

1           **Age trends in direct medical costs of pediatric asthma: a population study**

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13 **To the Editor**

14 Asthma symptoms is prevalent in 11.5% and 14.1% of children at ages 6-7 and 13-14,  
15 respectively<sup>1</sup>. Although 80% of patients with persistent asthma trace their symptoms to  
16 the first 3 years of life, asthma is often overlooked or misdiagnosed during infancy and  
17 early childhood<sup>2</sup>. Evidence on the health economic implications of this strong age trend is  
18 limited. Further compounding this picture is the potential effect of biologic sex and  
19 socioeconomic status (SES) on such trends, which are yet to be studied under Canada's  
20 universal health care system. This study estimated the age trends of direct medical costs  
21 (DMC) of pediatric asthma, and evaluated the influences of sex and SES on such trends  
22 in the secondary analyses.

23 Data were retrieved between January 1, 1997 and December 31, 2015 from the health  
24 administrative databases of the province of British Columbia, Canada (total population  
25 4.77M in 2015 - *Appendix 1*)<sup>3-7</sup>. All inferences, opinions and conclusions drawn in this  
26 study are those of the authors, and do not reflect the opinions or policies of the Data  
27 Steward(s). During every 2-year rolling window, we identified children who had  $\geq 2$   
28 outpatient physician visits or  $\geq 1$  hospitalization between 0 to 12 years of age, with  
29 asthma being the most responsible diagnosis (International Classification of Diseases  
30 [ICD] code, 9<sup>th</sup> edition [ICD-9]: 493, or tenth revision [ICD-10]: J45) (*Appendix Figure*  
31 *E1*). We followed them from the first diagnosis of asthma or wheezing (ICD-9: 786.0, or  
32 ICD-10: R06) until age 18, the administrative end of the study, the last date of presence  
33 in the registration database, or date of death.

34 Direct medical costs (referred to as ‘costs’ hereafter for brevity) were summed from three  
35 components: inpatient episodes, outpatient healthcare visits, and filled prescriptions,  
36 including all costs regardless of the payer. Inpatient costs were calculated using the case  
37 mix methodology<sup>8</sup>. Costs of outpatient visits and medication dispensations were directly  
38 available in the data. Most emergency department encounters (78%) were already  
39 captured by fee-for-service payments to healthcare practitioners within the outpatient  
40 encounter database, and the rest were captured within hospitalization costs<sup>9</sup>. All costs  
41 were adjusted to 2016 Canadian dollars using the Consumer Price Index<sup>10</sup>. The primary  
42 outcome was asthma-related costs. For inpatient and outpatient costs these were sum of  
43 costs associated with inpatient or outpatient records with asthma or wheezing being the  
44 most responsible diagnosis; for medications, we used a specific list of commonly  
45 dispensed asthma-related drugs (*Appendix Table E1*). The secondary outcome was costs  
46 of other respiratory conditions, including acute respiratory infections, influenza,  
47 pneumonia, other chronic respiratory conditions, lung diseases due to external agents,  
48 suppurative and necrotic respiratory conditions, other disorders and diseases of the  
49 respiratory system (ICD-9, 460-519, ICD-10, J00 – J99 – excluding asthma), other  
50 respiratory symptoms (ICD-9, 786, ICD-10, R05, R07, R09 – excluding wheezing), as  
51 well as other respiratory-related medications based on the American Hospital Formulary  
52 Service major drug category<sup>11</sup>. We applied generalized linear models to estimate the  
53 population-averaged costs per child-year (*Appendix E2*). Generalized Estimating  
54 Equations were applied to account for correlated measurements over time within each  
55 child. All analyses were performed using SAS 9.3 (SAS Institute Inc, Cary, NC, United  
56 States).

57 The final analysis included 44,552 children with asthma (62.8% boys), 39.9%, 42.9%,  
58 and 17.2% of children had the first asthma or wheezing diagnosis at between 0 to 3 years,  
59 4 to 7 years, and 8 to 12 years of age, respectively (**Table 1**). Per child-year and averaged  
60 over the follow-up period, costs related to asthma were estimated as \$208.0 (95% CI,  
61 204.7–211.3) and related to other respiratory conditions as \$128.7 (95% CI, 121.8–135.6)  
62 (**Table 2**). From age 0 to 3 years, there was a substantial decrease in asthma-related costs  
63 (from \$1035.6/child-year to \$381.6/child-year, decreased by 28.9% every year), mainly  
64 driven by hospitalization costs (decreased by -30.8% every year) (**Figure 1, left panel**).  
65 Between 4 and 18 years of age, per child-year asthma-related costs steadily declined, but  
66 at a slower rate of 14.1%, while hospitalization costs declined by 30.0% every year.  
67 Overall, children below 3 years of age incurred 3.6 times higher asthma costs and in  
68 particular 9.3 times higher asthma-related hospitalization costs compared to those aged 4  
69 and above. Meanwhile, the average costs of outpatient visits and medications were,  
70 respectively, 3.7 times and 1.7 times higher in children aged below 3 compared to those  
71 aged 4 and older. For other respiratory conditions, children also incurred the highest costs  
72 in their first 3 years of life, which decreased from \$1,144.6/child-year at age 0 to \$215.9/  
73 child-year at age 3, corresponding to a decline of 42.3% per year (**Figure 1, right panel**).  
74 The age trends persisted after the removal of wheezing-related healthcare encounters  
75 from both the definition of index date and asthma-related costs (**Appendix Figure E2**).

76 **Appendix Figure E3 and 4** respectively present the sex- and SES-stratified age trends of  
77 costs related to asthma and other respiratory conditions. The overall patterns of both  
78 asthma and other respiratory costs over age were similar between boys and girls  
79 (interaction term p-values>0.05) except that, costs of asthma medications steadily

80 declined in boys (-7.9%/year), whereas these costs initially declined in girls between age  
81 0 and 14 (-7.9%/year) but increased between age 15 and 17 (18.5%/year) (*Appendix*  
82 *Figure E3*). Such age trends were generally parallel across SES status (*Appendix Figure*  
83 *E4*).

84 Overall, these results depict a highly dynamic picture of the economic burden of asthma  
85 in children. The highest direct medical costs were found in children younger than 3. Age  
86 trends were generally consistent between sex and across socioeconomic status. The  
87 substantially higher costs in the first 3 years of life reflect the challenge of managing  
88 asthma in young children because, despite the early diagnosis, they were frequently  
89 hospitalized for asthma and other respiratory conditions. A similarly high burden has also  
90 been reported among children from Nordic countries<sup>12</sup>. In our study, starting around  
91 puberty, costs of asthma-related medications increased again in girls when compared to  
92 boys, which is consistent with the evidence that in their adolescence, boys are more likely  
93 to experience a remission of asthma symptoms than girls<sup>13</sup>. Interestingly, the SES-  
94 related inequalities in pediatric asthma costs were found to be minimal, supporting the  
95 recent report of Canadian Institutes for Health Information that, British Columbia  
96 appeared to be more effective compared to other provinces with regard to the elimination  
97 of income-related inequalities in the hospitalization rate of pediatric asthma<sup>14</sup>.

98 Our study has some limitations. First, we identified children with asthma through health  
99 resource use records<sup>15</sup> instead of objective measures of airflow obstruction. Second,  
100 several important risk factors related to pediatric asthma outcomes, such as family  
101 education status and environmental smoke exposure, were not recorded in our data.

102 Finally, other non-medical direct costs, indirect costs and overall intangible costs were  
103 not included in this study.

104 Both in Canada and worldwide, there is significant enthusiasm towards developing  
105 asthma prevention strategies such as antibiotic stewardship and breastfeeding promotion.  
106 There is scarcity of evidence on the economic burden of pediatric asthma, which is  
107 needed to establish the population-level ‘value for money’ potential of such prevention  
108 strategies. Future studies need to evaluate to what extent the future burden of pediatric  
109 asthma can be modified through evidence-informed disease management.

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111 Sincerely,

112 Wenjia Chen, Hamid Tavakoli, J Mark FitzGerald, Padmaja Subbarao, Stuart E. Turvey,  
113 Mohsen Sadatsafavi.

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119 **CONFLICT OF INTEREST STATEMENT**

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

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122 Dr.Wenjia Chen conceptualized and designed the study, wrote the first draft of  
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129 Dr.Mohsen Sadatsafavi conceptualized and designed the study, coordinated and  
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132 All authors approved the final manuscript as submitted and agree to be accountable for all  
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134 All authors agreed be accountable for all aspects of the work in ensuring that questions  
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186 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 (1 <sup>st</sup> and 2 <sup>nd</sup> quintile)	19,592 (44.0)
Middle (3 <sup>rd</sup> quintile)	9,068 (26.0)
High (4 <sup>th</sup> and 5 <sup>th</sup> quintile)	15,217 (34.7)
Missing	675 (1.5)

187 N, number

188 \*Measured by the quintiles of median neighbourhood household income of each personal  
189 record, categorized into 3 levels: low [the lowest 2 quintiles], middle, high [the highest 2  
190 quintiles]

191 Table 2. Direct medical costs for pediatric asthma patients

	Costs (\$/child-year) (95% CI)
<b>Asthma-related costs</b>	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)
<b>Other respiratory-related costs</b>	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)

192 **Figure legends**

193 Figure 1. Age trends of pediatric asthma costs. Left panel, direct medical costs related to  
194 asthma, total and by components. Right panel, direct medical costs related to other  
195 respiratory conditions, total and by components.