

Effect of asthma exacerbations on health care costs among asthmatic patients with moderate and severe persistent asthma

Jasmina I. Ivanova, MA,^a Rachel Bergman, BA,^a Howard G. Birnbaum, PhD,^b Gene L. Colice, MD,^c Robert A. Silverman, MD,^d and Kimmie McLaurin, MS^e *New York, NY, Boston, Mass, Washington, DC, and Gaithersburg, Md*

Background: Health care costs increase in patients with more severe asthma, but the effect of asthma exacerbations on costs among patients with more severe asthma has not been quantified.

Objective: This study compared direct health care costs between patients with moderate/severe persistent asthma with and without exacerbations.

Methods: Patients who had an asthma diagnosis (International Classification of Diseases–ninth revision–Clinical Modification code 493.x), were 12 to 64 years old, and were receiving controller therapy were identified from a large administrative claims database. Patients were categorized as having moderate/severe persistent asthma and were further evaluated for exacerbations during a 12-month exacerbation identification period. Patients with 1 or more exacerbations (asthma-related inpatient or emergency department visit or corticosteroid prescription) were matched to patients without exacerbations on demographic characteristics and asthma severity. Total and asthma-related health care costs during the 1-year study period after the exacerbation index date were calculated.

Results: Patients with exacerbations had significantly higher total health care costs (\$9223 vs \$5011, $P < .0001$) and asthma-related costs (\$1740 vs \$847, $P < .0001$). The cost differences remained significant after controlling for patient differences by using multivariate models. Patients with exacerbations ($n = 3830$) had higher rates of sinusitis, allergy-related diagnoses or medications, pneumonia, and mental disorders and higher average Charlson Comorbidity Index scores at baseline. Patients with exacerbations filled their prescriptions for controllers more often and had higher asthma-related drug costs.

Conclusions: Patients with moderate/severe persistent asthma who had exacerbations had higher total and asthma-related health care costs than those without exacerbations. Moreover, controller medication use was higher in patients with exacerbations. (*J Allergy Clin Immunol* 2012;■■■■:■■■-■■■.)

Key words: Moderate persistent asthma, severe persistent asthma, asthma-related costs, asthma-related resource use, asthma exacerbations

Asthma is a common and increasingly expensive disease in the United States. Recent estimates suggest that 22.9 million Americans had asthma in 2007.¹ Total direct and indirect costs attributed to asthma in the United States were approximately \$6.2 billion per year in 1990² but increased to \$20 billion per year in 2009.³ Previous studies have documented that the economic burden of asthma is greater in patients with more severe disease.⁴⁻⁸ In patients with severe persistent asthma, higher costs occur in patients with poorly controlled disease.⁹

The effect that asthma exacerbations have on health care costs among patients with moderate and severe persistent asthma has not been quantified. We used a previously established algorithm^{5,8,10} to identify patients with moderate and severe persistent asthma from a large claims database and evaluated the effect of exacerbations on resource use and health care costs. We hypothesized that exacerbations would increase health care costs in patients with moderate and severe persistent asthma. Establishing these economic costs could help direct development of alternative approaches or treatments intended specifically to decrease exacerbation rates in patients with more severe asthma. As Moore and Pascual¹¹ have observed, it is becoming increasingly clear that moderate-to-severe persistent asthma cannot be entirely managed with the currently available guideline-endorsed pharmacotherapy.¹¹

METHODS

Data source

The study sample was selected from a claims database (Ingenix Employer Solutions) covering more than 8 million privately insured beneficiaries (including employees, spouses, and dependents) from 40 United States–based companies for 1999–2007. The companies operate nationwide in a broad array of industries and job classifications. The database contains deidentified patients' demographics, monthly enrollment histories, and medical and pharmacy claims. Medical services use was recorded with date of service, up to 2 associated diagnoses, performed procedures, and actual payment amounts. The database also includes pharmacy claims, with prescribed medications identified by National Drug Code, date of fill, days supplied, quantity, and actual payment amounts.

From ^aAnalysis Group, Inc, New York; ^bAnalysis Group, Inc, Boston; ^cWashington Hospital Center, Washington; ^dNorth Shore–LIJ Health System, New York; and ^eMedImmune, Gaithersburg.

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Corresponding author: Jasmina I. Ivanova, MA, Analysis Group, Inc, 10 Rockefeller Plaza, 15th Floor, New York, NY 10020. E-mail: jivanova@analysisgroup.com. 0091-6749/\$36.00

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Abbreviations used

CCI:	Charlson Comorbidity Index
ED:	Emergency department
GINA:	Global Initiative for Asthma
HEDIS:	Health Plan Employer Data and Information Set
ICS:	Inhaled corticosteroid
LABA:	Long-acting inhaled β_2 -agonist
LM:	Leukotriene modifier
SABA:	Short-acting inhaled β_2 -agonist

Sample selection

Patients included in the study sample had an asthma diagnosis (International Classification of Diseases—ninth revision—Clinical Modification code 493) from January 1, 2003, to December 31, 2007, but no diagnosis of chronic obstructive pulmonary disease in their available medical claims data ($n = 361,390$). The analysis was limited to patients aged 12 to 62 years at the time of first asthma diagnosis ($n = 210,717$). Patients younger than 12 years were excluded because asthma guidelines have different treatment recommendations for this age group. Patients older than 62 years were excluded because database cost information might be incomplete for patients 65 years and older with dual Medicare eligibility. Study sample patients were also required to have at least 36 months of continuous coverage eligibility after the first asthma diagnosis ($n = 61,118$).

A 3-step process was used to identify patients with moderate and severe persistent asthma in the database. First, patients had to meet the Health Plan Employer Data and Information Set (HEDIS) criteria for persistent asthma during the 12-month entry eligibility period after the first asthma diagnosis ($n = 28,390$).^{12–14} The HEDIS criteria for persistent asthma require patients to have (1) at least 1 inpatient hospitalization with asthma as a primary discharge diagnosis, (2) at least 1 emergency department (ED) visit with a primary asthma diagnosis, (3) at least 4 claims for asthma prescription medications dispensed, or (4) at least 4 outpatient visits with an asthma diagnosis and at least 2 claims for asthma prescription medications dispensed. Asthma prescription medications included quick-relief medications (short-acting inhaled β_2 -agonists [SABAs] and other relievers), controllers (inhaled corticosteroids [ICSs], combination ICS plus long-acting inhaled β_2 -agonist [LABA], and other controllers), biologic agents, and systemic corticosteroids. Prescriptions filled with more than a 30-day supply were counted as multiple 30-day prescriptions (eg, a 90-day supply prescription was considered 3 prescriptions).

Second, to minimize the likelihood of misclassifying intermittent asthma as persistent with the HEDIS method,^{15,16} patients were also required to meet the Leidy criteria.¹⁷ These criteria further diminish inclusion of patients with intermittent asthma by requiring 2 or more SABA prescriptions or 1 or more oral corticosteroid prescriptions dispensed during the 12-month entry eligibility period ($n = 18,905$).

Third, patients were required to be categorized as having moderate ($n = 10,681$) or severe ($n = 1,951$) persistent asthma based on their controller medication use and treatment recommendations in the Global Initiative for Asthma (GINA) guidelines.¹⁸ According to the GINA-recommended stepwise approach for long-term management of asthma, patients receiving low-dose ICSs and either a LABA, leukotriene modifier (LM), or theophylline or medium- or high-dose ICSs were categorized as having moderate persistent asthma. Patients receiving a medium- or high-dose ICS plus a LABA along with other controllers were categorized as having severe persistent asthma.

All patients meeting the HEDIS and Leidy criteria for persistent asthma and categorized by the GINA treatment criteria as having moderate and severe persistent asthma were evaluated over a 12-month exacerbation identification period, which immediately followed the entry eligibility period ($n = 12,632$). Patients who had an exacerbation, which was defined in standard fashion as an inpatient stay or ED visit with an asthma diagnosis or an oral corticosteroid prescription, were identified as the asthma exacerbation group ($n = 4,317$). The control group was derived from the patients with moderate and severe persistent asthma who did not have an exacerbation during the 12-month exacerbation identification period and the 12-month study period. Patients

with exacerbations were matched to control patients 1:1 based on sex, region, asthma severity, index year (within 12 months), and age within 3 years, resulting in a study sample of 3830 patients with moderate/severe persistent asthma in the exacerbation group and 3830 matched control patients.

There were 3 time periods: 12 months were allowed for entry eligibility, 12 months for exacerbation identification, and 12 months for the study. The index date for the exacerbation group was the date of the first exacerbation during the 12-month exacerbation identification period. The baseline period was defined as the 12 months before the index date and the study period as the 12 months after the index date. Consequently, there was overlap for the 12-month entry eligibility and 12-month baseline periods. The index date for control patients was assigned to match the time from the end of the entry eligibility period to index exacerbation for the corresponding exacerbation patient. Control patients could have had an exacerbation during the 12-month entry eligibility period (which could have been captured in the baseline period) but could not have had an exacerbation during either the 12-month exacerbation period or the 12-month study period.

Patients' characteristics

Patients' characteristics compared between the exacerbation and control groups included variables on which the exacerbation and control groups were matched (ie, age, sex, index year, and region) and baseline comorbidities.

The Charlson Comorbidity Index (CCI) score was calculated from comorbidities not including asthma.^{19,20}

Resource use

Resource use during the baseline and study periods was compared between the exacerbation and control groups. Resource use counts included the occurrence of any inpatient, ED, and outpatient/other visit. Medical services with an asthma diagnosis were classified as asthma related.

Costs

Total health care costs included medical and prescription drug costs. Medical and asthma-related costs were calculated by type of service. Cost analyses were conducted from the third-party payer's perspective (ie, costs were defined as payments to providers by third-party payers). All costs were inflation adjusted to 2007 US dollars by using the medical care component of the Consumer Price Index.

Statistical analyses

Unadjusted patients' characteristics, resource use, and costs during the baseline and study periods were compared descriptively for matched patients with moderate and severe persistent asthma with exacerbations and control patients without exacerbations. Categorical variables were compared by using χ^2 tests. Costs and resource use counts were compared descriptively by using Wilcoxon rank sum tests.

Multivariate generalized linear models with a log link and gamma distribution were used to compare adjusted total and asthma-related health care costs controlling for age, sex, region, index year and index quarter, baseline asthma comorbidities, baseline CCI score, prior resource use (ie, any all-cause and asthma-related inpatient, ED, and outpatient visits), use of quick-relief or specific controller medications, number of different classes of drugs used during the baseline period, and log of baseline total health care costs.

All analyses were conducted with SAS version 9.2 software (SAS Institute, Inc, Cary, NC). *P* values of less than or equal to .05 were considered to indicate statistically significant differences.

RESULTS**Exacerbations**

Among the patients with moderate ($n = 10,681$) and severe ($n = 1,951$) persistent asthma identified during the entry eligibility period, 34.2% ($n = 4,317$) had at least 1 asthma exacerbation during the exacerbation identification period, 1.9% had at

TABLE I. Patients' baseline characteristics

	Patients with moderate/severe asthma with ≥ 1 exacerbation (n = 3830)	Patients with moderate/severe asthma without exacerbations (n = 3830)	P value
Demographic characteristics			
Age (y), mean (SD)	40.09 (15.43)	39.93 (15.49)	.6432
Sex (%), male	1444 (37.7%)	1444 (37.7%)	1.0000
Year of index date			.7247
2004	1790 (46.7%)	1786 (46.6%)	
2005	1543 (40.3%)	1523 (39.8%)	
2006	492 (12.8%)	516 (13.5%)	
2007	5 (0.1%)	5 (0.1%)	
Region			1.0000
New England and Middle Atlantic	802 (20.9%)	802 (20.9%)	
South Atlantic	672 (17.5%)	672 (17.5%)	
Central	1655 (43.2%)	1655 (43.2%)	
Mountain, Pacific, Hawaii, and Alaska	701 (18.3%)	701 (18.3%)	
Asthma-related comorbidities*			
Otitis media	315 (8.2%)	230 (6.0%)	.0002
Acute sinusitis	936 (24.4%)	630 (16.4%)	<.0001
Chronic sinusitis	537 (14.0%)	290 (7.6%)	<.0001
Allergic-related diagnoses or medications	3020 (78.9%)	2694 (70.3%)	<.0001
Eczema	255 (6.7%)	230 (6.0%)	.2408
Allergic conjunctivitis	68 (1.8%)	51 (1.3%)	.1163
Allergic rhinitis	1491 (38.9%)	1298 (33.9%)	<.0001
Angina	18 (0.5%)	15 (0.4%)	.6007
Pneumonia	152 (4.0%)	81 (2.1%)	<.0001
GERD	282 (7.4%)	252 (6.6%)	.1783
Obesity	107 (2.8%)	82 (2.1%)	.0656
Mental disorders	780 (20.4%)	644 (16.8%)	<.0001
CCI score, mean (SD)	0.99 (1.00)	0.87 (0.84)	<.0001

GERD, Gastroesophageal reflux disease.

*Values are presented as numbers (percentages) of patients with asthma-related comorbidities.

least 1 inpatient stay with an asthma diagnosis, 5.5% had at least 1 ED visit with an asthma diagnosis, and 31.5% had at least 1 systemic corticosteroid prescription. Patients with severe persistent asthma had a higher rate of exacerbations (43.7%) than those with moderate persistent asthma (32.4%).

Baseline comparisons

Baseline demographics were similar across matched patients with exacerbations and control patients (Table I). However, patients with exacerbations had significantly higher rates of otitis media, acute sinusitis, chronic sinusitis, allergic rhinitis, pneumonia, and mental disorders than control patients. Patients with exacerbations also had a significantly higher CCI score than control patients (0.99 vs 0.87, respectively; $P < .0001$).

Patients with exacerbations had significantly higher all-cause and asthma-related resource use than control patients during the baseline period (Table II). Patients with exacerbations had excess average baseline total health care costs of \$2198 compared with those of control patients ($P < .0001$) and excess baseline asthma-related health care costs of \$274 ($P < .0001$). Although

TABLE II. Patients' baseline resource use and costs

	Patients with moderate/severe asthma with ≥ 1 exacerbation (n = 3,830)	Patients with moderate/severe asthma without exacerbations (n = 3,830)	P value
All-cause resource use			
No. (%) of patients with ≥ 1 :			
All-cause inpatient stay	411 (10.7%)	269 (7.0%)	<.0001
All-cause ED visit	1,231 (32.1%)	912 (23.8%)	<.0001
All-cause outpatient/other visit	3,767 (98.4%)	3,734 (97.5%)	.0082
Any medication use	3,821 (99.8%)	3,807 (99.4%)	.0131
Asthma-related medical services resource use			
No. (%) of patients with ≥ 1 :			
Asthma-related inpatient stay	86 (2.2%)	36 (0.9%)	<.0001
Asthma-related ED visit	278 (7.3%)	125 (3.3%)	<.0001
Asthma-related outpatient/other visit	2,658 (69.4%)	2,487 (64.9%)	<.0001
Asthma-related medication use			
No. (%) of patients with ≥ 1 :			
Asthma quick-relief medication	2,924 (76.3%)	2,992 (78.1%)	.0639
SABA prescription	2,908 (75.9%)	2,984 (77.9%)	.0393
Other quick-relief medication	92 (2.4%)	56 (1.5%)	.0028
Asthma controller	3,380 (88.3%)	3,471 (90.6%)	.0007
ICS	998 (26.1%)	983 (25.7%)	.6955
LM	1,636 (42.7%)	1,425 (37.2%)	<.0001
ICS+LABA	2,455 (64.1%)	2,494 (65.1%)	.3514
LABA	239 (6.2%)	237 (6.2%)	.9246
Other controller	168 (4.4%)	128 (3.3%)	.0177
Biologic agent	27 (0.7%)	8 (0.2%)	.0013
Systemic corticosteroid	1,706 (44.5%)	786 (20.5%)	<.0001
Total direct costs, mean (SD)	\$7,047 (\$19,841)	\$4,849 (\$7,811)	<.0001
Asthma-related direct costs, mean (SD)	\$1,221 (\$2,337)	\$947 (\$1,289)	<.0001

there were statistically significant differences in asthma-related medication use during the baseline period between patients with exacerbations and control patients (eg, SABA prescriptions, other quick-relief medication, LM, and biologic agents), the absolute differences in these rates were small. During the baseline period, patients with exacerbations had a similar number of SABA and (3.1 vs 2.9, $P = .7852$) controller prescriptions (8.0 vs 7.9, $P = .2111$) filled compared with control patients. Patients with exacerbations had higher rates of systemic corticosteroid use compared with control patients (44.5% vs 20.5%, respectively; $P < .0001$). On average, patients with exacerbations

TABLE III. Health care resource use in the 12-month study period

	Patients with moderate/severe asthma with ≥ 1 exacerbation (n = 3830)	Patients with moderate/severe asthma without exacerbations (n = 3830)	P value
All-cause resource use			
No. (%) of patients with ≥ 1 :			
All-cause inpatient stay	616 (16.1%)	252 (6.6%)	<.0001
All-cause ED visit	1579 (41.2%)	779 (20.3%)	<.0001
All-cause outpatient/other visit	3782 (98.7%)	3687 (96.3%)	<.0001
Any medication use	3822 (99.8%)	3762 (98.2%)	<.0001
Asthma-related resource use			
Asthma-related exacerbations			
No. (%) of patients with ≥ 1 :			
Asthma-related inpatient stay, ED visit, or systemic corticosteroid	3830 (100.0%)	0 (0.0%)	<.0001
Asthma-related medical services resource use			
No. (%) of patients with ≥ 1 :			
Asthma-related inpatient stay	255 (6.7%)	0 (0.0%)	<.0001
Asthma-related ED visit	683 (17.8%)	0 (0.0%)	<.0001
Asthma-related outpatient/other visit	2794 (73.0%)	2122 (55.4%)	<.0001
Asthma-related medication use			
No. (%) of patients with ≥ 1 :			
Asthma quick-relief medication	2797 (73.0%)	2642 (69.0%)	<.0001
SABA prescription	2791 (72.9%)	2635 (68.8%)	<.0001
Other quick-relief medication	116 (3.0%)	31 (0.8%)	<.0001
Asthma controller	3167 (82.7%)	3130 (81.7%)	.2690
ICS	841 (22.0%)	759 (19.8%)	.0212
LM	1700 (44.4%)	1343 (35.1%)	<.0001
ICS+LABA	2261 (59.0%)	2141 (55.9%)	.0055
LABA	193 (5.0%)	159 (4.2%)	.0635
Other controller	170 (4.4%)	104 (2.7%)	<.0001
Biologic agent	40 (1.0%)	9 (0.2%)	<.0001
Systemic corticosteroid	3569 (93.2%)	0 (0.0%)	<.0001

had 1.0 prescriptions filled of systemic corticosteroids versus only 0.27 for those without exacerbations.

Study period unadjusted resource use comparisons

Patients with exacerbations had higher resource use during the 12-month study period (Table III). Notably, patients with exacerbations compared with patients without exacerbations had a

significantly higher rate of all-cause inpatient stays (16.1% vs 6.6%, $P < .0001$) and all-cause ED visits (41.2% vs 20.3%, $P < .0001$) and a higher average number of inpatient visits (0.25 vs 0.10, $P < .0001$) and average number of ED visits (0.86 vs 0.31, $P < .0001$).

Among patients with exacerbations, 6.7% had asthma-related inpatient stays (0.08 inpatient stays on average), and 17.8% had asthma-related ED visits (0.26 ED visits on average, Table III). Patients with exacerbations used significantly more asthma quick-relief medications (73.0% vs 69.0%, $P < .0001$) and filled a higher number of 30-day SABA prescriptions (3.0 vs 2.5, $P < .0001$). Patients with exacerbations used significantly more ICSs, LMs, and ICSs plus LABAs than those without exacerbations and filled, on average, significantly more controller prescriptions compared with control patients (8.0 vs 7.2, $P = .0001$). Among patients with exacerbations, 93.2% had at least 1 systemic corticosteroid prescription, and the average supply per patient over the study period was 27.8 days.

Study period: Unadjusted cost comparisons

Patients with exacerbations had significantly higher average all-cause total health care costs during the study period (\$9223 vs \$5011, $P < .0001$), yielding an excess of \$4212 per patient compared with costs for control patients (Table IV). This difference was driven primarily by \$1818 higher outpatient/other costs and \$1222 higher hospital inpatient costs. Patients with exacerbations also had significantly higher average asthma-related health care costs (\$1740 vs \$847, $P < .0001$), an excess of \$893 compared with that seen in control patients, with the difference mainly attributable to higher hospital inpatient costs. Controller costs for patients with exacerbations were also higher (\$846 vs \$666, $P < .0001$).

In the subgroup of patients with moderate persistent asthma, patients with exacerbations had, on average, \$9,068 annual all-cause health care costs per patient compared with \$4,835 among patients without exacerbations, an excess of \$4,233 per patient ($P < .0001$). Asthma-related health care costs were also significantly higher among patients with moderate persistent asthma with exacerbations (\$1,580 vs \$769, $P < .0001$), a difference of \$812. Among patients with severe persistent asthma, all-cause health care costs were, on average, \$10,121 per patient with exacerbations and \$6,026 per patient without exacerbations, a difference of \$4,095 per patient ($P < .0001$). Asthma-related health care costs were also significantly higher among patients with severe persistent asthma with exacerbations (\$2,663 vs \$1,297, $P < .0001$), a difference of \$1,366.

Study period: Adjusted cost comparisons

Multivariate analysis using generalized linear regressions provided similar results to the descriptive comparisons of total health care costs and asthma-related health care costs (Fig 1). Adjusted total all-cause health care costs (\$8318 vs \$5465, respectively) and adjusted asthma-related health care costs (\$1672 vs \$868, respectively) were significantly higher for patients with exacerbations than for control patients ($P < .0001$ for both comparisons).

In the subgroup of patients with moderate persistent asthma, adjusted total all-cause health care costs (\$8118 vs \$5234, respectively) and adjusted asthma-related health care costs

TABLE IV. Direct costs in the 12-month study period

	Patients with moderate/severe asthma with ≥ 1 exacerbation (n = 3,830)			Patients with moderate/severe asthma without exacerbations (n = 3,830)			P value
	Mean	SD	Median	Mean	SD	Median	
Total direct costs	\$9,223	\$16,964	\$4,440	\$5,011	\$11,055	\$2,509	<.0001
Drug costs	\$2,831	\$4,209	\$1,691	\$1,950	\$2,886	\$1,194	<.0001
Medical costs	\$6,392	\$15,440	\$2,098	\$3,061	\$10,054	\$843	<.0001
Hospital inpatient costs	\$1,954	\$9,419	\$0	\$733	\$7,400	\$0	<.0001
ED costs	\$408	\$1,616	\$0	\$116	\$504	\$0	<.0001
Outpatient/other costs	\$4,030	\$9,194	\$1,573	\$2,212	\$5,181	\$759	<.0001
Asthma-related direct costs	\$1,740	\$3,570	\$970	\$847	\$1,314	\$607	<.0001
Drug costs	\$924	\$1,834	\$608	\$716	\$1,085	\$517	<.0001
Quick-reliever costs	\$72	\$203	\$15	\$50	\$271	\$8	<.0001
SABA costs	\$69	\$195	\$15	\$48	\$265	\$8	<.0001
Other quick-relief medication	\$3	\$27	\$0	\$2	\$25	\$0	<.0001
Controller costs	\$846	\$1,793	\$542	\$666	\$1,030	\$480	<.0001
ICS costs	\$75	\$230	\$0	\$60	\$170	\$0	.0182
LM costs	\$211	\$309	\$0	\$173	\$290	\$0	<.0001
LABA costs	\$19	\$109	\$0	\$17	\$101	\$0	.0721
Combo ICS/LABA costs	\$410	\$518	\$182	\$376	\$483	\$145	.0067
Other controller costs	\$131	\$1,607	\$0	\$40	\$784	\$0	<.0001
Biologic agent costs	\$124	\$1,604	\$0	\$35	\$783	\$0	<.0001
Systemic corticosteroid costs	\$6	\$23	\$0	\$0	\$0	\$0	<.0001
Medical costs	\$816	\$3,004	\$135	\$131	\$698	\$22	<.0001
Hospital inpatient costs	\$321	\$2,363	\$0	\$0	\$0	\$0	<.0001
ED costs	\$112	\$505	\$0	\$0	\$0	\$0	<.0001
Outpatient/other costs	\$383	\$1,724	\$94	\$131	\$698	\$22	<.0001

(\$1536 vs \$781, respectively) were significantly higher for those with exacerbations than for control patients ($P < .0001$ for both comparisons). Among patients with severe persistent asthma, patients with exacerbations also had significantly higher adjusted total all-cause health care costs (\$9350 vs \$6917, respectively) and adjusted asthma-related health care costs (\$2398 vs \$1434, respectively) compared with those seen in patients without exacerbations ($P < .0001$ for both comparisons).

DISCUSSION

In this large retrospective cohort study of patients with moderate and severe persistent asthma, we found that exacerbations were associated with significantly higher average annual total health care and asthma-related health care costs. The patients with moderate and severe persistent asthma in the exacerbation group differed from those without exacerbations. They were significantly more likely to have had a history of sinusitis, otitis media, other allergy-related diseases (eg, rhinitis), and pneumonia. They also had higher CCI scores. A novel finding in this analysis was that patients with exacerbations, on average, refilled their controller medications more often than the comparison group without exacerbations, suggesting that the exacerbation group might have less asthma control.

Compared with nonasthmatic control subjects, patients with persistent asthma have significantly higher average annual direct health care costs.⁵ Patients with severe persistent asthma generate higher costs than patients with mild and moderate persistent asthma.⁴⁻⁸ Patients with poorly controlled asthma also have higher health care costs.^{9,21} The results of this analysis add to this previous body of work by showing that exacerbations are associated with significantly increased annual total and

asthma-related health care costs in patients with moderate and severe persistent asthma. The effect of exacerbations on total health care costs was substantial. Patients with exacerbations had \$2853 more total health care costs than patients without exacerbations. Because we did not take into account work-loss and productivity costs, this analysis underestimates the total economic effect of exacerbations.²² Also, patients with exacerbations had more comorbidities than those without exacerbations. An increased and more complex burden of comorbidities in asthmatic patients has been previously described in both small reports²³⁻²⁵ and large population studies.^{26,27} These findings strongly support the need for new approaches to reducing exacerbations in patients with moderate and severe persistent asthma and an improved understanding of the interaction between asthma exacerbations and comorbid disease.

The exacerbation cohort in this analysis resembles the patient with refractory or severe asthma described in an American Thoracic Society workshop.²⁸ The patients in the exacerbation group experienced exacerbations, despite receiving seemingly adequate controller medication per GINA recommendations. The American Thoracic Society workshop proposed that registries be initiated to compile information on patients with severe asthma in hopes that a clinical phenotype for this group might be defined. In this analysis otitis media, sinusitis, allergic rhinitis, and pneumonia were reported significantly more often in the exacerbation group but not gastroesophageal reflux disease or obesity. This observation is intriguing because it supports the association between upper airway disease and asthma exacerbations. Differences in mental disorders and CCI scores between the 2 cohorts were also noted but were small and of uncertain significance. Unfortunately, a consistent clinical phenotype is not emerging from this and other observational studies describing

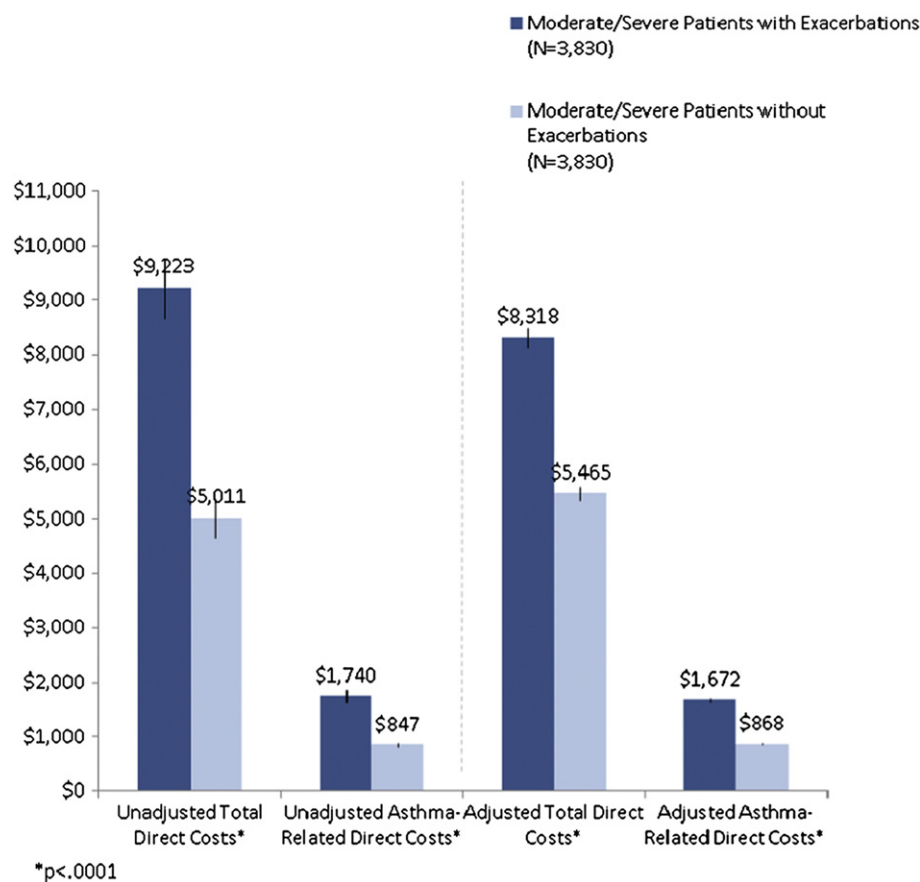


FIG 1. Unadjusted and adjusted total direct and asthma-related costs in the 12-month study period.

patients with severe,²⁹⁻³¹ difficult-to-treat,³² and refractory³³ asthma. Patients in the Severe Asthma Research Program more often reported gastroesophageal reflux disease and sinopulmonary infections and were less likely to have positive skin test results.²⁹ The European multicenter study of the clinical phenotype of chronic severe asthma (ENFUMOSA) also found less atopy but lower rates of allergic rhinitis.^{30,31} In a subanalysis of The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study, patients with severe asthma with persistent airflow limitation were less likely to have positive skin test results and allergic rhinitis.³² A recent report from the United Kingdom described wide variability in skin test reactivity, history of atopy, and rhinitis among patients with refractory asthma from 4 participating specialty asthma centers.³³ Pulmonary function test results were not available in this analysis. Previous work has suggested that air trapping^{30,34} or enhanced small-airway closure³⁵ might distinguish patients with severe asthma.

Asthmatic patients characteristically rely on SABA use to relieve their symptoms rather than controller medications to control their disease. Reports from the United States³⁶ and around the world³⁷ have consistently described poor adherence with controller medication use by patients with persistent asthma, surprisingly so in patients with difficult-to-treat asthma.³⁸ Nonadherence to controller medication use in asthmatic patients has been directly related to poor outcomes, such as ED visits and hospitalizations.³⁹ Conversely, previous database analyses have found that patients with persistent asthma who have a medication refill

pattern reflecting a higher (>0.5) controller/total asthma medication ratio (defined as the number of controllers dispensed divided by the total number of controllers plus SABAs refilled) were less likely to have exacerbations.⁴⁰⁻⁴² The results of this analysis appear to contradict in 2 important ways this prior work. The exacerbation group refilled their controller medications more often than the comparison cohort without exacerbations. The exacerbation group had a controller/total asthma medication ratio of greater than 0.5 not only for the study period but also for the baseline period. This more clearly defines the exacerbation group as those whose asthma is not adequately controlled by currently available therapies, including long-term controller use.

Claims database analyses provide clinically relevant observational information for large numbers of asthmatic patients.⁴³ This information reflects treatment decisions clinicians have made on a daily basis in their practice (eg, choice of controllers) and choices patients have made in how they manage their disease (eg, refill rates for controllers and SABAs).⁴³ A concern with claims database analyses is whether the sample selection approach accurately identifies patients with persistent asthma. Guidelines recommend using symptoms and lung function to categorize asthma severity, but this information was not available in the database used for this analysis. However, previous work has shown that SABA use and controller/total asthma medication ratio can be used as asthma quality-of-care markers,⁴² and lung function does not appreciably alter asthma severity categorization determined by a claims-based algorithm.⁸ Used sequentially, the HEDIS and Leidy criteria effectively identify persistent asthma patients.^{5,8,10} Relying on

patterns of medication use to categorize patients as having moderate and severe persistent asthma is consistent with GINA guidelines.¹⁸ Use of oral corticosteroids, a commonly used indicator of asthma exacerbations, for acute sinusitis is unlikely to explain differences between the 2 populations because the exacerbation group also had more asthma-related ED visits, hospitalizations, and outpatient visits. Because the exacerbation group had more asthma-related comorbidities, a higher CCI score and larger health care costs during the baseline period, multivariate analysis controlling for baseline differences was used to compare adjusted costs between patients with and without exacerbations. The adjusted analysis confirmed the initial findings that patients with exacerbations have significantly higher total all-cause and asthma-related health care costs.

In conclusion, this analysis shows that patients with moderate and severe persistent asthma who have exacerbations have increased total health care and asthma-related health care costs. The exacerbation group had different clinical characteristics than the comparison group without exacerbations, including more comorbidities. Surprisingly, the exacerbation group had a controller-to-total asthma medication refill rate of greater than 0.5 and refilled their controller medications significantly more often than the group without exacerbations. These findings support the need for new asthma treatment approaches, which would effectively reduce exacerbations in patients with moderate and severe persistent asthma.

Clinical implications: Currently available therapies do not adequately prevent exacerbations for all asthmatic patients. Given the higher health care costs among patients with exacerbations, these patients require novel approaches to reduce asthma morbidity.

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