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The Direct Expenditures and Indirect Costs Associated with Treating Asthma in the United States

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Introduction

Asthma is one of the most commonly diagnosed chronic conditions in the U.S. The National Centers for Health Statistics (NCHS) estimated that asthma prevalence was 8.2 percent (24.6 million) of the U.S. population in 2009, of which 7.7 percent were adults and 9.6 percent were children. Within population subgroups it was higher among females, children, persons of non-Hispanic black and Puerto Rican race or ethnicity, persons with family income below the poverty level, and those residing in the Northeast and Midwest Regions. In 2008, persons with asthma missed 14.2 million work days due to their asthma. In 2007, there were 1.75 million asthma-related emergency department visits and 456,000 asthma hospitalizations. Asthma emergency visit and hospitalization rates were higher among females than males, among children than adults, and among black than white persons [1].

The current cost-of living literature gives a wide range of estimates for the direct medical costs of asthma ranging from $3.6 billion to $30.8 billion [2-7] and indirect costs ranging from $673 million to $8.2 billion [3,7,8]. Some studies have reported only direct medical care expenditures thereby underestimating the economic impact of asthma in U.S [6,9,10]. Others have recognized the importance of incorporating the indirect cost burden of asthma with direct cost estimates to gain an accurate and complete view of the societal impact of the disease [3,5,11-15]. This observed inconsistency across the cost-of-illness studies might be due to variation in the methods used in the calculation of costs.

Cost of Illness Methodology

There are two methods to perform cost of illness (COI) studies. Those are incidence- and prevalence-based approaches. The incidence-based approach captures lifetime costs of a disease [16]. The prevalence based approach captures costs in a given year [17]. COI measures the economic burden of disease and gives estimates at the national level. It translates burden of disease into dollar amounts and has been used by policy makers in decision making and to estimate the magnitude effect of disease on society [16]. COI assists policy makers by providing important information to prioritize the diseases that need to be addressed. The different ways of conducting COI depend on perspective, source of data, and inclusion of indirect costs [17].

Historically, COI was based on one of two types of costs, total cost or incremental cost. Total costs provide estimates of the total healthcare expenditure of patients diagnosed with a disease. Incremental cost includes healthcare expenditures solely attributable to the disease. The Sum All Medical and Sum Diagnostic methods are used for the total cost approach. These methods add all costs of the patients diagnosed with disease irrespective of whether or not the costs directly related to disease. The Sum Diagnosis method, adds up the expenditures directly related to the primary diagnosis of the disease.

The Matched Control and Regression are the methods used for the incremental approach. Only the incremental approach uses a control group without disease [18]. The Matched Control method calculates the average sum of all medical costs among patients with the disease and subtracts the average sum of all medical costs among similar patients without the disease. The matched control method isolates disease-specific costs by subtracting the costs of control group from the case group, using a matching algorithm to adjust for confounders. In observational studies, the ”treatment”groups (or ”exposure” groups) often exhibit imbalance on covariates.

This covariate imbalance is confounded with treatments: It is difficult to attribute differences in responses to the ”treatment” or ”exposure” because the covariates are also believed to influence the response. In research studies, a researcher gets two opportunities to control the covariates. One is at the design level, and other is at the data analysis stage.

According to Trojano et al. “To deal with confounding and to improve validity, several methodological improvements (regression adjustment, stratification and matching) have been suggested in the absence of randomization” [19]. At the design level, matching techniques allow one to match individual cases with disease of interest with individual controls without disease of interest that have similar confounding factors in order to reduce the effect of these on the association being investigated in analytical studies. It is commonly seen in case-control studies and when there are only limited numbers of cases and a much larger number of controls. The propensity score matching is an example of such a technique which attempts to reduce the confounding effects of covariates, and so allow differences of responses to be attributed to differences of treatments (exposures).

However, matching methods of adjustment are often limited since they can only use a small number of covariates for adjustment or if there is extreme imbalance in the background characteristics. At the data analysis stage, a regression method can be used to determine COI estimates from the estimated coefficients of relevant variables, while also controlling for covariate confounding. The regression method is prone to bias, however, if the properties of the underlying cost distribution are not considered properly, because often the cost data are highly skewed. In addition there is much discussion in the literature about the challenges and limitations of cost estimation techniques such as ordinary least square (OLS) regression technique

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with log-transformation and two-part modeling [15,20]. The indirect modeling, log-transformation and retransformation of cost variables poses a threat of under- or over-estimation of the predicted costs, even after factoring in Duan smearing estimators. The Generalized Linear Model (GLM) method is efficient in modeling cost data with the appropriate choice of the variance function. The Park test can be used as a diagnostic test to examine the model fit. This diagnostic test reveals which is the most appropriate model specification within Generalized Linear Models with different variance function: Poisson, negative binomial, or gamma variance functions [15,21-23].

The proper matching algorithm used incrementally in combination with a regression method maybe a way to assuage both the problems of cost distribution and control of confounding variables, thereby capturing costs solely attributable to the disease of interest. This suggests that a combined incremental method may be the best approach to performing COI studies. This hybrid methodology has been used in health economics and epidemiological studies [24-26]. Those studies initially used a matched cohort technique, propensity score matching, to select the control patients from the pool of the patients without the disease of interest. Then, they tested all the covariates differences. When too many covariates were not controlled by propensity matching they used generalized linear modeling to estimate health care costs.

Limited research exists, however, on a combined incremental approach to COI for asthma in the United States [7]. Most incremental studies used either the matched control or a regression approach [4,6,12]. The purpose of this study was to use a combined covariate controlled incremental approach to determine the direct expenditures and indirect costs of asthma and to determine the influence of age, gender, race, ethnicity, poverty level, insurance, educational level, and comorbidity on these direct expenditures and indirect costs in the United States in 2007.

Methods

A retrospective two group case control design was used to measure the cost of illness (COI) for asthma in the U.S. from 2007 MEPS data and to determine the effects of demographic and comorbidity variables on COI for asthma. COI for asthma was defined as the combination of direct expenditures and indirect costs. Direct expenditures included outpatient, inpatient, office-based visits, emergency room, prescription, home healthcare, and other medical expenditures. Indirect costs were based upon productivity lost by the individual who is ill (missed work days) or family member who cares for the individual (bed days). Demographic and comorbidity variables were age, gender, race, region, area (MSA), income, insurance, education, and Charlson-comorbidity index score (CCI). Figure 1 shows data extraction methods used and how covariates were controlled. The same asthma and non-asthma cohorts were used to determine both direct expenditures and indirect costs.

Data source

This study used the 2007 Medical Expenditure Panel Survey (MEPS), a national probability sample survey whose main objective is to provide nationally representative estimates of healthcare use, expenditures, sources of payments, and prevalence rates of disease for the non-institutionalized US population [27]. The 2007 MEPS dataset contains variables and frequency distributions for 30,964 respondents. MEPS data provide four advantages. First, it captures all the medical

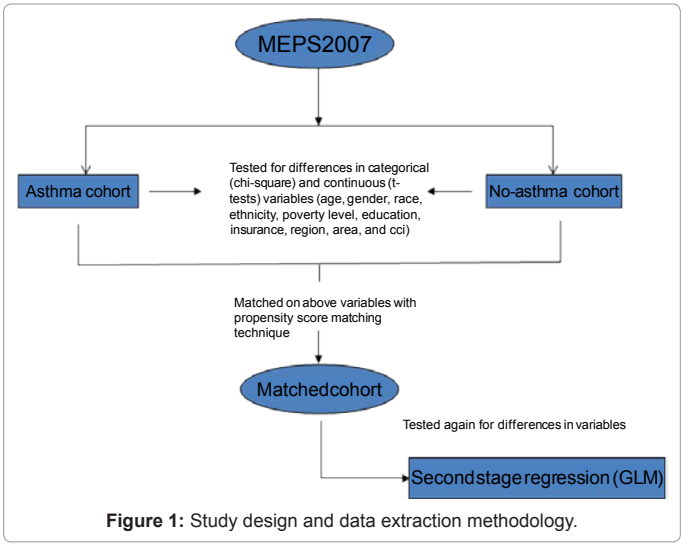

Figure 1: Study design and data extraction methodology.

events a respondent had, including inpatient, outpatient, emergency room, office-based provider, and prescription drug use. Second, a medical event is linked to the primary condition for which the medical care was sought. Third, costs incurred by society were derivable from all payers covered in the MEPS. Finally, its complex sampling design makes it possible to extrapolate the estimates and results to a U.S. civilian non-institutionalized population by applying appropriate person-level weights to individuals in the dataset.

The MEPS survey comprised of three survey components: The Household Component (HC), The Medical Provider Component (MPC), and The Insurance Component (IC). The HC collects nationally representative data on demographic characteristics, health conditions, health status, use of medical care services, charges and payments, access to care, satisfaction with care, health insurance coverage, income, and employment. The MPC collects data from a sample of providers (physicians, hospitals, home health agencies, and pharmacies) who provided medical care to MEPS Household Component respondents. The MPC data are dates of visits/services, use of medical care services, charges and sources of payments and amounts, and diagnoses and procedure codes for medical visits/encounters. The IC collects data on health insurance plans.

A computer-assisted personal interview (CAPI) is used in the MEPS to obtain data from the survey respondents. In this process, a respondent sits in front of a computer and answers all of the questions that appear on a computer monitor. This method is considered to be a personal interview technique because the interviewer guides the process throughout. CAPI technology is also used to obtain the information from medical providers to validate the respondent's responses. With the patient's consent, samples of providers are contacted for additional information.

The full year consolidated file states that "a sample representing about three-eighths of the National Health Interview Survey (NHIS) responding households is made available for use in the MEPS. A subsample of these households is then drawn for MEPS interviewing." The overall response rate in 2007 MEPS was 56.9%.

The Agency for Healthcare Research and Quality (AHRQ) validates MEPS as a self-reported instrument by administering many quality

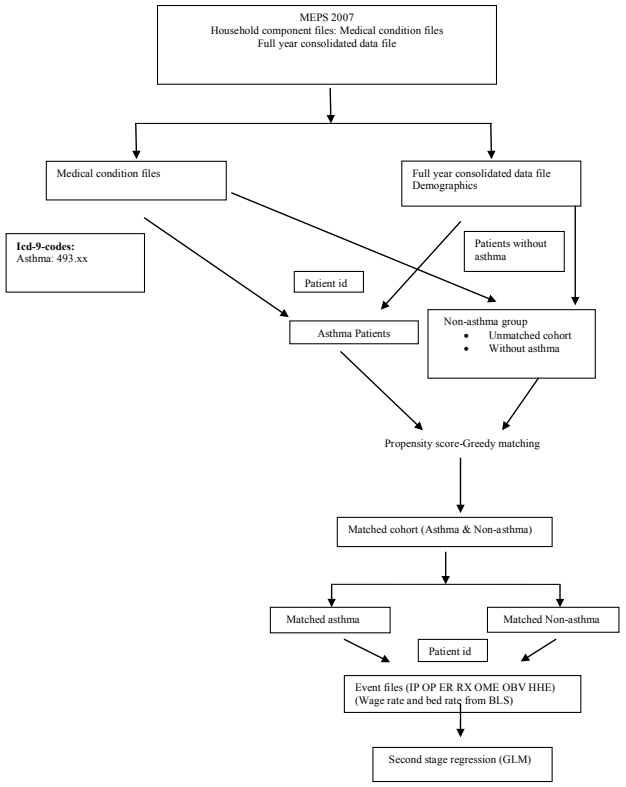

Figure 2: Data extraction flowchart for direct cost (indirect cost) of asthma.

assurance procedures like validation of interviewer's work and also comparing MEPS numbers with other data sources numbers like the Census Bureau and NHIS. Data collection is designed in such a way that interview frequency validates the responses.

Inclusion/Exclusion criteria

MEPS 2007 and Bureau of Labor Statistic (wage rate file for absenteeism) data were used to achieve study objectives. A flowchart describing the data extraction process used to compute direct and indirect COI estimates associated with asthma in the U.S. in 2007 is shown in Figure 2. SAS® transport format was used to download the data from the AHRQ website. The downloaded files were uncompressed with unzip software. Data files were converted into SAS® data sets using suitable SAS® codes provided in the MEPS.

A full year consolidated file contains one record for each patient who participated in the survey. This file contains patient's demographic characteristics, insurance, employment status, quality of life variables. Each patient in the data set has a unique identification number. All utilization and expenditure files also contained a unique patient identification number. All data sets, except the full year consolidated file, had multiple records per patient. Patients who did not use any health care resources do not appear in the data sets except in full year consolidated file. If the patient uses a particular service multiple times, however, that patient record appears the same number of times in the data set. Asthma patients were identified from the medical data file and the full year consolidated file using ICD-9-CM code 493.xx, and files were linked using a unique patient identification number. ICD-9-CM codes 493.xx include extrinsic asthma (unspecified, with status asthmaticus, or with acute exacerbation), intrinsic asthma (unspecified, with status asthmaticus, or with acute exacerbation), chronic obstructive asthma (unspecified, with status asthmaticus, or with acute exacerbation), exercise-induced bronchospasm, cough variant asthma, and asthma (unspecified, unspecified with status asthmaticus, or unspecified with acute exacerbation). The remaining patients in the dataset were classified as non-asthma (control) patients. Self-reporting asthma respondents in the 2007 full year consolidated file were also included in the study. Patients were divided into an asthma cohort and a non-asthma cohort based on the above criteria. Patients who did not complete the entire condition survey were excluded from the study. The two cohorts were tested for the differences in categorical (gender, race, ethnicity, region, area, poverty level, insurance, education) and continuous variables (age, comorbidity). The cohorts were then matched for further analysis.

Independent and dependent (outcome) variables, and covariates

The main independent variable was asthma and its referent no asthma as defined above. The dependent variables measuring direct COI expenditures for the analysis included Inpatient visits (IP), Prescription medications (RX), Outpatient visits (OP), Emergency room visits (ER), Office based visits (OBV), Home health visits (HHE), and Other medical (OME) expenditures as defined in The MEPS database. The dependent variables used to calculate indirect COI cost for the analysis included Missed work days (number of days of missed work reported during the year), Bed days (number of days reported being in bed for the year), Wage rate (hourly wages paid to an employee according to the Bureau of Labor Statistics), and Value of a bed day (the dollar amount assigned to the bed per day by the Bureau of Labor Statistics). Covariates in the analyses included respondent's age, gender, race, ethnicity, education status, income (poverty level), insurance status, Metropolitan Statistical Area, and geographic region as defined in the MEPS database.

The D'Hoore et al. adaptation of the Charlson comorbidity index was added [28]. It is defined as the score assigned to each patient based on the sum of weights of comorbidities. This version of the Charlson was used because it uses three-digit ICD code system, the way medical conditions were reported in the MEPS data. The 17 comorbidities considered (with weights) are myocardial infarction (1), congestive heart failure (1), peripheral vascular disease (1), dementia (1), cerebrovascular disease (1), chronic pulmonary disease (1), connective tissue disease (1), ulcer disease (1), mild liver disease (1), diabetes (1), hemiplegia (2), moderate or severe renal disease (2), any tumor (2), leukemia (2), lymphoma (2), moderate or severe liver disease (3), and metastatic tumor (6).

Data extraction

Figure 2 is a flowchart that describes the data extraction process. Propensity score matching is a matched control method used to estimate treatment effects when treatment assignment is not random, but can be assumed to be unconfounded. It is accomplished by selecting the first treated subject and finding the non-treated subject (control) with the closest propensity score. Propensity scores are widely used in pharmacoepidemiological and health-economic analyses, particularly to test drug effects in many therapeutic areas. The propensity score method uses logistic regression which estimates each patient's likelihood of being in the asthma group. For this study, a matched

control cohort was generated from the donor pool of non-asthma patients. Patients with no asthma were matched by a propensity score algorithm to patients in the asthma group using a 1:1 greedy matching technique. It was accomplished by selecting the first treated subject and finding the non-treated subject (control) with the closest propensity score. Both subjects were then removed from consideration for matching and the next treated subject was selected. The patients from both cohorts who were not matched were removed. For this propensity score algorithm, the dependent variable used was dichotomous (asthma=1, no asthma=0) and independent variables were age, gender, race, region, area (MSA), income, insurance, education, and Charlson-comorbidity index score (CCI).

A second-stage regression, Generalized Linear Model (GLM) method, was chosen to model the cost data and to assess the incremental expenditures associated with asthma while controlling for any remaining differences between the cohorts after matching. In this model, the dependent variables were total direct expenditures and total indirect costs, respectively, while independent variables were same used in the propensity score plus dummy indicators to denote asthma and non-asthma patients. The final matched cohorts of asthma and non-asthma were used for both direct and indirect COI estimates. For direct COI, the final matched cohorts of asthma and non-asthma were linked to the individual healthcare expenditure files: Inpatient visits (IP), Prescription medications (RX), Outpatient visits (OP), Emergency room visits (ER), Office based visits (OBV), Home health visits (HHE), and Other medical (OME) expenditures.

Costs related to loss in productivity were calculated for indirect COI. Value of lost productivity in the workforce for the final matched asthma and non-asthma cohorts was measured by calculating the number of missed work days multiplied with persons' daily wage rate (DW). Wage rates were obtained from the Bureau of Labor Statistics (BLS) which provides rates based on the occupation, region, state, age, race, and gender [29]. Missed work days were the number of days of missed work reported by respondents in the MEP consolidated file.

For patients who are not in workforce, but had lost productivity due to days spent in bed, value of lost productivity was calculated by multiplying number of bed days with the value of bed day. Bed days were the number of days being in the bed reported by respondents in the consolidated file of the MEPS. Wage data (age, race, gender) from BLS was used to calculate the value of bed day.

Data analysis

Descriptive statistics were used to describe demographic and comorbidity variables. A Greedy macro used nearest-neighbor matching (1:1) on the estimated propensity scores to match asthma and non-asthma patients. Chi-square and two-sample t-tests were used to assure identical asthma and non-asthma groups. Second

	Before matching			After matching		
Characteristics	**Asthma(n=2525)**	**Non-asthma(n=21700)**	**p value**	**Asthma(n=2257)**	**Non-asthma(n=2257)**	**p value**
Demographics						
Mean age	33.697	37.647	0.0001	36.898	35.483	0.0329†
Males (%)	41.82	46.16	0.0001	39.83	38.86	0.5027
Race (%):			0.0001			0.0087†
White	68.83	76.66		70.14	71.87	
Black	23.33	15.57		22.33	20.25	
American Indians	0.87	0.87		0.84	0.84	
Asians	2.81	4.46		2.84	4.39	
Native Hawaiian	0.48	0.34		0.49	0.4	
Multiple Races	3.68	2.1		3.37	2.26	
Hispanics (%)	18.97	23.18	0.0001	18.25	17.59	0.5605
Region (%)			0.0006			0.0444†
Northeast	16.91	14.57		17.24	14.98	
Midwest	20.88	21.73		21.27	24.24	
South	38.58	37.18		37.66	37.44	
West	23.63	26.52		23.84	23.35	
Area –MSA (%)	83.41	82.97	0.5715	83.61	82.19	0.2059
Education	n/a	n/a	0.0001			0.7921
Poverty categories (%)			0.0001			0.3659
Poor/Negative	27.37	17.97		25.48	23.84	
Near poor	5.39	5.91		5.23	6.34	
Low income	16.71	15.45		16.57	16.3	
Middle Income	27.01	29.35		27.65	27.29	
High Income	23.52	31.33		25.08	26.23	
CCI	0.5339	0.4122	0.0001	0.576	0.4843	0.0142†
Insurance Coverage (%)			0.0001			0.0001†
Any Private	50.85	60.11		52.55	57.86	
Public Only	40.2	26.65		37.93	29.33	
Uninsured	8.95	13.24		9.53	12.8	

† Variables those were significant even after applying matching algorithm, CCI-Charlson comorbidity index, and MSA-Metropolitan statistical area

Table 1: Demographic and comorbidity characteristics of asthma and non-asthma cohorts before and after matching.

Parameter‡	Parameter Estimate	SE	95% Confidence interval	P value
Asthma	1.75	.169	1.45-2.21	0.0001*
No asthma†	1.0	_	1.0	_
Age	1.017	.0029	1.01-1.02	0.0001*
Female	1.06	.134	.83-1.36	0.624
Male†	1.0	_	1.0	_
White	.375	.196	.133-1.05	0.06
Black	.372	.202	.127-1.08	0.07
Asian	.257	.142	.086-.765	0.015*
American Indian	.575	.381	.155-2.12	0.405
Multiple races	.933	.180	.767-1.494	0.063
Native Hawaiian/ Pacific				
Islander†	1.0	_	1.0	_
Non-Hispanic	1.07	.181	.767-1.49	0.686
Hispanic†	1.0	_	1.0	_
MSA	.956	.104	.772-1.18	.682
Non-MSA†	1.0	_	1.0	_
South	1.14	.112	.942-1.38	0.172
West	0.883	.100	.706-1.105	0.280
Midwest	1.30	.222	.928-1.821	.126
Northeast†	1.0	_	1.0	_
Poor	1.045	.188	.732-1.49	0.805
Lower income	.841	.154	.586-1.20	0.347
Middle income	.874	.173	.592-1.29	0.50
High income	.999	.200	.673-1.48	0.997
Near poor†	1.0	_	1.0	_
Private insured	.847	0.096	.677-1.06	0.147
Uninsured	.380	.068	.267-.542	.0001*
Public insured†	1.0	_	1.0	_
Elementary	.726	.130	.510-1.03	.07
High school	1.11	.221	.759-1.651	.567
Grade 12	1.001	.200	.675-1.48	.994
1 year college	.81	.147	.566-1.15	0.247
2 year college	1.42	.385	.834-2.42	. 195
3 year	.966	.219	.618-1.51	.881
4 year college	.8522	.174	.570-1.27	.435
>5 year college	.970	.223	.617-1.525	.897
No school†	1.0	_	1.0	_
CCI score	1.017	.0029	1.011-1.023	.0001*

†Referent category; ‡Results based on generalized linear model with log link Poisson distribution; *significant at alpha = 0.05

Table 2: Results of regression analysis to estimate the direct costs associated with asthma.

stage regression, GLM MFX command, was used to model the direct expenditure and indirect cost data, while controlling for any remaining differences between the cohorts after matching. The modified Park test was used as a diagnostic to select the variance function for the GLM. To calculate the total cost of illness of asthma, all direct expenditures and indirect costs components were summed. The association of demographic and comorbidity variables with asthma COI were determined from regression results. In all the analyses, the results were projected to the U.S. civilian non-institutionalized population using the sampling weights provided by MEPS. Because of the complex sample design of the MEPS, Taylor series variance estimation method was used to calculate sampling errors of estimates and 95% confidence intervals (CI) [30]. All analyses were conducted using SAS version 9.1.3 [31] or STATA version 10.0 [32]. An a priori alpha value of 0.05 was used for all statistical tests.

Service	Incremental estimate	SE	95% CI	P value
Inpatient visits	703.40	185.44	339.938- 1066.85	0.000*
Prescription medications	624.81	62.043	503.211- 746.417	0.000*
Outpatient visits	61.32	45.304	-27.4725- 150.117	0.176
Emergency room visits	52.27	21.735	9.66835 - 94.8689	0.016*
Office based visits	335.73	85.362	168.429- 503.04	0.000*
Home health visits	208.34	78.322	148.235- 412.54	0.015*
Other medical expenditures	13.30	23.711	-33.1775 -59.7685	0.575
Total	1999.17	320.59	1370.83- 2627.51	0.000*

*significant at alpha = 0.05

Table 3: Results of regression analyses to estimate the incremental direct expenditure of asthma by service category.

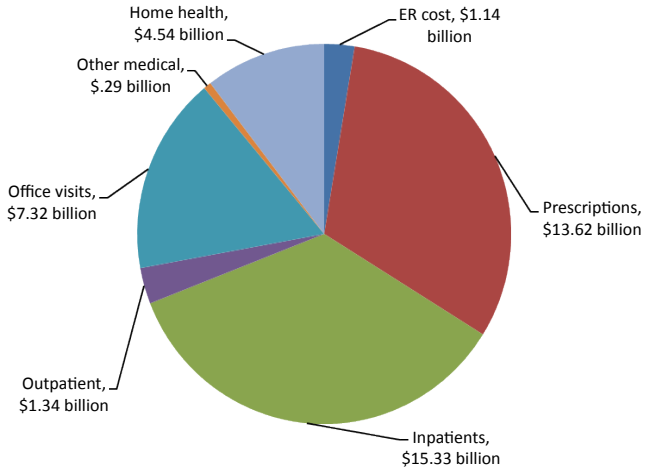

Figure 3: National direct cost of illness of asthma, breakdown of costs.

Results

A total of 2,525 patients with asthma and 21,700 patients without asthma were identified from the medical and full year consolidated file of MEPS 2007. Before matching, age, gender, race, ethnicity, region, poverty categories, insurance coverage, and Charlson comorbidity index (CCI) were significantly different between asthma and non-asthma cohorts. After matching, the variables age, race, region, insurance coverage, and CCI were still significant (Table 1). As a result, second stage regression models were used to control for the remaining significant variables and to assess the incremental direct expenditures and indirect costs of illness of asthma. Based upon MEPS data, the prevalence of asthma in the US for 2007 was estimated at 21,796,120 individuals. When compared to an estimated U.S. population of 301,139,947 for 2007 [33], the asthma prevalence was 7.24%.

Direct expenditures

After further adjusting for age, gender, race, ethnicity, education, insurance, region, MSA, income, and Charlson comorbidity index, patients with asthma had 75% higher direct expenditures than those with no asthma (parameter estimate: 1.75; $p < 0.0001$) (Table 2). Variables age, uninsured (compared to public insurance) and Charlson comorbidity score showed significant influence on the direct expenditures associated with asthma ($p < 0.05$).

Table 3 shows the results from individual regression models of incremental direct expenditures associated with asthma for total

Parameter‡	Parameter Estimate	SE	95% Confidence interval	P value
Asthma	2.08	.401	1.43-3.04	0.0001*
No asthma†	1.0	_	1.0	_
Age	1.007	.0043	.987-1.007	0.085
Female	0.973	.183	.671-1.42	0.887
Male	1.0	_	1.0	_
White	.970	.447	.391-2.40	0.9483
Black	1.264	.589	.496-3.55	0.615
Asian	.478	.239	.178-1.281	0.142
American Indian	3.932	2.73	1.003-15.40	0.049*
Multiple races	1.41	0.709	.525-3.79	0.494
Native Hawaiian/Pacific				
Islander†	1.0	_	1.0	_
Non-Hispanic	1.484	.417	.854-2.75	0.161
Hispanic†	1.0	_	1.0	_
MSA	1.355	.298	.878-2.09	0.208
Non-MSA†	1.0	_	1.0	_
South	1.902	.460	1.18-3.06	0.008*
West	1.313	.359	.767-2.24	0.319
Midwest	1.22	.332	.715-2.08	0.462
Northeast†	1.0	_	1.0	_
Poor	1.14	.357	.615-2.11	0.615
Lower income	.761	.275	.373-1.55	0.395
Middle income	.789	.275	.428-1.59	0.565
High income	.594	.234	.272-1.29	0.188
Near poor†	1.0	_	1.0	_
Private insured	0.605	0.132	.396-.934	0.023*
Uninsured	.576	0.167	.317-1.01	0.056
Public insured†	1.0	_	1.0	_
Elementary	.419	.216	.152-1.15	0.094
High school	1.365	.830	.413-4.51	0.608
Grade 12	1.58	.802	.588-4.28	0.360
1 year college	.636	.298	.253-1.599	0.336
2 year college	.965	.426	.404-2.300	0.936
3 year	.479	.257	.166-1.377	0.172
4 year college	.759	.406	.264-2.17	0.608
>5 year college	1.59	.976	.475-5.31	0.450
No school†	1.0	_	1.0	_
CCI score	1.28	0.047	1.18-1.36	.0001*

†referent category; ‡Results based on generalized linear model with log link Poisson distribution; *significant at alpha = 0.05

Table 4: Results of regression analysis to estimate the incremental indirect total costs associated with asthma.

expenditures and for each category of service. The annual mean direct incremental expenditure associated with asthma was $1,999.17 ($p < 0.0001$) per person. (Table 3) Inpatient visits accounted for the largest component of the total expenditures at $703.39 ($p < 0.0001$), followed by prescription medication at $624.81 ($p < 0.0031$). These two categories constituted approximately two thirds (66%) of the total expenditures associated with asthma patients. Although it accounted for a small amount of total expenditures, emergency room visits was statistically significant ($p < 0.016$). Office-based and home health visits accounted for 27% of the total expenditures associated with asthma patients ($p < 0.05$). Outpatient and other medical expenditures were not significant and accounted for approximately 3.6% of the total expenditures associated with asthma.

The total direct cost of illness associated with asthma in the United States in 2007 was estimated to be $43.57 billion. This was calculated by multiplying the asthma prevalence number (21,796,120) with the per-person total direct incremental expenditure ($1,999.17) associated with asthma. The estimate breaks down to $15.33 billion in inpatient expenditures, $13.62 billion in prescription medication expenditures, $7.32 billion in office-based visit expenditures, $1.34 billion in outpatient expenditures, $4.54 billion in home health expenditures, $1.14 billion in emergency room visit expenditures, and $0.29 billion other medical expenditures (Figure 3).

Service	Incremental estimate	SE	95% CI	P value
Total indirect costs	628.84	147.64	339.48-918.21	0.0001

Table 5: Results of regression analysis to estimate the incremental total indirect cost of asthma.

Indirect costs

After further adjusting for age, gender, race, ethnicity, education, insurance, region, MSA, income, and Charlson comorbidity index, patients with asthma had 100% higher indirect costs than those without asthma (parameter estimate: 2.08; $p < 0.0001$) (Table 4). Variables insurance (private compared to public), region (South compared to Northeast), and Charlson comorbidity score showed significant influence on the indirect costs associated with asthma ($p < 0.05$).The annual mean incremental indirect cost associated with asthma was $628.84 ($p < 0.0001$) per person (Table 5). The total indirect cost of illness associated with asthma in the United States in 2007 was $13.7 billion. This was calculated by multiplying the asthma prevalence number (21,796,120) with the per-person total indirect incremental cost ($628.84) associated with asthma.

National estimate of asthma COI

The total cost of illness (direct expenditures and indirect costs) associated with asthma in the United States in 2007 was $57.28 billion.

Discussion

The national direct cost of illness associated with asthma in 2007 was estimated to be $43.57 billion. This estimate was relatively higher than previously reported direct cost estimates of $5.76 billion-$37.2 billion, in inflation adjusted 2007 dollars [7,34]. The national indirect cost of illness estimates associated with asthma in 2007 was $13.7 billion. This estimate was relatively higher than previously reported indirect cost estimates of $673 million to $8.2 billion [3,11]. The total cost of illness (direct expenditures and indirect costs) was $57.28 billion. When compared to this study, those differences in the direct expenditures, indirect cost and total COI for asthma could be due to the prevalence of asthma at those times and the methodological approaches used to estimate the cost of illness of asthma. Others did utilize regression as an incremental approach to estimate the COI for asthma [7]. This study, however, used an efficient combination incremental method which combined matched controlled propensity scoring along with a robust second stage regression technique (GLM) to model highly skewed cost data. Since this study used expenditures instead of charges to calculate the estimates, comparisons to previous studies also may be problematic [5,35].

This study estimated the prevalence of asthma in the U.S. in 2007 to be 7.2 percent (21.8 million). This compares to an average 7.8 percent reported by the Census Bureau for years 2006-2008 [36]. By 2009 asthma prevalence was reported to be 8.2% of the U.S. population (24.6 million) [1]. This suggests that the cost of asthma illness of

noninstitutionalized patients in the U.S. for 2007 may have been underestimated.

Higher inpatient and prescription expenditures for patients with asthma in this study were also consistent with the literature [3,5,6]. Inpatient expenditures contributed the most to the direct cost of asthma illness, with prescription expenditures a close second. Overall, this combination contributed to 64.4 percent of total direct expenditures. Office-based visits contributed another 17 percent. Similar overall contributions of inpatient, prescription, and office-based visits expenditures to the direct cost of asthma are often found in the literature [6,11,14]. Some have found that office-based visit expenditures have contributed more than inpatient expenditures to direct costs, particularly when related to adult patients with asthma [7].

While this study is similar to earlier studies, in which inpatient expenditure was found to be the highest contributing expenditure to direct cost of asthma illness [34], more recent studies, however, have found that prescription expenditures accounted for the largest share of the total direct expenditures for asthma [4,7,14]. That shift in direct asthma expenditures may have been due to the introduction of newer, more expensive medications which allowed patients to remain ambulatory. While it is too early to determine whether inpatient expenditures will again trend to be the highest contributing expenditure to the direct cost of asthma illness, this study suggests that prescription use may be suffering from lowering adherence rates or concurrent mismanagement of ambulatory patients with asthma. As a result, the dilemma of the cost of asthma illness continues to be whether the ability of patients with asthma to remain ambulatory with proper, affordable medication use or will divert from this path toward the more expensive inpatient expenditures.

U.S. non institutionalized patients with asthma in 2007 had 75% higher direct expenditures and over 100% higher indirect costs than those with no asthma. This compares favorably with a recent study which found 92 percent higher direct asthma expenditures. Additionally, results of the current study show a significant association of age, comorbidity, and insurance with direct asthma expenditures and comorbidity with indirect asthma costs. It suggests that as age and comorbidity increase, their contributions to direct asthma expenditures increase, while a similar increase occurs from the comorbidity contribution to indirect costs. Conversely, uninsured patients contributed to lower direct expenditures when compared to publically insured patients, while privately insured patients contributed less to indirect asthma costs. The association of insurance with direct expenditures of asthma may be one in which uninsured patients are less likely to have access into the medical system thereby contributing less to direct expenditures. Privately insured patients, however, having greater access to the system, thereby needing less off work time, may explain their lower contribution to indirect asthma costs.

Accurate assessment of cost-of-illness expenditures associated with a disease is important to establish cost-effectiveness of medications and interventions to manage the disease. The results of this study show that both direct and indirect expenditures could be useful in cost-benefit analyses to justify expenditures and control costs for asthma disease management programs.

Limitations

The major limitation of this study is that the patients with asthma were identified using ICD-9 codes in the MEPS which were collapsed to three-digit codes to preserve the patient confidentiality. Three-digit codes are less accurate in the identifying the conditions that the five-digit codes. Some patients with milder or intermittent asthma symptoms might not have been coded with ICD-9 asthma codes. This could underestimate asthma prevalence and incremental expenditures. Because total expenditures and costs were calculated, no attempt was made to differentiate respondents by age (i.e. adult vs. child). The MEPS does not collect information on over-the-counter medications and therefore, only the cost of prescribed medicines was included. This study did not capture all the indirect expenditures associated with asthma, such as presenteeism and premature deaths. So this study might have underestimated the incremental expenditures and costs associated with asthma. Future studies should incorporate the costs of over the counter products, presenteeism expenditures, and mortality expenditures. The results and conclusions are also limited to those who responded to the asthma severity question in the MEPS data. Finally, this study is limited to the operational definitions used.

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