Economic burden of impairment in children with severe or difficult-to-treat asthma

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Background: The cost associated with asthma impairment in children with severe asthma has not been determined.

Objective: To assess the asthma cost burden in children with severe or difficult-to-treat asthma based on asthma impairment.

Methods: Children aged 6 to 12 years in The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens study with available data at baseline ($n = 628$), month 12 ($n = 385$), and month 24 ($n = 280$) corresponding to the National Heart, Lung, and Blood Institute asthma guidelines' impairment domain were included. Children were categorized as either very poorly controlled (VPC), not well controlled (NWC), or well controlled (WC) and assessed cross-sectionally and longitudinally. Mean total asthma costs based on direct (medication usage, unscheduled office visits, emergency department visits, hospitalizations) and indirect (school/work days lost) asthma costs were assessed.

Results: Mean annual total asthma costs were more than twice as high in the VPC group compared with NWC and WC groups (baseline: $7,846, $3,526, $3,766.44, respectively; month 12: $7,326, $2,959, $2,043, respectively; month 24: $8,879, $3,308, $1,861, respectively (all $P < .001$). Indirect costs accounted for approximately half the total asthma costs for VPC asthma patients at each time point. Significantly lower costs were observed for patients whose impairment status improved or temporarily improved from VPC after baseline.

Conclusion: The economic burden of severe or difficult-to-treat asthma in children is associated with VPC asthma and improvement in asthma control and is associated with reducing cost. Further attention to patients with poorly controlled asthma, through better management strategies or more effective medications, may significantly reduce this burden of illness.

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INTRODUCTION

Asthma, one of the most common chronic diseases, affects 20% of children worldwide.[1,2] Among children younger than 18 years of age in the United States, 13.0% have been diagnosed with asthma, and 8.9% (6.5 million) currently have asthma.[3] Recent analysis of data from the 2003/2004 National Survey of Children's Health demonstrated a significant relationship between severe asthma and lower health-related quality of life ($P = .005$).[4]

In 2007, the total incremental cost of asthma to society was $56 billion, with direct costs accounting for $50.1 billion, productivity losses attributable to morbidity accounting for $3.8 billion, and productivity losses attributable to mortality accounting for $2.1 billion.[5] More than 80% of healthcare resources are used by 20% of asthma patients,[6] likely reflecting a patient subgroup with severe or uncontrolled disease, because overall costs are related to severity[7] and uncontrolled disease.[8]

Studies of children with asthma indicate that high rates of medication use and healthcare utilization (HCU) are related to uncontrolled disease[9] and increased cost burden.[9-12] Although studies have assessed the costs associated with pediatric asthma as a whole,[13-15] none has focused on the costs of uncontrolled asthma or whether changes in control affect costs. The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) observational study assessed a large cohort of patients with severe or difficult-to-treat asthma and provided relevant data regarding this understudied population.[9,16,17] The current analysis assessed the burden in children aged 6 to 12 years in relation to

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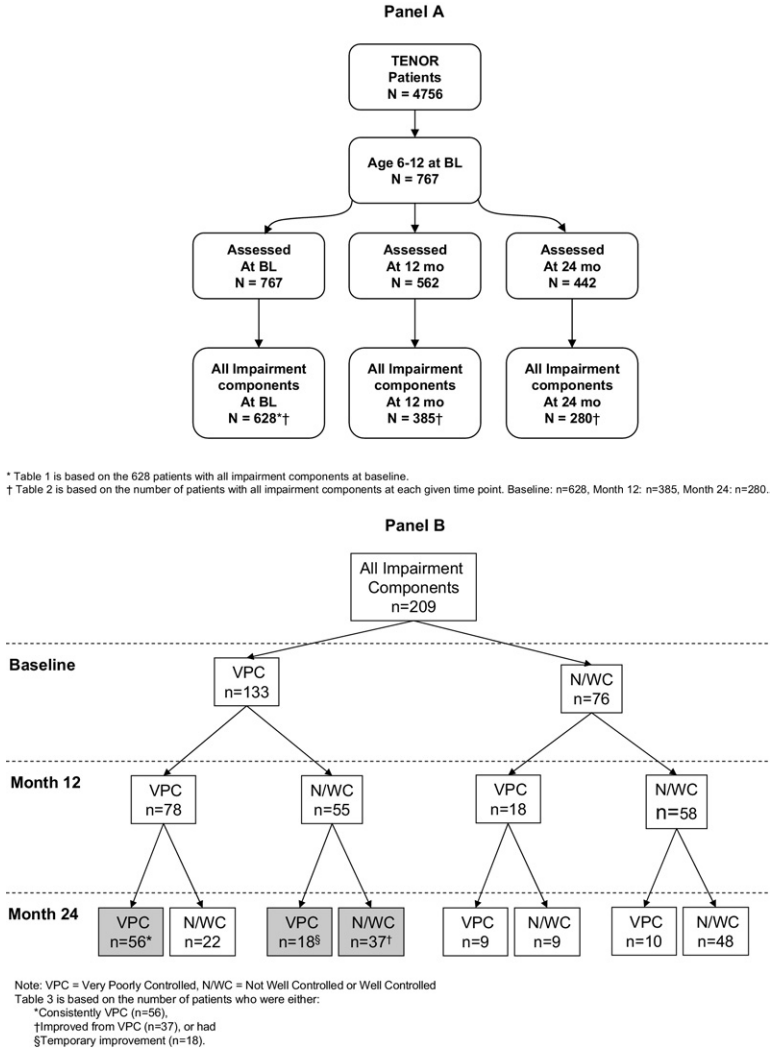


Figure 1. Flow diagram of analysis inclusion criteria for cross-sectional analysis (A) and longitudinal analysis (B). BL indicates baseline; N/WC, not well controlled or well controlled; TENOR, The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens; and VPC, very poorly controlled.

asthma control, as defined by the impairment domain of the National Heart, Lung, and Blood Institute (NHLBI) guidelines.[18] We hypothesized that costs increase with increasing impairment and that improvement in impairment status would be associated with reduced costs.

METHODS

TENOR Participants and Study Design

TENOR was a 3-year, observational, prospective study of patients from community and academic sites in the United States between 2001 and 2004. Full details of the study design are described elsewhere.[16] Briefly, TENOR patients were at least 6 years of age with severe asthma or with mild/moderate asthma considered difficult-to-treat. Patients had received care from their healthcare providers for at least 1 year and had either high use of the healthcare system (≥2 unscheduled asthma care visits or ≥2 oral steroid bursts) or high medication use (≥3 medications to control asthma or long-term, daily high doses [as defined by the American Thoracic Society] of inhaled steroids, or use of ≥5 mg/day of oral prednisone) in the past 12 months. The TENOR protocol and study design were reviewed and approved by a central institutional review board and by individual institutional review boards.

Analysis Inclusion/Exclusion Criteria

This analysis included children aged 6 to 12 years with data available to evaluate asthma control based on the impairment domain components of the 2007 NHLBI guidelines[18] at baseline ($n = 628$), month 12 ($n = 385$), and month 24 ($n = 280$).

Assessment of Asthma Impairment

Impairment metrics were obtained from data collected at baseline and annual visits. Symptoms, nighttime awakenings,

Table 1. Demographics and clinical variables of patients with all impairment domain components at baseline assessment by asthma control status ($N = 628$)

Characteristic	Very poorly controlled	Not well controlled	Well controlled	*P*
Total patients, n (%)	386 (61.5)	219 (34.9)	23 (3.7)	
Age: years at baseline, mean ± SD	9.5 ± 1.81	9.4 ± 1.90	9.0 ± 1.86	.41
Obesity[a], n (%)				
Not obese	289 (75.1)	192 (87.7)	20 (87.0)	<.001
Obese	96 (24.9)	27 (12.3)	3 (13.0)	
IgE IU/mL at baseline				
Geometric mean	227.0	140.6	154.4	.005
95% confidence levels for mean	191.49–269.21	110.76–178.44	67.74–351.83	
Sex, n (%)				
Female	125 (32.4)	81 (37.0)	6 (26.1)	.38
Male	261 (67.6)	138 (63.0)	17 (73.9)	
Race/ethnicity, n (%)				
White	207 (53.6)	150 (68.5)	20 (87.0)	<.001
Black	119 (30.8)	44 (20.1)	1 (4.3)	
Other	60 (15.5)	25 (11.4)	2 (8.7)	
Spirometry, mean ± SD				
Race-adjusted, prebronchodilator, % predicted FEV_1	85.3 ± 19.03	96.8 ± 14.46	104.6 ± 10.70	NA[d]
Prebronchodilator, actual FEV_1/FVC ratio	75.7 ± 11.17	84.7 ± 7.24	87.2 ± 4.43	NA[d]
Race-adjusted, prebronchodilator, % predicted FEF_{25-75}	64.3 ± 31.72	87.9 ± 25.06	114.3 ± 36.19	<.001
Steroid bursts[b], n (%)				
0	168 (43.5)	139 (63.5)	14 (60.9)	<.001
1	129 (33.4)	48 (21.9)	6 (26.1)	
2+	89 (23.1)	32 (14.6)	3 (13.0)	
Number of long-term controllers, n (%)				
0	1 (0.3)	1 (0.5)	0 (0.0)	.55
1	30 (7.8)	22 (10.0)	1 (4.3)	
2	113 (29.3)	74 (33.8)	10 (43.5)	
3+	242 (62.7)	122 (55.7)	12 (52.2)	
Medication adherence[c], n (%)				
I take it every day	234 (82.4)	128 (86.5)	15 (88.2)	.60
Some days I take it, but other days I don't	34 (12.0)	11 (7.4)	1 (5.9)	
I used to take it, but now I don't	10 (3.5)	4 (2.7)	0 (0.0)	
I only take it when I have symptoms	6 (2.1)	5 (3.4)	1 (5.9)	

Abbreviations: ED, emergency department; FEF_{25-75}, forced expiratory flow during the middle half of the forced vital capacity; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IgE, immunoglobulin E; NA, not applicable; SD, standard deviation.

[a] Obesity defined as body mass index for age (calculated using the Centers for Disease Control and Prevention growth charts[34]) in the 95th percentile or greater.

[b] During the 3 months before baseline.

[c] Medication adherence was measured using a proxy from the Asthma Therapy Assessment Questionnaire (ATAQ), "What best describes how you take this medicine now?"

[d] Definition of asthma control impairment domain involves an FEV_1 component; thus, assessing differences between categories is not meaningful.

and interference with normal activity were obtained from the Pediatric Asthma Quality of Life Questionnaire with Standardized Activities (PAQLQ[S]).[19] The PAQLQ(S), a validated questionnaire for asthma patients aged 7 to 17 years, was based on recall of the previous 1-week period. Although the age range for use of this instrument does not include 6-year-olds, the individual items provided requisite data for mapping responses to the guidelines for the current analysis of 6- to 12-year-olds (see eTable 1).[18] Lung function was measured using spirometry in accordance with American Thoracic Society guidelines.[20] Medication adherence was measured using a proxy from the Asthma Therapy Assessment Questionnaire (ATAQ),[21] "What best describes how you take this medicine now?"

At baseline and 12- and 24-month follow-up, patients were grouped by asthma impairment status into 1 of 3 categories defined by the impairment domain of the NHLBI guidelines[18]: very poorly controlled (VPC), not well controlled (NWC), and well controlled (WC) (Fig 1A). In addition to this cross-sectional analysis, we compared cumulative costs for patients who were consistently VPC at baseline, 12 months, and 24 months (VPC-VPC-VPC) with costs for patients who improved and remained improved (Fig 1B). Four improvement categories were defined by improvement from baseline to 12 and 24 months and were compared with the consistently VPC group: improvement to NWC at 12 months and remaining NWC at 24 months (VPC-NWC-NWC); improvement to

Table 2. Mean annual number of healthcare utilization visits and costs by cross-sectional asthma control status[a]

	Baseline				Month 12
	Very poorly controlled (n = 386)	Not well controlled (n = 219)	Well controlled (n = 23)	P[b]	Very poorly controlled (n = 179)
Direct asthma costs					
Physician visits					
n	386	219	23		179
Mean (SD)	12.1 ± 14.1	9.4 ± 10.6	10.4 ± 8.4	.042	8.8 ± 7.1
Subcost($)	934.97	725.04	807.44		681.29
95% CI subcost($)	825, 1,047	630, 835	560, 1083		606, 763
Hospital nights					
n	386	219	23		179
Mean (SD)	1.8 ± 6.2	0.4 ± 2.4	1.0 ± 5.0	.006	1.2 ± 3.3
Subcost($)	1,341.45	322.42	767.49		871.11
95% CI subcost($)	917, 1,811	119, 577	0, 2522		523, 1238
ED Visits					
n	386	219	23		179
Mean (SD)	2.0 ± 5.1	0.9 ± 2.7	0.5 ± 1.8	.005	1.2 ± 2.2
Subcost($)	586.89	255.94	152.31		339.23
95% CI subcost($)[c]	452, 747	164, 365	0, 389		255, 441
Mean drug cost[d]	2,119.57	1,948.53	1,860.71	<.001	2310.33
95% CI subcost($)	2,062, 2,177	1,878, 2,015	1,681, 2,041		2,225, 2,405
Mean direct cost[e]	4,982.88	3,235.93	3,587.95	<.001	4,201.95
95% CI subcost($)	4,429, 5,559	2,943, 3,629	2,454, 5,676		3,754, 4,695
Indirect asthma costs					
School/work days lost					
n	320	179	20		152
Mean (SD)	17.9 ± 45.4	2.1 ± 11.0	0.0 ± 0.0	<.001	18.1 ± 43.7
Subcost($)	3,077.79	369.32	0.00		3,118.15
95% CI subcost($)	2,250, 3,996	140, 680	0, 0		1,958, 4,463
Mean indirect cost	3,077.79	369.32	0.00		3,118.15
95% CI subcost($)	2,250, 3,996	140, 680	0, 0		1,958, 4,463
Mean total asthma cost[f]	7,846.03	3,526.38	3,766.44	<.001	7,326.07
95% CI cost($)	6,809, 9,005	3,105, 4,012	2,453, 6,025		5,958, 8,841

Abbreviations: SD, standard deviation; CI, confidence interval; ED, emergency department.

[a] Table 2 is based on the number of patients with all impairment components at each given time point. Baseline: n = 628, Month 12: n = 385, Month 24: n = 280 (See Fig 1A); Burden and associated costs were calculated per year for each measure.

[b] Significance was assessed by analysis of variance.

[d] Drug costs included inhaled corticosteroids, oral/systemic corticosteroids, short- and long-acting beta agonists, methylxanthines, cromolyns, and leukotriene modifiers.

[f] Mean total cost includes variables relating to indirect costs (school days lost), and direct costs (healthcare utilization and medication use). Mean costs of the two components do not sum to the total because it is only for patients with both components.

[c] Confidence intervals are based on 1,000 bootstrap samples.

[e] Direct costs include costs from healthcare utilization and medication use.

NWC at 12 months and WC at 24 months (VPC-NWC-WC); improvement to WC at 12 months, but reverting to NWC at 24 months (VPC-WC-NWC); and improvement to WC at 12 months and remaining WC at 24 months (VPC-WC-WC). We also examined patients who demonstrated temporary improvement to NWC or WC at 12 months, but reverted back to VPC at 24 months (VPC-NWC-VPC) and (VPC-WC-VPC) (Fig 1B). The results for this group should be interpreted with caution because of the small sample size (n = 18).

Primary Outcomes and Assessment of Cost

The primary outcome was mean annual total asthma costs for the various asthma control groups, which was based on direct asthma costs (asthma-related medications, unscheduled physician visits, hospitalizations, and emergency department [ED] visits) and indirect asthma costs (school/work days lost). Use of asthma-related medications was captured on the assessment date. School/work days lost because of asthma were measured by recall for the previous 7 days using an asthma-specific adaptation of the Work Productivity and Activity Impairment instrument,[22] a self-reporting tool validated for measuring asthma-related work or classroom productivity impairment. Asthma-related hospitalizations, ED visits, and unscheduled physician visits were self-reported for the 3-month period before the assessment date. One-year cost was assessed using data collected at an annual and a previous semi-annual visit.

Table 2. (*Continued*) Mean annual number of healthcare utilization visits and costs by cross-sectional asthma control status[a]

	Month 12			Month 24			
	Not well controlled (n = 172)	Well controlled (n = 34)	P[b]	Very poorly controlled (n = 120)	Not well controlled (n = 134)	Well controlled (n = 26)	P[b]
Direct asthma costs							
Physician visits							
n	172	34		120	134	26	
Subcost($)	5.8 ± 7.9	3.2 ± 2.8	<.001	8.0 ± 8.5	5.0 ± 5.5	3.4 ± 4.0	<.001
Mean (SD)	445.38	250.35		619.04	385.75	261.90	
95% CI subcost($)	362, 547	183, 331		504, 740	318, 458	149, 386	
Hospital nights							
n	172	34		120	134	26	
Mean (SD)	0.2 ± 2.1	0.0 ± 0.0	<.001	1.8 ± 6.0	0.4 ± 1.9	0.0 ± 0.0	.013
Subcost($)	119.73	0.00		1,348.44	307.38	0.00	
95% CI subcost($)	0, 399	0, 0		601, 2,266	97, 593	0, 0	
ED Visits							
n	172	34		120	134	26	
Mean (SD)	0.4 ± 1.6	0.1 ± 0.3	<.001	1.1 ± 2.5	0.5 ± 1.3	0.1 ± 0.4	.003
Subcost($)	128.99	17.17		330.85	130.71	22.46	
95% CI subcost($)[c]	69, 210	0, 57		213, 468	75, 208	0, 76	
Mean drug cost[d]	1,984.58	1,640.03	<.001	2,298.19	1,994.55	1,605.16	<.001
95% CI subcost($)	1,893, 2,060	1,452, 1,832		2,174, 2,416	1,882, 2,097	1,355, 1,859	
Mean direct cost[e]	2,681.84	1,907.55	<.001	4,596.52	2,815.27	1,889.52	<.001
95% CI subcost($)	2,388, 3,122	1,696, 2,105		3,691, 5,629	2,491, 3,168	1,607, 2,186	
Indirect asthma costs							
School/work days lost							
n	154	27		104	122	24	
Mean (SD)	1.4 ± 8.0	1.0 ± 5.0	<.001	24.8 ± 59.8	2.8 ± 15.5	0.0 ± 0.0	<.001
Subcost($)	247.38	166.00		4,277.18	477.58	0.00	
95% CI subcost($)	49, 504	0, 560		2,445, 6,434	72, 1,014	0, 0	
Mean indirect cost	247.38	166.00		4,277.18	477.58	0.00	
95% CI subcost($)	49, 504	0, 560		2,445, 6,434	72, 1,014	0, 0	
Mean total asthma cost[f]	2,959.78	2,043.60	<.001	8,879.73	3,308.40	1,861.22	<.001
95% CI cost($)	2,560, 3,486	1,713, 2,480		6,623, 11,370	2,764, 3,949	1,571, 2,149	

Cost of school absences was estimated by applying sex-specific dollar amounts for one parent's lost days of work.[23] Costs were inflated and adjusted to 2002 dollars to match other considered costs, using data from the Bureau of Labor Statistics Inflation Calculator,[24] and were determined as follows: (1) Cost of a lost day of work for a male adult: $208.94; (2) Cost of a lost day of work for a female adult: $125.37; (3) Blended cost for male or female: $172.38. For this analysis, the number of school days missed in the past week was extrapolated to calculate the number of school days missed in a year. This result was then multiplied by the inflation-adjusted blended cost to obtain the cost for the number of school days lost per patient for the year.

Average transaction prices for resource use were derived from an administrative claims database (PharMetrics Integrated Outcomes Database, 2002) containing patient-level reimbursement claims for more than 22 million managed-care patients in the United States during a 4-year period. Medication cost estimates were based on US average wholesale prices minus 15% to approximate actual acquisition costs. Total medication cost estimates were calculated using average recommended daily dose by medication (standard dose per day) and were not adjusted to account for patient compliance. All costs were adjusted to 2002 dollars.[24]

Statistical Methods

Demographic and clinical characteristics were stratified by 3 groups of asthma impairment (VPC, NWC, and WC) and evaluated by descriptive statistics. P values comparing differences among these groups were computed using χ^2 tests for categorical variables and analysis of variance for continuous variables. Costs were summarized by outcome at each timepoint by asthma control category. The n, mean, and standard deviation were reported for each HCU outcome and converted into costs. Costs were added to mean drug costs to compute the mean total cost estimates, and 95% confidence intervals (CIs) were computed based on 1,000 bootstrap samples. Because of the skewed distribution of costs, bootstrap CIs are preferred and were computed instead of parametric CIs.[25]

Patients were excluded from the cross-sectional analyses if the assessment did not occur or if a component of impairment was missing; patients missing asthma impairment data at any time were excluded from the longitudinal analysis (see On-

line Repository for additional information regarding patients excluded from the analysis and lost to follow-up). Patients excluded from the analysis were not appreciably different from those included, but were slightly older (10.0 ± 1.9 years vs 9.4 ± 1.8 years; $P = .0005$) and heavier (43.8 ± 17.2 kg vs 40.6 ± 16.5 kg; $P = .0415$).

RESULTS

Patient Characteristics

Baseline demographics and clinical characteristics for 628 eligible children are presented in Table 1. Based on NHLBI criteria, most children (61.5%) were VPC, fewer were NWC (34.9%), and very few (3.7%) were WC. Children in the VPC group were more likely to be obese ($P < .001$) than children in the NWC and WC groups. Children in the VPC group also had higher immunoglobulin E (IgE) levels ($P = .005$), were more likely to be of nonwhite race/ethnicity ($P < .001$), to have greater pulmonary obstruction (FEF_{25-75}; $P < .001$), and to have had 2 or more steroid bursts in the 3 months before baseline ($P < .001$) than children in the NWC and WC groups. Patient age, sex, long-term controller use, and medication adherence were similar among the 3 groups.

Association of Asthma Impairment Status with Burden

Baseline assessments indicated that the mean number of HCU visits was significantly greater for the VPC group than for the NWC and WC groups ($P < .05$; Table 2). The largest differences were seen in the mean number of school/work days lost across asthma control groups, with the VPC group demonstrating substantially higher mean number of days lost compared with the NWC and WC groups (17.9 ± 45.4 vs. 2.1 ± 11.0 vs. 0.0 ± 0.0, respectively; $P < .001$). These differences persisted at month 12 and month 24.

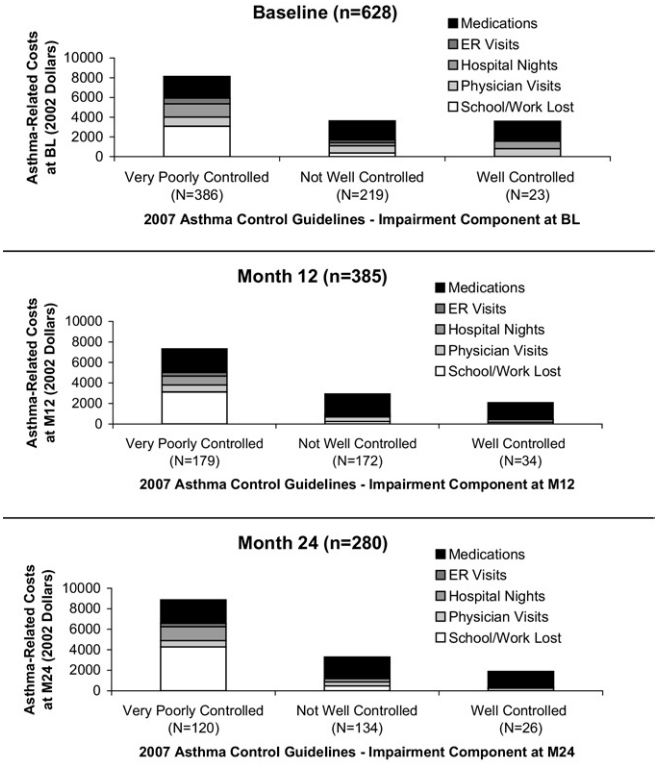
In general, the number of HCU visits was fewer at each timepoint for the 3 asthma control groups, reflecting a trend toward regression to the mean, likely attributable to the prospective, observational nature of TENOR's study design.

Direct Asthma Costs

Greater impairment was associated with greater cost burden. Increased annual HCU visits in the VPC group reflected a higher overall mean annual direct cost in this group compared with the NWC and WC groups (VPC: $4,983, $4,202, $4,597; NWC: $3,236, $2,682, $2,815; WC: $3,588, $1,908, $1,890; all $P < .001$) (Table 2, Fig 2). Mean drug costs consumed the highest portion of the direct costs, with the VPC group incurring the greatest cost: ($2,120, $2,310, and $2,298 at baseline, month 12, and month 24, respectively; $P < .001$), followed by the NWC group ($1,949, $1,985, and $1,995, respectively; $P < .001$), and the WC group ($1,861, $1,640, and $1,605, respectively; $P < .001$).

Indirect Asthma Costs

At baseline, month 12, and month 24, the VPC group exhibited an over 8-fold increase in costs attributable to school/work days lost compared with NWC patients (VPC: $3,078, $3,118, and $4,277; $P < .001$; NWC: $369, $247, $478, respectively $P < .001$) (Table 2, Fig 2). Patients with WC asthma exhibited no or negligible costs because of school/work days lost.



Note: Exact cost values are listed in Table 2.

Figure 2. Burden of cost in relation to asthma control status. BL indicates baseline; ER, emergency room; M12, month 12; M24, month 24; and VPC, very poorly controlled.

Total Asthma Costs

Mean annual total asthma costs were more than twice as high in the VPC group compared with NWC and WC groups (baseline: $7,846, $3,526, $3,766, respectively ($P < .001$); month 12: $7,326, $2,960, $2,044, respectively ($P < .001$); month 24: $8,880, $3,308, $1,861, respectively, ($P < .001$) (Table 2, Fig 2). Indirect costs accounted for almost half the total costs at baseline and month 12 for VPC asthma patients and more than half the total costs at month 24.

Change in Cost Associated with Change in Impairment Status

At each timepoint, significantly lower direct and indirect asthma costs were observed for patients whose impairment status improved from VPC after baseline and those patients who demonstrated temporary improvement in their asthma control compared with patients who remained consistently VPC (Table 3). Significant differences in total mean asthma costs per year were marginally higher between patients whose asthma control improved temporarily and those whose asthma control improved from VPC and remained improved over the course of the study. Patients

Table 3. Mean annual number of healthcare utilization visits and costs by longitudinal asthma control status[a]

	Baseline				Month 12
	Consistently very poorly controlled [a] (*n* = 56)	**Temporary improvement [b] (*n* = 18)**	**Improved from very poorly controlled [c] (*n* = 37)**	***P*[b] [a] vs. [b] [a] vs. [c] [b] vs. [c]**	**Consistently very poorly controlled [a] (*n* = 56)**
Direct asthma costs					
Physician visits					
n	56	18	37		56
Mean (SD)	13.4 ± 10.6	8.7 ± 10.1	8.4 ± 6.3	.10, .012, .92	9.9 ± 7.1
Subcost($)	1033.58	670.63	652.50		768.27
95% CI subcost($)	845, 1,233	376, 1063	497, 815		626, 900
Hospital nights					
n	56	18	37		56
Mean (SD)	2.6 ± 8.1	1.3 ± 4.1	0.0 ± 0.0	.51, .050, .052	1.1 ± 3.0
Subcost($)	1,943.85	980.68	0.00		814.31
95% CI subcost($)	623, 3,637	0, 2522	0, 0		305, 1430
ED visits					
n	56	18	37		56
Mean (SD)	2.4 ± 3.6	0.9 ± 2.2	0.4 ± 1.6	.088, .002, .38	1.2 ± 1.8
Subcost($)	708.97	259.49	126.24		354.49
95% CI subcost($)	467, 982	0, 556	0, 292		226, 494
Mean drug cost[c]	2,474.70	2,145.79	2,088.59	<.001, <.001, .63	2,509.31
95% CI cost($)	2,326, 2,626	1,962, 2,306	1,905, 2,259		2,347, 2,680
Mean direct cost[d]	6,161.10	4,056.59	2,867.33	.11, <.001, .27	4,446.38
95% CI subcost($)	4,689, 8,081	2,580, 6,228	2,535, 3,192		3,817, 5,211
Indirect asthma costs					
School days lost					
n	44	17	32		47
Mean (SD)	16.4 ± 44.0	0.0 ± 0.0	26.8 ± 50.2	.13, .34, .033	13.6 ± 43.3
Subcost($)	2,826.64	0.00	4,621.94		2,336.30
95% CI subcost($)[e]	879, 5,466	0, 0	1,635, 7,794		647, 4,818
Mean indirect cost	2,826.64	0.00	4,621.94		2,336.30
95% CI subcost($)	879, 5,466	0, 0	1,635, 7,794		647, 4,818
Mean total asthma cost[f]	8,963.77	4,138.05	7,534.49	.012, 0.48, .082	6,977.91
95% CI cost($)	6,310, 12,111	2,577, 6,446	4,508, 10,853		5,055, 9,514

Abbreviations: SD, standard deviation; CI, confidence interval; ED, emergency department.

[a] Table 3 is based on the number of patients who were either: Consistently VPC (*n* = 56), Improved from VPC (*n* = 37), or had Temporary improvement (*n* = 18); Burden and associated costs were calculated per year for each measure.

[b] Significance was assessed by Student's *t*-test for each pairwise comparison of units. Significance of costs assessed by computing one-tailed *P*-values based on the proportion of bootstrap samples with positive differences and multiplying by 2 to obtain a two-tailed *P*-value.

[c] Drug costs included inhaled corticosteroids, oral/systemic corticosteroids, short- and long-acting beta agonists, methylxanthines, cromolyns, and leukotriene modifiers.

[f] Mean total cost includes variables relating to indirect costs (productivity loss), and direct costs (healthcare utilization and medication use). Mean costs of the 2 components do not sum to the total because it is only for patients with both components.

[e] Confidence intervals are based on 1,000 bootstrap samples.

[d] Direct costs include costs from healthcare utilization and medication use.

who remained consistently VPC exhibited the highest total mean annual asthma costs compared with those whose asthma control improved temporarily and those whose asthma control improved and remained improved from VPC. Total mean asthma costs appeared to increase over time for patients who were consistently VPC and to decrease for patients who remained improved during the course of the study.

The difference in total asthma costs was primarily attributable to the difference in school/work days lost between the consistently VPC and improved from VPC groups.

Table 3. (Continued) Mean annual number of healthcare utilization visits and costs by longitudinal asthma control status[a]

	Month 12			Month 24			
	Temporary improvement [b] (n = 18)	Improved from very poorly controlled [c] (n = 37)	P[b] [a] vs. [b] [a] vs. [c] [b] vs. [c]	Consistently very poorly controlled [a] (n = 56)	Temporary improvement [b] (n = 18)	Improved from very poorly controlled [c] (n = 37)	P[b] [a] vs. [b] [a] vs. [c] [b] vs. [c]
Direct asthma costs							
Physician visits							
n	18	37		56	18	37	
Mean (SD)	4.7 ± 3.9	4.4 ± 2.9	.004, <.001, .80	8.4 ± 6.9	5.6 ± 8.5	4.8 ± 4.0	.15, .005, .64
Subcost($)	361.11	342.98		652.20	429.89	368.08	
95% CI subcost($)	232, 500	270, 416		511, 793	190, 810	264, 472	
Hospital nights							
n	18	37		56	18	37	
Mean (SD)	0.0 ± 0.0	0.0 ± 0.0	.12, .025, —	3.3 ± 8.3	0.0 ± 0.0	0.3 ± 1.4	.10, .036, .32
Subcost($)	0.00	0.00		2,390.41	0.00	238.54	
95% CI subcost($)	0, 0	0, 0		989, 4,047	0, 0	0, 592	
ED visits							
n	18	37		56	18	37	
Subcost($)	0.1 ± 0.5	0.2 ± 0.6	.013, .002, .53	1.5 ± 2.7	0.3 ± 0.8	0.5 ± 1.1	.079, .035, .60
Mean (SD)	32.44	63.12		437.90	97.31	142.02	
95% CI subcost($)	0, 103	15, 131		245, 643	0, 209	51, 251	
Mean drug cost[c]	2,013.18	1,996.75	<.001, .002, .91	2,450.32	2,146.81	1,909.15	.098, <.001, .25
95% CI cost($)	1,821, 2,209	1,780, 2,187		2,288, 2,625	1,816, 2,447	1,702, 2,106	
Mean direct cost[d]	2,406.72	2,402.85	<.001, <.001, .98	5,930.83	2,674.01	2,657.79	<.001, <.001, .91
95% CI subcost($)	2,130, 2,701	2,154, 2,649		4,269, 7,852	2,237, 3,110	2,198, 3,177	
Indirect asthma costs							
School days lost							
n	17	34		46	18	35	
Mean (SD)	0.0 ± 0.0	3.8 ± 12.9	.20, .21, .23	20.2 ± 52.0	20.2 ± 47.7	0.0 ± 0.0	.99, .024, .014
Subcost($)	0.00	659.10		3,483.20	3,485.91	0.00	
95% CI subcost($)[e]	0, 0	0, 1,547		1,131, 6,187	0, 7,712	0, 0	
Mean indirect cost	0.00	659.10		3,483.20	3,485.91	0.00	
95% CI subcost($)	0, 0	0, 1547		1,131, 6,187	0, 7,712	0, 0	
Mean total asthma cost[f]	2,333.04	3,034.50	<.001, <.001, .12	9,399.39	6,159.91	2,640.95	.27, <.001, .082
95% CI cost($)	2,079, 2,618	2,239, 4,104		6,046, 13,237	2,441, 10,684	2,164, 3,197	

DISCUSSION

This is the first analysis to assess the economic burden of asthma, as defined by the impairment domain of the NHLBI guidelines,[18] in children with severe or difficult-to-treat asthma. We observed that greater impairment was associated with greater total cost burden. Mean annual total asthma costs were more than twice as high in the VPC group compared with the NWC and WC groups, with indirect costs accounting for approximately half the total costs for VPC asthma patients. Patients with VPC asthma had a higher mean annual number of HCU visits compared with NWC and WC groups, reflecting a 2 to 3 times higher overall mean annual direct asthma cost in this group. Mean drug costs consumed approximately half the direct costs. At all timepoints, the VPC group exhibited a more than 8-fold increase in costs because of school/work days lost compared with NWC patients. When examined longitudinally, patients who remained consistently VPC exhibited the highest total mean annual asthma costs compared with those whose asthma control improved temporarily and those whose asthma control improved and remained improved from VPC.

Importantly, we found that indirect costs accounted for almost half the total costs at baseline and month 12 for the VPC asthma patients, and more than half the total costs at month 24. Although direct costs are most closely scrutinized by third-party payers, indirect costs should not be overlooked, because they appear to be a significant portion of the economic burden of asthma, particularly VPC asthma, in the pediatric population. In addition, our measure of indirect costs was based on the number of school/work days lost, reemphasizing the impact of loss of daily activity on the healthcare system and missed educational opportunities for

the pediatric population. A recent analysis of Missouri students ($N = 3,812$; aged 8–17 years) demonstrated a strong inverse relationship between absenteeism and performance ($P < .001$) on the Missouri Assessment Program (MAP) test.[26] Children absent for a mean of 7 days of the 176-day school year achieved a Missouri Assessment Program test level of "proficient"; those absent for a mean of 12 days achieved a level of "below progressing."

Mean total annual costs for patients whose impairment status improved or temporarily improved after baseline were significantly lower compared with patients whose condition remained very poorly controlled during the study period. Although some of these differences were apparent at baseline, indicating an association and not necessarily a cause-and-effect relationship, the data suggest that even an improvement from VPC to NWC could result in a reduction of associated costs. In fact, the disparity in total costs became more evident longitudinally in patients who sustained their asthma control status, that is, total mean asthma costs appeared to increase over time for patients who remained consistently VPC and to decrease for patients who remained improved during the course of the study, demonstrating a long-term reduction in cost burden in patients who maintain improvement in their asthma control.

Medication costs accounted for nearly half of direct asthma costs. Indeed, approximately half to two-thirds of pediatric patients in TENOR were using 3 or more long-term controller medications. Despite the use of multiple medications in this severe or difficult-to-treat asthma population, patients continue to experience a high level of morbidity.[9] These findings could mean that physicians treat patients with higher morbidity with increased numbers of controller medications; however, they also suggest that the prescribed medications do not prevent morbidity adequately. Nonadherence with increased numbers of prescribed medications cannot be excluded, however. Although we attempted to capture medication compliance in this analysis, no direct measure was made of medication adherence in TENOR. Thus, we relied on a proxy from the self-reported ATAQ, which indicated that medication adherence was high in children and adolescents. Still, in children, low adherence often has been noted in self-reported assessments and in assessments submitted by their parents.[27-29] We recommend close monitoring of the 6- to 12-year age group in their asthma management program to reinforce adherence to medication. Assessments should include pulmonary function tests and asthma questionnaires (eg, the Asthma Control Test)[30] and should be performed frequently. Recently, 85% of children who actively participated in a comprehensive structured program of regular asthma care achieved asthma control within 6 visits.[31]

Overall, total asthma costs in children are higher than those in adults. Although the findings in the current analysis are not directly comparable to those in adults with severe or difficult-to-treat asthma (different impairment criteria were used),[8] our data suggest that improvement of asthma control may have greater impact on total cost reduction in children than in adults. In the adult analysis, mean total costs were consistently approximately 2-fold greater for the VPC than for the WC impairment group at baseline ($5,964 vs $2,422), 12 months ($4,530 vs $2,410), and 24 months ($4,046 vs $2,194). In contrast, the total costs in our pediatric analysis were also approximately 2-fold greater for the VPC than for the WC impairment group at baseline ($7,846 vs $3,766), but this difference increased to 4- and 5-fold at 12 and 24 months, respectively ($7,326 vs $2,044 and $8,880 vs $1,861).

Although the sample size and breadth of variables in TENOR provided a unique, real-world opportunity to analyze an array of clinical and patient-reported outcomes within the context of the NHLBI guidelines, our evaluation of economic burden has inherent limitations. Lost school/work time was noted to be a large component of cost in our study. Because of the challenges in "fixing" a cost for a child not attending school (including missed education) for 1 day, this measure should be interpreted with caution. Namely, one could argue that parents of these children may not be working or may continue to go to work even if the child misses school. In addition, the reported number of school days lost reflected only the 7-day period immediately preceding each annual visit. Because we did not have complete information on parent occupation and missed work because of sick children, further study is warranted. Other limitations include the relatively small sample size of the asthma control groups for the longitudinal analysis, particularly patients who temporarily improved, the inability to directly measure or adjust for medication compliance, possibly inflating the reported cost of medications, and the introduction of recall bias with self-report of HCU data.

An objective of TENOR has been to understand the unmet needs of patients with severe or difficult-to-treat asthma. To this end, data from pediatric asthma patients in TENOR have revealed high rates of HCU and loss of lung function despite treatment with long-term controllers,[9] and have demonstrated that consistently poorly controlled asthma, as defined by the impairment domain of the 2007 NHLBI asthma guidelines, is a robust predictor of future severe exacerbations in this age group.[32] Furthermore, consistently VPC children are less likely to have private insurance, more likely to be treated by a pulmonologist, more likely to have a history of atopic dermatitis, and tend to take more long-term controller medications than patients improved from VPC.[33] The current analysis provides further insight into this underserved population of children and highlights the burden of cost associated with inadequate asthma control.

In summary, our report indicates a direct association of increased asthma impairment with increased total cost and asthma burden in children with severe or difficult-to-treat asthma. Also, improvement in asthma control and associated reduced impairment results in lower total costs. Cost of parent productivity loss attributable to school/work days lost and medication use are the largest contributors to this cost burden. These findings emphasize the importance of identifying and monitoring children with VPC asthma, vis-a-vis the

increased likelihood for obesity, high IgE, and poorer lung function in this group, to reduce impairment and, ultimately, total costs of care. Attention to better management strategies including careful monitoring of control and adherence, as well as the identification of new medications are needed to reduce asthma burden in this population of children.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.anai.2011.04.008.

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eTable 1. National Heart, Lung, and Blood Institute (NHLBI) impairment assessment of asthma control in patients 5 to 11 years of age[a]

Assessment of impairment	Classification of asthma control (Children 5–11 years)			TENOR assessment (patients 6–12 years)
	Well controlled	Not well controlled	Very poorly controlled	
Symptoms	≤2 d/wk but not more than once daily	>2 d/wk or multiple times on ≤2 d/wk	Throughout the day	
Nighttime awakenings	≤1 time/mo	≥2 time/mo	≥2 time/wk	PAQLQ(S)[b]
Interference with normal activity	None	Some limitation	Extremely limited	
Short-acting β_2-agonist use for symptom control	≤2 d/wk	>2 d/wk	Several times daily	Medication use
FEV_1 or peak flow	>80% predicted/personal best	60%–80% Predicted/personal best	<60% Predicted/personal best <75%	Spirometry
FEV_1/FVC	>80%	75%–80%	<75%	

FEV_1 indicates forced expiratory volume in 1 second; FVC, forced vital capacity; PAQLQ(S), Pediatric Asthma Quality-of-Life Questionnaire with Standardized Activities.

[a] National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Full Report 2007.* Publication 97-4051. Bethesda, MD: National Institutes of Health; 2007.

[b] For this study, items numbered 4, 10, 12, 14, 18, and 23 from the patient-reported Pediatric Asthma Quality of Life Questionnaire [PAQLQ(S)] were used to determine the Symptom component of the impairment domain of the 2007 NHLBI guidelines definition of asthma control in children aged 6-12 years. Similarly, items numbered 16 and 20 were used to determine the Nighttime Awakenings component, and items 1, 3, 13, 19, and 22 were used to determine the Normal Activities Interference component. Patients responded to questions such as "In general, how often during the last week did you feel out of breath because of your asthma?" or "How bothered have you been during the last week by wheezing?" on a 7-point ordinal scale with 1 corresponding to either "All of the time" or "Extremely bothered" and 7 corresponding to either "None of the time" or "Not bothered." A symptom component score of 1 or 2 ("Extremely or very bothered" and "All or most of the time") was used to approximate the very poorly controlled category ("Throughout the day"); 3 ("Quite bothered" and "Quite often") the not well controlled category ("Greater than 2 days per week"); 4, 5, 6, or 7 ("Somewhat, A bit, Hardly at all, or Not bothered" and "Some, Once in a while, Hardly any, or None of the time") the well controlled category ("Less than or equal to 2 days per week"). A nighttime awakening component score of 1 or 2 ("Extremely or Very bothered" and "All or Most of the time") was used to approximate the very poorly controlled category ("Greater than or equal to 2 times per week"); 3 or 4 ("Quite or Somewhat bothered" and "Quite often or Some of the time") the not well controlled category ("Greater than or equal to 2 times per month"); 5, 6, or 7 ("A bit, Hardly at all, or Not bothered" and "Once in a while, Hardly any, or None of the time") the well controlled category ("Less than or equal to 1 time per month"). A normal activity interference component score of 1 or 2 ("Extremely or Very bothered" and "All or Most of the time") was used to approximate the very poorly controlled category ("Extremely limited"); 3, 4, 5, or 6 ("Quite, Somewhat, A Bit, or Hardly bothered" and "Quite often, Some of the time, Once in a while, or Hardly any of the time") the not well controlled category ("Some limitation"); 7 ("Not bothered" and "None of the time") the well controlled category ("No limitation"). For each of these components, as well as for the short acting beta agonist use and lung function components, patients were assigned to 1 of the 3 asthma control categories. Overall level of asthma control for each patient was assigned based on the most severe impairment category.

eMethods

Patients were excluded from the cross-sectional analyses only if the assessment did not occur (12 months, $n = 205$; 24 months, $n = 325$) or if a component of impairment was missing at the assessment (baseline, $n = 139$; month 12, $n = 180$; month 24, $n = 162$). Patients were excluded from the longitudinal analysis if they were not in the consistently very poorly controlled group or the improved from very poorly controlled group. In addition, patients who were missing the outcome variable of interest for a time point were excluded from that calculation.

Of the children in the very poorly controlled group at baseline ($n = 386$), 282 (73.4%) and 228 (59.4%) remained in the study at 12 and 24 months, respectively; of the children in the not well controlled group at baseline ($n = 219$), 167 (76.3%), and 131 (59.8%) remained at 12 and 24 months, respectively; and of the children in the well controlled group at baseline ($n = 23$), 17 (73.9%) and 13 (56.5%) remained at 12 and 24 months, respectively.

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