Dose-Response Relationship Between Long-Term Systemic Corticosteroid Use and Related Complications in Patients with Severe Asthma

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ABSTRACT

BACKGROUND: Systemic corticosteroids are a leading cause of drug-related complications, yet little has been done to quantify the dose-response relationship between systemic corticosteroid exposure and complications in patients with severe asthma.

OBJECTIVES: To (a) evaluate the risk of developing systemic corticosteroid-related complications by corticosteroid exposure in severe asthma and (b) quantify the associated health care resource utilization and costs.

METHODS: This is a retrospective study using administrative claims data from a large commercial database between 2003 and 2014. Multivariate generalized estimating equation models were used to compare corticosteroid-related complications in patients continuously exposed to at least 5 mg of prednisone or equivalent for ≥6 months with a 1:1 ratio of propensity score-matched patients with asthma who did not use corticosteroids.

RESULTS: A total of 12,697 corticosteroid users and as many matched nonusers were identified. The odds of developing associated complications increased significantly in a dose-dependent manner with systemic corticosteroid exposure: odds ratios were 2.50, 2.95, and 3.32 (*P* values <0.05) for low (defined as <5 mg/day), medium (≥5-10 mg/day), and high (>10 mg/day) exposure, respectively, relative to no exposure. Health care resource utilization increased significantly with levels of systemic corticosteroid exposure. Hence, incidence rate ratios for inpatient visits with low, medium, and high exposure relative to none were estimated to be 1.86, 2.40, and 3.37, respectively (*P*<0.05).

CONCLUSIONS: A significant dose-response relationship was found between the long-term use of systemic corticosteroids and the risk of developing systemic corticosteroid-related complications in patients with severe asthma, resulting in increased burden and costs on the health care system that intensified with systemic corticosteroid exposure.

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What is already known about this subject

- Long-term use of systemic corticosteroids is a leading cause of drug-related complications.
- Asthma patients on maintenance corticosteroids have higher health care costs and notably higher nonmedication and non-asthma-related medication costs.

What this study adds

- This study shows that patients with severe asthma had a significantly higher risk of developing systemic corticosteroid-related complications compared with those not exposed to systemic corticosteroids.
- The identified risk significantly increased with systemic corticosteroid exposure, resulting in an incremental burden on health care resources, although the benefit of using systemic corticosteroid for asthma control was not assessed in the current study.

Systemic corticosteroids (SCSs) are widely used as frontline treatment in a variety of chronic inflammatory and autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, or Crohn's disease because of their potent anti-inflammatory and immunosuppressive properties.[1-3] They are also recommended for treatment of severe asthma (evidence level D) when other treatments have failed to control the disease.[4] However, long-term use of corticosteroids is associated with short- and long-term complications such as fractures, susceptibility to infections, obesity, stroke, cataract, and skin thinning.[5] According to data from the Healthcare Cost and Utilization Project, corticosteroids were the most common cause of drug-related complications in 2004, accounting for 10% of all drug-related complications and 141,000 hospital stays in the United States.[6] However, as reported in a recent literature review, evidence for the risks and costs associated with SCS therapy is sparse and inconsistent, particularly in patients with asthma.[5,7] Very few studies have considered the cumulative dose-response relationship between SCSs and their related complications, and no study has measured the association between the magnitude of SCS exposure and health care resource utilization.

In this study, we investigated the risk of developing SCS-related complications for different degrees of SCS exposure compared with no SCS exposure and quantified the associated health care resource utilization and costs in severe asthma patients from a large U.S. commercially insured population.

Methods

Data Sources

The Truven Health MarketScan Research Databases contain claims from >300 contributing employers and 25 contributing health plans across all regions of the United States. The present study used a subset of asthma patients from 2 core Truven databases: the Commercial Claims and Encounters database (2003-2014) and the Medicare Supplemental and Coordination of Benefits database (2006-2013). These databases include information on enrollment history, patient demographic characteristics (e.g., date of birth, region, and gender), claims for medical and pharmacy services, and complete payment information. For the purpose of this study, the total gross payment, including covered payer costs and patients' copays and deductables, was used. The databases were de-identified and complied with the Health Insurance Portability and Accountability Act of 1996 to preserve patient anonymity and confidentiality.

Study Design and Patient Groups

A retrospective, longitudinal, open-cohort study was conducted using de-identified claims from the Truven Health MarketScan Research Databases. Eligible patients were aged ≥12 years and had ≥2 administrative charges associated with a diagnosis for asthma (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] code 493.xx). SCS users were required to have ≥6 months of continuous chronic SCS use (identified by claims with daily doses of at least 5 mg prednisone equivalent with no gap of ≥14 days between 2 SCS claims. Doses of 0.6 mg betamethasone, 0.375 mg budesonide, 25 mg cortisone, 0.75 mg dexamethasone, 20 mg hydrocortisone, 4 mg methylprednisolone, 5 mg prednisolone, and 4 mg triamcinolone were considered equivalent to 5 mg prednisone).[8,9] These first 6 months constituted the baseline period, and the index date was defined as the first day with a daily dose of ≥5 mg prednisone equivalent following this period. Among asthma patients never exposed to SCS, those with ≥1 prescription for an asthma medication other than SCS were eligible for the control group (SCS nonusers). The index date was defined as the initiation of this medication. All patients were required to be continuously covered by their health plans for ≥6 months (baseline period) before their index dates. The follow-up period spanned from the index date to the earliest of disenrollment from health plan or data cutoff. Patients with conditions other than asthma that are commonly treated with SCS were excluded from the study (i.e., cancer of the respiratory and intrathoracic system, rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, and multiple sclerosis). Patients with a dose per claim higher than the 99th percentile were excluded to avoid the effects of outliers. Figure 1 summarizes the patient selection process.

Data Collection

To appropriately account for the fact that a patient's asthma severity and SCS exposure may change over time, follow-up periods were divided into quarterly time intervals over which patient level of SCS exposure was categorized according to the cumulative SCS dose intensity (i.e., no exposure; low exposure <5 mg/day; medium exposure ≥5-10 mg/day; and high exposure >10 mg/day). These quarters were also used to assess the occurrence of SCS-related complications, complication-related health care resource utilization, and complication-related health care costs.

Outcomes

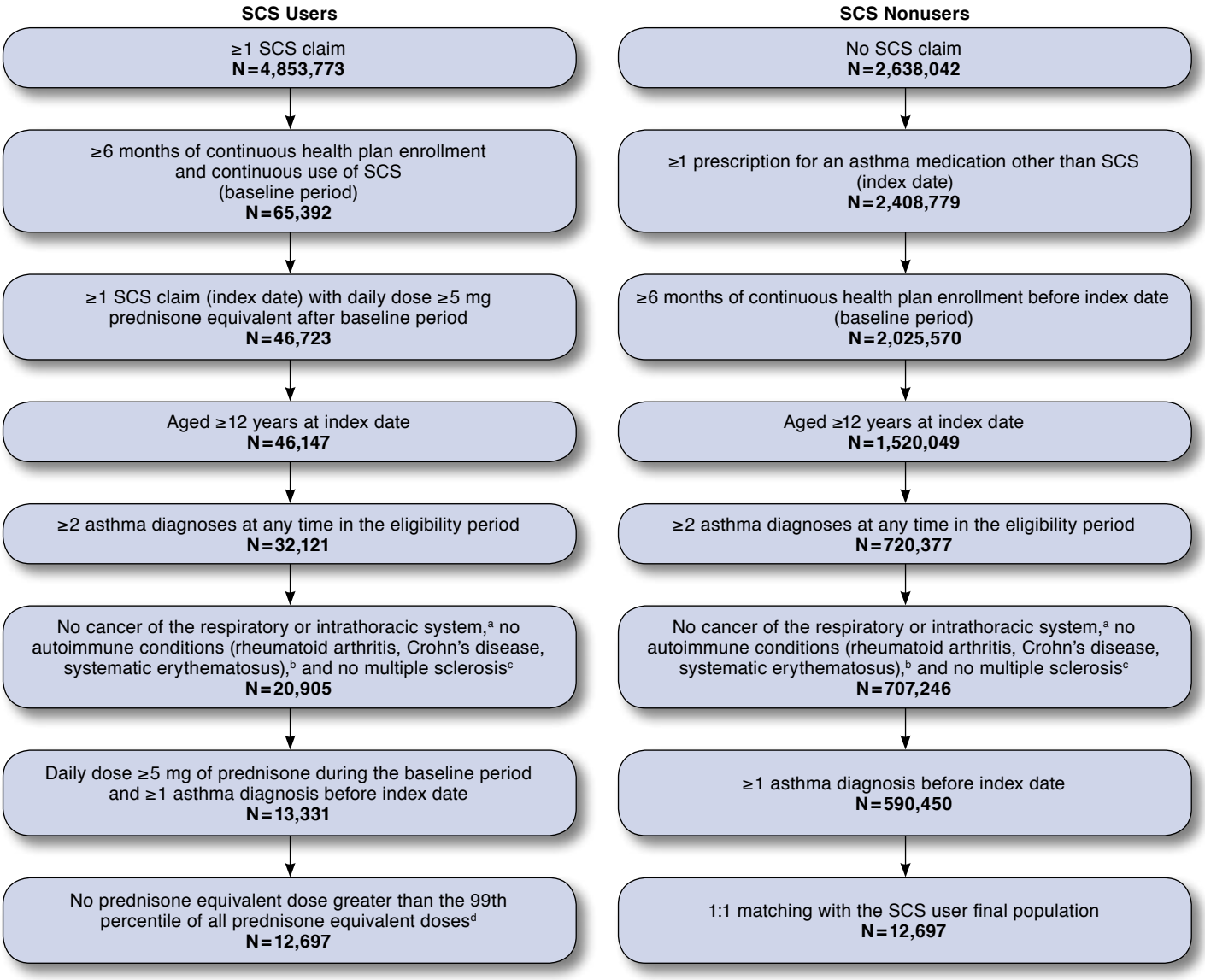
The study outcomes were the risk of developing acute and chronic SCS-related complications and associated health care resource utilization and costs. Acute complications included infections and gastrointestinal complications, whereas chronic complications included cardiovascular, metabolic, bone- and muscle-related, psychiatric, ocular, skin-related, adrenal, and other (bladder cancer, epistaxis, and non-Hodgkin's lymphoma) conditions (Appendix A, available in online article). The outcomes were calculated over the follow-up period on a quarterly basis, and health care costs were further annualized. Health care resource utilization and costs because of SCS-related complications, grouped into pharmacy dispensings, outpatient visits, emergency room visits, hospitalizations, and other visits, were calculated using (a) medical claims with a diagnosis (ICD-9-CM codes) for SCS-related complications (Appendix A) or (b) pharmacy claims for medications used to treat SCS-related complications (Appendix B, available in online article). Costs were adjusted to 2014 U.S. dollars using the medical care component of the Consumer Price Index.[10]

Statistical Analysis

Descriptive statistics were generated to summarize the patient baseline characteristics at the index date. Baseline characteristics included age, gender, region, calendar year of index date, pre-existing conditions that may influence the occurrence of SCS-related complications (i.e., history of falls, fractures, or diagnosis of osteoporosis; diagnosis of cognitive impairment or depression; diagnosis of epilepsy, cerebrovascular disease, or Parkinson's disease; diagnosis of diabetes mellitus; and diagnosis of chronic cardiovascular conditions), history of SCS-related complications, Charlson Comorbidity Index (CCI),[11] and all-cause and asthma-related health care costs. Frequency counts and percentages were used to summarize categorical variables, while means and standard deviations were used for continuous variables.

Standardized differences, which are the commonly accepted metrics to evaluate balance in propensity score matching,[12] were used to compare the baseline characteristics between SCS users and SCS nonusers. Baseline characteristics with

FIGURE 1 Sample Selection Flowcharts



[a]ICD-9-CM diagnosis codes 160.xx-165.xx were used to identify cancer of the respiratory and intrathoracic system.
[b]ICD-9-CM diagnosis codes 714.0x, 714.2x (rheumatoid arthritis), 555.xx (Crohn's disease), and 710.0x (systemic lupus erythematosus) were used to identify autoimmune conditions.
[c]ICD-9-CM diagnosis code 340.xx was used to identify multiple sclerosis.
[d]The 99th percentile of all prednisone equivalent dose per claim was 3,600 mg of prednisone equivalent.
ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; SCS = systemic corticosteroids.

standardized differences below 10% were considered well balanced, as commonly found in the literature.[12] SCS users and SCS nonusers were matched exactly with a ratio of 1:1 based on the propensity score. The propensity score modeled the probability of SCS use given demographic (age, gender, region, and year of index date) and clinical (CCI and pre-existing conditions) covariates, as well as baseline asthma-related health care costs.

The association between SCS exposure and outcomes was estimated through multivariate generalized estimating equation (GEE) models. 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 further controlled for key baseline characteristics (gender, age, region, total health care costs, whether the patient had at least 1 emergency room or inpatient visit)—to account for potential differences in the characteristics of patients with different degrees of SCS exposure—and time-dependent variables (quarter of observation, CCI, and cost of concomitant medications).

Odds ratios (ORs), estimated with a GEE model using a binomial distribution with logit link function and exchangeable correlation structure, were used to assess the risk of developing SCS-related complications for patients with low, medium, and high SCS exposure relative to patients without exposure to SCS. The GEE model used to estimate the incidence rate ratios of health care resource utilization because of SCS-related complications was based on a Poisson distribution with independent correlation structure. Adjusted cost differences between patients with low, medium, and high SCS exposure and SCS nonusers were assessed with a GEE model using a normal distribution with exchangeable correlation structure. Nonparametric bootstrap procedures with 999 replications were used to estimate 95% confidence intervals (CIs) and *P* values. In addition to the aforementioned key baseline characteristics and time-dependent variables, the GEE models controlled for the baseline CCI, the year of index date, and the presence of an SCS-related complication of interest or pre-existing conditions at baseline, where applicable (see Figures 2-4 for details regarding the covariates used in each GEE model). All outcomes were assessed for linear trends in continuous SCS exposure.

All analyses were conducted using SAS software version 9.3 of the SAS System for Windows (SAS Institute, Cary, NC). Statistical significance was declared at a 2-sided test at α-level of 0.05 or less.

Results

Baseline Characteristics

The initial unmatched asthma population included 12,697 SCS users and 590,450 SCS nonusers (Figure 1), and both groups differed significantly on most baseline characteristics (Table 1). The final propensity score-matched asthma population, which included all SCS users and an equal number of SCS nonusers, was more homogenous, since the standardized differences of the matching covariates were all smaller than 10%, except for asthma-related health care costs. SCS users and SCS nonusers were aged on average (median) 62.4 (61.9) and 62.6 (62.9) years, respectively, and both groups included 58.8% female patients. Mean (median) CCI was 1.9 (1.0) and 1.8 (1.0) for SCS users and nonusers, respectively.

Risks of Developing SCS-Related Complications

Compared with SCS nonusers, SCS users were significantly more likely to develop any SCS-related complication, and this likelihood increased with SCS exposure: ORs were 2.50 (95% CI = 1.22-5.10), 2.95 (95% CI = 2.60-3.35), and 3.32 (95% CI = 2.90-3.80) for low, medium, and high SCS exposure, respectively, compared with no exposure (Figure 2A). A significant linear relationship between increasing SCS exposure and increasing risk of developing SCS-related complications was also observed based on continuous SCS doses ($P < 0.0001$). Similar results were observed for the risks of developing acute and chronic complications, although the OR for chronic complications was not significant for low SCS exposure. The odds of developing infections (e.g., fungal and herpes zoster); bone/muscle-related complications (e.g., avascular necrosis and fractures); and skin diseases (e.g., bruising and striae) increased by at least 36%, 42%, and 66% for low, medium, and high SCS exposure, respectively, compared with no exposure. For medium and high SCS exposure compared with no SCS exposure, the odds for cardiovascular complications (e.g., hypertension and myocardial infarction) and psychiatric complications (e.g., depression and sleep disturbances) increased by at least 73%, whereas they increased by at least 96% for gastrointestinal complications (e.g., ulcers and gastritis with hemorrhage) and 32% for metabolic complications (e.g., obesity and dyslipidemia; Figure 2B).

Health Care Resource Utilization Because of SCS-Related Complications

Exposure to SCSs was associated with significant increases in health care resource utilization because of SCS-related complications, and these increases were more pronounced with higher degrees of SCS exposure (Figure 3). In fact, significant linear trends were observed between increasing SCS exposure, as a continuous variable, and increasing resource utilization of all types ($P < 0.0001$). This was also reflected in inpatient visits (incidence rate ratios for low, medium, and high SCS exposure relative to no exposure: 1.86 [95% CI = 1.70-2.04], 2.40 [95% CI = 2.26-2.56], and 3.37 [95% CI = 3.18-3.59]) and emergency room visits (incidence rate ratios for low, medium, and high SCS exposure relative to no exposure: 1.57 [95% CI = 1.39-1.78], 1.78 [95% CI = 1.65-1.92], and 2.17 [95% CI = 2.00-2.35]).

Health Care Costs of SCS-Related Complications

Table 2 presents the quarterly health care costs of SCS-related complications estimated by SCS exposure and quarter, and the annualized cost differences between SCS users and SCS nonusers are reported in Figure 4. A significant trend of increasing costs with increasing SCS exposure based on continuous SCS doses was observed ($P < 0.0001$), and annual health care costs of SCS-related complications were estimated to be $2,670, $4,639, and $9,162 higher for patients with low, medium, and

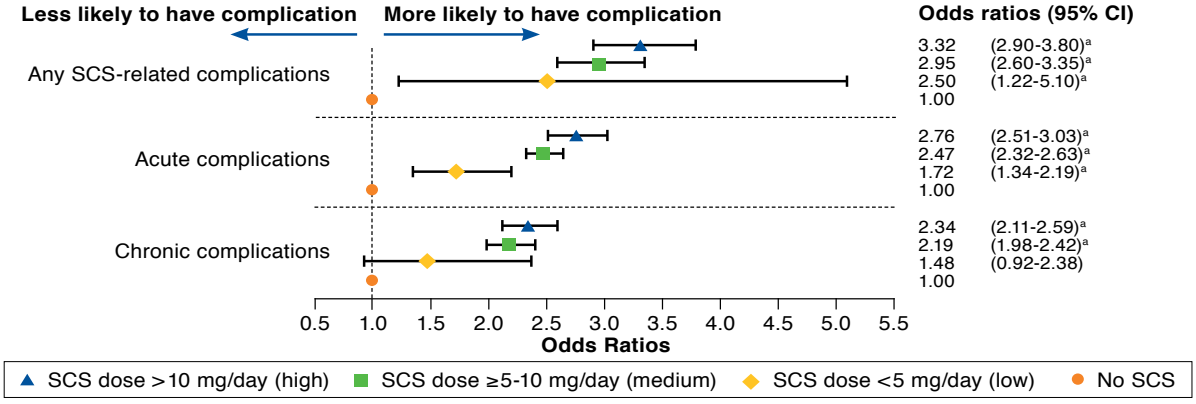
TABLE 1 Demographic and Clinical Baseline Characteristics at Index Date for Unmatched and Matched Populations

	Unmatched Populations			Matched Populations		
	SCS Users (N = 12,697)	SCS Nonusers (N = 590,450)	Std. Diff. (%)	SCS Users (N = 12,697)	SCS Nonusers (N = 12,697)	Std. Diff. (%)
Age at index date, mean ± SD [median], years	62.4 ± 15.2 [61.9]	37.7 ± 19.1 [36.5]	143.24	62.4 ± 15.2 [61.9]	62.6 ± 15.1 [62.9]	1.48
Age categories, years, n (%)						
12-17	114 (0.9)	130,956 (22.2)	66.61	114 (0.9)	110 (0.9)	0.34
18-34	451 (3.6)	151,282 (25.6)	62.52	451 (3.6)	388 (3.1)	2.78
35-44	900 (7.1)	90,105 (15.3)	25.94	900 (7.1)	786 (6.2)	3.61
45-54	2,218 (17.5)	92,035 (15.6)	5.07	2,218 (17.5)	2,116 (16.7)	2.14
55-64	3,851 (30.3)	83,577 (14.2)	38.89	3,851 (30.3)	3,851 (30.3)	0.00
≥ 65	5,163 (40.7)	42,495 (7.2)	78.44	5,163 (40.7)	5,446 (42.9)	4.52
Female, n (%)	7,471 (58.8)	337,397 (57.1)	3.44	7,471 (58.8)	7,465 (58.8)	0.10
Region, n (%)						
North Central	3,999 (31.5)	134,223 (22.7)	19.71	3,999 (31.5)	3,986 (31.4)	0.22
South	3,990 (31.4)	154,063 (26.1)	11.78	3,990 (31.4)	4,086 (32.2)	1.62
Northeast	2,345 (18.5)	139,604 (23.6)	12.69	2,345 (18.5)	2,361 (18.6)	0.32
West	2,177 (17.1)	149,590 (25.3)	20.02	2,177 (17.1)	2,084 (16.4)	1.96
Unknown	186 (1.5)	12,970 (2.2)	5.46	186 (1.5)	180 (1.4)	0.40
Follow-up period duration, mean ± SD [median], years	2.0 ± 1.9 [1.5]	1.2 ± 0.9 [1.1]	55.63	2.0 ± 1.9 [1.5]	1.1 ± 0.9 [1.1]	60.51
Year of index date, n (%)						
2003-2004	652 (5.1)	27,533 (4.7)	2.19	652 (5.1)	660 (5.2)	0.28
2005-2006	1,250 (9.8)	41,572 (7.0)	10.09	1,250 (9.8)	1,265 (10.0)	0.40
2007-2008	2,168 (17.1)	74,401 (12.6)	12.59	2,168 (17.1)	2,212 (17.4)	0.92
2009-2010	3,031 (23.9)	119,421 (20.2)	8.80	3,031 (23.9)	3,143 (24.8)	2.06
2011-2012	3,748 (29.5)	197,601 (33.5)	8.50	3,748 (29.5)	3,639 (28.7)	1.89
2013-2014	1,848 (14.6)	129,922 (22.0)	19.27	1,848 (14.6)	1,778 (14.0)	1.58
Pre-existing conditions, n (%)						
Diagnosis of chronic cardiovascular conditions	6,916 (54.5)	132,057 (22.4)	66.00	6,916 (54.5)	7,106 (56.0)	3.01
Diagnosis of diabetes mellitus	3,044 (24.0)	37,930 (6.4)	48.88	3,044 (24.0)	3,186 (25.1)	2.60
Diagnosis of cognitive impairment or depression	1,646 (13.0)	53,041 (9.0)	12.74	1,646 (13.0)	1,670 (13.2)	0.56
History of falls, fractures, or diagnosis of osteoporosis	1,561 (12.3)	18,001 (3.0)	34.74	1,561 (12.3)	1,505 (11.9)	1.35
Diagnosis of epilepsy, cerebrovascular disease, or Parkinson's disease	873 (6.9)	9,813 (1.7)	25.79	873 (6.9)	852 (6.7)	0.66
≥ 1 SCS-related complication, n (%)	12,454 (98.1)	413,066 (70.0)	76.77	12,454 (98.1)	11,615 (91.5)	29.71
≥ 1 acute SCS-related complication, n (%)	11,178 (88.0)	276,758 (46.9)	87.86	11,178 (88.0)	8,094 (63.7)	56.79
Infections	10,296 (81.1)	238,450 (40.4)	83.36	10,296 (81.1)	6,815 (53.7)	58.48
Gastrointestinal	6,584 (51.9)	87,213 (14.8)	78.68	6,584 (51.9)	3,841 (30.3)	43.92
≥ 1 chronic SCS-related complication, n (%)	11,960 (94.2)	321,067 (54.4)	91.11	11,960 (94.2)	10,971 (86.4)	26.32
Cardiovascular	9,192 (72.4)	136,261 (23.1)	98.74	9,192 (72.4)	7,748 (61.0)	24.13
Bone- and muscle-related	7,905 (62.3)	139,356 (23.6)	78.10	7,905 (62.3)	5,397 (42.5)	39.55
Psychiatric	7,143 (56.3)	139,731 (23.7)	66.54	7,143 (56.3)	4,859 (38.3)	36.03
Metabolic	6,921 (54.5)	128,089 (21.7)	67.57	6,921 (54.5)	6,883 (54.2)	0.60
Ocular	2,003 (15.8)	22,971 (3.9)	39.91	2,003 (15.8)	1,841 (14.5)	3.56
Skin diseases	614 (4.8)	14,364 (2.4)	12.84	614 (4.8)	442 (3.5)	6.79
Adrenal	91 (0.7)	56 (0.0)	11.76	91 (0.7)	1 (0.0)	11.80
Other	950 (7.5)	6,216 (1.1)	31.81	950 (7.5)	531 (4.2)	14.08
Health care costs, mean ± SD [median], 2014 $US						
All-cause health care costs	19,961 ± 38,109 [9,333]	3,820 ± 13,417 [1,289]	56.50	19,961 ± 38,109 [9,333]	12,418 ± 31,575 [3,744]	21.56
Asthma-related total health care costs	3,348 ± 8,058 [1,532]	736 ± 2,865 [213]	43.20	3,348 ± 8,058 [1,532]	2,423 ± 9,341 [523]	10.61
CCI, mean ± SD [median]	1.9 ± 1.6 [1.0]	0.8 ± 0.9 [1.0]	87.29	1.9 ± 1.6 [1.0]	1.8 ± 1.8 [1.0]	0.83

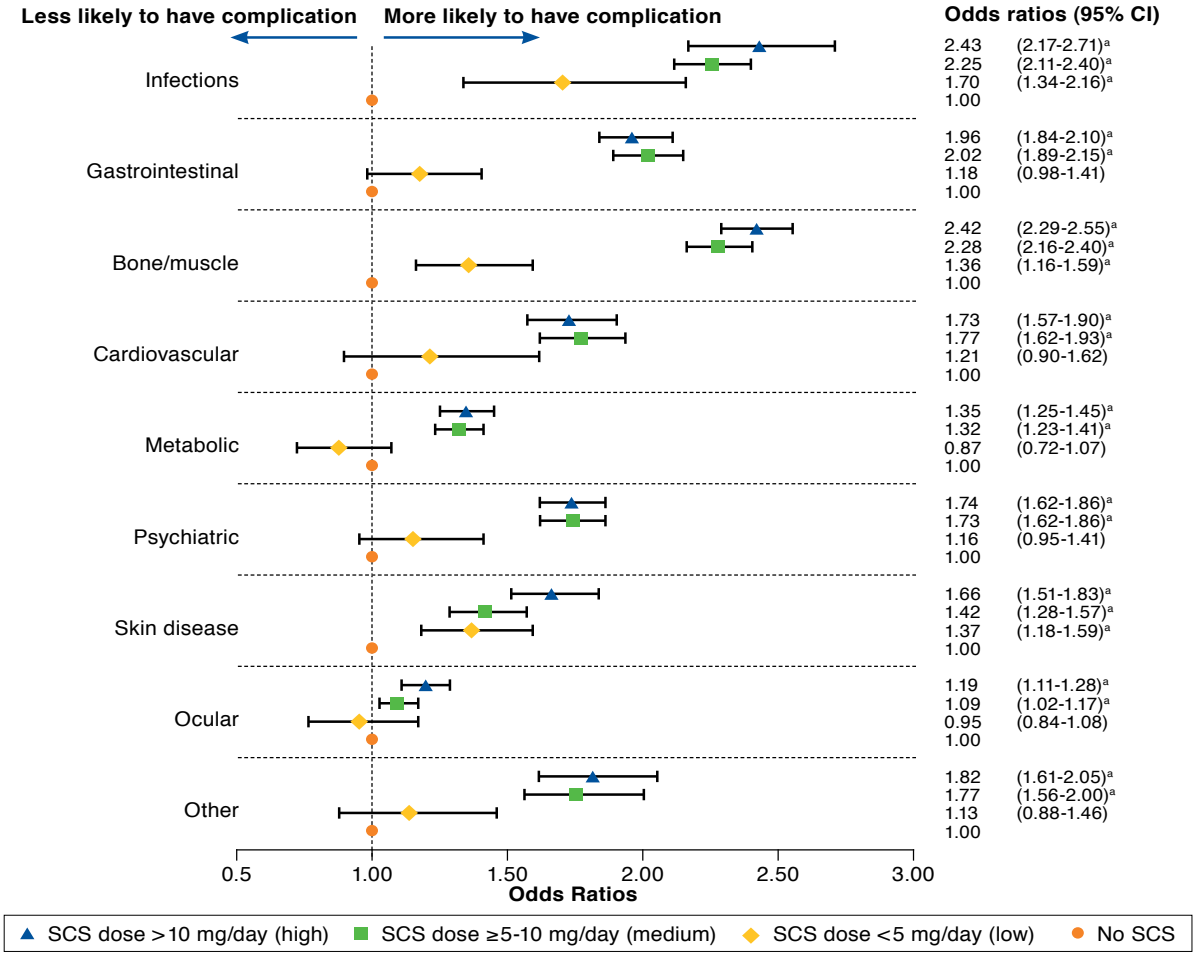
CCI = Charlson Comorbidity Index; SCS = systemic corticosteroids; SD = standard deviation; Std. Diff. = standardized difference; $US = U.S. dollars.

FIGURE 2 Risk of Developing SCS-Related Complications by SCS Exposure

A. Acute and Chronic Complications



B. Stratified Complications

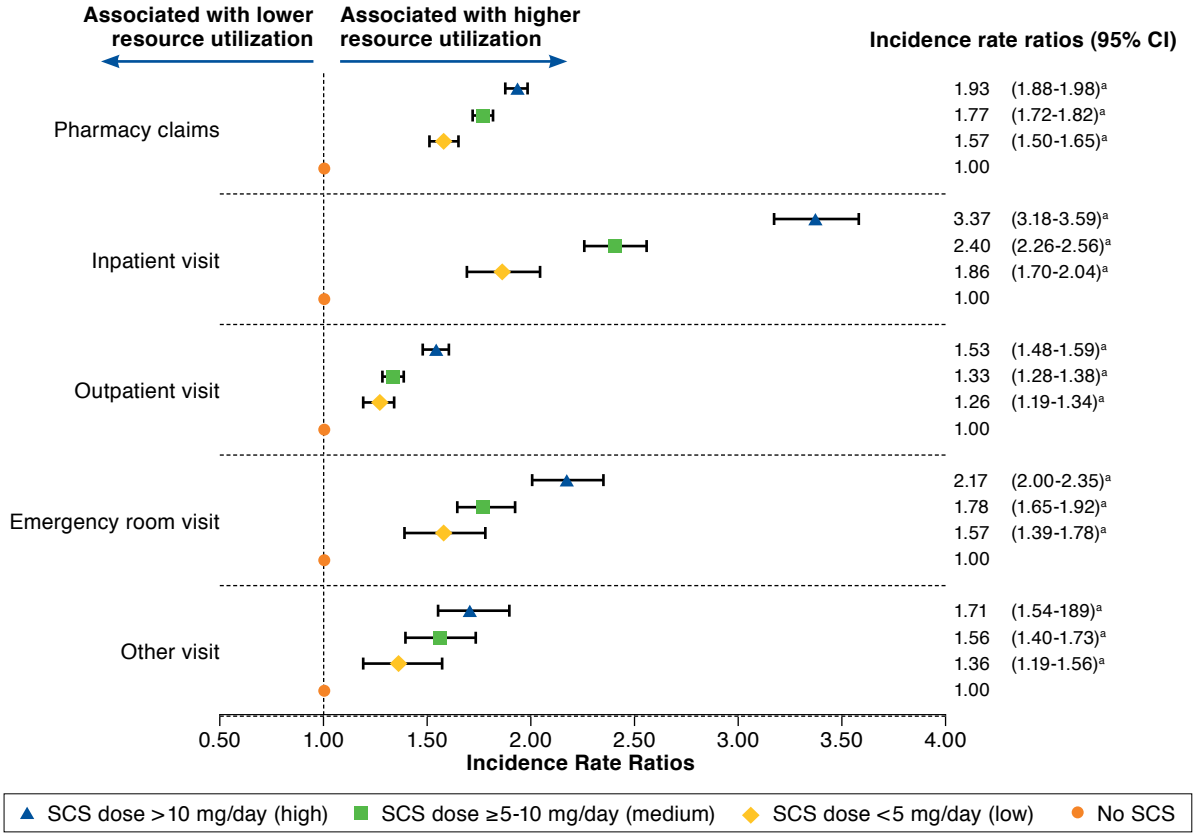


Note: Error bars represent 95% CIs. In addition to controlling for key baseline characteristics (gender, age, region, total health care costs, and whether the patient had ≥1 emergency room or inpatient visit at baseline) and time-dependent variables (quarter, Charlson Comorbidity Index, and cost of concomitant medications), the GEE model used to estimate the risk of developing SCS-related complications by SCS exposure controlled for occurrence of the SCS-related condition of interest at baseline and for the year of index date. Odds ratios of developing adrenal complications were not reported in Figure 2B because the resulting scale of the figure would not have allowed the other odds ratios to be properly read and compared. They were 3.87 (95% CI=0.93-16.06; P=0.0624), 20.95 (95% CI=7.62-57.63; P<0.0001), and 40.67 (95% CI=15.12-109.35; P<0.0001) for low, medium, and high SCS exposure, respectively, relative to no SCS exposure. Other category represents the conditions bladder cancer, epistaxis, and non-Hodgkin's lymphoma.

[a]Indicates statistical significance at a level of 0.05.

CI=confidence interval; GEE=generalized estimating equation; SCS=systemic corticosteroids.

FIGURE 3 Health Care Resource Utilization Because of SCS-Related Complications by SCS Exposure Compared with No SCS Exposure



Note: Error bars represent 95% CIs. In addition to controlling for key baseline characteristics (gender, age, region, total health care costs, and whether the patient had ≥1 emergency room 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 utilization because of SCS-related complications by SCS exposure controlled for pre-existing conditions at baseline and baseline Charlson Comorbidity Index.

[a]Indicates statistical significance at a level of 0.05.

CI = confidence interval; GEE = generalized estimating equation; SCS = systemic corticosteroids.

high SCS exposure, respectively, than for SCS nonusers. These cost differences were mainly driven by incremental pharmacy costs and inpatient visit costs.

Discussion

In this large retrospective open-cohort study of severe asthma patients, we found a significant dose-response relationship between degrees of SCS cumulative dose intensity and the risk of developing SCS-related complications. As expected, the magnitude of the dose-response relationship differed across categories of complications.

Previous asthma studies focusing on SCS-related complications were found either to be conducted on small sample sizes, to be of short duration in SCS exposure or in follow-up, or to examine a limited number of complications.[5,13,14] Nevertheless, many previous studies found a dose and time relationship for serious long-term corticosteroid-related complications.[13,15-18] In particular, fractures were often studied in the literature.[19-23] The present study found that patients with low, medium, and high SCS exposure had a 1.36-fold, 2.28-fold, and 2.42-fold risk, respectively, of developing bone- and muscle-related complications, such as fractures, relative to patients without exposure to SCSs. De Vries et al. (2007) reported a significantly increased risk of developing fractures among obstructive airway disease patients exposed to an SCS compared with those who were never exposed to an SCS.[19] Depending on the type of fracture, they estimated a relative risk varying from 1.37 to 5.65 for patients with a cumulative dose of SCS between 1 gm and 5 gm, and from 3.00 to 10.61 for patients with a cumulative dose >5 gm.[19]

TABLE 2 Association Between Health Care Costs Because of SCS-Related Complications and SCS Exposure

Health Care Costs (2014 $US)	Unadjusted Costs Mean ± SD [median]	Unadjusted Cost Difference Relative to No SCS	Adjusted Cost Difference Relative to No SCS Exposure[a]	
			Mean[b] (95% CI)	*P* Value
Pharmacy and medical costs				
No SCS	1,754 ± 10,749 [265]			
SCS dose: < 5 mg/day (low)	3,033 ± 16,406 [576]	1,279	**667** (257-937)	0.0020
SCS dose: ≥ 5-10 mg/day (medium)	3,284 ± 12,287 [715]	1,531	**1,160** (1,038-1,427)	< 0.0001
SCS dose: > 10 mg/day (high)	4,702 ± 19,382 [872]	2,948	**2,291** (2,044-2,532)	< 0.0001
Pharmacy costs				
No SCS	412 ± 1,041 [82]			
SCS dose: < 5 mg/day (low)	709 ± 1,538 [257]	297	**342** (302-397)	< 0.0001
SCS dose: ≥ 5-10 mg/day (medium)	850 ± 1,907 [350]	438	**422** (393-460)	< 0.0001
SCS dose: > 10 mg/day (high)	956 ± 2,032 [403]	544	**416** (382-447)	< 0.0001
All medical costs				
No SCS	1,342 ± 10,672 [21]			
SCS dose: < 5 mg/day (low)	2,324 ± 16,216 [95]	982	390 (-33-629)	0.0721
SCS dose: ≥ 5-10 mg/day (medium)	2,434 ± 12,047 [113]	1,092	**760** (629-1,013)	< 0.0001
SCS dose: > 10 mg/day (high)	3,746 ± 19,178 [150]	2,404	**1,872** (1,633-2,096)	< 0.0001
Inpatient visit costs				
No SCS	813 ± 10,104 [0]			
SCS dose: < 5 mg/day (low)	1,511 ± 15,648 [0]	698	233 (-143-467)	0.2162
SCS dose: ≥ 5-10 mg/day (medium)	1,570 ± 11,062 [0]	757	**467** (331-683)	< 0.0001
SCS dose: > 10 mg/day (high)	2,688 ± 18,474 [0]	1,875	**1,433** (1,212-1,635)	< 0.0001
Outpatient visit costs				
No SCS	337 ± 2,035 [0]			
SCS dose: < 5 mg/day (low)	478 ± 2,343 [63]	141	**82** (12-142)	0.0300
SCS dose: ≥ 5-10 mg/day (medium)	536 ± 2,989 [74]	199	**182** (150-230)	< 0.0001
SCS dose: > 10 mg/day (high)	686 ± 3,297 [90]	348	**282** (244-325)	< 0.0001
Emergency room visit costs				
No SCS	59 ± 739 [0]			
SCS dose: < 5 mg/day (low)	102 ± 810 [0]	44	**24** (11-45)	< 0.0001
SCS dose: ≥ 5-10 mg/day (medium)	97 ± 712 [0]	38	**30** (24-44)	< 0.0001
SCS dose: > 10 mg/day (high)	135 ± 1,084 [0]	76	**61** (49-72)	< 0.0001
Other visit costs				
No SCS	133 ± 1,337 [0]			
SCS dose: < 5 mg/day (low)	232 ± 2,147 [0]	99	**55** (6-93)	0.0240
SCS dose: ≥ 5-10 mg/day (medium)	232 ± 1,937 [0]	99	**75** (52-103)	< 0.0001
SCS dose: > 10 mg/day (high)	238 ± 1,809 [0]	105	**95** (78-122)	< 0.0001

[a] *In addition to controlling for key baseline characteristics (gender, age, region, total health care costs, whether the patient had ≥1 emergency room 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, baseline Charlson Comorbidity Index, and pre-existing conditions at baseline.*

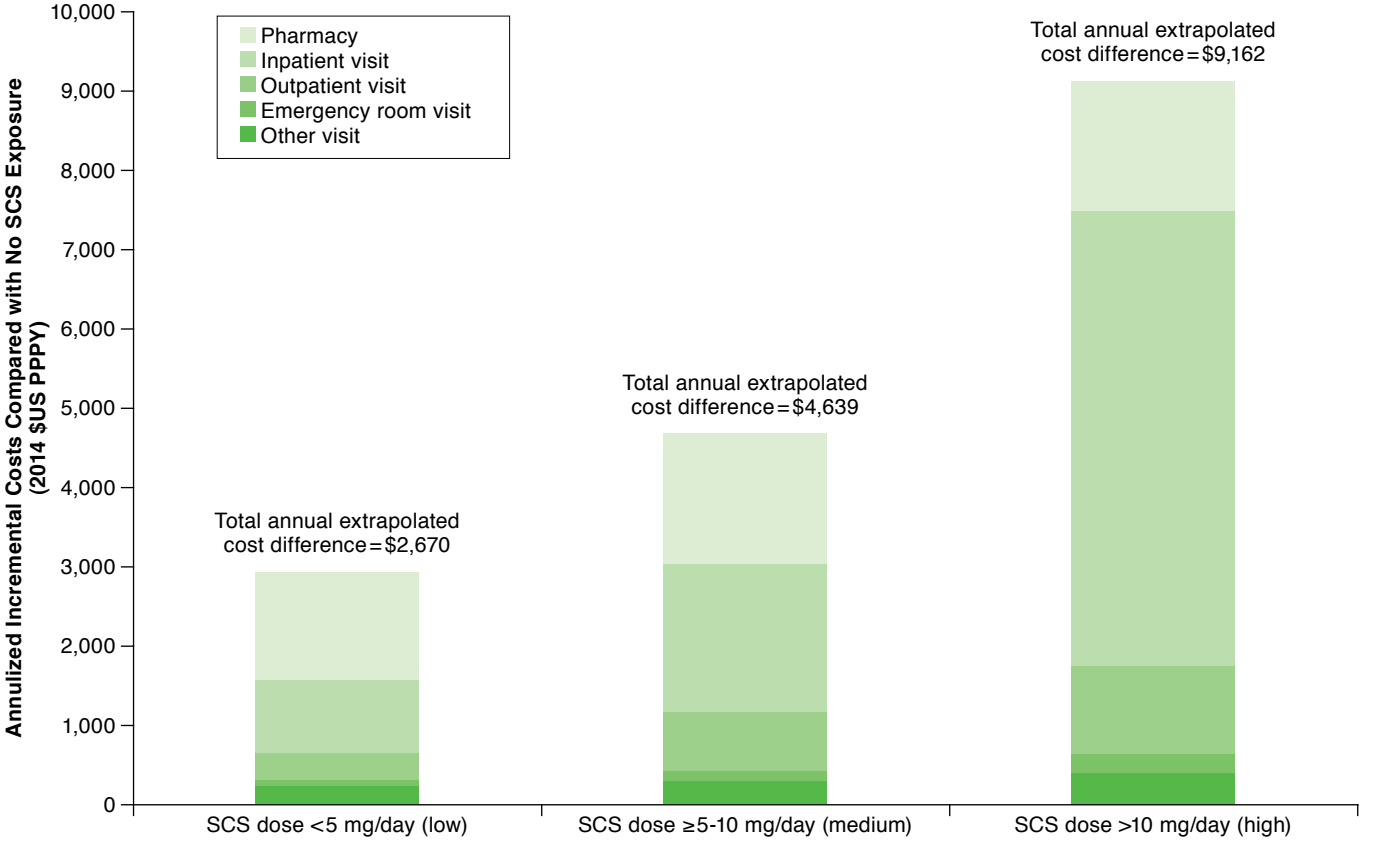
[b] *Estimates in bold are significant (P < 0.05).*

CI = confidence interval; GEE = generalized estimating equation; SCS = systemic corticosteroid; SD = standard deviation.

In their report, O'Neill et al. (2015) estimated the direct health care treatment costs from a National Health Service perspective using data from the British Thoracic Society Difficult Asthma Registry (n = 596) and examined factors that explain variations in costs.[14] They found that costs for patients on maintenance oral corticosteroids were 43% higher than for those not receiving maintenance oral corticosteroids. For those patients on maintenance steroids, asthma-related medications were more expensive, but notably, their nonmedication costs and those for nonasthma-related medications were significantly higher. Interestingly, nonasthma medication included proton pump inhibitors and bisphosphonates, which are examples of therapies used to manage side effects of oral corticosteroid-induced morbidity. Recurrent exacerbations were also a significant driver of costs; costs for patients with > 2 exacerbations requiring oral corticosteroids were approximately 31% higher than for patients with < 2 courses of rescue oral corticosteroids.

In the current study, higher cumulative doses of SCS significantly increased all types of SCS-related health care resource utilization with a significant dose-response

FIGURE 4 Annualized Incremental Costs of SCS-Related Complications by SCS Exposure Compared with No SCS Exposure



PPPY = per person per year; SCS = systemic corticosteroids; $US = U.S. dollars.

relationship. Patients with low, medium, and high SCS exposure were estimated to have $2,670, $4,639, and $9,162, respectively, annual incremental costs attributable to SCS-related complications relative to those without SCS exposure. These are comparable with the annual mean treatment costs among severe refractory asthma patients reported by O'Neill et al. (£2,912-£4,217) after conversion to U.S. dollars.[14] These results regarding health care utilization and costs are important for health care policy makers and payers, since they suggest that chronic SCS use, particularly at a high dose, imposes a large burden on health care systems. The report by Sarnes et al. (2011), which evaluated the burden of complications associated with corticosteroid use across different diseases, provided a similar conclusion.[5] The authors estimated that reducing daily doses of oral and parenteral corticosteroids may result in a cost reduction of $1.76 million per 10,000 persons by avoiding 96 fractures per 10,000 persons. This finding is in line with our results, since we estimated that a reduction from high to medium exposure and from medium to low exposure may result in a cost reduction of $968,579 and $3.93 million per 10,000 persons, respectively, by avoiding bone- and muscle-related complications.

There is an ongoing debate on the toxicity and safety of SCS use at daily doses ≤ 10 mg prednisone equivalent, in particular in the treatment of chronic diseases such as rheumatoid arthritis.[24-26] Of note, patients with rheumatoid arthritis rarely receive any other source of exogenous corticosteroid, whereas patients with severe asthma generally additionally receive daily doses of moderate- to high-dose inhaled corticosteroids. Although several large retrospective studies have shown that long-term corticosteroid use, even at daily doses < 5 mg prednisone equivalent, is a significant independent predictor of SCS-related complications,[16,20,27] no clinical trial in a rheumatoid arthritis setting has found statistically significant evidence of this relationship in low-dose SCS.[26] However, in the current study, we found that low exposure significantly increased the risk of developing 3 types of SCS-related complications compared with no SCS exposure (i.e., bone- and

muscle-related complications, skin diseases, and infections). Furthermore, the present study found a significant increase in health care resource use and costs associated with SCS-related complications compared with no SCS use for SCS doses < 5 mg. One explanation is that this significant increase in the health care resource utilization and cost burden could stem from follow-up visits or treatments for SCS-related complication episodes that may have happened before the low SCS exposure period, since all SCS users were continuously exposed to doses ≥ 5 mg prednisone equivalent during at least 6 months before their index dates. These results may indicate a lasting impact of SCS-related complications on health care resource utilization and costs associated with doses of SCS ≥5 mg, thereby supporting the need to develop corticosteroid-sparing therapies.

Limitations

There are limitations in this study that are commonly associated with the use of administrative claims data, including coding errors and reliance on ICD-9-CM codes to identify SCS-related complications that might not have reflected confirmed clinical diagnoses. Moreover, it was assumed that a prescription claim for SCS indicated use of SCS. However, patients might not have adhered to the SCS treatment regimen as prescribed. Additionally, pharmacy costs because of SCS-related complications were identified using the claims for medications used to treat each category of SCS-related complications. But, these medications could have been used for reasons other than treating complications because of SCS use. For example, antidepressants such as selective serotonin reuptake inhibitors, which were used to identify psychiatric SCS-related complications in the database, can sometimes be used to treat menopausal symptoms instead of depression.[26,28] Similarly, we identified complications and health care resource utilization using claims with a diagnosis of SCS-related complications. It is possible that these services were associated with other conditions. For example, although gastrointestinal conditions have been reported in the literature as potential complications of SCS use, some gastrointestinal disorders considered in the current study may not be associated with SCS use. The same limitation may apply to the psychiatric disorders assessed in this study. Also, it is possible that some of the differences estimated between the 2 groups may be partly attributable to asthma severity. Unfortunately, health care claims do not provide detailed clinical information related to asthma severity to control for potential confounding that may remain between the 2 groups.

This study was also subject to limitations related to the study design. Inhaled corticosteroids were not included in the list of SCSs, consistent with previous literature excluding inhaled corticosteroids from a systematic literature review of corticosteroid-associated adverse event costs, based on the assumption that they would lack significant systemic absorption.[5] Therefore, it is possible that SCS exposure was underestimated in the current study. Furthermore, patients with SCS-related complications before SCS initiation were not excluded. Consequently, the diagnosis of a complication occurring during the follow-up period may actually have referred to a follow-up visit for a condition that had developed before the use of an SCS. Finally, the study compared observable SCS-related complications associated with resource use and costs between SCS users and nonusers; however, the potential benefit of corticosteroids in terms of asthma control and related morbidity was not assessed.

Conclusions

We found that among a large U.S. commercially insured population, patients with severe asthma who had been treated for at least 6 months with a daily dose of at least 5 mg of prednisone had a significantly higher risk of developing SCS-related complications compared with those not exposed to SCSs and that this risk significantly increased with SCS exposure. We also found a significant incremental burden on health care resources and costs associated with SCS-related complications for SCS users compared with SCS nonusers and that this effect was significant even at daily doses < 5 mg prednisone equivalent.

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DISCLOSURES

Funding for this study was provided by GlaxoSmithKline, Study number HO-15-15930, to Analysis Group for the conduct of this study. Lefebvre, Duh, and Gozalo are employees of Analysis Group, a contract research organization that has received research grants from GlaxoSmithKline. Robitaille was employed by Analysis Group at the time of this study. Yancey, Forshag, Lin, and Albers are employees of GlaxoSmithKline and own company stock. Dalal and Ortega were employed by GlaxoSmithKline at the time of this study. Lefebvre 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. Additionally, all listed authors meet the criteria for authorship set forth by the International Committee for Medical Journal Editors.

Study concept and design were contributed by Dalal, Duh, Albers, Yancey, Ortega, Forshag, and Lefebvre. Data acquisition was by Dalal, Gozalo, Robitaille, Forshag, and Lefebvre and was analyzed and interpreted by Dalal, Gozalo, Robitaille, Albers, Yancey, Ortega, Forshag, and Lefebvre. The manuscript was drafted and approved by Dalal, Duh, Gozalo, Robitaille, Albers, Yancey, Ortega, Forshag, Lin, and Lefebvre.

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APPENDIX A ICD-9-CM Codes for SCS-Related Complications

Category	Condition	ICD-9 Code	Description
Gastrointestinal	Nausea/vomiting	787.0x	Nausea and vomiting
		536.2x	Persistent vomiting
		569.87	Vomiting of fecal matter
	Gastrointestinal bleeds/ ulcers	456.0x	Esophageal varices with bleeding
		456.2	Esophageal varices in diseases classified elsewhere
		530.2x	Ulcer of esophagus with bleeding
		530.4x	Perforation of esophagus
		530.82	Other specified disorders of esophagus with esophageal hemorrhage
		531.xx-534.xx	Gastric, duodenal, peptic, gastrojejunal ulcers
		535.01	Acute gastritis with hemorrhage
		535.11	Atrophic gastritis with hemorrhage
		535.21	Gastric mucosal hypertrophy with hemorrhage
		535.31	Alcoholic gastritis with hemorrhage
		535.41	Other specified gastritis with hemorrhage
		535.51	Unspecified gastritis and gastroduodenitis with hemorrhage
		535.61	Duodenitis with hemorrhage
		535.71	Eosinophilic gastritis with hemorrhage
		537.83	Angiodysplasia of stomach and duodenum with hemorrhage
		537.84	Dieulafoy lesion (hemorrhagic) of stomach and duodenum
		538.xx	Gastrointestinal mucositis (ulcerative)
		556.xx	Ulcerative enterocolitis
		557.0x	Acute vascular insufficiency of intestine
		562.02	Diverticulosis of small intestine with hemorrhage
		562.12	Diverticulosis of colon with hemorrhage
		562.13	Diverticulitis of colon with hemorrhage
		569.82	Ulceration of intestine
		569.83	Perforation of intestine
		569.85	Angiodysplasia of intestine with hemorrhage
		569.86	Dieulafoy lesion (hemorrhagic) of intestine
		578.xx	Gastrointestinal hemorrhage
	Dyspepsia	536.8	Dyspepsia and other specified disorders of function of stomach
Infections	Fungal infections	110.xx	Dermatophytosis
		111.xx	Dermatomycosis other and unspecified
		112.xx	Candidiasis
		117.xx	Other mycoses
		118.xx	Opportunistic mycoses
		202.1x	Mycosis fungoides
		370.05	Mycotic corneal ulcer
		484.7x	Pneumonia in other systemic mycose
		V75.4	Screening examination for mycotic infections
	Pneumonia	3.22	Salmonella pneumonia
		011.6x	Tuberculous pneumonia
		020.5x	Pneumonic plague, unspecified
		055.1x	Postmeasles pneumonia
		073.0x	Ornithosis with pneumonia
		112.4x	Candidiasis of lung
		115.15	Infection by Histoplasma duboisii, pneumonia
		115.95	Histoplasmosis, unspecified, pneumonia
		136.3x	Pneumocystosis
		480.xx	Viral pneumonia
		481.xx	Pneumococcal pneumonia [Streptococcus pneumoniae pneumonia]
		482.xx	Other bacterial pneumonia
		483.xx	Pneumonia due to other specified organism
		484.xx	Pneumonia in infectious diseases classified elsewhere
		485.xx	Bronchopneumonia, organism unspecified

APPENDIX A ICD-9-CM Codes for SCS-Related Complications *(continued)*

Category	Condition	ICD-9 Code	Description
Infections	Pneumonia	486.xx	Pneumonia, organism unspecified
		487.0x	Influenza with pneumonia
		488.01	Influenza due to identified avian influenza virus with pneumonia
		488.11	Influenza due to identified 2009 h1n1 influenza virus with pneumonia
		514.xx	Pulmonary congestion and hypostasis
		517.1x	Rheumatic pneumonia
		518.3x	Pulmonary eosinophilia
		V12.61	Personal history of pneumonia (recurrent)
		V73.9	Screening examination for unspecified viral and chlamydial disease
	Sepsis	038.xx	Septicemia
		670.2x	Puerperal sepsis
		995.91	Sepsis
		995.92	Severe sepsis
	Tuberculosis	010.xx-018.xx	Tuberculosis
		795.5x	Nonspecific reaction to test for tuberculosis
		V01.1	Contact with or exposure to tuberculosis
		V03.2	Need for prophylactic vaccination and inoculation against tuberculosis
		V71.2	Observation for suspected tuberculosis
		V74.1	Screening examination for pulmonary tuberculosis
	Urinary tract infection	599.0x	Chronic pyelonephritis
		997.5x	Urinary complications, not elsewhere classified
	Varicella infection	052.xx	Chickenpox
		053.xx	Herpes zoster
		V05.4	Need for prophylactic vaccination and inoculation against varicella
		V01.71	Contact with or exposure to varicella
	Bursitis	095.7x	Syphilis of synovium, tendon, and bursa
		98.52	Gonococcal bursitis
		726.19	Other specified disorders of bursae and tendons in shoulder region
		727.3x	Other bursitis
Adrenal	Cushing's syndrome	255.0x	Cushing's syndrome
Skin conditions	Bruising	920.xx-924.xx	Contusions with intact skin surface
	Impaired wound healing	998.83	Non-healing surgical wound
		782.9	Other symptoms involving skin and integumentary tissues
	Striae	701.3	Striae atrophicae
	Skin thinning	701.8x	Other specified hypertrophic and atrophic conditions of skin
		701.9x	Unspecified hypertrophic and atrophic conditions of skin
Bone- and muscle-related	Avascular necrosis	733.4x	Aseptic necrosis of bone
	Muscle weakness	728.87	Muscle weakness (generalized)
	Osteoporosis	733.0x	Osteoporosis
	Back pain	724.2x	Lumbago
		724.5x	Backache, unspecified
		724.3	Sciatica
	Fractures	733.1x	Pathologic fracture
		733.93	Stress fracture of tibia or fibula
		733.94	Stress fracture of the metatarsals
		733.95	Stress fracture of other bone
		733.96	Stress fracture of femoral neck
		733.97	Stress fracture of shaft of femur
		733.98	Stress fracture of pelvis
		800.xx-804.xx	Fracture of skull
		805.xx-809.xx	Fracture of spine and trunk
		810.xx-819.xx	Fracture of upper limb
		820.xx-829.xx	Fracture of lower limb

APPENDIX A ICD-9-CM Codes for SCS-Related Complications *(continued)*

Category	Condition	ICD-9 Code	Description
Cardiovascular	Atrial fibrillation/flutter	427.3x	Atrial fibrillation and flutter
	Hypertension	401.xx-405.xx	Hypertensive heart disease
	Myocardial infarction	410.xx	Acute myocardial infarction
		412.xx	Old myocardial infarction
Other	Bladder cancer	188.xx	Malignant neoplasm of bladder
	Epistaxis	784.7	Epistaxis
	Non-Hodgkin's lymphoma	202.8x	Other malignant lymphomas
Metabolic	Hyperglycemia	790.29	Other abnormal glucose
	Dyslipidemia	272.4x	Other and unspecified hyperlipidemia
	Obesity	278.xx	Overweight, obesity, and other hyperalimentation
		V77.8	Screening for obesity
		V85.3	Body mass index between 30-39, adult
		V85.4	Body mass index 40 and over, adult
	Diabetes mellitus	249.xx	Secondary diabetes mellitus
		250.xx	Diabetes mellitus
	Metabolic syndrome	277.7x	Dysmetabolic syndrome
		V77.99	Screening for other and unspecified endocrine, nutritional, metabolic, and immunity disorders
Ocular	Cataracts	366.xx	Cataract
	Glaucoma	365.xx	Glaucoma
Psychiatric	Bipolar disorder	296.0x	Bipolar I disorder, single manic episode
		296.4x	Bipolar I disorder, most recent episode (or current) manic
		296.5x	Bipolar I disorder, most recent episode (or current) depressed
		296.6x	Bipolar I disorder, most recent episode (or current) mixed
		296.7x	Bipolar I disorder, most recent episode (or current) unspecified
		296.8	Bipolar disorder, unspecified
		296.89	Other bipolar disorders
	Depression	292.84	Drug-induced mood disorder
		296.2x	Major depressive disorder single episode
		296.3x	Major depressive affective disorder, recurrent episode, unspecified
		298.0x	Depressive type psychosis
		300.0x	Anxiety states
		301.12	Chronic depressive personality disorder
		309.28	Adjustment disorder with mixed anxiety and depressed mood
		311.xx	Depressive disorder, not elsewhere classified
	Sleep disturbances	780.5x	Sleep disturbances
		307.4x	Specific disorders of sleep of nonorganic origin
	Steroid psychosis	292.1x	Drug-induced psychotic disorders
		292.89	Other specified drug-induced mental disorders
		292.9x	Unspecified drug-induced mental disorder

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; SCS = systemic corticosteroids.

APPENDIX B GPI Codes to Identify Medications Used for SCS-Related Complications

Condition	GPI Code	Description
Gastrointestinal disorders (nausea/vomiting, GI ulcers/bleeds, dyspepsia)	50xx	Antiemetics
	49xx	Ulcer drugs
	3017xx	Somatostatic agents
	48xx	Antacids
Infections (fungal infections, pneumonia, sepsis, tuberculosis, varicella infection, urinary tract infection)	01xx	Penicillins
	02xx	Cephalosporins
	03xx	Macrolides
	04xx	Tetracyclines
	05xx	Fluoroquinolones
	07xx	Aminoglycosides
	08xx	Sulfonamides
	09xx	Antimycobacterial agents
	11xx	Antifungals
	12xx	Antivarials
	13xx	Antimalarials
	14xx	Amebecides
	15xx	Antihelmintics
	16xx	Anti-infective agents - miscellaneous
	18xx	Toxoids
	19xx	Passive immunizing agents
	53xx	Urinary antiinfectives
	54xx	Urinary antispasmodics
	5510xx	Vaginal antiinfectives
	8610xx	Ophthalmic antiinfectives
	8810xx	Antiinfectives-throat
	9010xx	Antibiotics-topical
	9015xx	Antifungals-topical
	9035xx	Antivirals-topical
	92xx	Antiseptics and disinfectants
	9810xx	Antimicrobial agents
Adrenal (Cushing's syndrome)	–	N/A
Skin conditions (acne)	–	N/A
Bone- and muscle-related (bursitis, fractures, osteoporosis, avascular necrosis, muscle weakness, back pain)	3004xx	Bisphosponates
	64xx	Analgesics-non-narcotic
	65xx	Analgesics-opioid
	66xx	Analgesics-anti-inflammatory
	7910xx	Calcium
Cardiovascular (atrial fibrillation/flutter, myocardial infarction, hypertension)	32xx	Antianginal agents
	33xx	Beta blockers
	34xx	Calcium channel blockers
	35xx	Antiarrythmics
	36xx	Antihypertensives
	37xx	Diuretics
Other (bladder cancer, non-Hodgkin's lymphoma, epistaxis)	21xx	Antineoplastic agents
	3009xx	GnRH/LHRH antagonists
	9037xx	Antineoplastic topical agents
Ocular (cataract, glaucoma)	8625xx	Ophthalmic agents
Metabolic (hyperglycemia, obesity, diabetes, metabolic syndrome, hyerlipidemia)	39xx	Antihyperlipidemics
	27xx	Antidiabetics
	6125xx	Anti-obesity agents
Psychiatric (bipolar disorder, depression, sleep disturbances, steroid psychosis)	57xx	Antianxiety agents
	58xx	Antidepressants
	59xx	Antipsychotic/antimanic agents
	60xx	Hypnotics
	6200xx	Psychotherapeutic and neurological agents - miscellaneous
	6256xx	Restless leg syndrome agents

GI = gastrointestinal; GnRH = gonadotropin-releasing hormone; GPI = Generic Product Identifier; LHRH = luteinizing hormone-releasing hormone; N/A = not applicable; SCS = systemic corticosteroids.