Title

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The Burden of Glucocorticoids: Patterns of Use, Adverse Health Conditions, and Health Care Use in Two Cohorts With Systemic Lupus Erythematosus

Patricia Katz,[1] Sofia Pedro,[2] Joonsuk Park,[1] Jiyoon Choi,[3] and Kaleb Michaud[4]

Objective. Glucocorticoids (GCs) can be beneficial from both clinical and patient perspectives, but side effects are well documented. We examined patterns of GC use over 15 years (2006–2021) and occurrence of adverse health conditions (AHCs) and health care use by GC exposure in two longitudinal cohorts with systemic lupus erythematosus (SLE).

Methods. Data from the Lupus Outcomes Study (LOS; 2003–2015) and FORWARD cohort (2015–2021) were used. AHCs examined were diabetes, osteoporosis, nontraumatic fractures, cataracts, and infections. Health care use measures examined were the number of rheumatology and other provider visits, hospitalizations, and specific diagnostic tests. Kaplan–Meier analyses examined time to occurrence of each AHC. Cox regression analyses estimated the risk of occurrence of AHCs, controlling for covariates by GC use and by GC dose (0, 1–5, 5–7.5, and ≥7.5 mg).

Results. GC use was relatively consistent over time. At baseline, individuals who used GCs in the LOS were more likely to report osteoporosis (adjusted odds ratio [aOR] 1.7, 95% confidence interval [CI] 1.2–2.6) and cataracts (aOR 1.6, 95% CI 1.04–2.6); individuals who used GCs in the FORWARD cohort were more likely to report diabetes (aOR 5.1, 95% CI 2.2–12.0), osteoporosis (aOR 4.5, 95% CI 2.6–8.0), and fractures (aOR 6.5, 95% CI 3.8–11.1). Individuals who used high doses of GCs in the LOS had greater incidence of osteoporosis, fracture, and cataracts. In the FORWARD cohort, a significant difference in incidence was noted only for infections. In both cohorts, individuals who used GCs had more rheumatology and other physician visits, and greater risk of hospitalization.

Conclusion. Despite recommendations on steroid sparing, a large portion of people with SLE appear to remain on steroids. These analyses provide additional evidence of the potential health and health care burden of GC use, underscoring the need for other effective treatments for individuals with SLE.

INTRODUCTION

In spite of the recent introductions of new medications for individuals with systemic lupus erythematosus (SLE), glucocorticoids (GCs) remain a mainstay of SLE treatment. A study from the Systemic Lupus International Collaborating Clinic (SLICC) reported that over an average of seven years of follow-up, 81% of patients with SLE in the SLICC inception cohort, recruited between 1999 and 2011, received GCs.[1] The authors also reported that there were no changes in the proportion of patients who received GCs or in the average GC dose over time.

GCs can be beneficial from both clinical and patient perspectives.[2–4] However, side effects and adverse events from GCs are also well documented. Based on existing evidence and patient perspectives, the Outcome Measures in Rheumatology Glucocorticoid Impact Working Group defined a core domain set to capture the effects of GCs that included infection, bone fragility, hypertension, diabetes, weight, fatigue, mood disturbance, and death as mandatory domains.[5] The side effects have led efforts to develop steroid-sparing treatment protocols and guidelines that emphasize the limited use of GCs.[6,7] The health care

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SIGNIFICANCE & INNOVATIONS

- In two longitudinal cohorts with systemic lupus erythematosus (SLE), covering the years 2003 to 2021, glucocorticoid (GCs) use was relatively consistent over time despite efforts to develop steroid-sparing treatment protocols.
- In these two noninception cohorts, individuals who used GCs were more likely to have adverse health conditions commonly associated with receiving GCs, such as osteoporosis, diabetes, cataracts, and fractures, at study entry and over time had greater incidence of adverse health conditions associated with GC use.
- Individuals who used GC had more health care use, including physician visits and greater risk of hospitalization.
- Despite recommendations on steroid sparing, a large portion of people with SLE remain on steroids, with a significant portion remaining on high doses. Findings underscore the potential health and health care burden of GC use and the need for other effective treatments for SLE.

costs associated with use of GCs also suggest that longer use and higher doses may lead to substantial increases in health care utilization.[8] This analysis leverages data from two longitudinal cohorts composed of individuals with physician-confirmed SLE to examine patterns of GC use over a 15-year period from 2006 through 2021, as well as the occurrence of adverse health conditions known to be associated with GC use and health care use among individuals with different levels of GC exposure.

PARTICIPANTS AND METHODS

Data sources. Data from two large longitudinal observational cohorts formed the basis for analysis. The first, the Lupus Outcomes Study (LOS), collected data annually from 2003 to 2015. The second, FORWARD, collected data from 2015, when an SLE-specific patient-reported measure of disease damage was added to the questionnaires, through 2021.

LOS. The LOS was a longitudinal, observational cohort established at the University of California San Francisco (UCSF). Participants of the LOS were recruited from an existing cohort of individuals with confirmed SLE diagnoses based on medical chart reviews supervised by a rheumatologist.[9] Except for the initial confirmation of SLE diagnostic criteria, data for the LOS were primarily collected via annual standardized telephone interviews. Enrollment began in 2003 (year 1) and continued through 2010 (year 8), although 80% of the participants were enrolled before 2006 (year 4). Wave 4 will be used as the baseline for analyses in this report. LOS interviews continued through 2014 (year 12). Annual retention rates, including deaths, were ≥92%. All LOS procedures were approved by the UCSF Committee on Human Research (Institutional Review Board [IRB] 11-05717).

FORWARD. Data were derived from a longitudinal, observational cohort study, FORWARD, The National Databank for Rheumatic Diseases.[10] All participants were at least 18 years of age at study entry, and SLE diagnoses were physician confirmed. Data were obtained initially from participants and validated, when required, from hospital and physician sources and from national death records. All rheumatic disease diagnoses were confirmed by participants' physicians. Participants were surveyed by questionnaire at six-month intervals. Questionnaires included a broad range of data including demographics, health care use, medications, and patient-reported outcomes. Among participants with SLE in the most recent questionnaire waves, approximately 60% responded online and 40% by mail questionnaire. All responses to a specific questionnaire (eg, July 2019) received before release of the next questionnaire (eg, January 2020) are considered to be part of the July 2019 phase. FORWARD procedures were approved by Ascension Via Christi Hospitals Wichita IRB (IRB00001673).

Inclusion criteria. For both cohorts, inclusion criteria for the reported analyses were as follows: (1) for cross-sectional analyses, at least one questionnaire completed; and (2) for longitudinal analyses, at least two questionnaires completed. Because of differences in the reporting intervals and variables available, results from FORWARD and the LOS are presented separately in the reporting below.

Variables. *Primary independent variable: GC use.* For both cohorts, detailed information was collected at each interview or questionnaire. The LOS included GC use ever during the year before interview, use at the time of the interview, and current dosage (in milligrams per day). FORWARD collected more detailed information including dosage, average days using GCs, when use started, and when use stopped. Variables used in analyses were having ever used GCs (yes or no), using GCs at each interview or questionnaire (yes or no), and GC dosage at each phase categorized as 0, >0 to <5, ≥5 to <7.5, and ≥7.5 mg/day.[11,12]

Adverse health condition outcomes. In both cohorts, we examined the occurrence of three health conditions that are recognized to be potential adverse effects of long-term GC use and were available in both data sources: diabetes, osteoporosis, and nontraumatic fractures. Additionally, we examined the occurrence of cataracts in the LOS and infections (blood, fungal, skin, urinary tract, kidney, bladder, bone, or joint infections; pneumonia; or tuberculosis) in FORWARD. The presence of each of these was self-reported at each interview/questionnaire.

Health care use outcomes. In both cohorts, we examined self-reports of the number of rheumatology visits and hospitalization. In the LOS, we also examined reports of the number of visits

to general medicine providers. In the FORWARD cohort, we also examined self-reports of the number of visits to all other physicians, physical and occupational therapy visits, and nontraditional therapy visits, as well as the number of specific lung, bone density, blood, and urine tests (zero, one, two, three, four, or more than four, which was analyzed as five). In FORWARD, instead of the actual number of visits, reporting options were 0, 1 to 2, 3 to 4, 5 to 6, 7 to 8, or >8, except for nontraditional visits, which were reported as 0, 1 to 4, 5 to 8, 9 to 12, 13 to 16, 17 to 20, and ≥21. Length of hospitalization was reported as 1, 2 to 3, 4 to 6, 7 to 13, or ≥14 days. For each, the midpoint of the range was used in analyses.

Other variables. Variables used as covariates in analyses included sociodemographic factors (age, sex), comorbid conditions, and SLE-specific variables. Comorbid conditions in the LOS analyses included current hypertension, other cardiovascular disease, cancer, fibromyalgia, or recent myocardial infarction or stroke. For the FORWARD cohort, the Rheumatic Disease Comorbidity Index was calculated.[13] When used in regression analyses to determine predictors of side effects, the outcome condition was excluded from calculation. SLE-specific factors were SLE duration, self-reported disease activity (0 being not at all active and 10 being very active), and self-reported disease damage measured with the validated Brief Index of Lupus Damage (BILD).[14,15]

Statistical analysis. The frequency of GC use, overall and by dosage, was presented by data collection period. Additional summary statistics were calculated, including the percentage of observations in which GCs were used. Analyses were conducted with Stata SE version 17.0.

Adverse health conditions. Frequency of each of the four adverse conditions (diabetes, cataracts, osteoporosis, or nontraumatic fractures) was calculated. Kaplan–Meier analyses examined the time to reporting of the occurrence of each side effect among individuals who did and did not report the condition at the baseline year. Cox regression analyses were then calculated to estimate the risk of the occurrence of each condition, controlling for covariates (age, sex, obesity, comorbid conditions, SLE duration, SLE disease activity, and SLE disease damage). Two sets of Kaplan–Meier analyses and Cox regression analyses were conducted. The first used GC use at baseline as the primary independent variable. The second used time-varying lagged GC information. Each set examined both any GC use (no use vs any use) and GC dosage (0, 0–5, 5–7.5, and ≥7.5 mg/day) in separate analyses.

Table 1. Participant characteristics at first observation*

	LOS, 2006				FORWARD, 2015			
Variable	Total (n = 797)	Did not receive GCs, 355 (44.5%)	Received GCs, 442 (55.5%)	*P* value	Total (n = 512)	Did not receive GCs, 275 (53.7%)	Received GCs, 237 (46.3%)	*P* value
Demographic characteristics								
Male, n (%)	61 (7.7)	31 (6.6)	30 (9.2)	0.18	30 (5.9)	22 (8.0)	8 (3.4)	0.026
Race, n (%)								
Asian	72 (9.0)	26 (7.3)	46 (10.4)	0.063	5 (1.0)	1 (0.4)	4 (1.7)	0.043
Black non-Hispanic	60 (7.5)	19 (5.4)	41 (9.3)	0.063	49 (9.6)	20 (7.3)	29 (12.2)	0.043
Hispanic	72 (9.0)	31 (8.7)	41 (9.3)	0.063	19 (3.7)	6 (2.2)	13 (5.5)	0.043
White	547 (68.6)	346 (73.5)	201 (64.7)	0.063	428 (83.6)	243 (88.4)	185 (78.1)	0.043
Other	46 (5.8)	18 (5.1)	28 (6.3)	0.063	11 (2.1)	5 (1.8)	6 (2.5)	0.043
Age, mean ± SD, y	49.7 ± 12.7	51.3 ± 12.3	47.6 ± 12.8	<0.0001	58.5 ± 13.0	58.0 ± 13.0	59.6 ± 13.3	0.172
College graduate, n (%)	39.9%	185 (39.3)	133 (40.8)	0.67	245 (47.9)	132 (48.0)	113 (47.7)	0.942
General health characteristics								
BMI, mean ± SD, kg/m^2	26.1	27.1 ± 7.1	26.5 ± 6.7	0.23	29.4	29.2 ± 7.9	29.6 ± 9.3	0.561
Ever smoked, n (%)	329 (41.5)	206 (43.7)	123 (37.4)	0.14	177 (34.8)	103 (37.5)	74 (31.2)	0.139
SLE characteristics, mean ± SD								
SLE duration, y	15.7 ± 8.5	14.9 ± 8.5	16.8 ± 8.3	0.0015	24.2 ± 12.7	23.6 ± 12.4	25.6 ± 13.1	0.083
How active is your lupus today (0–10 rating)	4.2 ± 2.7	4.0 ± 2.7	4.6 ± 2.8	0.001	2.8 ± 2.7	2.4 ± 2.5	3.3 ± 2.8	0.000
SLAQ	12.6 ± 7.9	12.2 ± 7.9	13.1 ± 7.7	0.11	4.6 ± 4.3	3.7 ± 3.8	5.6 ± 4.5	0.000
BILD score	2.1 ± 2.0	1.9 ± 2.0	2.6 ± 2.0	<0.0001	3.4 ± 2.2	3.1 ± 2.1	4.00 ± 2.4	0.000
Medications								
Hydroxychloroquine, n (%)	425 (53.3)	245 (52.0)	180 (55.2)	0.37	299 (59.8)	159 (57.8)	140 (59.1)	0.774
Immunosuppressives, n (%)	227 (29.2)	76 (16.1)	151 (48.2)	<0.0001	156 (30.1)	54 (19.6)	102 (43.0)	0.000
Dose of GC at first observation, mean ± SD, mg/d	–	–	8.6 ± 9.1	–	–	–	9.1 ± 12.2	–
Received high doses (≥7.5 mg/day) at baseline, n (%)	–	–	232 (29.1)	–	–	–	144 (28.1)	–

*P values are from *t*-tests or chi-square analyses. Immunosuppressive medications included cyclophosphamide, cyclosporine, mycophenolate, methotrexate, rituximab, and any biologic such as etanercept. BILD, Brief Index of Lupus Damage; BMI, body mass index; GC, glucocorticoid; LOS, Lupus Outcomes Study; SLAQ, Systemic Lupus Activity Questionnaire; SLE, systemic lupus erythematosus.

Health care use. Analyses examined use according to GC use/non-use, as well as by GC dosage (0, 0–5, 5–7.5, and ≥7.5 mg/day). Generalized estimating equation (GEE) regression analyses were used to model health care use in the LOS. Because of the difference in the health care use variables in FORWARD, Poisson GEE with log link was used for count outcomes and logistic GEE for hospitalizations. Two series of models were calculated: the first used concurrent reports of GC use, both referring to the past year; and the second used lagged GC reports and health care use in the next reporting period. Analyses controlled for the same covariates listed above.

RESULTS

Both cohorts were predominantly female (Table 1). The LOS cohort was about 10 years younger and had a shorter SLE duration than the FORWARD cohort, included fewer college graduates, and was more diverse in terms of race and ethnicity. The LOS cohort also reported greater SLE disease activity by both the Systemic Lupus Activity Questionnaire[16] and the single-item rating. BILD scores were lower in the LOS cohort.

At baseline, 56% of the LOS cohort and 46% of the FORWARD cohort reported GC use at the time of data collection (Table 1). Baseline GC dosage was similar in the two cohorts (LOS: 8.6 ± 9.1 mg/day; FORWARD: 9.1 ± 12.2 mg/day). A similar portion reported using ≥7.5 mg GC at baseline (LOS: 29.1%; FORWARD: 28.1%). GC use by observation period is shown in Supplementary Table 1. The proportion of individuals using any GCs and the proportion using high doses of GCs were relatively consistent over time within each cohort.

In both cohorts, the proportion of individuals using GCs was relatively consistent over the observation periods. In both cohorts,

Table 2. Presence of adverse health events (AHE) possibly related to GC at first year of observation.

	Adverse health events									
	Diabetes		Osteoporosis		Fracture		Cataract		Infection	
No GC use vs. Use, unadjusted analyses										
	% (n)	*p*	% (n)	*p*	% (n)	*p*	% (n)	*p*	% (n)	*p*
LOS										
No GC use	6.2 (22)		25.4 (90)		4.0 (13)		27.2 (88)		–	
GC use	8.4 (37)	0.28	39.9 (172)	<0.0001	5.0 (20)	0.59	31.9 (128)	0.19	–	–
FORWARD										
No GC use	3.4 (11)		9.4 (31)		10.6 (35)		–		21.3 (70)	
GC use	16.9 (31)	<0.0001	30.0 (55)	<0.0001	39.9 (73)	<0.0001	–		35.5 (65)	0.003
No GC use vs. Use, adjusted analyses										
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
LOS										
GC use	1.1 (0.6, 2.3)	0.73	1.7 (1.2, 2.6)	0.004	1.0 (0.4, 2.5)	0.99	1.6 (1.04, 2.6)	0.03	–	–
FORWARD										
GC use	5.1 (2.2, 12.0)	0.000	4.5 (2.6, 8.0)	0.000	6.5 (3.8, 11.1)	0.000	–	–	1.5 (0.9, 2.3)	0.10
By GC dose (mg/day), unadjusted analysis										
	% (n)	*p*	% (n)	*p*	% (n)	*p*	% (n)	*p*	% (n)	*p*
LOS										
0	6.7 (32)		28.1 (131)		23.2 (100)		27.5 (119)		–	
>0 to <5	11.8 (6)		35.3 (18)		25.9 (14)		31.5 (17)		–	
≥5 to <7.5	6.1 (9)		38.2 (55)		23.8 (30)		32.3 (41)		–	
≥7.5	9.4 (12)	0.45	47.2 (58)	<0.0001	39.8 (45)	0.004	36.3 (41)	28.3	–	
FORWARD										
0	3.4 (11)		8.8 (31)		9.7 (31)		–		21.9 (70)	
>0 to <5	11.9 (5)		23.8 (10)		33.3 (14)		–		31.0 (13)	
≥5 to <7.5	13.9 (11)		34.2 (27)		32.9 (26)		–		34.2 (27)	
≥7.5	21.1 (15)	0.000	29.6 (21)	0.000	52.1 (37)	0.000	–		35.2 (25)	0.028
By GC dose (mg/day), adjusted analysis										
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
LOS										
0	Reference		Reference		Reference		Reference		–	
>0 to <5	1.7 (0.6, 5.0)	0.35	1.4 (0.7, 2.7)	0.38	1.0 (0.5, 2.0)		1.1 (0.5,2.5)	0.75	–	
≥5 to <7.5	0.9 (0.4, 2.1)	0.80	1.4 (0.9, 2.2)	0.12	0.9 (0.5, 1.5)	0.74	1.6 (0.9, 2.7)	0.11	–	
≥7.5	1.6 (0.7, 3.7)	0.24	2.2 (1.3, 3.6)	0.002	1.7 (1.0, 2.9)	0.039	2.0 (1.1, 3.8)	0.28	–	
FORWARD										
0	Reference		Reference		Reference		–		Reference	
>0 to <5	3.6 (0.96, 13.5)	0.06	3.5 (1.4, 8.4)	0.006	5.9 (2.6, 9.8)	0.000	–		1.3 (0.6, 2.9)	0.46
≥5 to <7.5	4.6 (1.7, 12.9)	0.003	5.7 (2.8, 11.6)	0.000	4.3 (2.1, 85)	0.000	–		1.5 (0.8, 2.8)	0.19
≥7.5	6.9 (2.5, 18.9)	0.000	4.3 (2.0, 8.9)	0.000	10.4 (5.2, 20.7)	0.000	–		1.5 (0.8, 2.8)	0.19

Adjusted analyses controlled for age, sex, SLE disease duration, comorbid conditions, obesity, use of other medications, self-rated SLE disease activity, and self-rated SLE damage using the Brief Index of Lupus Damage. CI, confidence interval; GC, glucocorticoid; LOS, Lupus Outcomes Study; OR, odds ratio; SLE, systemic lupus erythematosus.

White individuals were more likely to report not using GCs at baseline, and those with longer disease duration, more active SLE, and more SLE damage were more likely to report GC use at baseline. Individuals who reported GC use were also more likely to report the use of other immunosuppressive medications (eg, cyclophosphamide, cyclosporine, or mycophenolate).

Adverse health condition baseline. At baseline, individuals who used GCs in the LOS were more likely to report osteoporosis (adjusted odds ratio [aOR] 1.7, 95% confidence interval [CI] 1.2–2.6) and cataracts (aOR 1.6, 95% CI 1.04–2.6; Table 2), but there were no differences in the baseline prevalence of diabetes or fractures by GC use. In analyses by dosage group, differences in the proportion with osteoporosis and fracture were noted in the group who received the highest doses of GCs (aOR osteoporosis 2.2, 95% CI 1.3–3.6; aOR fracture 1.7, 95% CI 1.0–2.9) compared to the group with no GC use. There were no significant differences in the proportion of participants with diabetes or cataracts at baseline by GC dose.

In FORWARD, at baseline, individuals who used GCs were significantly more likely to report having diabetes (aOR 5.1, 95% CI 2.2–12.0), osteoporosis (aOR 4.5, 95% CI 2.6–8.0), and fractures (aOR 6.5, 95% CI 3.8–11.1). Differences in the presence of these adverse effects were also noted by GC dosage. After adjustment, the prevalence of infections was not significantly different by GC use/non-use or by GC dosage.

Adverse health condition follow-up. Over the nine years of observation for the LOS, survival analyses revealed increased incidence of osteoporosis, fracture, and cataracts among individuals who used GCs (Supplementary Figure 1) and significant differences in incidence by GC dosage for all four adverse conditions (Figures 1 and 2). After adjustment for covariates, osteoporosis incidence was significantly greater among individuals who used GCs at the baseline observation (aOR 2.1, 95% CI 1.5–3.1; Table 3). Differences in osteoporosis incidence were also noted in the groups who received dosages of ≥5 to <7.5 mg/day GCs and ≥7.5 mg/day GCs (aOR 2.3, 95% CI 1.4–3.5, and aOR 2.4, 95% CI 1.5–4.0, respectively). Incidence of cataracts was greater for individuals who ever used GCs (aOR 1.3, 95% CI 1.1–1.7) and those who used high doses of GCs (aOR 1.4, 95% CI 1.1–2.0). Incidence of fractures was elevated for individuals

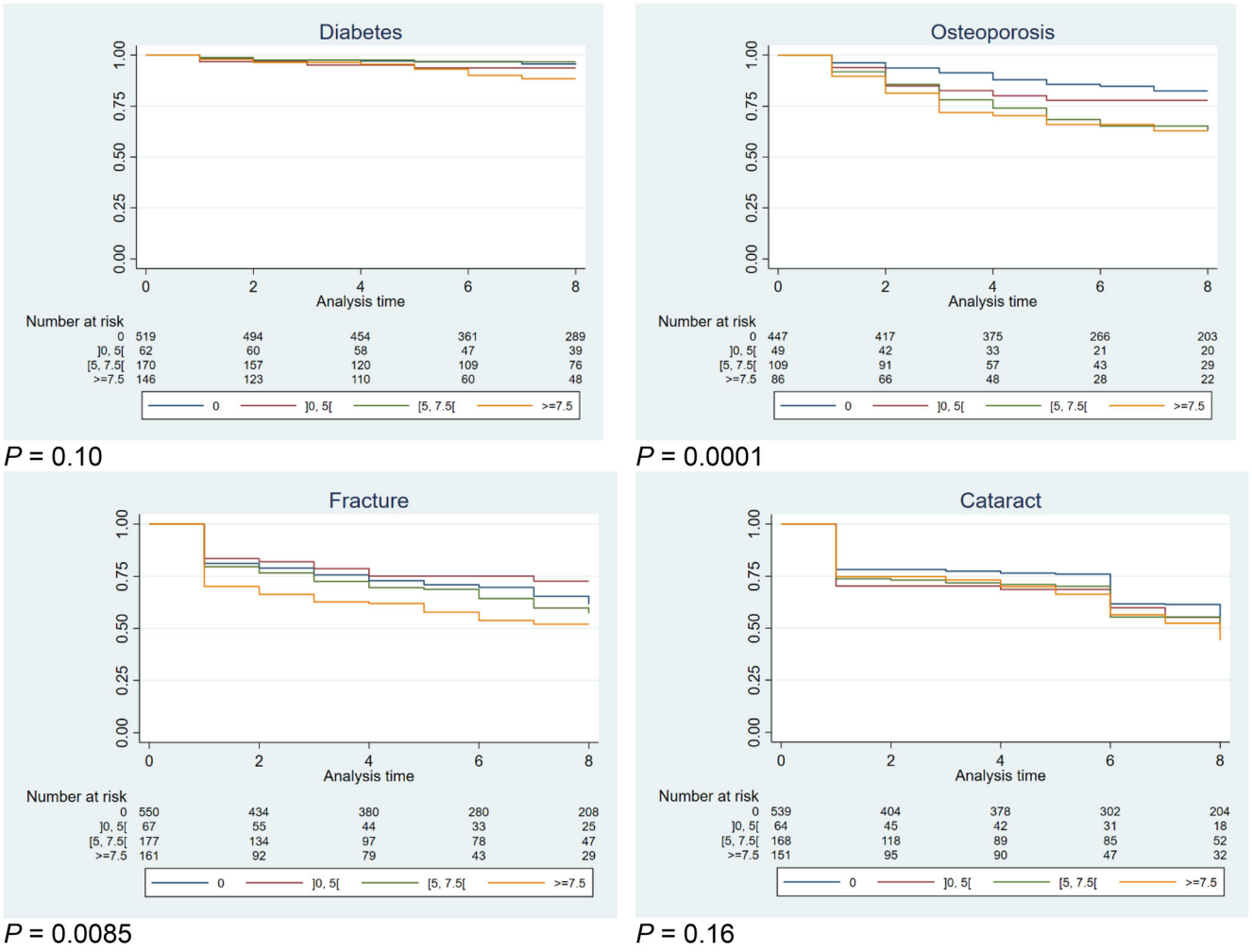

Figure 1. Incidence of adverse events by GC dose based on baseline GC reception: Lupus Outcomes Study. GC, glucocorticoid.

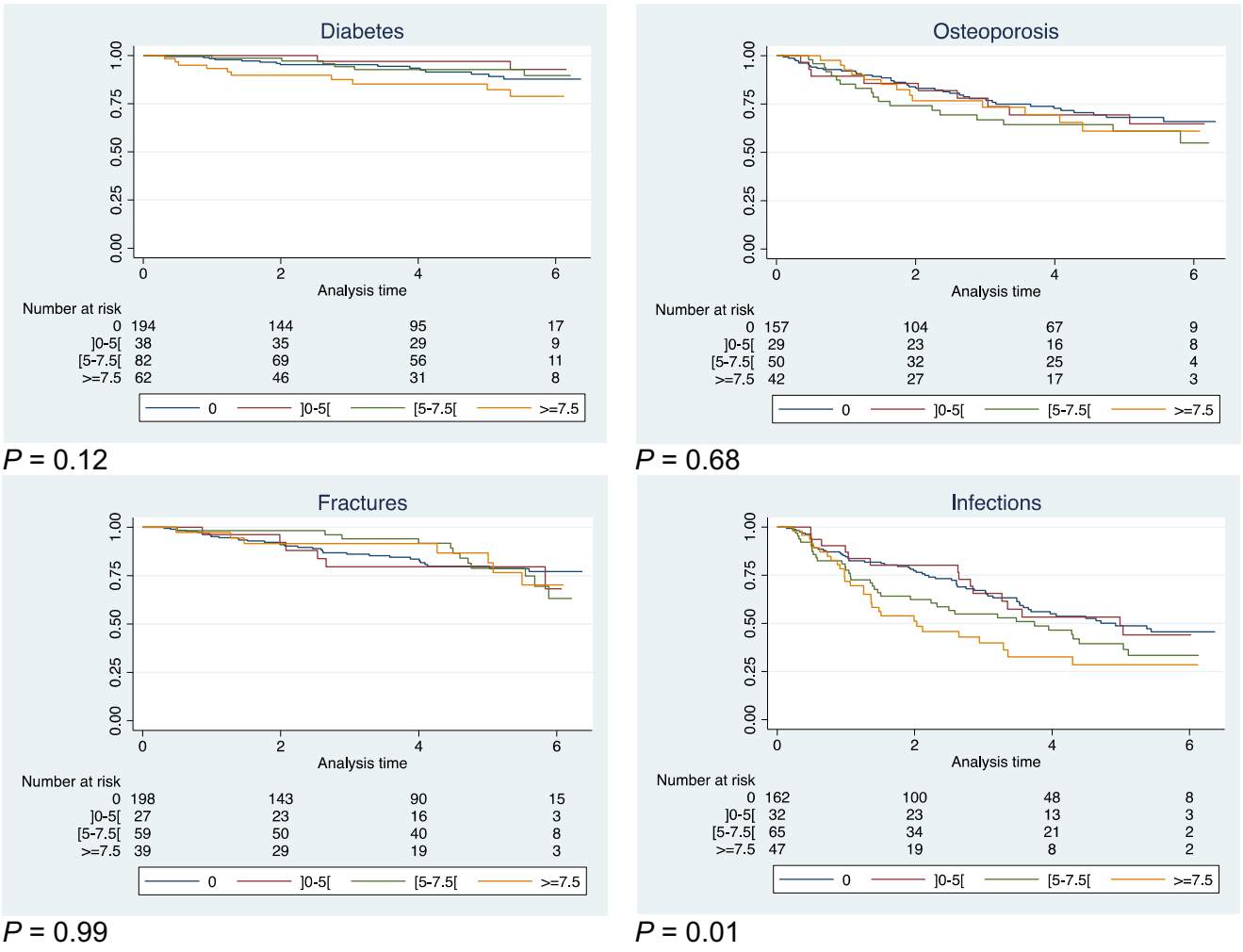

Figure 2. Incidence of adverse events by GC dose based on baseline GC reception: GC, glucocorticoid.

who used high doses of GCs (aOR 1.3, 95% CI 1.0–1.8). The only significant difference in incidence of adverse effects in the FORWARD cohort was for infections (any GC use aOR 1.5, 95% CI 1.1–2.2; high-dose use aOR 2.0, 95% CI 1.2–3.2). There were no substantive differences in models using time-varying GC use in either cohort (Supplementary Table 2).

Health care use. In both cohorts, any GC use was associated with a greater number of rheumatology visits and other physician

Table 3. Incidence of adverse health events possibly related to receiving GCs over follow-up based on baseline GC reception*

	Not receiving vs receiving GCs		GC dosage					
Variable	HR (95% CI)	*P* value	0–5 mg/day, HR (95% CI)	*P* value	5–7.5 mg/day, HR (95% CI)	*P* value	≥7.5 mg/day, HR (95% CI)	*P* value
LOS								
Diabetes	1.4 (0.7–2.7)	0.39	1.1 (0.3–3.8)	0.895	0.8 (0.3–2.2)	0.650	1.9 (0.8–4.2)	0.124
Osteoporosis	2.1 (1.5–3.1)	<0.0001	1.4 (0.7–2.8)	0.297	2.3 (1.4–3.5)	<0.001	2.4 (1.5–4.0)	<0.001
Fractures	1.2 (0.92–1.5)	0.19	0.7 (0.4–1.2)	0.198	1.1 (0.8–1.5)	0.575	1.3 (1.0–1.8)	0.05
Cataracts	1.3 (1.1–1.7)	0.008	1.4 (0.9–2.1)	0.109	1.1 (0.9–1.5)	0.366	1.4 (1.1–2.0)	0.017
FORWARD								
Diabetes	0.8 (0.3–1.6)	0.58	0.5 (0.1–2.3)	0.37	0.6 (0.2–1.6)	0.28	1.3 (0.5–3.4)	0.53
Osteoporosis	1.2 (0.7–1.9)	0.46	0.9 (0.5–2.0)	0.87	1.3 (0.7–2.5)	0.37	1.3 (0.7–2.6)	0.39
Fractures	0.8 (0.5–1.4)	0.52	1.1 (0.4–2.6)	0.89	0.7 (0.3–1.5)	0.40	0.8 (0.3–1.9)	0.65
Infection	1.5 (1.1–2.2)	0.023	1.1 (0.6–1.9)	0.85	1.5 (1.0–2.4)	0.06	2.0 (1.2–3.2)	0.006

*All models were adjusted for age, sex, SLE disease duration, comorbid conditions, obesity, other received medications, self-rated SLE disease activity, and self-rated SLE damage using the Brief Index of Lupus Damage. CI, confidence interval; GC, glucocorticoid; HR, hazard ratio; LOS, Lupus Outcomes Study; SLE, systemic lupus erythematosus.

Table 4. Health care use for GC users vs. non-users.

	Non-GC user	GC user		Adjusted analyses	
LOS					
N observations	3177	3662			
	Mean ± SD		*p**	β (95% CI)	*p***
Rheumatology visits	2.2 ± 2.6	4.0 ± 3.8	<0.0001	1.1 (0.92, 1.30)	<0.0001
General medicine visits	3.3 ± 3.9	4.4 ± 5.4	<0.0002	0.7 (0.4, 1.0)	<0.0001
General medicine visits related to lupus	1.5 ± 3.3	1.8 ± 3.8	<0.0001	0.3 (0.04, 0.6)	0.02
	% (n)			OR (95% CI)	*p***
Any ER visit related to lupus	12.7 (307)	28.0 (816)	<0.0001	2.0 (1.6, 2.5)	<0.0001
Any hospitalization	13.8 (439)	25.1 (922)	<0.0001	1.7 (1.4, 2.0)	<0.0001
FORWARD					
N observations	2980	2240			
	Mean ± SD		*p**	IRR (95% CI)	*p***
Rheumatology visits	3.2 ± 2.7	4.5 ± 3.1	<0.0001	1.2 (1.1, 1.3)	0.002
Other doctors	3.3 ± 3.3	4.7 ± 4.1	<0.0001	1.2 (1.1, 1.4)	0.002
PT/OT visits	2.0 ± 3.7	2.6 ± 4.3	0.12	1.2 (1.0, 1.5)	0.10
Non-traditional therapy visits	1.4 ± 3.1	2.3 ± 6.2	0.053	1.2 (0.9, 1.6)	0.20
Lung tests	0.3 ± 0.9	0.4 ± 1.2	0.24	1.8 (1.3, 2.4)	<0.0001
Bone density tests	0.8 ± 0.9	0.9 ± 0.8	0.09	1.1 (0.9, 1.3)	0.47
Blood tests	4.2 ± 2.7	5.7 ± 2.9	<0.0001	1.2 (1.1, 1.3)	<0.0001
Urine tests	2.7 ± 2.3	3.8 ± 2.8	<0.0001	1.3 (1.2, 1.5)	<0.0001
	% (n)			OR (95% CI)	*p***
Any hospitalization	33.2 (90)	51.3 (121)	<0.0001	1.7 (1.3, 2.3)	<0.0001
Number of days hospitalized (mean over observation period)	3.5 ± 2.6	5.2 ± 6.1	0.04		

CI, confidence interval; ER, emergency room; GC, glucocorticoid; GEE, generalized estimating equation; IRR, incidence rate ratio; LOS, Lupus Outcomes Study; OR, odds ratio; PT/OT, physical therapy or occupational therapy.
**p* from unadjusted GEE regression analyses
***p* from multivariable GEE regression analyses, controlling for age, sex, obesity, number of comorbidities, lupus disease duration, other medication use, self-rated lupus disease activity, and self-reported disease damage by the BILD.

visits (Table 4), even after adjusting for covariates. In the LOS, participants who used GCs were twice as likely to report at least one emergency department visit compared to individuals who did never used GCs (aOR 2.0, 95% CI 1.6–2.5). In FORWARD, the number of lung, blood, and urine tests were higher for individuals who used GCs. In both cohorts, the odds of a hospital visit were elevated by 70% for individuals who used GCs (LOS OR 1.7, 95% CI 1.4–2.0; FORWARD OR 1.7, 95% CI 1.3–2.3). The number of hospital days was also significantly longer (FORWARD, 3.5 ± 2.6 days vs 5.2 ± 6.1 days) for participants who used GCs. Hospital length of stay and use of specific tests was not collected in the LOS.

When examining health care use by GC dose, similar patterns were seen (Supplementary Table 3). Individuals who used GCs, particularly those who used high doses, reported significantly more rheumatology and other doctor visits. Hospitalizations were significantly more likely for individuals who used high doses of GCs (≥7.5 mg/day; LOS OR 2.3, 95% CI 1.3–4.3; FORWARD OR 3.1, 95% CI 1.2–4.5). In the LOS, emergency department visits were more common among patients who received high doses of GCs, but the difference was not statistically significant after adjustment. In FORWARD, physical/occupational therapy visits, lung tests, blood tests, and urine tests were significantly more likely among patients who received high doses of GCs.

The analyses using lagged GC reports with health care use in the next reporting period did not yield substantially different results and are not shown.

DISCUSSION

In these two large cohorts, which covered 15 years of observation, we noted a number of similarities in both the patterns of GC use and the health and health care burden associated with GC use in spite of differences in the cohorts' ages, disease duration, year of interview, and current reported disease activity. Roughly half of the participants in each cohort reported GC use at each interview. As might be expected, GC use was higher among individuals with greater disease activity and damage. Probably reflecting greater disease activity, individuals who used GCs were also more likely to be using other immunosuppressive medications. Before 2017, about 10% to 17% patients reported high-doses GC use (≥7.5 mg/day). After 2017, high dose use dropped to 6% to 9%. Patterns of GC use within individuals, however, were relatively stable, so this decrease may represent the differential loss of individuals who used GC or individuals who used high doses of GCs from the cohorts.

Results complement findings from earlier studies of clinical cohorts and administrative data sources and demonstrate that despite the recognition of the negative effects of GCs, they continue to be widely prescribed. Although GC use tends to be more common among individuals with greater disease severity or activity, additional factors contribute to variation in use. For example, Little et al[1] found significant differences in GC use by treatment center among the 33 centers in the SLICC consortium. Patients may be willing to tolerate the negative effects of GCs to obtain

the perceived benefits such as reduction in disease flares and physical symptoms and ability to maintain usual activities.[2,17] There also appear to be significant disparities in GC use, such that individuals who are White, well insured, and/or have higher incomes are less likely to receive persistent high doses of GCs.[18] Even though both of our cohorts were composed predominantly of White individuals, White participants in both cohorts were significantly less likely to report GC use.

Significantly more of the adverse health conditions examined were reported at baseline for the individuals who reported GC use in the FORWARD cohort, whereas only osteoporosis was more common among patients who used GCs in the LOS at baseline. This difference may be attributable to the older age and longer disease duration for participants of the FORWARD cohort. Incidence of each of the adverse conditions was more likely for participants who used GCs, particularly those using high doses, although findings were not always consistent across cohorts or between GC use definitions (any use vs dosage groups). The clearest and most consistent trend was the association of GC use with the presence and incidence of osteoporosis in the LOS and infection in FORWARD. In the LOS, individuals who used low to moderate doses of GCs had twice the risk of incident osteoporosis after controlling for covariates; individuals who used high doses of GCs had 2.5 times the risk. Similarly, individuals who used high doses of GCs in FORWARD had double the risk of a serious infection.

A survey of individuals who used GCs published in 2006 reported that more than 90% reported at least one GC-associated adverse event.[19] Cataracts and fractures were reported by 15% and 12%, respectively. A systematic review of GC use in rheumatoid arthritis noted that the risk of osteoporotic fractures, serious infections, and diabetes was increased for persons who used GCs across all studies included in the review. Our findings support previous studies showing the relatively high prevalence of these adverse events in individuals who used GCs in more recent years in spite of the well-known risks.

Although different dosages have been used to define high GC doses, ranging from ≥7.5 to >15 mg/day or even higher, side effects have been consistently found to be more common in individuals receiving high doses or receiving GCs for a long duration. Some have suggested that some lower doses of GCs may be considered safe, but data on safe daily dosing and/or duration have been conflicting.[6] Our results also showed that although the risk of incident side effects was higher, particularly for osteoporosis, individuals in the low/moderate dose range also had increased risk.

In our study, GC use was also associated with greater health care use, again after controlling for covariates. For variables measured the same way in both cohorts (rheumatology visits and hospitalizations), the results were remarkably similar. GC use was associated with one to two additional rheumatology visits per year, and the odds of hospitalization were increased by 70% in both cohorts. These differences were even more pronounced in the group who received high doses of GCs. For example, in the groups who received high doses of GCs, the odds of hospitalization were 2.3 to 3 times higher compared to individuals who did not receive GCs. Hospital length of stay was collected in FORWARD and showed significantly longer hospitalizations for those who received GCs, especially for those who received high doses. Our findings extend the time periods examined previously but show similar increased health care use for individuals who received GCs, especially for those who received high doses.

These analyses do have limitations. With the exception of SLE diagnosis, all data were self-reported. However, in FORWARD, a subset of health care use and diagnostic data were validated by review of medical records. Although all data collection measures were well tested, some measurement error always exists. Although both cohorts were large, some individuals with lupus have been underrepresented, limiting generalizability. For example, individuals with severe disease may have been underrepresented because they were too ill to complete surveys/interviews. All respondents were English speaking, and the majority were White, so other racial and ethnic groups were underrepresented. The FORWARD cohort was also older than many SLE cohorts, which may affect disease activity and treatments. Some of these issues were balanced by including analysis of the LOS. The LOS cohort was younger, more racially and ethnically diverse, and observed over a longer period of time. There were other adverse health conditions we might have included such as depression/mood disorders or cardiovascular events. However, these conditions have multiple etiologies, were not consistently assessed, and/or could not be tied as closely to GC use, so we chose to omit them in analyses. Finally, our measurements of GC use may not have been adequate. GC use can vary considerably over even short periods of time. It is possible that our methods did not adequately capture changes that could be important in identifying effects on outcomes. We also were unable to capture GC use before study entry or to develop estimates of cumulative GC dose.

These limitations are balanced by several strengths. The LOS and FORWARD are among the largest cohorts with SLE in the United States, with broad geographic representation that includes longitudinal observations with extensive coverage of medication use, other health conditions, and health care use. Participants in both cohorts had physician-confirmed SLE diagnoses. Both cohorts included detailed information on GC use, as well as relevant information on other health conditions and health care use. The two cohorts complemented each other in terms of time of data collection, age, disease duration, and other demographic characteristics. Many cohort studies are limited to single centers; both of these cohorts have drawn participants from a broad range of clinical and geographic settings and may thus be representative of general clinical practice.

Despite recommendations on steroid sparing, a large portion of people with SLE appeared to continue receiving steroids, with a significant portion continuing to receive higher doses. There may be multiple reasons for this, including lack of other treatments to address some SLE manifestations or symptoms, lack of access to other medications, or patient preference. Regardless, these analyses provide additional evidence of the potential health and health care burden of GC use, underscoring the need for other effective treatments for SLE.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr Katz had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Katz, Michaud.
Acquisition of data. Michaud.
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ROLE OF THE STUDY SPONSOR

Bristol Myers Squibb had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Bristol Myers Squibb.

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