

ORIGINAL ARTICLE

AIRWAY DISEASES

Ten-year trends in direct costs of asthma: a population-based study

H. Tavakoli^{1,2,3}, J. M. FitzGerald^{1,2}, W. Chen¹, L. Lynd¹, T. Kendzerska⁴, S. Aaron⁵, A. Gershon^{6,7}, C. Marra⁸ & M. Sadatsafavi^{1,2,3} for the Canadian Respiratory Research Network

¹Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC; ²Centre for Clinical Epidemiology and Evaluation, The University of British Columbia; ³Department of Medicine, Institute for Heart and Lung Health, The University of British Columbia; ⁴The Institute for Clinical Evaluative Sciences, Toronto, ON; ⁵The Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON; ⁶The Hospital for Sick Children; ⁷Dalla Lana School of Public Health, University of Toronto, Toronto, ON; ⁸School of Pharmacy, Memorial University of Newfoundland, St. John's, NF, Canada

To cite this article: Tavakoli H, FitzGerald JM, Chen W, Lynd L, Kendzerska T, Aaron S, Gershon A, Marra C, Sadatsafavi M, for the Canadian Respiratory Research Network. Ten-year trends in direct costs of asthma: a population-based study. *Allergy* 2016; DOI: 10.1111/all.12993.

Keywords

asthma; burden of diseases; cohort studies; costs; observational studies.

Correspondence

Mohsen Sadatsafavi, Centre for Clinical Epidemiology and Evaluation, 7th Floor, 828 West 10th Avenue, Research Pavilion, Vancouver, BC V5Z 1M9, Canada.
Tel.: 604 875 5178
Fax: 604 875 5179
E-mail: msafavi@mail.ubc.ca

Accepted for publication 21 July 2016

DOI:10.1111/all.12993

Edited by: Douglas Robinson

Abstract

Introduction: There is little information on recent trends in the economic burden of asthma. Our objective was to estimate the excess costs of asthma and their trend in British Columbia, Canada, from 2002 to 2011.

Methods: A retrospective cohort of individuals aged 5–55 years was constructed from the provincial administrative health databases, consisting of patients with physician-diagnosed asthma and a propensity-score-matched comparison sample from the general population. Total direct medical costs were calculated as the sum of hospitalizations, outpatient visits and medication costs, adjusted to 2012 Canadian dollars (\$). Excess costs were defined as the difference in costs between the asthma and comparison groups.

Results: A total of 341 457 individuals (mean age at entry 27.3, 54.1% female) were equally divided into the asthma and comparison groups. Excess costs in patients with asthma were \$1028.0 (95% CI \$982.7–\$1073.4) per patient-year (PY). Medications contributed to the greatest share of excess costs (\$471.7/PY), whereas hospitalization and outpatient costs were, respectively, \$272.2/PY and \$284.1/PY. Only \$192.9/PY was attributable to asthma itself. There was a 2.9%/year increase in excess costs ($P < 0.001$), a combination of asthma-attributable costs declining by 0.8%/year while nonasthma excess costs increasing by 3.8%/year. The most dramatic trend was observed in asthma-related outpatient costs, which decreased by %6.6/year.

Conclusions: A significant share of excess costs in asthma is not attributable to the disease itself. The pattern of costs changed significantly during the study period. The burden of comorbid conditions should be considered in developing evidence-based policies for management of patients with asthma.

Asthma is an inflammatory disease of the airways characterized by recurring symptoms including cough, wheezing and shortness of breath. In 2014, around 2.4 million individuals aged 12 or older suffered from asthma in Canada (1). Asthma has cost Canada \$2.10 billion in 2010 (2).

Burden of disease studies provides critical information that enables converting per-individual measures of intervention effectiveness to the impact of implementing treatments, programs and policies on population health and healthcare

costs. The burden of asthma is the result of the interplay of multiple causes including the prevalence of risk factors, the availability of health technologies for prevention, diagnosis, and treatment of the condition, access to care, care providers' adherence to evidence-based guidelines and patients' adherence to care providers' recommendations. All such factors are likely to vary over time, creating a dynamic landscape requiring an ongoing reassessment of the burden of a disease.

The primary objective of this study was to calculate the excess costs and their trends in patients with asthma in the context of the public healthcare setting of Canada over a 10-year period. We pursued several secondary objectives: to evaluate the excess costs attributable to asthma (*vs* those attributable to all other conditions), to evaluate the distribution of excess costs across sex and age groups and to evaluate the contribution of inpatient care, outpatient care and medications to excess costs (3).

Methods

Study design and setting

This study was based on the population-based administrative health data of British Columbia (BC), a Canadian province with a population of 4.5 million (as of 2012) (4). The administrative needs of the province's public healthcare system have resulted in the creation of centralized databases that capture the health services use of all the residents of the province. The quality of the data is high with no selection bias and very low levels of missing or duplicates records (5). The following data sources were available for this study: (i) Discharge Abstracts Database (DAD), containing information on admission and discharge dates and up to 25 discharge diagnoses in international classification of diseases, 9th (ICD-9) or 10th (ICD-10) revisions (6); (ii) Medical Services Plan, which contains outpatient services information including service date and diagnostic codes (in ICD-9) and costs (7); (iii) PharmaNET, which contains dispensation dates, unique drug identifier, dispensed quantity and costs (8); (iv) Vital Statistics, which contains information about births and deaths (9); (v) Registry and demographics (10), which contain information about the enrolment of individuals with the healthcare system as well as basic demographic variables (date of birth, sex) and socio-economic status (income quintiles determined from the geographic neighbourhood). Data from 1997 to 2012 were available. However, the first 5 years of data were not used for cost calculation to allow sufficient time for identification of prevalent patients with asthma. The last year was also not used as the 2-year follow-up required for the case definition of asthma results in an incomplete verification of cases in this year. The follow-up was therefore from 1 January 2002 to 31 December 2011 (10 years).

We used these data to create a retrospective matched cohort of adults 5–55 years of age with and without a diagnosis of asthma. The choice of the upper age limit was to ensure patients with chronic obstructive pulmonary disease (COPD) without asthma, who might have similar health resource use patterns, are not overrepresented in the data. However, once in the data, the individual could develop COPD without being excluded from the analysis. The lower age limit was imposed as attributing respiratory symptoms in the younger groups to asthma can be challenging. The Clinical Research Ethics Board at the University of British Columbia approved this study (H08-01287). All inferences, opinions and conclusions drawn in this research are those of the authors and do not reflect the opinions or policies of the Data Steward(s).

Asthma and comparison cohorts

A schematic illustration of the design is provided in Appendix S1. We applied a validated case definition of physician-diagnosed asthma (11): patients with one asthma-related hospitalization or two or more physician visits with the main diagnosis of asthma or three or more dispensation records for asthma-related medications (in different dates) in a rolling 12-month window were considered asthmatic (see Appendix S2 for the list of asthma –medications) (12). From the first date this definition was satisfied, we applied a look-back algorithm, as performed in our previous studies, to find the first date of asthma-related resource use (13). This process involved going back in time in asthma-related resource use records until the earliest of the first asthma-related resource use, subject's fifth birthday, or the start of the follow-up period. This date was considered the *index date*, marking the beginning of follow-up. Individuals with <1 year of data before the index date were excluded as this time span was required for covariate ascertainment.

We also had access to the records of 100 000 randomly selected individuals from the general nonasthma population. Each individual in this comparison pool was assigned an index date as 365 days after the first date of appearing in the data, start of the study period or individual's fifth birthday, whichever occurred the latest. This criterion was imposed to match the criteria used for the determination of the index date in patients with asthma.

Matching and follow-up

For each patient in the asthma cohort, we matched an individual from the comparison cohort based on sex, date of birth (± 5 years) and propensity score. The propensity score estimated the probability of being in the asthma cohort and was calculated using a logistic regression model with dependent variable being the presence in the asthma group, and independent variables being age (on index date), socio-economic status (neighbourhood household income quintile on index date), as well as the following variables ascertained in the 365 days prior to the index date: number of nonrespiratory-related hospitalizations, physician visits and modified Charlson score (14) (excluding respiratory-related diseases). One individual from the comparison cohort was matched with each individual in the asthma cohort by calliper matching on propensity score (with calliper width of 0.005) (15). Given the smaller size of the comparison cohort compared with the asthma cohort, matching with replacement was performed with proper adjustment for repeated selection of the same individuals from the comparison group (16). Matching with replacement is recommended when the pool of unexposed/control is smaller than the pool of exposed/case, as it results in the most efficient use of available data (17, 18). Standardized differences were calculated between the matched pairs for each of the variables included in the propensity score, and difference of <10% were considered satisfactory (19).

Follow-up continued to the earliest of dates of death, end of study period, unregistration from the healthcare system or

last resource use of any type. Follow-up time was divided into adjacent 12-month periods (with the last period potentially being truncated) to facilitate cost calculation and statistical analyses.

Outcomes

The primary outcome was excess direct medical costs (referred to as excess costs hereafter) in patients with asthma. Excess costs were defined as the difference in all-cause medical costs between the asthma cohort and the comparison cohort. An advantage of calculating the excess costs, as opposed to attributable costs as performed in previous studies (13, 20–24), is that excess costs properly incorporate both costs due to the disease of interest and costs due to coexisting conditions (25). Matching by propensity means the excess costs estimates are controlled for many potential confounding variables, including pre-existing comorbidity. For medication and outpatient services, cost data were available in the original data records. Case Mix Methodology (CMG) was applied to calculate hospitalization costs. Each hospitalization record comes with a resource intensity weight (RIW) (26). We calculated hospitalization costs by multiplying RIW by average costs of hospitalization in the given year. In case there was no RIW allocated to given hospitalization, we used estimated costs per CMG groups for the corresponding fiscal year (27).

Secondary outcomes included excess costs attributable to asthma itself (*vs* excess costs attributable to all other conditions), as well as excess costs by cost components (hospitalizations, outpatient visits and medication dispensations). Attributing individual health resource use records to asthma was based on ICD codes for hospitalization and outpatient visits, and the use of a dictionary table for asthma-related medications (Appendix S2). All costs were adjusted to the 2012 Canadian dollars (\$) using the medical components of the consumer price index (28). Attributing excess costs to specific comorbid conditions was out of the scope of the present work; however, we provided an overall estimate of the intensity of excess recourse use for each major disease category (the highest level IDC-10 chapters) by summing up the number of diagnostic codes in inpatient and outpatient databases within disease categories.

Statistical analysis

We used SAS Enterprise Guide to perform the analyses (version 6.1; Cary, NC, USA). The unit of observation was follow-up periods (person-years). Generalized linear models with generalized estimating equations with normal distribution and identity link function were used to account for the clustered nature of the data, with the cluster defined as each unexposed individual and all their matched exposed individuals. The choice of the normal distribution is justified given the large sample size, which assures the normality of sample means (18). The coefficient for cohort membership in the regression model corresponds to the excess costs of asthma per patient-year (PY). In addition to matching on sex, age

and propensity score, the regression model was further adjusted for the calendar year of the follow-up period and two binary variables indicating whether death occurred in a given period, or whether the (last) period was truncated. The death indicator was included to ensure any chance imbalance in the number of deaths, and the associated expensive end of life care would not affect the estimates. Trend in costs was estimated through an interaction term between cohort membership status and calendar year, converted to percentage of change per year by dividing the coefficient over the average excess costs during the follow-up period. Subgroup analysis was performed by running the same models separately within sex groups as well as age groups of 5–14, 15–45 and more than 45 years of age.

To evaluate the robustness of the results against design features, we performed sensitivity analyses. These included removing all cases of COPD [based on a validated case definition (29)], performing an unmatched analysis based on including all asthma and comparison cases, and not adjusting for the impact of mortality on costs.

Results

Population characteristics

Figure 1 provides the flow chart of sample selection. Initially, there were 361 501 individuals who satisfied the case definition of asthma. Of which, 341 457 (94.5%) met the inclusion criteria. These individuals were matched on a 1 : 1 basis to the comparison group.

The mean age on the index date for asthma and non-asthma cohorts was 27.2 [standard error (SE) = 0.03] and 27.1 (SE = 0.03), respectively; 54.1% of the both groups were female. The average follow-up time was 9.7 years (SE = 0.01) for the asthma and 11.1 years (SE = 0.01) for the comparison group. Table 1 presents the baseline characteristics of the asthma and comparison groups.

Excess costs in patients with asthma

Table 2 shows the excess costs in patients with asthma in total and across cost components. The asthma cohort accrued on average \$2217.5/PY (SE = \$4.0) in all-cause medical costs. The comparison group generated all-cause medical costs of \$1153.0/PY (SE = \$2.4).

After further adjustment for calendar year, death and truncated follow-up periods, the estimated excess costs were \$1028.0/PY (95% CI \$982.7–\$1073.4; $P < 0.001$). The largest cost component was medications, with \$471.7/PY (95% CI \$450.5–\$493.0; $P < 0.001$), or 46.0% of excess costs. Outpatient visits and hospitalizations were responsible for, respectively, \$284.1/PY (95% CI \$272.7–\$295.5; $P < 0.001$) and \$272.2/PY (95% CI \$247.7–\$296.7; $P < 0.001$) in excess costs, corresponding to 28.0% and 26.0% of excess costs, respectively. Across age groups, the highest excess costs belonged to individuals 45 years of age or older, with \$1895.3/PY (95% CI \$1750.4–\$2040.1; $P < 0.001$), followed by age groups of 15–45, at \$1209.9/PY (95% CI \$1149.0

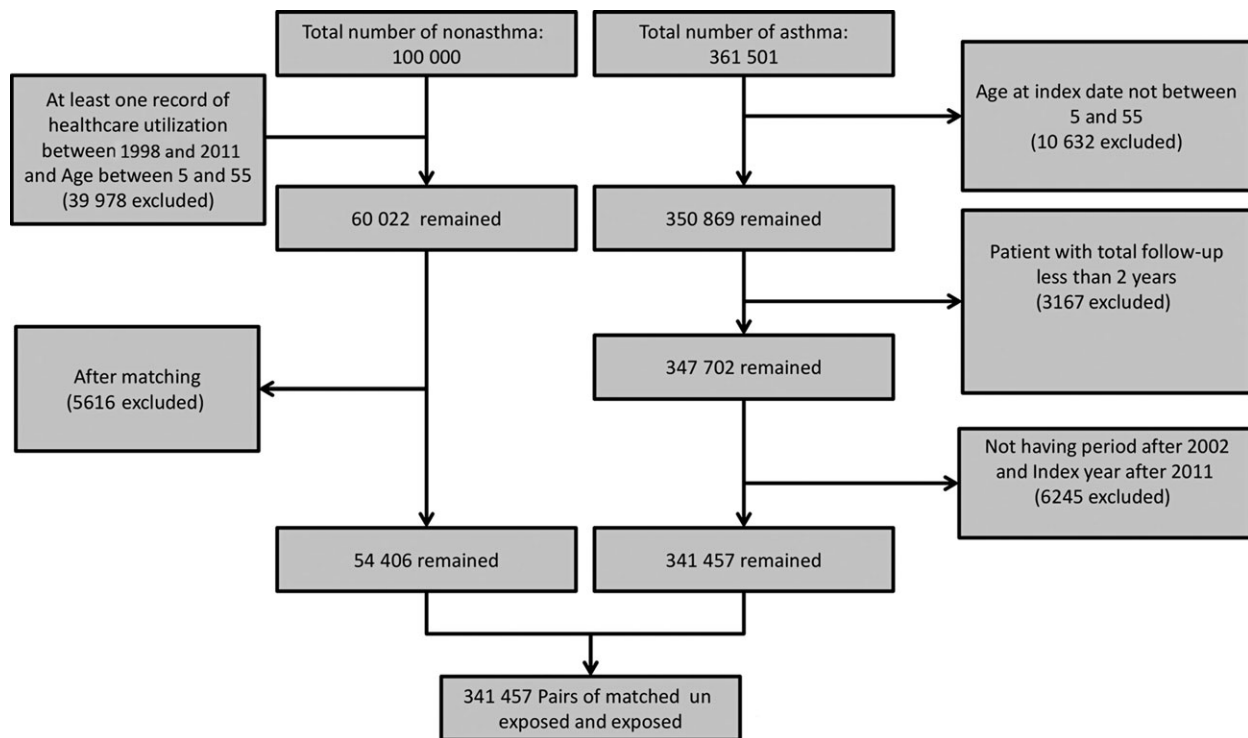


Figure 1 Flow chart of the cohort construction.

\$1270.8; $P < 0.001$), and 5–14 years, at \$363.2/PY (95% CI \$319.3–\$407.0; $P < 0.001$).

Asthma-attributable excess costs were \$192.9/PY (95% CI \$191.0–\$194.9; $P < 0.001$). Of which, hospitalizations, outpatient visits and medications were \$8.8/PY (95% CI \$8.3–\$9.3; $P < 0.001$), \$34.7/PY (95% CI \$34.5–\$34.9; $P < 0.001$) and \$149.5/PY (95% CI \$147.8–\$151.2; $P < 0.001$), respectively.

Figure 2 left panel presents excess costs in patients with asthma by calendar year, overall and across cost components. There was a positive (increasing) trend in all-cause per-patient excess costs, increasing by 2.9%/year (95% CI 2.0–3.8%; $P < 0.001$). Within cost components, this increasing trend was observed in all-cause medications (2.4%/year; $P < 0.001$) and all-cause hospitalizations (7.4%/year; $P < 0.001$). The outpatient services costs did not change significantly over the study period (–0.5%/year; $P = 0.23$).

Figure 2 right panel presents the trend of asthma-attributable excess costs, in total and across cost components. Unlike all-cause excess costs, asthma-attributable excess costs decreased over time, by an average of 0.8%/year (95% CI 0.6–0.9%; $P < 0.001$). Medication and outpatient visit costs showed reduction over time by 6.6%/year (95% CI 6.4–6.8%; $P < 0.001$) and 0.6%/year (95% CI 0.5–0.8%; $P < 0.001$), but there was no observable trend in hospitalization costs.

Figure 3 presents the breakdown of excess costs of medications by major drug classes. Single-inhaler combination of inhaled corticosteroids (ICS) and long-acting beta-agonists (LABA) demonstrated the greatest increase in annual per-patient costs overall, by 6.5%/year (95% CI 6.4–6.6%;

$P < 0.001$). As its introduction in the province in 2004, the excess costs of omalizumab, a targeted biologic therapy, increased by 21.5%/year (95% CI 20.6–22.0%; $P < 0.001$). Costs attributable to short-acting beta-agonists decreased through the study period by 3.7%/year (95% CI 3.5–3.9%; $P < 0.001$). Long-acting antimuscarinic agents (LAMA) demonstrated a significant increase trend by 10.6%/year (95% CI 10.3–10.9%; $P < 0.001$).

Figure 4 shows the number of discrete diagnostic hospitalizations and outpatient visit codes by major ICD-10 chapters in the asthma and comparison groups. Patients with asthma generally had higher number of diagnostic codes for all comorbidity groups, but the difference was particularly prominent for respiratory diseases other than asthma and mental health disorders.

Results of the sensitivity analyses are provided in the Appendix S3. Estimates of excess costs were lower in the unmatched analysis (\$657.4) and when COPD patients were excluded (\$735.3), and higher when adjustment for death was removed from the analysis (\$1032.8). The relative contribution of cost components to the overall costs remained the same in all scenarios.

Discussion

We calculated the excess costs and their trends in patients with asthma over a 10-year period (2002–2011) for the entire population of a well-defined geographic area. With an average difference of \$1028 per patient-year, patients with asthma

Table 1 Demographic characteristics of the study

Variable	No asthma N = 341 457	Asthma N = 341 457	Standardized difference
Female; N (%)	184 817 (54.1)	184 817 (54.1)	0.0*
Age at index date mean (SE)	27.1 (0.03)	27.2 (0.03)	1.1%*
Socio-economic status; N (%)			
Quintile 1	70 356 (20.6)	73 906 (21.6)	3.8%
Quintile 2	81 508 (23.9)	70 546 (20.7)	
Quintile 3	65 305 (19.1)	66 856 (19.6)	
Quintile 4	62 185 (18.2)	63 604 (18.6)	
Quintile 5	55 277 (16.2)	57 947 (17)	
Unknown	6826 (2)	8598 (2.5)	
Variables estimated in the 12-month period before the index date			
Modified Charlson Comorbidity score mean (SE), patient-year	0.12 (0.00)	0.15 (0.00)	2.0%
Nonrespiratory- related hospitalizations; mean (SE), patient-year	0.15 (0.00)	0.15 (0.00)	1.4%
Nonrespiratory- related outpatient services; mean (SE), patient-year	10.5 (0.02)	10.3 (0.02)	−1.6%

*Samples were matched directly on sex and age group.

incurred significantly higher direct medical costs over and beyond the medical expenditure of the comparable general population. Of note, 81% of such excess costs were attributable to diseases other than asthma, despite the fact that asthma and comparison cohorts were similar in many characteristics including the burden of comorbid conditions at the start of follow-up. Importantly, there was a statistically significant increase of 2.9% per year in all-cause excess costs,

whereas costs attributable to asthma decreased by 0.8% per year. Trends in costs of major classes of asthma therapies showed a very dynamic picture, with costs of combination ICS + LABA therapy increasing by 6.5% per year. This was concurrent with an equal decline in the utilization of ICS, such that overall, the costs of ICS either as monotherapy or as combination therapy remained roughly constant. The use of omalizumab, introduced to the provincial formulary in 2004, has increased but given that only a small fraction of patients (fewer than 200) take this medication, the contribution of this otherwise expensive medication to the overall costs remains small.

The increase in total excess costs in patients with asthma despite the decrease in asthma-attributable excess costs requires further interpretation and investigations. The declining direct costs attributable to asthma itself are in line with some other observations in the same timeline (30). The trend of the overall excess costs in asthma parallels the trends of general medical expenditure in the comparison cohort (results not shown) and the reported trends in the Canadian population. The observed 2.9%/year increase in excess costs is close to the 2.1%/year increase in overall medical expenditure in Canada (31). One interpretation is that individuals with asthma have a somewhat fixed 'relative' increase in all-cause medical expenditures. This can be due to having more encounters with the healthcare system. This hypothesis was supported by the observation of higher frequency of receiving ICD codes for almost all comorbid conditions as well as more generic codes such as the use of laboratory services (Fig. 4). Overall, the paradoxical trend of asthma-attributable and all-cause excess costs demonstrates the importance of calculating excess costs in reporting the burden of diseases, as a sole reliance on asthma-attributable costs would result in the interpretation that the economic burden of asthma on patients has been decreasing (13, 20, 32), which is not the case when all-cause medical utilization is concerned.

Other investigators have estimated the direct economic burden of asthma in Western countries in recent years, with widely varying results (13, 20, 21, 33–35). When converting to the currency used in our study (2012 \$CAD), the range of annual costs varies from \$140/PY (13) to \$2109/PY (33). While several factors (e.g. age criteria, severity of asthma in the included sample) can be responsible for the observed patterns, a very likely source of disparity is the methodology of cost calculation. Studies that estimated asthma-attributable costs (13,20,21) reported lower values (between \$168/PY and

Table 2 Excess costs and their trends in patients with asthma, in total and across cost categories*

Title	Excess costs per year (\$) (95% CI)	P-value	Trend, per year (%) (95% CI)	P-value
Total costs	\$1028 (\$982.7–\$1073.4)	<0.0001	2.9 (2, 3.8)	<0.0001
Hospitalization costs	\$272.2 (\$247.7–\$296.7)	<0.0001	7.4 (5.2, 9.3)	<0.0001
Outpatient services costs	\$284.1 (\$272.7–\$295.5)	<0.0001	−0.5 (−1.4, 0.3)	0.2383
Medication costs	\$471.7 (\$450.5–\$493)	<0.0001	2.4 (1.9, 2.9)	<0.0001

CI, confidence interval.

*All costs are in 2012 Canadian dollars.

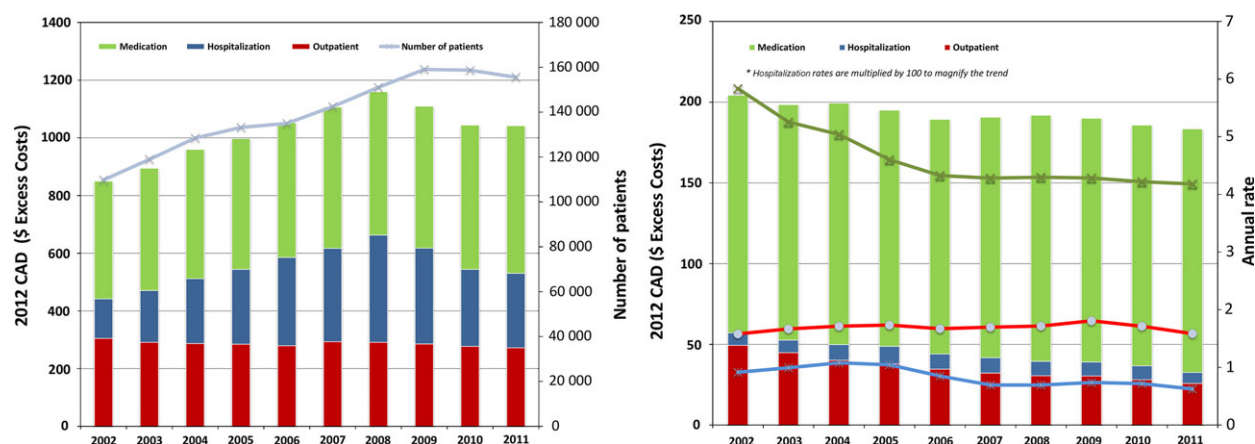


Figure 2 Trends in excess costs in patients with asthma; left panel: excess costs in total and by component; right panel: excess costs attributable to asthma, in total and by cost components. Stacked bars represent excess costs (value on left vertical axis). Marked lines represent total number of individuals within the asthma group (left panel) or rate of service utilization (right panel).

Hospitalization rate is admission rate in 100 people per patient-year. Rate of medication is calculated by average number of asthma-related medication units (puffs for inhalers and quantity of units for rest of drugs) within patient-year for 100 units of drugs. *All costs are in 2012 Canadian dollars.

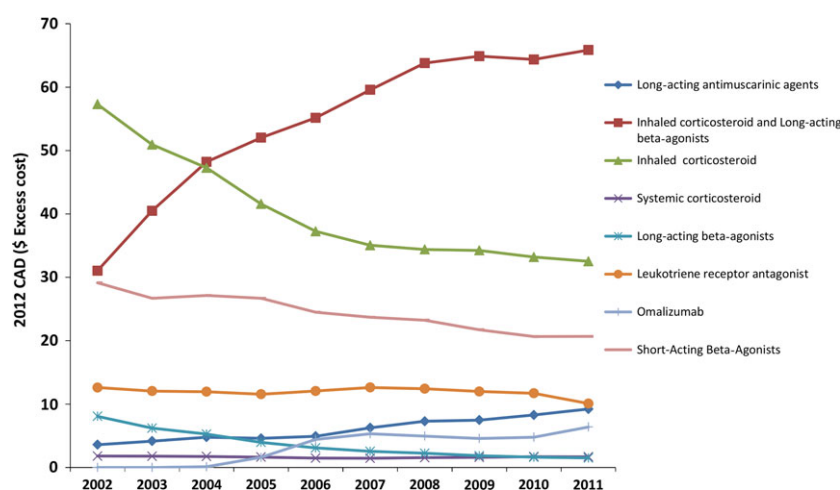


Figure 3 Excess cost of asthma-related medications (per patient-year). *All costs are in 2012 Canadian dollars.

\$1716/PY) than those reporting on all-cause excess costs (between \$710/PY and \$3848/PY) (33–35). Attributable costs do not take into account the costs of comorbid conditions, which, as observed in the present work, are responsible for the greater share of the burden.

This study has several strengths. To the best of our knowledge, our study has the longest follow-up time among the recent North American studies on the economic burden of asthma (13, 20, 21, 30, 33–35), providing a unique picture of the dynamic pattern of burden in total and across cost components. The administrative databases used in this study capture the entire population of a geographic area, thus are not susceptible to selection bias. Using a matched cohort design, we took into account the burden of pre-existing comorbidity and many other potentially confounding factors (e.g. socio-economic status). The use of matched design enabled us to

calculate the excess costs that are inherently agnostic to the underlying reason for medical services utilization.

The limitations of this study should be acknowledged. Like any other study based on administrative health data, the verification of asthma status based on health resource use records is an inexact science. It is likely that some of patients with mild asthma would never satisfy the case definition, thus making it likely that our sample is biased towards a higher proportion of patients with moderate–severe asthma. Emergency Department visits are not systematically captured in our data set, although their associated health services use is largely captured through outpatient service codes (36). Finally, we did not investigate the causes behind the excess nonasthma-related costs in patients with asthma. This was a *a priori* design decision due to our concerns for multiple hypothesis testing and interpretability of results.

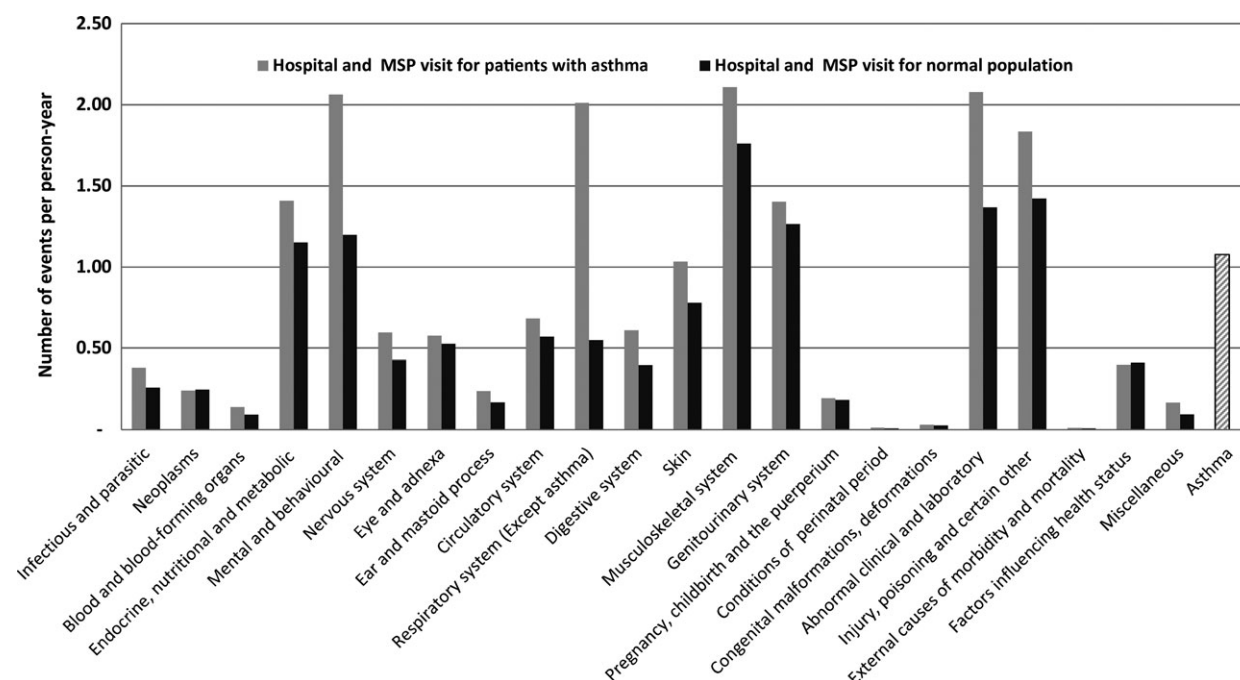


Figure 4 Number of discrete hospitalization and outpatient visits by major disease categories.

In the sensitivity analyses (Supplementary Material), excess costs were reduced by 28.5% when patients who satisfied a case definition of diagnosed COPD were excluded. Another significant change in this sensitivity analysis was the utilization of LAMA, which its excess cost declined by 83% and its increase cost rate plunged to 50%. We decided not to exclude patients who develop COPD during the follow-up in the main analysis as asthma can be on the causal pathway in developing fixed airflow obstruction, a phenotype described as the asthma COPD overlap syndrome (37). Therefore, the excess COPD-related economic burden, compared with the general nonasthma population, is likely a real component of the excess costs of asthma.

In summary, our long-term longitudinal population-based study provides updated evidence on the high and changing burden of asthma and depicts a very dynamic picture of the burden of asthma highlighted by significant shifts in its costs components. The costs of all-cause inpatient care and medication use have increased, but the costs of asthma-related inpatient and outpatient care as well as medications have significantly dropped during the study period, with outpatient care experiencing the most dramatic decline. These results are not only informative for policy makers, but also generate hypotheses regarding the changes in the severity of diagnosed asthma and evolution of comorbid conditions in asthma. Research into the reason behind such changes, as well as into the burden of comorbid conditions in asthma, should continue.

Author contributions

MS, JMF, TT, AG and SA conceptualized the study idea. MS designed the study. MS, HT and TK developed the data

analysis plan. HT performed all the analyses. MS, JMF, SA, TK, TT and AG provided critical feedback at the design stage. MS wrote the first version of the manuscript. All authors critically reviewed the manuscript and approved the final version. MS is the guarantor of the study.

Funding

This study was funded by the Canadian Respiratory Research Network (CRRN); the CRRN is supported by grants from the Canadian Institutes of Health Research (CIHR) – Institute of Circulatory and Respiratory Health; Canadian Lung Association (CLA)/Canadian Thoracic Society (CTS); British Columbia Lung Association; and Industry Partners including Boehringer-Ingelheim Canada Ltd, AstraZeneca Canada Inc., and Novartis Canada Ltd. Funding for the training of graduate students and new investigators within the network was supported by the above funding sponsors and as well by GlaxoSmithKline Inc. The funders had no role in the study design, data collection and analysis, or preparation of the manuscript.

Conflicts of interest

JMF has served on advisory boards for GlaxoSmithKline, AstraZeneca, Pfizer, Novartis, Boehringer-Ingelheim, Takeda, Merck and Amiral. He has also been a member of speakers' bureaus for Glaxo-SmithKline, AstraZeneca, Boehringer-Ingelheim, Pfizer and Merck. He has received research funding paid directly to the University of British Columbia from the Canadian Institutes of Health Research, AstraZeneca,

Glaxo-SmithKline, Boehringer-Ingelheim, Merck, Ono, Janssen and Janssen, Amgen and Genentech. Dr. FitzGerald is the chair of the Global Initiative for Asthma (GINA) Executive and a member of its Science Committee. Dr. Sadatsafavi receives salary support from the Canadian Institutes of Health Research and Michael Smith Foundation for Health Research.

References

- Health indicator profile, annual estimates, by age group and sex, Canada, provinces, territories, health regions (2013 boundaries) and peer groups, Table 105-0501. Statistics Canada.
- The Conference Board of Canada. Cost risk analysis for chronic lung disease in Canada. <http://www.conferenceboard.ca/e-library/abstract.aspx?did=4585> (accessed 26 January 2014).
- Voshaar T, Kostev K, Rex J, Schröder-Bernhardi D, Maus J, Munzel U. A retrospective database analysis on persistence with inhaled corticosteroid therapy: comparison of two dry powder inhalers during asthma treatment in Germany. *Int J Clin Pharmacol Ther* 2012;**50**:257–264.
- Population Estimates, BC Stats, central statistical agency of the Province of British Columbia. 2015. <http://www.bcstats.gov.bc.ca/StatisticsBySubject/Demography/PopulationEstimates.aspx>.
- (CIHI) CI for HI. CIHI data quality study of the DAD 2009-2010 discharge abstract database. <https://secure.cihi.ca/estore/productFamily.htm?pf=PFC1762&lang=en&media=0>.
- Canadian Institute for Health Information. *Discharge abstract database (hospital separations)*. Population Data BC. Data Extract. MOH (2014); 2014. <http://www.popdata.bc.ca/data>.
- British Columbia Ministry of Health. *Medical Services Plan (MSP) payment information file*. Population Data BC. Data Extract. MOH (2014); 2014. <http://www.popdata.bc.ca/data>.
- BC Ministry of Health. *PharmaNet*. BC Ministry of Health. Data Extract. Data Stewardship Committee (2013); 2014. <http://www.popdata.bc.ca/data>.
- British Columbia Ministry of Health, BC Vital Statistics Agency. *Vital statistics deaths*. Population Data BC. Data Extract BC Vital Statistics Agency (2013); 2013. <http://www.popdata.bc.ca/data>.
- British Columbia Ministry of Health. *Consolidation file (MSP registration & premium billing)*. Population Data BC. Data Extract. MOH (2014); 2013. <http://www.popdata.bc.ca/data>.
- Prosser RJ, Carleton BC, Smith MA. Identifying persons with treated asthma using administrative data via latent class modelling. *Health Serv Res* 2008;**43**:733–754.
- Lougheed MD, Lemiere C, Ducharme FM, Licskai C, Dell SD, Rowe BH et al. Canadian Thoracic Society 2012 guideline update: diagnosis and management of asthma in preschoolers, children and adults. *Can Respir J* 2012;**19**:127–164.
- Bedouch P, Marra CA, FitzGerald JM, Lynd LD, Sadatsafavi M. Trends in asthma-related direct medical costs from 2002 to 2007 in British Columbia, Canada: a population based-cohort study. *PLoS One* 2012;**7**:e50949.
- Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi J-C et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005;**43**:1130–1139.
- Austin PC, Lee DS. The concept of the marginally matched subject in propensity-score matched analyses. *Pharmacoepidemiol Drug Saf* 2009;**18**:469–482.
- Austin PC. A critical appraisal of propensity-score matching in the medical literature between 1996 and 2003. *Stat Med* 2008;**27**:2037–2049.
- Dehejia RH, Wahba S. *Propensity score matching methods for non-experimental causal studies*. National Bureau of Economic Research, 1998. <http://www.nber.org/papers/w6829> (accessed 19 November 2015).
- Mihaylova B, Briggs A, O'Hagan A, Thompson S. Review of statistical methods for analysing healthcare resources and costs. *Health Econ* 2011;**20**:897–916.
- Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multi-var Behav Res* 2011;**46**:399–424.
- Sadatsafavi M, Lynd L, Marra C, Carleton B, Tan W, Sullivan S et al. Direct health care costs associated with asthma in British Columbia. *Can Respir J* 2010;**17**:74–80.
- Accordini S, Corsico AG, Braggion M, Gerbase MW, Gislason D, Gulsvik A et al. The cost of persistent asthma in Europe: an international population-based study in adults. *Int Arch Allergy Immunol* 2013;**160**:93–101.
- Alzaabi A, Alseieri M, Mahboub B. Economic burden of asthma in Abu Dhabi: a retrospective study. *Clinicoecon Outcomes Res* 2014;**6**:445–450.
- Kim C-Y, Park H-W, Ko S-K, Chang S-I, Moon H-B, Kim Y-Y et al. The financial burden of asthma: a nationwide comprehensive survey conducted in the republic of Korea. *Allergy Asthma Immunol Res* 2011;**3**:34–38.
- Lee Y-H, Yoon S-J, Kim E-J, Kim Y-A, Seo H-Y, Oh I-H. Economic burden of asthma in Korea. *Allergy Asthma Proc* 2011;**32**:35–40.
- Akobundu E, Ju J, Blatt L, Mullins CD. Cost-of-illness studies: a review of current methods. *Pharmacoeconomics* 2006;**24**:869–890.
- Manitoba Center for Health Policy. Calculating hospital costs using cost per weighted case (CPWC) values. <http://mchp-appserv.cpe.umanitoba.ca/viewConcept.php?conceptID=1100>.
- Canadian Institute for Health Information. Patient cost estimator. <https://www.cihi.ca/en/spending-and-health-workforce/spending/patient-cost-estimator>.
- Bank of Canada. Consumer price index. <http://www.bankofcanada.ca/en/cpi.html>.
- Gershon AS, Wang C, Guan J, Vasilevska-Ristovska J, Cicutto L, To T. Identifying individuals with physician diagnosed COPD in health administrative databases. *COPD* 2009;**6**:388–394.
- Tan NC, Nguyen HV, Lye WK, Sankari U, Nadkarni NV. Trends and predictors of asthma costs: results from a 10-year longitudinal study. *Eur Respir J* 2016 Mar;**47**:801–809.
- Canadian Institute of Health Information. National health expenditure trends, 1975 to 2014. https://www.cihi.ca/en/nhex_2014_report_en.pdf (accessed 29 November 2015).
- Accordini S, Bugiani M, Arossa W, Gerzeli S, Marinoni A, Olivieri M et al. Poor control increases the economic cost of asthma. A multicentre population-based study. *Int Arch Allergy Immunol* 2006;**141**:189–198.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Schematic illustration of the design.

Appendix S2. List of asthma-related medications.

Appendix S3. Sensitivity analyses.

33. Kamble S, Bharmal M. Incremental direct expenditure of treating asthma in the United States. *J Asthma* 2009;**46**:73–80.
34. Barnett SBL, Nurmagambetov TA. Costs of asthma in the United States: 2002–2007. *J Allergy Clin Immunol* 2011;**127**:145–152.
35. Jang J, Gary Chan KC, Huang H, Sullivan SD. Trends in cost and outcomes among adult and pediatric patients with asthma: 2000–2009. *Ann Allergy Asthma Immunol* 2013;**111**:516–522.
36. McKendry R, Reid RJ, McGrail K, Kerluke KJ. Emergency rooms in British Columbia: a pilot project to validate current data and describe users | UBC CHSPR. <http://www.chspr.ubc.ca/pubs/report/emergency-rooms-british-columbia-pilot-project-validate-current-data-and> (accessed 8 October 2015).
37. Bujarski S, Parulekar AD, Sharafkhaneh A, Hanania NA. The asthma COPD overlap syndrome (ACOS). *Curr Allergy Asthma Rep* 2015;**15**:509.