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ECONOMICS

Measuring the cost of poor asthma control and exacerbations

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ABSTRACT

Background: Previous studies have shown an association between cost and poor asthma control. However, longitudinal studies of general populations are lacking. **Objective:** To examine the cost of poor asthma control and exacerbations across a broad spectrum of asthma patients. **Methods:** The Observational Study of Asthma Control and Outcomes (OSACO) was a prospective survey of persistent asthma patients in Kaiser Colorado in 2011–2012. Patients received a survey 3 times in one year, which included the Asthma Control Questionnaire (ACQ) and questions on exacerbations. Self-reported exacerbations were compared to actual oral corticosteroid (OCS) use. Regression analyses examined the association of control (ACQ-5 scores) and exacerbations with healthcare expenditures, controlling for sociodemographics and smoking. Analyses of expenditures used Generalized Linear Models (GLM) with log-link. **Results:** 2681 individuals completed at least one survey; 1799 completed all three. ACQ-5 scores were associated with higher all-cause and asthma-specific expenditures across all categories of costs (medical, outpatient, ER, pharmacy) except for inpatient expenditures. Each 1-point increase in the ACQ-5 score (i.e., worse control) was associated with a corresponding increase in all-cause annual healthcare and asthma-specific expenditures of \$1443 and \$927 (\$US 2013). Asthma exacerbations with documented OCS use were associated with an increase of \$3014 and \$1626 over 4 months, while self-reported exacerbations were \$713 and \$506. **Conclusion:** Results demonstrate that poor asthma control and exacerbations are strongly associated with higher healthcare expenditures. Results also confirm that collection of validated measures of control such as the ACQ-5 may provide valuable information toward improving clinical and economic outcomes.

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Medical expenditures; exacerbations; asthma control; Asthma Control Questionnaire; oral corticosteroids

Background

Asthma, a chronic inflammatory disorder of the airways characterized by recurring episodes of wheezing, breathlessness, chest tightness, and coughing, affects 25 million individuals in the United States, of whom more than 12 million experience an asthma attack every year [1–3]. Asthma symptoms cause significant burden leading to chronic, episodic, and often dramatic impact on patients' lives. Many studies have documented the significant negative impact of asthma on healthcare resource utilization and expenditures [4,5]. The extent of the impact is determined not only by the severity of the underlying disease, but also the degree of asthma control. Recognizing the distinction between asthma control and severity, the National Asthma Education and Prevention Program guidelines have redirected the focus of asthma treatment toward achieving and maintaining asthma control, reflected in the frequency of

everyday asthma symptoms (e.g., chest tightness, wheezing, nighttime awakenings) and use of rescue medications [6–8]. Consequently, standardized tools, such as the Asthma Therapy Assessment Questionnaire (ATAQ) [9], the Asthma Control Test [10], and the Asthma Control Questionnaire (ACQ) [11] have been developed to measure asthma control by assessing symptoms and rescue medication use.

Lack of asthma control is associated with increased healthcare costs [12]. One study found that patients with more than three control problems had at least twice the expenditures of those with fewer problems [13]; however, this study population was restricted to severe, “difficult to treat” patients who are not representative of most asthma patients.

Previous studies using a validated measure of asthma control have typically been conducted in clinical trials and specialty or severe populations. These populations may

not be generalizable to the broader persistent asthma population. For example, patterns of care, treatment choices, pulmonary function testing, etc. may be different in a specialty clinic population compared to a general population; likewise, clinical trial populations reflect the more restrictive inclusion and exclusion criteria of the trial (typically restricted to less controlled and more severe asthma patients). Other previous studies conducted in real-world settings have used surrogate markers of control (such as beta agonist use or exacerbations) instead of validated measures of control [4,12–14]. Our study approach is novel because it uses a validated measure of asthma control in a real-world setting in a general persistent asthma population.

The current study was designed to expand understanding of the cost of poor asthma control and exacerbations across a broad spectrum of patients using a valid measure of asthma control (ACQ-5). Multiple waves of survey administration across different allergy and flu seasons increased the range of possible ACQ scores, providing more data points to estimate this relationship. The objectives of the study were to examine 1) the cost of poor asthma control (as measured by the ACQ-5) and 2) the cost of asthma exacerbations.

Methods

Data source

Details of the OSACO study have been published previously [15]. The Observational Study of Asthma Control and Outcomes (OSACO) was a prospective survey and retrospective claims-based analysis of patients with persistent asthma ≥ 12 years of age in Kaiser Permanente of Colorado (KPCO). Eligible patients were sent surveys during three waves over the course of one year between April 2011 and June 2012. The survey included questions on asthma control, exacerbations, smoking status, sex, family income level, race, educational attainment, and ethnicity. Exacerbations were ascertained by asking: “In the last 6 weeks, have you experienced serious asthma symptoms requiring you to take oral steroid medications?”

Expenditures from the KPCO claims data were aggregated into 4-month panels (2 months prior and 2 months after survey completion) with three waves of surveys, resulting in three 4-month panels in one year. For example, total expenditures for Wave 1 were calculated as the sum of all expenditures incurred during the 2 months preceding and 2 months after completion of the first survey. Although actual health resource utilization (HRU) was obtained directly from the KPCO administrative and contracted claims data, expenditures associated with each utilization event were imported from an exogenous data

source, which is more representative of the cost of typical care in the United States. KPCO offers pre-paid health insurance and owns its own clinics and pharmacies and contracts for emergency and inpatient care. KPCO uses proprietary internal billing and costing methods atypical of other health insurance organizations. Expenditure data was derived from an exogenous commercial claims database. Each KPCO utilization event (e.g., office visit or IV administered in the ED) was matched by the respective billing code (CPT) and place of service; the average amount paid was then used to represent expenditures per event in the KPCO data.

Study variables

Study variables for this analysis included asthma control, exacerbations, expenditures and sociodemographic characteristics. ACQ scores and self-reported exacerbations were based on survey responses. Prescription-based exacerbations were defined as any prescription for oral corticosteroids (OCS) during the wave. Expenditures were categorized as medical- or pharmacy-related and as all-cause or asthma-related. Asthma-related medical expenditures were defined by claims with an ICD-9 code for asthma; asthma-related pharmacy expenditures included expenditures on all asthma medications. All-cause expenditures included all diagnoses and prescriptions (including asthma). Medical expenditures included inpatient, outpatient, and emergency room (ER) expenditures.

Asthma control was assessed by the ACQ-5, which includes five patient reported symptom questions (7-day recall of (1) frequency of nighttime awakening, (2) severity of asthma symptoms upon awakening, (3) extent of activity limitations, (4) frequency of shortness of breath, and (5) frequency of wheezing) and results in a continuous score from 0 to 6 with lower scores representing better control. The ACQ-6 adds a question about the average number of puffs of rescue medication used each day and the ACQ-7 adds provider performed FEV₁. The authors of the ACQ demonstrated that the ACQ-5, ACQ-6, and ACQ-7 produce clinically equivalent results, concluding that one can be used without preference over another [16]. Additional items in the survey included questions about exacerbations, smoking status, sex, family income level, race, educational attainment, and ethnicity. Patient reported exacerbations were determined by the survey question: “In the last 6 weeks, have you experienced serious asthma symptoms requiring you to take oral steroid medications?”

Statistical analysis

Unadjusted mean expenditures and standard deviations were calculated across ACQ-5 levels. To address

the skewed and censored characteristics of expenditure data, adjusted analyses of expenditures used Generalized Linear Models (GLM) with log link controlling for wave/group fixed effects, age, sex, family income level, race, educational attainment, ethnicity, and smoking status. Due to the extreme skewness of expenditure data, logarithmic transformation of the dependent variable is critical. However, simple log-transformation of expenditures with use of Ordinary Least Squares (OLS) is problematic due to clustering at zero (a sizable number of patients have zero cost). GLM with log link is robust to both skewness and clustering. Although OLS looks into the expected log of expenditures ($E[\log(Y)]$), GLM estimates the log of expected expenditures $\log(E[Y])$. The analysis has also used time and group specific fixed effects. In addition, the “robust” option was specified to correct for any possible clustering of data within groups and calculate more efficient standard errors. Regressions were run with the ACQ-5 treated as a continuous dependent variable. Exacerbation analyses treated exacerbation (yes/no) as a binary independent variable. The monthly health care inflation index was used to express all expenditures in 2013 dollars.

Results

Study population

Of the 5951 individuals eligible for the study, 2681 completed the first survey (Wave 1); 2681 were eligible for the second survey and 2186 completed the survey (Wave 2); 2158 were eligible for the third survey and 1799 completed it (Wave 3). 1799 individuals completed all three surveys; 387 completed only two and 495 completed only one (for a total of 6666 completed surveys). The mean age of the study population was 48 years, 65% were female, and 85% were white (Table 1). Approximately 19% of individuals reported having an exacerbation requiring the use of oral corticosteroids in the previous 6 weeks. Most ACQ-5 scores were between 0 and 1 (55%) or 1 and 2 (30%). The mean and median ACQ-5 scores were 0.99 and 0.80, respectively. Few individuals ($n = 34$) in the sample had an ACQ-5 ≥ 4.0 .

Mean unadjusted healthcare expenditures increased with increasing ACQ-5 scores (Figure 1 and Table 2). The majority of expenditures came from medical expenditures (\$2628; most of which were due to outpatient expenditures), followed by prescription expenditures (\$848) (Table 2). Because of the skewed and censored nature of expenditure data, the median is a better approximation of central tendency than the mean.

After controlling for wave and group fixed effects, age, sex, family, income level, race, educational attainment,

Table 1. Baseline sample characteristics.

	N = 2681
Female	65%
Age (years), mean	47.9
Race	
White	85%
Asian	2%
African American	4%
American Indian	4%
Native Hawaiian	1%
Multiple Race	0%
NA	4%
Ethnicity	
Hispanic	13%
Non-Hispanic	86%
NA	1%
Income (\$ per year)	
<\$10 000	2%
\$10 000 – \$30 000	8%
\$30 000 – \$50 000	16%
\$50 000 – \$70 000	15%
\$70 000 – \$90 000	16%
> \$90 000	31%
NA	4%
No answer	8%
Education	
< 8th Grade	3%
High School but did not graduate	5%
High school graduate or GED	14%
Some College	27%
College Graduate	25%
Post-graduate	25%
NA	1%
Smoking history	
Never Smoked	66%
Current Smoker	5%
Previous Smoker	28%
Exacerbation ^a	19%
ACQ-5 (mean; median)	0.99 (.80)
ACQ-5 0-1 N (%)	3654 (55)
ACQ-5 1-2 N (%)	1984 (30)
ACQ-5 2-3 N (%)	759 (11)
ACQ-5 3-4 N (%)	191 (3)
ACQ-5 4-5 N (%)	29 (.4)
ACQ-5 5-6 N (%)	5 (.1)

Note. Data represent proportion of patients unless otherwise indicated.

^aExacerbation of asthma requiring the use of oral corticosteroids in the previous six weeks (self-reported).

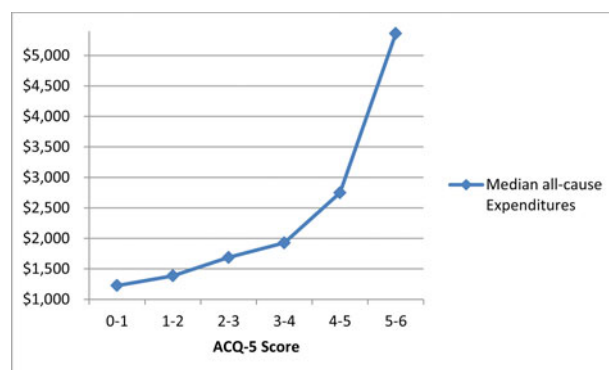


Figure 1. Unadjusted median all-cause expenditures by ACQ-5 score category.

Table 2. Unadjusted healthcare expenditures by ACQ-5 score (per 4 months).

	ACQ-5 0–1.0 N = 3654 Mean (SD) Median	ACQ-5 1.0–2.0 N = 1984 Mean (SD) Median	ACQ-5 2.0–3.0 N = 759 Mean (SD) Median	ACQ-5 3.0–4.0 N = 191 Mean (SD) Median	ACQ-5 4.0–5.0 N = 29 Mean (SD) Median	ACQ-5 5.0–6.0 N = 5 Mean (SD) Median	Total N = 6622 Mean (SD) Median
All-cause	\$3161 (6984) \$1225	\$3549 (7640) \$1385	\$4223 (8949) \$1686	\$5261 (11 371) \$1926	\$6607 (11 545) \$2748	\$4682 (2494) \$5359	\$3476 (7622) \$1349
Medical	\$2342 (6557) \$500	\$2709 (7335) \$560	\$3253 (8707) \$745	\$4333 (11 184) \$966	\$5389 (11 416) \$1356	\$3584 (2020) \$4649	\$2628 (7271) \$552
Inpatient	\$454 (3487) \$0	\$472 (3585) \$0	\$671 (5204) \$0	\$1359 (8574) \$0	\$2703 (8750) \$0	\$0 (0) \$0	\$520 (4017) \$0
Outpatient	\$1450 (4052) \$385	\$1613 (4723) \$435	\$1664 (4366) \$539	\$1891 (3686) \$720	\$1812 (2286) \$1066	\$2936 (1859) \$2376	\$1539 (4283) \$424
Prescription	\$819 (1437) \$588	\$841 (994) \$605	\$970 (1045) \$698	\$928 (968) \$697	\$1218 (811) \$987	\$1098 (762) \$1148	\$848 (1262) \$610
Asthma-specific	\$1257 (4307) 496	\$1513 (4621) 513	\$2128 (7342) 572	\$2868 (9937) 710	\$3512 (8289) 1022	\$1244 (1062) 1117	\$1490 (5106) 513
Medical	\$828 (4257) \$0	\$1066 (4566) \$0	\$1643 (7265) \$0	\$2363 (9904) \$188	\$2739 (8303) \$208	\$647 (748) \$407	\$1406 (5052) \$0
Inpatient	\$402 (3305) \$0	\$384 (3061) \$0	\$671 (5204) \$0	\$1309 (8553) \$0	\$1526 (6330) \$0	\$0 (0) \$0	\$458 (3773) \$0
Outpatient	\$260 (1745) \$0	\$357 (1920) \$0	\$419 (2721) \$0	\$434 (1257) \$0	\$555 (937) \$208	\$529 (752) \$407	\$314 (19119) \$0
Prescription	\$429 (425) \$391	\$446 (473) \$331	\$485 (491) \$344	\$505 (493) \$389	\$773 (618) \$574	\$597 (529) \$365	\$444 (451) \$358

ethnicity, and smoking status, the association between poor asthma control and expenditures was significant (Table 3). Each 1-point increase in the ACQ-5 was associated with an additional \$481 in all-cause healthcare expenditures and an additional \$309 in asthma-specific

healthcare expenditures over four months. A one-point increase in ACQ-5 score was associated with higher all-cause and asthma specific expenditures across all categories of healthcare costs except for inpatient expenditures.

Of those reporting having had an exacerbation requiring use of OCS, only 28% actually filled a prescription for OCS in the 4-month window (Table 4). Individuals who reported having an exacerbation incurred an additional \$713 (all cause) and \$506 (asthma-specific) in healthcare expenditures over 4 months compared to

Table 3. Regression results: Expenditures (incremental effect for a one-point change in ACQ-5 score per 4 months).

	Mean (SE)	95% CI	P Value
All-cause Healthcare Expenditures	\$482 (107)	(272 – 691)	0.00
Medical	\$444 (107)	(232 – 652)	0.00
ER	\$201 (48)	(107 – 294)	0.00
Inpatient	– \$332 (540)	(–1390 – 726)	0.54
Outpatient	\$179 (59)	(63 – 295)	0.003
Prescription	\$62 (18)	(27 – 97)	0.00
Asthma-specific Healthcare Expenditures	\$309 (69)	(173 – 445)	0.00
Medical	\$295 (81)	(136 – 454)	0.00
ER	\$319 (97)	(129 – 508)	0.001
Inpatient	– \$3419 (8772)	(–20 611 – 13 772)	0.70
Outpatient	\$86 (25)	(38 – 135)	0.00
Prescription	\$41 (7)	(27 – 54)	0.00

Note. Controlling for wave and group, age, sex, family income level, race, educational attainment, ethnicity and smoking status. ER = emergency room. Subcategories may not sum to the total for the category because there are other smaller components of expenditures that were not explicitly included in the results.

Table 4. Number of individuals reporting exacerbations and filling OCS prescriptions.

Self-reported Exacerbations ^a	OCS Use ^b		Total
	No	Yes	
No (n)	4,957	420	5,377
% (row)	92.2%	7.8%	100%
% (column)	85.5%	55.9%	82.1%
Yes (n)	842	332	1,174
% (row)	71.7%	28.3%	100%
% (column)	14.5%	44.2%	17.9%
Total	5,799	752	6,551

^aExacerbation of asthma requiring the use of oral corticosteroids in the previous 6 weeks (self-reported).

^bUse of Oral Corticosteroids (OCS) within the panel (4 months).

Table 5. Regression results: Cost of asthma exacerbation per four months.

	Mean	SE	P	95% CI	95% CI	Mean	SE	P	95% CI	95% CI
	Self-reported Exacerbations ^a					OCS Use ^b				
All-cause Expenditures										
Healthcare	\$713	213	0.00	295	1131	\$3014	278	0.00	2469	3560
Medical	\$702	205	0.00	301	1104	\$2650	271	0.00	2118	3182
Outpatient	\$362	115	0.00	135	588	\$1517	155	0.00	1214	1821
ER	\$251	75	0.00	105	397	\$428	76	0.00	278	578
Inpatient	\$162	250	0.52	− 327	651	\$1186	453	0.01	298	2075
Prescription	\$62	33	0.06	− 3	127	\$431	40	0.00	353	510
Asthma-specific Expenditures										
Healthcare	\$506	137	0.00	238	774	\$1626	170	0.00	1294	1958
Medical	\$538	142	0.00	259	817	\$1584	206	0.00	1179	1988
Outpatient	\$154	46	0.00	64	243	\$476	60	0.00	359	593
ER	\$276	79	0.00	121	431	\$457	109	0.00	243	671
Inpatient	\$316	271	0.24	− 215	848	\$1510	712	0.03	115	2906
Prescription	\$59	16	0.00	27	90	\$225	17	0.00	193	257

Note. Subcategories may not sum to the total for the category because there are other smaller components of expenditures that were not explicitly included in the results.

^aExacerbation of asthma requiring the use of oral corticosteroids in the previous 6 weeks (self-reported).

^bUse of ORAL CORTICOSTEROIDS (OCS) within the panel (4 months).

those who did not (Table 5). Individuals who actually filled a prescription for oral corticosteroids during the 4-month period incurred an additional \$3014 (all cause) and \$1626 (asthma-specific) in healthcare expenditures over 4 months compared to those who did not.

Prescription use of OCS appeared to be more strongly associated with expenditures than self-reported exacerbations for all expenditure categories. All categories were statistically significantly associated with exacerbations except inpatient expenditures with self-reported exacerbations. Individuals who had an exacerbation requiring a documented prescription for oral corticosteroids had significantly higher expenditures than those who self-reported an exacerbation (Figure 2).

Discussion

The results of this study show that poor asthma control and exacerbations are very expensive. Similar to findings in previous publications, the total cost per patient

was higher when asthma was poorly controlled [4,12–14]. Our study expands the understanding of the cost of poor asthma control and exacerbations by assessing a wide range of asthma control in a general population. It also provides detailed quantification of the cost associated with each one-point difference in ACQ-5 score.

The study findings are strengthened by the use of a validated measure of asthma control in a real-world setting in a general asthma population. Most previously published studies using a validated measure of asthma control have been conducted in clinical trials of specialty or severe populations, which may not be generalizable to a broader asthma population. Other studies have been conducted in real-world settings but have used surrogate markers of control such as beta agonist use or exacerbations [4,12–14,17] rather than validated instruments. When alluding to a “general” population, we refer to a real-world setting of patients receiving asthma care from a mix of primary care and specialty providers that matches the distribution in the community.

Results of studies conducted in general populations may differ from clinical trial or specialty clinic populations. For example, patterns of care, treatment choices, pulmonary function testing, etc. may be different in a specialty clinic population compared to a general population; likewise, clinical trial populations reflect the more restrictive inclusion and exclusion criteria of the trial (typically restricted to less controlled and more severe asthma patients). A general population such as in this research includes a broader spectrum of controlled and uncontrolled patients. As expected for a general sample, few individuals had an ACQ score > 4.0. Individuals with this level of very poor control would likely be admitted to the hospital or ER and unable to

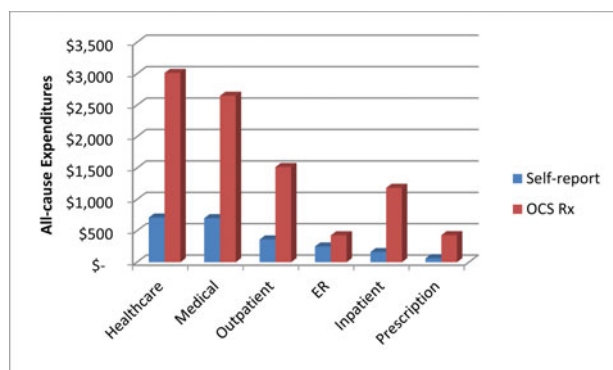


Figure 2. Adjusted all-cause expenditures comparing self-reported exacerbation to OCS prescription.

participate in a community survey. As a result, conclusions regarding patients with ACQ-5 scores > 4.0 must be made with caution. There were only 5 patients with ACQ-5 score 5–6. Although the results of this small sample are presented in Table 2, they should be interpreted with caution.

Although previous research has indicated that asthma costs increased in direct proportion to the number of asthma control problems (multilevel ATAQ control score) in patients with severe asthma [13], limited data on the relationship between healthcare expenditures and asthma control across the full spectrum of asthma control and over time have been published. Our study quantified specifically how each 1-point increase in the ACQ was associated with an increase in cost.

Each one-point increase in the ACQ-5 was associated with an additional \$1443 all-cause and \$927 asthma-related healthcare expenditures annually, representing a significant increase that may justify investment in interventions aimed at improving asthma control (on a financial basis alone). Moreover, asthma and associated symptoms and clinical sequelae have a wider impact on expenditures than asthma-specific costs alone. Clinic visits and expenditures not directly diagnosed as asthma (such as bronchitis) would not be included in asthma-specific expenditures.

For example, a patient without asthma may recover from a cold within 1 week without any need for medical attention, whereas a patient with asthma may develop bronchitis from the same cold, requiring a baseline and follow-up physician office visit as well as antibiotics. Although these associated office visits and antibiotics are attributable to the patient's asthma, as evidenced by the different outcomes, they would not be captured in analyses restricted to asthma-specific expenditures; however, the regression results of all-cause healthcare expenditures would capture them.

The beta coefficient of the ACQ-5 score in the regression analyses reflects the incremental impact of asthma control. Hence, the coefficient of the ACQ-5 suggests an increase of \$1443 in all-cause healthcare expenditures attributable to a 1-point increase in the ACQ-5, likely a very real financial impact attributable to poor asthma control. Although unmeasured confounders associated with asthma control and expenditures could potentially bias the coefficient, the statistical structure of the regression analyses permitted control for a variety of sociodemographic characteristics and smoking status, mitigating the potential impact of this bias.

The impact of having an asthma exacerbation on healthcare costs was significant (\$3014 over 4 months). This is not surprising, considering the additional utilization that accompanies an exacerbation. Medical costs

(including office visits, ER and inpatient visits) were the main driver of the cost of an exacerbation.

A novel and interesting finding in the results is the stark difference in the number and cost of self-reported exacerbations compared to exacerbations with a documented prescription for OCS (Tables 4 and 5; Figure 2). Individuals who had an exacerbation requiring a documented prescription for oral corticosteroids had significantly higher expenditures than those who self-reported an exacerbation (Figure 2). There seemed to be incongruence in the number of individuals self-reporting an exacerbation compared to the number actually filling a prescription. For example, only 28% of those reporting an exacerbation actually filled an OCS prescription. Expenditures associated with prescription-based exacerbations were also significantly greater than those associated with self-reported exacerbations. There are several possible explanations for these discrepancies. First, the window for aggregating cost was the same between the two methods (4 months), but the analytic window for reporting an exacerbation was different. The recall window for self-reported exacerbations was 6 weeks prior to the survey date.

Prescription-based exacerbations were measured based on any prescription fill during the 4 months (2 months pre- and 2 months post-survey). This difference in recall window would likely result in underreporting of exacerbations under the self-reported method because the recall window was shorter: a given individual is more likely to have an exacerbation over four months than 6 weeks because the exposure time is longer. If this were the case, we would expect a significant percentage of individuals who filled an OCS prescription would report not having an exacerbation (because they had an exacerbation outside of the 6-week window of self-report); but only 8% of individuals fit this pattern. In addition, this underreporting would result in a lower cost of self-reported exacerbation by a commensurate degree. However, the cost difference is much more substantial than would be expected by this factor alone.

It is possible that the difference is at least partially due to recall bias or other forms of bias associated with self-report and patient perspective. Perhaps an exacerbation that can be self-managed is inherently less severe and therefore less costly than an exacerbation that requires a physician visit (a necessary condition for receiving an OCS prescription). It is also possible that a self-managed exacerbation would be less expensive due to the reduced need for medical encounters like outpatient visits, ER visits and prescriptions. This presumes that the patient has OCS at home and is capable of knowing how to properly manage the exacerbation. Another potentially confounding limitation is the possibility that some patients were

filling OCS prescriptions for chronic use rather than an exacerbation. Future research on the source of these differences in both the cost and reporting of exacerbations would be beneficial. In addition, the difference in self-reported exacerbations should be considered by clinicians and researchers who rely on patient report.

Estimates of the specific relationship between the ACQ and exacerbations and economic outcomes may be beneficial for population health and future applications. Estimates provided in this research may enable public health authorities or large health organizations to quantify the potential cost impact of disease interventions that improve asthma control via an estimation of the impact on ACQ scores. In addition, these estimates may be useful to model the impact of improvement or decline in asthma control in future cost-effectiveness models, which often attempt to model cost and effectiveness of treatment on asthma control and outcomes. Such models could use our results to quantify specifically how a one-point improvement in ACQ-5 score would impact cost.

Results of the current study are limited to ACQ-5 scores. Juniper et al. has recommended that the ACQ-5, ACQ-6 and ACQ-7 can be used interchangeably because their psychometric performances are not clinically different [16]. As a result, we chose to report results for the ACQ-5 rather than the ACQ-6 because the ACQ-5 is the most parsimonious, given comparable scores.

There was a statistically significant association between higher ACQ-5 scores and all expenditure categories (all-cause and asthma-specific: total, medical, ER, outpatient and pharmacy) except inpatient expenditures. Although inpatient expenditures appeared to increase with increasing ACQ-5 score in unadjusted analyses, they were not statistically significant in the full adjusted regression results. This is likely due to the very small numbers of individuals who are admitted to the hospital and the wide variability in inpatient expenditures. For example, individuals with ACQ-5 4-5 had unadjusted mean inpatient expenditures of \$2703 with a standard deviation of \$8750. The median was \$0 for all ACQ-5 categories because more than half of the sample had no hospitalization. Future studies would need a very large sample to detect significant differences in inpatient expenditures across ACQ levels.

Other limitations include the survey response rate, geographical location, sociodemographic distribution and general potential for selection bias. Individuals who were willing to participate in the survey may be different than the broader population. Although we controlled for survey administration timing and sociodemographic characteristics, the potential for selection bias still exists. The KPCO population is generally representative of the

Colorado population, but this sample may not be generalizable to other populations. The sample in this study was less likely to be African American, Hispanic and poor compared to the U.S. general population.

Despite these limitations, this research provides important insight into the specific cost of poor asthma control (as measured by a validated instrument) and exacerbations in a general population with persistent asthma. Overall, the results of this study demonstrate a strong association between poor asthma control and increasing costs. The study results also suggest that collection of validated measures of control such as the ACQ may provide important clinical and economic insight without undue clinical and respondent burden. In addition, specific quantification of the relationship between ACQ scores and economic outcomes may help inform future public health applications such as disease management programs and cost-effectiveness analyses.

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Declaration of interest

Patrick Sullivan reports receiving research grants from Amgen Inc. during the conduct of the study and also reports grants and consultancy fees from Amgen Inc. Jonathan Campbell reports receiving consulting fees from Amgen Inc. related to the conduct of this study. Vahram Ghushchyan has nothing to declare. Gary Globe is an employee and stockholder of Amgen Inc. Bruce Bender has nothing to declare. David Magid has received research grants from Amgen, Inc. during the conduct of this study. The authors alone are responsible for the content and writing of the article.

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References

1. Fanta CH. Asthma. *N Engl J Med* 2009;360(10):1002–1014.
2. National Heart Lung, and Blood Institute. Expert Panel Report 3: Guidelines for the Diagnosis and Treatment of Asthma In: National Heart Lung, and Blood Institute, ed. Available from: <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf> [last accessed 10 July 2013].
3. Centers for Disease Control, Prevention. Vital signs: asthma prevalence, disease characteristics, and self-management education: United States, 2001–2009. *MMWR. Morbid Mortal Weekly Rept* 2011;60(17):54–55.

4. Bahadori K, Doyle-Waters MM, Marra C, Lynd L, Alasaly K, Swiston J, FitzGerald JM. Economic burden of asthma: a systematic review. *BMC Pulm Med* 2009;9:24.
5. Sullivan PW, Ghushchyan VH, Slejko JF, Belozeroff V, Globe DR, Lin S-L. The burden of adult asthma in the United States: Evidence from the Medical Expenditure Panel Survey. *J Allergy Clin Immunol* 2011;127(2):363–369.e363.
6. Cockcroft DW, Swystun VA. Asthma control versus asthma severity. *J Allergy Clin Immunol* 1996;98(6 Pt 1):1016–1018.
7. Pakhale S, Mulpuru S, Boyd M. Optimal management of severe/refractory asthma. *Clinical medicine insights. Circ Respir Pulmon Med* 2011;5:37–47.
8. Carranza Rosenzweig JR, Edwards L, Lincourt W, Dorinsky P, ZuWallack RL. The relationship between health-related quality of life, lung function and daily symptoms in patients with persistent asthma. *Respir Med* 2004;98(12):1157–1165.
9. Vollmer WM, Markson LE, O'Connor E, Sanocki LL, Fitterman L, Berger M, Buist AS. Association of asthma control with health care utilization and quality of life. *Am J Respir Crit Care Med* 1999;160(5 Pt 1):1647–1652.
10. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, . . . Pendergraft TB. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol* 2004;113(1):59–65.
11. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14(4):902–907.
12. Campbell JD, Spackman DE, Sullivan SD. Health economics of asthma: assessing the value of asthma interventions. *Allergy* 2008;63(12):1581–1592.
13. Sullivan SD, Rasouliyan L, Russo PA, Kamath T, Chipps BE, for the TSG. Extent, patterns, and burden of uncontrolled disease in severe or difficult-to-treat asthma. *Allergy* 2007;62(2):126–133.
14. Sullivan PW, Slejko JF, Ghushchyan VH, Sucher B, Globe DR, Lin SL, Globe G. The relationship between asthma, asthma control and economic outcomes in the United States. *J Asthma* 2014;51(7):769–778.
15. Sullivan PW, Campbell JD, Globe G, Ghushchyan VH, Bender B, Schatz M, . . . Magid DJ. Measuring the effect of asthma control on exacerbations and health resource use. *J Allergy Clin Immunol* 2015 Nov;136(5):1409–11.
16. Juniper EF, Svensson K, Mork AC, Stahl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med* 2005;99(5):553–558.
17. Vollmer WM, Markson LE, O'Connor E, Frazier EA, Berger M, Buist AS. Association of asthma control with health care utilization: a prospective evaluation. *Am J Respir Crit Care Med* 2002;165(2):195–199.