

Asthma costs and utilization in a managed care organization

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Background: Medical costs and health care utilization associated with asthma and the variation by treatment are poorly understood.

Objective: To compare single controller inhaled corticosteroid (ICS) to other asthma drug regimens on medical costs and utilization.

Methods: Direct medical costs and utilization were captured from administrative electronic databases from continuously enrolled members with asthma age 5 years or older with drug coverage. Asthma patients were identified during 2002, categorized into 14 asthma drug groups on the basis of 2003 prescription records, and had total medical costs and utilization determined in 2004 adjusting for demographics, insurance types, asthma risk, comorbidity, and propensity scores.

Results: A total of 96,631 patients met the study eligibility criteria. Patients were (mean $\pm$ SD) age 38 ± 23 years and were 57% female, 14% Medicare, 4% Medicaid, and had a median family income (mean $\pm$ SD) of $\$64,967 \pm \$29,285$. Total unadjusted direct medical costs/patient/year averaged $\$3745$ ($\$3298$ low asthma risk vs $\$6797$ high asthma risk; $P < .001$). Adjusted total and asthma drug costs were significantly lower with single controller ICS compared with single controller

leukotriene modifiers, long-acting β -agonists, and theophylline and most combination controller regimens ($P < .001$ for all comparisons). In addition, single controller ICS compared with single controller leukotriene modifiers and combination controllers was associated with significantly lower asthma-related utilization.

Conclusion: Total direct costs and asthma-related utilizations are meaningfully less in the year after being dispensed single controller ICS compared with single controller leukotriene modifiers or most combination controllers. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Asthma, combination controllers, drugs, health care costs, inhaled corticosteroids, leukotriene modifiers, long-acting β -agonists, managed care organization, health resource utilization

Asthma cost and resource utilization are major public health issues. In the United States, asthma affects about 16 million adults (7%) and 6.5 million (9%) children, has increased over the past decades, and accounts yearly for $\frac{1}{2}$ million hospitalizations, 2.8 million emergency department (ED) or hospital outpatient department visits, and 13.6 million office-based physician visits (<http://www.cdc.gov/nchs/fastats/asthma.htm>). Total annual expenditures for asthma were nearly \$13 billion, with \$7.4 billion or 62% a result of direct costs, of which 43% were for drugs.¹

Newer, more costly controller therapies, such as more potent inhaled corticosteroids (ICSs), leukotriene modifiers (LMs), long-acting β -agonists (LABAs), and combinations of these drugs are being dispensed more frequently, but their cost/benefit profiles and effect on total and asthma-related costs and utilization are poorly understood.² This study assesses the effect of being dispensed single controller ICS compared with other asthma drugs in the year before determination of total direct medical costs and asthma-related utilization in a large managed care organization (MCO).

METHODS

Study design

This is a retrospective cohort study among members of the Kaiser Permanente Southern California (KPSC) health plan of direct medical costs and asthma-related utilizations obtained from administrative electronic databases and approved by the KPSC Institutional Review Board. Data collected from 2002 to 2004 were used as follows:

1. 2002: Asthma case identification (inclusions and exclusions).
2. 2003: Stratification into intention-to-treat (ITT) drug groups by dispensing, and determination of predictors: asthma risk levels, age, years of membership, insurance type, education, household income, comorbidities, and treatment selection propensity scores.
3. 2004: Determination of medical costs and health care utilization.

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Abbreviations used

COPD: Chronic obstructive pulmonary disease
 ED: Emergency department
 ICD-9: International Classification of Diseases, 9th Revision
 ICS: Inhaled corticosteroid
 ITT: Intention-to-treat
 KPSC: Kaiser Permanente Southern California
 LABA: Long-acting β -agonist
 LM: Leukotriene modifier
 MCO: Managed care organization
 MCS: Mast cell stabilizer
 SABA: Short-acting β -agonist

Patients

Eligible members were 5 years of age and older, had KPSC drug coverage, met the study definition of asthma, and were continuously enrolled during the period 2002 to 2004 (no more than 1 gap of less than 45 days in coverage in a year; <http://web.ncqa.org>). Patients who died in 2004 after continuous enrollment in the period 2002 to 2003 were included. Of the KPSC members with asthma and potentially eligible for this study, 95% had KPSC drug coverage, a percentage similar to the KPSC membership as a whole. Patients were identified as having asthma if they met 1 or more of the following criteria³ in 2002:

- Any discharge diagnosis (principal or other diagnosis) of asthma in the KPSC and contracting hospital database (International Classification of Diseases, 9th Revision [ICD-9] code: 493.xx).
- Two or more asthma-related drug dispensed (excluding oral steroids) in the pharmacy database, including β -agonists (excluding oral terbutaline), ICS, other inhaled anti-inflammatory asthma drugs, and LM and theophylline.
- ED or outpatient asthma-related diagnosis.

Patients were excluded if they had cystic fibrosis or chronic obstructive pulmonary disease (COPD).

Patient characteristics included age, sex, length of KPSC membership, and insurance type. 2004 census block group level family household income and education attainment estimates were supplied by Claritas, Inc (San Diego, Calif, www.claritas.com) and obtained in more than 95% of members through geocoding, a technique that links members' addresses to census geographic areas. KPSC administrative databases do not capture smoking history of patients.

Drug categories/groups

Asthma drug use was preclassified into 14 asthma drug ITT categories on the basis of 2003 prescription records of the following classes of drugs: no asthma drug dispensed (no drugs dispensed), only rescue short-acting β -agonists (SABAs), single asthma controllers (ICS, LM, mast cell stabilizers [MCSs], theophylline, and LABA) and various controller combinations (Table I). We could not determine whether drug combinations were taken together, only that they were prescribed in 2003 to specific patients; however, given the care management practices in the MCO, it is likely that the combination drugs were generally used together. Patients dispensed controller drugs may or may not have also received SABA. Asthma treatment recommendations based on national guidelines are developed by KPSC and distributed to providers to use in their individual practices. However, there is still variability in the treatment patterns practiced. Although KPSC has a medication formulary, there is no restriction to providers in prescribing asthma medication.

Asthma risk stratification

Asthma risk stratification was based on criteria previously validated by us.⁴ The severity risk groups captured in 2003 were (1) high risk: any asthma ED or hospitalization and/or >14 β -agonist canisters dispensing and any oral corticosteroids dispensing; (2) medium risk: no asthma ED or hospitalization and

>14 β -agonist canisters dispensing or any oral corticosteroids dispensing; and (3) low risk: no asthma ED or hospitalization and <15 β -agonist canisters and no oral corticosteroids.

Data analyses

Medical costs and resource utilization. Administrative electronic databases captured all KPSC and outside claims inpatient and outpatient services as summarized in this article's Table E1 in the Online Repository at www.jacionline.org. An asthma hospitalization was defined as an inpatient stay with a primary diagnosis of asthma (493.xx) or secondary diagnosis of asthma when the primary diagnosis was related to a respiratory disease. An asthma ED visit was defined as an ED visit with an asthma diagnosis recorded. KPSC ED diagnosis coding includes diagnoses relevant to the visit and therefore represents uncontrolled asthma and is relevant in capturing asthma ED visit as an outcome.

Cost definitions. Total costs were the sum of (1) asthma-related inpatient, ED, and drug costs; (2) nonasthma inpatient, ED, and drug costs; and (3) residual costs. Asthma drug costs were costs associated with the dispensing of asthma drugs. Residual costs (outpatient costs including visits, medical equipment, laboratory tests, physical therapy, nursing home care, home care, and so forth) were costs of all services for which there was inadequate specificity in the databases to partition into asthma and nonasthma costs.

Medical costs. We examined the net effect of different ITT treatment groups on estimated direct medical costs, after adjusting for asthma risk level,⁴ demographics, comorbidities, RxRisk disease cost severity scores,^{5,6} and treatment selection propensity scores.^{7,8} The RxRisk model, a validated measure for health care cost analyses, incorporates both the Chronic Disease Score algorithm (limited to adults) and the Pediatric Chronic Disease Score.⁷ It measures comorbidity and relative disease severity by identifying 28 chronic conditions among adults and 24 among children on the basis of outpatient prescription drug fills. A cost score is produced from a regression equation that estimates expected previous year healthcare cost as a function of age, sex, and the chronic condition classes in which drug fills are observed. To adjust further for comorbidity cost variation, we included indicators for 18 ICD-9 disease comorbidity categories based on individual inpatient and outpatient utilization information (see this article's Table E2 in the Online Repository at www.jacionline.org).

For enhanced generalizability of findings, costs were assigned to health care services and pharmaceuticals by using the Medicare Resource Based Relative Value Scale and Diagnosis-Related Groups (posted at www.CMS.gov), respectively. Drug costs were estimated by matching Redbook drug prices to pharmacy National Drug Codes by using typical managed care drug price discounts because Medicare did not cover most drugs until the Part D program began in 2006. Medical treatment costs were generated for 2004 by applying 2004 national Medicare reimbursement rates (Diagnosis-Related Groups, Resource Based Relative Value Scales, and so forth) to individual reported medical service utilizations.

Asthma resource utilization. Asthma-related utilization was determined as any asthma hospitalization or asthma ED visit (see definitions) in either KPSC or non-KPSC facilities. Oral corticosteroid dispensing as a categorical variable (yes or no) was also determined as an indicator of increased asthma utilization.

Statistical analysis

Descriptive analyses for individual resource use items entered as a dichotomous variable (eg, hospitalization = yes or no) or a count variable (eg, how many physician visits) were conducted to illustrate the resource utilization associated with asthma. Both simple ANOVA and least-squares analysis were used to test between-group differences in individual patient costs. Multivariate analyses adjusted for asthma risk level, baseline demographics, insurance types, comorbidities, RxRisk, and treatment selection propensity scores as described. Treatment patterns were included as endogenous explanatory variables using instrumental variables and propensity score estimators to detect and correct for selection bias.⁸

Nearly all health care cost samples are highly skewed, with a small percentage of patients accounting for a large proportion of total costs.

Logarithmic transformation of the cost variables is an appropriate correction, but this adjustment creates additional complexities. When one transforms costs to the log-scale, one cannot simply take the exponent of the estimated treatment coefficient to predict the treatment effect on the raw cost scale. Log-transformations create a “retransformation bias” that must be accounted for in calculating treatment effects in the cost scale.⁹ Multivariate log-normal cost regressions and log-cost regressions in conjunction with smearing estimates for retransformation were estimated and compared with untransformed ordinary least-squares cost regressions to determine the robustness of the model functional specification. Asthma utilization was determined by using multivariate analyses adjusted for the same covariates as in the cost analyses.

RESULTS

Asthma cohort

Of the 2.8 million continuously enrolled members between 2002 and 2004 age 5 or greater in 2002, 96,631 (3.5%) met the study asthma eligibility criteria. Patients averaged (mean $\pm$ SD) 37.5 ± 23.1 years of age and were 57% female, 14% Medicare, and 4% Medicaid and were health plan members for a mean ($\pm$ SD) of 12.8 ± 9.4 years. On the basis of geocoding, 79% of adults had at least a high school diploma and a median family household income (mean $\pm$ SD) of $\$64,967 \pm \$29,285$ (Table I).

Drug groups

Incidences. The distribution of patients with asthma identified in 2002 in the ITT drug groups based on 2003 dispensing data were 33% with no drug dispensing, 28 % single controller ICS, 22% SABA only, 8% combination controller ICS and LABA, and less than 2% other single controllers or other controller combinations (Table I).

Asthma risk level. The majority of the identified members with asthma were low-risk (79%), with only 5% high-risk (Table I), consistent with our previous findings.⁴ The distribution of asthma risk levels varied among the different drug groups, lowest in the no drug dispensed and SABA-only groups and highest in the controller combination groups (Table I; $P < .001$ across all drug groups).

Comorbidity. The 18 defined ICD-9 comorbidity groups varied significantly across drug groups ($P < .001$; Table E2).

Costs of care

Unadjusted costs. Total 2004 medical costs/patient/year averaged \$3745 and varied by asthma risk level with an average across all drug groups of \$3298 for low risk, \$4962 for medium risk, and \$6797 for high risk ($P < .001$) (see this article's Table E3 in the Online Repository at www.jacionline.org). Asthma-related costs also directly paralleled increases in asthma risk for most drug groups (Table E3).

Final adjusted regression model

Costs varied by age, sex, insurance type, length of health plan membership, RxRisk score, asthma risk level, and drug group (Table II).

Relationship to demographics and other characteristics. Relative to patients 5 to 11 years of age, total cost and most asthma and nonasthma component costs were increasingly greater for higher age category patients. Patients with supplemental private insurance had significantly lower asthma drug

costs. Female subjects cost significantly more than male subjects for total costs, nonasthma costs (drug, inpatient, and ED), and residual costs, but significantly less for asthma drug costs. Higher household income was significantly associated with higher total costs, nonasthma-related costs, and residual costs (Table II). Length of membership was directly and significantly related to total costs, asthma drug costs, and residual costs but negatively related to asthma inpatient costs. All costs significantly increased with higher comorbidity RxRisk score. Total costs and asthma-related drug costs directly and significantly increased with increasing asthma risk level (Table II).

Differential costs of single controller ICS versus other drug groups (Fig 1). Adjusted total costs in 2004 were lowest for patients in 2003 treated with single controller ICS compared with other drugs with the exception of those classified in the no asthma drug or SABA categories, or those using MCS or MCS + ICS. The MCS and MCS + ICS groups were the least frequently used asthma drug categories (382 and 303 patients, respectively) and included only 1 and 4 patients, respectively, with inpatient stays. Moreover, for both MCS and MCS + ICS patients, the reduced level of nonasthma-related costs accounted for more than the differential in total average costs relative to ICS patients. The estimated annual total health plan cost savings in 2004 was \$33 million with a weighted average of about \$2089/patient/year with the use in 2003 of single controller ICS compared with other controller drug groups (Fig 1; see this article's Table E5 in the Online Repository at www.jacionline.org).

Total costs. Total costs were significantly less with single controller ICS compared with single controllers LM, LABA, and theophylline, and all controller combinations except the combination ICS and MCS, but were significantly more than for the SABA only and no drug dispensed groups (Fig 1, A).

Asthma-related costs. Asthma drug costs for single controller ICS were significantly less than for all single controllers except MCS and all combination controllers ($P < .001$ for all comparisons) and significantly more than the no drug dispensed, MCS, and SABA only groups (Fig 1, B). Asthma inpatient and asthma ED costs were generally less but not significantly for single controller ICS than other single and combination controllers (Fig 1, C and D).

Other costs. Nonasthma drug, inpatient, and ED costs were significantly greater for single controller ICS than for the no drug dispensed, SABA only, and single controller MCS groups, but significantly less or insignificantly different for all other drug groups (Fig 1, E). Residual costs were significantly more for single controller ICS than the no drug dispensed and SABA only groups, but significantly less or insignificantly different for all other drug groups (Fig 1, F).

Asthma-related utilization

The 2004 incidence of at least 1 utilization was 0.7% ($n = 714$) for an asthma-related hospitalization, 2.9% ($n = 2755$) for an asthma ED visit, 16.7% ($n = 16,097$) for an oral corticosteroid dispensing, and 17.8% ($n = 17,240$) for any 1 of these 3 events. In multivariable analyses, asthma-related utilizations were independently and directly associated with female sex, age 5 to 11 years, lower family income, higher RxRisk score, and higher asthma risk level (see Table E4 in the Online Repository at www.jacionline.org).

Comparison with single controller ICS (adjusted multivariate model). Significant increases in asthma-related utilization in 2004

TABLE I. Patient demographics, insurance plans, and 2003 asthma risk levels by drug groups defined in 2003

Characteristic	No asthma drugs dispensed	SABA only	LABA	ICS	LM	MCS	THEO
Patients, no. (%)	32,294 (33.4%)	21,642 (22.4%)	680 (0.7%)	26,879 (27.8%)	848 (0.9%)	382 (0.4%)	579 (0.6%)
Age, mean (SD)	35.5 (22.7)	32.6 (22.7)	51.7 (20.1)	39.0 (23.3)	37.2 (22.7)	19.9 (19.1)	60.8 (14.4)
Female (%)	57	54	62	56	61	46	66
≥High school diploma (%)	79	78	79	79	79	79	78
Median household income (\$) (SD)	64,794 (28,997)	63,309 (28,613)	67,665 (32,846)	65,379 (29,675)	70,164 (32,259)	70,198 (29,654)	60,877 (27,402)
Years as member, mean (SD)	12.0 (9.1)	12.0 (7.3)	14.0 (10.1)	13.3 (9.7)	12.7 (9.7)	11.1 (8.2)	19.5 (11.0)
Medicaid (%)	3	5	2	4	2	8	2
Medicare (%)	12	11	30	15	14	5	44
RxRisk score, mean (SD)	1802 (3105)	2314 (3056)	3836 (3707)	2690 (3108)	2399 (2545)	1608 (1599)	4755 (3623)
High asthma risk (%)	1	3	5	7	5	3	5
Medium asthma risk (%)	5	15	21	24	20	14	19
Low asthma risk (%)	94	82	74	69	75	83	76

ICS, Budesonide, fluticasone, beclomethasone, flunisolide, triamcinolone; LABA, formoterol, salmeterol; LM, montelukast, zafirlukast, zileutin; MCS, cromolyn, nedocromil; SABA only, only albuterol, levalbuterol, bitolterol, pirbuterol; THEO, theophylline.

Percentages were rounded to single integers.

* $P < .001$ for any differences between drug groups and not differences between specific drug groups for each of the characteristics.

were seen for the use in 2003 of single controller LM and most combination controller groups compared with single controller ICS (Table III). Conversely, asthma-related utilization was significantly less for the no drug dispensed or SABA only groups compared with single controller ICS (Table III). However, >6 β -agonist canister dispensing/year, an indicator of inadequate asthma control,¹⁰ occurred at a 35% higher frequency in 2004 (odds ratio, 1.35; 95% CI, 1.26-1.44; $P < .001$, adjusted) in the SABA only compared with the single controller ICS group.

DISCUSSION

Use of our comprehensive electronic administrative databases allowed the most complete assessment to date of direct total and asthma-related costs and asthma-related utilization. After adjusting for an extensive list of potential confounders, single controller ICS use in 2003 was associated with the lowest total and asthma-drug costs in 2004 compared with the single controller alternative (except MCS) or combination controller drug category (Fig 1; Table E5). Single controller ICS use in 2003 was associated with an estimated total annual cost savings in 2004 of about \$33 million or about \$2089/patient/year compared with patients in 2003 on other single or combined controllers. Because indirect costs such as work loss could not be captured, the reported cost advantages of single controller ICS are only conservative estimates.

Asthma drug costs were the major contributor to asthma-related cost differences between single controller ICS and other controller drug groups (Fig 1), consistent with other studies.^{2,11-14} Furthermore, compared with single controller ICS, markedly higher nonasthma drug, inpatient, and ED costs occurred in certain other drug groups, suggesting potential yet unknown characteristics of patients within these drug groups that may be responsible for driving these costs. The cost savings associated with MCS or MCS + ICS relative to single controller ICS are more than fully accounted for by the lower nonasthma-related costs for these drug treatment groups, suggesting that MCS

therapy is used in patients with less severe comorbidities. Moreover, significantly lower asthma-related utilization in 2004 was associated with use in 2003 of single controller ICS compared with single controller LM and most other combination controller drug categories, including combinations of ICS and LABA or ICS and LM (Table III).

Similar to our previous findings, a large minority of patients with asthma do not fill asthma prescriptions in a subsequent year (no asthma drug dispensed group), which may result from the low asthma risk level of almost 95% in this group. It is possible that the episodic nature of asthma in this low asthma risk group leads to only episodic care, not just for asthma but for other conditions as well.

The reliability and generalizability of our cost findings are supported by previous reports.^{13,15-22} The total cost/patient/year of \$3745 in the present study is similar to the cost of \$3180 found in an earlier smaller cross-sectional study of randomly sampled Northern California adults with asthma.²³ The total cost savings/patient/year reported here of \$749 with single controller ICS versus single controller LM compares well to the differential cost between these drugs of \$1080 reported in a meta-analysis of 6 smaller MCO claim studies¹¹ and of \$1197 found in a study of 2.6 million privately insured individuals.¹²

In the current study, single controller ICS compared with combination controllers ICS and LABA was associated with less total cost/patient/year (\$1811 less; $P < .001$) and asthma-drug costs (\$398 less; $P < .001$; Fig 1; Table E5). These findings are similar to a smaller administrative health insurance claims study in which single controller ICS use was significantly associated with less asthma drug costs (\$357 less) than combination ICS and LABA, without a difference in asthma exacerbations.¹⁴

The major limitation of the study is the potential residual confounding by severity, despite extensive adjustments, because asthma management programs in this MCO follow National Asthma Education and Prevention Program recommendations (<http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm>) and

TABLE I. (Continued)

ICS + LABA	ICS + LM	ICS + MCS	ICS + THEO	ICS + LABA + LM	ICS + LABA + THEO	Other controller combinations	Total
8125 (8.4%)	1235 (1.3%)	303 (0.3%)	779 (0.8%)	1735 (1.8%)	405 (0.4%)	745 (0.8%)	96,631 (100%)
47.1 (19.9)	33.8 (23.5)	27.7 (23.6)	60.3 (12.8)	44.6 (20.5)	58.8 (13.9)	47.2 (18.8)	37.5 (23.1)
61	57	48	62	65	66	63	57
79	79	79	78	79	79	80	79
67,944 (30,429)	65,986 (30,083)	68,032 (27,964)	61,440 (27,275)	64,898 (27,889)	65,169 (28,972)	66,343 (28,591)	64,967 (29,285)
14.6 (10.2)	11.8 (9.1)	12.9 (8.9)	20.2 (10.4)	14.1 (10.1)	18.6 (10.9)	15.8 (10.6)	12.8 (10.6)
3	5	11	2	4	3	6	4
20	11	10	38	16	34	18	14
3479 (3217)	2561 (2585)	2151 (1979)	4780 (4272)	3701 (3369)	4542 (3039)	3953 (3095)	2438 (3175)
13	13	11	14	21	21	24	5
31	34	25	31	37	29	32	17
56	53	64	55	42	49	44	79

TABLE II. 2004 Cost category regression coefficient (–, SE) comparisons by demographic, insurance plan, RxRisk and asthma risk level determined in 2003 (final adjusted model*)

Comparisons or continuous variables	Total costs		Asthma drug costs		Asthma inpatient costs		Asthma ED costs		Nonasthma drug, inpatient, and ED costs		Residual costs	
	\$	P value	\$	P value	\$	P value	\$	P value	\$	P value	\$	P value
Age 12-17 vs 5-11 y	537	<.001	–10	.009	–391	.46	20	.03	818	<.001	93	<.001
Age 18-34 vs 5-11 y	1387	<.001	30	<.001	551	.32	8	.40	1571	<.001	275	<.001
Age 35-64 vs 5-11 y	2224	<.001	38	<.001	1484	.002	37	<.001	2367	<.001	445	<.001
Age 65+ vs 5-11 y	2468	<.001	26	.001	1362	.08	53	.002	2654	<.001	528	<.001
Female vs male	138	<.001	–29	<.001	37	.89	9	.10	52	.01	94	<.001
Education level	9	<.001	1	<.001	20	.23	1	.08	8	<.001	1	.02
Household income	2	<.001	0	.24	–2	.73	0	.50	2	<.001	1	<.001
Years as member	12	<.001	1	<.001	–28	.04	0	.76	10	<.001	3	<.001
Non-Medicaid vs Medicaid	14	.89	–4	.72	–1934	.20	28	.23	134	.17	–13	.60
Non-Medicare vs Medicare	22	.92	–7	.80	442	.81	18	.81	106	.63	82	.18
Nonprivate pay vs private pay	28	.54	30	<.001	324	.66	–18	.24	89	.05	–5	.69
RxRisk score	253	<.001	5	<.001	93	.04	3	.004	224	<.001	41	<.001
Medium vs low asthma risk level	187	<.001	44	<.001	97	.78	–10	.21	21	.47	75	<.001
High vs low asthma risk level	236	<.001	60	<.001	621	.07	20	.007	–128	.006	5	.68

*Multivariate analysis log-cost model adjusted for asthma risk level, drug group, age, sex, geocode household income and education level, insurance types, 18 comorbidities and RxRisk score, and propensity scores that predict probabilities of drug treatment.

advocate treatment with higher ICS doses or additional controllers for patients with greater severity and poorer control. The potential confounding effects of smoking could not be adjusted because our databases do not capture smoking history. Moreover, the current design captured costs and utilization a year after ascertainment of drug ITT groups to avoid confounding by indication that occurs when treatment, costs, and utilization are determined in the same year. We purposely excluded patients with a diagnosis of COPD but cannot completely rule out the inclusion of patients with asthma in this cohort with coexisting but undiagnosed COPD. Given that 95% of the potential patients with asthma identified had drug coverage, our findings strong support the generalizability of the findings to patients with asthma in MCOs.

The 14 asthma treatment groups were prespecified before the multivariate cost regressions, on the basis of review of drug use frequencies in the sample. The group sizes ranged from 303 to >32,000 per drug category. Even 303 is considered a relatively large sample size in the existing literature on asthma treatment costs. We did not adjust for multiple comparisons because epidemiologists and health services researchers have differences of opinion regarding the importance of adjusting for multiple comparisons in prespecified retrospective data analyses, relative to evaluation of prospective randomized controlled trials. Specifically, the editor of *Epidemiology* states that “A policy of not making adjustments for multiple comparisons is preferable because it will lead to fewer errors of interpretation when the data

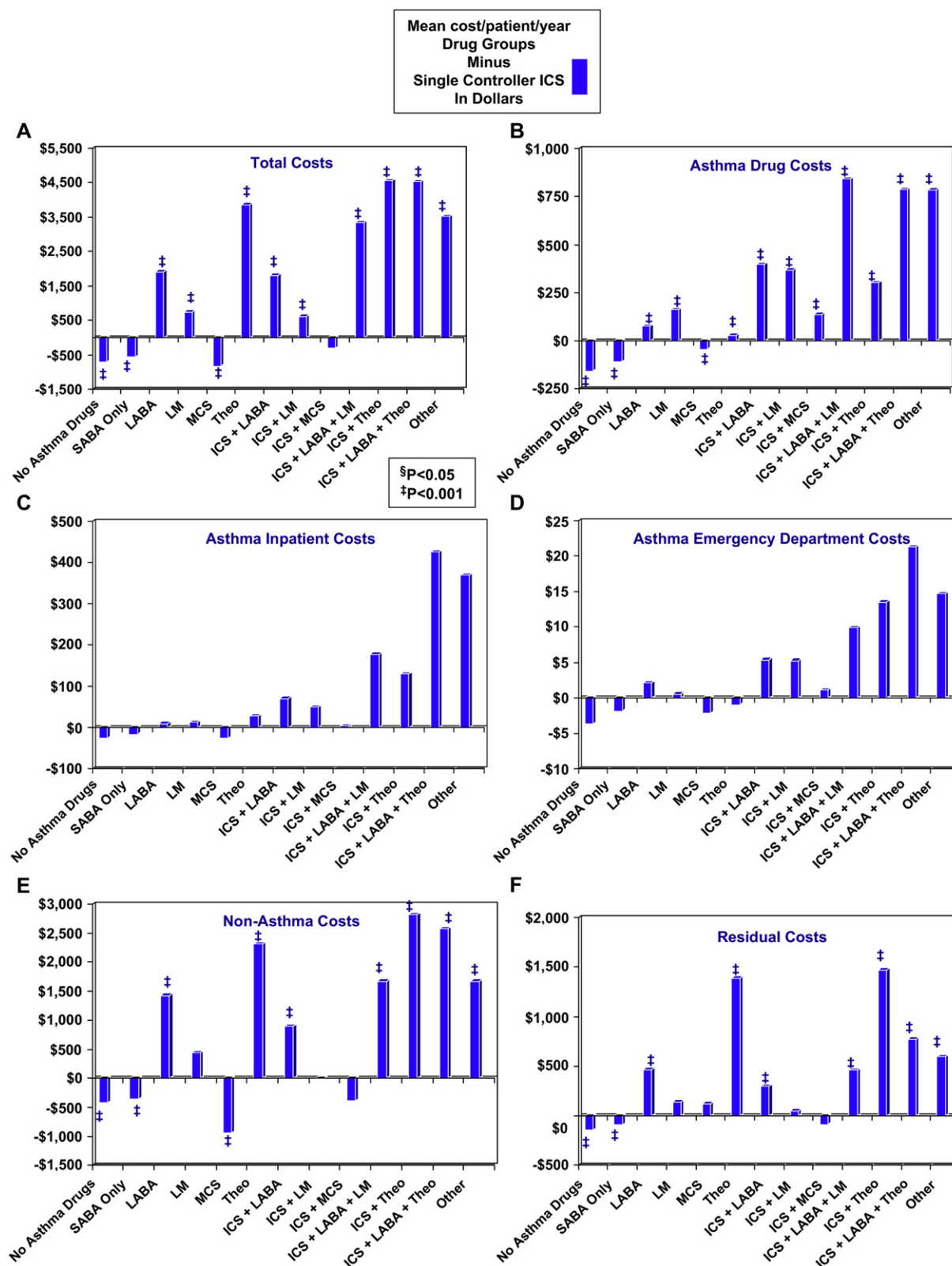


FIG 1. Differential cost (\$) comparisons of single controller ICS versus other drug groups (\$ other drug groups – \$ ICS) in 2004 in multivariate log-normal cost regressions and log-cost regressions in conjunction with smearing estimates for retransformation in final adjusted model (see Methods). *No drugs*, No asthma drugs dispensed; *Other*, other asthma drug combinations; *Theo*, theophylline.

TABLE III. Comparison of asthma utilization in 2004 between 2003 defined ITT single controller ICS and other drug groups (final adjusted model*)

Drug treatment vs single controller ICS	Any asthma inpatient visit			Any asthma ED visit			Any oral corticosteroid dispensing			Any asthma utilization event†		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
No asthma drugs dispensed	0.48	0.25-0.90	.02	0.45	0.34-0.60	<.001	0.61	0.53-0.69	<.001	0.61	0.54-0.70	<.001
SABA only	0.76	0.58-0.99	.04	0.84	0.74-0.94	.005	0.80	0.76-0.84	<.001	0.80	0.76-0.85	<.001
LABA	1.32	0.61-2.84	.48	0.89	0.56-1.40	.61	0.96	0.79-1.17	.67	0.97	0.80-1.17	.72
LM	1.37	0.67-2.80	.39	1.20	0.82-1.73	.35	1.17	0.99-1.39	.07	1.23	1.04-1.45	.02
MCS	0.43	0.06-3.24	.42	0.72	0.35-1.47	.36	0.92	0.69-1.23	.57	0.94	0.71-1.24	.64
Theophylline	1.48	0.68-3.20	.32	0.69	0.38-1.23	.21	0.71	0.56-0.90	.005	0.74	0.59-0.93	.01
ICS + LABA	1.78	1.42-1.23	<.001	1.33	1.17-1.51	<.001	1.38	1.29-1.47	<.001	1.39	1.31-1.45	<.001
ICS + LM	2.00	1.31-3.06	.001	1.34	1.04-1.74	.03	1.54	1.35-1.75	<.001	1.57	1.38-1.78	<.001
ICS + MCS	0.82	0.23-2.84	.75	0.83	0.45-1.54	.55	1.07	0.81-1.42	.63	0.97	0.74-1.29	.85
ICS + theophylline	1.93	1.21-3.09	.006	1.50	1.10-2.03	.01	1.14	0.96-1.35	.13	1.22	1.04-1.44	.02
ICS + LABA + LM	2.28	1.65-3.15	<.001	1.50	1.22-1.84	.001	1.81	1.62-2.02	<.001	1.81	1.62-2.03	<.001
ICS + LABA + theophylline	2.39	1.36-4.19	.002	1.33	0.89-2.02	.17	1.38	1.10-1.73	.005	1.41	1.13-1.76	.003
Other controller combinations	2.83	1.89-4.25	<.001	1.48	1.10-1.98	.009	1.61	1.37-1.91	<.001	1.57	1.33-1.85	<.001

OR, Odds ratio.

*Logistic multivariate analysis model adjusted for asthma risk level, drug group, age, sex, geocode household income and education level, insurance types, 18 comorbidities and RxRisk score, and propensity scores that predict probabilities of drug treatment.

†Any utilization refers to at least 1 asthma related-hospitalization or ED visit and/or oral corticosteroid dispensing.

under evaluation are not random numbers but actual observations on nature.”²⁴

We did test the robustness of our model specification by comparing the results of regression models with costs, log-costs, and log-costs with retransformation corrections. We ran sequential stepwise regression models with treatment groups + demographics + comorbidities + asthma risk groups + propensity scores to determine the additional explanatory value of each set of potential confounding factors. After adjustment for treatment groups, demographics, and comorbidities, the addition of asthma risk groups and propensity scores did not have a substantial effect on cost differences by treatment group.

Prospective, particularly randomized, cost analysis studies would be more definitive, but such studies are challenged by their own limitations, including smaller cohorts that decrease generalizability,²⁵ fewer drug group comparisons, and increased cost and study duration. However, our findings are supported by many meta-analyses of clinical trials,^{26,27} but not all^{28,29}; and by some³⁰⁻³² but not all³³ recent individual multicenter randomized clinical trials; and by some³⁴⁻³⁶ but not all³⁷⁻³⁹ cost analyses associated with these trials.

Objective measures, such as spirometry, to confirm the diagnosis of asthma are rarely captured in electronic databases and therefore are not commonly available for such studies.⁴⁰ Nonetheless, the criteria used to define asthma in this study, physician-diagnosed asthma recorded as ICD-9 coding for asthma and pharmacy dispensing of asthma drugs, are a valid way to identify patients with asthma in epidemiologic studies in this MCO and elsewhere.^{2,12}

In summary, within the limitations inherent in retrospective administrative economic analyses, direct total costs and asthma-related utilizations are significantly and meaningfully less in the year after being dispensed single controller ICS compared with single controller LM or combination asthma controllers except ICS and MCS, supportive of national and international guidelines (<http://www.ginasthma.com>) that recommend ICS as the preferred single asthma controller treatment. In addition, efforts

should be made to assess periodically the continued need for combination controllers to optimize asthma care and potentially reduce medical costs.

Clinical implications: These findings support national guidelines that recommend single controller ICS as the preferred single asthma controller treatment.

REFERENCES

- Weiss KB, Sullivan SD. The health economics of asthma and rhinitis, I: assessing the economic impact. *J Allergy Clin Immunol* 2001;107:3-8.
- Wang SW, Liu X, Wiener DJ, Sennett C, Bowers BW, Legorreta AP. Comparison of prevalence, cost, and outcomes of a combination of salmeterol and fluticasone therapy to common asthma treatments. *Am J Manag Care* 2001;7:913-22.
- Schatz M, Zeiger RS, Vollmer WM, Mosen D, Apter AJ, Stibolt TB, et al. Development and validation of a medication intensity scale derived from computerized pharmacy data that predicts emergency hospital utilization for persistent asthma. *Am J Manag Care* 2006;12:478-84.
- Schatz M, Nakahiro R, Jones CH, Roth RM, Joshua A, Petitti D. Asthma population management: development and validation of a practical 3-level risk stratification scheme. *Am J Manag Care* 2004;10:25-32.
- Meenan RT, Goodman MJ, Fishman PA, Hornbrook MC, O'Keeffe-Rosetti MC, Bachman DJ. Using risk-adjustment models to identify high-cost risks. *Med Care* 2003;41:1301-12.
- Fishman PA, Goodman MJ, Hornbrook MC, Meenan RT, Bachman DJ, O'Keeffe-Rosetti MC. Risk adjustment using automated ambulatory pharmacy data: the RxRisk model. *Med Care* 2003;41:84-99.
- Foster EM. Propensity score matching: an illustrative analysis of dose response. *Med Care* 2003;41:1183-92.
- Hay JW. Evaluation and review of pharmacoeconomic models. *Exp Opin Pharmacother* 2004;5:1867-80.
- Duan N. Smearing estimate: a nonparametric retransformation method. *J Am Stat Assoc* 1983;78:605-10.
- Schatz M, Zeiger RS, Vollmer WM, Mosen D, Cook EF. Determinants of future long-term asthma control. *J Allergy Clin Immunol* 2006;118:1048-53.
- Halpern MT, Khan ZM, Stanford RH, Spayde KM, Golubiewski M. Asthma: resource use and costs for inhaled corticosteroid vs leukotriene modifier treatment—a meta-analysis. *J Fam Pract* 2003;52:382-9.
- Orsini L, Limpa-Amara S, Crown WH, Stanford RH, Kamal K. Asthma hospitalization risk and costs for patients treated with fluticasone propionate vs montelukast. *Ann Allergy Asthma Immunol* 2004;92:523-9.

13. O'Connor RD, Parasuraman B, Roberts C, Leibman C. Inhaled corticosteroids vs leukotriene receptor antagonists: health care costs across varying asthma severities. *Ann Allergy Asthma Immunol* 2006;97:236-43.
14. Friedman HS, Yawn BP. Resource utilization in asthma: combined fluticasone propionate/salmeterol compared with inhaled corticosteroids. *Curr Med Res Opin* 2007;23:427-34.
15. Stempel DA, Kruzikas DT, Manjunath R. Comparative efficacy and cost of asthma care in children with asthma treated with fluticasone propionate and montelukast. *J Pediatr* 2007;150:162-7.
16. Pathak DS, Davis EA, Stanford RH. Economic impact of asthma therapy with fluticasone propionate, montelukast, or zafirlukast in a managed care population. *Pharmacotherapy* 2002;22:166-74.
17. Allen-Ramey FC, Duong PT, Goodman DC, Sajjan SG, Nelsen LM, Santanello NC, et al. Treatment effectiveness of inhaled corticosteroids and leukotriene modifiers for patients with asthma: an analysis from managed care data. *Allergy Asthma Proc* 2003;24:43-51.
18. Allen-Ramey FC, Anstatt DT, Sajjan SG, Markson LE. Asthma-related health care resource use among patients starting fluticasone or montelukast therapy. *Pharmacotherapy* 2005;25:1752-60.
19. Allen-Ramey FC, Markson LE, Riedel AA, Sajjan S, Weiss KB. Patterns of asthma-related health care resource use in children treated with montelukast or fluticasone. *Curr Med Res Opin* 2006;22:1453-61.
20. Allen-Ramey FC, Bukstein D, Luskin A, Sajjan SG, Markson LE. Administrative claims analysis of asthma-related health care utilization for patients who received inhaled corticosteroids with either montelukast or salmeterol as combination therapy. *J Manag Care Pharm* 2006;12:310-21.
21. Balkrishnan R, Nelsen LM, Kulkarni AS, Pleasants RA, Whitmire JT, Schechter MS. Outcomes associated with initiation of different controller therapies in a Medicaid asthmatic population: a retrospective data analysis. *J Asthma* 2005;42:35-40.
22. Bukstein DA, Henk HJ, Luskin AT. A comparison of asthma-related expenditures for patients started on montelukast versus fluticasone propionate as monotherapy. *Clin Ther* 2001;23:1589-600.
23. Cisternas MG, Blanc PD, Yen IH, Katz PP, Earnest G, Eisner MD, et al. A comprehensive study of the direct and indirect costs of adult asthma. *J Allergy Clin Immunol* 2003;111:1212-8.
24. Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology* 1990;1:43-6.
25. Kennedy WA, Laurier C, Malo JL, Ghezzi H, L'archeveque J, Contandriopoulos AP. Does clinical trial subject selection restrict the ability to generalize use and cost of health services to "real life" subjects? *Int J Technol Assess Health Care* 2003;19:8-16.
26. Ducharme FM. Inhaled corticosteroids versus leukotriene antagonists as first-line therapy for asthma: a systematic review of current evidence. *Treat Respir Med* 2004;3:399-405.
27. Guevara JP, Ducharme FM, Keren R, Nihitanova S, Zorc J. Inhaled corticosteroids versus sodium cromoglycate in children and adults with asthma. *Cochrane Database Syst Rev* 2006;2:CD003558.
28. Ni CM, Greenstone IR, Danish A, Magdolinos H, Masse V, Zhang X, et al. Long-acting beta2-agonists versus placebo in addition to inhaled corticosteroids in children and adults with chronic asthma. *Cochrane Database Syst Rev* 2005;4:CD005535.
29. Masoli M, Weatherall M, Holt S, Beasley R. Moderate dose inhaled corticosteroids plus salmeterol versus higher doses of inhaled corticosteroids in symptomatic asthma. *Thorax* 2005;60:730-4.
30. Zeiger RS, Bird SR, Kaplan MS, Schatz M, Pearlman DS, Orav EJ, et al. Short-term and long-term asthma control in patients with mild persistent asthma receiving montelukast or fluticasone: a randomized controlled trial. *Am J Med* 2005;118:649-57.
31. Sorkness CA, Lemanske RF Jr, Mauger DT, Boehmer SJ, Chinchilli VM, Martinez FD, et al. Long-term comparison of 3 controller regimens for mild-moderate persistent childhood asthma: the Pediatric Asthma Controller Trial. *J Allergy Clin Immunol* 2007;119:64-72.
32. Ostrom NK, Decotiis BA, Lincourt WR, Edwards LD, Hanson KM, Carranza R Jr, et al. Comparative efficacy and safety of low-dose fluticasone propionate and montelukast in children with persistent asthma. *J Pediatr* 2005;147:213-20.
33. O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, Runnerstrom E, Sandstrom T, Svensson K, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. *Am J Respir Crit Care Med* 2001;164:1392-7.
34. Menendez R, Stanford RH, Edwards L, Kalberg C, Rickard K. Cost-efficacy analysis of fluticasone propionate versus zafirlukast in patients with persistent asthma. *Pharmacoeconomics* 2001;19:865-74.
35. Pieters WR, Wilson KK, Smith HC, Tamminga JJ, Sondhi S. Salmeterol/fluticasone propionate versus fluticasone propionate plus montelukast: a cost-effective comparison for asthma. *Treat Respir Med* 2005;4:129-38.
36. Sheth K, Borker R, Emmett A, Rickard K, Dorinsky P. Cost-effectiveness comparison of salmeterol/fluticasone propionate versus montelukast in the treatment of adults with persistent asthma. *Pharmacoeconomics* 2002;20:909-18.
37. Jonsson B, Berggren F, Svensson K, O'Byrne PM. An economic evaluation of combination treatment with budesonide and formoterol in patients with mild-to-moderate persistent asthma. *Respir Med* 2004;98:1146-54.
38. Akazawa M, Stempel DA. Single-inhaler combination therapy for asthma: a review of cost effectiveness. *Pharmacoeconomics* 2006;24:971-88.
39. Lyseng-Williamson KA, Plosker GL. Inhaled salmeterol/fluticasone propionate combination: a pharmacoeconomic review of its use in the management of asthma. *Pharmacoeconomics* 2003;21:951-89.
40. Macy E, Schatz M, Gibbons C, Zeiger R. The prevalence of reversible airflow obstruction and/or methacholine hyperactivity in random adult asthma patients identified by administrative data. *J Asthma* 2005;42:213-20.

TABLE E1. Categories of costs by utilization determined from administrative electronic databases in 2004

Inpatient costs	Outpatient costs	ED costs	Drug costs	Other costs
KP and contracting hospital inpatient based on DRG	KP outpatient physician fee	KP ED physician fee	KP outpatient drug cost	SNF per diem
Claims inpatient based on DRG	Claims outpatient physician fee	Claims ED physician fee		SNF professional visit
KP inpatient physician fee	KP outpatient procedure other than laboratory and radiology department services	KP ED procedure		Hospice per diem
Claims inpatient physician fee	Claims outpatient procedure including laboratory and radiology department services	Claims ED procedure		Hospice professional visit
KP inpatient procedure other than laboratory and radiology department services	KP outpatient laboratory services	ED laboratory services		Home health professional visit
Claims inpatient procedure other than laboratory and radiology department services	KP outpatient radiology department services	ED radiology department services		Durable medical equipment

Claims, Non-Kaiser Permanente services for emergencies and referrals; *DRG*, diagnosis-related group; *hospice*, services for near the end of life care; *KP*, Kaiser Permanente; *SNF*, skilled nursing facility.

TABLE E2. Comorbidity frequency (%) by drug group*

Comorbidities (ICD-9 codes)	No asthma drugs dispensed	SABA only	LABA	ICS	LM	THEO	MCS	ICS + LABA	ICS + LM	ICS + MCS	ICS + THEO	ICS + LABA + LM	ICS + LABA + THEO	Other combination controllers	Total
Infections (001-139)	16	19	15	18	18	14	19	16	20	22	16	18	14	19	17
Neoplasms (140-239)	8	7	14	9	10	15	5	12	8	5	15	12	16	13	9
Endocrine/immune (240-279)	21	20	36	25	22	39	8	30	22	14	39	32	37	34	23
Blood (280-289)	4	3	6	4	3	6	2	5	3	1	6	5	5	5	4
Mental (290-319)	17	18	23	19	20	19	12	22	19	16	21	23	19	23	18
Central nervous system (320-389)	38	39	47	43	45	48	39	45	45	42	49	47	52	51	41
Circulatory (390-459)	21	19	38	25	21	44	6	31	22	14	42	30	42	35	23
Respiratory (460-519)	41	62	71	78	72	55	63	85	89	84	78	93	85	87	63
Digestive (520-579)	16	16	24	19	21	21	11	24	17	10	27	28	25	26	18
Genitourinary (580-629)	19	17	28	19	20	29	9	24	19	13	27	25	21	27	19
Perinatal-pregnancy* (630-677 and 760-779)	1	1	1	0.9	0.7	0.5	0.8	1	1	0.7	0.3	0.9	0.7	0.5	1
Dermatological (680-709)	23	23	32	26	29	30	20	30	26	21	31	31	27	31	25
Muscle/bone/connective tissue (710-739)	28	26	43	30	31	42	16	38	27	24	41	40	42	38	30
Congenital problems (740-759)	2	2	1	1	2	0.7	3	2	2	2	1	3	2	2	2
Ill-defined (780-799)	34	35	49	41	41	43	26	48	41	32	49	53	47	53	38
Injury/poison (800-999)	24	25	26	25	26	23	23	26	29	23	24	28	22	27	25
Supplementary (V-codes V01-V85)	51	52	60	57	60	57	51	61	59	56	61	66	58	68	54
External injury/poison (E-codes E800-E999)	3	3	4	3	4	4	3	4	4	4	4	5	5	5	3

THEO, Theophylline.

Percentages >1 were rounded to single integers.

* $P < .001$ for any differences between drug groups and not differences between specific drug groups for each ICD-9 grouping.

TABLE E3. Mean costs (\$) by drug group and asthma risk level (unadjusted)

Cost	Asthma severity risk level	No asthma drugs dispensed	SABA only	LABA	ICS	LM	MCS	THEO	ICS + LABA	ICS + LM	ICS + MCS	ICS + THEO	ICS + LABA + LM	LABA + ICS + THEO	Other combined controllers	Total
Total		3129	3346	5465	3630	4635	2506	8711	5414	4478	2976	7722	6808	7924	7666	3745
	High	7579	5649	8161	5329	7628	1687	9344	7967	5350	3640	14018	8350	11305	10013	6797
	Medium	6489	4862	5349	3809	5244	5713	11,405	5588	4731	3373	7460	7159	8880	7651	4962
	Low	2925	2994	5310	3401	4276	1988	8014	4738	4112	2713	6237	5737	5900	6424	3298
Asthma drug		21	73	276	195	366	152	219	599	573	349	513	1033	980	1009	178
	High	42	145	329	304	445	252	371	692	588	395	726	1092	1113	1169	485
	Medium	35	127	311	234	446	262	323	618	592	358	581	1051	1036	1070	324
	Low	20	61	263	171	339	129	184	567	556	339	419	989	890	880	128
Asthma inpatient		9	21	44	36	63	8	78	118	88	39	182	226	473	434	41
	High	276	180	167	142	339	0	219	443	326	262	526	759	1541	1363	354
	Medium	21	46	68	40	91	58	78	97	72	0	238	75	396	150	59
	Low	7	10	29	24	38	0	68	56	42	18	62	96	60	144	18
Asthma ED		2	4	7	6	7	3	5	12	12	5	20	17	29	24	5
	High	27	27	33	24	36	17	27	43	42	22	52	56	96	70	36
	Medium	2	5	4	6	8	7	3	8	8	2	27	10	13	16	7
	Low	1	3	6	4	4	2	4	6	7	4	8	5	10	5	3
Nonasthma drug, inpatient, ED		2284	2308	3542	2453	3051	1078	5470	3388	2736	1648	4852	4118	4644	4515	2544
	High	6215	3912	5631	3650	5736	851	6034	5067	3220	1411	7902	4807	6651	5784	4425
	Medium	4817	3224	3567	2492	3346	1877	7426	3480	2924	2068	4818	4545	5170	4403	3253
	Low	2126	2088	3390	2323	2796	950	4958	2956	2502	1523	4080	3402	3467	3920	2277
Residual		814	940	1595	939	1149	1265	2939	1297	1071	934	2155	1414	1797	1683	977
	High	1019	1385	2000	1210	1072	568	2692	1722	1173	1549	4811	1641	1905	1627	1498
	Medium	1613	1460	1398	1036	1353	3509	3574	1384	1135	945	1797	1478	2265	2013	1320
	Low	770	832	1622	879	1098	907	2800	1152	1006	829	1667	1245	1473	1474	872

THEO, Theophylline. $P < .001$ for differences between drug groups and not differences between specific drug groups for all severity levels except for high-risk and nonasthma costs ($P = .03$). Validated criteria for asthma severity risk levels defined in Methods.

TABLE E4. Odds ratio (95% CI) for dichotomous or coefficient estimate (SE) for continuous comparisons of 2004 utilization by demographic, other characteristics, and asthma risk level determined in 2003 (final adjusted model*)

Demographics and risk levels	Any asthma inpatient visit		Any asthma ED visit		Any oral corticosteroid dispensing		Any asthma utilization event†	
	OR (95% CI) or coefficient estimate (SE)	P value	OR (95% CI) or coefficient estimate (SE)	P value	OR (95% CI) or coefficient estimate (SE)	P value	OR (95% CI) or coefficient estimate (SE)	P value
Age 12-17 vs 5-11 y	0.63 (0.45-0.88)	.007	1.00 (0.87-1.15)	.99	0.67 (0.62 -0.72)	<.001	0.69 (0.65-0.74)	<.001
Age 18-34 vs 5-11 y	0.53 (0.37-0.75)	<.001	1.06 (0.91-1.23)	.48	0.798 (0.74-0.86)	<.001	0.83 (0.77-0.89)	<.001
Age 35-64 vs 5-11 y	0.61 (0.45-0.82)	.001	0.66 (0.57-0.77)	<.001	0.994 (0.93-1.06)	.85	0.97 (0.91-1.04)	.40
Age 65+ vs 5-11 y	0.75 (0.47-1.20)	.23	0.57 (0.43-0.75)	<.001	0.894 (0.79 -1.01)	.08	0.87 (0.77-0.98)	.02
Female	1.36 (1.15-1.61)	<.001	1.09 (1.00-1.19)	.05	1.06 (1.01-1.10)	.006	1.05 (1.01-1.09)	.01
Education level	0.007 (0.005)	.22	0.003 (0.003)	.24	0.001 (0.001)	.73	0.001 (0.001)	.32
Household income	-8.6E-6 (1.7E-6)	<.001	-5.7E-6 (8.3E-7)	<.001	-8.7E-7 (3.5E-7)	.01	-1.0E-6 (3.5E-7)	.003
Years as member	-0.002 (0.004)	.62	-0.004 (0.002)	.12	-0.001 (0.001)	.25	-0.001 (0.001)	.53
Non-Medicaid vs Medicaid	1.08 (0.46-2.53)	.86	0.71 (0.50-1.01)	.06	0.96 (0.80-1.15)	.65	0.91 (0.76-1.09)	.32
Non-Medicare vs Medicare	1.56 (0.47-5.26)	.47	0.61 (0.21-1.78)	.36	1.01 (0.66-1.54)	.96	0.94 (0.62-1.42)	.77
Nonprivate vs private pay	1.14 (0.72-1.81)	.59	1.08 (0.86-1.36)	.49	1.10 (1.00-1.21)	.05	1.09 (0.99-1.20)	.06
RxRisk score	4.0E-5 (1.2E-5)	<.001	1.9E-5 (7.5E-6)	.01	2.6E-5 (3.7E-6)	<.001	2.6E-5 (3.6E-6)	<.001
Medium vs low asthma risk level	1.70 (1.37-2.12)	<.001	1.51 (1.34-1.69)	<.001	2.71 (2.58-2.85)	<.001	2.63 (2.51-2.77)	<.001
High vs low asthma risk level	5.37 (4.32-6.66)	<.001	4.91 (4.36-5.52)	<.001	3.22 (2.99-3.46)	<.001	3.47 (3.23-3.72)	<.001

OR, Odds ratio.

*Logistic multivariate analysis model adjusted for asthma risk level, drug group, age, sex, geocode household income and education level, insurance types, 18 comorbidities and RxRisk score, and propensity scores that predict probabilities of drug treatment.

†Any utilization refers to at least 1 asthma related-hospitalization or ED visit and/or oral corticosteroid dispensing. Values for income and RxRisk are measured in dollars; a coefficient of $\pm 4\text{E-}5$ means that \$1000 of additional income (or RxRisk) increases/decreases the annual odds of utilizing that service (inpatient, ED, rescue medications, and so forth) by 4% (or \$1 of additional income by 0.004%).

TABLE E5. Comparison of mean differential costs (\$) between single controller ICS and other drug groups (drug groups - ICS) (final adjusted model*)

Differential average costs (\$) (drug group - ICS)	No asthma drugs dispensed vs ICS	SABA only vs ICS	LABA vs ICS	LM vs ICS	MCS vs ICS	Theo vs ICS	ICS + LABA vs ICS	ICS + LM vs ICS	ICS + MCS vs ICS	ICS + LABA + LM vs ICS	ICS + Theo vs ICS	ICS + LABA + Theo vs ICS	Other combinations vs ICS
Total	-711	-549	1914	749	-825	3863	1811	618	-308	3346	4553	4525	3519
<i>P</i> value	<.001	<.001	<.001	.001	.008	<.001	<.001	.001	.22	<.001	<.001	<.001	<.001
Asthma drug	-156	-109	77	162	-43	30	398	369	138	841	303	785	784
<i>P</i> value	<.001	<.001	<.001	.001	<0.001	.004	<.001	<.001	<.001	<.001	<.001	<.001	<.001
Asthma inpatient	-26	-16	10	13	-25	28	71	50	5	177	131	425	369
<i>P</i> value	.95	.97	.99	.99	ND	.97	.88	.91	.99	.78	85	.88	.81
Asthma ED	-3.6	-1.8	2.2	0.6	-2.1	-0.9	5.4	5.3	1.2	9.9	13.5	21.3	14.7
<i>P</i> value	.73	.80	.97	.98	.88	.98	.57	.84	.97	.66	.68	.78	.53
Nonasthma inpatient, ED, drug	-418	-353	1425	444	-945	2311	898	-14	-386	1667	2820	2574	1666
<i>P</i> value	<.001	<.001	<.001	.06	<0.001	<.001	<.001	.93	.18	<.001	<.001	<.001	<.001
Residual	-147	-88	464	141	123	1389	299	48	-87	463	1470	774	595
<i>P</i> value	<.001	.001	<.001	.10	.60	<.001	<.001	.40	.28	<.001	.001	<.001	<.001

Theo, Theophylline.

*Multivariate analysis log-cost model adjusted for asthma risk level, drug group, age, sex, geocodes household income and education level, insurance types, 18 comorbidities and RxRisk score, and propensity scores that predict the probabilities of each drug treatment.