

Utilization and Costs of Severe Uncontrolled Asthma in a Managed-Care Setting



Robert S. Zeiger, MD, PhD^a, Michael Schatz, MD, MS^a, Anand A. Dalal, MBA, PhD^b, Lei Qian, PhD^a, Wansu Chen, MS^a, Eunice W. Ngor, MS^c, Robert Y. Suruki, ScD^b, and Aniket A. Kawatkar, PhD^a San Diego and Pasadena, Oakland, Calif; and Research Triangle Park, NC

What is already known about this topic? The high utilization and cost of severe asthma is in disproportion to its frequency among persistent asthmatics, but little is known of the burden of severe uncontrolled asthma (SUA) in a managed-care setting.

What does this article add to our knowledge? The present study identified, characterized, and determined the clinical and economic burden of SUA compared with non-SUA in a cohort of adolescents and adults with persistent asthma in a large managed-care organization. It was found that patients with SUA comprised a minority of persistent asthmatics but had significantly more comorbidities, asthma exacerbations, utilization, and direct total and asthma-related costs in a follow-up year despite being dispensed more controller medications than patients with non-SUA.

How does this study impact current management guidelines? The study highlights that patients with SUA require more intensive interventions, including higher step-level care, better adherence, more specialist care, and specific attention to comorbidities to reduce asthma burden.

BACKGROUND: Clinical and economic burden of patients with severe uncontrolled asthma (SUA) in a real-world managed-care setting required further documentation.

OBJECTIVE: The objective of this study was to determine the characteristics, clinical, and economic burden of SUA in a managed-care setting.

METHODS: This observational study identified patients with persistent asthma aged 12 years or more (N = 25,935) using the

International Classification of Diseases, 9th Revision asthma codes and Healthcare Effectiveness Data and Information Set administrative criteria. An SUA subgroup was identified when all of the following 3 criteria were met in 2012: (1) 2 or more asthma exacerbations; (2) 6 or more medium- or high-dose dispensed canisters of inhaled corticosteroid (ICS) as monotherapy or with long-acting β_2 -agonist; and (3) 3 or more dispensed non-ICS controllers. Health care utilization and direct costs (all-cause and asthma-related) in 2013 were compared between SUA and non-SUA subgroups using multivariable regression.

RESULTS: Compared with the non-SUA subgroup (N = 25,350, 97.7%), the SUA subgroup (N = 585, 2.3%) at baseline was significantly older and had more comorbidities, asthma specialist care, controller medication dispensed, and asthma exacerbations. During follow-up, patients with SUA exhibited significantly more asthma exacerbations and short-acting β_2 -agonist use, and higher all-cause and asthma-related costs than patients with non-SUA. The adjusted asthma-related average direct cost per patient at follow-up was significantly higher for SUA (mean $\pm$ SE) (\$2325 $\pm$ \$75) than non-SUA (\$1261 $\pm$ \$9) with an incremental cost of \$1056 (95% CI, \$907-\$1205). Asthma drugs accounted for the major difference (incremental cost of \$848/patient; 95% CI, \$737-\$959).

CONCLUSION: Increases and disparities in health care utilization and direct cost by SUA status suggest that patients with SUA require more intensive therapy, greater attention to adherence and comorbidities, more specialist care, and, possibly, personalized treatment approaches including novel biologic treatments. © 2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;4:120-9)

Key words: Antiasthma agents; Asthma control; Asthma cost; Asthma impairment; Asthma risk; Asthma guidelines; Controller medication; Persistent asthma; Severe asthma

^aKaiser Permanente Southern California Region, San Diego and Pasadena, Calif

^bGlaxoSmithKline, Research Triangle Park, NC

^cKaiser Permanente Northern California Region, Oakland, Calif

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Corresponding author: Robert S. Zeiger, MD, PhD, Director of Allergy Research, Department of Allergy, Kaiser Permanente Medical Center, 7060 Clairemont Mesa Blvd, San Diego, CA 92111. E-mail: robert.s.zeiger@kp.org.

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Abbreviations used

CI- Confidence interval
ED- Emergency department
GERD- Gastroesophageal reflux disease
ICD-9- The International Classification of Diseases, 9th Revision
ICS- Inhaled corticosteroids
KPSC- Kaiser Permanente Southern California
LABA- Long-acting β_2 -agonist
LM- Leukotriene modifiers
MCO- Managed-care organization
OCS- Oral corticosteroids
PA- Persistent asthma
RR- Risk ratio
SABA- Short-acting β_2 -agonists
SARP- Severe Asthma Research Program
SUCAS- Burden of Illness in Severe Uncontrolled Asthma Study

Most patients with asthma have mild to moderate disease that is generally treated with anti-inflammatory controllers such as low- to medium-dose inhaled corticosteroids (ICS) or leukotriene modifiers (LM) and rescue short-acting β_2 -agonists (SABA). Patients whose asthma cannot be controlled with ICS alone are treated with the addition of other controllers (eg, long-acting β_2 -agonists [LABA] and LM). However, approximately 5%-10% of patients with asthma have severe asthma¹ and only approximately 3.6% have severe refractory asthma.² Although severe asthma accounts for only a small portion of the asthmatic population, it causes considerable morbidity and disproportionate burden on health care resources, with a 1.7- to 4-fold higher direct asthma-related cost than for mild persistent asthma (PA).³

To improve the care of patients with severe asthma, the American Thoracic Society developed a set of criteria to characterize severe refractory asthma that take into consideration baseline asthma medication requirements, asthma exacerbations, and lung function among other criteria.⁴ This definition of severe asthma has subsequently been adopted by the European Respiratory Society and World Health Organization.⁵ Severe or difficult-to-treat asthma has been categorized into 5 specific clinical phenotypic clusters based on sex, ethnicity, asthma onset, obesity, biomarkers, lung function reversibility, aspirin sensitivity, controller medication use, and health care utilization by the Severe Asthma Research Program (SARP) in adults⁶ and children,⁷ the Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens study,⁸ and the British Thoracic Society Severe Refractory Asthma Registry.⁹ The relationship of these cluster phenotypes in severe asthma to outcomes has been reported in some studies in adults^{8,10}; however, the SARP study found that they did not behave differently with respect to asthma-control-related outcomes.¹¹

Among managed-care organizations (MCO), little is known about the characteristics and asthma burden of severe uncontrolled asthma (SUA) phenotypes with multiple asthma exacerbations and intensive asthma controller therapy. In addition, given the advent of new therapies directed at patients with severe or difficult-to-treat asthma, it is important to better understand the prevalence and characteristics of such patients in a general asthma population who may be in need of such novel treatments. To address these needs, we conducted the Burden of Illness in Severe UnControlled Asthma Study (SUCAS) to determine the

clinical and economic burden of SUA in adolescents and adults in a real-world setting.

METHODS

Study design

SUCAS was an observational study that characterized and compared the clinical and economic burden of SUA to non-SUA in adolescent and adult patients. Pharmacy and health care utilization data were captured with the use of the Kaiser Permanente Southern California (KPSC) research data warehouse that allowed identification of adolescents and adults with PA. With waiver of written consent, SUCAS was approved by the KPSC Institutional Review Board.

Patients

Patients 12 years or older who had PA in the baseline year 2012 were identified based on an asthma International Classification of Diseases, 9th Revision (ICD-9) code (493.xx excluding 493.2, chronic obstructive asthma) and Healthcare Effectiveness Data and Information Set PA criteria¹² (Figure 1, A). Patients had to have continuous health plan enrollment and pharmacy benefit in 2012-2013 (no enrollment gap of >45 days within each calendar year),¹³ and no chronic obstructive lung disease or other chronic conditions commonly applied to clinical trials (Figure 1, panel A legend). Patients with SUA were identified from the PA cohort if they met all of the following 3 criteria in 2012 (baseline period): (a) 2 or more asthma exacerbations (see below for definition), (b) 6 or more medium- or high-dose ICS canisters dispensed as monotherapy or in combination with LABA, and (c) 3 or more non-ICS controller canisters dispensed. The SUA definition was created to approximate using administrative data the severity inclusion criteria implemented in the pivotal trial of mepolizumab for severe refractory asthma (ClinicalTrials.gov NCT01691521). Patients with PA who did not meet the above criteria for SUA were classified as patients with non-SUA (Figure 1, panel B for the consort diagram).

Study measures characterizing clinical burdens

Address information was geocoded to the census block level and linked to census-based block group-level socioeconomic information that included head of household education level and household income. The asthma medication ratio, an administrative-data quality marker predictive of future asthma emergency department (ED) or hospital care, was defined as the number of dispensed asthma controller units (inhaled controller medication canisters or 30-day supplies of oral controller medications) divided by the total number of controller units and SABA canisters dispensed. A ratio of ≥ 0.5 is the minimum quality measure cutpoint for determining controller medication dispensing.¹⁴ ICS products were categorized into low-, medium-, and high-dose, based on the calculated daily dosage and their individual potency using the estimated comparative daily dosages recommended by the Global Initiative for Asthma guideline for the diagnosis and management of adolescent and adult asthma.¹⁵ Prescription of 9 or more units of controllers per year, equivalent to at least 75% adherence, was used as a proxy for adherence to treatment.¹⁶ An asthma exacerbation was defined as an outpatient visit with uncontrolled asthma (ie, acute exacerbation, status asthmaticus, acute asthma attack, uncontrolled asthma, or asthmatic bronchitis indicated by KPSC-specific encounter codes) that required oral corticosteroids dispensed 7 days before or after the visit or an ED visit or hospitalization with a primary asthma diagnosis (ICD-9 493.xx). Asthma exacerbations at least 8 days after discharge

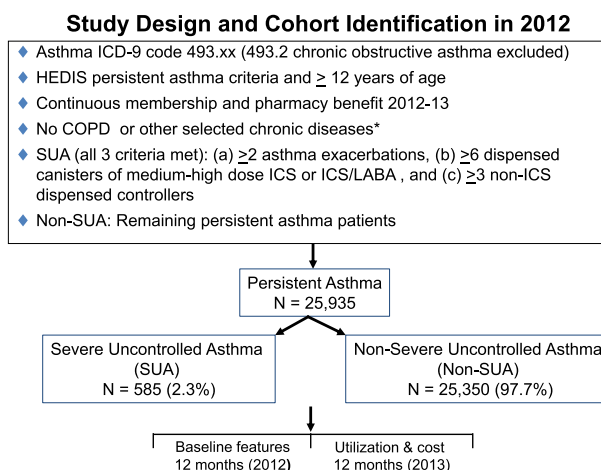
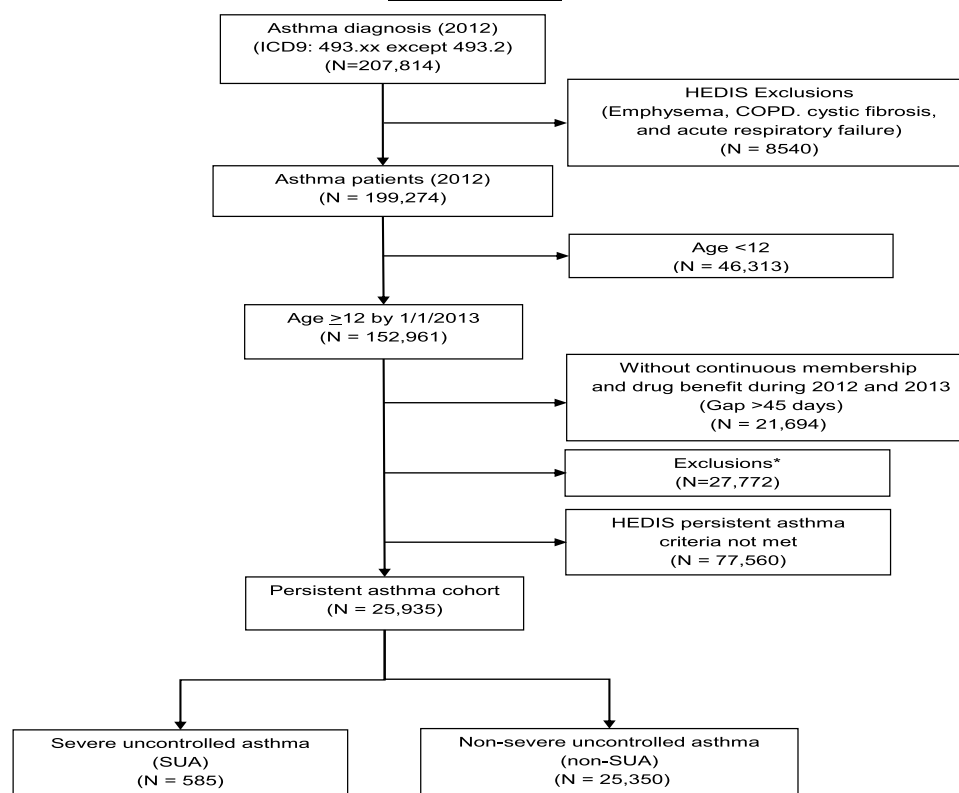
A**B****Consort Diagram**

FIGURE 1. A, The study design and number of patients identified with administrative databases. *Excluded conditions: chronic obstructive pulmonary disease, chronic obstructive asthma, emphysema, cystic fibrosis, chronic bronchitis, bronchiolitis obliterans, hypereosinophilic syndromes (eosinophilic granulomatosis with polyangiitis or eosinophilic esophagitis), cardiovascular conditions (angina pectoris, heart failure, acute myocardial infarction), endocrine disorders (systemic lupus erythematosus, rheumatoid arthritis, Crohn's disease), hepatic conditions (ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices or persistent jaundice, cirrhosis, known biliary abnormalities with the exception of Gilbert's syndrome or asymptomatic gallstones, pregnancy, granulomatosis with polyangiitis, sarcoidosis, other autoimmune disorders, immune deficiency, HIV, drug addiction, active respiratory cancer requiring any therapy except for antihormonal therapy, and immunosuppressant therapy). **B**, Consort diagram depicting the administrative logistics used to identify the study adolescent and adult persistent asthma cohort and its subgroups of patients with severe uncontrolled asthma (SUA) and non-severe uncontrolled asthma (non-SUA) amongst the 3,523,389 Kaiser Permanente Southern California 2012 members. *COPD*, Chronic obstructive lung disease; *HEDIS*, Healthcare Effectiveness Data and Information Set; *ICD-9*, International Classification of Diseases, 9th Revision; *ICS*, inhaled corticosteroid; *LABA*, long-acting β_2 -agonist.

from the hospital or ED, or outpatient visit were considered separate exacerbations.¹⁷ Seven or more SABA canisters dispensed per year, equivalent to 4 or more puffs per day/year, were defined as excessive SABA use because it has been associated with poorer asthma control and quality of life.¹⁸

Study measures characterizing economic burdens

Total health care resource utilization included all hospitalizations, ED visits, outpatient visits, asthma drugs, laboratory, radiology, skilled nursing facility, and home health. Asthma-related health care resource utilization with the associated laboratory and radiology services included hospitalizations and ED visits with a primary discharge diagnosis of asthma and outpatient visits coded for uncontrolled asthma to assure that the visit was asthma-related. An outpatient visit with an asthma ICD-9 code does not assure that the visit was asthma-related because visits unrelated to asthma may also contain such codes. Total costs captured these outpatient visits. Asthma-related drugs included asthma controllers and SABA and were captured through pharmacy databases.

Only direct costs were calculated because indirect costs, including time lost from work or school, were not captured in our health plan's administrative data. For enhanced generalizability of the findings, health care service costs were estimated by using the Medicare Resources Based Relative Values Scale on Diagnosis Related Groups and Current Procedural Terminology codes (Centers for Medicare & Medicaid Services). Asthma drug costs were estimated by mapping the National Drug Codes of the selected medications to the discounted Average Wholesale Prices published in RED BOOK.¹⁹ All costs are in 2013 US dollars. Nonasthma drug costs were not determined because of resources and time constraints.

Statistical analyses

Patient demographics, comorbidities, asthma characteristics, and features during baseline (2012) and follow-up (2013) periods were compared between patients with SUA and non-SUA by using the χ^2 or Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Poisson regression models with robust error variance estimated unadjusted and adjusted outcome rate and risk ratios for the follow-up year (2013).¹⁵ Covariates determined in 2012 and adjusted for in the regression model included age (categorical: 12-17, 18-64, and ≥ 65 years), gender, geocoded education, ethnicity, insurance type, obesity (BMI ≥ 30 kg/m² in adults and ≥ 95 percentile for age in adolescents), Charlson comorbidity index, gastroesophageal reflux disease (GERD), any rhinitis, chronic sinusitis, any upper respiratory infection (acute upper respiratory infection, pharyngitis, or acute sinusitis), pneumonia, nasal polyps, anxiety or depression, 7 or more SABA canisters dispensed, and asthma specialist care.

Total and asthma-related annual cost analyses used a 1- or 2-part generalized linear model (GLM) with log link and Gamma or Poisson family or a 2-part GLM with inverse link and Poisson family. Analyses for cost outcomes were conducted by using Stata 12 (StataCorp LP, College Station, Tex). All other analyses were conducted using SAS (version 9.3 for Windows, SAS Institute, Cary, NC). All tests were 2-tailed and significance was set at $P < .05$.

RESULTS

Identification of SUA and non-SUA cohort

After applying all the inclusion and exclusion criteria in the baseline period, 25,935 patients with PA at least 12 years of age

were identified (Figure 1, B). Within this PA cohort, 585 (2.3%) had SUA and 25,350 (97.7%) did not have SUA (non-SUA).

Comparison of demographic, comorbidities, and clinical burden at baseline (2012) between patients with SUA and non-SUA (Table I)

Compared with the non-SUA subgroup, the SUA subgroup was significantly older (50.6 ± 16.9 vs 46.7 ± 20.2 years, $P < .001$), was slightly more ethnically diverse ($P = .03$), and had longer health plan enrollment ($P = .03$). Gender, geocoded income, type of health insurance, and smoking status were not significantly different between the 2 subgroups. The SUA subgroup exhibited significantly more comorbidities compared with the non-SUA subgroup ($P \leq .001$ for all comparisons for SUA versus non-SUA groups, respectively): obesity (53.5% vs 44.6%), GERD (31.8% vs 16.4%), any rhinitis (65.1% vs 37.3%), chronic sinusitis (39.1% vs 15.1%), acute upper respiratory infections (48.7% vs 27.9%), pneumonia (12.8% vs 5.1%), nasal polyposis (5.6% vs 1.5%), and anxiety or depression (26.3% vs 21.8%). Significantly higher clinical burden was observed in the SUA compared with non-SUA subgroup (respectively): asthma exacerbation rate per year (2.7 ± 1.3 vs 0.5 ± 0.8), asthma hospitalization (6.7% vs 1.3%), asthma ED visits (23.8% vs 11.1%), asthma outpatient visits with uncontrolled asthma (98.5% vs 41.3%), 7 or more SABA canisters dispensed (33.0% vs 15.9%), ICS or ICS/LABA dispensed (100% vs 86.0%), 9 or more controller canisters equivalent dispensed (71.3% vs 23.0%), medication controller ratio ≥ 0.5 (85.6% vs 62.6%), oral corticosteroids at a dose of ≥ 5 mg/day (17.6% vs 1.5%), and asthma specialist care (63.1% vs 25.9%) (all $P < .001$).

Comparison of clinical burden in the follow-up year (2013) between patients with SUA and non-SUA (Table II)

Univariate analyses. Asthma exacerbations, outpatient visits with uncontrolled asthma, excessive SABA use, controller medications dispensed, oral corticosteroids (OCS) dispensed at ≥ 5 mg/day, and asthma specialist care were significantly greater in patients with SUA than in those with non-SUA during the follow-up year (all $P < .001$) (Table II).

Multivariable analyses. Compared with the patients with non-SUA, patients with SUA experienced significantly higher clinical burden (all $P < .001$): asthma exacerbations (rate ratio, 2.8; 95% CI, 2.5-3.2), 1 or more asthma exacerbations (risk ratio [RR], 2.1; 95% CI, 1.9-2.3), 2 or more asthma exacerbations (RR, 3.2; 95% CI, 2.7-3.8), 1 or more asthma hospitalizations (RR, 2.9; 95% CI, 1.8-4.7), 1 or more asthma ED visits (RR, 2.3; 95% CI, 1.8-2.9), OCS ≥ 5 mg/day (RR, 2.8; 95% CI, 2.1-3.7), and 7 or more SABA canisters dispensed (RR, 1.5; 95% CI, 1.3-1.82). Asthma specialist care (RR, 1.3; 95% CI, 1.2-1.4) and an asthma medication ratio of ≥ 0.5 (RR, 1.2; 95% CI, 1.1-1.2) were more common in the patients with SUA (Table II). Baseline covariates that were significantly associated with an increase in the asthma exacerbations in the follow-up period included age groups 18-64 and 65 years or older versus 12-17 years, female sex, Asian/Pacific Islanders, non-Hispanic blacks, and Hispanics versus non-Hispanic whites, GERD, obesity, pneumonia, chronic sinusitis, upper respiratory infections, nasal polyps, and 7 or more SABA canisters dispensed (Table E1, available in this article's Online

TABLE I. Comparison of demographics, comorbidities, and asthma burden in 2012 among patients with severe uncontrolled (SUA) and non-severe uncontrolled (non-SUA) persistent asthma (PA) [Data as N (%) or mean $\pm$ SD]

Demographics/clinical features	PA cohort (N = 25,935)	SUA (N = 585)	Non-SUA (N = 25,350)	P value*
Age (y)				<.001
	46.8 $\pm$ 20.2	50.6 $\pm$ 16.9	46.7 $\pm$ 20.2	
12-17	3669 (14.1)	48 (8.2)	3621 (14.3)	
18-64	16,995 (65.5)	431 (73.7)	16,564 (65.3)	
≥ 65	5271 (20.3)	106 (18.1)	5165 (20.4)	
Female sex	15,920 (61.4)	372 (63.6)	15,548 (61.3)	.27
Ethnicity				.04
White	10,509 (40.5)	225 (38.5)	10,284 (40.6)	
Hispanic	7781 (30.0)	178 (30.4)	7603 (30.0)	
Black	3731 (14.4)	89 (15.2)	3642 (14.4)	
Asian Pacific Island	2339 (9.0)	69 (11.8)	2270 (9.0)	
Others/unknown	1575 (6.1)	24 (4.1)	1551 (6.1)	
Estimated median household income by geocoding (US dollars), mean $\pm$ SD	64,201 $\pm$ 27,251	62,846 $\pm$ 26,012	64,232 $\pm$ 27,279	.20
Estimated family education level < high school diploma by geocoding, mean %	20.1 $\pm$ 14.5	21.2 $\pm$ 14.2	20.0 $\pm$ 14.5	.01
Insurance†				
Commercial	20,916 (80.6)	481 (82.2)	20,435 (80.6)	.33
Medicaid or state sponsored	2524 (9.7)	60 (10.3)	2464 (9.7)	.67
Medicare	5066 (19.5)	100 (17.1)	4966 (19.6)	.13
Private pay	2580 (9.9)	45 (7.7)	2535 (10.0)	.07
Length of health plan enrollment, y	16.4 $\pm$ 11.7	17.3 $\pm$ 11.5	16.4 $\pm$ 11.7	.03
Smoking status				.89
Ever	6217 (24.4)	144 (24.6)	6073 (24.4)	
Never	19,297 (75.6)	441 (75.4)	18,856 (75.6)	
	(N = 25,514)	(N = 585)	(N = 24,929)	
Comorbidities				
Charlson comorbidity index	1.4 $\pm$ 0.90	1.4 $\pm$ 0.87	1.4 $\pm$ 0.90	.19
Obesity, BMI ≥ 30 kg/m ² (≥ 95 percentile for age in adolescents)	11,629 (44.8)	312 (53.5)	11,317 (44.6)	<.001
Gastroesophageal reflux disease	4338 (16.7)	186 (31.8)	4152 (16.4)	<.001
Any rhinitis	9831 (37.9)	381 (65.1)	9450 (37.3)	<.001
Chronic sinusitis	4054 (15.6)	229 (39.1)	3825 (15.1)	<.001
Acute upper respiratory infection, pharyngitis, or acute sinusitis	7361 (28.4)	285 (48.7)	7076 (27.9)	<.001
Pneumonia	1369 (5.3)	75 (12.8)	1294 (5.1)	<.001
Nasal polyposis	405 (1.6)	33 (5.6)	372 (1.5)	<.001
Anxiety or depression	5682 (21.9)	154 (26.3)	5528 (21.8)	.001
Controller medications				
ICS monotherapy or ICS/LABA	22,396 (86.4)	585 (100)	21,810 (86.0)	<.001
Leukotriene modifiers	4590 (17.7)	272 (46.5)	4318 (17.0)	<.001
Theophylline	251 (1.0)	11 (1.9)	240 (0.9)	.02
≥ 9 controller canister equivalents	6237 (24.0)	417 (71.3)	5820 (23.0)	<.001
Controller medication ratio ≥ 0.5	16,176 (63.1)	501 (85.6)	15,675 (62.6)	<.001
Oral corticosteroids ≥ 5 mg/d	487 (1.9)	103 (17.6)	384 (1.5)	<.001
≥ 7 SABA canisters	4218 (16.3)	193 (33.0)	4025 (15.9)	<.001
Asthma exacerbations, Rate	0.5 $\pm$ 0.8	2.7 $\pm$ 1.3	0.5 $\pm$ 0.8	<.001
≥ 1	9355 (36.1)	585 (100)	8770 (34.6)	<.001
≥ 2	2505 (9.7)	585 (100)	1920 (7.6)	<.001
≥ 1 ED visit	2943 (11.3)	139 (23.8)	2804 (11.1)	<.001
≥ 1 hospitalization	370 (1.4)	39 (6.7)	331 (1.3)	<.001
≥ 1 asthma ED/hospitalization	3002 (11.6)	143 (24.4)	2859 (11.3)	<.001
Uncontrolled asthma (outpatient), Rate	0.8 $\pm$ 1.2	3.5 $\pm$ 2.0	0.7 $\pm$ 1.1	<.001
≥ 1	11,050 (42.6)	576 (98.5)	10,474 (41.3)	<.001

(continued)

TABLE I. (Continued)

Demographics/clinical features	PA cohort (N = 25,935)	SUA (N = 585)	Non-SUA (N = 25,350)	P value*
Asthma specialist care				
Allergist	5419 (20.9)	274 (46.8)	5145 (20.3)	<.001
Pulmonologist	1750 (6.7)	150 (25.6)	1600 (6.3)	<.001
Care manager	370 (1.4)	15 (2.6)	355 (1.4)	.02
Any specialist care	6933 (26.7)	369 (63.1)	6564 (25.9)	<.001

ED, Emergency department; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; SABA, short-acting β_2 -agonist.

Bold values indicate significant differences between comparisons at $P < .05$.

*P value: χ^2 test or Fisher's exact test for the categorical and Wilcoxon rank-sum test for continuous comparisons.

†Patients may have more than 1 insurance plan.

TABLE II. Unadjusted and adjusted* rate or risk ratio of asthma utilization and other outcomes in 2013 in patients with severe uncontrolled asthma (SUA) and non-severe uncontrolled asthma (non-SUA)

Asthma utilization/outcomes (2013)	SUA (N = 585)	Non-SUA (N = 25,350)	Unadjusted rate or risk ratio (95% CI)†	Adjusted* rate or risk ratio (95% CI)†
Asthma exacerbation, rate/year, mean $\pm$ SD	1.1 $\pm$ 1.6	0.3 $\pm$ 0.7	3.97 (3.52-4.48)	2.80 (2.46-3.18)
Any asthma exacerbation, N (%)	309 (52.8)	4929 (19.4)	2.72 (2.51-2.94)	2.12 (1.94-2.32)
≥ 2 asthma exacerbations, N (%)	153 (26.2)	1310 (5.2)	5.06 (4.37-5.86)	3.22 (2.73-3.81)
≥ 1 asthma emergency department visit, N (%)	65 (11.1)	1026 (4.0)	2.75 (2.17-3.48)	2.27 (1.78-2.90)
≥ 1 asthma hospitalization, N (%)	22 (3.8)	210 (0.8)	4.54 (2.95-6.99)	2.92 (1.83-4.67)
≥ 1 asthma emergency department visit or hospitalization, N (%)	66 (11.3)	1060 (4.2)	2.70 (2.13-3.41)	2.25 (1.77-2.86)
Outpatient visits with uncontrolled asthma‡, N (%)	346 (59.1)	6897 (27.2)	2.17 (2.03-2.33)	1.71 (1.59-1.85)
Oral corticosteroid ≥ 5 mg/day, N (%)	65 (11.1)	414 (1.6)	6.80 (5.31-8.72)	2.80 (2.12-3.69)
≥ 7 SABA canisters dispensed, N (%)	103 (17.6)	1803 (7.1)	2.48 (2.07-2.97)	1.54 (1.30-1.82)
Asthma medication ratio ≥ 0.5 , N (%)	498 (87.8)	16,417 (73.2)	1.20 (1.16, 1.24)	1.16 (1.12-1.20)
≥ 9 controller canister equivalent, N (%)	347 (59.3)	6234 (24.6)	2.41 (2.25, 2.59)	1.80 (1.67-1.94)
Controller medications proportion of days covered ≥ 0.8 , N (%)	205 (37.2)	3466 (17.8)	2.09 (1.87, 2.34)	1.66 (1.47-1.86)
Asthma specialist care, N (%)	302 (51.6)	5391 (21.3)	2.43 (2.24, 2.63)	1.25 (1.15-1.35)

ED, Emergency department; SABA, short-acting β_2 -agonists.

Bold values indicate significant differences between comparisons at $P < .05$.

*Adjustments included: age group, sex, ethnicity, geocoded education, health insurance, obesity, gastroesophageal reflux disease, any rhinitis, chronic sinusitis, any upper respiratory infection (acute upper respiratory infection, pharyngitis, or acute sinusitis), nasal polyposis, anxiety or depression, ≥ 7 SABA canisters dispensed, and asthma specialist care.

†Poisson regression models with robust error variance were used to estimate the unadjusted and adjusted rate ratio and risk ratio, their 95% confidence intervals (CI) and to derive the P values (all comparisons, $P < .001$ and bolded).

‡Outpatient visits with uncontrolled asthma: outpatient visits with KPSC-specific diagnosis codes of uncontrolled asthma.

Repository at www.jaci-inpractice.org). Baseline covariates associated with asthma medication dispensed and asthma specialist care are noted in Table E2, available in this article's Online Repository at www.jaci-inpractice.org.

Comparisons of average all-cause and asthma-related direct costs per patient in the follow-up year (2013) between patients with SUA and non-SUA

Univariate analyses (Table E3, available in this article's Online Repository at www.jaci-inpractice.org). The average all-cause annual direct cost per patient was significantly higher for the SUA (\$5851 $\pm$ \$5230) than the non-SUA (\$3411 $\pm$ \$5162) subgroups ($P \leq .001$). The difference in the average cost was mostly explained by the cost differences in hospitalizations, ED and outpatient visits, laboratory, and asthma medications. Consistent with the above, the average annual asthma-related direct costs per patient were also significantly higher for the patients with SUA (\$2965 $\pm$ \$2273) than those with non-SUA (\$1261 $\pm$ \$1420) ($P < .001$) with asthma hospitalizations, asthma ED visits, asthma outpatient visits, and

asthma medications contributing to the majority of this difference (all $P \leq .001$).

Multivariable analyses (Table III and Figure 2). Compared with patients with non-SUA, the patients with SUA exhibited significantly higher economic burden per patient. The estimated incremental annual costs per patient were \$1339 (95% CI, \$973-\$1704) for all-cause direct costs, \$31 (95% CI, \$7-\$53) for ED visits, and \$129 (95% CI, \$48-\$210) for outpatient visits (Figure 2, A). Similarly, the estimated incremental annual costs per patient related to asthma were significantly higher for the patients with SUA compared with patients with non-SUA with respect to asthma hospitalizations (\$127, 95% CI, \$26-\$228), ED visits (\$15, 95% CI, \$7-\$23), outpatient visits (\$82, 95% CI, \$66-\$98), asthma drug dispensed (\$848, 95% CI \$737-\$959), and overall cost estimates of these 4 costs (\$1056, 95% CI, \$907-\$1205) (Figure 2, B).

DISCUSSION

SUCAS characterized and compared patients with SUA who had more asthma exacerbations and higher level of controller

TABLE III. Adjusted average direct costs and incremental costs per patient in 2013 US dollars (\$USD) by type of utilization in patients with severe uncontrolled asthma (SUA) and non-severe uncontrolled asthma (non-SUA): (A) all-cause, (B) asthma-related (mean $\pm$ SE)

Adjusted all-cause and asthma-related direct costs*	SUA (N = 585) (\$USD)	Non-SUA (N = 25,350) (\$USD)	Incremental cost (95% CI) (\$USD)	P value
(A) All-cause				
Total all-cause	4800 $\pm$ 185	3461 $\pm$ 32	1339 (973-1704)[†]	<.001
Hospitalization including laboratory and radiology	1043 $\pm$ 141	844 $\pm$ 25	199 (–83 to 4481) [‡]	.17
Emergency department including laboratory and radiology	105 $\pm$ 12	75 $\pm$ 1	31 (7-53)[§]	.010
Outpatient visits including laboratory and radiology	1235 $\pm$ 41	1107 $\pm$ 7	129 (48-210)	.002
Asthma drug (nonasthma drugs not captured)	2007 $\pm$ 56	1159 $\pm$ 7	848 (737-959)	<.001
Laboratory not accounted by above visit encounters	93 $\pm$ 7	64 $\pm$ 1	28 (15-42)	<.001
Other: radiology, skilled nursing, hospital outpatient, and home health	191 $\pm$ 36	183 $\pm$ 7	8 (–62 to 78) [¶]	.82
(B) Asthma-related				
Total asthma-related	2325 $\pm$ 75	1269 $\pm$ 9	1056 (907-1205)	<.001
Asthma hospitalization including laboratory and radiology	179 $\pm$ 51	52 $\pm$ 4	127 (26-228)[‡]	.014
Asthma emergency department including laboratory and radiology	21 $\pm$ 4	6 $\pm$ 0.3	15 (7-23)[§]	<.001
Asthma outpatient visits including laboratory and radiology	133 $\pm$ 8	51 $\pm$ 1	82 (66-98)[§]	<.001
Asthma drug	2007 $\pm$ 56	1159 $\pm$ 7	848 (737-959)	<.001

Bold values indicate significant differences between comparisons at $P < .05$.

*All the cost estimates were generated by using generalized linear models (GLM) with adjustment of the following covariates in 2012: age group, gender, ethnicity, geocoded education, health insurance, Charlson comorbidity index, obesity, gastroesophageal reflux disease, any rhinitis, chronic sinusitis, any upper respiratory infection (acute upper respiratory infection, pharyngitis, or acute sinusitis), nasal polyposis, anxiety or depression, ≥ 7 SABA canisters dispensed, and asthma specialist care.

[†]One part: GLM with log link and Gamma family.

[‡]Two part: GLM with inverse link and Poisson family.

[§]Two part: GLM with log link and Poisson family.

^{||}One part: GLM with log link and Poisson family.

[¶]Two part: GLM with log link and Gamma family.

medication dispensed with patients with non-SUA who had less severe asthma, among adolescents and adults with PA (Figure 1). The SUA subgroup made up 2.3% of the entire PA cohort, similar in magnitude to the 3.6% prevalence found recently in a severe refractory adult asthma cohort.² The SUA subgroup compared with the non-SUA subgroup evidenced statistically more relevant comorbidities, asthma exacerbations, and controller medication dispensed during the baseline year (Table I) and after a year follow-up (Table II).

The average all-cause (absent nonasthma drugs) annual direct cost for the SUA subgroup was \$1339/patient higher than that for the non-SUA subgroup (Figure 2, A). Asthma-related direct costs contributed to most of the incremental differences seen in all-cause cost between the subgroups. Specifically, after adjusting for baseline covariates, the average asthma-related incremental annual direct cost for the SUA subgroup was \$1056/patient higher than that for the non-SUA subgroup, with asthma drugs accounting for the major difference (incremental mean cost \$848/patient) (Figure 2, B).

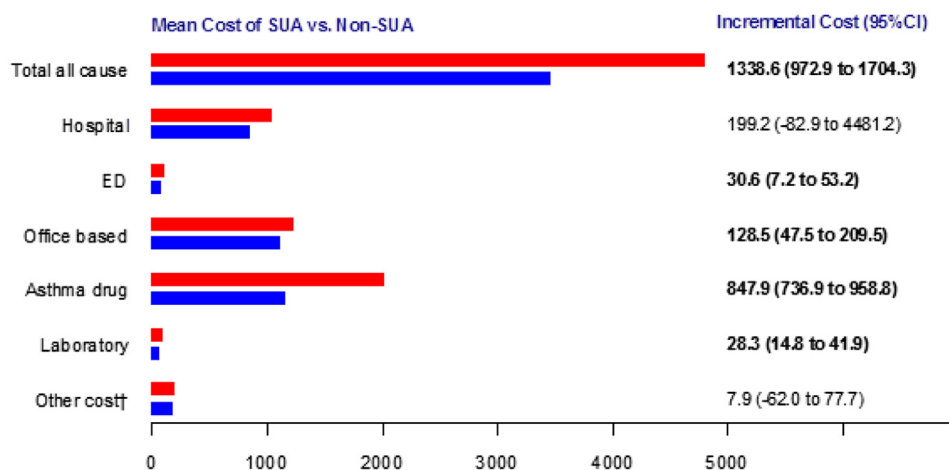
These findings are consistent with prior reports of costs in severe asthma²⁰ and uncontrolled asthma.²¹ The unadjusted average all-cause direct cost exclusive of nonasthma drugs in the SUCAS PA cohort was \$3466 (Table E3, available in this article's Online Repository at www.jaci-inpractice.org), which was similar to the cost reported in our previous study.²² The unadjusted and adjusted direct asthma-related mean costs in the patients with SUA (\$2965 and \$2325, respectively) were slightly higher than reported in a recent claims database study (\$2107 and \$2025 in 2013 US dollars, respectively).²¹ However, that study analyzed privately insured patients with less

uncontrolled moderate to severe PA who were required to evidence only 1 or more asthma exacerbations in the baseline year.

Other clinically relevant observations were gleaned from SUCAS regarding SUA in an MCO. Although the frequency of identified SUA was low, patients with SUA evidenced more frequent comorbidities that by themselves were risk factors for future asthma exacerbations (Table I and Table E1, available in this article's Online Repository at www.jaci-inpractice.org) and greater asthma burden and costs compared with patients with non-SUA.

Within a PA cohort, 2.3% patients were identified as having SUA based on the manifestations of 2 or more asthma exacerbations and dispensing of high levels of ICS or ICS/LABA in the same year. These clinical criteria were similar to those used to identify severe asthmatics in biological therapy trials.²³ The prevalence of SUA in SUCAS was lower than the typically reported prevalence of 5%-10% of severe asthma among general asthmatics.²⁴ More recently, a nationwide Danish adult study reported a severe asthma prevalence of 8.1% among asthmatics based on a high level of controller medications.²⁵ A more comprehensive Dutch study that applied pharmacy databases of 500,000 patients and questionnaires to a random sample noted a 3.6% (95% CI, 3.0% to 4.1%) prevalence of severe refractory asthma (10.4 patients per 10,000 inhabitants) among asthmatics based on high-dose ICS/LABA combination or medium-high dose ICS/LABA and oral corticosteroids.² Differences in the reported prevalence of severe asthma probably relate to differences in more stringent diagnostic criteria, populations studied, and available asthma care management. The lower prevalence

A All-cause direct costs



B Asthma-related direct costs

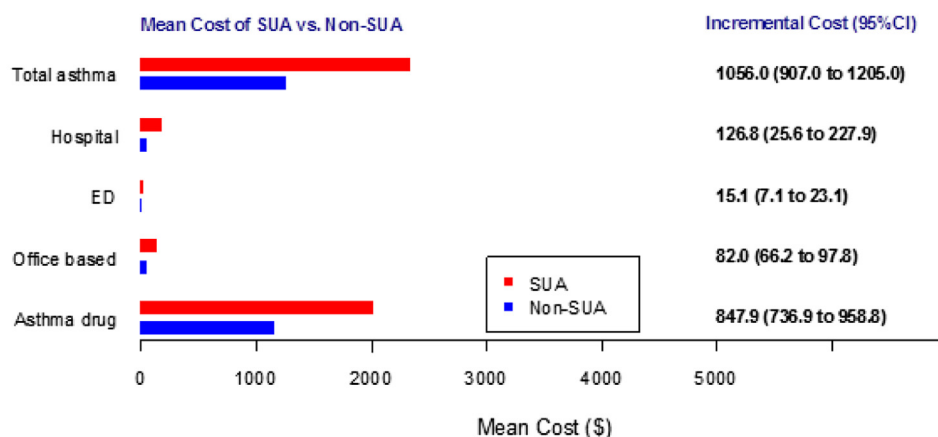


FIGURE 2. Adjusted average direct costs and incremental cost per patient in 2013 (US dollars) by type of utilization in severe uncontrolled asthma (SUA) and non-severe uncontrolled asthma (non-SUA) subgroups in 2013. **A**, All-cause except nonasthma drugs. **B**, Asthma-related. *CI*, Confidence interval; *ED*, emergency department.

found in SUCAS might be due in part to the promotion by the MCO of multiple asthma management strategies to improve care (specific task forces, physician champions, care managers, and easy access to electronic medical records with disease registries), the demographics of the enrollees (eg, higher median household income than the general United States),²⁶ and other unrecognized factors.

Comorbidities related to uncontrolled asthma such as GERD, pneumonia, chronic sinusitis, frequent upper respiratory infections, and nasal polyposis occurred more often in the patients with SUA than those with non-SUA (Table I), and were risk factors for future asthma exacerbations (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). Greater attention to the control of comorbidities in asthma, despite the asthma guidelines, is often overlooked.²⁷

The SUA subgroup evidenced a high occurrence of asthma exacerbations and burden in 2012 as expected based on the SUA identification criteria. However, the patients with SUA

continued to experience significantly more asthma utilization including asthma exacerbations, ED visits, and hospitalizations compared with the patients with non-SUA in the follow-up year 2013 even, after adjusting for demographic factors, comorbidities, and asthma features that are well-known risk factors for future exacerbations in SUCAS (Table II and Table E1, available in this article's Online Repository at www.jaci-inpractice.org).²⁸ These events occurred in spite of significantly higher adjusted risk ratios for 9 or more controller canister equivalents dispensed, asthma medication ratio of 0.5 or more, and asthma specialist care (Table II). However, the level of controller medication dispensed and frequency of asthma specialist care achieved were still suboptimal (Table II) based on asthma guidelines. These limitations to achieving optimal care and asthma control highlight that more intensive asthma care management is needed to improve outcomes in patients with SUA in managed-care and other settings. The challenges to achieving better control than that reported in the current study are not insubstantial given that the present managed-care setting has already instituted many

strategies to improve asthma care. Some of these approaches include system wide pharmacy coverage that enhances access to controller medication; presence of asthma task forces, physician champions, and care managers; use of electronic medical records and disease registries to aid in determining individual patient adherence in real time; and periodic physician notification of their asthma medication ratio score and relationship to benchmark goals. However, more intensive efforts are needed to facilitate more optimal controller prescribing at a higher step-level of care combined with better patient adherence and commitment to treatment, better and faster identification of high-risk patients, more frequent referral to asthma specialists, and when indicated, more access to novel therapies. Moreover, efforts to improve adherence must be promoted in managed-care and other settings. Specifically, these efforts should be directed at gaining a better understanding of the barriers to adherence in individual patients with SUA. Using the recent validated Adult Asthma Adherence Questionnaire that identifies barriers to adherence, outreach programs directed at individual patients with SUA could administer, evaluate, and act on the identified barriers to improve adherence.²⁹ The suboptimal asthma outcomes of patients with SUA observed in this MCO were also found in other medical care settings.³⁰⁻³² The present study noted that the management of patients with SUA could be enhanced by the institution of higher step-level care as recommended by asthma guidelines. The Gaining Optimal Asthma Control study demonstrated that despite the significant increase in cost of medication needed to obtain optimal control, the improvement in control was associated with cost per quality adjusted life year comparable to figures used to justify health care resources for many other chronic diseases.³³ The major limitation of SUCAS was its observational design. However, the design with baseline and follow-up periods being in successive years allows adjustment for baseline differences in evaluation of follow-up year outcomes, which improves its study's validity. This retrospective administrative study allowed only capture of controller dispensings and not actual controller use or proper use including inhaler technique.² Although spirometry data were not available for more specific asthma diagnosis and adjustments in the multivariable analyses, as with most administrative data studies, we included important variables shown to influence asthma exacerbations.^{30,34} It is often difficult to compare precisely the costs of care determined in a closed medical care system, such as studied in SUCAS, with studies using other methodology such as Medical Expenditure Panel Surveys³⁵⁻³⁷ or claims^{21,38} assessments due to differences in coding, completeness of capture of utilizations, cost structure, and accuracy of data capture.³⁹ Except for our earlier published study of costs in KPSC,²² we could not find comparable studies that have used data exclusively from a capitated revenue system such as KPSC (see Online Repository for further discussion).

In summary, we found that severe uncontrolled adolescent and adult asthma, though less frequent than anticipated, was associated with future substantial and clinically significant disease burden and costs. To better manage patients with SUA, health professionals need to address relevant comorbidities, intensify guideline recommended controller therapies, improve adherence, increase asthma specialist care, and when appropriate, consider biological agents that can target and improve outcomes in specific subgroups of these patients.²³

REFERENCES

- Wenzel SE, Busse WW. Severe asthma: lessons from the Severe Asthma Research Program. *J Allergy Clin Immunol* 2007;119:14-21.
- Hekking PP, Wener RR, Amelink M, Zwiderman AH, Bouvy ML, Bel EH. The prevalence of severe refractory asthma. *J Allergy Clin Immunol* 2015;135:896-902.
- Bahadori K, Doyle-Waters MM, Marra C, Lynd L, Alasaly K, Swiston J, et al. Economic burden of asthma: a systematic review. *BMC Pulm Med* 2009;9:24.
- Proceedings of the ATS Workshop on Refractory Asthma Current Understanding, Recommendations, and Unanswered Questions. *Am J Respir Crit Care Med* 2000;162:2341-51.
- Bousquet J, Mantzouranis E, Cruz AA, Ait-Khaled N, Baena-Cagnani CE, Bleecker ER, et al. Uniform definition of asthma severity, control, and exacerbations: document presented for the World Health Organization Consultation on Severe Asthma. *J Allergy Clin Immunol* 2010;126:926-38.
- Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med* 2010;181:315-23.
- Fitzpatrick AM, Teague WG, Meyers DA, Peters SP, Li X, Li H, et al. Heterogeneity of severe asthma in childhood: confirmation by cluster analysis of children in the National Institutes of Health/National Heart, Lung, and Blood Institute Severe Asthma Research Program. *J Allergy Clin Immunol* 2011;127:382-9.
- Schatz M, Hsu JW, Zeiger RS, Chen W, Dorenbaum A, Chipps BE, et al. Phenotypes determined by cluster analysis in severe or difficult-to-treat asthma. *J Allergy Clin Immunol* 2014;133:1549-56.
- Newby C, Heaney LG, Menzies-Gow A, Niven RM, Mansur A, Bucknall C, et al. Statistical cluster analysis of the British Thoracic Society Severe refractory Asthma Registry: clinical outcomes and phenotype stability. *PLoS One* 2014;9:e102987.
- Ortega H, Li H, Suruki R, Albers F, Gordon D, Yancey S. Cluster analysis and characterization of response to mepolizumab. A step closer to personalized medicine for patients with severe asthma. *Ann Am Thorac Soc* 2014;11:1011-7.
- Bourdin A, Molinari N, Vachier I, Varrin M, Marin G, Gamez AS, et al. Prognostic value of cluster analysis of severe asthma phenotypes. *J Allergy Clin Immunol* 2014;134:1043-50.
- National Committee of Quality Assurance, 2015. HEDIS and performance measures. Available from: <http://www.ncqa.org/HEDISQualityMeasurement.aspx>. Accessed April 19, 2015.
- Mosen DM, Macy E, Schatz M, Mendoza G, Stibolt TB, McGaw J, et al. How well do the HEDIS asthma inclusion criteria identify persistent asthma? *Am J Manag Care* 2005;11:650-4.
- Schatz M, Zeiger RS, Vollmer WM, Mosen D, Mendoza G, Apter AJ, et al. The controller-to-total asthma medication ratio is associated with patient-centered as well as utilization outcomes. *Chest* 2006;130:43-50.
- Zeiger RS, Schatz M, Li Q, Zhang F, Purdum AS, Chen W. Step-up care improves impairment in uncontrolled asthma: an administrative data study. *Am J Manag Care* 2010;16:897-906.
- Agency for Health Research Quality, 2015. National quality measures clearinghouse. Available from: <http://www.qualitymeasures.ahrq.gov/content.aspx?id=48617>. Accessed April 19, 2015.
- Fuhlbrigge A, Peden D, Apter AJ, Boushey HA, Camargo CA Jr, Gern J, et al. Asthma outcomes: exacerbations. *J Allergy Clin Immunol* 2012;129(Suppl):S34-48.
- Schatz M, Zeiger RS, Vollmer WM, Mosen D, Apter AJ, Stibolt TB, et al. Validation of a beta-agonist long-term asthma control scale derived from computerized pharmacy data. *J Allergy Clin Immunol* 2006;117:995-1000.
- Red Book, 2015. Available from: <http://sites.truvenhealth.com/redbook/index.html>. Accessed April 19, 2015.
- O'Neill S, Sweeney J, Patterson CC, Menzies-Gow A, Niven R, Mansur AH, et al. The cost of treating severe refractory asthma in the UK: an economic analysis from the British Thoracic Society Difficult Asthma Registry. *Thorax* 2015;70:376-8.
- Ivanova JI, Bergman R, Birnbaum HG, Colice GL, Silverman RA, McLaurin K. Effect of asthma exacerbations on health care costs among asthmatic patients with moderate and severe persistent asthma. *J Allergy Clin Immunol* 2012;129:1229-35.
- Zeiger RS, Hay JW, Contreras R, Chen W, Quinn VP, Seal B, et al. Asthma costs and utilization in a managed care organization. *J Allergy Clin Immunol* 2008;121:885-92.
- Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012;380:651-9.

24. Chanez P, Wenzel SE, Anderson GP, Anto JM, Bel EH, Boulet LP, et al. Severe asthma in adults: what are the important questions? *J Allergy Clin Immunol* 2007;119:1337-48.
25. von Bulow A, Kriegbaum M, Backer V, Porsbjerg C. The prevalence of severe asthma and low asthma control among Danish adults. *J Allergy Clin Immunol Pract* 2014;2:759-67.
26. Household income in the United States, 2015. Available from: http://en.wikipedia.org/wiki/Household_income_in_the_United_States. Accessed April 19, 2015.
27. Expert Panel 3 Report for the National Asthma Education Prevention Program, 2007. Available from: <http://www.nhlbi.nih.gov/files/docs/guidelines/asthgdln.pdf>. Accessed April 19, 2015.
28. Zeiger RS, Schatz M, Li Q, Chen W, Gossage D, Khaty D, et al. High blood eosinophil count is a risk factor for future asthma exacerbations in adult persistent asthma. *J Allergy Clin Immunol Pract* 2014;2:741-50.
29. Schatz M, Zeiger RS, Yang SJ, Weinstein AG, Chen W, Saris-Baglama RN, et al. Development and preliminary validation of the Adult Asthma Adherence Questionnaire. *J Allergy Clin Immunol Pract* 2013;1:280-8.
30. Schatz M, Meckley LM, Kim M, Stockwell BT, Castro M. Asthma exacerbation rates in adults are unchanged over a 5-year period despite high-intensity therapy. *J Allergy Clin Immunol Pract* 2014;2:570-4.
31. Hasegawa K, Sullivan AF, Tovar HE, Gaeta TJ, Fee C, Turner SJ, et al. A multicenter observational study of US adults with acute asthma: who are the frequent users of the emergency department? *J Allergy Clin Immunol Pract* 2014;2:733-40.
32. Calhoun WJ, Haselkorn T, Mink DR, Miller DP, Dorenbaum A, Zeiger RS. Clinical burden and predictors of asthma exacerbations in patients on guideline-based steps 4-6 asthma therapy in the TENOR cohort. *J Allergy Clin Immunol Pract* 2014;2:193-200.
33. Briggs AH, Bousquet J, Wallace MV, Busse WW, Clark TJ, Pedersen SE, et al. Cost-effectiveness of asthma control: an economic appraisal of the GOAL study. *Allergy* 2006;61:531-6.
34. Zeiger RS, Schatz M, Li Q, Solari PG, Zazzali JL, Chen W. Real-time asthma outreach reduces excessive short-acting beta2-agonist use: a randomized study. *J Allergy Clin Immunol Pract* 2014;2:445-56.
35. Sullivan PW, Ghushchyan VH, Slejko JF, Belozeroff V, Globe DR, Lin SL. The burden of adult asthma in the United States: evidence from the Medical Expenditure Panel Survey. *J Allergy Clin Immunol* 2011;127:363-9.
36. Barnett SB, Nurmagambetov TA. Costs of asthma in the United States: 2002-2007. *J Allergy Clin Immunol* 2011;127:145-52.
37. Rank MA, Liesinger JT, Ziegenfuss JY, Branda ME, Lim KG, Yawn BP, et al. Asthma expenditures in the United States comparing 2004 to 2006 and 1996 to 1998. *Am J Manag Care* 2012;18:499-504.
38. Van GE, Laforest L, Pietri G, Boissel JP, Gormand F, Ben-Joseph R, et al. Persistent asthma: disease control, resource utilisation and direct costs. *Eur Respir J* 2002;20:260-7.
39. Akinbami LJ, Sullivan SD, Campbell JD, Grundmeier RW, Hartert TV, Lee TA, et al. Asthma outcomes: healthcare utilization and costs. *J Allergy Clin Immunol* 2012;129(Suppl):S49-64.

ONLINE REPOSITORY METHODS

Cost assignment

Integrated health care organizations such as Kaiser Permanente may generally have capitated revenue streams or do not bill external payers for some of their services. Thus, health care delivery is not tracked with the same bill-generating precision as that provided in a typical fee-for-service environment. Tracking health care expenditures in closed systems such as KPSC can be achieved by either direct estimation of production costs, micro-costing, step-down allocation, or standardized resource use assignment. The pros and cons of each of these labor-intensive costing approaches have been described.¹ Because of the advantages of generalizability, replicability, and comparability of estimates across different studies, we chose standardized resource use assignment as the method to assign dollar values to utilization units. Standardized resource use assignment typically relies on relative value units (RVUs) that are specific to each component of health services production and delivery.

RVUs for physician services draw on Current Procedural Terminology (CPT) codes for which separate scales for evaluation and management, surgery, pathology, and radiology related codes are available.¹ The expected physician time, skill, and risk associated with delivering services represented by the code determine the relative value for that service. In-patient services draw on Diagnosis Related Group (DRG) codes and are weighted by both the relative complexity of the services related to the diagnoses on which the DRG is based and the mean length of stay for those services along with other chronic conditions afflicting the patients. Relative values for pharmaceuticals are based on National Drug Code, and therapeutic class designations

that often reflect mean prices paid at the wholesale level. These wholesale prices are discounted to represent the typical discount offered by pharmaceutical manufacturers when the interest is in understanding cost.

Cost outcomes

Economic burden (ie, direct healthcare costs) was characterized based on the setting of care. Burden was characterized in terms of annual visits during follow-up to emergency department (ED), in-patient stays, and office-based visits each of which was further classified as specific to asthma or defined as “all cause” if nonasthma. Length of hospital stay was defined as the number of nights between the date of admission and the date of discharge. Medical expenditures were calculated by multiplying units of service by standardized resource-based relative value multipliers. Resource-based relative value multipliers are based on CPT codes and are published under the Physician Fee Schedule in the Federal Register. All expenditures were tallied up to the visit level. Thus, the analytic file contained annual cost outcomes that were captured for the following: (1) all-cause in-patients stays, (2) all-cause ED visits, (3) all-cause office visits, (4) all-cause laboratory visits, (5) other ancillary costs related to radiology, skilled nursing, hospital-based outpatient visits, and paid home health visits. We also identified a subset of these outcomes specific to asthma that included (1) asthma-related in-patient stays, (2) asthma-related ED visits, (3) asthma-related office visits, and (4) asthma-related pharmacy expenditure.

REFERENCE

1. Fishman PA, Hornbrook MC. Assigning resources to health care use for health services research: options and consequences. *Med Care* 2009;47(Suppl 1):S70-5.

TABLE E1. Adjusted rate ratio and risk ratio (95% CI)* for asthma utilizations in 2013 for each covariate determined in 2012 in the regression models with severe uncontrolled asthma (SUA) and non-severe uncontrolled asthma (non-SUA)

Covariates (2012)	Adjusted rate and risk ratios (95% CI) for asthma utilization (2013)				
	Exacerbation rate (number/y)	≥1 exacerbation	≥2 exacerbations	≥1 emergency department visit	≥1 hospitalization
Ages 18-64 vs 12-17	1.23 (1.12-1.35)	1.09 (1.01-1.18)	1.49 (1.24-1.79)	0.80 (0.67-0.94)	1.08 (0.67-1.75)
Ages ≥ 65 vs 12-17	1.37 (1.16-1.62)	1.18 (1.03-1.34)	1.73 (1.29-2.30)	0.88 (0.64-1.20)	2.77 (1.39-5.52)
Female vs male	1.17 (1.10-1.25)	1.18 (1.12-1.24)	1.16 (1.04-1.29)	1.19 (1.04-1.34)	1.49 (1.11-2.00)
Asian/Pacific Islander vs white	1.15 (1.03-1.28)	1.13 (1.03-1.24)	1.28 (1.06-1.55)	1.31 (1.04-1.66)	2.13 (1.41-3.23)
Black vs white	1.39 (1.27-1.52)	1.23 (1.14-1.32)	1.52 (1.32-1.76)	2.16 (1.82-2.56)	1.75 (1.20-2.55)
Hispanic vs white	1.30 (1.20-1.40)	1.25 (1.17-1.33)	1.34 (1.17-1.53)	1.65 (1.40-1.94)	1.34 (0.93-1.91)
Geocoded < high school diploma	1.0 (1.00-1.01)	1.0 (1.0-1.0)	1.01 (1.00-1.01)	1.01 (1.00-1.01)	1.01 (1.00-1.02)
Medicare (Y/N)	0.84 (0.73-0.98)	0.87 (0.78-0.98)	0.86 (0.68-1.10)	0.90 (0.68-1.20)	0.80 (0.45-1.43)
Private insurance (Y/N)	0.98 (0.88-1.09)	0.98 (0.90-1.07)	1.01 (0.84-1.21)	0.79 (0.62-1.01)	0.83 (0.53-1.30)
Obesity (Y/N)	1.16 (1.09-1.23)	1.15 (1.09-1.21)	1.18 (1.07-1.31)	1.11 (0.98-1.25)	1.62 (1.23-2.11)
Gastroesophageal reflux disease (Y/N)	1.11 (1.03-1.20)	1.07 (1.00-1.14)	1.09 (0.96-1.23)	1.16 (1.00-1.35)	1.38 (1.01-1.87)
Rhinitis (Y/N)	1.03 (0.96-1.10)	1.03 (0.97-1.09)	1.06 (0.94-1.19)	0.77 (0.67-0.88)	0.95 (0.70-1.29)
Chronic sinusitis (Y/N)	1.29 (1.19-1.39)	1.22 (1.15-1.30)	1.32 (1.17-1.50)	0.91 (0.77-1.08)	0.76 (0.53-1.10)
Acute upper respiratory infections (Y/N)	1.24 (1.17-1.32)	1.20 (1.14-1.26)	1.34 (1.20-1.49)	1.10 (0.97-1.25)	1.02 (0.76-1.37)
Pneumonia (Y/N)	1.57 (1.41-1.75)	1.40 (1.28-1.52)	1.64 (1.38-1.94)	1.50 (1.22-1.84)	2.21 (1.48-3.30)
Nasal polyps (Y/N)	1.44 (1.16-1.78)	1.16 (1.00-1.35)	1.55 (1.19-2.00)	1.48 (1.00-2.20)	2.13 (1.06-4.31)
Anxiety or depression (Y/N)	1.06 (0.99-1.13)	1.05 (0.99-1.11)	1.15 (1.02-1.29)	1.22 (1.06-1.40)	1.18 (0.88-1.59)
≥7 SABA dispensed canisters (Y/N)	1.43 (1.33-1.54)	1.31 (1.24-1.39)	1.59 (1.42-1.79)	1.57 (1.37-1.80)	2.19 (1.65-2.90)
Asthma specialist care (Y/N)	1.08 (1.00-1.16)	1.03 (0.97-1.09)	1.12 (0.99-1.27)	1.15 (0.99-1.33)	1.22 (0.89-1.67)

SABA, Short-acting β_2 -agonist.

Bold values indicate significant differences between comparisons at $P < .05$.

*Poisson regression models with robust error variance were used to estimate the adjusted rate and risk ratios and their 95% confidence intervals (CI).

TABLE E2. Adjusted risk ratios (RR) (95% CI)* for asthma medication dispensed and asthma specialist care in 2013 for each covariate determined in 2012 in the regression models with severe uncontrolled asthma (SUA) and non-severe uncontrolled asthma (non-SUA)

Covariates (2012)	Adjusted risk ratio (95% CI) for asthma medication or asthma specialty care (2013)				
	Oral corticosteroid ≥ 5 mg/d	Controller proportion of days covered ≥ 0.8	Asthma medication ratio ≥ 0.5	≥7 SABA canisters dispensed	Asthma specialist care
Ages 18-64 vs 12-17	7.71 (3.64-16.32)	1.64 (1.44-1.88)	1.12 (1.08-1.15)	1.88 (1.56-2.26)	1.12 (1.04-1.20)
Ages ≥ 65 vs 12-17	9.01 (3.85-21.10)	1.90 (1.59-2.28)	1.13 (1.08-1.18)	2.47 (1.95-3.14)	1.26 (1.13-1.40)
Female vs male	0.89 (0.73-1.07)	1.12 (1.05-1.19)	1.02 (1.00-1.03)	0.90 (0.84-0.98)	1.08 (1.04-1.13)
Asian/Pacific Islander vs white	1.13 (0.82-1.55)	0.78 (0.70-0.87)	1.01 (0.99-1.04)	0.74 (0.63-0.86)	0.98 (0.92-1.05)
Black vs white	1.41 (1.10-1.80)	0.72 (0.66-0.79)	0.93 (0.91-0.95)	0.98 (0.88-1.10)	0.91 (0.86-0.97)
Hispanic vs white	0.97 (0.76-1.23)	0.63 (0.58-0.68)	0.93 (0.91-0.95)	0.87 (0.79-0.97)	0.89 (0.85-0.94)
Geocode < high school diploma	1.00 (0.99-1.01)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.01)	1.00 (1.00-1.00)
Medicare (Y/N)	1.09 (0.70-1.69)	1.16 (1.02-1.33)	1.05 (1.02-1.09)	1.15 (0.98-1.36)	1.10 (1.00-1.20)
Private insurance (Y/N)	1.12 (0.85-1.49)	0.92 (0.83-1.01)	0.96 (0.93-0.98)	0.95 (0.84-1.07)	0.99 (0.93-1.06)
Obesity (Y/N)	1.12 (0.93-1.34)	1.02 (0.96-1.08)	1.01 (0.99-1.02)	1.09 (1.00-1.18)	0.99 (0.95-1.03)
Gastroesophageal reflux disease (Y/N)	1.28 (1.05-1.56)	1.13 (1.05-1.21)	1.04 (1.02-1.05)	1.11 (1.00-1.22)	1.10 (1.05-1.16)
Rhinitis (Y/N)	0.84 (0.67-1.05)	1.05 (0.98-1.13)	1.05 (1.03-1.07)	0.91 (0.82-1.00)	1.21 (1.15-1.27)
Chronic sinusitis (Y/N)	1.82 (1.48-2.23)	1.14 (1.06-1.23)	1.03 (1.01-1.05)	0.89 (0.79-1.00)	1.05 (1.00-1.10)
Acute upper respiratory infections (Y/N)	0.97 (0.80-1.19)	0.93 (0.87-0.99)	0.98 (0.96-1.00)	0.93 (0.84-1.02)	1.02 (0.97-1.06)
Pneumonia (Y/N)	1.38 (1.00-1.91)	0.92 (0.80-1.05)	0.98 (0.94-1.01)	1.10 (0.93-1.31)	1.01 (0.93-1.10)
Nasal polyps (Y/N)	1.86 (1.30-2.67)	1.19 (1.01-1.40)	1.06 (1.02-1.11)	1.27 (0.95-1.70)	1.11 (1.00-1.23)
Anxiety or depression (Y/N)	1.15 (0.94-1.41)	1.00 (0.93-1.07)	0.96 (0.94-0.98)	0.94 (0.86-1.04)	1.01 (0.96-1.06)
≥7 SABA dispensed canisters (Y/N)	2.41 (1.99-2.92)	1.26 (1.18-1.35)	0.78 (0.76-0.80)	14.3 (12.9-15.86)	1.30 (1.24-1.37)
Asthma specialist care (Y/N)	3.27 (2.62-4.08)	1.61 (1.51-1.72)	1.13 (1.11-1.15)	1.03 (0.93-1.14)	5.15 (4.87-5.45)

SABA, Short-acting β_2 -agonist.

Bold values indicate significant differences between comparisons at $P < .05$.

*Poisson regression models with robust error variance were used to estimate the adjusted rate ratio and risk ratio and their 95% confidence intervals (CI).

TABLE E3. Unadjusted average direct costs per patient in 2013 US dollars (\$USD) by type of utilization in patients with severe uncontrolled asthma (SUA) and non-severe uncontrolled asthma (non-SUA) (mean $\pm$ SD): (A) all-cause and (B) asthma-related

All-cause and asthma-related direct costs (2013)	PA cohort (N = 25,935) (\$USD)	SUA (N = 585) (\$USD)	Non-SUA (N = 25,350) (\$USD)	P value*
(A) All-cause costs				
Total-all cause costs†	3466 $\pm$ 5177	5851 $\pm$ 5230	3411 $\pm$ 5162	<.001
Hospitalization including laboratory and radiology	849 $\pm$ 3947	1262 $\pm$ 4007	840 $\pm$ 3945	<.001
Hospital outpatient	78 $\pm$ 401	92 $\pm$ 335	78 $\pm$ 403	0.02
Emergency department including laboratory and radiology	75 $\pm$ 225	127 $\pm$ 335	74 $\pm$ 222	<.001
Outpatient visits including laboratory and radiology	1110 $\pm$ 1138	1626 $\pm$ 1365	1099 $\pm$ 1130	<.001
Laboratory not accounted by above visit encounters	65 $\pm$ 129	112 $\pm$ 206	64 $\pm$ 127	<.001
Radiology not accounted by above visit encounters	60 $\pm$ 168	72 $\pm$ 166	59 $\pm$ 168	.002
Asthma medication†	1183 $\pm$ 1214	2522 $\pm$ 1610	1152 $\pm$ 1186	<.001
Home health	11 $\pm$ 79	12.4 $\pm$ 61	10.8 $\pm$ 80	.002
Skilled nursing facility	35 $\pm$ 1075	27 $\pm$ 642	35 $\pm$ 1083	.39
(B) Asthma-related costs				
Total asthma-related costs	1299 $\pm$ 1467	2965 $\pm$ 2273	1261 $\pm$ 1420	<.001
Asthma hospitalization including laboratory and radiology	56 $\pm$ 679	247 $\pm$ 1404	52 $\pm$ 652	<.001
Asthma emergency department including laboratory and radiology	7 $\pm$ 47	25 $\pm$ 118	6 $\pm$ 44	<.001
Asthma outpatient visits including laboratory and radiology	54 $\pm$ 119	172 $\pm$ 232	51 $\pm$ 114	<.001
Asthma medication	1183 $\pm$ 1214	2525 $\pm$ 1610	1152 $\pm$ 1186	<.001

Bold values indicate significant differences between comparisons at $P < .05$.

*P value: Wilcoxon rank-sum test.

†Nonasthma medication was not captured.

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