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Saving in medical costs by achieving guideline-based asthma symptom control: a population-based study

Authors: Mohsen Sadatsafavi^{1,2}, Wenjia Chen³, Hamid Tavakoli¹, J Douglass Rolf⁴, Roxanne Rousseau¹, J Mark FitzGerald^{1,2}, *for the Economic Burden of Asthma Study Group*

Affiliations:

1. Institute for Heart and Lung Health, Department of Medicine, the University of British Columbia, Vancouver, Canada
2. Centre for Clinical Epidemiology and Evaluation, the University of British Columbia, Vancouver, Canada
3. Faculty of Pharmaceutical Sciences, the University of British Columbia, Vancouver, Canada
4. Kelowna Allergy & Respiriology Research

Corresponding author:

Mohsen Sadatsafavi
Centre for Clinical Epidemiology and Evaluation
7th Floor, 828 West 10th Avenue
Research Pavilion
Vancouver, BC V5Z 1M9
Tel: 604.875.5178 | Fax: 604.875.5179
Email: msafavi@mail.ubc.ca

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Authors' contribution: MS and JMF came up with the study question. MS, JMF, and RR designed the study. RR was the primary study coordinator who collected the data of the study. JDR supervised the progression of the study and at the satellite site. WC and HT extracted and cleaned the data for the current research. HT, WC, and MS conducted the statistical analyses. MS wrote the first draft of the manuscript. All authors significantly contributed to the manuscript and approved the final version.

Abstract

Background: Asthma control is increasingly used as an outcome measure in asthma trials. Economic evaluations of asthma interventions require converting the impact on control to impact on resource use. The purpose of this study was to estimate the savings in direct costs by achieving asthma symptom control as defined in the Global Initiative for Asthma (GINA) 2014 management strategy.

Methods: Adolescents and adults with asthma were recruited through random digit dialing. Asthma control per GINA and the use of health-care resources were assessed at baseline and three-monthly visits up to one year. We used regression models to associate costs with symptom control, adjusting for potential confounding variables.

Results: The final sample included 517 individuals (average age 48.9, 65.8% female) with mostly mild-moderate asthma contributing 2,033 follow-up visits. In 598 (29.4%), 809 (39.8%), and 626 (30.8%) of visits asthma was symptomatically controlled, partially controlled, or uncontrolled, respectively. The

average three-month costs of asthma were \$134.5. Of these, 20.5% were attributable to inpatient care, 47.8% to outpatient care, and 31.5% to medication. Compared to controlled asthma, partially controlled asthma was associated with a non-significant increase of \$9.5 (95%CI -\$13.6 – \$32.6) in adjusted three-month costs and uncontrolled asthma with a statistically significant increase of \$81.7 (95%CI \$48.5 – \$114.9).

Conclusion: A substantial fraction of this population-based sample of largely mild-moderate asthmatics was symptomatically uncontrolled. Achieving symptom control was associated with a reduction in direct costs. The adjusted values from this study can be used to inform cost-effectiveness analyses of asthma treatments.

Keywords: asthma, costs, cost-effectiveness, outcomes

Introduction

Asthma is a prevalent disease of the airways affecting more than 300 million individuals across the world[1]. While rarely fatal, frequent symptoms such as cough, wheeze, shortness of breath, and episodes of intensified disease activity (referred to as exacerbation) can cause significant morbidity[2], resulting in high medical costs as well as loss of productivity and reduced quality of life[2].

While asthma is considered a non-curable disease, the conventional wisdom is that it is largely a controllable disease[3]. With proper management such as avoidance of triggers and use of anti-inflammatory agents (asthma controller therapies), symptom control can be achieved in the majority of individuals[4]. As such, the difference between the burden of uncontrolled and controlled asthma can be interpreted as the 'preventable' burden[5]. Unfortunately, the reality of asthma management is highlighted by poor adherence to guidelines among care providers and poor adherence to and

inappropriate use of controller therapies among patients[6]. As a result, a significant proportion of the asthma population remains uncontrolled[6].

While several studies have attempted to estimate the costs of asthma[7], very few studies have measured the preventable burden associated with uncontrolled asthma[8,9]. The latter is a more relevant figure of merit from a policy perspective as it determines the return on investment from strategies aimed at improving asthma control. A few studies have reported medical costs across control levels[8–14]. However, a simple reporting of costs across control level does not directly relate to the preventable burden. This is because of the impact of confounding variables that can affect both the chance of control as well as resource utilisation without being on a direct causal pathway. An example of such confounding variable is socio-economic status (SES). Individuals across levels of SES are different in the rate of asthma outcomes[15], and SES is also a predictor of medical costs[16]. Very few studies have reported differences (or ratios) of costs across control levels adjusted for confounding variables[10,11]. Of those that have, the study focus has been on severe or difficult-to-treat individuals[11] or less standard definitions of asthma control have been employed[17]. This is despite the critical role of adjusted estimates in the evaluation of the cost-effectiveness of asthma treatments. For example, such estimates can be used to convert the effectiveness of treatments on asthma control to their effect on costs; this, combined with estimates of their effect on quality of life can be used to inform economic evaluation of asthma interventions.

The present study aims at informing such evidence gap in the literature. We have used a prospectively recruited sample, longitudinal evaluation of costs and control, and updated definitions of asthma control (according to the Global Initiative for Asthma [GINA] 2014 management strategy[4]) to address the following question: "what is the expected reduction in direct medical costs of asthma by achieving asthma symptom control in a patient with uncontrolled asthma?"

Methods

We used the longitudinal data from the Economic Burden of Asthma (EBA - University of British Columbia Human Ethics #H10-01542). The details of EBA are presented elsewhere[5]. In summary, individuals 1 – 85 years old with a self-reported physician-diagnosed history of asthma were detected through random digit dialing of both land lines and cell phones at Vancouver census subdivision and Central Okanagan census subdivision, with a 2006 population of, respectively, 578,014 and 162,276[18]. Individuals who agreed to participate were invited to the study centers and upon consent were enrolled in study which involved a baseline visit as well as five follow-up visits at three-month intervals, for a one-year follow-up. For this analysis, we restricted the sample to individuals 12 years or older.

The baseline visit included detailed information about patients' socio-demographic status. In all visits, asthma control was estimated based on the 2014 Global Initiative for Asthma (GINA) Management Strategy[4]. This symptom-based classification is based on four components of asthma symptoms with a recall period of 4 weeks: daytime asthma symptoms for more than a few minutes, any activity limitation, need for reliever medications more than once a week, and any night awakening or night coughing. Individuals were classified as well controlled if none of the symptoms are present, partially controlled if, 1-2 symptoms are present, and uncontrolled otherwise.

The baseline and follow-up visits also included detailed information regarding the health-care resource use. The recall period for resource use questionnaire was one year at baseline and three months during the follow-up. Given the three-month interval between visits, this approach provided us with continuous resource use records from the twelve months prior to the baseline visit to the end of follow-up. Asthma-related hospitalisations, emergency department (ED) visits, outpatient physician visits, and medications were captured through self-report using cost diaries. For medication use, we used an incremental approach, capturing current medication lists in the baseline visits and recording any subsequent changes

(whether self-initiated or through care provider's advice) during the follow-up. A reference list of respiratory-related drugs was used to determine whether a particular medication should be considered asthma-related (list provided in Appendix).

Estimating unit costs: Direct medical costs were calculated by assigning unit costs to each resource use record. The average costs of asthma-related hospitalisation were determined from a separate analysis of British Columbia's administrative health data for corresponding fiscal years. Details of this study are published elsewhere[19]. We retrieved all records of hospitalisations with asthma as the main discharge diagnosis (International Classification of Diseases [ICD] codes of 493.x (ICD-9), J45, J46 (ICD10)) between 2008 and 2012 from the Ministry of Health. Each record is accompanied by a resource intensity weight (RIW). The RIW was multiplied by the average cost of hospitalisation (across all conditions) in the province for the corresponding fiscal year to estimate the cost of each hospitalisation. Details of this method is provided elsewhere[19]. Similarly, to calculate the cost of physician visits, we used the Medical Services Plan database for 2008 to 2012. Physicians charge fee codes for a variety of services. While there are published fee codes for outpatient services, the costs of an actual visit are a mixture of code such as the visit itself (whether it is consultation or follow-up), physical exam, spirometry, and so on. To calculate the average costs of visits, we grouped all such services with the same date and physician identifier and summed their costs, separately for general practitioner (GP) and specialist visits. For medication use, we cross-linked all medications according to their Drug Identification Number (DIN) to the Provincial Drug Master Plan database to estimate the costs per dose of the medication[20].

Analysis: Three-month costs associated with each follow-up visits were calculated as the sum of the product of resource use records and their associated unit costs. All costs were adjusted to 2012 Canadian dollars using the medical component of the Consumer Price Index[21]. We adopted a societal

perspective, thus disregarding whether the costs were covered by the health-care provider, third-party insurer, or patient.

Each observation unit for the analysis was a follow-up visit with corresponding asthma control and three-month costs. The data from the baseline were not used as an outcome, but were used for adjusting the analysis for the previous history of asthma control and costs as potential confounding variables. We used regression methods with period-specific medical costs as the dependent variable and asthma control (entered as two dummy variables representing partially controlled or uncontrolled asthma with controlled asthma as the reference category) as independent variables. Generalized Linear Models with Generalized Estimating Equations were used to estimate the marginal (population-level) impact of asthma control on costs, taking into account the clustering of observations within individuals.

All regression models were adjusted for the following variables: asthma control and costs at baseline, SES (annual income for the household – cut-off point of \$60,000), education (post-secondary or less), sex, age, year since asthma diagnosis, urban v. rural residence, and whether the individual was covered by third-part insurance or not. SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for all analyses. Two-tailed P-values (P) at 0.05 level were considered to determine statistical significance.

Results

The study sample included a total of 532 individuals 12 years of age or older. Of these, 1 was excluded because of missing asthma control variables, and 14 were excluded as they only participated in the baseline visit. The remaining 517 individuals contributed 2,033 follow-up visits (contributing 506.5 patient-years of data to the analysis). 499 (96.5%) patients had all four follow-up visits. 7 (1.4%), 5 (1.0%), and 6 (1.1%) had, respectively, 3, 2, and 1 follow-up visits. 472 (91.3%) of the sample was adult.

The average age at baseline visit was 48.9 (SD 17.3), and 340 (65.8%) of the sample was female. The frequency of controlled, partially controlled, and uncontrolled asthma at baseline was 128 (24.8%), 209 (40.4%), and 180 (34.8%), respectively. The average medical costs for the year before baseline were \$473.0 (SD \$1360.7), with minimum of \$0.0 and maximum of \$23,321. Overall, consistent with the population-based nature of sampling, the study mostly consisted of subjects with mild to moderate asthma: only 7.1% of patients had any history of asthma-related hospitalisation or emergency department visits in the year prior to entry. During this period, 13.9% of individuals used at least 6 canisters of inhaled corticosteroids; 8.3% used at least 6 canisters of a combined inhaled corticosteroid and long-acting beta agonist, and 7.9% used 6 or more canisters of short-acting beta-agonists.

In administrative health records, there were a total of 5,297 asthma-related hospitalisations in British Columbia between 2008 and 2012, with average costs of \$3,310.1. In the same period, there were 880,116 GP visits and 151,268 specialist visits, with average costs of \$43.2 for GP and \$117.1 for specialist visits.

Rate of outcomes and unadjusted comparisons: Of the 2,033 follow-up visits, in 598 (29.4%), 809 (39.8%), and 626 (30.8%) asthma was symptomatically controlled, partially controlled, or uncontrolled, respectively. As follow-up visits were equidistant, these figures approximate the percentage of follow-up time individuals experienced a given asthma control level. The average costs of asthma per three-month period were \$134.4 (SD \$379.8, range \$0.0 - \$7,518.2). Of these, \$27.6 (20.6%) were due to hospital admission/ED visits, \$64.3 (47.8%) due to outpatient visits, and \$42.4 (31.5%) due to medication use. In the unadjusted comparison, three-month costs of controlled asthma were \$63.1; for partially controlled asthma they were \$92.6, and for uncontrolled asthma they were \$256.4. In the unadjusted analysis, partially controlled and uncontrolled asthma were associated with incremental costs of, respectively, \$28.0 ($P=0.016$) and \$192.9 ($P<0.001$).

Adjusted analysis: Results of the regression analysis are provided in Table 3. Compared to controlled asthma, partially controlled asthma was associated with a non-significant increase in three-month costs of \$9.5 (95%CI -13.6 – 32.6, $P=0.420$) and uncontrolled asthma with \$81.7 (95%CI 48.5 – 114.9, $P<0.001$). Among the other covariates included in the regression model, baseline costs were positively associated with follow-up costs, whereas female sex and FEV₁ were negatively associated with follow-up costs.

Figure 1 provides the results of costs component and subgroup analyses. When the comparison between the partially controlled and controlled asthma was concerned, the only three-month costs component with a statistically significant difference was medication costs (\$19.0 higher in the partially controlled group). For the comparison between the uncontrolled and controlled asthma, all components except hospitalisation costs were statistically significantly higher for uncontrolled asthma. The results remained largely the same in the adults subgroup. On the other hand, no costs component was statistically significantly different between uncontrolled or partially controlled and controlled asthma among the adolescents, although only 45 individuals (177 observation units) contributed to the latter analysis.

Discussion

We estimated the 'preventable burden' due to uncontrolled asthma, defined as the savings in the direct medical costs that can be gained by achieving asthma symptom control. After adjustment, there was no statistically significant difference in direct costs between partially controlled and controlled asthma; on the other hand, compared to controlled asthma, uncontrolled asthma was associated with an excess three-month costs of \$81.7. This is a much smaller value than the unadjusted difference of \$192.8 in the three-month costs of uncontrolled and controlled asthma, and shows that impact of confounding factors in such associations. Assuming that we have sufficiently adjusted for potentially confounding variables, the value of \$81.7 can be considered as potential gain in achieving asthma control in an uncontrolled

patient for three month. Other findings of our study were the observation that in more than 30% of follow-up person-time asthma was uncontrolled and that females on average had \$45.7 lower three-month costs compared to males.

Several other authors have reported on the direct costs of asthma[8,9,11–14,17]. For the most part, these studies did not adjust for the potentially confounding variables[8,9,13,14,17]. In Briggs et al., the association between costs and control was assessed based on the data of a large randomized trial[12]. However, the randomisation on treatment *per se* does not protect against confounding of the association between exposure (control) and outcomes (costs). The investigators adjusted for severity but not for demographics or socio-economic factors. Overall, the analysis by Campbell et al. seems to be the one that has used both validated definition of asthma control, reliable costs estimation methods, and rigorous adjustment for multiple covariates[11]. Of note, the adjusted regression coefficients for uncontrolled v. controlled asthma were around \$800 (per year) lower than the unadjusted ones. This study, however, was in a sample of difficult-to-treat asthma, whereas our sample was largely made of milder asthma patients.

The strengths of our study include a prospectively recruited population-based sample, longitudinal follow-up that allowed us to use the previous history of asthma control and costs (baseline values) as surrogates for asthma severity in the regression analysis, and the use of an up-to-date and internationally accepted definition of asthma control. Our very high retention rate (96% of individuals were successfully followed for one year) minimizes the bias that arises from informative censoring, i.e., the chance of attrition being correlated with the exposure and/or outcome. Assuming that the set of variables used for adjustment in the regression is sufficient for controlling for potential confounding, our adjusted estimates of costs can have causal interpretation and can be used in estimating the impact of an intervention on costs through its impact on asthma symptom control. The validity, feasibility and

popularity of asthma control as an outcome variable in interventional asthma studies make it a central component representing the efficacy and effectiveness of asthma treatments[4,12,22]. High quality evidence relating asthma control to costs and quality of life is therefore a key piece as it enables the translation of impact on asthma control to cost and effectiveness outcomes.

Our study has several limitations. Costs were estimated using validated cost diaries, but the chance of recall bias cannot be excluded. Imperfect recall can weaken the significance of associations as it adds noise to the estimates of costs. On the other hand, if the recall is preferential with individuals' responses to the asthma control questionnaire (e.g., if individuals who report the presence of asthma symptoms also exaggerate their resource use) it can result in biased estimates of the impact of asthma control on costs. Furthermore, our sample consisted of individuals with mild asthma, as evidenced by low rate of hospitalisation and ED visits at baseline and during follow-up. This might be due to differential preference of study participants to enroll depending on their level of asthma severity. On the other hand, the rapid decline of hospital admissions and ED visits in British Columbia might indicate that the low rate of inpatient care is a reality[19]. Despite the relatively large sample size, we did not have enough samples in subgroups such as adolescents to draw reliable inference. The absence of evidence on the relation between asthma control and costs in this subgroup should not therefore be taken as evidence of absence, until further studies with larger sample sizes are conducted. Another concern is that for feasibility reasons, follow-up visits were scheduled on a three-month basis, while the recall period for GINA symptom control is four weeks. Accordingly, the interpretation of the results of our study is in terms of potential saving in direct costs during the past three-month if an individual's asthma is symptomatically controlled at present. Another quantity of interest might be the potential saving if the individual's asthma remains controlled in the entire three-month period. This quantity could not be readily estimated using our data.

The results of our study can have important implications especially in evaluating the burden of uncontrolled asthma and estimating the cost-effectiveness profile of asthma interventions. Prevalence of partially controlled and uncontrolled asthma at a jurisdiction of interest can be combined with adjusted estimates of cost difference to provide an overall estimate of the excess direct costs that can be avoided by improving the level of asthma control. Providing evidence on cost-effectiveness is a requirement in many jurisdictions for the approval of new health technologies. This is usually performed through decision-analytic modeling. Asthma control is a central variable in decision models of asthma and transition rates across control levels are well established[12]. Such models should be populated with the adjusted difference in direct and indirect costs as well as quality of life weights across levels of asthma control. Up-to-date and valid estimates for such variables are required, and our study provides critical evidence in this direction. Further studies of this type are required to generate similar evidence on the preventable burden of uncontrolled asthma in terms of loss of quality of life and excess exacerbations, in general and across different asthma phenotypes and patients subgroups. These statistics are required for evidence-informed policy making and efficient allocation of our scarce health care resources.

Table 1: Baseline demographic characteristics of the study population <back to text>

Variable	Controlled (n= 128)	Partially controlled (n= 209)	Uncontrolled (n=180)	Total (n=517)	P
Female N (%)	74 (57.8%)	133 (63.6%)	133 (73.9%)	340 (65.7%)	0.001*
Age at baseline mean (SD)	49.8 (17.8)	46.9 (17.6)	50.5 (16.5)	48.9 (17.3)	0.093
High (v. low) income† N (%)	67 (52.3%)	118 (56.5%)	85 (47.2%)	270 (52.2%)	0.191
High (v. low) education‡ N (%)	83 (64.8%)	149 (71.2%)	196 (70.0%)	358 (69.2%)	0.444
Full (v. no/partial) third-party	27 (21.1%)	42 (20.1%)	38 (21.1%)	117 (20.7%)	0.962

insurance coverage N (%)					
Forced Expiratory Volume at 1 second mean (SD)	2.72 (0.81)	2.78 (0.87)	2.47 (0.92)	2.66 (0.88)	0.016*
% predicted Mean (SD)	88.0%(16.1)	87.6%(17.7)	83.1%(20.2)	86.2% (18.3)	0.022*
Health services use and outcomes in the year prior to recruitment					
Patients with history of hospital admissions, N,%	0 (0.00%)	2 (0.96%)	10 (5.56%)	12(2.32%)	0.001*
Patients with history of ED visits, N (%)	3 (2.34%)	8 (3.83%)	23 (12.78%)	34 (6.58%)	0.002*
Total costs mean (SD)	\$203.2 (\$405.6)	\$287.0 (496.7)	\$880.8 (\$2161.9)	\$473.0 (\$1360.7)	<0.001*
Hospital/ED visits costs mean (SD)	\$15.0 (\$119.5)	\$48.5 (\$352.8)	\$398.6 (\$1949.5)	\$162.1 (\$1184.2)	0.004*
Outpatient visits costs mean (SD)	\$50.3 (\$181.3)	\$58.5 (\$72.5)	\$152.4 (\$213.5)	\$162.1 (\$1184.2)	<0.001*
Medication costs mean (SD)	\$137.7 (\$346.4)	\$180.0 (\$309.4)	\$330.0 (\$521.0)	\$89.2 (\$167.8)	<0.001*
				\$221.7 (\$410.9)	

*Significant at 0.05 level

† Cut-off of 60,000, close to the Canadian median household income

‡ Low education was defined as post-secondary or less

SD: standard deviation, **P:**p-value, **ED:** emergency department, **ICS:** inhaled corticosteroids,

LABA: inhaled long-acting beta-agonist, **SABA:** inhaled short-acting beta-agonist

Table 2: The unadjusted rate of outcomes during the follow-up period# <back to text>

Variable	Controlled (n=135)	Partially controlled (n=234)	Uncontrolled (n=196)	Total (n=565)	P
Hospitalisations					
<i>N with any hospitalisation</i>	1 (0.17%)	1 (0.12%)	10 (1.60%)	12 (0.59%)	<0.001
<i>(%)</i>	0.002 (0.041)	0.001	0.018 (0.143)	0.006 (0.085)	*
<i>mean (SD)</i>		(0.035)			<0.001
					*
Emergency Department visits					
<i>N with any visits (%)</i>	3 (0.50%)	6 (0.74%)	25 (3.99%)	34 (1.67%)	<0.001
<i>mean (SD)</i>	0.005 (0.071)	0.009 (0.086)	0.053 (0.284)	0.021 (0.172)	*
Outpatient visits					
<i>mean (SD)</i>	0.41 (1.36)	0.55 (1.21)	1.31 (2.16)	0.74 (1.65)	<0.001
General Practitioner					*
<i>mean (SD)</i>	0.36 (1.30)	0.49 (1.10)	0.98 (1.48)	0.60 (1.31)	
Specialist					<0.001
<i>mean (SD)</i>	0.05 (0.29)	0.06 (0.38)	0.33 (1.32)	0.14 (0.79)	*
					<0.001
					*
Total costs					
<i>mean (SD)</i>	\$63.1 (180.1)	\$92.6	\$256.4	\$134.4	<0.001
Hospital/ED visits		(198.5)	(604.1)	(379.8)	*
<i>mean (SD)</i>	\$7.1 (149.5)				
Outpatient visits		\$6.5	\$74.5 (521.1)	\$27.6 (312.7)	0.001*
<i>mean (SD)</i>	\$21.6 (68.5)	(130.0)			
Medication use			\$80.7 (178.0)	\$42.4 (116.9)	<0.001
<i>mean (SD)</i>	\$34.3 (72.0)	\$28.2			*
		(68.4)	\$101.2	\$64.3 (128.5)	
			(167.7)		<0.001
		\$58.0			*
		(119.1)			

*Significant at 0.05 level

All costs are adjusted to 2012 Canadian dollars

SD: standard deviation, P:p-value, ED: emergency department

Table 3: Regression coefficients for the association between costs and control# <back to text>

Variable	Coefficient	95% confidence interval	P
Age at baseline	-\$0.7	-\$2.2 , \$0.7	0.315
Sex (female v. male)	-\$45.7	-\$89.5 , -\$1.8	0.041*
Income (high v. low) †	-\$1.7	-\$27.8 , \$24.4	0.899
Education (high v. low) ‡	\$1.9	-\$29.2 , \$33.0	0.905
Third-party insurance (full v. partial or no)	\$3.8	-\$26.8 , \$34.4	0.809
Control at baseline partially controlled v. controlled	\$1.5	-\$13.3 , \$16.2	0.847
uncontrolled v. controlled	\$36.9	-\$2.1 , \$75.8	0.064
Cost at baseline	\$0.2	\$0.1 , \$0.2	<0.001*
Forced expiratory volume at 1 second	-\$47.1	-\$85.8 , -\$8.3	0.017*
Asthma control during follow-up			
Partially controlled v. controlled	\$9.5	-\$13.6 , \$32.6	0.420
Uncontrolled v. controlled	\$81.7	\$48.5 , \$114.9	<0.001*

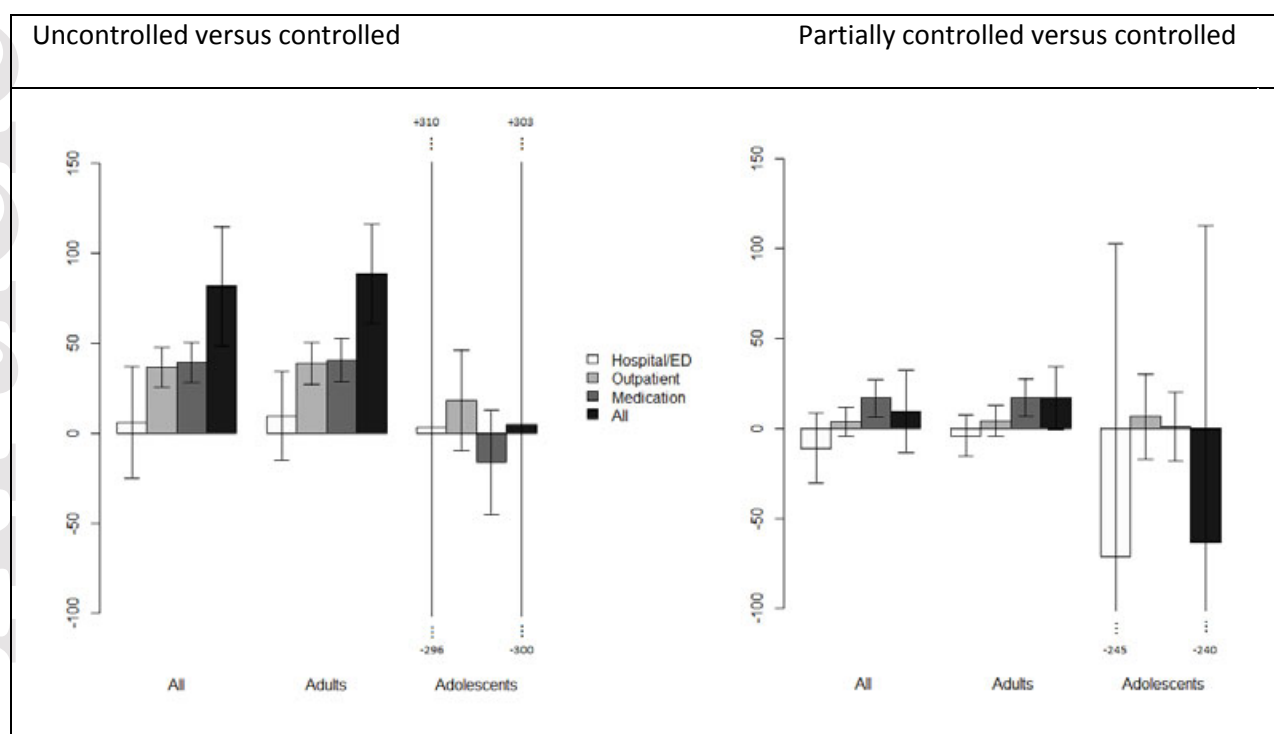
*Significant at 0.05 level

† Cut-off of 60,000, close to the Canadian median household income

‡ Low education was defined as post-secondary or less

All costs are adjusted to 2012 Canadian dollars

Figure 1: subgroup and cost component analysis <back to text>



All costs are adjusted to 2012 Canadian dollars

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Table E1. Asthma-related medications per categories

Co de	Categor y	genericName	BrandName	Rout	Input	Price (per dose)
171	XAN	Theophylline	Theolair	ORA L	oral	0.0273
160	SABA	Salbutamol	Albuterol	INHA LE	inhaler	0.0324
197	SABA	Salbutamol	Asthavent	INHA LE		0.0324
201	SABA	Salbutamol	Airomir	INHA LE	inhaler	0.0324
212	SABA	Salbutamol	Salbutamol	INHA LE	inhaler	0.0324
234	SABA	Salbutamol	Proventil	INHA LE	Inhaler/ NFA	0.0324
176	SABA	Salbutamol	Ventolin	INHA LE	inhaler	0.0351
138	OTHER	Oxtriphylline	Choledyl		exlixir	0.04
184	CS	Beclomethasone	Beclonase	NAS AL	Nasal spray	0.0662
239	CS	Beclomethasone	Beclomethasone	NAS AL	Nasal spray	0.0662
240	CS	Beclomethasone Dipropionate	Alanase	NAS AL	Nasal spray	0.0662
140	CS	Prednisone	Deltasone	ORA L	Oral	0.02994165
155	CS	Prednisone	Orasone	ORA L	oral	0.06757082 5
156	CS	Prednisone	Prednisone (tab)	ORA L	tab	0.06757082 5
157	CS	Prednisone	Prednisone (liq)	ORA L	liquid	0.06757082 5
217	SABA	Terbutaline	Terbutaline	INHA LE	Inhaler	0.0825
219	SABA	terbutaline	Bricanyl	INHA LE	inhaler	0.0825
229	SABA	terbutaline	Bricanyl	INHA LE	turbuhal er	0.0825
185	CS	Budesonide	Rhinocort AQ	NAS AL	Nasal	0.0965
195	CS	Budesonide	Budesonide	INHA LE	inhaler	0.09725

198	CS	Budesonide	Inflammid	INH A L E	inhaler	0.09725
203	CS	Budesonide	Budeflam	INH A L E	inhaler	0.09725
116	XAN	Theophylline	Nuelin	ORA L	oral	0.100225
143	XAN	Theophylline	Elixophyllin	ORA L	Oral	0.100225
112	ACH	Ipratropium	Atrovent	INH A L E	inhaler	0.1006
227	ACH	Ipratropium	Atrovent nebulizer	NEB U L	nebulizer	0.1006
179	CS	Budesonide	Rhinocort	INH A L E	turbuhal er	0.1287
163	OTHER	guaifenesin and theophylline	Quibron			0.129866667
167	XAN	Theophylline	Slo-Bid	ORA L	oral	0.129866667
168	XAN	Theophylline	T-Phyl	ORA L	oral	0.129866667
169	XAN	Theophylline	Theo-24	ORA L	oral	0.129866667
170	XAN	Theophylline	Theochron	ORA L	oral	0.129866667
233	XAN	Theophylline	Theodur	ORA L	oral	0.129866667
139	SABA	Salbutamol	Apo Salvent	INH A L E	inhaler	0.133466667
241	CS	Prednisone sodium phosphate	Pediapred	ORA L	Pill	0.1372
189	CS	Mometasone	Nasonex	NAS A L	nasal	0.223
118	CS	Beclomethasone	Beclomethasone	INH A L E	inhaler	0.2427
133	CS	Beclomethasone	Beclovent	NAS A L	nasal spray	0.2427
164	CS	beclomethasone	Qvar	INH A L E	inhaler	0.2427
187	CS	Beclomethasone	Beclonase AQ	NAS A L		0.2427
228	CS	Beclomethasone	Becloforte	INH A L E	inhaler	0.2427
236	CS	Beclomethasone	Clenil modulate	INH A L E	Inhaler	0.2427
103	XANx	Theophylline Derivative	Aminophylline	ORA L		0.2808

126	SABA	Salbutamol	Albuterol	NEB UL	nebulizer	0.33235454 5
158	SABA	Salbutamol	Proventil	NEB UL	Nebulizer	0.33235454 5
177	SABA	Salbutamol	Volmax	ORA L	oral	0.33235454 5
222	SABA	Salbutamol	Salbutamol	NEB UL	nebulizer	0.33235454 5
162	CS	Budesonide	Pulmicort	INHA LE	inhaler	0.374
146	CS	Fluticasone	Flovent	INHA LE	inhaler	0.44326666 7
237	CSLAB A	Mometason+Formoterol	Zenhale	INHA LE	Inhaler	0.468
120	CS	ciclesonide	Alvesco	INHA LE	inhaler	0.52605
111	ACH	Ipratropium	Ipratropium bromide	NAS AL	Nasal spray	0.530075
225	CS	Budesonide	Pulmicort suspension 0.5mg	NEB UL	nebulizer	0.54683333 3
174	XAN	Theophylline	Uniphyll	ORA L	Oral	0.59465
230	CS	Fluticasone	Flovent	INHA LE	nebulizer	0.60882857 1
180	CS	Flunisolide	Nasalide	NAS AL	nasal	0.6415
183	CS	Flunisolide	Nasarel	NAS AL	nasal	0.6415
221	CS	Flunisolide	Flunisolide	NAS AL	Nasal spray	0.6415
131	ACHSABA	Ipratropium/albuterol	Combivent	INHA LE	Inhaler	0.6512
182	CSLAB A	Budesonide+Formoterol	Symbicort	INHA LE	inhaler	0.6545
223	MCS	Ketotifen	Ketotifen	ORA L	pill	0.6842
210	LLABA	Formoterol	Oxeze	INHA LE	Inhaler	0.70605
224	CS	Fluticasone	Flovent	INHA LE	diskus	0.733
175	SABA	Salbutamol	Ventolin	ORA L	oral	0.837675
144	LABA	Formoterol	Foradil	INHA LE	inhaler	0.9095
207	LABA	Formoterol	Formoterol	INHA LE	inhaler	0.9095

121	LABA	Salmeterol	Serevent	INH ALE	inhaler	1.0097
238	LABA	Salmeterol	Serevent	INH ALE	Discus	1.0097
215	CSLAB A	Fluticasone+salmeter ol	Advair	INH ALE	inhaler	1.0452
152	OTHER	N-acetylcysteine	N-acetylcysteine			1.0782154
226	SABA	Salbutamol	Ventolin	NEB UL	nebulizer	1.1052
113	OTHER	Methotrexate	Methotrexate			1.174925
200	CSLAB A	Fluticasone+salmeter ol	Advair	INH ALE	diskus	1.8747
196	ACH	Tiotropium	Spiriva	INH ALE	handyhal er	2.304
231	OTHER		Soframycin		Nasal spray	2.808