



Asthma control and disease burden in patients with asthma and allergic comorbidities

Lulu K. Lee, Engels Obi, Brandee Paknis, Abhishek Kavati & Bradley Chipps

To cite this article: Lulu K. Lee, Engels Obi, Brandee Paknis, Abhishek Kavati & Bradley Chipps (2017): Asthma control and disease burden in patients with asthma and allergic comorbidities, Journal of Asthma, DOI: [10.1080/02770903.2017.1316394](https://doi.org/10.1080/02770903.2017.1316394)

To link to this article: <http://dx.doi.org/10.1080/02770903.2017.1316394>



© 2017 The Author(s). Published with license by Taylor & Francis© Lulu K. Lee, Engels Obi, Brandee Paknis, Abhishek Kavati, and Bradley Chipps.



Published online: 06 Jun 2017.



Submit your article to this journal [↗](#)



Article views: 757



View related articles [↗](#)



View Crossmark data [↗](#)

Asthma control and disease burden in patients with asthma and allergic comorbidities

Lulu K. Lee, PhD^a, Engels Obi, PhD, BPharm^b, Brandee Paknis, PharmD^d, Abhishek Kavati, PhD^b, and Bradley Chipps, MD^c

^aHealth Outcomes Research, Kantar Health, Foster City, CA, USA; ^bUS Health Economics and Outcomes Research, Novartis Pharmaceuticals Corp., East Hanover, NJ, USA; ^cUS Medical Affairs, Novartis Pharmaceuticals Corp., East Hanover, NJ, USA; ^dAllergy and Respiratory Disease, Capital Allergy & Respiratory Disease Center, Sacramento, CA, USA

ABSTRACT

Objective: To assess asthma control and associations with health-related quality of life (HRQoL) and economic outcomes among patients with asthma and allergic comorbidities treated with inhaled corticosteroids (ICS) and long-acting beta-agonists (LABA) combination therapy. **Methods:** Data from the 2011–2013 US National Health and Wellness Survey were used to identify patients with asthma currently treated with ICS and LABA combination therapy (N = 1923). Patients were included if they self-reported a physician diagnosis of asthma and at least one allergic/asthma-related comorbid condition (e.g., nasal allergies, atopic dermatitis). Asthma Control Test scores categorized patients as very poorly (scores ≤ 15; 29.3%), not well (16–19; 25.1%), or well controlled (20–25; 45.7%). Outcomes included HRQoL (SF-36v2; SF-12v2), work productivity and activity impairment, healthcare utilization (HRU), and annual indirect and direct costs. Generalized linear models, controlling for covariates, examined whether outcomes differed by asthma control. **Results:** Over half of the patients had very poorly or not well-controlled asthma (54.4%). Patients with very poorly controlled versus well-controlled asthma reported significantly greater decreases in HRQoL, greater overall work impairment, and higher HRU (all, $p < 0.05$). Very poorly controlled patients incurred over double the indirect costs and nearly one and a half times the direct and total costs of well-controlled patients. **Conclusions:** Increasing level of asthma control was related to improved HRQoL and lower costs. The considerably high prevalence of uncontrolled asthma among patients on ICS and LABA suggests poor treatment adherence or unmet needs in current treatment and may require step-up therapy in appropriate patients according to clinical guidelines.

ARTICLE HISTORY

Received 6 February 2017
Revised 24 March 2017
Accepted 2 April 2017

KEYWORDS

Costs; health-related quality of life; inhaled corticosteroids; long-acting beta-agonists; work productivity loss

Introduction

Asthma is characterized by chronic wheezing and air-flow obstruction, which occurs because of swelling and inflammation in the lining of the bronchial tubes [1]. Asthma can be triggered by contact with an allergen; common triggers include dust mites, animal dander, and cockroach debris [2]. Between 2001 and 2009, the prevalence of asthma in the US general population increased from 7.3% to 8.2%, with the prevalence of asthma at 7.7% for US adults [3]. According to the National Health, Lung, and Blood Institute (NHLBI), for adults, poorly controlled asthma entails frequent asthma symptoms (i.e., symptoms experienced >2 days per week requiring a short-acting beta-agonist to control) and may be associated with a progressive decline in pulmonary function [4].

Previous research indicated that adults with poorly controlled asthma had significantly lower HRQoL, with

higher work productivity loss and activity impairment than those with well-controlled asthma [5, 6]. Asthma has also been associated with poorer health status. The rate of depression among patients with asthma was significantly higher than that for matched controls [7]. Additionally, after controlling for comorbidities (e.g., gastroesophageal reflux disease and sleep apnea), asthma patients reported poor sleep quality, which was even worse with more severe symptoms [8]. Regardless of asthma severity, poor sleep quality was found to be linked to inadequate asthma control and lower HRQoL. Overall, these research findings suggest that achieving asthma control is integral to improving HRQoL and health status. However, this may be challenging, given almost 40% of US adults with asthma had poor asthma control [5].

Asthma is also associated with a considerable economic burden. Data from the 2003 and 2005 Medical

CONTACT Lulu K. Lee  Lulu.Lee@kantarhealth.com  Health Outcomes Research, Kantar Health, 1810 Gateway Drive, Suite 120, San Mateo, CA 94404, USA.

© 2017 Lulu K. Lee, Engels Obi, Brandee Paknis, Abhishek Kavati, and Bradley Chipps. Published with license by Taylor & Francis

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited, and is not altered, transformed, or built upon in any way.

Expenditures Panel Survey (MEPS) showed that costs associated with asthma among adults in the US totaled \$18 billion annually in 2008 US dollars [9]. Among US adults, those with poorly controlled asthma had significantly higher healthcare resource use (HRU; i.e., emergency room [ER] visits, hospitalizations, and visits to healthcare providers [HCPs]) than adults with well-controlled asthma [5, 6]. Nevertheless, only a third of US adults with asthma were found to be actively managing their symptoms with long-term control medications [11]; indicating that asthma may be sub-optimally treated in the US. Insufficient treatment may serve to increase the burden of this disease.

Long-term maintenance medications are used daily with the goal being to achieve symptom control for persistent asthma [4]. In contrast, short-term treatments (e.g., short-acting beta-agonists) are available to quickly relieve acute incidents of airflow obstruction. Patients with persistent asthma need a combination of these medications. NHLBI guidelines recommend that adult asthma patients step up 1 step for not well-controlled asthma [10]. Patients not well controlled on step 3 preferred treatment (low-dose ICS +LABA OR medium-dose ICS) need to step up to step 4 therapy (medium-dose ICS +LABA or alternatively low-dose ICS +either Leukotriene Receptor Antagonist [LTRA], Theophylline, or Zileuton). Patients not well controlled on step 4 preferred treatment (medium-dose ICS +LABA) need to step up to step 5 therapy (high-dose ICS + LABA AND consider omalizumab for patients who have allergies).

Despite available studies on the burden of asthma in the US, noticeable gaps still exist. Most studies underestimate asthma burden by exclusively focusing on just symptoms or costs, rather than a comprehensive assessment of burden. Furthermore, all forms of asthma and asthma medication regimens are frequently aggregated together when estimating prevalence and burden. This approach is problematic, as asthma is a complex disease with multiple phenotypes that can differ by medication requirements and age of onset, among other characteristics [11]. ICS and LABA combination therapy is the mainstay of controller treatment for moderate-to-severe asthmatics [4], yet the burden of these patients, particularly among those with asthma-related and allergic comorbidities, is unexplored. Clarifying the extent of the burden attributed to asthma and related comorbidities, by level of asthma control, in patients on ICS and LABA combination therapy will provide clinicians, patients, and payers with important information on additional unmet need in patients optimized on these therapies. Such information can help to guide better and more cost-effective treatment decisions in asthma patients.

Objectives

The current study had three key objectives. First, the study examined level of asthma control among patients with asthma and asthma-related or allergic comorbidities on ICS and LABA combination therapy. Second, this study examined the association between level of asthma control and health burden, controlling for patient characteristics, among patients with asthma and asthma-related or allergic comorbidities on ICS and LABA combination therapy. Third, this study examined the association between level of asthma control and economic burden, controlling for patient characteristics, among patients on ICS and LABA combination therapy.

Methods

Data source

This retrospective observational study included data from the 2011–2013 US National Health and Wellness Survey (2011 NHWS $N = 75,000$; 2012 NHWS; $N = 71,157$ and 2013 NHWS; $N = 75,000$). The NHWS is a representative, large-scale survey of the adult population (≥ 18 years) assessing health status and outcomes across a wide array of diseases. The NHWS uses random stratified sampling framework to ensure that the demographic composition is similar to the US general population [5]. To maximize sample size of asthma patients, 3 years of NHWS data were pooled. Since it was possible for a single respondent to have participated in consecutive survey years, only the most recent year of survey data of the respondent were kept in such instances. The current study received approval from the Essex Institutional Review Board (Lebanon, New Jersey). Informed consent was obtained from all participants.

Sample

Patients with asthma currently on ICS and LABA combination therapy were included in the analyses ($N = 1923$). Asthma was defined by a self-reported physician diagnosis of asthma. Asthma with asthma-related or allergic comorbidities (here after referred to as “allergic asthma”) was defined by a self-reported physician diagnosis of asthma and at least one of the following comorbid conditions: chronic hives, dermatitis, nasal allergies, hay fever, atopic dermatitis, eczema, or skin allergies. ICS and LABA combination therapy included patients who were currently on a combination inhaler (ICS and LABA in one inhaler/device) or those on two separate inhalers (one ICS only inhaler plus one LABA

only inhaler); patients may also have been taking other asthma prescription medications.

Measures

Asthma control

Patients were grouped by asthma control, according to their Asthma Control Test scores (scores ≤ 15 : very poorly controlled; 16–19: not well-controlled; 20–25: well-controlled asthma) [12].

Demographics and patient characteristics

Participants provided data on age, gender, race/ethnicity (non-Hispanic black, Hispanic, other, vs. non-Hispanic white), marital status (married/living with partner vs. not married), insurance (do not have vs. have), education (university degree vs. less than university degree), household income ($< \$25K$, $\$25$ – $\$50K$, $\$50$ – $\$75K$, or decline to answer vs. $\$75K+$), and employment status (employed vs. unemployed).

Participants self-reported smoking status (currently smoke, former smoker vs. never smoker), alcohol use (drink vs. do not drink alcohol), and exercise behavior (exercise vs. do not exercise for 20 minutes or more, one or more times in the past month). Body mass index (BMI; underweight, overweight, obese, unknown vs. normal weight) and comorbidities (Charlson Comorbidity Index [CCI] scores) [13], were calculated. Higher total CCI index score indicate more comorbidity burden on the patient. Additionally, participants were asked how many years since they were diagnosed with asthma, time(s) of the year asthma was experienced (spring, summer, autumn, and/or winter), frequency of problems in the seasons when experiencing asthma, and main causes of asthma attacks (e.g., allergies, exercise, etc.).

Health burden

Health status. Eight health domain scores (bodily pain, general health, mental health, physical functioning, role emotional, role physical, social functioning, and vitality), physical component summary score (PCS), mental component summary score (MCS), and Short Form-6 Dimension (SF-6D) health utilities were derived from the Medical Outcomes Study Short Form-12 Item Health Survey version 2 (SF-12v2; survey year 2011) or the Short Form-36 Item Health Survey version 2 (SF-36v2; survey years 2012–2013) [14–18]. The norm-based MCS, PCS, and health domains have a population mean of 50 and a standard deviation of 10 [16]. Previous research reported a population mean of 0.79–0.81 for health utilities [19]. Additionally, 3 points for MCS and PCS, 5 points on health domains, and 0.041 points for health utilities represent minimally important differences (MIDs) [16, 20].

Psychological symptoms. Participants self-reported presence or absence of depression, anxiety, and sleep problems (insomnia and sleep difficulties) were experienced in the past 12 months.

Economic burden

Work productivity and activity impairment. The Work Productivity and Activity Impairment-General Health Scale (WPAI-GH v2.0) [21] includes the following metrics: absenteeism (% of time missed from work due to health in the past 7 days), presenteeism (% of impairment while at work due to health in the past 7 days) overall work impairment (aggregate of absenteeism and presenteeism), and activity impairment (% of impairment in daily activities due to health in the past 7 days).

HRU. The frequency of various forms of all-cause (i.e., for any reason) HRU in the past 6 months was self-reported, specifically, ER visits, hospitalizations, and traditional HCP visits (includes general/family practitioners, internists, and specialists).

Estimated annual direct costs. All-cause HRU costs were calculated from MEPS data by applying 2012 age-specific unit cost to each HRU event for each NHWS respondent [22].

Estimated annual indirect costs. Similar calculations were performed for estimates of indirect costs. In this case, 2012 age- and gender-specific wages from the Bureau of Labor Statistics were applied to work hours lost with presenteeism and absenteeism from the WPAI-GH [23].

Estimated annual total costs. For employed participants, estimated total costs included the total of direct and indirect costs. Total costs for unemployed respondents only included direct costs.

Statistical analysis

Overall one-way analysis of variance (ANOVA; for continuous variables) and chi-square tests (for categorical variables) were used to compare demographics, health characteristics, and health and economic outcomes by asthma control groups. All multiple pair-wise comparisons were conducted with t-tests (continuous variables) or binomial proportion tests (z-tests; categorical variables) with Bonferroni correction.

Generalized linear models (GLMs) were then used to predict differences in outcomes between asthma control groups, controlling for age, gender, ethnicity, education, income, partner status, insurance, BMI category, smoking, alcohol use, exercise, CCI scores, and years diagnosed with asthma. GLMs specifying identity link distributions were used to predict health domains, physical and MCSs, and health utilities. GLMs specifying a binominal distribution with logit link functions were used to predict the

presence/absence of depression, anxiety, or sleep problems. GLMs specifying negative binomial distributions with log-link functions were used to predict WPAI-GH scores, HRU visits, and costs (due to pronounced skew). Adjusted means were reported, along with 95% confidence intervals (CIs) for all multivariable models. Any two-sided p -value, less than 0.05, was considered statistically significant.

Results

Demographic and patient characteristics

Among all asthma patients, the mean age was 49.8 years, 66.3% were female, and 75.9% were white (Table 1). There were 563 (29.3%) very poorly controlled, 482 (25.1%) not well-controlled, and 878 (45.7%) well-controlled asthma patients. Compared with well-controlled asthma patients, a higher proportion of very poorly controlled asthma patients were single, had less than a 4-year college degree, and had lower income. Compared to well-controlled asthma patients, a higher proportion of very poorly controlled asthma patients were obese, current smokers, and did not exercise. In terms of comorbidity burden, a higher proportion of very poorly controlled asthma patients had a score of 3+ on the CCI than not well or well-controlled asthma patients. The most common allergic conditions across the groups were nasal allergies, hay fever, skin allergies, and eczema. Compared with well-controlled asthma patients, very poorly controlled asthma patients had a longer history of asthma and experienced asthma problems more on a daily basis. Although asthma patients in this analysis were all treated with ICS and LABA, many were also taking other asthma medications. Among the other asthma medications taken by allergic asthma patients, 75.2% were on a short-acting beta-agonist (SABA), 25.1% on leukotriene antagonists, 8.7% on an anticholinergic, 1.1% on a theophylline, 1.1% on anti-IgE, and less than 1% on an oral corticosteroids (See Table A1 in Appendix).

Health and economic burden of allergic asthma

Among asthma patients in the study sample, mean MCS was 45.9, PCS was 42.5, and health utilities was 0.66; all were below established population norms of 50 for MCS and PCS and 0.79–0.81 for health utilities (Table 2). All of the mean scores for the eight health domains were also below population norms of 50. More than a third of the allergic asthma patients experienced any anxiety disorder or depression, and half experienced sleep problems.

Among asthma patients, the mean percentage of overall work impairment was 25.6%, which was largely driven

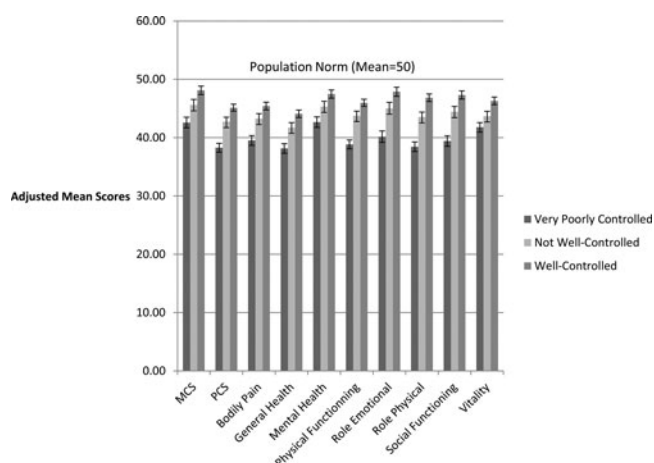


Figure 1. HRQoL by asthma control, adjusted for covariates. Models were adjusted for age, gender, ethnicity, education, income, partner status, insurance, BMI, smoking, alcohol, exercise, and years diagnosed with asthma. Error bars depict 95% CIs. All pairwise comparisons between asthma control groups significantly differed at $p < 0.001$, except for very poorly controlled vs. not well-controlled on vitality, which differed at $p = 0.001$.

by presenteeism (22.6%), rather than absenteeism (6.3%) (Table 2). The mean percentage of activity impairment was 40.0%. Additionally, on average, patients visited a traditional HCP approximately eight times in the past 6 months and incurred annual total costs of \$33 228.

The eight health domain scores, MCS, PCS, and health utilities were lowest among patients with very poorly controlled, followed by patients with not well controlled, and highest in patients with well-controlled asthma (Table 2). Patients with very poorly controlled and not well-controlled asthma had greater incidences of experiencing any anxiety disorder, depression, and sleep problems than patients with well-controlled asthma.

WPAI-GH scores (presenteeism, overall work impairment, and activity impairment), HRU (ER visits and hospitalizations), and annual estimated costs (indirect, direct, and total) were highest among patients with very poorly controlled, followed by patients with not well controlled, and lowest in patients with well-controlled asthma (Table 2).

Adjusted associations between asthma control and HRQoL

After adjusting for covariates, very poorly controlled, compared with not well-controlled and well-controlled, asthma patients had lower MCS, PCS (Figure 1), and health utilities (adjusted means = 0.61 vs. 0.66 and 0.70, $p < 0.001$). Not well-controlled patients also had significantly lower MCS, PCS, and health utilities (adjusted means = 0.66 vs. 0.70, $p < 0.001$) than well-controlled patients. Findings for the eight health domain scores

Table 1. Demographic and patient characteristics by asthma control among diagnosed asthma patients with asthma-related/allergic comorbidities on ICS and LABA combination therapy.

	Asthma Control							
	Very poorly controlled asthma N = 563 (a)			Not well controlled asthma N = 482 (b)		Well controlled asthma N = 878 (c)		a p-value
	Mean / %	SD / N	Mean / %	SD / N	Mean / %	SD / N		
Demographics								
Age	49.8	15.4	51.4 _b	14.2	48.3 _a	16.4	49.6	0.004
Gender								
Female	66.3%	1274	65.9%	371	66.0%	318	66.6%	0.949
Male	33.7%	649	34.1%	192	34.0%	164	33.4%	
Race/Ethnicity								
Non-Hispanic white	75.9%	1459	71.0% _c	400	75.5%	364	79.2% _a	0.016
Non-Hispanic black	10.1%	195	11.2% _c	63	9.8%	47	9.7%	85
Hispanic	7.1%	136	9.4% _c	53	6.8%	33	5.7% _a	50
Other ethnicity	6.9%	133	8.3% _c	47	7.9%	38	5.5%	48
Education								
< 4-yr college degree	60.3%	1159	74.2% _{b,c}	418	62.0% _{a,c}	299	50.3% _{a,b}	<0.001
4-yr college degree or higher	39.7%	764	25.8% _{b,c}	145	38.0% _{a,c}	183	49.7% _{a,b}	436
Annual Household Income								
< \$25k	23.9%	460	32.5% _{b,c}	183	26.8% _a	129	16.9% _a	148
\$25k to \$50k	26.3%	505	30.0% _c	169	26.1% _a	126	23.9% _a	210
\$50k to \$75k	19.6%	377	15.8% _c	89	18.3%	88	22.8% _a	200
\$75k or more	24.6%	474	18.1% _{b,c}	102	23.9% _a	115	29.3% _a	257
Decline to Answer	5.6%	107	3.6% _c	20	5.0%	24	7.2% _a	63
Marital Status								
Single	42.9%	825	47.2% _c	266	44.0%	212	39.5% _a	347
Married/living with partner	57.1%	1098	52.8% _c	297	56.0%	270	60.5% _a	531
Has Health Insurance	89.5%	1722	85.8% _c	483	87.6% _c	422	93.1% _{a,b}	817
Health Characteristics								
Charlson Comorbidity Index (CCI)	0.98	1.5	1.5 _{b,c}	1.8	0.88 _{a,c}	1.3	0.67 _{a,b}	1.2
CCI categories: 0	51.5%	991	34.3% _{b,c}	193	51.9% _{a,c}	250	62.4% _{a,b}	548
CCI categories: 1	24.3%	468	27.4% _c	154	26.80%	129	21.1% _a	185
CCI categories: 2	12.2%	234	17.1% _{b,c}	96	11.6% _{a,c}	56	9.3% _{a,b}	82
CCI categories: 3+	12.0%	230	21.3% _{b,c}	120	9.8% _{a,c}	47	7.2% _{a,b}	63
Allergic Comorbidities								
Chronic hives	2.2%	43	2.70%	15	1.20%	6	2.50%	22
Nasal allergies	76.1%	1464	77.10%	434	75.70%	365	75.70%	665
Atopic dermatitis	2.9%	55	3.00%	17	2.70%	13	2.80%	25
Dermatitis	3.3%	63	3.00%	17	2.70%	13	3.80%	33
Eczema	14.9%	286	14.20%	80	15.40%	74	15.00%	132
Skin allergies	20.3%	391	23.1% _c	130	22.20%	107	17.5% _c	154
Hayfever	43.9%	845	46.00%	259	41.70%	201	43.80%	385
(Continued on next page)								

(Continued on next page)

Table 1. Continued

	Asthma Control												a-p-value				
	Total N = 1923				Very poorly controlled asthma N = 563 (a)				Not well controlled asthma N = 482 (b)					Well controlled asthma N = 878 (c)			
	Mean / %	SD / N	Mean / %	SD / N	Mean / %	SD / N	Mean / %	SD / N	Mean / %	SD / N	Mean / %	SD / N					
Body Mass Index (BMI) Category																	
BMI: underweight	1.1%	22	1.8%	10	1.2%	6	0.7%	6	0.7%	6	0.7%	6	<0.001				
BMI: normal weight	21.5%	414	16.9% _c	95	17.8% _c	86	26.5% _{a,b}	233	26.5% _{a,b}	233	26.5% _{a,b}	233					
BMI: overweight	25.2%	484	24.0% _c	135	27.0% _c	130	24.9% _a	219	24.9% _a	219	24.9% _a	219					
BMI: obese	49.0%	943	53.5% _c	301	51.5% _c	248	44.9% _a	394	44.9% _a	394	44.9% _a	394					
BMI: unknown	3.1%	60	3.9% _c	22	2.5% _c	12	3.0% _a	26	3.0% _a	26	3.0% _a	26					
Smoking Status																	
Current Smoker	17.1%	329	25.2% _{b,c}	142	18.7% _{a,c}	90	11.0% _{a,b}	97	11.0% _{a,b}	97	11.0% _{a,b}	97	<0.001				
Former Smoker	35.7%	687	37.8% _c	213	36.5% _c	176	33.9% _a	298	33.9% _a	298	33.9% _a	298					
Never Smoker	47.2%	907	36.9% _{b,c}	208	44.8% _{a,c}	216	55.0% _{a,b}	483	55.0% _{a,b}	483	55.0% _{a,b}	483					
Drinks Alcohol	64.4%	1239	55.8% _{b,c}	314	63.7% _{a,c}	307	70.4% _{a,b}	618	70.4% _{a,b}	618	70.4% _{a,b}	618	<0.001				
Exercise 20+ minutes 1+ times in past month																	
Exercise: 0 times	40.6%	781	50.1% _{b,c}	282	38.6% _a	186	35.6% _a	313	35.6% _a	313	35.6% _a	313	<0.001				
Exercise: 1+ times	59.4%	1142	49.9% _{b,c}	281	61.4% _a	296	64.4% _a	565	64.4% _a	565	64.4% _a	565					
Years of asthma diagnosis	23.9	17.0	26.0% _{b,c}	17.7	22.1% _a	15.9	23.6% _a	17.0	23.6% _a	17.0	23.6% _a	17.0	0.001				
Time of the year suffer from asthma																	
In the spring	88.8%	1707	88.3%	497	88.4%	426	89.3%	784	89.3%	784	89.3%	784	0.798				
In the summer	82.5%	1586	88.3% _{b,c}	497	82.0% _a	395	79.0% _a	694	79.0% _a	694	79.0% _a	694	<0.001				
In the autumn	85.1%	1637	87.2% _c	491	83.2% _a	401	84.9% _a	745	84.9% _a	745	84.9% _a	745	0.182				
In the winter	80.3%	1544	80.3%	452	81.3%	392	79.7%	700	79.7%	700	79.7%	700	0.777				
Frequency of problems in the seasons when experience asthma																	
Daily	28.0%	538	48.5% _{b,c}	273	24.5% _{a,c}	118	16.7% _{a,b}	147	16.7% _{a,b}	147	16.7% _{a,b}	147	<0.001				
4-6 times a week	14.2%	274	21.8% _c	123	18.0% _c	87	7.3% _{a,b}	64	7.3% _{a,b}	64	7.3% _{a,b}	64					
2-3 times a week	20.0%	384	19.7% _{b,c}	111	29.9% _{a,c}	144	14.7% _{a,b}	129	14.7% _{a,b}	129	14.7% _{a,b}	129					
Once a week	8.7%	168	4.3% _{b,c}	24	9.3% _a	45	11.3% _a	99	11.3% _a	99	11.3% _a	99					
2-3 times a month	14.1%	271	4.4% _{b,c}	25	12.2% _{a,c}	59	21.3% _{a,b}	187	21.3% _{a,b}	187	21.3% _{a,b}	187					
Once a month or less often	15.0%	288	1.2% _{b,c}	7	6.0% _{a,c}	29	28.7% _{a,b}	252	28.7% _{a,b}	252	28.7% _{a,b}	252					
Main causes of asthma attacks																	
Allergies/Allergic reaction	77.6%	1493	80.5%	453	75.7%	365	76.9%	675	76.9%	675	76.9%	675	0.143				
Exercise/Physical activity	49.6%	954	57.2% _c	322	53.9% _c	260	42.4% _{a,b}	372	42.4% _{a,b}	372	42.4% _{a,b}	372	<0.001				
Illnesses/Conditions (e.g. colds, flu)	45.6%	876	51.7% _c	291	44.6% _c	215	42.1% _a	370	42.1% _a	370	42.1% _a	370	0.002				
Pollutants/Airborne irritants	60.1%	1155	69.8% _{b,c}	393	60.0% _a	289	53.9% _a	473	53.9% _a	473	53.9% _a	473	<0.001				
Second hand smoke	36.0%	692	38.4% _c	216	34.2% _a	165	35.4% _a	311	35.4% _a	311	35.4% _a	311	0.341				
Stress/Anxiety/Emotional states	36.9%	709	51.3% _{b,c}	289	38.6% _{a,c}	186	26.7% _{a,b}	234	26.7% _{a,b}	234	26.7% _{a,b}	234	<0.001				
Weather/Temperature	62.0%	1192	74.1% _{b,c}	417	61.8% _{a,c}	298	54.3% _{a,b}	477	54.3% _{a,b}	477	54.3% _{a,b}	477	<0.001				
None of these	2.2%	42	1.4% _c	8	2.5% _{a,c}	12	2.5% _a	22	2.5% _a	22	2.5% _a	22	0.338				

Note: Subscript (a, b, c) correspond to whether the value significantly differ at $p < 0.05$ (binomial proportion tests for categorical variables or t-tests for continuous variables) to the respective comparison group (a = very poorly controlled, b = not well controlled and c = well controlled). All pair-wise comparisons are adjusted with the Bonferroni correction. ICS: inhaled corticosteroid; LABA: Long-acting beta-agonist; SD: Standard deviation.

a p-value column represent values from omnibus/overall ANOVA or chi-square tests.

Table 2. Health and economic burden by asthma control among diagnosed asthma patients with asthma-related/allergic comorbidities on ICS and LABA combination therapy.

	Asthma control						^a p-value		
	Total N = 1923		Very poorly controlled asthma N = 563 (a)		Not well-controlled asthma N = 482 (b)			Well-controlled asthma N = 878 (c)	
	Mean/%	SD/N	Mean/%	SD/N	Mean/%	SD/N		Mean/%	SD/N
Health-related quality of life									
SF-36/SF-12 summary scores									
SF-36 mental component summary score (MCS)	45.9	11.7	41.8 _{b,c}	12.2	45.2 _{a,c}	11.1	48.8 _{a,b}	10.9	<0.001
SF-36 physical component summary score (PCS)	42.5	11.6	35.7 _{b,c}	11.4	43.0 _{a,c}	10.5	46.7 _{a,b}	10.2	<0.001
SF-6D health utilities	0.66	0.14	0.59 _{b,c}	0.12	0.65 _{a,c}	0.11	0.71 _{a,b}	0.13	<0.001
SF-36/SF-12 norm-based domain scores									
Bodily pain	43.1	11.3	37.5 _{b,c}	10.9	43.3 _{a,c}	10.5	46.7 _{a,b}	10.4	<0.001
General health	41.8	11.4	35.9 _{b,c}	10.9	41.7 _{a,c}	10.1	45.6 _{a,b}	10.7	<0.001
Mental health	45.5	11.4	41.8 _{b,c}	12.0	44.9 _{a,c}	10.3	48.3 _{a,b}	10.9	<0.001
Physical functioning	43.4	11.6	36.4 _{b,c}	11.5	44.0 _{a,c}	10.5	47.5 _{a,b}	10.0	<0.001
Role emotional	44.9	12.6	38.7 _{b,c}	14.1	44.9 _{a,c}	11.5	48.9 _{a,b}	10.2	<0.001
Role physical	43.6	11.8	36.2 _{b,c}	11.5	43.7 _{a,c}	10.7	48.2 _{a,b}	10.0	<0.001
Social functioning	44.3	12.0	37.8 _{b,c}	12.0	44.2 _{a,c}	11.2	48.5 _{a,b}	10.4	<0.001
Vitality	44.3	10.7	40.2 _{b,c}	10.3	43.6 _{a,c}	9.6	47.4 _{a,b}	10.5	<0.001
Experience of disorders in past 12 months									
Any anxiety disorder	37.7%	725	44.4% _c	250	44.2% _c	213	29.8% _{a,b}	262	<0.001
Depression	36.5%	702	48.1% _{b,c}	271	40.0% _{a,c}	193	27.1% _{a,b}	238	<0.001
Sleep problems (insomnia, sleep difficulties)	50.5%	971	61.5% _{b,c}	346	53.9% _{a,c}	260	41.6% _{a,b}	365	<0.001
Work productivity and activity impairment									
Absenteeism % ^b	6.3	16.9	12.3 _{b,c}	22.4	6.1 _a	17.2	3.7 _a	12.9	<0.001
Presenteeism % ^c	22.6	26.6	37.5 _{b,c}	30.8	23.4 _{a,c}	25.1	15.7 _{a,b}	22.4	<0.001
Overall work impairment % ^b	25.6	29.4	42.2 _{b,c}	33.1	26.3 _{a,c}	28.2	17.9 _{a,b}	24.9	<0.001
Activity impairment %	40.0	32.1	59.1 _{b,c}	28.8	39.6 _{a,c}	29.7	28.0 _{a,b}	29.3	<0.001
Healthcare resource use in past 6 months									
Number of visits to any traditional healthcare provider	8.1	10.2	9.8 _{b,c}	12.6	8.1 _a	10.2	7.0 _a	8.2	<0.001
Number of ER visits	0.48	1.3	0.79 _{b,c}	1.7	0.41 _a	1.3	0.32 _a	1.0	<0.001
Number of hospitalizations	0.21	0.72	0.39 _{b,c}	1.1	0.17 _{a,c}	0.52	0.10 _{a,b}	0.41	<0.001
Annualized estimated costs (\$)									
Total indirect costs ^b	8716	12 533	15 374 _{b,c}	16 926	8394 _{a,c}	10 811	5974 _{a,b}	9725	<0.001
Total direct costs	29 122	47 301	41 631 _{b,c}	67 375	27 222 _{a,c}	40 265	22 143 _{a,b}	30 886	<0.001
Total cost ^d	33 228	48 311	47 202 _{b,c}	68 124	31 297 _{a,c}	41 234	25 328 _{a,b}	31 917	<0.001

Note: Subscript (a, b, c) correspond to whether the value significantly differ at $p < 0.05$ (binomial proportion tests for categorical variables or t-tests for continuous variables) to the respective comparison group (a = very poorly controlled, b = not well controlled and c = well controlled). All pair-wise comparisons are adjusted with the Bonferroni correction. ICS: Inhaled corticosteroid; LABA: Long-acting beta-agonist; SD: Standard deviation; SF-6D: Short form-6 dimensions; SF-12: Medical Outcomes Study Short Form-12-item health survey version 2; SF-36: Short Form-36-item health survey version 2.

^a *P*-value column represent values from omnibus/overall ANOVA or chi-square tests.

^b Calculated for employed only: very poorly n = 197; not well n = 226; well n = 448.

^c Calculated for unemployed only: very poorly n = 195; not well n = 225; well n = 446.

^d Total costs for unemployed respondents include only direct costs.

Table 3. Experience of any anxiety disorder, depression, or sleep difficulties in the past 12 months by asthma control among diagnosed asthma patients with asthma-related/allergic comorbidities on ICS and LABA combination therapy, adjusting for covariates.

	OR	95% CI for OR		^b <i>p</i> -value	Adjusted means
		Lower	Upper		
<i>Experience of any anxiety disorder</i>					
Very poorly controlled	1.8	1.4	2.3	<0.001	41.9%
Not well-controlled	1.7	1.3	2.2	<0.001	41.4%
Well-controlled ^a					29.1%
<i>Experience of depression</i>					
Very poorly controlled	1.9	1.5	2.5	<0.001	43.1%
Not well-controlled	1.5	1.2	1.9	0.001	37.3%
Well-controlled ^a					28.2%
<i>Experience of any sleep problems (insomnia, sleep difficulties)</i>					
Very poorly controlled	1.7	1.3	2.2	<0.001	58.0%
Not well-controlled	1.5	1.2	1.9	0.001	54.2%
Well-controlled ^a					44.6%

Note. Presented are results summary from generalized linear models specifying a binominal distribution with logit link functions. Covariates included: age, gender (male vs. female), ethnicity (non-Hispanic black, Hispanic, other vs. non-Hispanic white), education (4 years or more vs. <4 years), income (<\$25K, \$25–50K, \$50–75K, declined to answer vs. \$75K or more), partner status (married/living together vs. single/separated/divorced/widowed), insurance (don't have vs. have), BMI (underweight, overweight, obese, unknown vs. normal weight), smoking (current, former vs. never), alcohol (drink vs. don't drink), exercise (1+ times vs. 0 times) and years diagnosed with asthma. OR: Odds ratio; CI: Confidence interval.

^aReference group in the multivariable model.

^b*p*-value represents comparison of GLM parameters.

followed a similar pattern (Figure 1). Notably, patients with very poorly controlled, compared with patients with well-controlled asthma, scored more than eight points lower on role-physical and nearly eight points lower on social functioning. Compared with those who were well-controlled, very poorly controlled patients experienced 1.8 times as much of any anxiety disorder, 1.9 times as much depression, and 1.7 times as much sleep problems (Table 3).

Adjusted associations between asthma control and economic outcomes

After adjusting for covariates, very poorly controlled asthma patients, compared with those not well-controlled and well-controlled, had greater overall work impairment and activity impairment (Figure 2). Very poorly controlled asthma patients, compared with those not well-controlled and well-controlled, had more ER visits and hospitalizations (Figure 3). Very poorly controlled asthma patients, compared with those well-controlled, had higher numbers of HCP visits.

Annual direct costs incurred by very poorly controlled asthma patients were 1.5-fold higher than annual direct costs for well-controlled patients (Figure 4). Annual indirect costs incurred by very poorly controlled asthma patients were 2.2-fold higher than annual indirect costs for well-controlled patients. Annual total costs incurred by very poorly controlled asthma patients were 1.5-fold higher than annual total costs for well-controlled patients. Annual indirect and total costs were similarly higher for very poorly controlled asthma patients, compared with not well-controlled patients.

Discussion

The current study aimed to examine associations between level of asthma control with HRQoL and economic outcomes, among asthma patients with asthma-related or allergic comorbidities on ICS and LABA combination therapy. Unlike prior research, this study provided a more comprehensive account of the health and economic burden specific to adults with asthma and related comorbidities on ICS and LABA combination therapy. Findings of less than optimal levels of asthma control and the positive impact of better asthma control on HRQoL, WPAI, HRU, and costs highlight considerable unmet need in this population.

Prior studies reported that poorly controlled symptoms were found among a sizeable percentage (40%) of US adults with asthma [5]. The current study found that among allergic asthma patients on an ICS plus LABA, over half (54.4%) reported very poorly controlled or not well-controlled asthma. It may be that patients with allergic asthma who are not well-controlled have comorbidities that were not well treated. However, in multivariable regression analyses, the CCI, a measure of comorbidity burden, was included as a covariate to control for the effect of CCI comorbidities. Thus, comorbidities or untreated comorbidities cannot fully account for high uncontrolled asthma finding. Another possibility is that patients on ICS plus LABA regimen were not adherent to their treatment and thus, there was a high prevalence of uncontrolled asthma found in the current study. It may be possible that there were differences in the formulations of fixed-dose combination medications used in the controlled vs. uncontrolled groups leading to possible differences

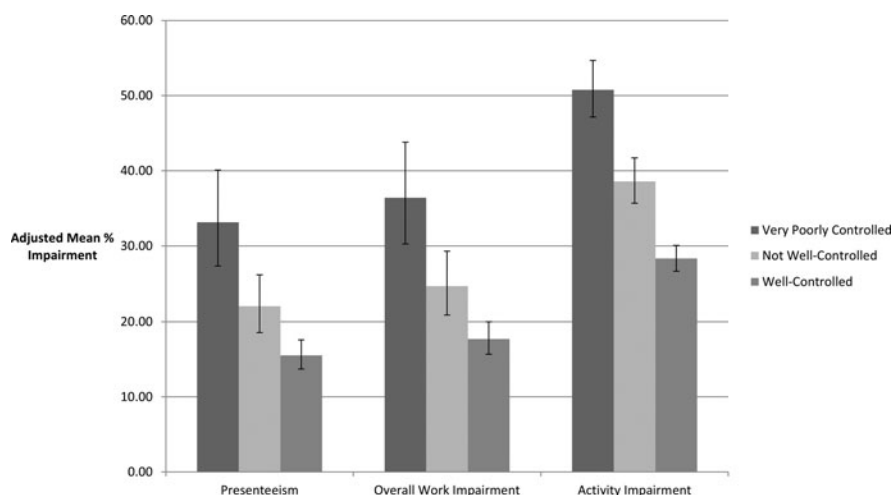


Figure 2. Work productivity and activity impairment by asthma control, adjusted for covariates. Models were adjusted for age, gender, ethnicity, education, income, partner status, insurance, BMI, alcohol, exercise, and years diagnosed with asthma. Error bars depict 95% CIs. Presenteeism and overall work impairment were calculated for employed respondents only. All pair-wise comparisons between asthma control groups significantly differed at $p < 0.01$.

in the effectiveness of fixed-dose combination medications in the controlled vs. uncontrolled groups. The higher rate of SABA and ipratropium inhalers in the uncontrolled group could be a result of patients confusing controller inhalers with rescue inhalers, though, we cannot be certain of this occurrence. Additionally, physicians may not be consistently abiding by guidelines to step-up therapy for uncontrolled patients with persistent asthma. Particularly, NHLBI guidelines (for the US) indicate that, as symptom severity and frequency increase, the dose of ICS (plus LABA) should likewise increase [4]. Furthermore, additional treatment options for appropriate

allergic asthma patients should be considered such as biologics and oral corticosteroids if needed (Steps 5 and 6) [4].

The current study's findings on allergic asthma agreed with prior research showing asthma to be associated with lower HRQoL [5, 6, 8]. Specifically, very poorly controlled compared with not well-controlled and well-controlled allergic asthma patients had lower MCS, PCS, and health utilities that exceeded MID. Not well-controlled patients also had significantly lower MCS, PCS, and health utilities than well-controlled patients; however, only health utilities reached MID thresholds. Moreover, differences in general health, bodily pain, physical functioning, role emotional, role physical, and social functioning health

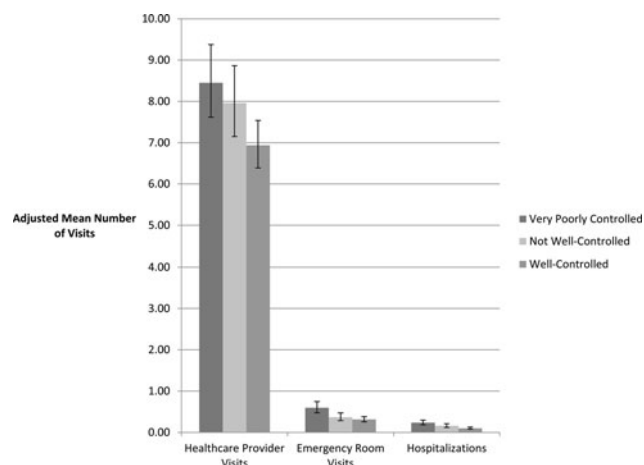


Figure 3. Six-month HRU by asthma control, adjusted for covariates. Models were adjusted for age, gender, ethnicity, education, income, partner status, insurance, BMI, smoking, alcohol, exercise, and years diagnosed with asthma. Error bars depict 95% CIs. All pair-wise comparisons between asthma control groups significantly differed at $p < 0.05$, except HCP (not well vs. very poorly controlled; $p =$ not significant) and ER (not well vs. well-controlled; $p =$ not significant) visits.

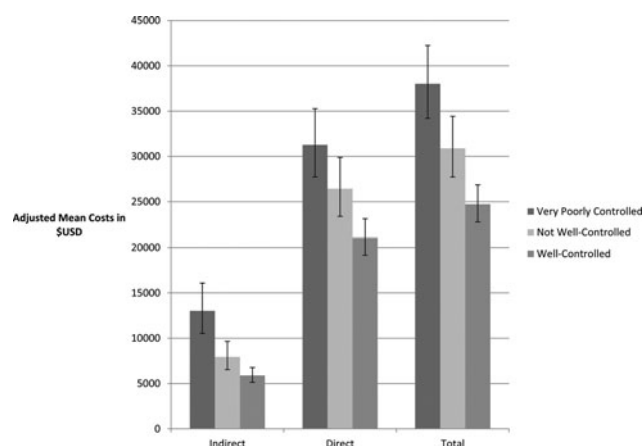


Figure 4. Annualized estimated costs by asthma control, adjusted for covariates. Models were adjusted for age, gender, ethnicity, education, income, partner status, insurance, BMI, smoking, alcohol, exercise, and years diagnosed with asthma. Error bars depict 95% CIs. All pair-wise comparisons between asthma control groups significantly differed at $p < 0.05$, except for direct costs for not well vs. very poorly controlled ($p = 0.06$).

domain scores exceeded MID between very poorly controlled and well-controlled patients [16, 20]. Also, in line with previous research, uncontrolled asthma patients experienced poorer sleep quality [8]. Thus, the large health-related burden of asthma was replicated in this study for allergic asthma.

Consistent with previous research, patients with uncontrolled asthma (i.e., very poorly controlled or not well-controlled asthma) had greater work productivity loss, activity impairment, and HRU [5, 6]. As a result of work productivity loss and HRU, very poorly controlled patients were found to have total costs over one and half times higher than patients with well-controlled symptoms. Specifically, the indirect costs of very poorly controlled patients were over double than those incurred by well-controlled patients. The direct costs of very poorly controlled patients were almost one and a half times higher than those of well-controlled patients. Thus, results from the present study contributed to the evidence demonstrating the high costs ascribed to asthma, especially for those with uncontrolled symptoms, and particularly for the allergic asthma subpopulation [5, 6, 9]. Overall findings underscored the considerable economic burden associated with poor asthma control among allergic asthma patients.

Implications of study findings can be contextualized using Link and Phelan's fundamental social causes of health theoretical framework, which posits that social factors (e.g., economic hardship, low educational attainment, racial discrimination, sexism, etc.) can fundamentally cause inequalities in health [24, 25]. According to this framework, high socioeconomic status and its associated resources of money, knowledge, power, and prestige are beneficial to maintaining a health advantage. Indeed, the current study found that there was a higher rate of uncontrolled asthma in the lower income and education brackets. Although not directly assessed in the current survey, it is possible the cost of medication may impact adherence which would impact asthma control. Additionally, the considerably high costs associated with uncontrolled asthma may place a particularly higher burden on low-income relative to high-income patients and their families. Thus, an appreciation of the high economic burden of uncontrolled asthma within the context of socioeconomic disparities further illustrates the impact of poor asthma disease management, and may help clinicians better understand potential individual and societal-level gains from long-term asthma control improvement.

Strengths and limitations

This study examined the health and economic burden of asthma from the patient's perspective. Patient self-report can be more readily used to assess subjective outcomes,

such as HRQoL, that cannot be evaluated using alternative means, like claims databases or are expensive to collect in clinical trials. Moreover, the study contributes to the limited real-world data on asthma patients with asthma-related or allergic comorbidities treated with ICS and LABA. By conceptualizing burden broadly to encompass health and economic outcomes, this study provided a more complete account of the unique burden experienced by patients with asthma and related comorbidities and demonstrated that asthma control has meaningful effects on both health and costs. This study contributed to the better understanding of the burden specifically associated with asthma in combination with asthma-related or allergic comorbidities and highlighted the need for improvement in disease management, including the assessment of treatment adherence and consideration of other treatment options.

There were some limitations to consider when making inferences about the results. Particularly, causal conclusions cannot be established from the findings, given this was a cross-sectional survey. Further, it was unknown if patients were being adherent to their prescribed treatment regimen. Thus, future research should examine treatment adherence in order to better understanding the factors contributing to the high prevalence of uncontrolled asthma among allergic asthma patients on ICS and LABA found in the current study. Recall bias may have also been introduced, due to the self-reported response format. Similarly, it was not possible to confirm the patient-reported responses regarding diagnosis and treatment, among other study variables. Certain psychiatric diagnoses such as depression may be particularly susceptible to self-reporting bias and may be under-reported. To better control for these shortcomings, future research could supplement self-report measures with more objective sources of data (e.g., medical records) to validate participants' responses.

The survey may selectively under-represent the asthma population, due to age-related limitations (e.g., very frail elderly patients are less likely to complete the survey) and limited access to the Internet (e.g., very low-income individuals and elderly asthma patients may not have computer access). While the NHWS was designed to mimic the demographic characteristics of the general adult population, whether it adequately represents the population of adults with asthma cannot be verified.

Conclusions

Among asthma patients on ICS and LABA, over half had very poorly or not well-controlled asthma. The substantial number of uncontrolled asthma patients demonstrates the importance of appropriate disease monitoring by the treating clinician, including assessment of

treatment adherence and consideration for stepping up therapy. Findings revealed lower levels of asthma control (i.e., very poorly controlled and not well-controlled) were associated with worse HRQoL, greater work productivity loss, activity impairment, HRU, and indirect, direct, and total costs. Even a modest increment in asthma control was associated with less work productivity loss, HRU, and costs. Overall, the current study highlights a considerable unmet need in asthma patients on ICS and LABA and should help inform both healthcare practitioner and payor understanding and decision-making with regard to alleviating disease burden.

Acknowledgment

The authors acknowledge the literature review and editing assistance of Martine C. Maculaitis, PhD, on behalf of Kantar Health. Poster presentations of sections of this work were given at the Academy of Managed Care Pharmacy (AMCP) Annual Meeting on April 19–22, 2016 and American Thoracic Society (ATS) Conference on May 13–18, 2016. A poster presentation of a third section of this work was also given at the American College of Chest Physicians (CHEST) Annual Meeting on October 22–26, 2016.

Declaration of interests

The study reported on this manuscript was funded by Novartis Pharmaceuticals Corporation. Lulu Lee is an employee of Kantar Health, who received funding from Novartis to conduct and report on this study. Engels Obi, Brandee Paknis, and Abhishek Kavati are employees of Novartis, who funded this study. Bradley Chippis serves as a consultant for Novartis, AstraZeneca, Boehringer Ingelheim, Circassia, Genetech, and Teva.

Funding

The authors acknowledge the funding from the Novartis Pharmaceuticals Corporation.

References

- Kim K, Jahan SA, Kabir E. A review of human health perspective of air pollution with respect to allergies and asthma. *Environ Int* 2013;59:41–52.
- Centers for Disease Control and Prevention. Vital signs: asthma prevalence, disease characteristics, and self-management education: United States, 2001–2009. *MMWR Morb Mortal Wkly Rep* 2011;60:547–552.
- World Health Organization. (2013). Asthma (Fact sheet #307). [Internet]. [cited 2016 Feb 5]. Available from: <http://www.who.int/mediacentre/factsheets/fs307/en/>
- National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program. Expert panel report 3: guidelines for the diagnosis and management of asthma, 2007. [Internet]. [cited 2016 Feb 5]. Available from: <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf>
- Vietri J, Burslem K, Su J. Poor asthma control among US workers: health-related quality of life, work impairment, and health care use. *J Occup Environ Med* 2014;56:425–430.
- Williams SA, Wagner S, Kannan H, Bolge SC. The association between asthma control and health care utilization, work productivity loss and health-related quality of life. *J Occup Environ Med* 2009;51:780–785.
- Walters P, Schofield P, Howard L, Ashworth M, Tylee A. The relationship between asthma and depression in primary care patients: a historic cohort and nested case control study. *PLoS One* 2011;6:e20750.
- Luyster FS, Teodorescu M, Bleeker E, Busse W, Calhoun W, Castro M, et al. Sleep quality and asthma control and quality of life in non-severe and severe asthma. *Sleep Breath* 2012;16:1129–1137.
- Sullivan PW, Ghushchyan VH, Slejko J, Belozeroff V, Globe DR, Lin S. The burden of adult asthma in the United States: evidence from the medical expenditure panel survey. *J Allergy Clin Immunol* 2011;127:363–369.e3.
- Thomas M, von Ziegenweid J, Lee AJ, Price D. High-dose inhaled corticosteroids versus add-on long-acting β -agonists in asthma: an observational study. *J Allergy Clin Immunol* 2009;123:116–121.e10.
- Moore WC, Meyers DA, Wenzel SE, Teague G, Li H, Li X, et al. Identification of asthma phenotypes using cluster analysis in the severe asthma research program. *Am J Respir Crit Care Med* 2010;181:315–323.
- Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the Asthma Control Test: a survey for assessing asthma control. *J Allergy Clin Immunol* 2004;113:59–65.
- Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–383.
- Ware JE, Kosinski M, Keller SD. A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996;34:220–233.
- Ware JE, Kosinski M, Turner-Bowker DM, Gandek B. How to score version 2 of the SF-12[®] health survey (with a supplement documenting version). Lincoln, RI: Quality Metric, Inc.; 2002.
- Ware JE, Kosinski M, Gandek B. SF-36 health survey: manual and interpretation guide. 2nd ed. Lincoln, RI: Quality Metric, Inc.; 2000.
- Brazier, JE & Roberts, J. The estimation of a preference-based measure of health from the SF-12. *Med Care* 2004;42:851–859.
- Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ* 2002;21:271–292.
- van den Berg, B. SF-6D population norms. *Health Econ* 2012;21:1508–1512.
- Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. *Qual Life Res* 2005;14:1523–1532.
- Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics* 1993;4:353–365.

22. Agency for Healthcare Research and Quality. Medical expenditure panel survey: center for financing, access and cost trends; 2012. [Internet]. [cited 2009 April 29]. Available from: <http://meps.ahrq.gov/mepsweb/index.jsp>
23. US Bureau of Labor Statistics. Highlights of women's earnings in 2012. [Internet]. [cited 2016 Nov 3]. Available from: http://www.bls.gov/opub/reports/womens-earnings/archive/womensearnings_2012.pdf
24. Link BG, Phelan JC. Social conditions as fundamental causes of disease. *J Health Soc Behav* 1995;35(Extra Issue):80–94.
25. Phelan JC, Link BG, Tehranifar P. Social conditions as fundamental causes of health inequalities: theory, evidence, and policy implications. *J Health Soc Behav* 2010;51 Suppl:S28–S40.

Appendix

Table A1. Asthma treatment by asthma control among diagnosed asthma patients with asthma-related/allergic comorbidities on ICS and LABA combination therapy.

	Asthma control								^a <i>p</i> -value
	Total N = 1923		Very poorly controlled asthma N = 563 (a)		Not well-controlled asthma N = 482 (b)		Well-controlled asthma N = 878 (c)		
			%	N	%	N	%	N	
Any ICS/LABA fixed-dose combination	97.2	1870	97.5	549	96.7	466	97.4	855	0.676
Fluticasone/salmeterol	59.4	1142	57.0 _c	321	53.1 _c	256	64.4 _{a,b}	565	<0.001
Budesonide/formoterol fumarate	17.7	340	20.6 _c	116	19.9 _c	96	14.6 _{a,b}	128	0.005
Fluticasone propionate/salmeterol (HFA)	15.1	290	14.9	84	16.6	80	14.4	126	0.537
Mometasone furoate/formoterol fumarate dihydrate	5.1	98	5.0	28	7.1	34	4.1	36	0.060
Any LABA	2.8	53	2.5	14	3.3	16	2.6	23	0.676
Salmeterol	1.8	35	1.6	9	2.3	11	1.7	15	0.673
Formoterol fumarate	0.9	18	0.9	5	1.0	5	0.9	8	0.964
Any ICS	2.8	53	2.5	14	3.3	16	2.6	23	0.676
Mometasone	0.8	15	0.9	5	0.8	4	0.7	6	0.902
Fluticasone propionate	0.8	15	0.5	3	0.8	4	0.9	8	0.721
Beclometasone dipropionate	0.4	7	0.4	2	0.4	2	0.3	3	0.976
Flunisolide	0.1	1	0.2	1	0.0	0	0.0	0	0.299
Triamcinolone	0.1	1	0.2	1	0.0	0	0.0	0	0.299
Budesonide	0.1	2	0.2	1	0.0	0	0.1	1	0.669
Fluticasone propionate	0.1	2	0.2	1	0.2	1	0.0	0	0.426
Ciclesonide	0.1	1	0.0	0	0.2	1	0.0	0	0.224
Fluticasone propionate (HFA)	0.5	9	0.0	0	0.8	4	0.6	5	0.123
Any SABA	75.2	1446	85.1_{b,c}	479	80.3_a	387	66.1_a	580	<0.001
Albuterol (generic)	38.1	732	47.4 _{b,c}	267	38.8 _{a,c}	187	31.7 _{a,b}	278	<0.001
Albuterol sulfate (branded; HFA)	20.4	393	25.0 _c	141	23.0 _c	111	16.1 _{a,b}	141	<0.001
Albuterol (branded)	8.5	164	10.5	59	8.1	39	7.5	66	0.134
Ipratropium bromide	5.1	99	9.1 _c	51	5.6 _c	27	2.4 _{a,b}	21	<0.001
Albuterol sulfate	6.6	127	9.1 _c	51	7.5	36	4.6 _a	40	0.002
Albuterol sulfate (branded; HFA)	5.9	114	8.3 _c	47	6.6	32	4.0 _a	35	0.002
Albuterol (HFA)	4.5	87	4.4	25	3.7	18	5.0	44	0.552
Levalbuterol	3.7	71	6.6 _{b,c}	37	2.9 _a	14	2.3 _a	20	<0.001
Pirbuterol	1.2	23	1.1	6	1.5	7	1.1	10	0.830
Any leukotriene antagonists	25.1	483	29.3_c	165	23.9	115	23.1_a	203	0.023
Montelukast	24.0	461	27.7	156	22.6	109	22.3	196	0.047
Zafirlukast	1.1	22	1.6	9	1.2	6	0.8	7	0.367
Any anticholinergic	8.7	168	16.9_{b,c}	95	8.5_{a,c}	41	3.6_{a,b}	32	<0.001
Tiotropium	6.8	131	13.1 _{b,c}	74	6.6 _{a,c}	32	2.8 _{a,b}	25	<0.001
Ipratropium bromide	2.2	43	4.6 _c	26	2.1	10	0.8 _a	7	<0.001
Theophylline	1.4	27	2.0	11	1.7	8	0.9	8	0.223
Anti-IgE									
Omalizumab	1.1	21	1.6	9	0.8	4	0.9	8	0.385
Oral corticosteroids									
Prednisone	0.4	7	0.9	5	0.0	0	0.2	2	0.039
Prednisolone	0.0	0	0.0	0	0.0	0	0.0	0	N/A

Note: Subscript (a, b, c) correspond to whether the value significantly differ at $p < 0.05$ (binomial proportion tests for categorical variables or t-tests for continuous variables) to the respective comparison group (a = very poorly controlled, b = not well controlled and c = well controlled). All pair-wise comparisons are adjusted with the Bonferroni correction. HFA: hydrofluoroalkane; ICS: Inhaled corticosteroid; LABA: Long-acting beta-agonist; SABA: Short-acting beta-agonist.

^ap-value column represent values from omnibus/overall ANOVA or chi-square tests.