age-standardized rate was the West Midlands (3.56 per 100,000; 95% CI 3.00, 4.13), and that with the highest was Northern Ireland (7.62 per 100,000; 95% CI 5.59, 9.65). Although SLE incidence has not been previously reported specifically for Northern Ireland, prevalence was estimated in 1993 to be 25.4 per 100,000 (95% CI 22.1, 28.7), which does not appear to be unusually high (19). It is unclear what factors may be involved with such geographic variation within the UK. Latitude gradients have been observed based on ecologic studies of other autoimmune diseases, such as multiple sclerosis (20,21) and RA (22), with increasing latitude being associated with higher rates of disease. We did not find a clear association between latitude and SLE incidence.

The biggest limitation of our study was the inability to apply ACR criteria to all cases for SLE classification, or to validate cases individually by performing detailed medical chart reviews. The ACR classification criteria would allow for more direct comparison with other studies that

have used the criteria, but their sensitivity was only 83% in an external population when compared with the gold standard of rheumatologist diagnosis (13). Therefore, it can be argued that our study fills an important gap in the data because it includes the subset of patients with SLE that would have been false negatives according to the ACR criteria. Nonetheless, it would have been preferable to also directly compare incidence estimates based on the ACR criteria had such data been uniformly available. Another limitation was the lack of data regarding laboratory results in the GPRD. Only 19 of the patients included in this study had mention of antinuclear antibody (ANA) or anti-DNA antibody positivity in their electronic records, which clearly precludes the ability to use autoantibody data in any fashion.

There were also limitations in using prescription drug data to assist in the validation of SLE diagnoses. Because drug exposure patterns vary considerably between patients with SLE, the lack of use of certain drugs cannot exclude the possibility that a person has SLE. Conversely, the use of certain antimalarials and immunosuppressive agents can be highly suggestive of a rheumatic disease diagnosis, but this information on its own cannot confirm an SLE diagnosis. The diagnosis and initial management of SLE occurs almost entirely in a hospital setting in the UK. However, even when drug treatments are initiated by a hospital consultant, continued long-term prescribing will be undertaken by the general practitioner and will therefore be recorded in the GPRD record. However, a small proportion of drugs will continue to be predominantly prescribed by hospital consultants, in particular immunosuppressive agents such as cyclophosphamide. Thus the GPRD record may not include all prescriptions related to a patient's SLE diagnosis.

Despite these issues, we attempted to estimate the extent of potential overlap between RA and SLE. Of the 1,638 patients with SLE, 203 (12.4%) also had a code for RA at some point in their medical record. Of these, 164 (80.8%) had the RA code prior to their SLE diagnosis. RA accompanied by ANA positivity or extraarticular involvement may infrequently be difficult to distinguish from SLE, although actual RA overlap ("rhupus") probably occurs in no more than 1.5% of patients with SLE (23,24) as cited by Wallace (25). It has also been observed that patients initially presenting with RA may evolve into having SLE after the initial prodrome. For the patients in our series who had an RA code prior to SLE diagnosis, it is possible that early features of their disease were mistaken for RA, but it is impossible to know how many patients with an RA code after their SLE diagnosis may have had RA but were initially misclassified as having SLE. Misclassification of RA as SLE is less likely than the converse because additional clinical features are required.

In summary, this study provides updated estimates for SLE incidence in the UK, with a high level of statistical precision and detailed investigation of time trends and geographic variation. To our knowledge, this surveillance study includes the largest number of incident SLE cases to date, particularly with regard to male patients with lupus. Population-based databases such as the GPRD are underutilized for the study of rheumatic diseases, and serve as important resources for cost-effective research that does not include referral biases inherent in tertiary care settings.

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AUTHOR CONTRIBUTIONS

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 design. Somers, Thomas, Smeeth, Schoonen, Hall.

Acquisition of data. Somers, Thomas, Smeeth, Hall.

Analysis and interpretation of data. Somers, Thomas, Schoonen, Hall.

Manuscript preparation. Somers, Thomas, Smeeth, Schoonen, Hall.

Statistical analysis. Somers.

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