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Quantifying the burden of steroid-related damage in SLE in the Hopkins Lupus Cohort

Julie E Davidson,[1] Qinggong Fu,[2] Sapna Rao,[3] Laurence S Magder,[4] Michelle Petri[5]

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[1]Real World Evidence, GlaxoSmithKline R&D, Stockley Park, Uxbridge, UK
[2]Real World Evidence, GlaxoSmithKline R&D, Upper Providence, Pennsylvania, USA
[3]Real World Evidence, GlaxoSmithKline R&D, Research Triangle Park, North Carolina, USA
[4]Department of Epidemiology and Public Health, University of Maryland, Baltimore, Maryland, USA
[5]Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Correspondence to
Dr Julie E Davidson;
juliedson10@hotmail.com

ABSTRACT

Objective Corticosteroids are a mainstay of SLE treatment; however, cumulative steroid exposure may lead to organ damage. This study aimed to quantify the risk of new diabetes, hypertension, cataracts, osteoporosis and avascular necrosis that is attributable to cumulative corticosteroid exposure in SLE.

Methods Using data from the Hopkins Lupus Cohort, a longitudinal study of lupus activity, organ damage and quality of life in patients with SLE, five matched case–control analyses nested within a prospectively enrolled SLE cohort were performed. Two randomly selected controls were matched to each case using incidence-density sampling from defined risk sets. Attributable risk was calculated for steroid exposure (dose and duration, separately). Cumulative steroid dose was modelled as a four-level categorical variable using clinically relevant thresholds: 0 g (no exposure); >0 and <3.65 g (<10 mg/day for a year); ≥3.65 g and <18.25 g (1–5 years at 10 mg/day); and ≥18.25 g (>5 years at 10 mg/day).

Results Eligible cases were identified for diabetes (n=42), hypertension (n=79), cataract (n=132), osteoporosis (n=118) and avascular necrosis (n=38). The unadjusted OR for a one-category increase in cumulative steroid exposure ranged from 1.157 (cataract (0.889 to 1.506); p=0.2779) to 2.183 (avascular necrosis (1.162 to 4.103); p=0.0153). After adjusting for confounding variables, a one-category increase in the cumulative steroid dose was significantly associated with risk of cataract (OR (95% CI) 1.855 (1.190 to 2.892); p=0.0064) and osteoporosis (OR (95% CI) 1.604 (1.067 to 2.412); p=0.0232). ORs for avascular necrosis, diabetes and hypertension suggested a moderately increased risk (not significant). Duration of steroid exposure was not associated with any of the outcomes. The proportion of risk attributable to steroid exposure after adjustment for covariates was 0.711 for cataract and 0.540 for osteoporosis.

Conclusions Cumulative steroid exposure was associated with an increased risk of cataract and osteoporosis in patients with SLE.

Trial registration number NCT01616472.

INTRODUCTION

SLE is a chronic, autoimmune system disease with fluctuating disease activity.[1] Multiple organ systems can be affected, including musculoskeletal, skin and renal manifestations.[1] The accrual of long-term organ damage is multifactorial, with corticosteroids, active disease and comorbid factors playing roles.[2]

Corticosteroids are a mainstay of SLE therapy and are commonly administered due to their ability to reduce inflammatory disease activity.[3 4] Prior studies on SLE treatment have shown an association between steroid exposure and unwanted outcomes, such as the development of osteoporotic fractures, symptomatic coronary artery disease and cataracts.[1 2 4] However, quantitative evidence assessing the degree to which adverse events (AEs) observed in SLE are related to corticosteroid exposure, rather than other SLE-related factors, and the relationship between dose exposure or duration of exposure is lacking.[5]

The Hopkins Lupus Cohort is a longitudinal study of lupus activity, organ damage and quality of life (QoL) in patients with SLE, which has followed up patients since 1987.[6] The effects of corticosteroids have been examined previously in the Hopkins Lupus Cohort. The association between cumulative prednisone dose and each damage item, as measured by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (ACR) Damage Index (SDI) score, plus hypertension, was assessed in 539 patients.[1] Prednisone dose was associated with the development of osteoporotic fractures, symptomatic coronary artery disease and cataracts after adjustment for several factors. High-dose steroid (≥60 mg/day) treatment was associated with an increased risk of avascular necrosis and stroke. However, disease activity was not controlled for in this study.[1]

A separate study assessed the association between cumulative steroid dose and organ damage (new SDI score) in 525 patients with incident SLE in the Hopkins Lupus Cohort after adjusting for several variables.[3] Low doses of prednisone were not associated with an increased risk of irreversible organ

damage; however, the data did not rule out substantial increased risk due to steroids.

The pattern of damage accrual over time was studied in the Toronto Lupus Cohort, and damage was classified as independent of steroid exposure in certain organ systems (renal/pulmonary, gastrointestinal, skin, gonadal/malignancy), possibly related to steroid exposure in some organ systems (cardiovascular, peripheral vascular, neuropsychiatric, diabetes) or definitely related to steroid exposure in ocular and musculoskeletal systems.[7] The damage was described as being related to steroid exposure accumulated over time, accounting for a high proportion of the damage that occurred after 15 years.

The current study performed a series of case–control studies nested within a prospectively enrolled Hopkins Lupus Cohort. The objectives were to quantify the relationship between the organ damage items believed to be 'possibly' or 'definitely' related to steroid exposure and steroid exposure over time, and to calculate the attributable risk of these events to steroid exposure over other factors.

METHODS

Study population and setting

The Hopkins Lupus Cohort is a prospective, longitudinal study of disease activity, organ damage and QoL in patients with SLE followed-up since 1987.[6] The cohort database is continually updated and includes socio-demographic information, medical and reproductive history, comorbidities, SLE complications, and treatment. Data collected at each patient visit include SLE clinical activity indices, laboratory data and treatment (medication and dose). Informed written consent is obtained from all participants. The median time of follow-up in the cohort for patients recruited between 1992 and 2010 is approximately 5 years.

For the present analysis (GSK study 116015; WEUKBRE5716; NCT01616472), all cases and controls were selected from the subpopulation of patients diagnosed with SLE as per the ACR criteria within 5 years of cohort enrolment in order to reduce the extent of prior steroid exposure. Patients with no history of outcomes of interest prior to cohort entry were included; those with a gap of ≥24 months between cohort visits were excluded, due to uncertainty about their prednisone exposure during that period.

Study design

Five matched retrospective case–control analyses were performed, nested within the Hopkins Lupus Cohort.

Cases and controls

The case events of incident diabetes, hypertension, cataract, osteoporosis (with fracture or vertebral column collapse) and avascular necrosis were recorded prospectively at each visit as part of the standard of care SDI.[8] Case at-risk time (look-back period for steroid exposure, disease activity and other covariates) was defined, in years, as the period of time from SLE diagnosis until case event date.

Two randomly selected controls, with no case event during the period from SLE diagnosis, were selected from the defined risk set and matched to each case using incidence-density sampling. Controls were selected from the risk set defined as those with no case event during the time period (in years) from SLE diagnosis, which was equivalent to the period of case at-risk time (years). The control look-back period post cohort entry was thus matched in length to that of the case (eg, if the case event occurred 3 years after cohort entry, the control look-back period would have been the first 3 years following cohort entry). Eligible controls were also matched to cases on decade of SLE diagnosis. Case and control eligibility for each case–control risk set were assessed independently. Cases may have served as controls if matched to cases at a time prior to their own case date. Controls may have served as controls in more than one case–control analysis, but may not have served as controls to more than one case within a case–control analysis.

Exposure variables

Daily steroid dose was recorded at each clinic visit; this dose was assumed to have remained constant from the time of the previous visit date. Cumulative steroid dose was calculated as the sum of the total prescribed steroid dose since SLE diagnosis and the total dose was summed across all exposure periods. All steroids were converted to prednisone equivalent. Cumulative years of steroid exposure were calculated by summing all steroid-exposed days (at any prednisone or prednisone-equivalent dose >0 mg) since SLE diagnosis and dividing by 365.25.

The exposure measures of cumulative duration were modelled as quartiles of years of exposure (based on the distribution of duration across the total cohort), while cumulative steroid dose (g) was modelled as a four-level categorical variable with cut-points based on clinical relevance: 0 g (corresponding to no exposure); >0 and <3.65 g (corresponding to <10 mg/day for a year); ≥3.65 g and <18.25 g (corresponding to 1–5 years at 10 mg/day); and ≥18.25 g (corresponding to >5 years at 10 mg/day). In order to better understand the relationship between steroid exposure and outcomes, other measures of steroid exposure were explored (cumulative dose and cumulative duration as continuous variables, highest daily steroid dose in milligram, cumulative years of exposure to daily doses >7.5 mg/day and cumulative years of exposure to daily doses >20 mg/day).

The following potential confounders of the relationship between steroid and outcomes were explored in each case–control model: age (years) at case date, sex, race/ethnicity, total SDI score at case date (excluding the score for the case outcome of interest), history of cyclophosphamide or other immunosuppressive agents, and years of education. Disease activity (SLE Disease Activity Index (SLEDAI)),[9] recorded at each study visit, was included as a key covariate given the strong association

between disease activity and steroid exposure. SLEDAI was modelled in two ways: a cumulative score (assuming a daily activity exposure level by carrying forward SLEDAI score between visits and summing the daily scores up to case date), in order to provide a comparable measure of accumulated insult over time to cumulative steroid exposure, and using the adjusted mean SLEDAI score[10] as a measure of average exposure over the study period. The diabetes case–control comparisons also included additional adjustment for obesity (at first clinic visit), total cholesterol, statin use (at first clinic visit) and hypertension (at first clinic visit). Hypertension case–control comparisons included additional adjustment for obesity and history of SLE renal activity (SLEDAI score).

Statistical analyses

Univariate conditional logistic regression models were used to explore the relationship between steroid exposure measures, potential covariates and case outcomes for each case–control analysis. Where the regression models indicated a significant effect of steroids, the proportion of cases considered to result from exposure to (1) cumulative steroid dose and (2) duration of steroid exposure in SLE was calculated using the method described by Bruzzi *et al*.[11] This method allows for calculation of attributable risk for a single variable, adjusted for other covariates, using coefficients from multiple conditional logistic regression models and frequency of the exposure in cases only. In sensitivity analyses, the possibility of a lagged effect of steroids on outcomes was explored in univariate conditional logistic regression models by censoring cases that occurred within 1 and within 5 years of first steroid exposure that might have been unlikely as a result of cumulative steroid exposure (models repeated for each lag period). Non-linearity in the association between continuous steroid exposure measures and case status was explored using univariate conditional logistic regression models with quadratic terms: cumulative steroid dose $(g)^2$ and exposure duration $(years)^2$ (separate models).

RESULTS

Patient population

Each matched case–control study had a fairly low number of cases (diabetes n=42, hypertension n=79, cataract n=132, osteoporosis n=118, avascular necrosis n=38); thus, the power to detect smaller ORs was limited. The majority of patients were female (73.7%–95.2%, across all cases), with a mean age range of 37.3–51.7 years (table 1). The mean cumulative SLEDAI ranged from 46.5 to 93.7 and the mean SDI score from 0.4 to 1.1. The total cumulative dose of steroids ranged from 6.1 to 11.1 g, with a mean number of years at >7.5 mg/day ranging from 1.4 to 2.7.

Unadjusted conditional logistic regression analyses

The univariate OR ranged in magnitude from 1.157 (cataract case–control comparison 95% CI (0.889 to 1.506); p=0.2779) to 2.183 (avascular necrosis 95% CI (1.162 to 4.103); p=0.0153) for cumulative dose (modelled as a four-level categorical variable), and 0.698 (diabetes case–control comparison 95% CI (0.134 to 3.643); p=0.670) to 1.227 (avascular necrosis case–control comparison 95% CI (0.408 to 3.692); p=0.7157) for duration of steroid exposure in years (quartiles). In the univariate analysis, cumulative steroid dose was found to be significantly associated with hypertension (OR (95% CI) 1.689 (1.160 to 2.459); p=0.0062), osteoporosis (OR (95% CI) 1.339 (1.019 to 1.759); p=0.0363) and avascular necrosis (OR (95% CI) 2.183 (1.162 to 4.103); p=0.0153), whereas duration of steroid exposure was not statistically significantly associated with any of the disease outcomes.

Multiple conditional logistic regression analyses

After adjustment for covariates, cumulative steroid dose was found to be significantly associated with risk for cataract (OR (95% CI) 1.855 (1.190 to 2.892); p=0.0064) and osteoporosis with fracture or vertebral column collapse (OR (95% CI) 1.604 (1.067 to 2.412); p=0.0232) (table 2). The association between cumulative steroid dose and the other study outcomes of avascular necrosis, diabetes and hypertension was consistent with the cataract and osteoporosis findings (ORs ranging from 1.427 to 1.618 were suggestive of a moderately increased risk), although these associations did not reach statistical significance. When the cumulative dose categories were modelled using dummy variables with 0 g (corresponding to no exposure) as the reference category adjusting for covariates, a non-significantly increasing monotonic response with increasing steroid dose was observed for hypertension and osteoporosis outcomes. No trend was observed for diabetes, cataract or avascular necrosis outcomes.

Cumulative duration of steroid exposure at any dose (modelled as quartiles of years exposed based on the distribution of steroid exposure duration in the entire Hopkins Lupus Cohort study population as quartile 1=1.17, quartile 2=3.21, quartile 3=3.21 and quartile 4=23.08) was not found to be statistically associated with any of the five outcomes in the univariate or the adjusted models (table 3). When the cumulative duration of steroid exposure was modelled using dummy variables with quartile 1 (1.17 years) as the reference category and adjusting for covariates, no trend was observed for any of the outcomes.

The attributable risk was calculated for the outcomes of cataract and osteoporosis only and for cumulative steroid dose (g) exposure based on statistically significant results from multiple conditional logistic regression results (table 4).

Sensitivity analyses

There was a marginal increase in the association of steroid dose with hypertension (OR (95% CI) 1.771 (1.172 to 2.678); p=0.0067) and avascular necrosis (OR (95% CI) 2.345 (1.164 to 4.727); p=0.0171) when a 1-year lag period was used. However, when compared with the univariate conditional logistic regression models without

Table 1 Patient demographics and clinical characteristics

	Diabetes		Hypertension		Cataract		Osteoporosis		Avascular necrosis	
Characteristics	Cases (n=42)	Controls (n=86)	Cases (n=79)	Controls (n=159)	Cases (n=132)	Controls (n=263)	Cases (n=118)	Controls (n=231)	Cases (n=38)	Controls (n=76)
Continuous variables, mean (SD)										
Age, years	47.1 (11.31)	40.3 (11.60)	38.2 (12.18)	37.3 (12.35)	51.7 (12.34)	39.9 (11.78)	48.5 (12.41)	41.3 (12.50)	40.6 (11.16)	42.7 (12.51)
Years of education	12.5 (2.47)*	13.1 (2.58)	13.3 (3.21)†	13.8 (2.61)‡	13.6 (2.98)§	14.0 (2.71)¶	13.8 (3.12)**	14.1 (3.08)††	13.5 (2.79)‡‡	13.4 (3.15)
Time since SLE diagnosis, years	12.8 (6.02)	14.5 (6.38)	13.8 (6.45)	12.6 (5.94)	11.7 (6.06)	11.9 (6.09)	12.2 (6.01)	12.8 (5.76)	11.6 (6.62)	12.4 (6.29)
Cumulative SLEDAI	77.3 (88.36)	89.9 (93.20)	60.3 (62.90)	46.5 (83.76)	76.5 (91.68)	68.1 (94.37)	88.6 (93.64)	69.1 (82.86)	93.7 (106.78)	66.6 (84.77)
Adjusted mean SLEDAI	2.6 (2.01)	2.8 (2.35)	4.3 (3.29)	3.3 (2.82)	2.7 (2.12)	2.8 (2.62)	2.7 (1.98)	2.5 (1.92)	3.3 (1.84)	2.6 (2.26)
Total cumulative dose of steroids, g	10.0 (13.06)	10.3 (14.30)	7.8 (9.35)	6.1 (11.72)	9.5 (13.77)	7.8 (12.13)	10.4 (14.03)	8.5 (12.99)	11.1 (13.32)	8.2 (13.32)
Steroid-exposed years, total	6.4 (5.30)	6.4 (5.18)	2.8 (2.56)	2.7 (2.61)	6.0 (5.35)	5.3 (4.99)	6.0 (4.73)	5.9 (4.64)	4.5 (4.81)	4.8 (4.79)
At >7.5 mg/day	2.3 (2.54)	2.7 (2.75)	1.4 (1.61)	1.6 (2.20)	2.4 (3.21)	2.0 (2.73)	2.4 (2.81)	2.4 (2.99)	2.4 (2.84)	2.4 (3.18)
At >20 mg/day	0.6 (0.84)	0.8 (1.02)	0.3 (0.22)	0.4 (0.60)	0.5 (0.54)	0.5 (0.50)	0.7 (0.76)	0.4 (0.40)	0.4 (0.52)	0.4 (0.26)
Highest daily steroid dose, mg	29.5 (54.84)	29.7 (80.05)	28.8 (42.46)	17.7 (19.51)	23.9 (24.36)	21.8 (21.64)	25.4 (22.08)	25.1 (56.54)	33.4 (23.97)	21.2 (22.05)
SDI score§§	1.0 (1.19)	1.1 (1.63)	0.6 (1.19)	0.4 (0.80)	1.0 (1.38)	0.6 (1.15)	1.1 (1.36)	0.7 (1.21)	0.9 (1.33)	0.6 (1.08)
Categorical variables, n (%)										
Gender, female	40 (95.2)	80 (93.0)	74 (93.7)	145 (91.2)	123 (93.2)	239 (90.9)	111 (94.1)	210 (90.9)	28 (73.7)	70 (92.1)
Black	21 (50.0)	33 (38.4)	50 (63.3)	61 (38.4)	52 (39.4)	107 (40.7)	29 (24.6)	109 (47.2)	16 (42.1)	26 (34.2)
White	18 (42.9)	50 (58.1)	27 (34.2)	93 (58.5)	71 (53.8)	140 (53.2)	83 (70.3)	112 (48.5)	20 (52.6)	47 (61.8)
Asian	2 (4.8)	1 (1.2)	2 (2.5)	3 (1.9)	6 (4.6)	8 (3.0)	2 (1.7)	6 (2.6)	1 (2.6)	0 (0)
Other	1 (2.4)	2 (2.3)	0 (0)	2 (1.3)	3 (2.3)	8 (3.0)	4 (3.4)	4 (1.7)	1 (2.6)	3 (4.0)
Ever steroid-exposed	33 (78.6)	63 (73.3)	67 (84.8)	113 (71.1)	108 (81.8)	191 (72.6)	96 (81.4)	170 (73.6)	33 (86.8)	55 (72.4)
Cyclophosphamide or other immunosuppressant in the last 12 months of at-risk time	16 (38.1)	23 (26.7)	21 (26.6)	30 (18.9)	51 (38.6)	74 (28.1)	50 (42.4)	67 (29.0)	19 (50.0)	27 (35.5)
Obesity prior to case date	32 (76.2)	61 (70.9)	58 (73.4)	91 (57.2)	87 (65.9)	164 (62.4)	84 (71.2)	148 (64.1)	31 (81.6)	62 (81.6)
Renal activity prior to case date	20 (47.6)	48 (55.8)	42 (53.2)	47 (29.6)	57 (43.2)	128 (48.7)	64 (54.2)	105 (45.5)	23 (60.5)	39 (51.3)
Renal activity in the last 12 months of at-risk time	15 (35.7)	17 (19.8)	26 (32.9)	22 (13.8)	18 (13.6)	52 (19.8)	19 (16.1)	29 (12.6)	13 (34.2)	16 (21.1)

*n=41.
†n=77.
‡n=156.
§n=130.
¶n=262.
**n=117.
††n=229.
‡‡n=36.
§§Excluding case outcome score.
SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI, SLE Disease Activity Index.

Table 2 Multiple conditional regression models: association between categories of cumulative steroid dose (g) and outcome

Study variable, OR (95% CI)	Diabetes	Hypertension	Cataracts	Osteoporosis	Avascular necrosis
Cumulative steroids dose categories, g	1.618 (0.790 to 3.312)	1.544 (0.963 to 2.509)	1.855 (1.190 to 2.892)**	1.604 (1.067 to 2.412)*	1.427 (0.580 to 3.512)
Age, years	1.069 (1.017 to 1.124)**	1.001 (0.973 to 1.029)	1.116 (1.080 to 1.153)***	1.057 (1.031 to 1.084)***	0.948 (0.895 to 1.003)
Gender, female	2.582 (0.237 to 28.192)	1.597 (0.480 to 5.310)	1.900 (0.701 to 5.151)	4.004 (1.209 to 13.267)*	0.068 (0.011 to 0.414)**
Black	1.379 (0.436 to 4.368)	2.408 (1.213 to 4.777)*	0.900 (0.510 to 1.588)	0.230 (0.119 to 0.443)***	1.088 (0.338 to 3.506)
Cyclophosphamide or other immunosuppressant in the last 12 months of at-risk time	2.666 (0.665 to 10.695)	0.772 (0.326 to 1.830)	1.391 (0.746 to 2.594)	1.256 (0.669 to 2.358)	2.516 (0.538 to 11.755)
Time since SLE diagnosis, years	0.838 (0.729 to 0.964)*	1.056 (0.995 to 1.122)	0.974 (0.896 to 1.058)	0.965 (0.894 to 1.043)	0.850 (0.730 to 0.990)*
SDI score	0.791 (0.517 to 1.211)	1.212 (0.833 to 1.763)	1.064 (0.829 to 1.367)	1.051 (0.850 to 1.300)	1.353 (0.770 to 2.378)
Cumulative SLEDAI	0.994 (0.985 to 1.004)	0.997 (0.992 to 1.002)	0.999 (0.995 to 1.003)	1.005 (1.000 to 1.009)*	1.002 (0.995 to 1.009)
Years of education	0.937 (0.724 to 1.214)	1.042 (0.923 to 1.176)	0.954 (0.863 to 1.053)	0.932 (0.849 to 1.023)	0.942 (0.773 to 1.149)
History of renal activity	–	2.125 (0.972 to 4.646)	–	–	–
Obesity	1.131 (0.311 to 4.116)	–	–	–	–
Total cholesterol	1.002 (0.993 to 1.012)	1.004 (0.999 to 1.009)	–	–	–
Statin use	1.327 (0.293 to 6.023)	–	–	–	–
Hypertension	1.544 (0.410 to 5.823)	–	–	–	–

*p<0.05, **p<0.01, ***p<0.001.
SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI, SLE Disease Activity Index.

Table 3 Multiple conditional logistic regression models: association between quartiles of cumulative steroid duration (years) and outcome

Study variable, OR (95% CI)	Diabetes	Hypertension	Cataracts	Osteoporosis	Avascular necrosis
Duration of steroid exposure quartiles, years	3.682 (0.234 to 57.836)	0.788 (0.433 to 1.436)	0.825 (0.383 to 1.775)	0.777 (0.317 to 1.902)	0.714 (0.148 to 3.442)
Age, years	1.074 (1.019 to 1.132)**	0.999 (0.972 to 1.027)	1.102 (1.071 to 1.135)***	1.052 (1.027 to 1.077)***	0.945 (0.894 to 1.000)*
Gender, female	2.431 (0.211 to 27.988)	1.591 (0.486 to 5.208)	1.612 (0.627 to 4.144)	3.130 (0.977 to 10.030)	0.062 (0.011 to 0.363)**
Black	1.668 (0.507 to 5.487)	2.602 (1.300 to 5.209)**	0.952 (0.543 to 1.670)	0.260 (0.137 to 0.496)***	1.360 (0.437 to 4.229)
Cyclophosphamide or other immunosuppressants in the last 12 months of at-risk time	3.404 (0.918 to 12.623)	0.927 (0.394 to 2.179)	1.708 (0.932 to 3.132)	1.586 (0.877 to 2.869)	2.778 (0.638 to 12.093)
Time since SLE diagnosis years	0.821 (0.702 to 0.959)*	1.062 (0.999 to 1.129)	0.983 (0.909 to 1.063)	0.974 (0.903 to 1.050)	0.846 (0.727 to 0.985)*
SDI score	0.809 (0.527 to 1.241)	1.238 (0.852 to 1.800)	1.123 (0.880 to 1.434)	1.129 (0.917 to 1.390)	1.495 (0.856 to 2.611)
Cumulative SLEDAI	0.997 (0.988 to 1.006)	0.998 (0.993 to 1.004)	1.001 (0.997 to 1.005)	1.006 (1.002 to 1.010)**	1.003 (0.996 to 1.010)
Years of education	0.946 (0.738 to 1.212)	1.048 (0.931 to 1.181)	0.948 (0.859 to 1.045)	0.940 (0.857 to 1.030)	0.949 (0.778 to 1.158)
History of renal activity ever	–	2.357 (1.086 to 5.116)*	–	–	–
Obesity	1.112 (0.290 to 4.260)	–	–	–	–
Total cholesterol	1.002 (0.994 to 1.011)	1.004 (0.999 to 1.009)	–	–	–
Statin use	1.337 (0.289 to 6.195)	–	–	–	–
Hypertension	1.468 (0.385 to 5.598)	–	–	–	–

*p<0.05, **p<0.01, ***p<0.001.
SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI, SLE Disease Activity Index.

Table 4 Attributable risk for proportion of cataracts and osteoporosis cases attributable to steroid exposure

Cumulative steroid dose categories, g	Cataracts			Osteoporosis		
	Exposed cases, n	Adjusted OR	Attributable risk	Exposed cases, n	Adjusted OR	Attributable risk
0 g	24	1.000	0.711	22	1.000	0.540
>0 and <3.65 g	44	4.401		31	1.234	
≥3.65 and <18.25 g	40	9.688		45	6.632	
≥18.25 g	24	586.187		20	58.164	

censoring for hypertension and avascular necrosis, there was only a marginal increase in the effect size. Duration of steroid exposure (years) did not affect any of the outcomes irrespective of the two lagging periods.

Steroid dose was found to have a non-linear association with hypertension (OR (95% CI) for a quadratic term in the model, 0.997 (0.995 to 1.00); p=0.0033) and avascular necrosis (OR (95% CI) for a quadratic term in the model, 0.998 (0.996 to 1.000); p=0.0300). The quadratic terms were found to have OR <1.0, indicating that the risk of hypertension and avascular necrosis plateaued over time.

Steroid duration was not found to have a non-linear association with any of the case outcomes.

DISCUSSION

SLE disease activity is known to be associated with long-term organ damage and linked to steroid exposure.[8 12 13] A quantitative review of published studies highlighted a strong correlation between avascular necrosis rate and total daily corticosteroid dose almost 30 years ago, and it is recommended to closely monitor patients with SLE with MRI.[14 15] However, certain types of organ damage might be more likely to be caused by disease activity and/or steroid exposure.[16] Corticosteroid risks have been identified in studies from other diseases and are included on product labels, but there remains a lack of quantitative information on the exact risks conferred, populations at highest risk and how risks might be mitigated through prescribing practice (eg, avoiding intensive treatment above a given level of mg/day or avoiding long, unremitting duration of exposure). In particular, the risk–benefit considerations of corticosteroid use must be evaluated specifically in SLE populations, where the risk of poor outcomes due to uncontrolled acute inflammatory disease activity should be considered against the risk of steroid-related AEs.

This study was designed to assess the effect of different patterns of steroid use on five SLE damage outcomes believed to be largely or partially caused by steroid exposure, and to quantify the proportion of the risk of these outcomes in SLE that could be attributable to cumulative steroid exposure. The study findings indicate that the risk of cumulative steroid dose may be more important to consider than duration of exposure.

Zonana-Nacach *et al*[1] performed a survival analysis using 539 incident patients with SLE enrolled in the Hopkins Lupus Cohort.[1] The authors found that cumulative prednisone dose was associated with the development of osteoporotic fractures (rate ratio (RR) (95% CI) 2.5 (1.7 to 3.7)) and cataracts (RR (95% CI) 1.9 (1.4 to 2.5)) for a 10-year exposure to 10 mg per day of prednisone, after adjustment for age, race and sex. The RR for hypertension, diabetes and avascular necrosis was ≥1 but not statistically significant. High-dose steroid (≥60 mg/day) use was associated with increased risk of avascular necrosis (RR (95% CI) 1.2 (1.1 to 1.4)). While our study used a matched case-control design with adjustment for a number of covariates, including disease activity, Zonana-Nacach *et al*[1] conducted a survival analysis adjusting for age, race and sex, but not disease activity. Despite the differences in study design, our results were consistent with findings from this paper. The increase in number of covariates (especially disease activity accounting for some of the steroid dose effect) may have accounted for the differences in strength of association between these studies.

Similar to the current study, the prior study by the coauthors in the Hopkins Lupus Cohort looked at the effect of the mean prior prednisone dose (≥7.5 mg/day vs <7.5 mg/day) on the overall damage and the specific outcomes of cataract and fracture.[2] These results found that the risk of cataract and fracture increased over two times in patients with a mean dose ≥7.5 mg/day compared with <7.5 mg/day. In another previous analysis restricted to patients under 60 years of age, disease activity, hypertension, duration of SLE, diabetes, smoking, cholesterol, renal involvement, immunological profile and medication history were adjusted for; cumulative prednisone dose, equivalent to 10 mg/day (3–10 years), increased the risk of cataract three times, while exposure equivalent to 10 mg/day for >10 years resulted in a fourfold increase in risk.[17] The current study further substantiates these findings by exploring the risk associated with different potential toxicological models of steroid exposure.

A key challenge for this study was to disentangle the effects of SLE disease activity and steroid exposure on the study outcomes. In addition, one of the key limitations of this study, or of any study that attempts to assess the association between steroid exposure and organ damage outcomes in SLE, is the potential for confounding by SLE disease activity and/or disease severity (or treatments associated with severe disease). These two factors are

closely related, as spikes in disease activity will often lead to an increase in steroid dose that should, in turn, lead to a decrease in disease activity.

Average disease activity has been shown to be associated with risk of new organ damage in SLE in several studies.[8 12] Previous studies have found steroid exposure to be significantly associated with organ damage in SLE.[10] The SDI score for SLE-related organ damage was developed to capture all major types of organ damage known to occur in SLE.[3]

In this study, cumulative duration of steroid exposure in years was lower than expected given that these SDI damage outcomes were thought to be largely steroid-related. The correlation between the average disease activity and the average daily steroid dose over a 1-year period in these data was <0.7. Therefore, it is believed that there should still be sufficient residual variance associated with steroid exposure for analysis, particularly given the enrichment for potentially steroid-associated case outcomes.

To account for possible confounding by severity, we adjusted for total prior organ damage burden (SDI score minus other than case outcome element), disease activity and exposure to immunosuppressive medications. Immunosuppressants are often used in severe, refractory cases of SLE, when steroid therapy plus first-line therapies such as antimalarials have failed to induce a response.

The Hopkins Lupus Cohort is a large and well-established lupus cohort with long-term outcome and steroid data available. Case numbers were small in this study as the study inclusion was restricted to SLE classification, as per the ACR criteria, in the 5 years prior to or after cohort entry, in order to establish a temporal relationship between exposure and outcome. The number of cases could have affected the stability of estimates from the fully adjusted model. To test any effect of the conservative assumption of at least 10 events per predictor variable on stability of estimates, we conducted a simplified analysis with fewer covariates in the adjusted model. While estimates from this simplified model changed the magnitude of effect (data not shown), it did not change the direction of association. The small number of events also limits the power to detect moderate associations for some conditions. For example, the CI for the OR for the relationship between a one-category increase in cumulative prednisone dose and avascular necrosis ranges from 0.6 to 3.5, indicating that, although there is no strong evidence in the data against the hypothesis that the relationship is null, the data are also at least marginally consistent with an OR as high as 3.5.

Another limitation of the study is that the Hopkins Lupus Cohort is based in the Baltimore catchment settlement, which is not necessarily representative in terms of demographic make-up of the entire US population. Lupus treatment and lupus care practices in this tertiary-referral lupus specialist centre may not reflect SLE treatment and care practices in other settings. Finally, the dose of glucocorticoids was recorded at the start of a new clinic visit via a question to patients 'what is your current dose of steroid?' An assumption was made that the dose had been constant since the previous visit. Although this captured the actual dose rather than the dose prescribed at the previous visit, in the event that the patient had downtitrated their dose since the last visit, this could have led to an underestimation of true dose exposure. Nonetheless, this study is the first of its kind to quantify the relationship between cumulative steroid exposure and the specific SDI damage outcomes that have been believed to be largely related to steroid exposure in patients with SLE,[7] after adjustment for key covariates.

Overall, the study showed that cumulative steroid dose was associated with a significantly increased risk of cataract and osteoporosis with fracture, while the risk of avascular necrosis, diabetes and hypertension was moderately increased. Cumulative steroid duration (at any dose) was not associated with an increased risk of the study outcomes. These findings support the notion that steroid-sparing is an important goal in the treatment of SLE, but the overall cumulative dose may be more impactful compared with duration. Future longitudinal studies could include the assessment of whether additional factors, such as poverty and antimalarial use, mediate the effect of steroids on organ damage outcomes.

Contributors The GSK authors led the development of the protocol, performed the statistical analyses and developed the study report. The Hopkins authors collected the data and contributed to both the protocol and the study report. JED, QF and MP were involved in the study design, and JED, QF, SR, LSM and MP were involved in the analysis or interpretation of data. All authors reviewed the manuscript and approved the final version to be submitted.

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Competing interests JED: shareholder of GSK; employee of GSK at the time of study. QF: employee and shareholder of GSK. SR: employee of GSK; student at the University of North Carolina at Chapel Hill. LSM: none. MP: received research funding from GSK and has served as a consultant to GSK.

Patient consent Patients provided written informed consent.

Ethics approval The study is approved on an annual basis by The Johns Hopkins University School of Medicine Institutional Review Board.

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Data sharing statement The results of this study are freely available from the GSK study register https://www.gsk-clinicalstudyregister.com

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