Age trends in direct medical costs of pediatric asthma: a population-based study

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest relevant to this article to disclose.

ABSTRACT

Background: Quantifying age trends in healthcare costs of pediatric asthma leads to better understanding of the natural history of the disease and informed decision-making on the allocation of healthcare resources.

Methods: We identified children with incident asthma from the health administrative data of British Columbia, Canada (Jan 1998 to Dec 2015), and followed them from their first diagnosis of asthma or wheezing until age 18. We estimated direct medical costs (in 2016 Canadian dollars [$]), including inpatient and outpatient encounters and pharmacy costs, attributed to asthma (primary outcome) and other respiratory diseases (secondary outcome). We assessed the impact of sex and socioeconomic status on age trends, adjusting for calendar effect.

Results: The final analysis included 44,552 children with asthma (62% boys). From age 0 to 18, costs of asthma/wheezing and other respiratory conditions decreased from $1,036 to $29/child-year, and from $1,145 to $31/child-year, respectively. Children under 3 years of age incurred 4–fold higher costs for asthma/wheezing and other respiratory conditions. In particular, costs of asthma hospitalizations were 10 times higher in this age group compared to older children. Age trends were generally similar between sex groups and across socioeconomic status. However, medication costs for asthma/wheezing

decreased in boys, whereas those in girls declined during childhood but increased during adolescence.

Conclusions: The highest costs of pediatric asthma are concentrated in children younger than 3. Age trends were generally consistent between sex and across socioeconomic status.

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Key words: pediatric asthma; healthcare costs; age trend; burden of diseases

KEY MESSAGES

Many children develop asthma symptom at an early age yet grow out of it over time. Evidence on the health economic aspects of this age trend is limited. The results of this study show that infants and toddlers with asthma incurred disproportionately high healthcare costs in particular for hospitalizations. Meanwhile, sex and socioeconomic status did not significantly modify age trends. This new evidence can be used to support the design and economic assessment of early preventive or therapeutic interventions for asthma.

INTRODUCTION

Asthma is a most prevalent chronic disease of the airways in children[1]. The global prevalence of asthma symptoms is estimated at 11.5% in children at age 6 to 7, and 14.1% at age 13 to 14[2]. In particular, asthma is a leading cause of hospitalization among children and youth in both Canada[3] and the US[4]. Pediatric patients contributed to nearly half of asthma-related hospitalization in Quebec, Canada[5]. In the US, the total direct costs of pediatric asthma amounted to $5.9 billion in 2013, with inpatient and emergency department (ED) visits particularly exerting a high cost burden[6].

Although 80% of patients with persistent asthma trace their symptoms to the first 3 years of life[7], asthma is often overlooked or misdiagnosed during infancy and toddlerhood[8]. Both in Canada and worldwide, there is significant activities towards developing and assessing prevention strategies such as antibiotic stepwarship[9] and breastfeeding promotion[10]. Before implementation of such interventions and policies, their 'value for money' potential should be demonstrated. The burden of asthma rapidly evolves as children age; consequently, its economic burden is likely to have strong age trends. Further compounding this picture is the potential effect of biologic sex on such trends, as it is generally demonstrated that boys are more likely to experience a full or temporary remission compared to girls[11]. Another factor of interest in this context is socioeconomic barriers under Canadian's provision of universal health care, which is yet to be studied.

Based on data from a well-defined population, the primary objective of this study was to estimate the age trends of healthcare costs of pediatric asthma, including costs

attributable to asthma and to other respiratory conditions. The secondary objective was to evaluate the influences of sex and SES on such trends.

METHODS

Data sources

We retrieved longitudinal data between January 1, 1997 and December 31, 2015 from the health administrative databases of British Columbia, which has 4.4 million residents as of 2016 (representing 13% of Canada's population) [12]. These databases provide linked, individual-level information on demographics, vital statistics, inpatient, outpatient, and pharmacy records of >98% of BC residents[13–17](details are provided in ***Appendix 1***). The prevalence of missing, under-reporting, or misclassified data is very low[18,19]. Ethics approval was obtained from the University of British Columbia Human Ethics Board (H17-00938). All inferences, opinions and conclusions drawn in this study are those of the authors, and do not reflect the opinions or policies of the Data Steward(s).

Study design and sample

This was a retrospective cohort study of pediatric patients with newly diagnosed asthma. ***Appendix Figure E1*** shows a schematic presentation of the study design. First, we identified children between 0 and 12 years of age who satisfied a case definition of asthma. In a large scale Canadian study of case verification for asthma patients between 0 and 18 years of age, one diagnosis code of asthma from physician service records in the Canadian administrative data was sufficiently sensitive (91.4%) and specific (82.9%) for identifying children with asthma[20]. To further enhance specificity, our current case definition extended the above-mentioned definition to include 2 or more outpatient

diagnosis or 1 or more inpatient diagnosis of asthma within a 2-year rolling window. Asthma-related inpatient and outpatient records were identified as those whose most responsible diagnostic International Classification of Diseases (ICD) code was due to asthma (ICD-9th edition [ICD-9]: 493, or tenth revision [ICD-10]: J45). Next, for each asthma case identified, we defined an *index date* as the first date in which the individual had the first diagnosis of asthma or wheezing (ICD-9: 786.0, or ICD-10: R06). The choice of including wheezing in the definition of index date, but not in the case definition of asthma itself, was to ensure we are using a valid definition for asthma, yet also capturing the time between the onset of asthma symptoms and the formal diagnosis, which is often delayed in pediatric population[21]. We evaluated the impact of this approach in a sensitivity analysis. Asthma cases remained in the study until the earliest of the following dates: the administrative end of the study, the last date of presence in the registration database, or date of death.

Cost variables

In BC, all inpatient and outpatient services are fully paid for by the government, while prescriptions are paid either by the patient, government (for selected subgroups), or third-party insurers. We adopted a societal perspective by including all costs regardless of the payer, including out-of-pocket medication costs. All costs were adjusted to 2016 Canadian dollars using the Consumer Price Index[22]. The direct medical costs were summed from three components, inpatient episodes, outpatient healthcare visits, and filled prescriptions. Inpatient costs were calculated using the case mix methodology[23]. Costs of outpatient visits and medication dispensations were directly available in the data.

Of note, most emergency department (ED) encounters (78%) were already captured by fee-for-service payments to healthcare practitioners within the outpatient encounter database (e.g., billing codes with emergency visits/consultation and one-day onsite hospital visits), and the rest were captured within hospitalization costs[24]. This approach has been used in previous analyses of the same data[25].

The primary outcome was asthma-related medical costs, including inpatient outpatient costs with asthma or wheezing being the most responsible diagnosis, as well as the aggregate costs of a specific list of commonly dispensed asthma-related medications (***Appendix Table E1***). Similarly, the secondary outcome was medical costs of other respiratory conditions , including acute respiratory infections, influenza and pneumonia, other chronic respiratory conditions, lung diseases due to external agents, suppurative and necrotic respiratory conditions, other disorders and diseases of the respiratory system (ICD-9, 460-519, ICD-10, J00 – J99 – excluding asthma codes as defined previously), and other respiratory symptoms (ICD-9, 786, ICD-10, R05, R07, R09 – excluding wheezing codes as defined previously), as well as costs of non-asthma respiratory-related medications based on the American Hospital Formulary Service major drug category[26].

Statistical analysis

All analyses were performed using SAS 9.3 (SAS Institute Inc, Cary, NC, United States).

We applied generalized linear models to estimate the longitudinal, population-averaged costs per child-year. The unit of observation was every 12-month period following the index date, with the last period truncated when less than 300 days. The dependent

variables were costs of asthma, or other respiratory conditions. The independent variables were age, sex, socioeconomic status (SES, measured by the quintiles of median neighbourhood household income of each personal record, categorized into 3 levels: low [the lowest 2 quintiles], middle, high [the highest 2 quintiles]). The model further controlled for calendar year effect and the high costs incurred at the first year of asthma onset. Normal distribution and identity link were used for the cost estimation. The normality assumption is robust when the sample size is large, and is a recommended approach[27]. Generalized Estimating Equations was applied to account for correlated cost measurements over time within each child. To test for age trends, we preformed the above-mentioned models by adding interaction terms between age and sex, and between age and SES levels.

RESULTS

The baseline characteristics are presented in ***Table 1***. A total of 44,552 asthma children were included in the analysis, 62% were boys. 40%, 43%, and 17% of children had the first asthma or wheezing diagnosis at between 0 to 3 years, 4 to 7 years, and 8 to 12 years of age, respectively.

Age trends of healthcare costs related to asthma and other respiratory conditions

Overall, per child-year and averaged over the follow-up period, healthcare costs related to asthma were estimated as $208.0 (95% CI, 204.7–211.3), those related to other respiratory conditions were $128.7 (95% CI, 121.8–135.6) (***Table 2***). Age had a significant impact on costs.

Figure 1 presents the age trends of per child-year asthma costs and other respiratory costs from 0 to 18 years of age. From age 0 to 3 years, there was a substantial decrease in asthma costs (from $1035.6/child-year to $381.6/child-year, decreased by 28.9% every year), which was mainly driven by hospitalization costs (decreased by -30.8% every year). Between 4 and 18 years of age, per child-year asthma costs steadily declined, but at a slower rate of 14.1%, while hospitalization costs declined by 30.0% every year. Overall, children below 3 years of age incurred 3.6 times higher asthma costs and in particular 9.3 times higher hospitalization costs compared to those aged 4 and above. Meanwhile, the average costs of outpatient visits and medications were, respectively, 3.7 times and 1.7 times higher in children aged below 3 compared to those aged above 4 (***Figure 1, left panel)***.

For costs of other respiratory conditions, children also incurred highest costs in their first 3 years of life, which decreased from $1144.6/child-year at age 0 to $215.9/child-year at age 3 by -42.3% per year. The average costs of other respiratory conditions were 4.1 times higher for children age below 3 than children age above 4. The average costs of hospitalizations and outpatient visits were respectively 6.7 and 2.8 times higher in children aged below 3 compared to those aged above 4 (from age 0 to 18, $741.6/child-year decreased to $2.0/child-year, $266.9/child-year decreased to $14.0/child-year, respectively). Meanwhile, costs of medications for other respiratory conditions were steadily low over time (***Figure 1, right panel)***.

Influences of sex and SES on age trends

Appendix Figures E2 – E3 respectively show the overall cost differences of asthma and other respiratory conditions between sex groups and across socioeconomic groups. The only statistical difference was found in children who lived in low-income neighborhoods, who incurred higher costs of other respiratory conditions than those living in middle- and high-income neighborhoods (per child-year, low income, $144.5, middle income, $119.5, high income, $106.7, decreased by 14.1% per income level, ***Appendix Figures E3***)

Figure 2 and 3 respectively present the sex- and SES-stratified age trends of healthcare costs related to asthma and other respiratory conditions. The overall patterns of both asthma and other respiratory costs over age were similar between boys and girls (interaction term p-values>0.05) except that, costs of asthma medications steadily declined in boys (-7.9%/year), whereas those costs first declined in girls between age 0 and 14 (-7.9%/year) but increased between age 15 and 17 (18.5%/year) (***Figure 2)***. Despite social gradients in pediatric asthma costs, age trends were generally parallel across SES status (***Figure 3)***.

Sensitivity analysis: excluding wheezing from asthma costs

The removal of wheezing-related healthcare encounters from both the definition of index date and asthma-related costs had resulted in a slight reduction of overall asthma costs (per child-year, from $208.0 to $196.3). However, the age trends remained persistent that children below 3 years of age incurred 3.5 times higher asthma costs, including 8.7 times higher hospitalization costs, compared to those aged 4 and above (***Appendix Figure E4)***.

DISCUSSION

In this retrospective population-based cohort study, we estimated that asthma cost about $208 per child-year in healthcare expenses in a Canadian setting. Moreover, children with asthma annually incurred $129 per child due to other respiratory conditions. Age of a child had a significant impact on costs, with children under 3 years of age incurring 4-fold higher costs for both asthma and other respiratory conditions, in particular over 10-fold higher costs of asthma hospitalizations, compared to children above age 4. The age trends of asthma and other respiratory costs were largely parallel across sex and SES groups.

Our study followed children as early as their first presentation of recurrent wheeze, and attributed costs related to wheezing to asthma costs. This attribution provided a more complete picture of the healthcare needs of young asthmatics. The substantially high costs of asthma in the first 3 years of life actually reflected to a certain extent the challenges in managing asthma in young children because, despite early diagnosis, they were still hospitalized for asthma and other respiratory conditions.

Consistent with recent evidence that boys are more likely to experience a remission of their asthma than girls in adolescence[11], in our analysis, starting around puberty, costs of asthma-related medications rose up again in girls and was higher than in boys. This pattern might suggest persistent or even increased asthma symptoms in girls in adolescence, and female onset of asthma which generally starts at puberty. Overall, it appears that the difference in the burden of asthma between boys and girls is mainly due to labeled diagnosis or medication use (which in turn might be due to symptom burden) rather than asthma attacks that might require outpatient or inpatient care.

Interestingly, the SES-related inequalities in pediatric asthma costs were found to be minimal. This finding is aligned with the recent report of Canadian Institutes for Health Information that, BC appeared to be more effective compared to other provinces with regard to the elimination of income-related inequalities in the hospitalization rate of pediatric asthma[28]. This finding seemingly contradicted with well-established evidence in the US that asthma-related health resource utilization was highest among ethnic minorities and low socioeconomic status[29], which may be explained by Canada's provision of universal healthcare coverage, whereas US provides a mix of private plans and Medicaid/HMO.

The current findings support more appropriate therapeutic options in young asthma children, such as researches to understand the heterogeneity in clinical phenotypes of early-life asthma; as well as broader-scope early-life programs that strive to improve microbiome, diet and regulate second-hand smoke and antibiotics. Moreover, our study provides direct evidence to assist the economic evaluation of those personalized medicine and public health interventions for pediatric asthma. Exact cost estimates are not transferrable to other jurisdictions due to the nuances of different healthcare systems. However, trends in costs by age group likely reflects the age-dependent epidemiology of asthma and should be more consistent across jurisdictions. Compared to similar recent North American studies[30], our study has the longest follow-up time, and captures the entire population of a representative geographic region which minimized selection bias.

Nonetheless, there are also several limitations. First, due to the nature of administrative health data and a lack of objective measures such as spirometry in the pediatric

242 population, we identified asthma children through a case definition that was based on
243 health resource use records[20]. In addition, the case definition algorithm required a two-
244 year assessment window, which led to an under-representation of asthma children who
245 were born between 1997 and 1999 (the first years of data). Second, this was an incidence
246 cohort of asthma children, but the first incidence of asthma may be uncertain if the child
247 was not born in BC. Finally, several important risk factors related to pediatric asthma
248 outcomes, such as family education status and environmental smoke exposure, were not
249 recorded in our data.

250 To conclude, children with asthma below 3 of years of age incurred significantly higher
251 costs due to asthma and other respiratory-related hospitalizations and outpatient visits,
252 compared to children aged above 4. Infants and preschool children with wheezing
253 disorders and asthma still had unmet medical needs and they might be a mixed group of
254 disorders.

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Dr.Wenjia Chen conceptualized and designed the study, wrote the first draft of manuscript, critically reviewed and revised the manuscript.

Mr. Hamid Tavakoli designed the study, collected data and performed the statistical analysis, critically reviewed the manuscript for important intellectual content.

Drs.J Mark FitzGerald, Padmaja Subbarao and Stuart E. Turvey conceptualized the study, provided critical clinical input, critically reviewed the manuscript for important intellectual content.

Dr.Mohsen Sadatsafavi conceptualized and designed the study, coordinated and supervised data collection and statistical analysis, critically reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

All authors agreed be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Table 1. Baseline characteristics of the study sample

	Overall Sample (N=44,552)
Age, n (%)	
0–3 years	17,796 (39.9)
4–7 years	19,093 (42.9)
8–12 years	7,663 (17.2)
Sex, n (%)	
Girls	16,597 (37.3)
Boys	27,955 (62.8)
Neighborhood household income, n (%)	
Low (1st and 2nd quintile)	19,592 (44.0)
Middle (3rd quintile)	9,068 (26.0)
High (4th and 5th quintile)	15,217 (34.7)
Missing	675 (1.5)

N, number

Table 2. Healthcare costs for pediatric asthma patients

	Costs ($/child-year) (95% CI)
Asthma-related costs	208.0 (204.7, 211.3)
Hospitalizations	58.1 (55.9, 60.3)
Outpatient visits	64.4 (63.7, 65.1)
Medications	85.5 (84.0, 87.0)
Other respiratory-related costs	128.7 (121.8, 135.6)
Hospitalization	64.0 (57.6, 70.4)
Outpatient visits	60.2 (59.5, 60.8)
Medication	4.5 (3.5, 5.6)

Figure legends

Figure 1. Age trends of pediatric asthma costs. Left panel, healthcare costs related to asthma, total and by components. Right panel, healthcare costs related to other respiratory conditions, total and by components.

Figure 2. Age trends of pediatric asthma costs, by sex. Left panel, costs related to asthma. Right panel, costs related to other respiratory conditions.

Figure 3. Age trends of pediatric asthma costs, by socioeconomic status. Left panel, costs related to asthma. Right panel, costs related to other respiratory conditions.