Acute and chronic systemic corticosteroid–related complications in patients with severe asthma

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Background: Many patients with severe asthma require maintenance treatment with systemic corticosteroids (SCSs) to control daily symptoms and prevent serious acute exacerbations, but chronic SCS use is associated with complications.

Objective: We sought to evaluate the risk of SCS-related complications by SCS exposure and quantify the associated health care costs and resource use in patients with severe asthma.

Methods: We performed a longitudinal, open-cohort, observational study using health insurance claims data (1997-2013: Medicaid) from Florida, Iowa, Kansas, Missouri, Mississippi, and New Jersey. Eligible patients were 12 years old or older with 2 or more asthma diagnoses and had more than 6 months of continuous SCS use. An open-cohort approach was used to classify patients' follow-up into low, medium, and high SCS exposure (≤6, >6-12, and >12 mg/d, respectively). Multivariate generalized estimating equation models were used to estimate the adjusted risk of SCS-related complications for patients with medium and high exposure compared with patients with low exposure and quantify the resulting health care resource use and costs.

Results: The study included 3628 patients (mean age, 57.6 years; 68% female). Patients with medium and high SCS exposure had significantly higher risks of SCS-related complications, including infections and cardiovascular, metabolic, psychiatric, ocular, gastrointestinal, and bone-related complications (odds ratio, 1.23-2.12 by complication; $P < .05$ for all but one) versus those with low (reference group) SCS exposure. Medium and high SCS exposure were also associated with significantly more emergency department visits (incidence rate ratios, 1.31 [$P = .0004$] and 1.78 [$P < .0001$]) and inpatient visits (incidence rate ratios, 1.25 [$P < .0001$] and 1.59 [$P < .0001$]) versus low SCS exposure.

Conclusions: A significant dose-response relationship was demonstrated between chronic SCS use and risk of SCS-related complications in patients with severe asthma. Effective SCS-sparing strategies might reduce the burden associated with SCS-related complications in patients with severe asthma. (J Allergy Clin Immunol 2015;136:1488-95.)

Key words: *Systemic corticosteroids, severe asthma, health care use, dose response, corticosteroid-related complications, cost*

Approximately 5% to 10% of asthmatic patients have severe asthma, which is associated with more asthma-related symptoms and increased risk of exacerbations.[1-3] Because of the higher risk of asthma exacerbations, patients with severe asthma have high asthma-related morbidity.[2,4] Moreover, it has been estimated that health care costs of patients with asthma exacerbations are at least 80% higher than those for patients without exacerbations and that exacerbations are associated with a disproportionate share of health care resource use.[4-6] Severe asthma is difficult to manage, and in 30% to 40% of patients with this condition, it requires regular use of oral corticosteroids.[2,6,7]

It is well established that chronic use of corticosteroids leads to both short- and long-term complications, such as osteoporosis, fractures, susceptibility to infections, obesity, symptomatic coronary artery disease, avascular necrosis, stroke, cataract, glucose metabolism changes, and skin thinning.[8] According to data from the Healthcare Cost and Utilization Project, corticosteroids were the most common cause of drug-related complications, accounting for 10% of such complications and 141,000 hospital stays in the United States in 2004.[9]

However, according to a recent literature review, evidence for the risks and costs associated with systemic corticosteroid (SCS) therapy is sparse and inconsistent, particularly in asthmatic patients.[8] Another review revealed that most studies assessing corticosteroid-related complications are of short duration, thus underestimating the long-term complications associated with SCS use.[10] Moreover, very few studies considered the cumulative dose-response relationship between SCSs and complications, and none of the studies measured the association between the magnitude of SCS exposure and health care resource use.

A longitudinal observational study of Medicaid beneficiaries from 6 states in the United States was performed to evaluate the risk of SCS-related complications by degree of SCS exposure (ie, for patients with higher levels of SCS exposure compared with patients with lower levels of exposure) and to quantify the associated health care costs and resource use among patients with severe asthma.

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Abbreviations used
CCI: Charlson Comorbidity Index
GEE: Generalized estimating equation
ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification
ICS: Inhaled corticosteroid
OR: Odds ratio
QIC: Quasilikelihood under the independence model criterion
SCS: Systemic corticosteroid

METHODS

Data source

This study used claims data from Medicaid health insurance beneficiaries from 6 US states: Florida (2001-2012), Iowa (1998-2013), Kansas (2001-2013), Missouri (1997-2013), Mississippi (2006-2013), and New Jersey (1997-2013). This data set was chosen because of the long enrollment duration of Medicaid recipients, which permitted observation of both short- and long-term SCS-related complications. Data elements used in the present analysis included information on enrollment history, patient demographic characteristics, date of death, and claims for medical and pharmacy services. Actual costs, which were calculated as the sum of costs reimbursed by Medicaid and patients' out-of-pocket expenses, were also included. The database was deidentified and complied with the Health Insurance Portability and Accountability Act of 1996 to preserve patient anonymity and confidentiality.

Study design and patient selection

A longitudinal, open-cohort, observational study design was used. Eligible patients were 12 years and older, had at least 2 administrative charges associated with a diagnosis of asthma (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 493.xx), and had at least 6 months of continuous chronic SCS use (identified by claims for oral, injectable, intravenous, or intramuscular corticosteroids with daily doses of ≥5 mg of prednisone equivalent with no gap of 14 days or more between 2 SCS claims) while being continuously eligible for Medicaid (see Table E1 in this article's Online Repository at www.jacionline.org for the prednisone equivalent dosage of SCSs). These first 6 months constituted the baseline period, and the index date was defined as the first day with a daily dose of at least 5 mg of prednisone equivalent after these first 6 months (see Fig E1 in this article's Online Repository at www.jacionline.org).

Patients with at least 1 claim associated with a diagnosis for any cancer of the respiratory and intrathoracic systems (ICD-9-CM code 160.xx-165.xx) at any time before the index date or at least 1 claim for rheumatoid arthritis (ICD-9-CM code 714.0x, 714.2x), Crohn disease (ICD-9-CM code 555.xx), systemic lupus erythematosus (ICD-9-CM code 710.x0), or multiple sclerosis (ICD-9-CM code 340.xx) at any time in the patient claim history were excluded from the study. These conditions were identified as exclusion criteria because they have SCSs as treatment alternatives and have a similar interlinked relationship of dose and occurrence of SCS-related complications.

The follow-up period of each patient was divided into quarterly time intervals to appropriately account for the fact that a patient's SCS exposure could change over time (with changes in disease state and consequent SCS dose titration). An open-cohort approach was then used to classify quarters of patients' follow-up periods into different degrees of SCS exposure measured based on cumulative SCS dose intensity, as previously reported by Thamer et al[11] (ie, low exposure, ≤6 mg/d; medium exposure, >6-12 mg/d; and high exposure, >12 mg/d). For this analysis, we used the low-exposure group as a reference group.

Outcomes

The study outcomes were the risk of acute and chronic SCS-related complications and associated health care resource use and costs. Acute complications included infections and gastrointestinal complications, and chronic complications included cardiovascular, metabolic, bone- and muscle-related, psychiatric, ocular, skin, adrenal, and other conditions (see Table E2 in this article's Online Repository at www.jacionline.org).

The outcomes were calculated over the follow-up period on a quarterly basis, and health care costs were further annualized. Health care resource use and costs caused by SCS-related complications and grouped into pharmacy dispensings, outpatient visits, emergency department visits, hospitalizations, and other visits were calculated by using (1) medical claims with a diagnosis (ICD-9-CM codes) for SCS-related complications (see Table E2) or (2) pharmacy claims for medications used to treat SCS-related complications (see Table E3 in this article's Online Repository at www.jacionline.org). Costs were adjusted to 2013 US dollars by using the medical care component of the Consumer Price Index.[12]

The power calculation performed during the study protocol development phase indicated that a sample size of 2861 was necessary to achieve 80% power in detecting a 3% effect on health care costs for each additional milligram of increased cumulative daily dose. Whereas the SD of the daily SCS-related complication-associated health care cost was assumed to be twice the expected mean ($4.30), the SD of the mean daily dose was assumed to be 7.5 mg, and the 2-sided α level was set at .05.

Statistical analysis

Descriptive statistics were generated to summarize the patients' baseline characteristics by SCS exposure at the index date. Frequency counts and percentages were used to summarize categorical variables, whereas means, medians, and SDs were used for continuous variables. Baseline characteristics included age, sex, region, race, state, calendar year of index date, pre-existing conditions that can influence the occurrence of SCS-related complications (ie, history of falls, fractures, or diagnosis of osteoporosis; diagnosis of cognitive impairment or depression; diagnosis of epilepsy, cerebrovascular disease or Parkinson disease; diagnosis of diabetes mellitus; and diagnosis of chronic cardiovascular conditions), the Charlson Comorbidity Index (CCI),[13] and all-cause and asthma-related health care costs.

Multivariate generalized estimating equation (GEE) models were used to evaluate the association between SCS exposure and outcomes in patients with medium and high SCS exposure compared with that in patients with low exposure. This approach was chosen to account for the longitudinal and correlated nature of repeated quarterly data for the same patient on SCS exposure and outcomes and for the potential progression of confounders over time. The GEE models controlled for key baseline characteristics (sex, age, race, state, total health care costs, CCI, and ≥1 emergency department or inpatient visit at baseline) and time-dependent variables (quarter of observation, CCI, and cost of concomitant medications).

Odds ratios (ORs), which were estimated with a GEE model by using a binomial distribution with logit link function and exchangeable correlation structure, were used to assess the risk of SCS-related complications assessed as a discrete binary variable for patients with medium and high SCS exposure relative to that of patients with low SCS exposure. The GEE model used to estimate incidence rate ratios, CIs, and *P* values of health care resource use because of SCS-related complications was based on a Poisson distribution with an independent correlation structure to account for the discrete nature of health care resource use event counts. Adjusted cost differences between patients with medium/high SCS exposure and patients with low SCS exposure were assessed with a GEE model by using a normal distribution with exchangeable correlation structure to account for the continuous nature of costs. In addition to the aforementioned key baseline characteristics and time-dependent variables, the GEE models controlled for the year of index date and presence of a SCS-related complication of interest or pre-existing condition at baseline, where applicable. Nonparametric bootstrap procedures with 999 replications were used to estimate 95% CIs and *P* values.

All analyses were conducted with SAS software, version 9.3, of the SAS System for Windows (SAS Institute, Cary, NC). The SAS "PROC GENMOD" procedure was used to conduct the GEE regressions and to calculate the quasilikelihood under the independence model criterion (QIC) measures

TABLE I. Demographic and clinical baseline characteristics by SCS exposure at the index date

	Overall study population (n = 3628)	Low SCS exposure (n = 368)	Medium SCS exposure (n = 1630)	High SCS exposure (n = 1630)
Age at index date (y), mean ± SD (median)	57.6 ± 16.3 (57.7)	62.4 ± 16.9 (62.6)	60.0 ± 16.0 (60.6)	54.2 ± 15.7 (54.1)
Age categories (y), no. (%)				
12-17	84 (2.3)	7 (1.9)	31 (1.9)	46 (2.8)
18-34	202 (5.6)	15 (4.1)	75 (4.6)	11 (6.9)
35-44	404 (11.1)	25 (6.8)	13 (8.5)	240 (14.7)
45-54	874 (24.1)	66 (17.9)	342 (21.0)	466 (28.6)
55-64	938 (25.9)	91 (24.7)	433 (26.6)	414 (25.4)
≥65	1,126 (31.0)	164 (44.6)	610 (37.4)	352 (21.6)
Female sex, no. (%)	2,478 (68.3)	260 (70.7)	1,136 (69.7)	1,082 (66.4)
Race/ethnicity, no. (%)				
White	2,190 (60.4)	226 (61.4)	968 (59.4)	996 (61.1)
Black	776 (21.4)	71 (19.3)	338 (20.7)	367 (22.5)
Hispanic	152 (4.2)	11 (3.0)	69 (4.2)	72 (4.4)
Other	402 (11.1)	48 (13.0)	210 (12.9)	144 (8.8)
Unknown	108 (3.0)	12 (3.3)	45 (2.8)	51 (3.1)
State, no. (%)				
Florida	797 (22.0)	61 (16.6)	352 (21.6)	384 (23.6)
Iowa	245 (6.8)	25 (6.8)	99 (6.1)	121 (7.4)
Kansas	288 (7.9)	30 (8.2)	113 (6.9)	145 (8.9)
New Jersey	1,072 (29.5)	115 (31.3)	523 (32.1)	535 (32.8)
Missouri	1,173 (32.3)	133 (36.1)	524 (32.1)	415 (25.5)
Mississippi	53 (1.5)	4 (1.1)	19 (1.2)	30 (1.8)
Follow-up period duration (y), mean ± SD (median)	3.8 ± 3.4 (2.7)	4.2 ± 3.4 (3.1)	3.9 ± 3.4 (2.8)	3.6 ± 3.3 (2.5)
Year of index date, no. (%)				
1997-1998	287 (7.9)	37 (10.1)	127 (7.8)	123 (7.5)
1999-2000	350 (9.6)	38 (10.3)	172 (10.6)	140 (8.6)
2001-2002	515 (14.2)	59 (16.0)	245 (15.0)	211 (12.9)
2003-2004	666 (18.4)	67 (18.2)	319 (19.6)	280 (17.2)
2005-2006	560 (15.4)	53 (14.4)	265 (16.3)	242 (14.8)
2007-2008	365 (10.1)	29 (7.9)	161 (9.9)	175 (10.7)
2009-2010	469 (12.9)	48 (13.0)	168 (10.3)	253 (15.5)
2011-2012	393 (10.8)	34 (9.2)	164 (10.1)	195 (12.0)
2013	23 (0.6)	3 (0.8)	9 (0.6)	11 (0.7)
Pre-existing conditions, no. (%)				
History of falls, fractures, or diagnosis of osteoporosis	401 (11.1)	33 (9.0)	161 (9.9)	207 (12.7)
Diagnosis of cognitive impairment or depression	645 (17.8)	55 (14.9)	236 (14.5)	354 (21.7)
Diagnosis of epilepsy, cerebrovascular disease, or Parkinson disease	275 (7.6)	26 (7.1)	132 (8.1)	117 (7.2)
Diagnosis of diabetes mellitus	1,082 (29.8)	109 (29.6)	455 (27.9)	518 (31.8)
Diagnosis of chronic cardiovascular conditions	1,953 (53.8)	191 (51.9)	861 (52.8)	901 (55.3)
All-cause health care costs	18,142 ± 28,668 (9,059)	13,638 ± 25,719 (7,181)	16,040 ± 25,414 (7,902)	21,261 ± 31,879 (10,660)
Asthma-related total medical costs	1,862 ± 7,066 (18)	1,314 ± 5,002 (0)	1,518 ± 6,100 (6)	2,329 ± 8,242 (37)
CCI, mean ± SD (median)	2.0 ± 1.7 (2.0)	1.9 ± 1.8 (1.0)	2.0 ± 1.7 (1.0)	2.1 ± 1.7 (2.0)

reported for the model's goodness of fit.[14] Statistical significance was declared as a 2-sided test result at an α level of .05 or less.

RESULTS

Baseline characteristics

A total of 3628 patients were included in the study (see Fig E2 in this article's Online Repository at www.jacionline.org). Table I presents their baseline characteristics grouped by SCS exposure at the index date (low, 368 [10.1%] patients; medium, 1630 [45.0%] patients; high, 1630 [45.0%] patients). Lower SCS exposure subgroups were older on average (low, 62.4 years; medium, 60.0 years; high, 54.2 years), included more female subjects (low, 70.7%; medium, 69.7%; high, 66.4%), and had a longer mean follow-up period (low, 4.2 years; medium, 3.9 years; high, 3.6 years). Patients with high SCS exposure at the index date had more pre-existing conditions compared with patients with lower SCS exposure.

Risks of SCS-related complications

Fig 1 presents ORs of SCS-related complications by SCS exposure. Compared with patients with low SCS exposure, those with medium and high SCS exposure had significantly higher risks of having any SCS-related complication, with the exception of other complications that included hematologic/oncologic problems, for

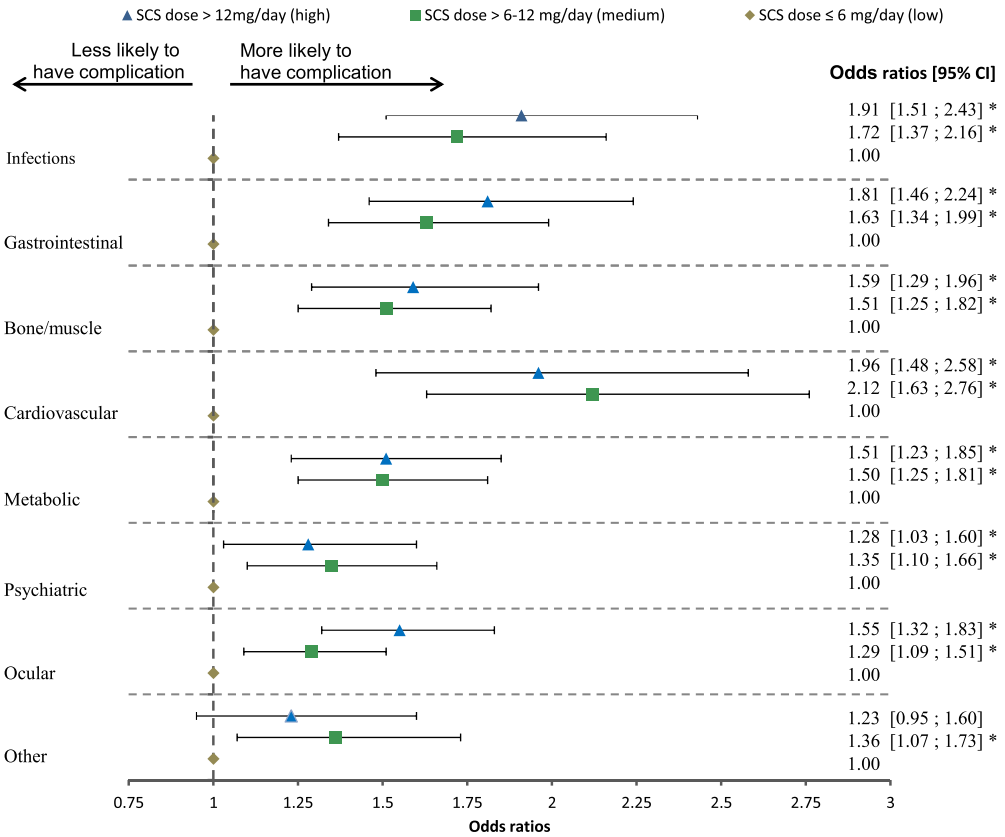

FIG 1. Risk of SCS-related complications by SCS exposure. In addition to controlling for key baseline characteristics (sex, age, race, state, total health care costs, and ≥1 emergency department or inpatient visit at baseline) and time-dependent variables (quarter, Charlson comorbidity index, and cost of concomitant medications), the GEE model used to estimate the risk of SCS-related complications by SCS exposure controlled for the year of index date and occurrence of the SCS-related complication of interest at baseline. *Error bars* represent 95% CIs. *Statistical significance at a *P* value of .05.

which the trend was not significant. In particular, patients with medium and high SCS exposure had higher risks of cardiovascular complications (ORs, 2.12 [95% CI, 1.63-2.76; $P < .0001$] and 1.96 [95% CI, 1.48-2.58; $P < .0001$]), infections (ORs, 1.72 [95% CI, 1.37-2.16; $P < .0001$] and 1.91 [95% CI, 1.51-2.43; $P < .0001$]), and gastrointestinal complications (ORs, 1.63 [95% CI, 1.34-1.99; $P < .0001$] and 1.81 [95% CI, 1.46-2.24; $P < .0001$]) compared with patients with low SCS exposure. Because of their low prevalence, the GEE models for adrenal and skin complications did not converge, and therefore ORs for these complications were not estimated. The estimated QIC for the chronic and acute complication models ranged from 1879 to 3958.

Health care resource use because of SCS-related complications

The incidence rate ratios of resource use because of SCS-related complications by SCS exposure are presented in Fig 2. Patients with medium and high SCS exposure were associated, respectively, with 31% (95% CI, 13% to 53%; $P = .0004$) and 78% (95% CI, 47% to 117%; $P < .0001$) more emergency department visits, 25% (95% CI, 15% to 35%; $P < .0001$) and 59% (95% CI, 44% to 76%; $P < .0001$) more inpatient visits, and 22% (95% CI, 14% to 29%; $P < .0001$) and 35% (95% CI, 26% to 44%; $P < .0001$) more pharmacy claims because of SCS-related complications compared with patients with low SCS exposure. The estimated QIC for the resource use outcomes models ranged from 13,570 to 45,214.

Health care costs of SCS-related complications

Health care costs of SCS-related complications by SCS exposure are presented in Table II.

Both unadjusted and adjusted results indicate that an increase in SCS exposure was associated with higher SCS-related complication costs. After adjustment, quarterly health care costs of patients with medium and high SCS exposure were $478 (95% CI, $256-$733; $P < .0001$) and $1,370 (95% CI, $1,018-$1,720; $P < .0001$) higher than those of patients with low SCS exposure, respectively. The estimated QIC for the health care costs models ranged from 57,776 to 59,707.

These results are mainly explained by differences in inpatient visit costs ($239 [95% CI, $102-$391; $P < .0001$] and $620 [95% CI, $403-$848; $P < .0001$]), outpatient visit costs ($136 [95% CI, $45-$215; $P < .0001$] and $398 [95% CI, $250-$514; $P < .0001$]), and pharmacy costs ($110 [95% CI, $36-$198; $P = .0040$] and $307 [95% CI, $208-$417; $P < .0001$]) between patients with medium and high SCS exposure relative to those with low SCS exposure.

The annualized incremental health care costs of SCS-related complications for medium and high SCS exposure relative to low

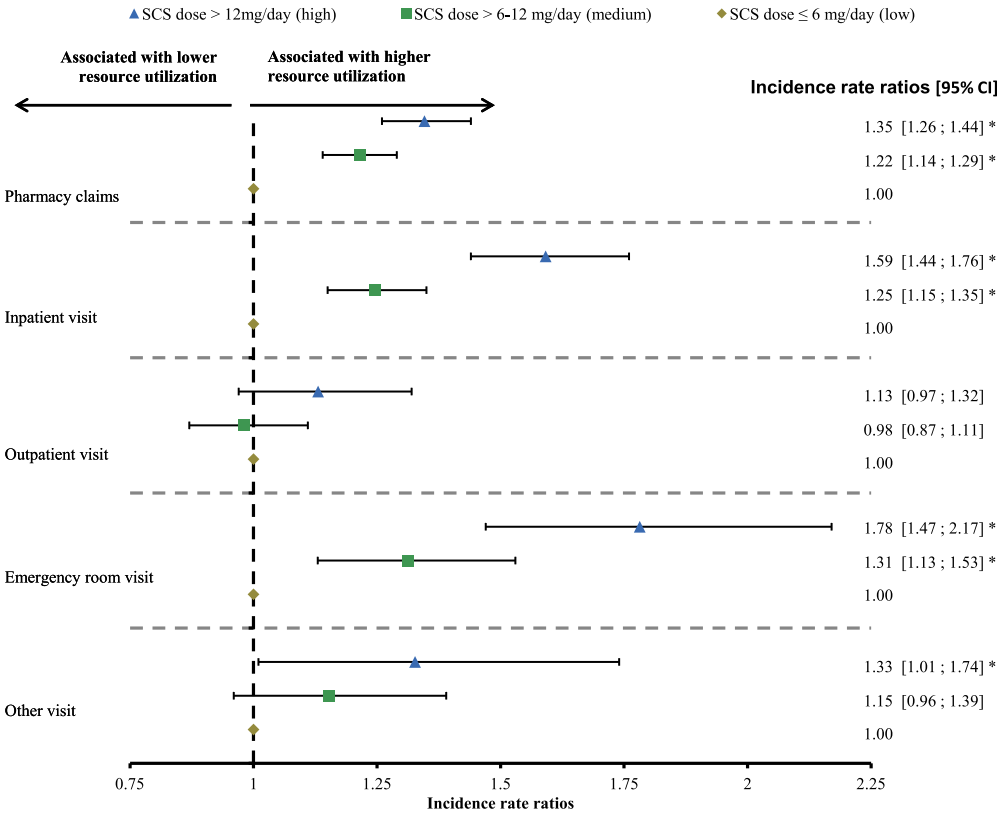

FIG 2. Health care resource use because of SCS-related complications by SCS exposure. In addition to controlling for key baseline characteristics (sex, age, race, state, total health care costs, and ≥1 emergency department or inpatient visit at baseline) and time-dependent variables (quarter, Charlson comorbidity index, and cost of concomitant medications), the GEE model used to estimate health care resource use because of SCS-related complications by SCS exposure controlled for pre-existing conditions at baseline. *Error bars* represent 95% CIs. *Statistical significance at a *P* value of .05.

SCS exposure by type of service and by SCS-related complication are shown in Fig 3. Total annualized incremental health care costs for medium and high SCS exposure were $1914 and $5479 relative to low SCS exposure, respectively. Health care costs of acute complications were $842 and $2953 higher for patients with medium and high SCS exposure than for patients with low SCS exposure. These differences were mostly driven by infection-related costs. For chronic complication costs, differences of $1767 and $4492 were observed between patients with medium and high SCS exposure and patients with low SCS exposure. The main drivers of these differences in chronic complication costs were cardiovascular, metabolic, and bone- and muscle-related complications.

DISCUSSION

Because of established clinical efficacy, SCSs are widely used to treat numerous inflammatory diseases, including asthma. However, their chronic use can lead to troublesome and severe complications.[8] This is the first longitudinal observational study evaluating the risk of SCS-related complications and their associated health care resource use and costs in a large US cohort of Medicaid beneficiaries with severe asthma and chronic SCS use.

Systematic literature reviews on SCS-related complications by Sarnes et al[8] and Hoes et al[10] reported that one shortcoming in the available published data is the short duration of studies on SCS-related complications, which leads to underestimation of long-term complications associated with corticosteroid use. The current study addressed this issue by using the Medicaid database, which contains information on all Medicaid beneficiaries from 6 states in the United States in the period of 1997 to 2013. It is important to highlight that the sample size used in this study is reassuringly large for a study with a long-term follow-up. In the meta-analysis by Hoes et al,[10] studies with long follow-up periods (>6 months) included no more than 235 patients each.

By using an open-cohort approach to classify patients' follow-up periods into different degrees of SCS exposure, this study allowed for the identification of a significant dose-response relationship between chronic use of SCSs and the risk of SCS-related complications. This finding is supported by data from previous studies that found a dose and time relation for more serious long-term corticosteroid-related adverse events.[11,15-19] In particular, fractures were often studied in the literature.[17,20-23] The results of the current study are in line with those of the study by Zonana-Nacah et al,[22] who found a 2.5-fold increased risk of fractures for each decade of prednisone at 10 mg/d in patients with systemic lupus erythematosus. Also, our findings are consistent with those of Richy et al,[19] who reported deleterious effects of inhaled corticosteroids (ICSs) on bone mineral density in clinical trials of patients with asthma/chronic obstructive pulmonary disease. Furthermore, cardiovascular complications were often given particular attention in the literature.[22,24-26] Similar to our findings, Souverein et al[26] reported an increased risk of cardiovascular complications with higher cumulative glucocorticoid doses, although the dose-response relation was not continuous.

TABLE II. Association between health care costs caused by SCS-related complications and SCS exposure

Health care costs (2013 $US) per quarter	Unadjusted costs, mean ± SD (median)	Unadjusted cost difference relative to low SCS exposure	Adjusted cost difference relative to low SCS exposure*	
			Mean† (95% CI)	*P* value
Pharmacy and medical costs				
Low SCS exposure (≤6 mg/d)	2,515 ± 5,528 (603)	—	—	—
Medium SCS exposure (>6-12 mg/d)	3,342 ± 6,149 (1,257)	827	**478** (256-733)	<.0001
High SCS exposure (>12 mg/d)	4,465 ± 8,254 (1,810)	1,950	**1,370** (1,018-1,720)	<.0001
Pharmacy costs				
Low SCS exposure (≤6 mg/d)	674 ± 1,534 (146)	—	—	—
Medium SCS exposure (>6-12 mg/d)	1,028 ± 1,711 (573)	353	**110** (36-198)	.0040
High SCS exposure (>12 mg/d)	1,336 ± 2,143 (783)	662	**307** (208-417)	<.0001
All medical costs				
Low SCS exposure (≤6 mg/d)	1,840 ± 5,081 (166)	—	—	—
Medium SCS exposure (>6-12 mg/d)	2,314 ± 5,658 (250)	474	**369** (168-600)	<.0001
High SCS exposure (>12 mg/d)	3,129 ± 7,804 (397)	1,289	**1,061** (731-1,402)	<.0001
Inpatient visit costs				
Low SCS exposure (≤6 mg/d)	571 ± 2,800 (0)	—	—	—
Medium SCS exposure (>6-12 mg/d)	881 ± 3,818 (0)	311	**239** (102-391)	<.0001
High SCS exposure (>12 mg/d)	1,324 ± 5,125 (0)	754	**620** (403-848)	<.0001
Outpatient visit costs				
Low SCS exposure (≤6 mg/d)	384 ± 2,951 (6)	—	—	—
Medium SCS exposure (>6-12 mg/d)	485 ± 2,654 (8)	101	**136** (45-215)	<.0001
High SCS exposure (>12 mg/d)	881 ± 4,813 (19)	498	**398** (250-514)	<.0001
Emergency department visit costs				
Low SCS exposure (≤6 mg/d)	6 ± 32 (0)	—	—	—
Medium SCS exposure (>6-12 mg/d)	9 ± 44 (0)	3	**2** (0-3)	.0100
High SCS exposure (>12 mg/d)	12 ± 48 (0)	6	**4** (2-6)	<.0001
Other visit costs				
Low SCS exposure (≤6 mg/d)	880 ± 2,742 (28)	—	—	—
Medium SCS exposure (>6-12 mg/d)	939 ± 3,058 (30)	60	35 (−88 to 173)	.4745
High SCS exposure (>12 mg/d)	911 ± 3,104 (47)	31	116 (−30 to 291)	.1181

$US, US dollars.

*In addition to controlling for key baseline characteristics (sex, age, race, state, total health care costs, and ≥1 emergency department or inpatient visit at baseline) and time-dependent variables (quarter, Charlson comorbidity index, and cost of concomitant medications), the GEE model used to estimate health care costs of SCS-related complications by SCS exposure controlled for the year of index date and pre-existing conditions at baseline.

†Boldface estimates are statistically significant ($P < .05$).

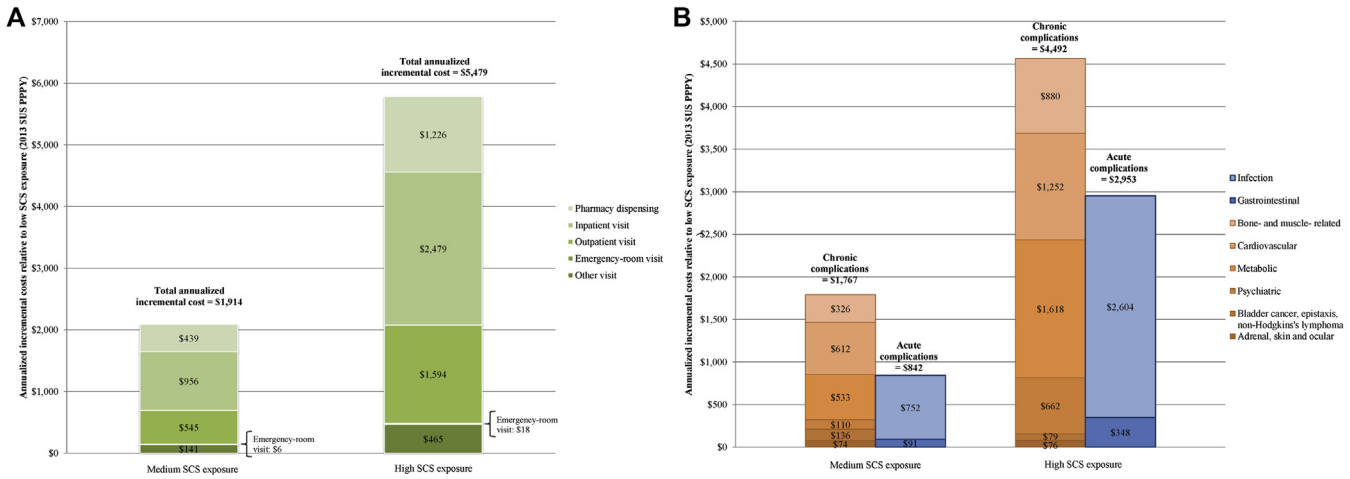

FIG 3. A, Annualized incremental costs of SCS-related complications for medium and high SCS exposure relative to low SCS exposure by type of service. **B,** Annualized incremental costs of SCS-related complications for medium and high SCS exposure relative to low SCS exposure by type of complication. Incremental costs of chronic and acute complications are not mutually exclusive because they were estimated through claims that could be associated with several diagnoses. As a consequence, costs associated with some claims were counted for both chronic and acute complication costs, whereas they were counted only once to estimate the incremental total health care costs. *$US PPPY*, US dollars per patient per year.

Results from this study also indicate that higher cumulative doses of SCSs tend to be associated with increased health care resource use and costs because of SCS-related complications. In the current study medium and high SCS exposure were associated with 31% and 78% more emergency department visits, 25% and 59% more inpatient visits, and 22% and 35% more pharmacy claims because of SCS-related complications, respectively, compared with low SCS exposure. Consequently, patients with medium and high SCS exposure had $1194 and $5479 in annual incremental costs relative to those with low SCS exposure. To the best of our knowledge, no study has previously investigated health care costs of corticosteroid-related complications grouped by exposure. O'Neill et al[27] estimated the direct health care treatment in the United Kingdom from a severe asthma registry in 596 patients and found that patients receiving maintenance oral corticosteroids are 43% more expensive than those not receiving maintenance oral corticosteroids. Among those receiving maintenance corticosteroids, asthma-related medications were more expensive, but notably, their nonmedication costs and non–asthma-related medication costs were significantly higher. These results on health care use and costs are important for both health care policymakers and payers because they suggest that chronic SCS use, particularly at high doses, is associated with a large burden on health care systems.

By stipulating at least 6 months of continuous SCS use before the index date, this study restricted the population to patients with severe asthma. These patients were included because they have particularly important unmet needs because they are associated with more asthma-related symptoms, increased risk of exacerbations, and higher asthma-related morbidity than other asthmatic patients.[1-4] Moreover, to take into account the fact that cumulative SCS exposure can change over time and that confounders can vary over time, patients' follow-up periods were split into quarters. Quarters were chosen because they were previously found to be short enough to be sensitive to changes in SCS dosing but long enough to enable observation of variations in time-dependent variables and outcomes.[22,28]

This study was subject to some limitations. First, pharmacy costs caused by SCS-related complications were identified by using claims for medications used to treat SCS-related complications. However, these medications could have been used for reasons other than treating complications caused by SCS use. For example, antidepressants, such as selective serotonin reuptake inhibitors, which were used to identify potential SCS-related depression complications, can sometimes be used to treat menopausal symptoms instead of depression.[29]

Second, ICSs, which have some degree of systemic bioavailability, were not included in our list of SCSs, and therefore total SCS exposure could have been underestimated.

Third, this study focused on the major known direct complications associated with SCS treatment but excluded important areas of SCS-associated negative effects, such as lost productivity and quality of life.

Fourth, because the study population consisted of Medicaid enrollees from 6 states, results from this study might not be generalizable to the general population. However, the 6 included states are geographically dispersed and represent a broad range of demography.

Fifth, the GEE approach might not have fully accounted for time-dependent confounding by indication bias. This type of confounding would have been more appropriately adjusted for by counterfactual models, such as a marginal structural model. Nonetheless, it was expected that no such important confounders in the causal pathway would be encountered. For example, even if asthma severity affected SCS dosage, it should not have affected SCS-related complications.

Sixth, matching the study populations at baseline was considered inappropriate with the choice of the open-cohort design. It is possible that SCS-related complications might have developed for some patients as a result of a more severe disease burden or a higher number of comorbidities at baseline rather than being associated with the level of SCS exposure. However, because the GEE models controlled for comorbidities at baseline, as well as conditions that developed over time, and our results consistently suggest a dose-response association while patients change SCS exposure cohorts over time, we believe that our study findings are robust to this limitation.

Seventh, the 6-month baseline period used in the current study might not be long enough to capture all pre-existing conditions at baseline (eg, in patients who can only consult annually). However, given the repeated nature of our analytic approach with an open-cohort design to control for time-dependent variables and update the patients' characteristics over time, the effect of the baseline period length is not as meaningful for our study.

Finally, although health insurance claims data are a rich, relatively inexpensive, and important source of information for studies of health care use and costs, because these data are generated for administrative billing purposes, the conversion of claims into research information deserves caution. The billing diagnoses might not always reflect confirmed clinical diagnoses, and SCS pharmacy dispensings do not necessarily indicate patients' consumption of the medicine. However, we expect these misclassification and measurement errors are nondifferential across the study treatment groups, and hence the biases should not materially affect their comparison.

This longitudinal observational study is the first to compare health care resource use and costs of SCS-related complications by SCS exposure in a large cohort of Medicaid beneficiaries with severe asthma chronically using SCSs. A significant dose-response relationship between the chronic use of SCSs and health care resource use and costs of SCS-related complications was found. In particular, annualized incremental health care costs of SCS-related complications for medium and high SCS exposure were $1194 and $5479 higher, respectively, relative to low SCS exposure. These results are consistent with findings from other studies about asthma or other diseases that found a relationship between long-term SCS use and deleterious complications, as well as increased costs. Consistent with current asthma treatment guidelines, which recommend the use of the lowest effective dose of ICSs or SCSs to maintain satisfactory symptom control and reduce exacerbations,[1,30] these data highlight that identifying effective strategies for SCS-sparing treatments might help reduce health care costs and resource use in patients with severe asthma.

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Clinical implications: A significant dose-response relationship exists between chronic SCS use and the risk of SCS-related complications in patients with severe asthma. Effective SCS-sparing strategies are needed to reduce this burden.

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