

QUALITY OF LIFE

Burden of illness of patients with allergic asthma versus non-allergic asthmaMarie-Hélène Lefebvre, MA¹, Jonathan Gravel, MSc¹, Maria Figliomeni, PhD², Jie Zhang, PhD², and Patrick Lefebvre, MA¹¹Groupe d'analyse, Ltée, Montréal, Québec, Canada and ²Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA**Abstract**

Objective: Allergic and non-allergic asthma share similar symptoms, but differ in that allergic asthma is triggered by inhaled allergens. This study compared healthcare resource utilization (HCRU) and costs between these groups using US employer-based claims data. **Methods:** Health insurance claims from Truven Marketscan database (2002Q1–2010Q2) were analyzed. Included patients had ≥ 2 asthma diagnoses and ≥ 1 year of eligibility prior to and following the date of first asthma diagnosis. Patients with ≥ 1 diagnosis for allergic asthma and ≥ 1 diagnosis for other allergic conditions formed the allergic asthma cohort whereas patients without any of these diagnoses formed the non-allergic asthma cohort. Allergic and non-allergic asthma patients were matched 1:1. HCRU and costs during the study period were compared between cohorts using incidence rate ratios (IRR) and bootstrap methods. **Results:** Sixty four thousand four hundred and seventy three allergic and non-allergic asthma patients were matched (mean age = 30; 57.1% female; mean CCI = 0.2), with 7.1% and 0.36% having received an allergy test during the baseline period, respectively. During the study period, allergic asthma patients had significantly more asthma-related pharmacy dispensings (IRR[95% CI] = 2.25[2.22–2.28], $p < 0.001$) and asthma-related outpatient visits (IRR[95% CI] = 2.29[2.27–2.32], $p < 0.001$). Allergic asthma patients incurred 39% greater per-patient-per-year all-cause costs (allergic: \$4008; non-allergic: \$2889, $p < 0.001$) and 79% greater asthma-related costs (allergic: \$1063; non-allergic: \$592, $p < 0.001$) than non-allergic asthma patients. **Conclusions:** These results indicate, even in a relatively healthy population, allergic asthma is associated with greater HCRU and costs. Guideline-recommended IgE allergy tests should be employed in distinguishing the two forms of asthma, to optimize patient management and reduce costs.

Keywords

Asthma, allergic conditions, claims data, healthcare costs, resource utilization

History

Received 31 August 2012

Revised 20 May 2013

Accepted 27 May 2013

Published online 9 July 2013

Introduction

Several types of asthma have been recognized clinically. Allergic asthma (or extrinsic asthma), generally recognized as the most common form of asthma, accounts for approximately two thirds of asthmatics, and half of patients suffering from severe asthma have allergic asthma [1–3]. The allergen sensitivity in susceptible individuals is initiated at the mucosal surface level where environmental allergens meet the mucosal epithelia [4]. The interaction of inhaled allergens with sensitized immune cells in the airway results in an allergic asthma response. However, allergic and non-allergic asthma hold many of the same symptoms. Thus allergy testing is often necessary to differentiate them clinically [5].

The prevalence of asthma in the United States (US) has been reported to be over 22 million (about 7.7% of the population) and the case fatality from the disease has been estimated at 5.2 per 100 000 asthmatic patients per year [6,7].

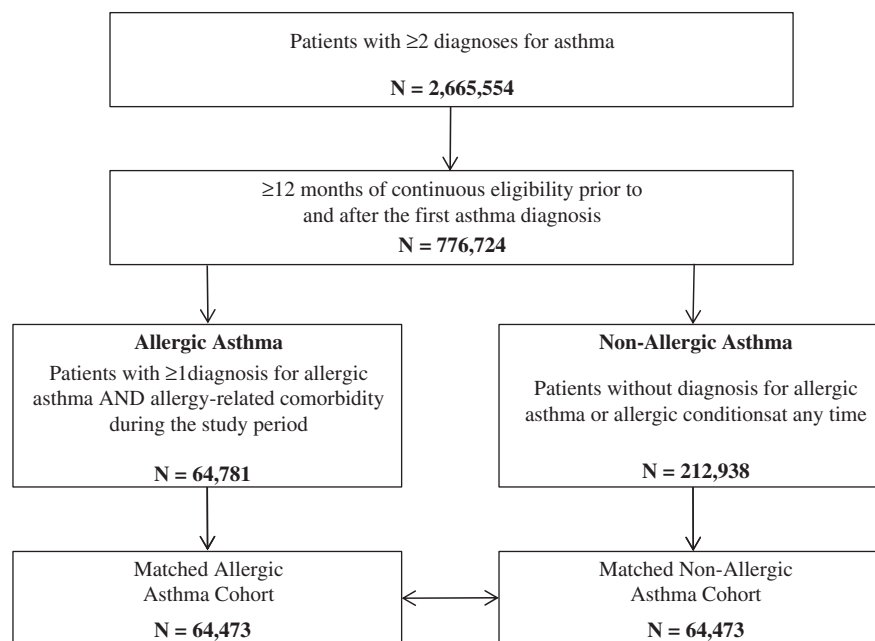
The economic implications of asthma treatment are estimated to rank as one of the highest among all chronic diseases due to both the prevalence of asthma and the large amount of health resource utilization associated with the condition, accounting for up to 2% of the economic cost of all diseases in developed countries [8,9]. A recent systematic review examined 68 articles on the economic burden of asthma between 1966 and 2008 and concluded that despite the availability of effective preventive therapies, the cost of asthma treatment has significantly increased over the last few decades [9].

In children, diagnosis of an allergic condition has been reported to be associated with increasing asthma severity but results seem to be equivocal [10,11]. It has been reported that non-allergic asthma is more severe both in terms of lower lung function and in terms of the persistency of symptoms compared with allergic asthma [3]. Many studies have examined resource utilization and costs of asthma patients as a homogenous group [9]; however, very limited information exists on the possible differential economic burden associated with allergic and non-allergic asthma.

This study aimed to (1) define and describe cohorts of allergic and non-allergic asthma patients and (2) quantify

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Figure 1. Study population flow chart.



differences in resource utilization and associated costs between these cohorts in a real-world setting using a large in US employer-based healthcare claims database.

Methods

Data source

The Truven Health MarketScan database, formerly known as the MedStat MarketScan database, is a large, Health Insurance Portability and Accountability Act fully compliant, integrated, de-identified, individual-level claims database containing data from approximately 45 large employers, health plans, and government and public organizations and covering over 18 million lives. Enrollees in the database include employees, dependents and retirees in the US with primary or Medicare supplemental coverage through privately insured fee-for-service, point-of-service or capitated health plans. All census regions are represented, although members predominantly represent the South and North Central (Midwest) regions. The data used in the current analysis covered the period from January 2002 through June 2010 and includes inpatient, outpatient, pharmacy, enrollment information and associated paid amounts for the Commercial Claims and Encounters (CCE) and the Medicare Supplemental and Coordination of Benefits (COB) databases. Institutional review board (IRB) and informed consent were not required for this study.

Patient selection

A retrospective matched-cohort study design was used to assess the burden of illness of patients considered newly diagnosed with allergic asthma compared to those considered newly diagnosed with non-allergic asthma. Patients were eligible for inclusion if they had at least two diagnoses for asthma (International Classification of Diseases, 9th Revision [ICD-9]: 493.x) at any time as to confirm diagnosis [12,13]. Eligible patients also had at least one-year of continuous insurance eligibility prior to and after the first diagnosis for

asthma in the database (index date). The one-year period prior to the index date was defined as the baseline period whereas the one-year period after the index date was defined as the study period. Figure 1 summarizes the study population flow chart.

The allergic asthma cohort was defined as the subset of patients with at least one diagnosis code for extrinsic (allergic) asthma (ICD-9 code: 493.0x) and at least one diagnosis code for the following allergic conditions, as defined by Gupta et al., during the study period: allergic rhinitis (ICD-9 code: 477.xx), anaphylaxis (ICD-9 code: 995.0, 999.4), conjunctivitis (ICD-9 code: 372.1x, 372.3x), eczema/dermatitis (ICD-9 code: 691.xx-692.xx), food allergy (ICD-9 code: 693.1) or urticaria/angioedema (ICD-9 code: 708.x, 995.1) [14].

The non-allergic asthma cohort was defined as asthmatic patients without any diagnoses for allergic asthma or any of the above allergic conditions at any time.

Patients from the allergic asthma cohort were matched 1:1 with patients in the non-allergic asthma cohort based on the following available exact matching factors: age categories, gender, region, year of index date and the Quan-Charlson comorbidity index (CCI) [15,16]. The demographic matching factors (age, gender, region and index date) were chosen, based on available data, to best enable a comparison of outcomes (resource utilization and costs) among allergic and non-allergic patients by reducing confounding due to non-disease factors. The CCI is a summary of scores associated with a range of comorbidities that predicts the ten-year mortality. Controlling for CCI allows for a reduction in confounding possibly due to non-asthma disease-related factors.

Outcomes and statistical analysis

Baseline characteristics

The demographic and clinical characteristics of the study population were evaluated during the one-year prior to the

Table 1. Baseline demographics and clinical characteristics of the matched cohorts.

	Matched cohorts						<i>p</i> Value ^a
	Allergic asthma			Non-allergic asthma			
	<i>N</i>	=	64 473	<i>N</i>	=	64 473	
Age categories, <i>N</i> (%)							
≤12 years	21 524		(33.4%)	21 524		(33.4%)	—
12–17 years	6707		(10.4%)	6707		(10.4%)	—
18–44 years	16 340		(25.3%)	16 340		(25.3%)	—
45–64 years	16 501		(25.6%)	16 501		(25.6%)	—
≥65 years	3401		(5.3%)	3401		(5.3%)	—
Female, <i>N</i> (%)	36 801		(57.1%)	36 801		(57.1%)	—
Region, <i>N</i> (%)							
North Central	14 205		(22.0%)	14 205		(22.0%)	—
North East	8760		(13.6%)	8760		(13.6%)	—
South	28 209		(43.8%)	28 209		(43.8%)	—
West	12 417		(19.3%)	12 417		(19.3%)	—
Unknown	882		(1.4%)	882		(1.4%)	—
Year of index date, <i>N</i> (%)							
2003	4125		(6.4%)	4125		(6.4%)	—
2004	5416		(8.4%)	5416		(8.4%)	—
2005	7435		(11.5%)	7435		(11.5%)	—
2006	7155		(11.1%)	7155		(11.1%)	—
2007	8739		(13.6%)	8739		(13.6%)	—
2008	10 146		(15.7%)	10 146		(15.7%)	—
2009	14 794		(22.9%)	14 794		(22.9%)	—
2010	6663		(10.3%)	6663		(10.3%)	—
Quan-Charlson comorbidity index, Mean ± SD [Median]	0.2	±	0.6 [0.0]	0.2	±	0.6 [0.0]	—
Asthma-related comorbidities ^b , <i>N</i> (%)							
Respiratory infections	36 845		(57.1%)	26 199		(40.6%)	<0.0001
Chronic sinusitis	6453		(10.0%)	1920		(3.0%)	<0.0001
Acute sinusitis	14 987		(23.2%)	6462		(10.0%)	<0.0001
Chronic obstructive pulmonary disease	1212		(1.9%)	2315		(3.6%)	<0.0001

ED = emergency department

^aStatistical differences between matched cohorts were calculated using McNemar tests for categorical variables and two sided paired Student's *t*-tests for continuous variables.^bEvaluated during the baseline period defined as 12 months prior to the index date.

study period. These characteristics included age, gender, region, year of index date, CCI and asthma-related comorbidities (respiratory infections, chronic sinusitis, acute sinusitis, chronic obstructive pulmonary disease) (Table 1). Descriptive statistics included mean ($\pm$ standard deviation [SD]) and median values for continuous data and relative frequencies for categorical data. Statistical comparisons between the matched groups were conducted using McNemar tests for categorical variables and two-sided paired Student's *t*-tests for continuous variables.

Asthma treatments

The use of asthma medication during the study period was evaluated and compared between matched cohorts by reporting the proportion of patients filling prescriptions for asthma medications and the mean number of claims from the following asthma treatment classes: inhaled corticosteroids (ICS), long-acting beta₂-agonists (LABA), short-acting beta₂-agonists (SABA), anticholinergics, oral corticosteroids (OCS), leukotriene modifiers, methylxanthines, mast cell stabilizers, monoclonal antibodies as well as fixed-dose combinations including ICS + LABA and SABA + anticholinergics (Table 2). McNemar tests for categorical variables and two-sided paired Student's *t*-tests for continuous variables were used for statistical comparison.

Healthcare resource utilization

To assess the burden of illness for allergic versus non-allergic asthma patients in the matched populations, the number of healthcare utilization services from both prescription and medical claims were compared between the two matched cohorts during the one-year study period. First, the frequency of patients receiving a range of different skin (percutaneous, intracutaneous and other) and blood (total serum IgE, specific IgE and other) allergy tests were compared. Then, overall and asthma-related healthcare resource utilization was compared, including pharmacy claims, outpatient services, hospitalizations and emergency-department (ED) visits. Asthma-related events were defined as services associated with a diagnosis of asthma (ICD-9: 493.x). Incidence rate ratios (IRRs) were calculated to compare the two groups as well as confidence intervals using conditional Poisson regression models accounting for matched pairs.

Healthcare costs

Healthcare costs from a payer perspective (i.e. the actual costs paid by the insurance plan) for each study cohort as well as cost differences between the matched cohorts were evaluated during the one-year study period. The total healthcare costs per-patient per-year (PPPY) were stratified into pharmacy costs, including pharmacy costs for asthma medication, and

Table 2. Asthma-related prescriptions during the one-year study period of the matched cohorts.

	Allergic asthma			Non-allergic asthma			
	<i>N</i>	=	64 473	<i>N</i>	=	64 473	<i>p</i> Value
Asthma treatments, <i>N</i> (%)							
ICS	42 307		(65.6%)	34 565		(53.6%)	<0.001
Number of claims, Mean ± SD [Median]	3.3	±	3.7 [2.0]	1.5	±	2.5 [0.0]	<0.001
Fixed-dose combination (LABA + ICS)	21 272		(33.0%)	13 865		(21.5%)	<0.001
Number of claims, Mean ± SD [Median]	1.1	±	2.2 [0.0]	0.7	±	1.8 [0.0]	<0.001
LABA	22 176		(34.4%)	14 609		(22.7%)	<0.001
Number of claims, Mean ± SD [Median]	1.2	±	2.2 [0.0]	0.7	±	1.8 [0.0]	<0.001
Fixed-dose combination (LABA + ICS)	21 272		(33.0%)	13 865		(21.5%)	<0.001
Number of claims, Mean ± SD [Median]	1.1	±	2.2 [0.0]	0.7	±	1.8 [0.0]	<0.001
SABA	46 416		(72.0%)	46 023		(71.4%)	0.013
Number of claims, Mean ± SD [Median]	2.0	±	2.4 [1.0]	1.8	±	2.5 [1.0]	<0.001
Fixed-dose combination (SABA + Anticholinergics)	2377		(3.7%)	2835		(4.4%)	<0.001
Number of claims, Mean ± SD [Median]	0.1	±	0.6 [0.0]	0.1	±	0.8 [0.0]	<0.001
Anticholinergics	6410		(9.9%)	6022		(9.3%)	<0.001
Number of claims, Mean ± SD [Median]	0.2	±	1.1 [0.0]	0.3	±	1.4 [0.0]	<0.001
Fixed-dose combination (SABA + Anticholinergics)	2377		(3.7%)	2835		(4.4%)	<0.001
Number of claims, Mean ± SD [Median]	0.1	±	0.6 [0.0]	0.1	±	0.8 [0.0]	<0.001
OCS	41 380		(64.2%)	20 992		(32.6%)	<0.001
Number of claims, Mean ± SD [Median]	1.1	±	1.5 [1.0]	0.7	±	1.2 [0.0]	<0.001
Leukotriene modifiers	26 549		(41.2%)	11 585		(18.0%)	<0.001
Number of claims, Mean ± SD [Median]	1.8	±	3.0 [0.0]	0.7	±	2.0 [0.0]	<0.001
Methylxantines	417		(0.6%)	566		(0.9%)	<0.001
Number of claims, Mean ± SD [Median]	0.0	±	0.4 [0.0]	0.0	±	0.5 [0.0]	<0.001
Mast cell stabilizers	659		(1.0%)	219		(0.3%)	<0.001
Number of claims, Mean ± SD [Median]	0.0	±	0.3 [0.0]	0.0	±	0.2 [0.0]	<0.001
Monoclonal antibodies (i.e. omalizumab)	392		(0.6%)	7		(0.0%)	<0.001
Number of claims, Mean ± SD [Median]	0.0	±	0.6 [0.0]	0.0	±	0.0 [0.0]	<0.001

ICS = inhaled corticosteroids; LABA = long-acting beta₂-agonist; SABA = short-acting beta₂-agonist; OCS = oral corticosteroids.

costs for all-cause and asthma-related outpatient services, ED visits, hospitalizations and other services. All costs were inflated using the Consumer Price Index (CPI) for medical care services and are expressed in constant 2010 US dollars. To address non-normal distribution of costs, cost differences with 95% CIs were estimated using non-parametric resampling (bootstrap) methods [17]. As a sensitivity analysis, a multivariate regression including baseline healthcare costs as covariates was conducted.

Statistical significance was assessed with a two-sided test at α -level of 0.05 or less. All analyses were conducted using SAS software version 9.2 (SAS Institute, Cary, NC).

Results

Baseline characteristics

A total of 64 781 and 121 938 patients were identified with allergic and non-allergic asthma conditions, respectively. Using age categories, gender, region, year of index date and CCI as exact matching factors, 64 473 (99.5%) allergic asthma patients were matched 1:1 to non-allergic asthma patients. 4564 (7.1%) and 233 (0.36%) allergic and non-allergic asthma patients received a skin or blood allergy test during the baseline period, respectively. Baseline demographic characteristics of the matched populations are presented in Table 1. Most prevalent allergic conditions for asthma patients at baseline were allergic rhinitis (38.8%) and eczema/dermatitis (12.2%). After matching, the allergic asthma cohort had a

greater proportion of patients suffering from respiratory infections (57.1% versus 40.6%, $p < 0.001$), chronic sinusitis (10.0% versus 3.0%, $p < 0.001$), and acute sinusitis (23.2% versus 10.0%, $p < 0.001$) during the baseline period.

Asthma treatments

Asthma treatments for the matched cohorts during the study period are presented in Table 2. During the one-year study period, allergic asthma patients were more likely to have filled a prescription for an asthma controller medication, including ICS (65.6% versus 53.6%, $p < 0.001$), LABA (34.4% versus 22.7%, $p < 0.001$), OCS (64.2% versus 32.6%, $p < 0.001$), leukotriene modifiers (41.2% versus 18.0%, $p < 0.001$), and the fixed-dose combination of LABA + ICS (33.0% versus 21.5%, $p < 0.001$). ICS was the most commonly filled asthma medication for allergic asthma patients with a mean (SD) number of 3.3 (3.7) pharmacy dispensings per patient whereas SABA was the most commonly filled asthma medication for non-allergic patients with a mean (SD) of 1.8 (2.5) pharmacy dispensings per patient.

Healthcare resource utilization

Healthcare resource utilization of both cohorts during the one-year study period is presented in Table 3. Of note, allergic patients were more likely to have had a claim for skin tests (IRR ranging from 28.12 to 66.35, $p < 0.001$ for all) or blood tests (IRR ranging from 2.78 to 10.65, $p < 0.001$ for all) with

Table 3. Healthcare resource utilization during the one-year study period of the matched cohorts.

	Total number of events		Incidence rate (number of events/number of patients)		Univariate incidence rate ratio (Poisson) [95% CI] ^a		<i>p</i> Value
	Allergic asthma	Non-allergic asthma	Allergic asthma	Non-allergic asthma			
Asthma-related test or procedure							
Skin tests							
Percutaneous tests	12 465	434	0.1933	0.0067	28.72	[26.04; 31.68]	<0.001
Intracutaneous tests	2853	43	0.0443	0.0007	66.35	[45.55; 96.64]	<0.001
Other skin tests ^b	47	17	0.0074	0.0003	28.12	[17.29; 45.73]	<0.001
Blood tests							
Total serum IgE	1225	146	0.0190	0.0023	8.39	[7.06; 9.97]	<0.001
Specific IgE test	895	84	0.0139	0.0013	10.65	[8.42; 13.48]	<0.001
Other blood tests ^c	217	78	0.0034	0.0012	2.78	[2.09; 3.69]	<0.001
Resource utilization							
Pharmacy claims							
All pharmacy claims	999 783	622 788	15.51	9.66	1.61	[1.59; 1.62]	<0.001
Asthma medication claims ^d	296 265	131 688	4.60	2.04	2.25	[2.22; 2.28]	<0.001
All medical services							
Outpatient services	1 418 193	672 665	22.00	10.43	2.11	[2.09; 2.13]	<0.001
Hospitalizations	14 282	17 880	0.22	0.28	0.80	[0.78; 0.82]	<0.001
ED visits	43 186	40 875	0.67	0.63	1.06	[1.03; 1.08]	<0.001
Other visits ^e	171 462	150 407	2.66	2.33	1.14	[1.12; 1.17]	<0.001
Asthma-related medical services ^f							
Outpatient services	246 782	107 555	3.83	1.67	2.29	[2.27; 2.32]	<0.001
Hospitalizations	2311	2173	0.04	0.03	1.06	[1.00; 1.13]	0.067
ED visits	7910	9282	0.12	0.14	0.85	[0.82; 0.88]	<0.001
Other visits ^e	32 465	25 860	0.50	0.40	1.26	[1.21; 1.30]	<0.001

ED = Emergency department.

^aStatistical differences between groups, as well as 95% confidence intervals [95% CI], were calculated using conditional Poisson regression models to account for matched pairs.^bOther skin tests includes skin patch and photo patch tests as well as photo, ophthalmic mucous membrane, direct nasal mucous membrane, inhalation bronchial challenge, ingestion challenge, and provocative tests.^cOther blood tests include RAST, MAST, FAST, ELISA and ImmunoCAP tests.^dAsthma medications were identified as pharmacy claims for SABA, LABA, ICS, OCS, leukotriene modifiers, methylxantines, mast cell stabilizers, anticholinergics, monoclonal antibodies, and fixed-dose combinations (LABA + ICS, SABA + Anticholinergics).^eOther visits include long-term care, skilled nursing facilities, rehabilitation centers, laboratory and tests.^fAsthma-related services were defined as visits associated with a diagnosis of asthma.

22.5% and 1.16% of allergic and non-allergic asthma patients receiving a skin or blood allergy tests. Allergic asthma patients also had significantly more all-cause pharmacy dispensings (IRR [95% CI] = 1.61 [1.59–1.62], $p < 0.001$), outpatient visits (IRR [95% CI] = 2.11 [2.09–2.13], $p < 0.001$), ED visits (IRR [95% CI] = 1.06 [1.03–1.08], $p < 0.001$) and other visits (IRR [95% CI] = 1.14 [1.12–1.17], $p < 0.001$), compared to non-allergic asthma patients. However, allergic asthma was associated with fewer all-cause hospitalizations (IRR [95% CI] = 0.80 [0.78–0.82], $p < 0.001$). Results were generally consistent in the subset of asthma-related services, with allergic asthma being associated with significantly more pharmacy dispensings (IRR [95% CI] = 2.25 [2.22–2.28], $p < 0.001$), outpatient visits (IRR [95% CI] = 2.29 [2.27–2.32], $p < 0.001$), and other visits (IRR [95% CI] = 1.26 [1.21–1.30], $p < 0.001$) relative to the non-allergic asthma group. By contrast, allergic asthma was associated with fewer asthma-related ED visits (IRR [95% CI] = 0.85 [0.82–0.88], $p < 0.001$) compared to non-allergic asthma.

Healthcare costs

Table 4 shows the healthcare costs of both cohorts during the one-year study period, whereas Figure 2 presents the

healthcare cost differences relative to the non-allergic asthma cohort. Compared with patients with non-allergic asthma, patients with allergic asthma incurred greater total healthcare costs PPPY (allergic: \$4008; non-allergic: \$2889; cost difference [95% CI] = \$1119 [1063–1180], $p < 0.001$) and asthma-related costs (allergic: \$1063; non-allergic: \$592; cost difference [95% CI] = \$470 [454–488], $p < 0.001$) corresponding to 39% greater all-cause and 79% greater asthma-related total healthcare costs. Main cost drivers were pharmacy costs (cost difference [95% CI] = \$598 [571–623], $p < 0.001$, 57% of the cost for the non-allergic asthma cohort) and outpatient costs (cost difference [95% CI] = \$677 [646–704], $p < 0.001$, 67% of the cost for the non-allergic asthma cohort). All-cause hospitalization costs were lower for the allergic asthma cohort (allergic: \$180; non-allergic: \$336; cost difference [95% CI] = –\$156 [–183–131], $p < 0.001$); however, asthma-related hospitalizations costs PPPY were similar between the two groups (\$45 versus \$56, $p = 0.124$). The multivariate analysis controlling for healthcare costs at baseline yielded consistent results.

Discussion

In this large retrospective matched-cohort study using a health insurance claims database, allergic asthma, as identified

Table 4. Healthcare costs for the matched cohorts during the one-year study period.

Total healthcare costs (US \$2010)	Per-patient per-year costs		Univariate cost difference [95% CI] ^a		p Value	Multivariate ^b cost difference [95% CI] ^b		p Value
	Allergic asthma	Non-allergic Asthma						
Pharmacy costs								
All pharmacy costs	\$1639	\$1042	\$598	[571; 623]	<0.001	\$329	[293; 361]	<0.0001
Asthma medication costs ^c	\$668	\$317	\$352	[340; 362]	<0.001	\$328	[317; 338]	<0.0001
All medical costs								
Outpatient costs	\$1688	\$1011	\$677	[646; 704]	<0.001	\$462	[403; 503]	<0.0001
ED costs	\$122	\$124	-\$3	[-11; 6]	0.441	-\$7	[-15; 0]	0.0681
Hospitalization costs	\$180	\$336	-\$156	[-183; -131]	<0.001	-\$164	[-194; -136]	<0.0001
Other costs ^d	\$379	\$376	\$3	[-20; 25]	0.782	-\$43	[-68; -21]	<0.0001
Asthma-related medical costs ^e								
Outpatient costs	\$276	\$132	\$145	[138; 151]	<0.001	\$142	[136; 148]	<0.0001
ED costs	\$36	\$43	-\$7	[-10; -5]	<0.001	-\$7	[-9; -4]	<0.0001
Hospitalization costs	\$45	\$56	-\$11	[-21; 3]	0.124	-\$11	[-21; 3]	0.1162
Other costs ^d	\$36	\$45	-\$8	[-13; -4]	<0.001	-\$9	[-1; -6]	<0.0001
Total asthma-related costs ^f	\$1063	\$592	\$470	[454; 488]	<0.001	\$443	[42; 460]	<0.0001
Total costs ^g	\$4008	\$2889	\$1119	[1063; 1180]	<0.001	\$577	[493; 647]	<0.0001

ED = Emergency department.

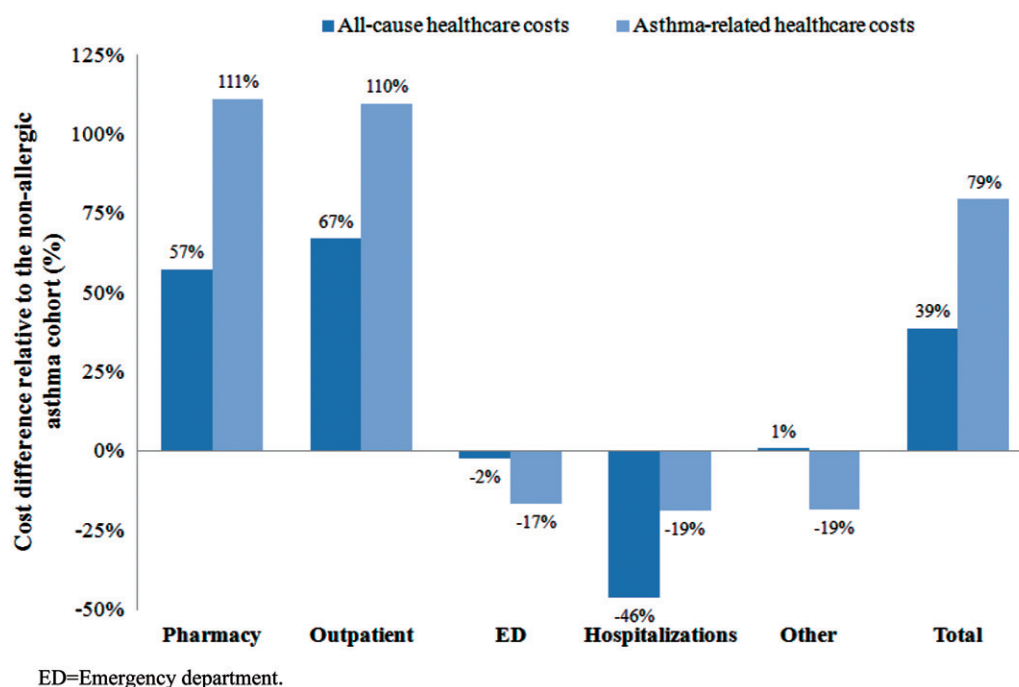
^aStatistical differences between groups, as well as 95% confidence intervals [95% CI], were calculated using a nonparametric re-sampling (bootstrap) methods with 499 replications.^bCovariates included baseline all-cause outpatient, emergency-room, hospitalization, and pharmacy costs.^cAsthma medications were identified as pharmacy claims for SABA, LABA, ICS, OCS, leukotriene modifiers, methylxanthines, mast cell stabilizers, anticholinergics, monoclonal antibodies, and fixed-dose combinations (LABA + ICS, SABA + Anticholinergics).^dOther costs include long-term care, skilled nursing facilities, rehabilitation centers, laboratory and tests.^eAsthma-related services were defined as visits associated with a diagnosis of asthma.^fTotal asthma-related costs include asthma-related pharmacy and medical costs.^gTotal costs include all pharmacy and medical costs.

Figure 2. Healthcare Cost differences during the observation period in the matched cohorts.

through ICD-9 codes, was associated with overall greater healthcare resource utilization compared to non-allergic asthma, including significantly more asthma-related pharmacy dispensings, and asthma-related outpatient and other services. Allergic asthma patients also incurred 39% greater all-cause healthcare costs and 79% greater asthma-related costs than non-allergic asthma patients.

With a limited loss in sample size (<1% of patients from baseline), the exact matching algorithm generally remedied

cohort differences and allowed for a direct comparison of burden between asthma types in similar populations with low overall morbidity (CCI = 0.2). Matching exactly on year of index date allowed for a potential reduction in bias due to changes in clinical practice across the years of data included in the analysis. It was decided to not match on healthcare costs at baseline in the base case scenario as these costs may be associated with the allergic conditions of interest as well as be part of the cost escalation associated with allergic asthma

diagnosis that may be different for non-allergic asthma. As a sensitivity analysis, multivariate regressions including baseline healthcare costs as covariates were conducted. Consistently, it was found that patients with allergic asthma incurred significantly more costs than those with non-allergic asthma.

The asthma-related costs reported in this study are in line with the majority of annual cost estimates for asthmatic patients from a systematic review published in 2009 that examined the economic burden of asthma [9]. Although this systematic review reports on a very heterogeneous group of studies with varying levels of asthma severity, its findings are generally in line with the current claims analysis. According to this literature review, many studies found that the greatest cost driver of total direct costs was hospitalizations, accounting for 52% to 86% of asthma-related costs in seven studies and 47% to 67% of total direct costs in five others [9]. Pharmacy claims were also reported as a principal component of total costs, which is in line with results reported here. Nevertheless, the fact that outpatient costs composed such a large proportion of total costs does corroborate the results of a study by Beyhun et al. (2007) that reported 49% of total asthma costs could be attributed to outpatient visits, and about 76% of these costs were due to laboratory examinations such as pulmonary function tests and skin-prick tests [18].

The fact that outpatient services and prescription treatments were the main cost drivers in the current study may be explained by our focus on newly diagnosed patients with few comorbidities who are enrolled full time in an employed-based health plan, who are therefore more likely to represent a healthier segment of the target population. As claims data do not provide information regarding the severity of the disease, it was not possible to assess whether allergic asthma patients were in higher National Heart, Lung, and Blood Institute (NHLBI) steps of care [19]; however, the fact that allergic asthma patients had on average 3.3 ICS prescriptions per year is an indicator of persistent asthma. In the current study, the allergic asthma patients showed a significantly greater number of outpatient visits, but the cost difference PPPY between the two groups for asthma-related ED visits and hospitalization ranged from $-\$7$ to $-\$11$. These results suggest that allergic asthma study patients may have been less severe and/or monitored closely and consequently had fewer uncontrolled asthma events requiring hospitalization or ED visits. As well, health plan coverage may have effectively reduced treatment costs. As one of the primary goals in the management of asthma is to mitigate the risk of exacerbations, potentially closer follow-up in allergic patients may be of interest from a public health standpoint [20]. In an allergic asthma population, skin and blood allergy testing should be considered more frequently than what is observed in our study population. Based on the results reported in this analysis, it may be inferred that better differentiation of asthma types through allergy testing may lead to better disease management and reduced downstream costs.

Despite the thorough study protocol and design, this study had several limitations including the usual caveats associated with retrospective claims data analysis. First, claims data may be subjected to inaccuracies in billing information and missing data. In addition, claims data do not include certain

information such as reasons for treatment, disease severity, lifestyle information such as smoking, adherence. Diagnoses associated with specific services have been used as a proxy for reasons for services. For example, it was not possible to assess whether anaphylaxis and urticaria were associated to an allergen or whether patients in the allergic asthma cohort had a non-allergic component to their disease. Also, as over-the-counter medications were not captured in the data, the cost burden for allergic asthma patients may have been underestimated as these patients are likely to use medications such as antihistamines and eye drops. Claims data also provide limited visibility into details of hospitalizations, such as the breadth of medications and tests administered during the inpatient stay. Furthermore, laboratory test results were not available in MarketScan database; therefore, it was impossible to confirm allergic asthma diagnoses using IgE levels. Thus, a fairly restrictive algorithm was employed to confirm allergic asthma diagnosis (diagnoses for both allergic asthma and allergic conditions) potentially explaining why allergic asthma was less common than non-allergic asthma in this study, which is in opposition to previous reports [2,3]. In addition, the patient history period to define a new asthma diagnosis in our study was one-year; it is possible that patients were diagnosed prior and did not seek care during this one-year timeframe. This study examined costs associated with allergic and non-allergic asthma but was limited by its inability to examine indirect costs, such as missed workdays or loss of effectiveness. In addition, this study is based on a one-year follow-up year after initial asthma diagnosis, which may be more susceptible to physicians' practice styles (i.e. some physicians may embark on a large workup to characterize asthma, whereas others would observe for several months to see if this is a transient episode). Finally, health plan information was not taken into account, which may have attenuated costs connected to health care resource utilization (e.g. bundling of services). Nevertheless, health insurance claims data remain a valuable source of information as they comprise a fairly valid, large sample of real-world practice data and allow outcomes to be examined in a real-world setting.

Conclusion

Based on health insurance claims, this large observational study found evidence that suffering from allergic asthma, as identified through ICD-9 codes, is associated with greater healthcare resource utilization and healthcare costs compared to non-allergic asthma, even in a relatively healthy, employed US population with low overall morbidity. Such information provides a more complete picture of the impact of different asthma types, and consequently provides evidence to support the importance of distinguishing these two types of asthma early in the progression of the disease using the recommended methods of skin and blood allergy IgE tests. Further research into more severe or high risk asthma is needed to understand the true differential in healthcare resource use and costs between non-allergic asthma and allergic asthma patients.

Acknowledgements

The authors wish to acknowledge Tara Nazareth and Stuart Turner of Novartis Pharmaceuticals Corporation for their

input into the data interpretation and assistance with development of the manuscript.

Declarations of interest

Lafeuille, Gravel, and Lefebvre are employees of Groupe d'analyse, Ltée, a consulting company that has received research grants from Novartis Pharmaceuticals Corporation. Figliomeni and Zhang are employees of Novartis Pharmaceuticals Corporation. This analysis was funded by Novartis Pharmaceuticals Corporation.

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