

Original Article

Systemic Corticosteroid-Related Complications and Costs in Adults with Persistent Asthma

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What is already known about this topic? Prior studies have shown that high use of systemic corticosteroids in the management of asthma is associated with complications and high health care costs.

What does this article add to our knowledge? The complications and costs associated with systemic corticosteroid use exist for patients with both 1 to 3 claims and 4+ prescription claims, although the burden increases with utilization. This burden also increases over time.

How does this study impact current management guidelines? These results highlight the clinical and economic consequences and cost of systemic corticosteroid use in persistent asthma and raise awareness of the potential benefits of minimizing systemic corticosteroid use in persistent asthma whenever possible.

BACKGROUND: Systemic corticosteroids (SCS) may cause complications for patients with asthma.

OBJECTIVE: We sought to better understand the burden of SCS use in persistent asthma, including health care costs.

METHODS: Adult patients with persistent asthma were identified in the IBM MarketScan Databases from January 2003 to July 2016. The index date was set as the first SCS prescription for SCS users or an algorithm-matched date for non-SCS users. Patients were required to have ≥ 1 year of data before and after the index date. Based on the number of SCS claims in the first year after index, patients were categorized into 3 SCS groups: 0 SCS claims, 1 to 3 claims, and 4+ claims. Inverse probability of treatment weights were applied to adjust for differences

between SCS and non-SCS users. Analyses included weighted and multivariate modeling to assess SCS-related complications and costs during a 3-year follow-up.

RESULTS: A total of 86,786 SCS users (1-3 claims: 76,690; 4+ claims: 10,096) and 91,409 non-SCS users were included; 45% remained 3 years after index. In multivariate analysis, the 3-year risk of developing any chronic complication was 6% greater for those with 1 to 3 claims and 26% greater for those with 4+ claims compared with non-SCS users ($P < .001$). Multivariate-adjusted health care costs over 3 years were significantly greater as 4+ users incurred \$22,311 greater total costs, \$4627 greater asthma-related costs, and \$2647 greater chronic complication-related costs than non-SCS users ($P < .001$).

CONCLUSIONS: In this study, adults with persistent asthma receiving SCS treatment had greater odds of complications and greater associated costs over 3 years than matched non-SCS asthma patients. © 2020 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). (J Allergy Clin Immunol Pract 2020;■:■-■)

Key words: Corticosteroids; Persistent asthma; Health care costs; Complications

Among patients with persistent asthma, inhaled corticosteroids (ICS) as monotherapy or combined with long-acting β_2 -agonists (LABA), and leukotriene modifiers (LMs), are the most common maintenance therapies.¹ Use of systemic corticosteroids (SCS) is reserved for treatment of asthma exacerbations and as a supplemental maintenance therapy for patients whose disease remains uncontrolled with maximum maintenance controller therapies.^{2,3} However, SCS therapy comes with known risks for acute and chronic complications, including osteoporosis, bone fracture, hypertension, diabetes mellitus, metabolic syndrome, weight gain, cataracts, glaucoma, gastrointestinal bleeds/ulcers, impaired wound healing, and psychological disorders.⁴⁻¹²

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Abbreviations used

CM- Clinical Modification
ED- Emergency department
HCRU- Health care resource utilization
HEDIS- Healthcare Effectiveness Data and Information Set
ICD- International Classification of Diseases
ICS- Inhaled corticosteroid
IPT- Inverse probability of treatment
LABA- Long-acting β_2 -agonist
LM- Leukotriene modifier
SABA- Short-acting β_2 -agonist
SCS- Systemic corticosteroid
SD- Standard deviation

Analysis of data from the Healthcare Cost and Utilization Project demonstrated that nearly 10% of adverse drug events presented at hospital admission are related to SCS use,¹³ and in cases of myocardial infarction and fractures, SCS are accompanied by substantial costs of care.¹⁴

Understandably, asthma has been shown to pose a substantial economic burden to society, with direct medical costs for the management of asthma exceeding \$50 billion annually in the United States alone.¹⁵ It is well established that patients with severe asthma are responsible for a disproportionate amount of the economic burden of asthma^{16,17}; however, less clear is the extent to which SCS use and its consequences specifically contribute to the cost burden of asthma.

Several large, retrospective studies have shown that patients with greater SCS exposure have greater health care utilization and expenditure after adjusting for baseline demographic and clinical characteristics,^{6-8,18-20} but further investigation is needed to understand the effects of exposure over time, complications, and costs from SCS use. The present large retrospective study used administrative claims data to follow patients for up to 3 years after an initial treatment with SCS and compared their complication rates, health care resource utilization (HCRU), and costs to similar patients who were not treated with SCS. We hypothesized that increased usage of SCS would lead to an increase in SCS complication rates with corresponding greater HCRU and costs.

METHODS

Study design and data source

This observational, retrospective matched-cohort study used deidentified health care claims from the IBM MarketScan Commercial and Medicare Supplemental Databases spanning the period of January 1, 2002, through July 31, 2017 (study period), to evaluate the relationship between SCS utilization and related complications and health care costs among adults with persistent asthma in the United States (see this article's Online Repository at www.jaci-inpractice.org for full description of the MarketScan databases).

Patient selection and cohort assignment

To be eligible for study inclusion, all patients were required to have ≥ 1 nondiagnostic claim with a diagnosis of asthma between January 1, 2003, and July 31, 2016 (enrollment period). Patients with ≥ 1 medical or pharmacy claim for an SCS during the enrollment period were eligible for inclusion in the SCS user cohort. SCS users were required to be aged ≥ 18 years and have continuous enrollment with medical and pharmacy benefits for ≥ 12 months

before and ≥ 12 months after their initial SCS claim. Patients with asthma who had ≥ 24 months of continuous MarketScan enrollment and no medical or pharmacy claims for an SCS any time during their enrollment were eligible for inclusion in the non-SCS cohort. All SCS users and non-SCS users were required to meet the Healthcare Effectiveness Data and Information Set (HEDIS) criteria for persistent asthma (see this article's Online Repository at www.jaci-inpractice.org for full details of patient selection, including description of the HEDIS criteria).

Patients with evidence of other specific respiratory conditions during the study period or evidence of autoimmune disorders, organ transplants, or chronic SCS complications in the 12-month baseline period were excluded (see this article's Online Repository at www.jaci-inpractice.org).

SCS users were further stratified into 2 cohorts based on the number of SCS claims in the first year after index: low-frequency SCS users (1-3 claims in the first year) and high-frequency SCS users (4+ claims in the first year). SCS exposure in the subsequent years (after the first year after index) was ignored for SCS group assignment purposes; individuals in the no SCS group had no SCS exposure during any study year. The threshold for the high-dosage steroid group was set at 4 or more claims, as an analysis of the sample's steroid utilization and dosing revealed that patients with 4+ claims were categorically different than those with 1 to 3 claims. Those with 4+ claims presented, on average, a similar annual cumulative dose as those with substantially more claims (eg, 12 or 13). Results suggest that those with a few short SCS bursts have much greater intensity of dosage, whereas those with more claims tend to be long-term SCS users on a much lower dosage.

Measures

Sample characteristics. Patient demographic characteristics were assessed on the index date and included age, sex, geographic region of residence (northeast, north-central, south, west, and unknown), urban or rural residency, primary payer (commercial or Medicare), and index year. Baseline patient clinical characteristics were assessed during the 12-month baseline period and included the Deyo-Charlson Comorbidity Index,²¹ presence of comorbid conditions of interest (allergic rhinitis, anxiety, chronic sinusitis, depression, gastroesophageal reflux disease, insomnia, ischemic heart disease, and nasal polyps), use of asthma medications (biologics, ICS, ICS/LABA combinations, LMs, and short-acting β_2 -agonists [SABA]), and confirmation of prevalent or incident asthma. Baseline HCRU was measured during the preindex period, and metrics included evidence of ≥ 1 hospitalization, ≥ 1 asthma-related hospitalization, ≥ 1 emergency department (ED) visit, ≥ 1 asthma-related ED visit, ≥ 1 outpatient office visit, ≥ 1 outpatient prescription fill, and use of SABA indicating poor asthma control (≥ 7 canisters).

Outcomes. The incidence of acute or chronic complications of SCS was assessed for all patients. Acute complications included anxiety/depression, fracture, and infection either as a primary diagnosis on inpatient claims or in any position on outpatient claims. Similarly, chronic complications included avascular necrosis, cataracts, type 2 diabetes, dyslipidemia, dyspepsia, gastrointestinal ulcers/bleeds, glaucoma, hypertension, metabolic syndrome, myocardial infarction, obesity, osteoporosis, renal disease, sepsis, stroke, or thromboembolism diagnoses either as a primary diagnosis on any position of an inpatient or outpatient medical claim. A list of International Classification of Diseases, 9th and 10th Revision, Clinical Modification (ICD-9-CM and ICD-10-CM) codes can be

found in [Table E1](#) (available in this article's Online Repository at www.jaci-inpractice.org).

All-cause HCRU was recorded for each cohort and included the presence of ≥ 1 hospitalization, ≥ 1 ED visit, ≥ 1 physician-administered SCS service, and ≥ 1 outpatient prescription claim for SCS. All-cause, asthma-related, and chronic SCS complication-related costs were calculated from the paid amounts of fully adjudicated claims, including insurer and health plan payments as well as patient cost-sharing in the form of copayment, deductible, and coinsurance. Asthma-related costs were estimated using hospital claims carrying an asthma diagnosis in the primary diagnosis position, outpatient medical claims carrying an asthma diagnosis in any diagnosis position, and asthma-related prescription claims. Chronic SCS complication-related costs were estimated using hospital claims carrying a diagnosis for a chronic complication of SCS use in the primary diagnosis position, outpatient medical claims carrying a diagnosis for a chronic complication of SCS use in any diagnosis position, and claims for prescriptions used to treat chronic complications. Prescriptions used to treat chronic complications were identified by therapeutic class categories matched to each complication; for example, bone resorption inhibitors for osteoporosis. All costs were reported per-person per-timeframe and were inflated to 2018 US dollars using the medical care component of the Consumer Price Index.²²

Statistical analysis

Inverse probability of treatment (IPT) weighting was used to account for differences in baseline patient characteristics between SCS users and non-SCS users. The following covariates were included in all models: all baseline demographic characteristics, all baseline clinical characteristics, all baseline HCRU metrics, and the duration of continuous enrollment.

Unweighted and weighted descriptive statistics were reported for demographics, clinical characteristics, and all outcome measures for each cohort. Continuous variables were summarized using means and standard deviations (SD). Categorical variables were reported using counts and percentages before weighting, and percentages only after weighting.

For all multivariable models, the ordinal primary SCS exposure was defined for each patient as none (reference), 1 to 3 claims, or 4+ claims within the first postindex year. Multivariable models were performed on the cohort of patients with 3 years of continuous enrollment (see this article's Online Repository at www.jaci-inpractice.org for full description of the statistical analytic approach).

RESULTS

Patient characteristics

Among eligible patients with asthma identified as SCS users, 86,786 had ≥ 1 year of follow-up data and 45,427 had ≥ 3 years of follow-up data. Of those with ≥ 1 year of follow-up data, 76,690 had 1 to 3 SCS claims and 10,096 patients had 4+ SCS claims in the first year of follow-up. Among non-SCS users, 91,409 had ≥ 1 year of follow-up and 34,570 had ≥ 3 years of follow-up. Details of patient selection are shown in [Figure E1](#) (available in this article's Online Repository at www.jaci-inpractice.org).

Among patients with ≥ 1 year of follow-up, during the preindex period and before weighting, SCS users were slightly older (mean $\pm$ SD: 42.1 $\pm$ 13.8 years vs 41.4 $\pm$ 14.9 years), were more likely to be female (63.8% vs 53.8%), had a greater comorbidity burden as measured by the Deyo-Charlson

Comorbidity Index (mean $\pm$ SD: 0.7 $\pm$ 0.7 vs 0.5 $\pm$ 0.7), had a greater prevalence of comorbid conditions of interest, and were more likely to have had ≥ 1 inpatient admission (5.5% vs 2.6%) or ≥ 1 ED visit (22.4% vs 12.5%) compared with non-SCS users (all, $P < .001$). These trends were consistent for all follow-up cohorts and SCS user cohorts when compared with their appropriate non-SCS user group, although differences were less pronounced between SCS users with 1 to 3 claims in the first year after index and non-SCS users than between SCS users with 4+ claims in the first year after index and non-SCS users (see [Table E2](#) in this article's Online Repository at www.jaci-inpractice.org).

After weighting, baseline differences in demographic and clinical characteristics were reduced or eliminated between SCS user cohorts and matched non-SCS user cohorts ([Table I](#)). SCS users with 4+ claims in the first year after index remained slightly older (mean $\pm$ SD: 42.4 $\pm$ 14.9 years vs 41.6 $\pm$ 14.8 years, $P < .001$) and more likely to have used a SABA in the baseline period (71.1% vs 69.1%, $P = .003$) compared with non-SCS users after the weighting. In addition, all SCS users remained more likely than non-SCS users to have had ≥ 1 all-cause hospitalization (3.9% vs 3.7%, $P < .03$) after weighting. Also, asthma-related health care costs were \$59 to \$68 more, and all-cause health care costs were \$179 to \$803 more for SCS users compared with non-SCS users in the baseline period. These differences were sustained in all follow-up cohorts; however, exact values and P values varied (see [Table E2](#) in this article's Online Repository at www.jaci-inpractice.org).

SCS utilization

In the first year of follow-up after the index date, 13.3% of all SCS users had ≥ 1 physician-administered SCS claim and 96.2% had ≥ 1 outpatient SCS prescription ([Table II](#)). By the end of 3 years of follow-up, 15.7% of all SCS users had ≥ 1 physician-administered SCS claim and 97.8% had ≥ 1 outpatient SCS claim. The cumulative likelihood of ≥ 1 physician-administered or outpatient SCS claim was lower among users with 1 to 3 claims in the first year after index and greater for SCS users with 4+ claims in the first year after index at all time points. For SCS users with 1 to 3 claims in the first year after index, the mean (SD) total number of physician-administered and outpatient SCS claims at year 3 were 1.30 (0.73) and 2.44 (1.90), respectively. Among SCS users with 4+ claims in the first year after index, the mean (SD) total number of physician-administered and outpatient SCS claims at year 3 were 1.95 (1.52) and 6.47 (4.31), respectively. The mean (SD) cumulative dose of steroids (prednisone equivalent dosage) over the initial 12-month follow-up period was 435 (536) mg across all patients using SCS, 346 (347) mg across patients with 1 to 3 claims, and 1110 (1022) mg across patients with 4+ claims.

Outcomes: IPT weighting analyses

[Figure 1](#), *A* (1-3 SCS claims) and *B* (4+ SCS claims) present postweighting differences between SCS users and their matched controls on the cumulative incidence of acute and chronic complications. The cumulative incidence of each acute and chronic complication over the 3-year follow-up may be viewed in [Table E3](#) (available in this article's Online Repository at www.jaci-inpractice.org). Postweighting differences between SCS users and their matched controls on the cumulative

TABLE I. Postweighting baseline characteristics among patients with at least 1 year of follow-up data

	All SCS users		Non-SCS users		<i>P</i> value	Low-frequency SCS users*		Non-SCS users		<i>P</i> value	High-frequency SCS users†		Non-SCS users		<i>P</i> value
	N = 86,786		N = 91,409			N = 76,690		N = 91,409			N = 10,096		N = 91,409		
	Mean	%/SD	Mean	%/SD		Mean	%/SD	Mean	%/SD		Mean	%/SD	Mean	%/SD	
Age (mean, SD)	41.8	14.4	41.7	14.5	.114	41.6	14.5	41.5	14.6	.145	42.4	14.9	41.6	14.8	<.001
Sex female (%)		58.5%		58.5%	.874		58.0%		57.9%	.865		55.0%		55.2%	.711
DCI (mean, SD)	0.6	0.7	0.6	0.7	.882	0.6	0.7	0.6	0.7	.975	0.5	0.7	0.5	0.7	.291
Comorbid conditions (%)															
Allergic rhinitis		23.8%		23.9%	.578		23.7%		23.7%	.766		22.6%		22.2%	.441
Anxiety		5.0%		5.0%	.937		4.9%		4.9%	.929		4.6%		4.6%	.816
Chronic sinusitis		12.6%		12.6%	.938		12.1%		12.1%	.888		10.4%		10.2%	.362
Depression		6.4%		6.4%	.979		6.3%		6.3%	.920		5.9%		5.8%	.753
GERD		5.3%		5.2%	.626		5.2%		5.1%	.578		4.8%		4.7%	.710
Insomnia		1.5%		1.5%	.758		1.4%		1.4%	.935		1.4%		1.3%	.540
Ischemic heart disease		1.0%		1.0%	.484		1.0%		1.0%	.561		1.1%		0.9%	.090
Nasal polyps		0.7%		0.7%	.414		0.6%		0.6%	.527		0.6%		0.5%	.270
Asthma medications (%)															
Biologics‡		0.4%		0.4%	.201		0.4%		0.4%	.039		0.5%		0.4%	.239
ICS		25.9%		25.9%	.910		26.1%		26.0%	.798		24.8%		25.5%	.238
ICS/LABA		46.6%		46.6%	.914		46.3%		46.5%	.535		45.9%		46.5%	.382
Leukotriene modifier		39.7%		39.6%	.850		39.3%		39.3%	.965		38.1%		38.6%	.419
SABA		72.6%		72.2%	.080		72.3%		71.9%	.072		71.1%		69.1%	.003
SABA use indicating poor asthma control§		9.7%		9.5%	.120		9.5%		9.4%	.213		8.8%		8.8%	.950
≥1 inpatient admission (%)		3.9%		3.7%	.025		3.7%		3.5%	.052		3.0%		3.1%	.941
≥1 emergency room visit (%)		17.3%		17.0%	.225		16.8%		16.6%	.316		14.4%		13.8%	.140
Total asthma-related costs (mean, SD)	\$1076	\$2285	\$1008	\$2409	<.001	\$1058	\$2279	\$998	\$2375	<.001	\$995	\$1903	\$937	\$2173	.016
Total costs (mean, SD)	\$6331	\$10,224	\$6070	\$11,158	<.001	\$6152	\$10,137	\$5974	\$11,010	.002	\$6458	\$9138	\$5655	\$10,591	<.001

DCI, Deyo-Charlson Comorbidity Index; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; SABA, short-acting β_2 -agonist; SCS, systemic corticosteroid; SD, standard deviation.

*Low-frequency SCS users had <4 claims for SCS in the first 12 months after index.

†High-frequency SCS users had 4+ claims for SCS in the first 12 months after index.

‡All patients on biologics for asthma were prescribed omalizumab. No patients had prescriptions for mepolizumab or reslizumab.

§≥7 SABA canisters during the baseline period.

||Costs for all claims with a primary diagnosis of asthma and claims for asthma medications.

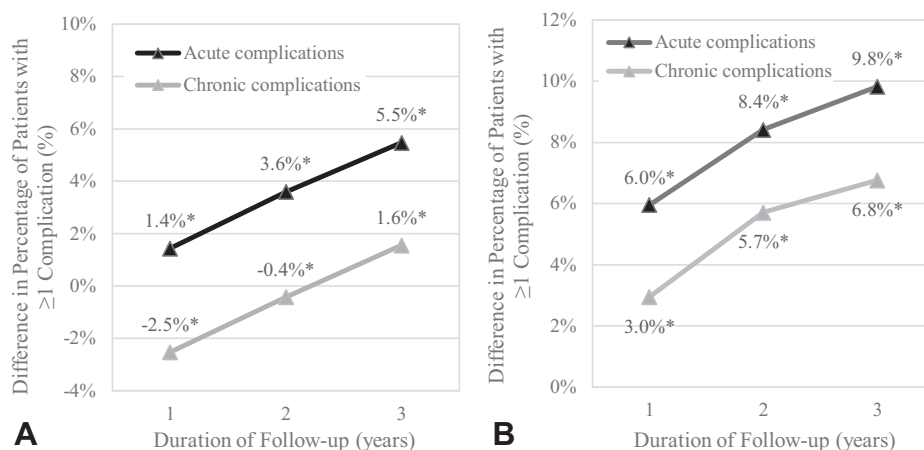
TABLE II. Postweighting cumulative systemic corticosteroid utilization

Years of follow-up	All SCS users		Low-frequency* SCS users		High-frequency† SCS users	
1	N = 86,786		N = 76,890		N = 10,096	
2	N = 62,190		N = 55,031		N = 7159	
3	N = 45,427		N = 40,315		N = 5112	
	Mean	% or SD	N or mean	% or SD	N or mean	% or SD
Patients with ≥ 1 physician-administered SCS claim (cumulative %)						
1		13.3%		11.1%		31.7%
2		14.7%		12.5%		33.1%
3		15.7%		13.5%		33.4%
Number of physician-administered SCS claims (mean, SD)						
1	1.19	0.52	1.09	0.31	1.46	0.79
2	1.33	0.80	1.21	0.56	1.71	1.19
3	1.45	1.02	1.30	0.73	1.95	1.52
Patients with ≥ 1 outpatient SCS prescription (cumulative %)						
1		96.2%		95.9%		98.4%
2		97.1%		96.9%		98.9%
3		97.8%		97.6%		99.3%
Number of outpatient SCS prescriptions (mean, SD)						
1	1.72	1.19	1.44	0.66	3.91	1.90
2	2.30	1.91	1.93	1.25	5.25	3.24
3	2.89	2.65	2.44	1.90	6.47	4.31

SCS, Systemic corticosteroids; SD, standard deviation.

*Low-frequency SCS users had <4 claims for SCS in the first 12 months after index.

†High-frequency SCS users had 4+ claims for SCS in the first 12 months after index.

**FIGURE 1.** Postweighting trends in the difference in the cumulative incidence of patients with ≥ 1 acute or ≥ 1 chronic complication related to systemic corticosteroid (SCS) use. **A**, Percentage of SCS users with 1-3 claims in baseline period – percentage of matched non-SCS users. **B**, Percentage of SCS users with 4+ claims in baseline period – percentage of matched non-SCS users. *Statistically significant difference between relevant SCS group (either low- or high-frequency) and non-SCS control group ($P < .01$).

asthma-related, SCS complication-related, and all-cause costs are shown in [Table E4](#) (available in this article's Online Repository at www.jaci-inpractice.org). For full details on IPT weighting analyses, please see this article's Online Repository at www.jaci-inpractice.org.

Outcomes: multivariable analyses

After adjusting for baseline demographic and clinical characteristics, SCS users with 1 to 3 claims in the first year after index had 6% greater odds, and SCS users with 4+ claims in the first year after index had 26% greater odds, of developing any chronic

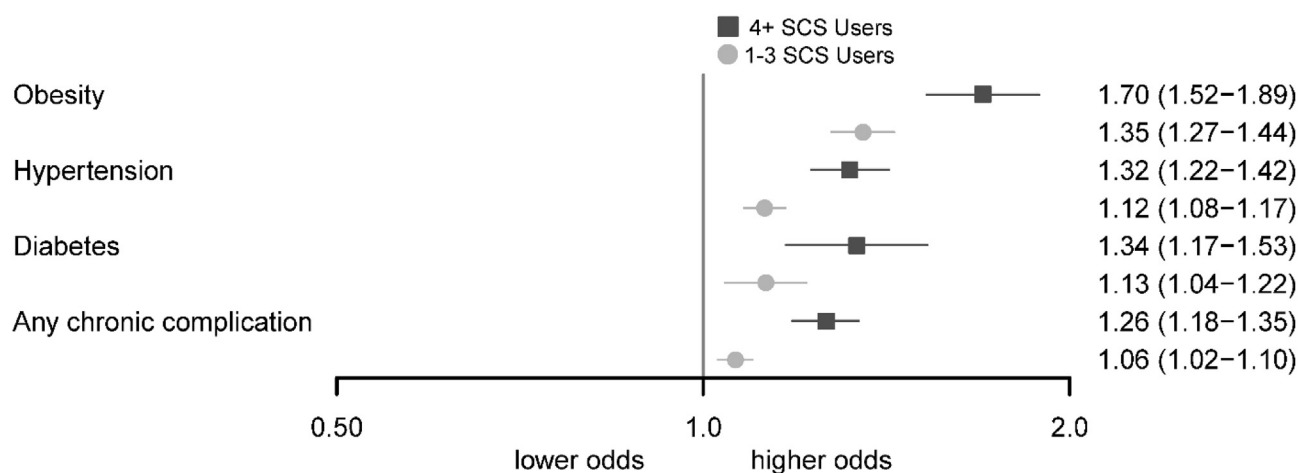


FIGURE 2. Multivariate adjusted odds of developing a chronic complication of systemic corticosteroid (SCS) use among SCS users and non-SCS users over a 3-year period. Low-frequency SCS users had 1-3 claims for SCS in the first 12 months after index. High-frequency SCS users had 4+ claims for SCS in the first 12 months after index.

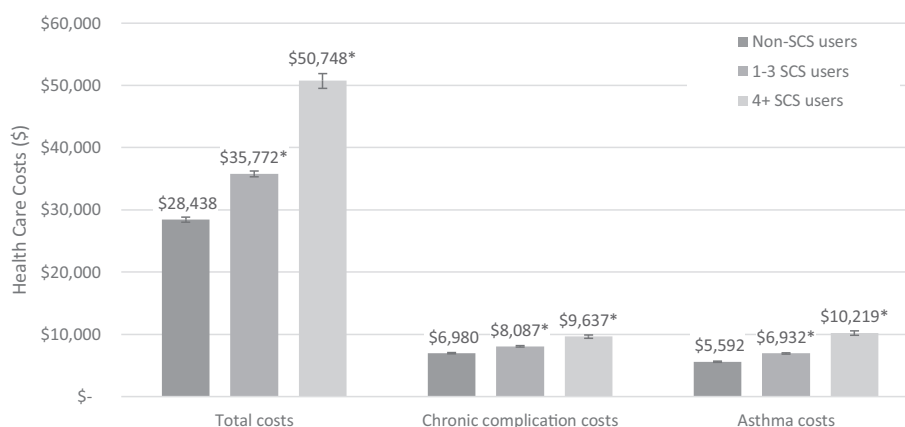


FIGURE 3. Multivariate adjusted 3-year health care costs among systemic corticosteroid (SCS) users and non-SCS users. Confidence intervals for covariate-adjusted costs were estimated using bootstrap resampling with 1000 replications. Low-frequency SCS users had 1-3 claims for SCS in the first 12 months after index. High-frequency SCS users had 4+ claims for SCS in the first 12 months after index. *Statistically significant difference between relevant SCS group (either low- or high-frequency) and non-SCS control group ($P < .01$).

complication within 3 years of the index date compared with non-SCS users (Figure 2). Similarly, compared with controls, SCS users (1-3 claims and 4+ claims) had significantly greater odds of developing diabetes (13% and 34%), hypertension (12% and 32%), and obesity (35% and 70%) within 3 years of the index date compared with non-SCS users. The magnitude of the relative odds of developing a complication was consistently greater among those with 4+ SCS claims in year 1 versus non-SCS users compared with those with 1 to 3 SCS claims in year 1 versus non-SCS users, although no direct comparison was made between the 2 SCS groups.

Among non-SCS users, the adjusted 3-year cumulative health care costs were \$28,438, of which \$6980 was attributable to chronic SCS complications and \$5592 was attributable to asthma (Figure 3). Compared with non-SCS users, adjusted 3-year cumulative total health care costs were 26% greater for those with 1 to 3 SCS claims in year 1 and 78% greater for those with 4+ SCS claims in year 1 (both, $P < .001$) (Figure 3).

Chronic SCS complication–related costs were 16% greater for those with 1 to 3 SCS claims in year 1 and 38% greater for those with 4+ SCS claims in year 1, whereas asthma-related costs were 24% greater and 83% greater compared with non-SCS users, respectively, for the 2 SCS groups (all $P < .001$).

DISCUSSION

This longitudinal retrospective study of adult patients with persistent asthma showed that SCS-related adverse complications and health care costs were greater among SCS users compared to controls in the 3 years after initial SCS exposure in the index year, irrespective of subsequent SCS exposure. The categorization of SCS exposure in the first year only, with outcomes captured in the SCS exposure year (year 1) as well as 2 subsequent years after exposure (years 2 and 3), is a study strength. Chronic SCS complication–related, asthma-related, and all-cause direct health care costs were greater for SCS users than propensity-matched

TABLE III. Summary of prior studies reporting clinical and economic outcomes associated with systemic corticosteroid use among patients with asthma

Author, year	Study design	Cohorts	Clinical outcomes	Economic outcomes
Lefebvre et al, 2015 ⁸	Retrospective cohort study using Medicaid claims data from 1997 to 2013 of 3628 patients ≥ 12 y old with ≥ 2 asthma medical claims and ≥ 6 mo of ≥ 5 mg SCS; a mean follow-up of 3.8 y	3 cohorts: ≥ 6 mo of SCS use at cumulative dose of 6 mg/d (low), >6 -12 mg/d (medium), and >12 mg/d (high). Cohort could change between quarters	Medium- and high-dosage SCS associated with greater adjusted odds of infections, gastrointestinal, bone/muscle, cardiovascular, metabolic, psychiatric, and ocular complications	Annual adjusted incremental cost compared with low SCS dose was \$1914 for medium SCS and \$5479 for high SCS dose (2013 USD)
Zazzali et al, 2015 ¹¹	Retrospective matched cohort study using US commercial claims data from 2008 (baseline year) to 2009 (follow-up year) of 3604 matched pairs of patients ≥ 18 y old with ≥ 2 asthma medical claims and ≥ 2 asthma prescription	2 cohorts: no OCS (none) and >30 d/y OCS exposure at any dosage (high)	High OCS dosage was associated with an increased incidence of osteoporosis, fractures, pneumonia, infections, hypertension, diabetes, cataracts, lipid disorders, and obesity	See Luskin et al, 2016 ¹⁹
Dalal et al, 2016 ⁶	Retrospective cohort study using MarketScan commercial claims data from 2003 to 2014 of 12,697 patients ≥ 12 y old with ≥ 2 asthma medical claims; a mean follow-up of 1.2 no SCS users vs 2.0 y SCS users	4 cohorts: no OCS (none) or >6 mo of SCS use at dosage of 5-6 mg/d (low), >6 -12 mg/d (medium), and >12 mg/d (high). Cohort could change between quarters	Chronic SCS use associated with greater adjusted odds of <i>acute</i> complications: low = 1.72 (1.34-2.19), medium = 2.47 (2.32-2.63), and high = 2.76 (2.51-3.03), <i>chronic</i> complications: low = 1.48 (0.92-2.38), medium = 2.19 (1.98-2.42), and high = 2.34 (2.11-2.59)	Annual adjusted incremental costs among SCS users was \$2670-\$9162 for SCS complication-related costs (2014 USD)
Luskin et al, 2016 ¹⁹	Retrospective cross-sectional matched cohort study using US commercial claims data from 2008 (baseline year) to 2009 (follow-up year) of 3604 matched pairs of patients ≥ 18 y old with ≥ 2 asthma medical claims and ≥ 2 asthma prescription and >30 d/y OCS exposure at any dosage (high)	2 cohorts: possible complications or no possible complications	See Zazzali et al, 2015 ¹¹	Annual adjusted incremental costs were \$25,168 (\$24,223-\$26,113) for patients with complications vs \$21,882 (\$19,644-\$24,121) for patients with no complications; $P = .009$ (2009 USD)
Sweeney et al, 2016 ¹⁰	Retrospective cohort study using UK primary care data from 2008 to 2013 of 7195 patients ≥ 12 y old with ≥ 2 y continuous data	3 cohorts: 4 OCS prescriptions in each of 2 consecutive years (severe), <0.8 mg/d SCS (mild/moderate), or non-SCS rhinitis patients (no asthma)	Patients with severe asthma had greater odds of dyspeptic disorders, obesity, psychiatric disorders, hypertension, osteoporosis, chronic kidney disease, type II diabetes, osteopenia, cardiovascular disease, fracture, cataract, and sleep disorders than patients with mild/moderate asthma or rhinitis controls	See Barry et al, 2017 ¹⁸

(continued)

TABLE III. (Continued)

Author, year	Study design	Cohorts	Clinical outcomes	Economic outcomes
Zeiger et al, 2016 ¹⁷	Retrospective study analyzing claims data of asthma patients 12 y of age or older in 2013; ≥ 2 y of continuous enrollment (2012-2013)	2 cohorts: severe uncontrolled and nonsevere asthma using the HEDIS criteria, consisting of meeting the following 3 criteria in 2012: 2 or more asthma exacerbations; 6 or more medium- or high-dosage dispensed canisters of inhaled corticosteroid (ICS) as monotherapy or with long-acting β_2 -agonist; and 3 or more dispensed non-ICS controllers	Patients with severe uncontrolled asthma exhibited significantly more asthma exacerbations and short-acting β_2 -agonist use	Patients with severe uncontrolled asthma exhibited significantly greater all-cause and asthma-related costs than patients with nonsevere asthma. The adjusted asthma-related average direct cost per patient at follow-up was significantly greater for severe uncontrolled patients (mean $\pm$ SE) (\$2325 $\pm$ \$75) than nonsevere (\$1261 $\pm$ \$9) with an incremental cost of \$1056 (95% CI, \$907-\$1205)
Barry et al, 2017 ¹⁸	Retrospective cohort study using UK primary care data from 2008 to 2013 of 7195 patients ≥ 12 y old with ≥ 2 y continuous data	3 cohorts: 4 OCS prescriptions in each of 2 consecutive years (severe), <0.8 mg/d SCS (mild/moderate), or non-SCS rhinitis patients (no asthma)	See Sweeney et al, 2016 ¹⁰	Estimated average health care costs PPPY were £2603-£4533 for severe, £978-£2072 for mild/moderate, and £560-£1324 for rhinitis controls; ranges generated from use of different costing models (2013 GBP)
Lefebvre et al, 2017 ⁷	Retrospective cohort study using Medicaid claims data from 1997 to 2013 of 3628 patients ≥ 12 y old with ≥ 2 asthma medical claims; a mean follow-up of 2.1 no SCS users vs 3.8 y SCS users	4 cohorts: no OCS (none) or >6 mo of SCS use at cumulative dosage of 6 mg/d (low), >6 -12 mg/d (medium), and >12 mg/d (high). Cohort could change between quarters	Medium- and high-dosage SCS associated with greater adjusted odds of infections, gastrointestinal, bone/muscle, cardiovascular, metabolic, psychiatric, and ocular complications	Annual adjusted incremental cost among SCS users was \$2712-\$8560 for all-cause costs and \$2424-\$6916 for chronic complications cost compared with non-SCS users (2013 USD)
Barry et al, 2018 ²³	Retrospective cohort study using UK primary care data from 2008 to 2013 of 7195 patients ≥ 12 y old with ≥ 2 y of continuous data	3 cohorts: 4 OCS prescriptions in each of 2 consecutive years (severe), <0.8 mg/d SCS (mild/moderate), or non-SCS rhinitis patients (no asthma)	Adjusted odds of specific complications from OCS use differed by age and sex. Differences in odds of complications were less detectable in patients over 70	Cost differences (severe – mild/controlled) were larger for younger patients (<46 y) than older patients (<70 y)
Bloechliger et al, 2018 ⁴	Retrospective observational nested case-control analysis using UK primary care data from 2000 to 2015 of 269,368 patients ≥ 18 y old with an asthma diagnosis requiring $\geq$ GINA 2-level treatment, >3 y of enrollment data, and no history of >4 prior OCS prescriptions in at least the last 3 years	Nested case-control (users vs nonusers) based on first code for a potential complication of SCS use subanalysis by cumulative exposure (<500 , 500-2000, and >2000 mg) and by average daily dosage (<1 , 1-5, and >5 mg)	Use of SCS associated with a greater risk of severe infection, peptic ulcer, affective disorders, cataracts, herpes zoster, cardiovascular events, type II diabetes, and bone complications. Risks tended to increase with increasing dosage. No association with glaucoma, chronic kidney disease, or hypertension	Not reported

(continued)

TABLE III. (Continued)

Author, year	Study design	Cohorts	Clinical outcomes	Economic outcomes
Sullivan et al, 2018 ⁹	Retrospective matched cohort study using MarketScan commercial claims data from 2000 to 2014 of 144,126 patients ≥ 12 y old with ≥ 3 y of continuous data, ≥ 1 asthma-related ER or hospitalization claim in baseline year; a mean follow-up of 1.2 no SCS users vs 2.0 y SCS users	2 cohorts: no OCS (none) and any OCS exposure at any dosage (OCS)	Use of OCS associated with increased odds of osteoporosis, hypertension, obesity, type 2 diabetes, cataracts, and gastrointestinal complications. Odds 29% greater for patients with 4+ OCS prescriptions with the year and odds increased 20% each year with 4+ OCS prescriptions	Not reported
Voorham et al, 2019 ²⁰	Retrospective matched cohort study using UK primary care and hospital linked data from 1997 to 2016 of 18,826 asthma patients ≥ 18 y old with ≥ 3 -y continuous data (1-y baseline and 2-y follow-up)	2 cohorts: no SCS (none) and ≥ 2 SCS prescriptions within 18 mo (SCS) subanalysis by average daily exposure (>0 to <0.5 , 0.5 - 2.5 , 2.5 - 5 , 5 to <7.5 , 7.5 to <15 , and ≥ 15)	Use of SCS associated with greater risk of cataracts, renal impairment, cardio-cerebrovascular disease, type II diabetes, and osteoporosis. Risks tended to increase with increasing dosage. No association with glaucoma or peptic ulcer	Annual complications-related costs: no SCS £1165, any SCS £1483, and ranged from £1210 to £4449 by dosage Annual asthma-related costs: no SCS £166, any SCS £403, and ranged from £273 to £1925 by dosage (2016 GBP)

CI, Confidence interval; ER, emergency room; GINA, Global Initiative for Asthma; HEDIS, Healthcare Effectiveness Data and Information Set; OCS, oral corticosteroid; PPPY, per person per year; SCS, systemic corticosteroid.

non-SCS users at all time points evaluated, and the difference in cost was greatest for those patients who received 4+ SCS treatments in the first year. Patients with 4+ SCS claims in year 1 had 26% greater odds of developing any chronic SCS-related complication and 70% greater odds of developing obesity within 3 years. Odds of other SCS-related complications such as hypertension and diabetes were 32% and 34% greater, respectively. The 3-year, adjusted, incremental, all-cause health care costs among those with 1 to 3 claims in year 1 and those with 4+ SCS claims in year 1 (based on exposure only during the first year) were \$7334 and \$22,310, respectively, compared with non-SCS users.

The study findings with respect to the number of SCS-associated complications over 1 and 3 years are consistent with a previous study that found that patients who had any SCS exposure were at greater risk of acute complications, and those whose 3-month cumulative dose exposure exceeding 5 mg/day were at the greatest risk of chronic complications of SCS use.⁶ In addition, results of this study are consistent with findings from Sullivan et al,⁹ which showed that receipt of 4+ oral corticosteroid prescriptions within a given year was associated with a greater likelihood of chronic complications in that year and in future years.

Previous studies have demonstrated that cumulative SCS exposure correlates with an increased risk of SCS complications (Table III).^{4,6-11,20,23} Overall, the risk of complications tends to increase with increasing exposure,^{4,6,7} but even patients on comparably low dosages of oral prednisone (daily dosage <1 mg/day or cumulative dose of <500 mg) had increased odds of bone-related conditions, severe infections, type 2 diabetes, affective disorders, and cardiovascular events compared with non-SCS users.⁴ This is slightly counter to what was observed in the present study, as comparable rates of chronic complications were

observed between the low-frequency SCS group (1-3 claims) and non-SCS controls in years 1 and 2, indicating that greater SCS exposure will result in a greater likelihood of developing adverse outcomes. Regardless, in addition to SCS dosage, both patient age and sex have also been associated with differences in odds of complications from SCS exposure.¹⁸

In addition to increased clinical adverse events, the present findings indicated an association between SCS use and increased health care costs. This is anticipated as new-onset acute or chronic complications require greater health care utilization, which drives costs. Furthermore, patients may become more difficult and costly to manage as they develop more chronic conditions.

We attempted to determine the source of increased expenditures by categorizing costs into different types: asthma-specific health care costs, SCS complication-related costs, and total health care costs. Although it is likely that each of these categories somewhat overlaps, the costs specific to SCS-related complications may be the best indicator of a direct effect of adverse effects from SCS use (within the limitations of retrospective observational analysis). On the other hand, it is known that asthma-related costs are greater for patients who require SCS therapy due to the inherently greater severity or poorer control typically associated with SCS use. The study found that patients who used SCS had greater asthma-specific costs over time compared with patients not taking SCS. The study used propensity score matching to adjust for differences in demographic characteristics, baseline clinical characteristics reflecting asthma severity and control, baseline HCRU metrics, and the duration of continuous enrollment. In addition, the adjusted analyses further controlled for confounding characteristics. Even after the propensity score adjustment and multivariate adjustment, our

results highlight that patients exposed to SCS had greater asthma-specific health care costs, SCS complication-related costs, and total health care costs.

SCS use has been shown to result in increased health care expenditures.^{6-8,18-20} A study of primary care medical records in the United Kingdom found that, after adjusting for morbidity unrelated to SCS use, greater SCS complication-related costs were associated with younger age, female sex, and receipt of 4+ prescriptions of oral corticosteroids.¹⁸ Similarly, a recent UK-based longitudinal analysis reported that the incremental annual complication-related costs increased over time from 7% in the first year, to 50% and 70% in years 5 and 10, respectively.²⁰ A retrospective claims analysis of patients with asthma that had continuous coverage from 2008 through 2009 found that, among patients with ≥ 2 prescriptions for a 30-day supply of oral corticosteroids, adjusted annual all-cause health care costs were \$3286 greater for patients with ≥ 1 complication compared with SCS users without any associated complications; however, asthma-related costs were similar between groups.¹⁹ Among Medicaid-insured patients, the annualized adjusted incremental cost of complications compared with non-SCS patients ranged from \$2712 to \$8560 in 2013 depending on SCS dosage.⁷

Studying the impact of SCS use on the development of complications and increased health care cost over time has some limitations. First, chronic SCS-related complications often develop after multiple years of use, and it is challenging to observe patients over a significant time horizon. Acute SCS complications could occur early after initiating treatment, but acute adverse events could also develop after long-term exposure. In addition, patients who require SCS for asthma may have more severe or more poorly controlled disease. Both of these characteristics may predispose a patient to incur greater health care costs and be more likely to develop other related conditions. We have attempted to mitigate this “selection bias” by using 2 methods. First, we used propensity score matching to adjust for differences in demographic characteristics, baseline clinical characteristics reflecting asthma severity and control, baseline HCRU metrics, and the duration of continuous enrollment; second, we used adjusted analyses to control for confounding characteristics in all multiple regression analyses. Nonetheless, the threat of selection bias is a limitation of our study.

In addition, the current study required a minimum of 2 years of continuous commercial health coverage or private Medicare supplemental coverage, and most analyses were based on patients with a minimum of 4 years of continuous coverage. Consequently, results of this analysis may not be generalizable to patients with asthma who change or lose insurance or are without any health insurance coverage. Also, although a subset of patients were followed for up to 3 years, this extended follow-up period may not completely capture the long-term clinical outcomes and costs of SCS-related complications in the population. It can take decades for some complications to develop, particularly when SCS treatment is started at a younger age.

In addition, administrative claims data are subject to data coding limitations and data entry error, which may result in missing or erroneous data. Medication utilization was based on records of physician treatment claims and filled prescriptions. Patients were assumed to take the medications as prescribed, though that could not be confirmed. Because of the large sample size used in this study, some differences identified between cohorts may be statistically significant but not clinically meaningful.

Finally, although baseline differences between cohorts were controlled for by IPT weighting and subsequently multivariable modeling, this adjustment was limited to those characteristics that can be measured from administrative claims. Differences in baseline health care utilization and costs after matching suggest that there were persistent systematic differences between the study cohorts that may account for differences found in health care costs, utilization, and clinical outcomes rather than SCS use.

In summary, this study shows that adult patients with persistent asthma treated with SCS are more likely to develop corticosteroid-associated complications and greater associated costs up to 3 years after exposure, and that this was likely dose dependent as those SCS users with 4+ SCS claims in year 1 had numerically greater complications and costs compared with those with 1 to 3 claims in year 1. These findings are consistent with previous research that has shown an association between SCS use and increased incidence of complications, as well as increased health care expenditures. Future research should examine the relationship between prolonged SCS use and adverse outcomes, as the current study limited this association with the amount of SCS prescribed in year 1. Similarly, exploring the impact on changes to asthma maintenance treatment and rescue medication use over time as they relate to both SCS use and the development of adverse outcomes is also warranted, and thus would allow for a proxy measurement of disease control. Regardless, taken together, current results provide clinicians with greater awareness of the potential deleterious clinical and economic effects of using SCS in patients with asthma.

CONCLUSIONS

Patients treated with SCS, particularly those with 4 or more claims in a 12-month period, were more likely to experience SCS-related clinical complications and increased asthma-specific, SCS complication-related, and all-cause health care costs. These results highlight the clinical and economic cost and consequences of SCS use in persistent asthma and raise awareness of the potential benefits of minimizing SCS use in persistent asthma whenever possible.

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ONLINE REPOSITORY

DATA SOURCE

The MarketScan Commercial Database contains the inpatient and outpatient medical, and the outpatient prescription-drug experience of several million employees and their dependents covered under a variety of fee-for-service and capitated health plans. The MarketScan Medicare Supplemental Database contains the same health care experience data for individuals with Medicare supplemental insurance paid for by employers. Reported costs include both the Medicare-covered and the employer-paid portions. All study data were obtained using International Classification of Diseases, 9th and 10th Revision, Clinical Modification (ICD-9-CM and ICD-10-CM) codes, Current Procedural Terminology 4th edition codes, Healthcare Common Procedure Coding System codes, and National Drug Codes. All database records are statistically deidentified and certified to be fully compliant with US patient confidentiality requirements set forth in the Health Insurance Portability and Accountability Act of 1996. As this study used only deidentified patient records and did not involve the collection, use, or transmittal of individually identifiable data, institutional review board approval to conduct this study was not necessary.

Sample selection

To be eligible for study inclusion, all patients were required to have ≥ 1 nondiagnostic claim with a diagnosis of asthma (ICD-9-CM: 493 and ICD-10-CM: J45) codes between January 1, 2003, and July 31, 2016 (enrollment period). Patients with ≥ 1 medical or pharmacy claim for a systemic corticosteroid (SCS) during the enrollment period were eligible for inclusion in the SCS user cohort. The date of the first claim for an SCS during the enrollment period was defined as the index date. SCS users were required to be ≥ 18 years old on the index date, have continuous enrollment with medical and pharmacy benefits for ≥ 12 months before and ≥ 12 months after the index date, and have no claims for SCS use during the 12-month baseline period.

Patients with asthma with ≥ 24 months of continuous MarketScan enrollment and no medical or pharmacy claims for an SCS for the treatment of asthma any time during their enrollment were eligible for inclusion in the non-SCS cohort. To establish their index date, each non-SCS user was matched to an eligible SCS user (with resampling) based on length of continuous enrollment during the study period. A target index date for each non-SCS user was assigned based on the time from the beginning of the matched SCS user's enrollment to their first SCS claim. The final index date was the date of any claim with an asthma diagnosis within 3 months of the target date. After the assignment of an index date, patient age (≥ 18 years old) and minimum continuous enrollment criteria (≥ 12 months before and after the index date) were verified.

All SCS users and non-SCS users were required to meet the Healthcare Effectiveness Data and Information Set (HEDIS) criteria for persistent asthma.

HEDIS defines a patient who meets ≥ 1 of the following criteria during both the 12-month pre- and postindex periods as having persistent asthma:

- (1) ≥ 1 inpatient admission or emergency room visit with a principal diagnosis of asthma

- (2) 4+ outpatient office visits with an asthma diagnosis in any position plus ≥ 2 asthma medication dispensing events
- (3) 4+ asthma medication dispensing events.

Patients with evidence of autoimmune disorders, organ transplants, or chronic SCS complications in the 12-month baseline period were excluded. In addition, patients with any of the following chronic respiratory conditions in either the 12-month pre- or postperiod were excluded: chronic obstructive pulmonary disease, cystic fibrosis, pulmonary fibrosis, bronchiectasis, lung cancer, other respiratory tract cancer, bronchopulmonary dysplasia, sarcoidosis, interstitial lung disease, pulmonary hypertension, or tuberculosis; exclusion based on interstitial lung disease and pulmonary fibrosis required ≥ 1 inpatient or 2 distinct outpatient nondiagnostic claims with the diagnosis code—all others required ≥ 1 nondiagnostic claim. SCS users with any claims for oral budesonide in the first 5 years after index or whose cumulative 1-year postindex SCS exposure was equal to 0 or above the 99th percentile were excluded. Non-SCS users with any physician-administered SCS claims in the first 5 years after index were also excluded.

All remaining SCS users and non-SCS users were assigned to 1 or more follow-up cohorts based on the duration of available continuous follow-up data: ≥ 1 year, ≥ 2 years, and ≥ 3 years.

Statistical analysis

Inverse probability of treatment weighting. Inverse probability of treatment (IPT) weighting was used to account for differences in baseline patient characteristics between SCS users and non-SCS users. Propensity scores were estimated using separate logistic regression models with an indicator of SCS use as a function of baseline demographic and clinical characteristics. Separate propensity score models were fit for each follow-up period (ie, samples of patients with at least 1, 2, and 3 years of continuous enrollment) and each SCS comparison (ie, all SCS users vs non-SCS users, low-frequency SCS users vs non-SCS users, and high-frequency SCS users vs non-SCS users), resulting in a total of 9 models and 9 sets of weights. For each patient, IPT weights were calculated as the inverse of the probability of treatment assignment (ie, $1/P$ for SCS users and $1/[1 - P]$ for non-SCS users, where P is the probability of treatment). The following covariates were included in all models: all baseline demographic characteristics, all baseline clinical characteristics, all baseline health care resource utilization metrics, and the duration of continuous enrollment.

Descriptive analyses. Unweighted and weighted descriptive statistics were reported for demographics, clinical characteristics, and all outcome measures for each cohort. Continuous variables were summarized using means and standard deviations (SD). Categorical variables were reported using counts and percentages before weighting, and percentages only after weighting. Statistically significant differences between groups assessed via 2-sample t -tests for continuous variables and χ^2 tests for categorical variables. Weighted t -tests and χ^2 tests employed robust standard error for postweighting descriptive analyses. For all measures, comparisons were made between SCS users and non-SCS users, low-frequency SCS users and non-SCS users, and high-frequency SCS users and non-SCS users.

Multivariable analyses. For all multivariable models, the ordinal primary SCS exposure was defined for each patient as

none (reference), low-frequency, and high-frequency within the first postindex year. Multivariable models were performed on the cohort of patients with 3 years of continuous enrollment.

Associations between SCS utilization with total health care costs, asthma-specific costs, and chronic SCS complication—related costs over a 3-year follow-up period were estimated using separate linear regression models with log-transformed costs as a function of SCS exposure and baseline clinical and demographic characteristics. Covariate-adjusted costs were estimated for each exposure group using the recycled prediction method. Duan's smearing estimator was used for back-transformation. Confidence intervals for covariate-adjusted costs were estimated using bootstrap resampling with 1000 replications.

The relationships between SCS exposure and the odds of developing any chronic complication and specific complications within a 3-year follow-up period were assessed using separate logistic regression models. Each logistic regression model included covariates for baseline and demographic characteristics. Given the ordinal nature of the exposure, IPT weights were not applied to the multivariable analyses. The alpha level for all statistical tests was 0.05.

Outcomes: IPTW analyses

Complications. In the first year of follow-up, low-frequency SCS users had a higher incidence of ≥ 1 acute complication(s) than matched non-SCS users (16.3% vs 14.9%, $P < .001$), and this difference was driven predominantly by a higher likelihood of infection (Figure 1, A). In contrast, low-frequency SCS users had a lower incidence of ≥ 1 chronic complication than non-SCS users (22.1% vs 24.7%, $P < .001$) with the difference ([users] – [controls]) in the incidence of specific chronic complications in the first year of follow-up ranging from 0.1% to –2.5%. The cumulative incidence of each acute and chronic complication over the 3-year follow-up is reported in Table E3.

As the duration of follow-up increased, the cumulative likelihood of an asthma patient to experience ≥ 1 acute or ≥ 1 chronic complication of SCS use increased at a faster rate for low-frequency SCS users than matched non-SCS users (Figure 1, A). After 3 years of follow-up, the cumulative incidence of ≥ 1 acute complication was 34.2% for low-frequency users compared with 28.7% for non-SCS users ($P < .001$) and cumulative incidence of ≥ 1 acute complication was 44.9% for low-frequency users compared with 43.4% for non-SCS users ($P < .001$). After 3 years, the most common acute complications among low-frequency users and non-SCS users were infection (17.7% vs 14.0%, $P < .001$) and anxiety/depression (15.9% vs 13.6%, $P < .001$), whereas the most common chronic complications were hypertension (20.8% vs 19.5%, $P < .001$), dyslipidemia (19.4% vs 21.2%, $P < .001$), and obesity (8.1% vs 6.2%, $P < .001$; see Table E3).

In contrast, high-frequency SCS users were more likely than matched non-SCS users to have ≥ 1 acute and ≥ 1 chronic complication at every time point ($P < .001$; Figure 1, B). After 3 years of follow-up, the cumulative incidence of ≥ 1 acute complication was 38.2% for high-frequency users compared with 28.4% for non-SCS users ($P < .001$) and cumulative incidence of ≥ 1 acute complication was 50.0% for high-frequency users compared with 43.2% for non-SCS users ($P < .001$). After 3

years, the most common acute complications among high-frequency users and matched non-SCS users were infection (20.5% vs 13.8%, $P < .001$) and anxiety/depression (17.9% vs 13.3%, $P < .001$), whereas the most common chronic complications were hypertension (24.6% vs 19.5%, $P < .001$), dyslipidemia (22.7% vs 21.3%, $P = .11$), and obesity (9.9% vs 6.3%, $P < .001$).

HCRU and costs. In the first year of follow-up, the percentage of low-frequency SCS users who had ≥ 1 emergency room visit was higher than non-SCS users (36.6% vs 28.2%, $P < .001$); however, there was no statistical difference between the percentage of patients with ≥ 1 inpatient admission (9.2% vs 9.0%, $P = .21$). A higher percentage of high-frequency SCS users had ≥ 1 emergency room visit (46.5% vs 25.8%, $P < .001$) and ≥ 1 inpatient admission (14.0% vs 8.5%, $P < .001$) compared with non-SCS users in the first year of follow-up. As with complications of SCS use, the cumulative likelihood of a patient with asthma to experience ≥ 1 emergency room visit or ≥ 1 inpatient admission increased at a faster rate for SCS users than non-SCS users as the duration of follow-up increased. Among patients with 3 years of follow-up, 51.5% of low-frequency SCS patients had ≥ 1 emergency room visit, and 18.6% had ≥ 1 inpatient admission over the full follow-up period compared with 39.4% and 14.7% of non-SCS users (both, $P < .001$). For high-frequency SCS users with ≥ 3 years of follow-up data, 60.7% had ≥ 1 emergency room visit, and 25.9% had ≥ 1 inpatient admission over the full follow-up period compared with 36.8% and 13.8% of non-SCS users (both, $P < .001$).

In the first year of follow-up, low-frequency SCS users incurred a mean (SD) of \$2822 (\$4608) in asthma-related costs, \$3353 (\$5041) in chronic SCS complication—related costs, and \$15,334 (\$23,124) in total health care costs (Table E4). This was \$256 more on asthma-related costs, \$127 more on chronic SCS complication—related costs, and \$1279 more on total health care costs than non-SCS users (all, $P < .001$). By the end of 3 years after index, low-frequency asthma patients had incurred a mean cumulative \$5387 (\$7469) in asthma-related costs, \$7348 (\$9470) in chronic SCS complication—related costs, and \$34,140 (\$47,851) in total health care costs, which equates to \$987, \$872, and \$6556 more than non-SCS users, respectively (all, $P < .001$; cumulative 3-year costs).

Among high-frequency SCS users, the trends were similar, but the differences between SCS users and non-SCS users were more pronounced. In the first year of follow-up, high-frequency SCS users incurred a mean (SD) of \$4003 (\$6478) in asthma-related costs, \$3907 (\$5666) in chronic SCS complication—related costs, and \$22,967 (\$33,918) in total health care costs (Table E4). This was \$1514 greater in asthma-related costs, \$657 greater in chronic SCS complication—related costs, and \$9357 greater in total health care costs compared with non-SCS users (all, $P < .001$). By the end of 3 years after index, high-frequency SCS users had incurred a mean cumulative \$7625 (\$9459) in asthma-related costs, \$9187 (\$11,666) in chronic SCS complication—related costs, and \$50,431 (\$73,172) in total health care costs, which equates to \$3303, \$2701, and \$23,877 more than non-SCS users, respectively (all, $P < .001$; cumulative 3-year costs).

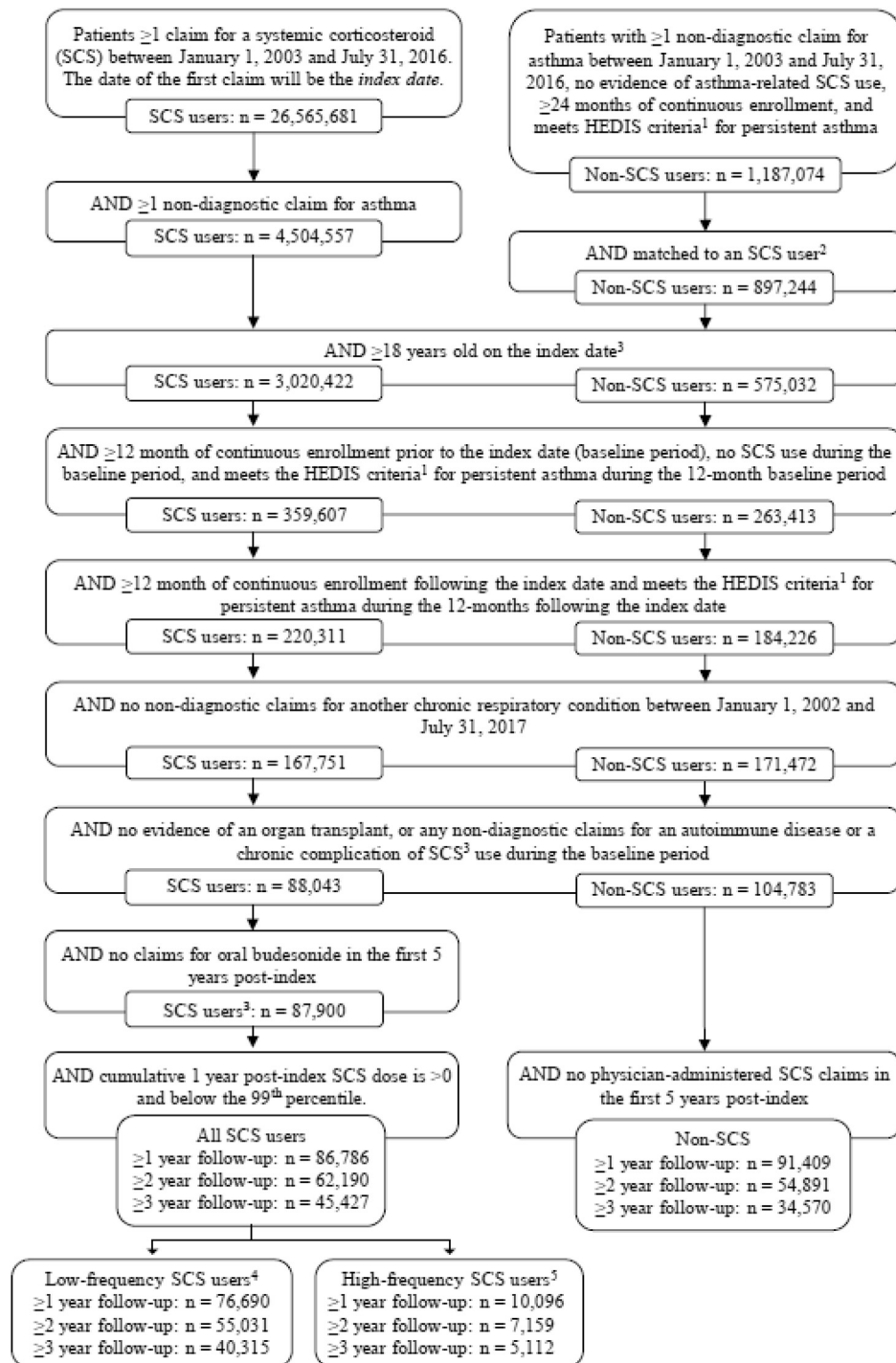


FIGURE E1. Patient selection diagram. ¹The patient meets ≥ 1 of the following criteria: ≥ 1 inpatient admission or ED visit with a principal diagnosis of asthma OR ≥ 4 outpatient office visits with an asthma diagnosis in any position, plus ≥ 2 asthma medication dispensing events OR 4+ asthma medication dispensing events. ²Non-SCS users were matched to SCS users based on length of enrollment. Non-SCS users' target index date is based on the time from the beginning of a matched SCS user's continuous enrollment to their index date. Non-SCS users' final index date was a date with an asthma claim within ± 3 months of the target date. ³Cohort used for direct matching on length of enrollment. ⁴Patient has < 4 claims for SCS in the first 12 months after index. ⁵Patient has 4+ claims for SCS in the first 12 months after index. ED, Emergency department; SCS, systemic corticosteroid.

TABLE E1. International Classification of Diseases, 9th and 10th Revision, Clinical Modification (ICD-9-CM and ICD-10-CM) codes for complications of systemic corticosteroid use

	ICD-9-CM	ICD-10-CM
Anxiety/depression	2962, 2963, 29682, 2980, 3000, 3004, 3091, 311	F32-F33, F341, F41
Fracture	7331X, 800-829	M4850XA-M4858XA, M800, M808, M844-M846, S02, S12, S22, S32, S42, S52, S62, S72, S82, S890-S893, S92
Infection	001-004, 008-104	A00-A99, B00-B99
Avascular necrosis	7334	M87, M905
Cataracts	366	E0836, E0936, E1036, E1136, E1336, H25, H26, H28
Type 2 diabetes	250	E11
Dyslipidemia	2720-2724	E780-E785
Dyspepsia	5368	K30
Gastrointestinal ulcers/bleeds	5310-5312, 5314-5316, 5320-5322, 5324-5326, 5330, 5332, 5334, 5336, 5340, 5342, 5344, 5346, 535, 53783, 53784, 56202, 56203, 56212, 56213, 56985, 56986	K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K2901, K2921, K2931, K2941, K2951, K2961, K2971, K2981, K2991, K31811, K3182, K5521, K5701, K5711, K5713, K5721, K5731, K5733, K5741, K5751, K5753, K5781, K5791, K5793, K625, K6381, K920, K921, K922
Glaucoma	365	H40
Hypertension	401-404	I10-I13
Metabolic syndrome	2777	E8881
Myocardial infarction	410	I21-I22
Obesity	27800, 27801, 27803, V8530-V8545	E660-E662, E669, E669
Osteoporosis	7330	M80-M81
Renal disease	403, 40402, 40403, 40412, 40413, 40492, 40493, 584-586	I12-I13, N17-N19, N990
Sepsis	99591, 99592	A40-A41
Stroke	99702, 430-434	I60-I63, I9781-I9782
Thromboembolism	4151-4162, 4511, 45181, 45182, 4534, 4535, 45372, 45382	I26, I2782, I801, I80201-I80209, I802, I824, I8262, I8272

TABLE E2. Baseline characteristics among of all patient cohorts before and after weighting

Patients with ≥1 year of follow-up	Unweighted											Weighted																				
	All SCS users				Low-frequency SCS users*		High-frequency SCS users†		Non-SCS users		P value SCS users vs non-SCS users	P value low-frequency vs non-SCS users	P value high-frequency vs non-SCS users	All SCS users				Non-SCS users		Low-frequency SCS users*				Non-SCS users		High-frequency SCS users†				Non-SCS users		
	N/mean	%/SD	N/mean	%/SD	N/mean	%/SD	N/mean	%/SD						Mean	%/SD	Mean	%/SD	P	Mean	%/SD	Mean	%/SD	P	Mean	%/SD	Mean	%/SD	Mean	%/SD	P		
	N =	86,786	N =	76,690	N =	10,096	N =	91,409					N =	86,786	N =	91,409	value	N =	76,690	N =	91,409	value	N =	10,096	N =	91,409	value	N =	10,096	N =	91,409	value
Age (mean, SD)	42.1	13.8	41.9	13.8	43.6	13.4	41.4	14.9	<.001	<.001	<.001		41.8	14.4	41.7	14.5	.114	41.6	14.5	41.5	14.6	.145	42.4	14.9	41.6	14.8	<.001					
Age (N, %)																																
18-24	11,621	13.4%	10,632	13.9%	989	9.8%	15,202	16.6%	<.001	<.001	<.001		15.4%		15.5%	.883		15.8%		15.8%	.860		16.0%		16.0%	.986						
25-34	15,123	17.4%	13,480	17.6%	1643	16.3%	16,915	18.5%	<.001	<.001	<.001		17.7%		17.8%	.741		17.8%		17.9%	.652		16.6%		18.3%	.002						
35-44	23,917	27.6%	21,083	27.5%	2834	28.1%	22,663	24.8%	<.001	<.001	<.001		25.9%		25.9%	.935		25.7%		25.8%	.730		24.9%		25.1%	.760						
45-54	21,107	24.3%	18,418	24.0%	2689	26.6%	19,738	21.6%	<.001	<.001	<.001		22.8%		22.8%	.963		22.5%		22.6%	.839		22.4%		22.1%	.580						
55-64	11,875	13.7%	10,362	13.5%	1513	15.0%	12,834	14.0%	.030	.002	.010		14.0%		14.0%	.924		13.9%		13.9%	.789		14.9%		14.1%	.120						
65-74	2229	2.6%	1920	2.5%	309	3.1%	2535	2.8%	.008	<.001	.103		2.7%		2.7%	.771		2.7%		2.7%	.719		3.1%		2.8%	.159						
75+	914	1.1%	795	1.0%	119	1.2%	1522	1.7%	<.001	<.001	<.001		1.5%		1.4%	.244		1.5%		1.4%	.164		2.1%		1.6%	.032						
Sex female (N, %)	55,332	63.8%	48,429	63.1%	6903	68.4%	49,167	53.8%	<.001	<.001	<.001		58.5%		58.5%	.874		58.0%		57.9%	.865		55.0%		55.2%	.711						
Geographic region (N, %)																																
Northeast	16,007	18.4%	14,367	18.7%	1640	16.2%	19,718	21.6%	<.001	<.001	<.001		20.2%		20.3%	.764		20.5%		20.5%	.974		20.9%		21.1%	.752						
North Central	23,909	27.6%	21,223	27.7%	2686	26.6%	23,277	25.5%	<.001	<.001	.013		26.2%		26.3%	.517		26.2%		26.4%	.449		24.8%		25.6%	.186						
South	26,340	30.4%	22,526	29.4%	3814	37.8%	21,364	23.4%	<.001	<.001	<.001		26.7%		26.5%	.350		26.0%		25.9%	.514		25.2%		24.8%	.474						
West	19,657	22.7%	17,804	23.2%	1853	18.4%	25,870	28.3%	<.001	<.001	<.001		25.7%		25.7%	.930		26.1%		26.1%	.939		27.7%		27.3%	.606						
Unknown	873	1.0%	770	1.0%	103	1.0%	1180	1.3%	<.001	<.001	.024		1.2%		1.2%	.768		1.2%		1.2%	.799		1.5%		1.3%	.197						
Rural residence indicator (N, %)																																
Urban	75,290	86.8%	66,707	87.0%	8583	85.0%	79,799	87.5%	<.001	.002	<.001		87.2%		87.1%	.782		87.3%		87.2%	.732		87.3%		87.3%	.900						
Rural	10,650	12.3%	9237	12.0%	1413	14.0%	10,256	11.2%	<.001	<.001	<.001		11.7%		11.7%	.767		11.5%		11.6%	.728		11.2%		11.5%	.486						
Unknown	846	1.0%	746	1.0%	100	1.0%	1174	1.3%	<.001	<.001	.014		1.2%		1.2%	.981		1.2%		1.2%	.977		1.5%		1.3%	.204						
Commercial payer (N, %)	83,121	95.8%	73,525	95.9%	9596	95.0%	86,870	95.0%	<.001	<.001	.973		95.2%		95.3%	.403		95.2%		95.3%	.336		94.1%		95.0%	.010						
Year of index date (N, %)																																
2003	5672	6.5%	4878	6.4%	794	7.9%	4188	4.6%	<.001	<.001	<.001		5.6%		5.6%	.901		5.5%		5.4%	.801		5.3%		4.9%	.203						
2004	5733	6.6%	5018	6.5%	715	7.1%	5114	5.6%	<.001	<.001	<.001		6.1%		5.9%	.229		6.0%		5.9%	.347		6.0%		5.7%	.439						
2005	5860	6.8%	5242	6.8%	618	6.1%	5011	5.5%	<.001	<.001	.008		6.1%		6.1%	.925		6.1%		6.1%	.964		5.6%		5.5%	.803						
2006	5226	6.0%	4635	6.0%	591	5.9%	4498	4.9%	<.001	<.001	<.001		5.4%		5.3%	.414		5.4%		5.3%	.527		4.6%		5.0%	.221						
2007	5730	6.6%	5054	6.6%	676	6.7%	5154	5.6%	<.001	<.001	<.001		6.0%		6.0%	.830		6.0%		6.0%	.900		5.5%		5.7%	.506						
2008	6087	7.0%	5400	7.0%	687	6.8%	5923	6.5%	<.001	<.001	.217		6.7%		6.7%	.964		6.7%		6.7%	.990		6.2%		6.5%	.330						
2009	8935	10.3%	7856	10.2%	1079	10.7%	10,177	11.1%	<.001	<.001	.181		10.7%		10.7%	.978		10.7%		10.7%	.965		11.6%		11.1%	.317						
2010	8569	9.9%	7583	9.9%	986	9.8%	9846	10.8%	<.001	<.001	.002		10.4%		10.3%	.587		10.5%		10.4%	.550		10.5%		10.7%	.715						
2011	8397	9.7%	7452	9.7%	945	9.4%	9726	10.6%	<.001	<.001	<.001		10.1%		10.1%	.890		10.2%		10.2%	.863		10.7%		10.5%	.689						
2012	7221	8.3%	6437	8.4%	784	7.8%	8192	9.0%	<.001	<.001	<.001		8.6%		8.7%	.525		8.7%		8.8%	.557		8.4%		8.8%	.326						
2013	6423	7.4%	5711	7.4%	712	7.1%	7418	8.1%	<.001	<.001	<.001		7.8%		7.8%	.661		7.8%		7.9%	.700		7.9%		8.0%	.767						
2014	5205	6.0%	4612	6.0%	593	5.9%	6237	6.8%	<.001	<.001	<.001		6.5%		6.5%	.451		6.5%		6.6%	.613		6.7%		6.7%	.908						
2015	4936	5.7%	4374	5.7%	562	5.6%	6322	6.9%	<.001	<.001	<.001		6.4%		6.4%	.784		6.5%		6.5%	.830		6.9%		6.8%	.699						
2016	2792	3.2%	2438	3.2%	354	3.5%	3603	3.9%	<.001	<.001	.034		3.6%		3.7%	.418		3.6%		3.7%	.567		4.0%		3.9%	.618						

DCI (mean, SD)	0.7	0.7	0.7	0.6	0.8	0.8	0.5	0.7	<.001	<.001	<.001	0.6	0.7	0.6	0.7	.882	0.6	0.7	0.6	0.7	.975	0.5	0.7	0.5	0.7	.291
Comorbid conditions (N, %)																										
Allergic rhinitis	22,404	25.8%	19,697	25.7%	2707	26.8%	19,771	21.6%	<.001	<.001	<.001		23.8%		23.9%	.578		23.7%		23.7%	.766		22.6%		22.2%	.441
Anxiety	4865	5.6%	4188	5.5%	677	6.7%	3938	4.3%	<.001	<.001	<.001		5.0%		5.0%	.937		4.9%		4.9%	.929		4.6%		4.6%	.816
Chronic sinusitis	14,136	16.3%	12,078	15.7%	2058	20.4%	8209	9.0%	<.001	<.001	<.001		12.6%		12.6%	.938		12.1%		12.1%	.888		10.4%		10.2%	.362
Depression	6470	7.5%	5595	7.3%	875	8.7%	4962	5.4%	<.001	<.001	<.001		6.4%		6.4%	.979		6.3%		6.3%	.920		5.9%		5.8%	.753
GERD	5289	6.1%	4570	6.0%	719	7.1%	4041	4.4%	<.001	<.001	<.001		5.3%		5.2%	.626		5.2%		5.1%	.578		4.8%		4.7%	.710
Insomnia	1486	1.7%	1264	1.6%	222	2.2%	1087	1.2%	<.001	<.001	<.001		1.5%		1.5%	.758		1.4%		1.4%	.935		1.4%		1.3%	.540
Ischemic heart disease	915	1.1%	805	1.0%	110	1.1%	776	0.8%	<.001	<.001	.016		1.0%		1.0%	.484		1.0%		1.0%	.561		1.1%		0.9%	.090
Nasal polyps	840	1.0%	675	0.9%	165	1.6%	326	0.4%	<.001	<.001	<.001		0.7%		0.7%	.414		0.6%		0.6%	.527		0.6%		0.5%	.270
Asthma medications (N, %)																										
Biologics [‡]	400	0.5%	334	0.4%	66	0.7%	368	0.4%	.065	.315	<.001		0.4%		0.4%	.201		0.4%		0.4%	.039		0.5%		0.4%	.239
ICS	22,474	25.9%	20,083	26.2%	2391	23.7%	23,509	25.7%	.395	.029	<.001		25.9%		25.9%	.910		26.1%		26.0%	.798		24.8%		25.5%	.238
ICS/LABA	41,760	48.1%	36,715	47.9%	5045	50.0%	42,215	46.2%	<.001	<.001	<.001		46.6%		46.6%	.914		46.3%		46.5%	.535		45.9%		46.5%	.382
Leukotriene modifier	36,489	42.0%	31,819	41.5%	4670	46.3%	34,559	37.8%	<.001	<.001	<.001		39.7%		39.6%	.850		39.3%		39.3%	.965		38.1%		38.6%	.419
SABA	66,133	76.2%	58,384	76.1%	7749	76.8%	62,357	68.2%	<.001	<.001	<.001		72.6%		72.2%	.080		72.3%		71.9%	.072		71.1%		69.1%	.003
SABA use indicating poor asthma control [§]	9678	11.2%	8460	11.0%	1218	12.1%	7746	8.5%	<.001	<.001	<.001		9.7%		9.5%	.120		9.5%		9.4%	.213		8.8%		8.8%	.950
Incident asthma (N, %)	28,721	33.1%	25,275	33.0%	3446	34.1%	54,242	59.3%	<.001	<.001	<.001		46.9%		47.1%	.608		47.8%		47.8%	.946		56.4%		56.8%	.530
≥1 inpatient admission (N, %)	4766	5.5%	4022	5.2%	744	7.4%	2333	2.6%	<.001	<.001	<.001		3.9%		3.7%	.025		3.7%		3.5%	.052		3.0%		3.1%	.941
≥1 emergency room visit (N, %)	19,406	22.4%	16,876	22.0%	2530	25.1%	11,449	12.5%	<.001	<.001	<.001		17.3%		17.0%	.225		16.8%		16.6%	.316		14.4%		13.8%	.140
Total asthma-related costs (mean, SD)	\$1250	\$2661	\$1241	\$2694	\$1322	\$2396	\$903	\$2068	<.001	<.001	<.001	\$1076	\$2285	\$1008	\$2409	<.001	\$1058	\$2279	\$998	\$2375	<.001	\$995	\$1903	\$937	\$2173	.016
Total costs (mean, SD)	\$7152	\$11,436	\$6955	\$11,389	\$8653	\$11,677	\$5399	\$10,080	<.001	<.001	<.001	\$6331	\$10,224	\$6070	\$11,158	<.001	\$6152	\$10,137	\$5974	\$11,010	.002	\$6458	\$9138	\$5655	\$10,591	<.001
Patients with ≥2 years of follow-up																										
	N =	62,190	N =	55,031	N =	7159	N =	54,891				N =	62,190	N =	54,891	N =	55,031	N =	54,891	N =	7159	N =	54,891			
Age (mean, SD)	42.9	13.7	42.7	13.8	44.4	13.3	41.9	14.9	<.001	<.001	<.001	42.5	14.3	42.4	14.5	.279	42.3	14.4	42.2	14.5	.345	43.2	14.9	42.2	14.8	<.001
Age (N, %)																										
18-24	7274	11.7%	6684	12.1%	590	8.2%	8739	15.9%	<.001	<.001	<.001		14.0%		14.1%	.847		14.4%		14.4%	.934		14.5%		15.0%	.451
25-34	10,182	16.4%	9056	16.5%	1126	15.7%	9549	17.4%	<.001	<.001	<.001		16.6%		16.7%	.822		16.7%		16.8%	.740		15.5%		17.2%	.011
35-44	17,253	27.7%	15,274	27.8%	1979	27.6%	13,755	25.1%	<.001	<.001	<.001		26.3%		26.2%	.868		26.2%		26.2%	.954		25.4%		25.3%	.936
45-54	15,970	25.7%	13,953	25.4%	2017	28.2%	12,372	22.5%	<.001	<.001	<.001		24.1%		24.1%	.882		23.8%		23.8%	.952		23.5%		23.2%	.625
55-64	8959	14.4%	7855	14.3%	1104	15.4%	7789	14.2%	.296	.697	.005		14.4%		14.4%	.980		14.3%		14.3%	.892		15.1%		14.3%	.208
65-74	1839	3.0%	1586	2.9%	253	3.5%	1700	3.1%	.168	.038	.051		3.1%		3.1%	.938		3.0%		3.0%	.928		3.7%		3.2%	.113
75+	713	1.1%	623	1.1%	90	1.3%	987	1.8%	<.001	<.001	.001		1.5%		1.5%	.778		1.6%		1.5%	.643		2.3%		1.8%	.046
Sex female (N, %)	39,826	64.0%	34,894	63.4%	4932	68.9%	29,100	53.0%	<.001	<.001	<.001		58.7%		58.7%	.863		58.1%		58.1%	.923		54.4%		54.8%	.619
Geographic region (N, %)																										
Northeast	11,464	18.4%	10,323	18.8%	1141	15.9%	12,391	22.6%	<.001	<.001	<.001		20.7%		20.7%	.848		21.0%		21.0%	.879		21.6%		21.8%	.776
North Central	17,304	27.8%	15,390	28.0%	1914	26.7%	13,965	25.4%	<.001	<.001	.019		26.4%		26.6%	.535		26.4%		26.6%	.458		24.8%		25.6%	.305
South	18,746	30.1%	16,015	29.1%	2731	38.1%	12,184	22.2%	<.001	<.001	<.001		26.3%		26.1%	.376		25.6%		25.4%	.512		24.1%		23.9%	.782
West	14,197	22.8%	12,882	23.4%	1315	18.4%	15,829	28.8%	<.001	<.001	<.001		25.8%		25.8%	.964		26.2%		26.2%	.996		28.9%		27.6%	.166
Unknown	479	0.8%	421	0.8%	58	0.8%	522	1.0%	<.001	<.001	.272		0.9%		0.9%	.817		0.9%		0.9%	.836		0.6%		1.0%	.003
Rural residence indicator (N, %)																										
Urban	54,066	86.9%	47,995	87.2%	6071	84.8%	48,310	88.0%	<.001	<.001	<.001		87.5%		87.5%	.836		87.7%		87.6%	.762		88.3%		87.6%	.185

(continued)

TABLE E2. (Continued)

Patients with ≥2 years of follow-up																													
	N =	62,190	N =	55,031	N =	7159	N =	54,891				N =	62,190	N =	54,891				N =	55,031	N =	54,891				N =	7159	N =	54,891
Rural	7667	12.3%	6634	12.1%	1033	14.4%	6063	11.0%	<.001	<.001	<.001		11.7%		11.7%	.941		11.5%		11.5%	.863		11.1%		11.4%		.584		
Unknown	457	0.7%	402	0.7%	55	0.8%	518	0.9%	<.001	<.001	.163		0.8%		0.9%	.609		0.8%		0.9%	.617		0.6%		1.0%		.003		
Commercial payer (N, %)	59,188	95.2%	52,432	95.3%	6756	94.4%	51,890	94.5%	<.001	<.001	.590		94.7%		94.8%	.718		94.8%		94.8%	.714		93.3%		94.5%		.007		
Year of index date (N, %)																													
2003	4909	7.9%	4218	7.7%	691	9.7%	3161	5.8%	<.001	<.001	<.001		7.0%		7.0%	.905		6.8%		6.8%	.826		6.9%		6.2%		.067		
2004	4010	6.4%	3528	6.4%	482	6.7%	2436	4.4%	<.001	<.001	<.001		5.5%		5.3%	.367		5.4%		5.3%	.482		4.5%		4.7%		.705		
2005	4913	7.9%	4396	8.0%	517	7.2%	3602	6.6%	<.001	<.001	.037		7.3%		7.2%	.982		7.2%		7.2%	.945		7.2%		6.7%		.263		
2006	4376	7.0%	3878	7.0%	498	7.0%	3249	5.9%	<.001	<.001	<.001		6.4%		6.3%	.432		6.4%		6.3%	.549		5.7%		6.0%		.432		
2007	4477	7.2%	3937	7.2%	540	7.5%	3349	6.1%	<.001	<.001	<.001		6.6%		6.6%	.748		6.5%		6.5%	.807		6.1%		6.3%		.668		
2008	4296	6.9%	3820	6.9%	476	6.6%	3233	5.9%	<.001	<.001	.012		6.4%		6.4%	.967		6.4%		6.4%	.999		5.5%		6.0%		.222		
2009	7028	11.3%	6191	11.3%	837	11.7%	7030	12.8%	<.001	<.001	.008		12.0%		12.0%	.960		12.0%		12.1%	.918		13.7%		12.7%		.096		
2010	6733	10.8%	5973	10.9%	760	10.6%	6944	12.7%	<.001	<.001	<.001		11.7%		11.7%	.785		11.8%		11.7%	.727		11.9%		12.4%		.373		
2011	5366	8.6%	4803	8.7%	563	7.9%	5218	9.5%	<.001	<.001	<.001		9.0%		9.0%	.932		9.1%		9.1%	.920		9.1%		9.3%		.715		
2012	5564	8.9%	4944	9.0%	620	8.7%	5530	10.1%	<.001	<.001	<.001		9.4%		9.6%	.437		9.5%		9.6%	.469		9.6%		9.9%		.598		
2013	4181	6.7%	3707	6.7%	474	6.6%	3939	7.2%	.002	.004	.090		6.9%		7.0%	.645		6.9%		7.0%	.652		6.8%		7.1%		.536		
2014	4139	6.7%	3684	6.7%	455	6.4%	4589	8.4%	<.001	<.001	<.001		7.5%		7.7%	.473		7.6%		7.7%	.665		8.3%		8.2%		.817		
2015	2198	3.5%	1952	3.5%	246	3.4%	2611	4.8%	<.001	<.001	<.001		4.2%		4.2%	.825		4.2%		4.3%	.946		4.6%		4.6%		.949		
2016	0	0.0%	0	0.0%	0	0.0%	0	0.0%	n/a	N/A	N/A		0.0%		0.0%	n/a		0.0%		0.0%	N/A		0.0%		0.0%		N/A		
DCI (mean, SD)	0.7	0.7	0.7	0.6	0.8	0.8	0.5	0.7	<.001	<.001	<.001	0.6	0.7	0.6	0.7	.958	0.6	0.7	0.6	0.7	.995	0.5	0.7	0.5	0.7		.438		
Comorbid conditions (N, %)																													
Allergic rhinitis	15,613	25.1%	13,745	25.0%	1868	26.1%	11,498	20.9%	<.001	<.001	<.001		23.3%		23.5%	.539		23.1%		23.3%	.693		21.8%		21.6%		.777		
Anxiety	3047	4.9%	2640	4.8%	407	5.7%	2099	3.8%	<.001	<.001	<.001		4.4%		4.4%	.890		4.4%		4.4%	.990		4.0%		4.1%		.831		
Chronic sinusitis	10,112	16.3%	8650	15.7%	1462	20.4%	4660	8.5%	<.001	<.001	<.001		12.6%		12.7%	.885		12.1%		12.2%	.905		10.2%		9.9%		.433		
Depression	4377	7.0%	3808	6.9%	569	7.9%	2756	5.0%	<.001	<.001	<.001		6.1%		6.1%	.801		6.0%		5.9%	.763		5.5%		5.4%		.749		
GERD	3755	6.0%	3258	5.9%	497	6.9%	2251	4.1%	<.001	<.001	<.001		5.1%		5.1%	.854		5.0%		5.0%	.856		4.4%		4.5%		.778		
Insomnia	972	1.6%	817	1.5%	155	2.2%	571	1.0%	<.001	<.001	<.001		1.3%		1.4%	.550		1.3%		1.3%	.754		1.2%		1.2%		.861		
Ischemic heart disease	736	1.2%	648	1.2%	88	1.2%	517	0.9%	<.001	<.001	.024		1.1%		1.1%	.426		1.1%		1.1%	.470		1.2%		1.0%		.278		
Nasal polyps	574	0.9%	463	0.8%	111	1.6%	166	0.3%	<.001	<.001	<.001		0.6%		0.7%	.356		0.6%		0.6%	.409		0.6%		0.5%		.375		
Asthma medications (N, %)																													
Biologics [‡]	283	0.5%	239	0.4%	44	0.6%	195	0.4%	.009	.041	.001		0.4%		0.4%	.713		0.4%		0.4%	.839		0.5%		0.4%		.146		
ICS	16,639	26.8%	14,891	27.1%	1748	24.4%	14,555	26.5%	.360	.043	<.001		26.8%		26.7%	.914		26.9%		26.9%	.864		25.9%		26.3%		.622		
ICS/LABA	30,209	48.6%	26,566	48.3%	3643	50.9%	25,295	46.1%	<.001	<.001	<.001		46.9%		46.9%	.792		46.6%		46.7%	.879		45.6%		46.6%		.247		
Leukotriene modifier	26,286	42.3%	22,953	41.7%	3333	46.6%	20,457	37.3%	<.001	<.001	<.001		39.8%		39.6%	.579		39.4%		39.2%	.626		37.4%		38.3%		.248		
SABA	47,253	76.0%	41,764	75.9%	5489	76.7%	37,138	67.7%	<.001	<.001	<.001		72.5%		72.1%	.172		72.2%		71.8%	.157		71.4%		68.7%		.001		
SABA use indicating poor asthma control [§]	6927	11.1%	6038	11.0%	889	12.4%	4558	8.3%	<.001	<.001	<.001		9.7%		9.4%	.102		9.6%		9.3%	.180		8.7%		8.7%		.980		
Incident asthma (N, %)	20,803	33.5%	18,317	33.3%	2486	34.7%	33,064	60.2%	<.001	<.001	<.001		46.3%		46.6%	.411		47.1%		47.3%	.631		56.7%		57.3%		.466		
≥1 inpatient admission (N, %)	3449	5.5%	2910	5.3%	539	7.5%	1374	2.5%	<.001	<.001	<.001		4.1%		3.8%	.036		3.9%		3.6%	.067		3.1%		3.1%		.989		
≥1 emergency room visit (N, %)	13,682	22.0%	11,938	21.7%	1744	24.4%	6548	11.9%	<.001	<.001	<.001		17.3%		17.0%	.281		16.8%		16.6%	.364		13.9%		13.4%		.309		
Total asthma-related costs (mean, SD)	\$1238	\$2586	\$1230	\$2630	\$1301	\$2216	\$878	\$1928	<.001	<.001	<.001	\$1074	\$2235	\$974	\$2093	<.001	\$1057	\$2244	\$966	\$2074	<.001	\$964	\$1650	\$914	\$2008		.040		
Total costs (mean, SD)	\$7242	\$10,971	\$7046	\$10,858	\$8755	\$11,698	\$5322	\$10,228	<.001	<.001	<.001	\$6457	\$9935	\$6110	\$11,475	<.001	\$6269	\$9782	\$6009	\$11,325	<.001	\$6518	\$9129	\$5636	\$10,861		<.001		

Patients with ≥3 years of follow-up																													
	N =	45,427	N =	40,315	N =	5112	N =	34,570				N =	45,427	N =	34,570				N =	40,315	N =	34,570				N =	5112	N =	34,570
Age (mean, SD)	43.8	13.6	43.6	13.6	45.3	13.2	42.6	14.9	<.001	<.001	<.001	43.3	14.2	43.3	14.4	.511	43.2	14.3	43.1	14.4	.570	44.1	15.0	43.0	14.8	.002			
Age (N, %)																													
18-24	4444	9.8%	4099	10.2%	345	6.7%	5012	14.5%	<.001	<.001	<.001		12.1%		12.2%	.660		12.5%		12.6%	.857		12.9%		13.5%	.507			
25-34	7025	15.5%	6266	15.5%	759	14.8%	5668	16.4%	<.001	.002	.005		15.7%		15.6%	.909		15.7%		15.7%	.982		15.0%		16.2%	.140			
35-44	12,788	28.2%	11,373	28.2%	1415	27.7%	8767	25.4%	<.001	<.001	<.001		26.7%		26.6%	.810		26.7%		26.6%	.969		25.1%		25.6%	.533			
45-54	12,231	26.9%	10,737	26.6%	1494	29.2%	8207	23.7%	<.001	<.001	<.001		25.4%		25.4%	.959		25.1%		25.1%	.978		24.6%		24.5%	.844			
55-64	6798	15.0%	5994	14.9%	804	15.7%	5002	14.5%	.051	.127	.019		14.9%		14.9%	.984		14.8%		14.8%	.899		15.4%		14.6%	.271			
65-74	1549	3.4%	1333	3.3%	216	4.2%	1241	3.6%	.175	.036	.027		3.5%		3.6%	.731		3.5%		3.5%	.772		4.4%		3.7%	.094			
75+	592	1.3%	513	1.3%	79	1.5%	673	1.9%	<.001	<.001	.056		1.7%		1.7%	.814		1.7%		1.7%	.600		2.6%		1.9%	.070			
Sex female (N, %)	29,173	64.2%	25,651	63.6%	3522	68.9%	18,160	52.5%	<.001	<.001	<.001		59.1%		59.0%	.780		58.5%		58.4%	.822		54.7%		54.6%	.959			
Geographic region (N, %)																													
Northeast	7986	17.6%	7205	17.9%	781	15.3%	7572	21.9%	<.001	<.001	<.001		19.7%		19.8%	.694		20.0%		20.1%	.933		20.9%		21.1%	.883			
North Central	12,944	28.5%	11,542	28.6%	1402	27.4%	8942	25.9%	<.001	<.001	.019		27.1%		27.3%	.632		27.1%		27.3%	.628		24.9%		26.1%	.183			
South	13,294	29.3%	11,397	28.3%	1897	37.1%	7127	20.6%	<.001	<.001	<.001		25.4%		25.0%	.272		24.6%		24.3%	.417		22.1%		22.7%	.438			
West	10,938	24.1%	9940	24.7%	998	19.5%	10,712	31.0%	<.001	<.001	<.001		27.2%		27.3%	.811		27.6%		27.7%	.830		31.4%		29.5%	.086			
Unknown	265	0.6%	231	0.6%	34	0.7%	217	0.6%	.449	.357	.826		0.6%		0.6%	.856		0.6%		0.6%	.910		0.7%		0.6%	.875			
Rural residence indicator (N, %)																													
Urban	39,504	87.0%	35,162	87.2%	4342	84.9%	30,607	88.5%	<.001	<.001	<.001		87.7%		87.7%	.966		87.8%		87.8%	.936		88.3%		88.1%	.809			
Rural	5676	12.5%	4937	12.2%	739	14.5%	3748	10.8%	<.001	<.001	<.001		11.8%		11.7%	.885		11.6%		11.6%	.994		11.1%		11.3%	.794			
Unknown	247	0.5%	216	0.5%	31	0.6%	215	0.6%	.162	.132	.971		0.6%		0.6%	.648		0.6%		0.6%	.689		0.6%		0.6%	.952			
Commercial payer (N, %)	42,909	94.5%	38,143	94.6%	4766	93.2%	32,426	93.8%	<.001	<.001	.127		94.0%		94.0%	.985		94.1%		94.1%	.882		92.2%		93.7%	.009			
Year of index date (N, %)																													
2003	4055	8.9%	3491	8.7%	564	11.0%	2268	6.6%	<.001	<.001	<.001		8.0%		8.1%	.838		7.8%		7.8%	.876		8.3%		7.2%	.035			
2004	3425	7.5%	3024	7.5%	401	7.8%	1830	5.3%	<.001	<.001	<.001		6.5%		6.3%	.416		6.4%		6.3%	.555		5.4%		5.6%	.651			
2005	4255	9.4%	3804	9.4%	451	8.8%	2829	8.2%	<.001	<.001	.128		8.9%		8.9%	.945		8.9%		8.9%	.946		8.8%		8.3%	.369			
2006	3577	7.9%	3159	7.8%	418	8.2%	2370	6.9%	<.001	<.001	<.001		7.3%		7.2%	.460		7.3%		7.2%	.552		6.8%		7.0%	.699			
2007	3487	7.7%	3094	7.7%	393	7.7%	2172	6.3%	<.001	<.001	<.001		7.0%		6.9%	.758		6.9%		6.9%	.774		6.1%		6.5%	.416			
2008	3457	7.6%	3092	7.7%	365	7.1%	2329	6.7%	<.001	<.001	.299		7.2%		7.2%	.893		7.2%		7.3%	.875		6.1%		6.7%	.149			
2009	5793	12.8%	5129	12.7%	664	13.0%	5365	15.5%	<.001	<.001	<.001		14.1%		14.1%	.993		14.1%		14.1%	.962		16.2%		15.2%	.252			
2010	4364	9.6%	3911	9.7%	453	8.9%	3732	10.8%	<.001	<.001	<.001		10.1%		10.1%	.785		10.2%		10.2%	.771		9.9%		10.5%	.340			
2011	4068	9.0%	3628	9.0%	440	8.6%	3450	10.0%	<.001	<.001	.002		9.3%		9.4%	.822		9.3%		9.4%	.799		9.8%		9.8%	.998			
2012	3765	8.3%	3361	8.3%	404	7.9%	3188	9.2%	<.001	<.001	.002		8.7%		8.8%	.505		8.7%		8.9%	.556		8.7%		9.1%	.565			
2013	3357	7.4%	2983	7.4%	374	7.3%	3053	8.8%	<.001	<.001	<.001		8.0%		8.1%	.633		8.0%		8.2%	.613		8.6%		8.6%	.922			
2014	1824	4.0%	1639	4.1%	185	3.6%	1984	5.7%	<.001	<.001	<.001		4.9%		5.0%	.740		5.0%		5.0%	.999		5.4%		5.5%	.879			
2015	0	0.0%	0	0.0%	0	0.0%	0	0.0%	N/A	N/A	N/A		0.0%		0.0%	n/a		0.0%		0.0%	N/A		0.0%		0.0%	N/A			
2016	0	0.0%	0	0.0%	0	0.0%	0	0.0%	N/A	N/A	N/A		0.0%		0.0%	n/a		0.0%		0.0%	N/A		0.0%		0.0%	N/A			
DCI (mean, SD)	0.7	0.7	0.7	0.6	0.8	0.8	0.5	0.7	<.001	<.001	<.001	0.6	0.7	0.6	0.7	.999	0.6	0.7	0.6	0.7	.994	0.5	0.7	0.5	0.7	.363			
Comorbid conditions (N, %)																													
Allergic rhinitis	10,836	23.9%	9561	23.7%	1275	24.9%	7000	20.2%	<.001	<.001	<.001		22.4%		22.7%	.484		22.3%		22.5%	.614		21.1%		20.9%	.815			
Anxiety	1950	4.3%	1695	4.2%	255	5.0%	1165	3.4%	<.001	<.001	<.001		3.9%		4.0%	.836		3.9%		3.9%	.967		3.6%		3.6%	.943			
Chronic sinusitis	7273	16.0%	6245	15.5%	1028	20.1%	2762	8.0%	<.001	<.001	<.001		12.5%		12.5%	.961		12.0%		12.0%	.970		9.8%		9.6%	.653			
Depression	3105	6.8%	2716	6.7%	389	7.6%	1645	4.8%	<.001	<.001	<.001		5.9%		5.9%	.918		5.8%		5.8%	.868		5.2%		5.1%	.940			

(continued)

TABLE E2. (Continued)

Patients with ≥3 years of follow-up																													
	N =	45,427	N =	40,315	N =	5112	N =	34,570				N =	45,427	N =	34,570				N =	40,315	N =	34,570				N =	5112	N =	34,570
GERD	2626	5.8%	2290	5.7%	336	6.6%	1347	3.9%	<.001	<.001	<.001		5.0%		4.9%	.931		4.9%		4.8%	.940		4.1%		4.3%		.616		
Insomnia	649	1.4%	554	1.4%	95	1.9%	322	0.9%	<.001	<.001	<.001		1.2%		1.3%	.608		1.2%		1.2%	.769		1.2%		1.1%		.575		
Ischemic heart disease	628	1.4%	557	1.4%	71	1.4%	352	1.0%	<.001	<.001	.020		1.2%		1.3%	.453		1.2%		1.3%	.505		1.3%		1.1%		.326		
Nasal polyps	417	0.9%	341	0.8%	76	1.5%	91	0.3%	<.001	<.001	<.001		0.6%		0.7%	.376		0.6%		0.7%	.387		0.5%		0.5%		.742		
Asthma medications (N, %)																													
Biologics [‡]	212	0.5%	182	0.5%	30	0.6%	107	0.3%	<.001	.002	.002		0.4%		0.3%	.052		0.4%		0.3%	.113		0.4%		0.3%		.282		
ICS	12,615	27.8%	11,315	28.1%	1300	25.4%	9535	27.6%	.561	.142	.001		27.7%		27.7%	.863		27.8%		27.9%	.797		26.9%		27.3%		.682		
ICS/LABA	22,148	48.8%	19,546	48.5%	2602	50.9%	15,879	45.9%	<.001	<.001	<.001		47.2%		46.9%	.394		47.0%		46.7%	.546		45.0%		46.5%		.172		
Leukotriene modifier	19,205	42.3%	16,804	41.7%	2401	47.0%	12,652	36.6%	<.001	<.001	<.001		39.6%		39.4%	.511		39.2%		38.9%	.555		37.4%		37.9%		.577		
SABA	34,475	75.9%	30,577	75.8%	3898	76.3%	23,354	67.6%	<.001	<.001	<.001		72.7%		72.3%	.309		72.4%		72.0%	.280		71.6%		68.6%		.004		
SABA use indicating poor asthma control [§]	5082	11.2%	4434	11.0%	648	12.7%	2859	8.3%	<.001	<.001	<.001		9.9%		9.5%	.159		9.6%		9.4%	.239		8.7%		8.8%		.921		
Incident asthma (N, %)	15,447	34.0%	13,602	33.7%	1845	36.1%	21,086	61.0%	<.001	<.001	<.001		46.0%		46.3%	.379		46.7%		47.0%	.530		57.6%		57.8%		.852		
≥1 inpatient admission (N, %)	3449	5.5%	2215	5.5%	373	7.3%	879	2.5%	<.001	<.001	<.001		4.3%		4.1%	.217		4.1%		3.9%	.287		3.1%		3.2%		.597		
≥1 emergency room visit (N, %)	13,682	22.0%	8607	21.3%	1190	23.3%	3987	11.5%	<.001	<.001	<.001		17.2%		16.9%	.385		16.8%		16.6%	.478		13.6%		13.1%		.341		
Total asthma-related costs (mean, SD)	\$1238	\$2586	\$1214	\$2551	\$1276	\$2234	\$849	\$1674	<.001	<.001	<.001	\$1076	\$2225	\$958	\$1895	<.001	\$1061	\$2232	\$949	\$1872	<.001	\$935	\$1623	\$889	\$1783		.098		
Total costs (mean, SD)	\$7242	\$10,971	\$7254	\$11,380	\$8746	\$11,154	\$5366	\$10,843	<.001	<.001	<.001	\$6684	\$10,455	\$6271	\$12,208	<.001	\$6512	\$10,417	\$6175	\$12,085	.001	\$6609	\$8999	\$5710	\$11,501		<.001		

DCI, Deyo-Charlson comorbidity index; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; N/A, not applicable; SABA, short-acting β_2 -agonist; SCS, systemic corticosteroid; SD, standard deviation.

*Low-frequency SCS users had <4 claims for SCSs in the first 12 months after index.

†High-frequency SCS users had ≥4 claims for SCSs in the first 12 months after index.

‡All patients on biologics for asthma were prescribed omalizumab. No patients had prescriptions for mepolizumab or reslizumab.

§≥7 SABA canisters during the baseline period.

||Costs for all claims with a primary diagnosis of asthma, and claims for asthma medications.

TABLE E3. Adjusted prevalence of complications of systemic corticosteroid (SCS) use in the full follow-up period among SCS users versus non-SCS users

	All SCS users		Non-SCS users		P value	Low-frequency SCS users*		Non-SCS users		P value	High-frequency SCS users†		Non-SCS users		P value
	N/mean	%/SD	N/mean	%/SD		N/mean	%/SD	N/mean	%/SD		N/mean	%/SD			
	N =	86,786	N =	91,409		N =	76,690	N =	91,409		N =	10,096	N =	91,409	
Patients with ≥1 year of follow-up															
Acute complications‡															
≥1 (N, %)		16.7%		14.9%	<.001		16.3%		14.9%	<.001		20.7%		14.8%	<.001
Number per patient§ (mean, SD)	1.08	0.27	1.07	0.26	.041	1.07	0.27	1.07	0.26	.210	1.1	0.3	1.1	0.3	<.001
Anxiety/depression (N, %)		7.7%		7.4%	.046		7.5%		7.4%	.754		10.0%		7.4%	<.001
Fracture (N, %)		2.3%		2.1%	.004		2.3%		2.1%	.011		2.4%		2.0%	.064
Infection (N, %)		8.0%		6.4%	<.001		7.8%		6.4%	<.001		10.4%		6.3%	<.001
Chronic complications‡															
≥1 (N, %)		22.7%		24.8%	<.001		22.1%		24.7%	<.001		28.0%		25.0%	<.001
Number per patient§ (mean, SD)	1.32	0.60	1.35	0.64	<.001	1.31	0.60	1.35	0.64	<.001	1.38	0.66	1.35	0.65	.132
Avascular necrosis (N, %)		0.0%		0.0%	.402		0.0%		0.0%	.978		0.1%		0.0%	<.001
Cataracts (N, %)		1.9%		2.0%	.043		1.8%		2.0%	.006		2.6%		2.0%	.009
Diabetes (type 2) (N, %)		1.8%		1.8%	.432		1.7%		1.8%	.226		2.3%		1.8%	.020
Dyslipidemia (N, %)		8.0%		10.4%	<.001		7.9%		10.4%	<.001		9.6%		10.7%	.017
Dyspepsia (N, %)		0.5%		0.5%	.869		0.5%		0.5%	.817		0.6%		0.5%	.167
Gastrointestinal ulcers/bleeds (N, %)		1.7%		1.6%	.032		1.7%		1.6%	.077		2.0%		1.5%	.012
Glaucoma (N, %)		1.0%		1.2%	<.001		1.0%		1.2%	<.001		1.4%		1.2%	.351
Hypertension (N, %)		9.7%		10.5%	<.001		9.4%		10.4%	<.001		12.4%		10.7%	<.001
Metabolic syndrome (N, %)		0.2%		0.2%	.979		0.2%		0.2%	.809		0.2%		0.2%	.612
Myocardial infarction (N, %)		0.1%		0.2%	.232		0.1%		0.2%	.105		0.3%		0.2%	.145
Obesity (N, %)		3.3%		3.3%	.649		3.2%		3.3%	.395		4.5%		3.3%	<.001
Osteoporosis (N, %)		0.6%		0.7%	.001		0.6%		0.7%	<.001		0.8%		0.7%	.499
Renal disease (N, %)		0.3%		0.3%	.598		0.3%		0.3%	.148		0.7%		0.4%	<.001
Sepsis (N, %)		0.1%		0.1%	.116		0.1%		0.1%	.668		0.3%		0.1%	<.001
Stroke (N, %)		0.2%		0.2%	.648		0.1%		0.2%	.107		0.4%		0.2%	.002
Thromboembolism (N, %)		0.4%		0.3%	<.001		0.4%		0.3%	.004		0.6%		0.3%	<.001
Patients with ≥2 years of follow-up															
	N =	62,190	N =	54,891		N =	55,031	N =	54,891		N =	7159	N =	54,891	
Acute complications‡															
≥1 (N, %)		26.8%		22.8%	<.001		26.3%		22.7%	<.001		31.0%		22.6%	<.001
Number per patient§ (mean, SD)	1.1	0.4	1.1	0.3	<.001	1.13	0.36	1.11	0.33	.002	1.15	0.37	1.11	0.33	.002
Anxiety/depression (N, %)		12.5%		11.1%	<.001		12.2%		11.1%	<.001		15.0%		11.0%	<.001
Fracture (N, %)		4.4%		3.7%	<.001		4.3%		3.7%	<.001		4.9%		3.7%	<.001
Infection (N, %)		13.5%		10.6%	<.001		13.3%		10.6%	<.001		15.7%		10.5%	<.001
Chronic complications‡															

(continued)

TABLE E3. (Continued)

Patients with ≥ 2 years of follow-up	N =	62,190	N =	54,891		N =	55,031	N =	54,891		N =	7159	N =	54,891	
≥ 1 (N, %)		35.7%		35.7%	.854		35.1%		35.5%	.195		41.3%		35.6%	<.001
Number per patient [§] (mean, SD)	1.5	0.8	1.5	0.8	.302	1.47	0.77	1.49	0.77	.046	1.57	0.90	1.50	0.78	.008
Avascular necrosis (N, %)		0.1%		0.1%	.232		0.1%		0.1%	.582		0.2%		0.1%	<.001
Cataracts (N, %)		3.6%		3.7%	.686		3.5%		3.7%	.366		4.6%		3.7%	.016
Diabetes (type 2) (N, %)		3.3%		3.1%	.104		3.2%		3.0%	.215		4.1%		3.0%	<.001
Dyslipidemia (N, %)		14.1%		16.4%	<.001		14.0%		16.3%	<.001		16.2%		16.5%	.594
Dyspepsia (N, %)		1.1%		0.8%	<.001		1.0%		0.8%	.001		1.3%		0.8%	.003
Gastrointestinal ulcers/bleeds (N, %)		3.3%		2.8%	<.001		3.2%		2.8%	<.001		3.6%		2.7%	.002
Glaucoma (N, %)		1.9%		2.2%	.004		1.8%		2.2%	.001		2.4%		2.1%	.382
Hypertension (N, %)		15.7%		15.5%	.504		15.3%		15.4%	.631		18.8%		15.6%	<.001
Metabolic syndrome (N, %)		0.4%		0.4%	.607		0.4%		0.4%	.611		0.3%		0.4%	.698
Myocardial infarction (N, %)		0.3%		0.2%	.076		0.3%		0.2%	.192		0.4%		0.3%	.024
Obesity (N, %)		6.0%		5.0%	<.001		5.8%		5.0%	<.001		7.5%		5.1%	<.001
Osteoporosis (N, %)		1.2%		1.4%	.019		1.1%		1.4%	.003		1.7%		1.3%	.047
Renal disease (N, %)		0.7%		0.6%	.747		0.6%		0.6%	.794		1.1%		0.6%	.003
Sepsis (N, %)		0.2%		0.1%	.012		0.2%		0.1%	.163		0.6%		0.1%	<.001
Stroke (N, %)		0.3%		0.3%	.752		0.3%		0.3%	.410		0.5%		0.3%	.095
Thromboembolism (N, %)		0.7%		0.5%	<.001		0.7%		0.5%	<.001		1.4%		0.5%	<.001
Patients with ≥ 3 years of follow-up	N =	45,427	N =	34,570		N =	40,315	N =	34,570		N =	5112	N =	34,570	
Acute complications [‡]															
≥ 1 (N, %)		34.7%		28.8%	<.001		34.2%		28.7%	<.001		38.2%		28.4%	<.001
Number per patient [§] (mean, SD)	1.2	0.4	1.1	0.4	<.001	1.17	0.40	1.15	0.38	<.001	1.21	0.43	1.15	0.37	<.001
Anxiety/depression (N, %)		16.2%		13.6%	<.001		15.9%		13.6%	<.001		17.9%		13.3%	<.001
Fracture (N, %)		6.5%		5.4%	<.001		6.3%		5.4%	<.001		7.8%		5.3%	<.001
Infection (N, %)		18.0%		14.0%	<.001		17.7%		14.0%	<.001		20.5%		13.8%	<.001
Chronic complications [‡]															
≥ 1 (N, %)		45.5%		43.6%	<.001		44.9%		43.4%	<.001		50.0%		43.2%	<.001
Number per patient [§] (mean, SD)	1.6	0.9	1.6	0.9	.098	1.62	0.89	1.62	0.88	.726	1.81	1.09	1.62	0.88	<.001
Avascular necrosis (N, %)		0.1%		0.1%	.024		0.1%		0.1%	.101		0.3%		0.1%	<.001
Cataracts (N, %)		5.6%		5.5%	.791		5.4%		5.5%	.774		7.2%		5.6%	.001
Diabetes (type 2) (N, %)		4.6%		4.3%	.049		4.5%		4.2%	.155		6.2%		4.1%	<.001
Dyslipidemia (N, %)		19.7%		21.3%	<.001		19.4%		21.2%	<.001		22.7%		21.3%	.108
Dyspepsia (N, %)		1.5%		1.2%	<.001		1.5%		1.2%	.002		1.9%		1.2%	.003
Gastrointestinal ulcers/bleeds (N, %)		4.9%		4.1%	<.001		4.8%		4.0%	<.001		5.4%		3.9%	<.001
Glaucoma (N, %)		2.8%		3.1%	.103		2.8%		3.0%	.066		3.5%		3.0%	.207
Hypertension (N, %)		21.1%		19.6%	<.001		20.8%		19.5%	<.001		24.6%		19.5%	<.001
Metabolic syndrome (N, %)		0.5%		0.5%	.971		0.5%		0.5%	.877		0.4%		0.5%	.145

Myocardial infarction (N, %)	0.5%	0.4%	.008	0.5%	0.4%	.045	0.8%	0.4%	<.001
Obesity (N, %)	8.3%	6.2%	<.001	8.1%	6.2%	<.001	9.9%	6.3%	<.001
Osteoporosis (N, %)	1.8%	2.1%	.048	1.8%	2.0%	.021	2.3%	1.9%	.187
Renal disease (N, %)	1.0%	0.9%	.416	1.0%	0.9%	.725	1.6%	0.9%	.007
Sepsis (N, %)	0.2%	0.2%	.077	0.2%	0.2%	.410	0.6%	0.2%	<.001
Stroke (N, %)	0.5%	0.5%	<.001	0.5%	0.5%	.536	0.8%	0.5%	.037
Thromboembolism (N, %)	1.1%	0.7%	<.001	1.0%	0.7%	<.001	2.2%	0.7%	<.001

SD, Standard deviation.

*Low-frequency SCS users had <4 claims for SCSs in the first 12 months after index.

†High-frequency SCS users had ≥4 claims for SCSs in the first 12 months after index.

‡Not present during the baseline period.

§Among patients with at least one complication.

TABLE E4. Cumulative costs in the 3-year follow-up period among systemic corticosteroid (SCS) users and non-SCS users

	All SCS users			Non-SCS users			<i>P</i> value
	Mean	SD	Median	Mean	SD	Median	
Cumulative asthma-related costs* (mean, SD)							
1 y	\$2973	\$4834	\$1947	\$2582	\$4865	\$1651	<.001
2 y	\$4312	\$6222	\$2936	\$3509	\$5750	\$2277	<.001
3 y	\$5661	\$7824	\$3950	\$4421	\$7001	\$2845	<.001
Cumulative chronic SCS complication—related costs† (mean, SD)							
1 y	\$3427	\$5119	\$2652	\$3224	\$5306	\$2506	<.001
2 y	\$5417	\$7296	\$4173	\$4851	\$6814	\$3756	<.001
3 y	\$7578	\$9815	\$5750	\$6502	\$8997	\$5000	<.001
Cumulative total costs (mean, SD)							
1 y	\$16,415	\$25,305	\$10,352	\$14,212	\$25,374	\$8649	<.001
2 y	\$25,869	\$37,296	\$16,988	\$20,889	\$33,659	\$13,412	<.001
3 y	\$36,285	\$51,562	\$24,166	\$27,845	\$45,749	\$18,293	<.001

	Low-frequency‡ SCS users			Non-SCS users			<i>P</i> value
	Mean	SD	Median	Mean	SD	Median	
Cumulative asthma-related costs* (mean, SD)							
1 y	\$2822	\$4608	\$1852	\$2566	\$4812	\$1640	<.001
2 y	\$4087	\$6002	\$2779	\$3492	\$5722	\$2262	<.001
3 y	\$5387	\$7469	\$3767	\$4400	\$6936	\$2825	<.001
Cumulative chronic SCS complication—related costs† (mean, SD)							
1 y	\$3353	\$5041	\$2616	\$3216	\$5295	\$2501	<.001
2 y	\$5257	\$7038	\$4095	\$4833	\$6792	\$3745	<.001
3 y	\$7348	\$9470	\$5615	\$6476	\$8993	\$4980	<.001
Cumulative total costs (mean, SD)							
1 y	\$15,334	\$23,124	\$9870	\$14,056	\$25,318	\$8551	<.001
2 y	\$24,226	\$34,317	\$16,174	\$20,668	\$33,498	\$13,267	<.001
3 y	\$34,140	\$47,851	\$23,075	\$27,584	\$45,687	\$18,096	<.001

	High-frequency§ SCS users			Non-SCS users			<i>P</i> value
	Mean	SD	Median	Mean	SD	Median	
Cumulative asthma-related costs* (mean, SD)							
1 y	\$4003	\$6478	\$2579	\$2489	\$4497	\$1585	<.001
2 y	\$5817	\$7006	\$4110	\$3438	\$5729	\$2204	<.001
3 y	\$7625	\$9459	\$5565	\$4322	\$6727	\$2748	<.001
Cumulative chronic SCS complication—related costs† (mean, SD)							
1 y	\$3907	\$5666	\$2813	\$3250	\$5333	\$2543	<.001
2 y	\$6477	\$8655	\$4728	\$4857	\$6698	\$3798	<.001
3 y	\$9187	\$11,666	\$6685	\$6487	\$8842	\$5030	<.001
Cumulative total costs (mean, SD)							
1 y	\$22,967	\$33,918	\$13,757	\$13,610	\$25,722	\$8195	<.001
2 y	\$35,993	\$50,952	\$22,961	\$19,935	\$33,012	\$12,619	<.001
3 y	\$50,431	\$73,172	\$32,153	\$26,554	\$45,254	\$17,198	<.001

SD, Standard deviation.

*Summed costs for all claims with a primary diagnosis of asthma and claims for asthma medications.

†Summed costs for all claims with a primary diagnosis of a chronic complication and claims for prescriptions to treat chronic complications.

‡Low-frequency SCS users had <4 claims for SCS in the first 12 months after index.

§High-frequency SCS users had 4+ claims for SCS in the first 12 months after index.