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Original article

Health-care utilization and costs in adults with systemic lupus erythematosus in the United Kingdom: a real-world observational retrospective cohort analysis

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Abstract

Objective. The aim was to describe direct health-care costs for adults with SLE in the UK over time and by disease severity and encounter type.

Methods. Patients aged ≥18 years with SLE were identified using the linked Clinical Practice Research Datalink–Hospital Episode Statistics database from January 2005 to December 2017. Patients were classified as having mild, moderate or severe disease using an adapted claims-based algorithm based on prescriptions and co-morbid conditions. We estimated all-cause health-care costs and incremental costs associated with each year of follow-up compared with a baseline year, adjusting for age, sex, disease severity and co-morbid conditions (2017 UK pounds).

Results. We identified 802 patients; 369 (46.0%) with mild, 345 (43.0%) moderate and 88 (11.0%) severe disease. The mean all-cause cost increased in the 3 years before diagnosis, peaked in the first year after diagnosis and remained high. The adjusted total mean annual increase in costs per patient was £4476 (95% CI: £3809, £5143) greater in the year of diagnosis compared with the baseline year ($P < 0.0001$). The increase in costs per year was 4.7- and 1.6-fold higher among patients with severe SLE compared with those with mild and moderate SLE, respectively. Primary care utilization was the leading component of costs during the first year after diagnosis.

Conclusion. The health-care costs for patients with SLE in the UK are substantial, remain high after diagnosis and increase with increasing severity. Future research should assess whether earlier diagnosis and treatment might reduce disease severity and associated high health-care costs.

Key words: SLE and autoimmunity; health economics; primary care rheumatology; DMARDs; immunosuppressants

Key messages

- The direct costs of health care for patients with SLE in the UK are substantial.
- The cost to manage patients with moderate and severe SLE doubled 10 years after diagnosis.
- Patients with SLE have increasingly high health-care costs driven by primary care and prescription drugs.

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Introduction

SLE is a chronic inflammatory autoimmune disease characterized by alternating periods of increased disease activity, SLE flares, disease inactivity and remission. SLE affects multiple organs, including the skin, musculoskeletal, renal, pulmonary and nervous systems, leading to a wide range of clinical manifestations [1]. Common co-morbidities include cardiovascular disease [2, 3], stroke [4], osteoporosis [5] and infection [6]. Involvement of the renal system, referred to as LN [7], occurs in ~60% of patients [8]. Organ damage in lupus can occur as a direct consequence of the disease or can be associated with long-term CS treatment [9–12], which offers rapid symptom relief and effective short-term disease control [13] but is associated with significant adverse effects. The high prevalence of SLE-related co-morbidities and the adverse effects associated with treatment can result in significant health-care resource utilization and costs. SLE has been associated with high health-care utilization and costs in several countries [12, 14–16]; however, evidence is currently limited in the UK. Furthermore, long-term longitudinal trends in health-care utilization and costs among patients with SLE are lacking.

We assessed the health-care utilization (primary care, hospitalizations, outpatient visits and selected prescription drugs) and costs among patients with SLE over a 13-year period (2005–2017), using population-based data for the UK from the linked Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES) database.

Methods

Study design and data

This study adopted an observational, retrospective cohort design using the UK CPRD- and HES-linked health-care administrative database and the Office for National Statistics mortality files between 1 January 2005 and 31 December 2017. The CPRD has been used previously to describe the epidemiology of SLE in the UK [3, 17–27]. It contains routinely collected primary care medical records data for ~5.5 million registered patients from ~590 general practices covering 8% of the UK population and has been shown broadly to be representative of the demographic distribution of the UK population. Linkage to HES is possible for approximately half of patients in the CPRD primary care database. Hospital data on the length, type, reasons and current diagnoses for all UK National Health Service (NHS) inpatient hospital admissions and outpatient clinic attendances were captured regardless of payer (private or government) or geographical residency of the patient [28]. Approval for this study was granted by the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency on 8 March 2018 (CPRD00023132 PROTOCOL 17_281R).

Study population

Adult patients aged ≥18 years and older who had a verified SLE diagnosis in the linked CPRD–HES database during the inclusion period were included in the study. Patients were required to have ≥12 months of prior history in the CPRD GOLD database without a diagnosis of SLE to confirm an incident diagnosis. Patients with a first diagnosis (index date) between 1 January 2005 and 31 December 2017 with ≥12 months of follow-up were selected.

Identification of SLE was based on the presence of one or more definitive diagnostic read codes in CPRD GOLD, confirmed by using International Classification of Diseases, 10th Revision (ICD-10) diagnosis codes in the HES data, by evidence of referral to a rheumatologist, or by treatment with one or more SLE-targeted prescription medications (including oral prednisolone, immunosuppressive therapy and antimalarials) using an algorithm modified from Nightingale *et al.* [23] (Supplementary Table S1 and S2, available at *Rheumatology Advances in Practice* online). An index date was assigned corresponding to the earliest SLE diagnosis anywhere in the linked CPRD–HES dataset. Prescriptions for SLE treatment alone were not considered enough to identify SLE incidence; however, if an SLE-specific prescription was identified before the first SLE diagnosis, the time of that prescription was taken to be the index diagnosis date.

Patients were excluded if they had read codes indicating cutaneous, drug-induced or discoid lupus rather than systemic lupus; if they did not have a definite code anywhere in their CPRD record or in HES to confirm diagnosis; or if they transferred out of the practice before the index event date.

Study time line

Patients were followed for 3 years before diagnosis (i.e. before their index diagnosis date) until the earliest of the following events: end of study period; leaving the database/date of patient's last observed visit; or death. Person-time denominators were used to handle the varying lengths of follow-up of patients.

Assessment of disease severity

Disease severity (mild, moderate or severe) was defined using an algorithm adapted from a US retrospective, observational study [16], which combined SLE medications with SLE-related conditions (Supplementary Table S3, available at *Rheumatology Advances in Practice* online). The assigned disease severity was the highest severity experienced by a patient during a 1-year baseline period (12 months before index). SLE disease severity was defined as mild, moderate or severe. SLE was categorized as severe if treatment included CYC or an oral CS (prednisone-equivalent) prescription of ≥60 mg/day, or diagnosis of a severe co-morbid condition (e.g. end-stage renal disease, arterial/venous thrombosis). A moderate SLE category was assigned if treatment did not include CYC or oral CSs ≥60 mg/day, if there was a presence

of a diagnosis of a moderate co-morbid condition (e.g. nephritis, haemolytic anaemia), or if treatment included an oral CS prescription of ≥7.5 to <60 mg/day or use of an immunosuppressive agent (excluding CYC). When patients did not meet criteria for moderate or severe disease, they were assigned mild SLE.

Assessment of health-care utilization and costs

Mean all-cause health-care costs were estimated using standard unit costing methods [29, 30]. We focused on all-cause health-care costs in order to capture the cost associated with treatment of SLE, related co-morbidities and adverse effects from treatment. Primary care costs were calculated by multiplying the duration of each consultation by the average cost per minute based on a comprehensive estimate of general practice expenses [31]. Outpatient attendances with and without procedures were assigned the appropriate unit costs from the NHS Reference Costs publication [32] by treatment specialty. Inpatient care was costed using the Health Resource Group 2017–2018 Reference Costs Grouper software [33] before applying reference costs for each category of stay, taken from the UK National Cost Schedule [32]. Medications were costed by mapping CPRD to British National Formulary codes [34] data and multiplying the quantity prescribed by the unit costs from the British National Formulary. Manual checks were carried out to examine the validity of quantity, strength and dosage of prescriptions.

Mean all-cause health-care costs per patient per year were estimated for the pre- and post-diagnosis periods for identified patients with SLE. Costs were examined for ≤10 years after the index date as the sum of costs by type of care (primary care, hospital inpatient, outpatient and prescription drugs) in the respective year. For patients with >12 months of pre-index disease-free data, we considered ≤3 years before diagnosis as reference for post-diagnosis cost comparisons.

To account for inflation and variations in pricing over time, 2017 unit costs were applied to all years from the UK NHS perspective. Additional detail on the methods used to estimate costs for each type of care is provided in Supplementary Table S4, available at *Rheumatology Advances in Practice* online.

Data analysis

We used means, standard deviations and frequencies to describe the characteristics of patients with SLE overall and by disease severity. We estimated unadjusted means and the 25th, 50th (median) and 75th quartiles to summarize annual counts by type of utilization, including inpatient and outpatient hospital and primary care visits, in addition to prescriptions. We estimated the unadjusted mean all-cause health-care costs per patient per year in the 3 years before the index date to 10 years after by type of care (primary care, inpatient, outpatient hospital and prescription drugs) and by disease severity (mild, moderate and severe SLE).

We used generalized estimating equations (GEEs) to compare mean all-cause health-care costs in each year with the reference year (3 years before the index date), adjusting for age and disease severity. We used the third year before diagnosis as a reference, to avoid distortion by the higher expected costs in the 24 months preceeding formal SLE diagnosis. Specifically, previous research has demonstrated that patients present with symptoms that might not be recognized immediately; for example, Al Sawah *et al.* [35] reported an average of 2.1 years between first lupus symptoms and seeking of medical care. We then used a random-effects (random intercepts) model to estimate patient-specific annual trends in mean all-cause health-care costs, adjusting for age and disease severity. Only the main effect from these models (trend in costs) is shown, because the effects of covariates were very similar to the ones from the GEE models. All available years of data were included for patients with variable amounts of pre-diagnosis and follow-up information. All analyses were conducted using SAS software v.9.4 (SAS Institute, Cary, NC, USA).

Results

Descriptive characteristics

A total of 802 individuals with 12 months of pre- and post-index data were identified, of whom 369 (46.0%) had mild SLE, 345 (43.0%) moderate SLE and 88 (10.9%) severe SLE. Table 1 presents descriptive information on patient characteristics, overall and by disease severity (mild, moderate and severe). About 88% were female, and the average age was 48.4 years. Patients had an average of 5.2 years of follow-up data after diagnosis. Of these 802 patients, 682 (85%) had ≥3 years of health records prior to the index diagnosis of SLE, and 569 (71%) had ≥3 years of follow-up data after diagnosis.

Direct health-care utilization

The average number of primary care visits, inpatient stays, outpatient visits and prescriptions in the year of diagnosis was 28.4, 1.2, 8.8 and 46.9, respectively (Fig. 1). For all types of health-care use, there was a pattern of increasing utilization in the 3 years before diagnosis, with a peak during the year of diagnosis, after which health-care utilization remained fairly constant over 10 years of follow-up (Fig. 1; Supplementary Table S5, available at *Rheumatology Advances in Practice* online).

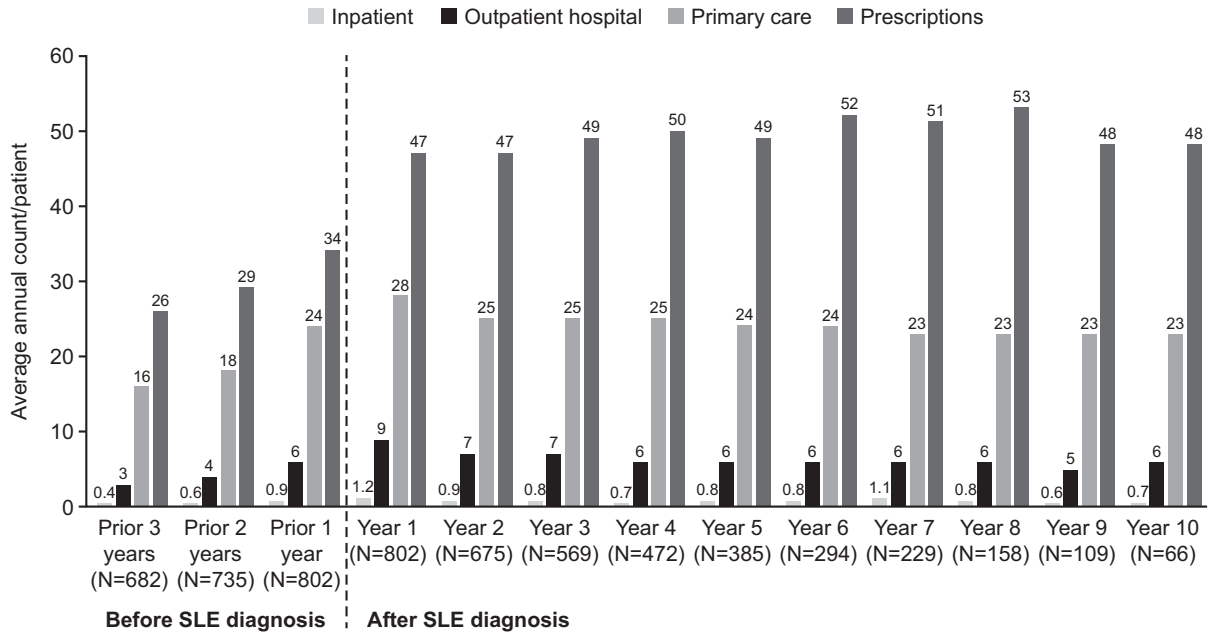
Mean all-cause direct health-care costs

The mean, unadjusted, all-cause health-care cost for patients with SLE increased progressively in the 3 years before diagnosis, and during the first year after diagnosis rose to £7532 (Table 2). The mean all-cause health-care cost held relatively steady throughout 7 years of follow-up. The highest health-care costs were observed

Table 1 Characteristics of patients with SLE (Clinical Practice Research Datalink–Hospital Episodes Statistics database, 2005–2017)

Characteristic	All patients (*n* = 802)	Mild disease (*n* = 369)	Moderate disease (*n* = 345)	Severe disease (*n* = 88)
Female, *n* (%)	709 (88.4)	326 (88.4)	311 (90.1)	72 (81.8)
Age at index, mean (S.D.), years	48.4 (15.3)	47.1 (14.4)	48.2 (15.7)	53.9 (16.0)
Age, *n* (%)				
18–44 years	348 (43.4)	169 (45.8)	152 (44.1)	27 (30.7)
45–64 years	321 (40.0)	149 (40.4)	134 (38.8)	38 (43.2)
≥65 years	133 (16.6)	51 (13.8)	59 (17.1)	23 (26.1)
Follow-up, years				
Mean (S.D.)	5.2 (3.0)	5.0 (3.0)	5.6 (3.0)	4.7 (2.8)

Fig. 1 Health-care utilization by category from 3 years before to 10 years after the index date (Clinical Practice Research Datalink–Hospital Episodes Statistics database, 2005–2017)



in years 8–10 (from fewer patient numbers) reaching £12 195 in year 10 (Table 2). The adjusted total mean annual increase in all-cause health-care costs from 3 years before the index date compared with each available follow-up year, adjusted for age, sex, disease severity and co-morbid conditions, followed a similar pattern. In the year after diagnosis, adjusted costs reached £4476 (95% CI: £3809, £5092; $P < 0.0001$) and remained higher in the years after diagnosis compared with the pre-diagnosis period (Table 2; Supplementary Table S6, available at *Rheumatology Advances in Practice* online).

Direct health-care costs by type of encounter

Primary care utilization was the leading component of health-care costs during the first year of diagnosis, representing an unadjusted mean cost of £2682 (Fig. 2). The proportion of health-care cost utilization attributable to primary care and the other utilization categories remained steady until year 6, after which the largest increase in health-care costs was observed (Fig. 2).

All-cause direct health-care costs by disease severity

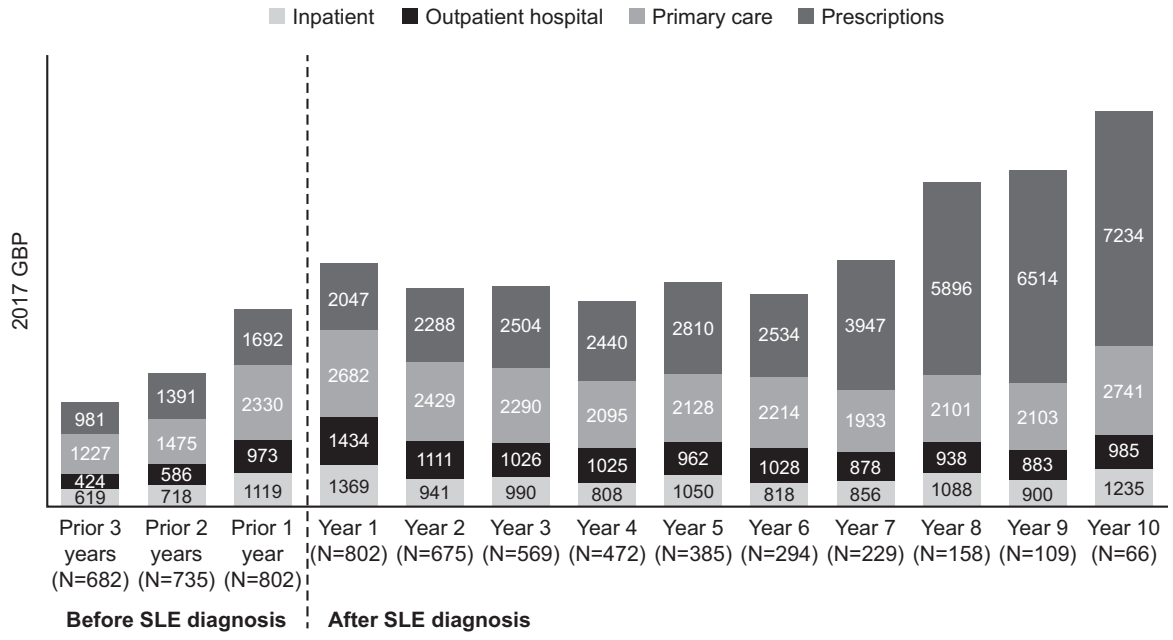
All-cause health-care costs increased over time for patients with severe and moderate SLE but remained relatively flat over the study period for patients with mild SLE. These unadjusted mean costs in the year of diagnosis were £14 125, £8323 and £5221, for severe, moderate and mild SLE, respectively (Fig. 3). Adjusted mean all-cause health-care costs were greater for patients

Table 2 Mean health-care costs from 3 years before to 10 years after the index date (Clinical Practice Research Datalink–Hospital Episodes Statistics database, 2005–2017)

Year (number of observations)	Unadjusted mean (s.d.) all-cause health-care costs per person per year, £[a]	Adjusted mean all-cause health-care costs *vs* 3 years before index[b]			
		Estimate, £[a,c]	95% CIs, £		*P* value
Before diagnosis					
Year −3 ($n = 682$)	3250 (4475)	–	–	–	–
Year −2 ($n = 735$)	4171 (6760)	1020	654	1386	<0.0001
Year −1 ($n = 802$)	6114 (8183)	3058	2545	3571	<0.0001
After diagnosis					
Year 1 ($n = 802$)	7532 (9634)	4476	3861	5092	<0.0001
Year 2 ($n = 675$)	6769 (11 502)	3898	3124	4672	<0.0001
Year 3 ($n = 569$)	6809 (12 325)	4172	3276	5069	<0.0001
Year 4 ($n = 472$)	6367 (10 028)	4043	3233	4854	<0.0001
Year 5 ($n = 385$)	6950 (11 442)	4950	3944	5957	<0.0001
Year 6 ($n = 294$)	6593 (8759)	4947	4014	5881	<0.0001
Year 7 ($n = 229$)	7614 (10 870)	6172	4889	7455	<0.0001
Year 8 ($n = 158$)	10 023 (14 807)	8506	6506	10 507	<0.0001
Year 9 ($n = 109$)	10 398 (17 777)	9239	6350	12 128	<0.0001
Year 10 ($n = 66$)	12 195 (20 286)	10 550	6592	14 508	<0.0001

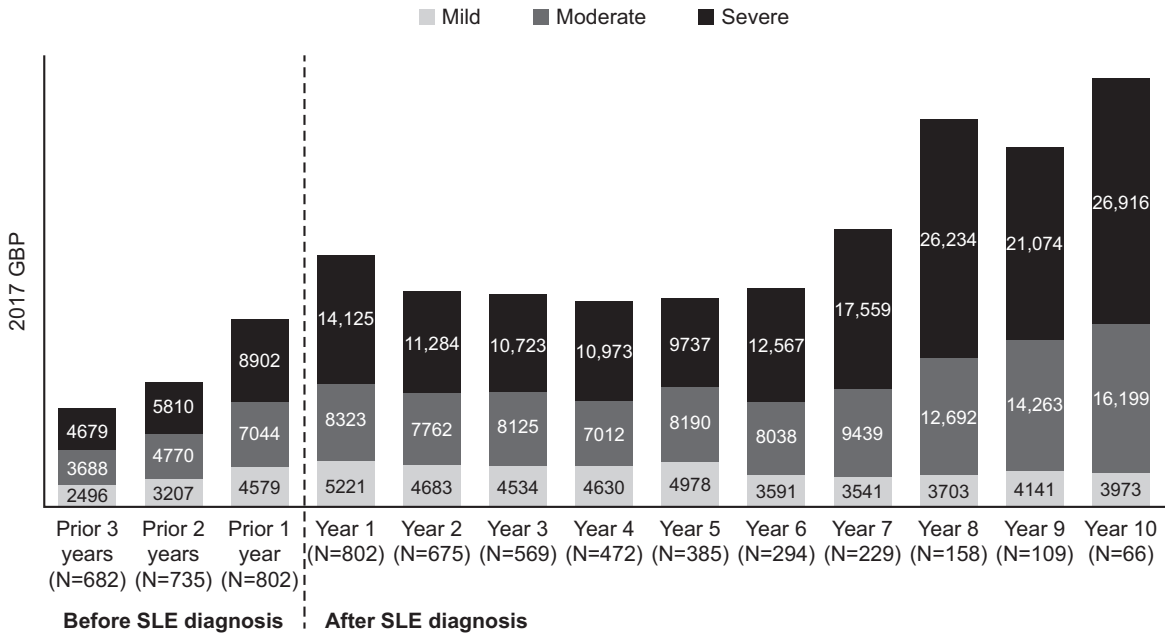
[a]Costs are expressed in 2017 UK pounds. [b]Person-time denominators were used to account for varying lengths of follow-up for individual patients.[c]Calculated using generalized estimating equations to compare mean all-cause health-care costs in each year with the reference year (3 years before the index date), adjusting for age and disease severity.

Fig. 2 Mean annual health-care costs by category before and after the index date (Clinical Practice Research Datalink–Hospital Episodes Statistics database, 2005–2017)



Unadjusted costs are expressed in 2017 UK pounds. Costs were estimated using a health system perspective and included direct medical resource use only. Other costs, such as out-of-pocket expenditure by patients and costs of informal and formal caregiving, were not captured. GBP: UK pounds.

FIG. 3 Mean annual total health-care costs by disease severity before and after the index date (Clinical Practice Research Datalink–Hospital Episodes Statistics database, 2005–2017)



Unadjusted costs are expressed in 2017 UK pounds. SLE disease severity was classified as mild, moderate or severe using an adapted claims-based algorithm that uses SLE-related conditions and medications. GBP: UK pounds.

TABLE 3 Change in total health-care costs per year by disease severity (Clinical Practice Research Datalink–Hospital Episodes Statistics database, 2005–2017)

Group	Change in all-cause health-care costs/year, £[a,b]	95% CIs, £		*P*-value
All patients ($n = 802$)	616	560	672	<0.0001
Mild SLE ($n = 369$)[c]	262	194	330	<0.0001
Moderate SLE ($n = 345$)[c]	788	699	878	<0.0001
Severe SLE ($n = 88$)[c]	1228	981	1476	<0.0001

[a]Costs are expressed in 2017 UK pounds. [b]Calculated using random intercept patient-specific models. [c]SLE disease severity was classified as mild, moderate or severe using an adapted claims-based algorithm that uses SLE-related conditions and medications.

with moderate *vs* mild SLE (£2786; 95% CI: £1737, £3835; $P < 0.0001$) and with severe *vs* mild SLE (£5207; 95% CI: £3277, £7138; $P < 0.0001$). Models of individual trajectories of mean all-cause health-care costs (Table 3) showed an increase of £616 (95% CI, £560, £672) per year, controlling for age, sex and disease severity. The increased costs were most pronounced among patients with severe SLE (£1228; 95% CI, £981, £1476), followed by moderate (£788; 95% CI, £699, £878) and mild SLE (£262; 95% CI, £194, £330).

Discussion

Direct health-care costs increased gradually in the 3 years before diagnosis, with high costs in the year after diagnosis, which remained relatively stable for several years, possibly reflecting the establishment of treatment regimens. Among patients who remained in the database, mean all-cause health-care costs rose sharply in follow-up years 8–10. This might represent costs associated with long-term SLE care and co-morbid disease; however, this rise should be viewed with caution given the smaller sample size in later years and

might be explained by outlier cases (e.g. those with organ damage as a result of SLE). Health-care costs increased with increasing severity. Patients with moderate or severe SLE consistently incurred greater all-cause health-care costs over time compared with patients with mild SLE during a 3-year pre-diagnosis period and after diagnosis, until 10 years of follow-up; costs doubled for patients with moderate and severe SLE, whereas the cost for mild SLE did not increase. The increase in adjusted mean all-cause health-care costs per year were 4.7- and 1.6-fold higher among patients with severe SLE compared with those with mild and moderate SLE, respectively.

There are limited data evaluating health-care costs associated with SLE over time. The substantial health-care costs found in the present study are consistent with studies from other countries that have reported a significant economic burden associated with SLE. A review of articles published between 2007 and 2013 reported high medical costs and high levels of unemployment and absenteeism associated with the disease [36]. An earlier review of 11 articles reported that average direct costs per patient-year ranged from $3735 to $14 410 (2008 US dollars), mostly driven by inpatient care [12]; in another review of 14 studies, the direct annual costs were between $2214 and $16 685 (2010 US dollars) [15]. A recent study also reported that the direct health-care costs associated with SLE were $13 038 (2013 Canadian dollars) [14]. Comparisons between the costs estimated in our study and those estimated in previous studies would need to account for the relevant currency exchange and inflation rates and should be made cautiously, owing to differences in the methodology used to estimate costs, in addition to structural differences in the underlying health-care delivery landscape across countries.

Our study also complements the limited literature on costs of SLE in the UK, which has been based on small samples. One cross-national comparison of patients in the US, Canada and UK, the Tri-Nation study [37], relied on self-reported data for 215 UK-based patients. Another study consisted of 86 patients recruited from four specialist rheumatology centres in England (the LUCIE study) [38, 39]. Detailed data on inpatient and specialist care were obtained from medical chart review for a cohort of patients with prevalent SLE over a follow-up period of 2 years. The LUCIE study was not designed to track either the impact on cost of a nascent diagnosis or the effect on costs over the medium to long term. Furthermore, primary care costs were not captured. We add to this literature by estimating costs across all settings covered by the NHS in the UK for an extended period before incident diagnosis of SLE and following patients for as long as data were available, $\leq$10 years after diagnosis.

In contrast to studies from other countries [12, 14–16], which found that the largest component of medical costs associated with SLE was inpatient hospitalization, we found that primary care utilization represented a larger share of the mean all-cause health-care cost compared with inpatient stays. This might reflect differences in care delivery, the generally lower costs of inpatient care in the UK compared with the USA, or differences among the costing methodologies used. Prescription medications made up a substantial and growing share of the mean all-cause cost over time in our study. This might be attributable to an increasing need to manage co-morbid conditions and/or the sequelae of SLE as the disease progresses.

Our study demonstrated an increase in adjusted mean all-cause health-care costs over time, with the increase in costs being most pronounced among patients with severe SLE, followed by those with moderate SLE. This is likely to reflect the extent of organ damage in these patients. Greater organ damage has been associated with increased health-care resource use [40]. Potentially, cost savings could be achieved by earlier diagnosis and treatment, including careful monitoring, to reduce the onset of irreversible organ damage and the occurrence of co-morbidities. This aligns with clinical guidelines that stress the goal of treatment aimed at improving long-term patient outcomes and quality of life, in addition to preventing damage accrual [41].

Observational studies using routinely collected electronic health record data are subject to several limitations, including the possibility of missing or misclassified data. To reduce potential misclassification of SLE diagnosis, we required that an SLE diagnosis be confirmed using an algorithm, modified from Nightingale *et al.* [23], to identify additional criteria in the patient record. It is possible to have underestimated the number of cases, because patients without active disease might have been excluded owing to lack of supporting data on treatment in the medical record. Electronic health records do not routinely include the information needed to generate established scores for disease severity and activity [23, 42]. However, we used a validated algorithm to assign patients to mild, moderate and severe disease categories in the year after index diagnosis [16, 43]. It is possible, given the criteria used in the algorithm, that we have underestimated the proportion of patients with severe SLE and overestimated those with moderate and mild disease. For example, one of the criteria for severe disease is a prescription of prednisolone of $>$60 mg/day. Other disease severity scores might use lower milligram per day thresholds for severe disease [44]. However, our analysis clearly shows an association between costs and severity.

CPRD GOLD linkage data are available for only 50% of contributing CPRD GOLD practices in the UK; therefore, health-care resource use is not available for all SLE patients captured in the CPRD database. Our study included health-care costs to the NHS only and did not include other societal costs, such as informal care (e.g. by family members and friends), out-of-pocket costs for non-prescription medications and other services not covered by the NHS, and a range of non-health-care costs, such as lost productivity. Other studies have

found these indirect costs in individuals with SLE to be much higher than the direct medical costs [45]. In addition, costs of biologics and drugs prescribed at specialty centres are not captured in the CPRD database. Together, these factors suggest that our results might be an underestimation of the true SLE costs in the UK.

Finally, our estimates are based on the missing-at-random assumption, implying that loss to follow-up was not related to health-care costs. As in most longitudinal studies, this assumption could not be tested directly, because cost data on patients after they left the dataset were not available. However, there is no reason to expect that leaving the dataset is associated with the severity of SLE and, therefore, with health-care utilization and cost of care.

Conclusions

Our findings suggest that the direct costs of health care for patients with SLE in the UK are substantial and increase in the years before and after diagnosis. Patients with moderate or severe SLE consistently incur greater all-cause health-care costs over time compared with patients with mild SLE during the 3 years before and after diagnosis, up to 10 years. For all patients, health-care costs gradually increase during the 3 years before diagnosis, suggesting that patients might initiate encounters with the health-care system in quest of a diagnosis. This study sheds light on the importance of disease management for the moderate to severe SLE patient. Earlier diagnosis and treatment might reduce disease severity and occurrence of co-morbidities and the high health-care costs associated with SLE.

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Data availability statement

This study is based in part on data from CPRD obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data are provided by patients and collected by the NHS as part of their care and support. The Office for National Statistics provided the mortality data. The interpretation and conclusions contained in this study are those of the authors alone. The authors do not own these data and hence are not permitted to share the data in the original form.

Supplementary data

Supplementary data are available at *Rheumatology Advances in Practice* online.

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