The direct costs of overdiagnosed asthma in a longitudinal population-based study

Running title: Costs of overdiagnosed asthma

Bryan C. Ng[1]; Mohsen Sadatsafavi, MD, PhD[1,2]; Abdollah Safari, PhD[1,2]; J. Mark FitzGerald, MD[2]; Kate M. Johnson, MSc[1]

Affiliations:

[1] Respiratory Evaluation Sciences Program, Collaboration for Outcomes Research and Evaluation, Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, Canada
[2] Institute for Heart and Lung Health, Department of Medicine, University of British Columbia, Vancouver, Canada

Corresponding Author: Kate M. Johnson
Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver Campus,
2405 Wesbrook Mall
Vancouver, BC Canada V6T 1Z3
Phone: 604-788-8575
Email: kate.johnson@alumni.ubc.ca

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1   **ABBREVIATIONS:**

2   BC: British Columbia

3   CI: Confidence Interval

4   FEV_1: Forced Expiratory Volume in 1 second

5   MPR: Medication Possession Ratio

6   SD: Standard Deviation

7   **ABSTRACT**

8   **Objectives:** A current diagnosis of asthma cannot be objectively confirmed in many patients

9   with physician-diagnosed asthma. Estimates of resource use in overdiagnosed cases of asthma

10   are necessary to measure the burden of overdiagnosis and evaluate strategies to reduce this

11   burden. We assessed the difference in asthma-related healthcare resource use between patients

12   with a confirmed asthma diagnosis and those with asthma ruled out.

13   **Design:** Population-based prospective cohort study.

14   **Setting:** Participants were recruited through random-digit dialling of both landlines and mobile

15   phones in BC, Canada.

16   **Participants:** We included 345 individuals ≥12 years of age with a self-reported physician

17   diagnosis of asthma which was confirmed by a bronchodilator reversibility or methacholine

18   challenge test at the end of the 12-month follow-up.

19   **Primary and secondary outcome measures:** Self-reported annual asthma-related direct

20   healthcare costs (2017 Canadian dollars), outpatient physician visits, and medication use from

21   the Canadian healthcare system perspective.

22   **Results:** Asthma was ruled out in 86 (24.9%) participants. Average annual asthma-related direct

23   healthcare costs for participants with confirmed asthma were $497.9 (SD $677.9), and $307.7

24   (SD $424.1) for participants with asthma ruled out. In the adjusted analyses, a confirmed

25   diagnosis was associated with higher direct healthcare costs (Relative Ratio [RR]=1.60, 95%CI

26   1.14-2.22), increased rate of specialist visits (RR=2.41, 95%CI 1.05-5.40) and reliever

27   medication use (RR=1.62, 95%CI 1.09-2.35), but not primary care physician visits (p=0.10) or

28   controller medication use (p=0.11).

29   **Conclusions:** A quarter of individuals with a physician diagnosis of asthma did not have asthma

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30   after objective re-evaluation. These participants still consumed a significant amount of asthma-

31   related healthcare resources. The population-level economic burden of asthma overdiagnosis

32   could be substantial.

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34   **Strengths and limitations of this study:**

35   • Participants were recruited through random sampling of the general population in the

36   province of British Columbia.

37   • Asthma diagnosis was confirmed or ruled out using sequential guideline-recommended

38   objective airway tests.

39   • Healthcare resource use was self-reported, potential recall bias may have led to reduced

40   accuracy.

41   • The study was unable to evaluate the indirect costs of overdiagnosis or the cost-savings

42   from correcting the diagnosis.

43   • The generalizability of the results may be limited by regional differences in medical costs

44   and practices.

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46   **Keywords:** Asthma, Costs, Misdiagnosis, Observational Studies, Overdiagnosis

47 **INTRODUCTION**

48 Over 300 million people worldwide have been diagnosed with asthma.[1] Patients with asthma

49 experience symptoms of wheezing, shortness of breath, chest tightness, and cough.[2] These

50 symptoms, and periods of intensified disease activity referred to as exacerbations, impose a

51 significant burden on healthcare resources and reduce patient quality of life.[3] A Canadian study

52 estimated the excess direct medical costs of asthma at $1,058 (2013 Canadian dollars) per

53 person-year.[4] The majority (74%) of asthma-attributed costs were due to medication use.[4]

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55 Multiple evidence-based guidelines recommend confirming a diagnosis of asthma with objective

56 testing for reversible airflow limitation or increased airway hyper responsiveness.[2,5] Despite

57 these recommendations, previous studies suggest that in the community, asthma is diagnosed

58 solely based on symptom history in over half of the cases.[6,7] The underuse of spirometry has

59 been documented in Canada,[8] the United States,[9] and Europe.[10] A recent population-based

60 study found that one in three patients with physician-diagnosed asthma did not meet the

61 guideline-recommended spirometric criteria for asthma diagnosis and could have their

62 medications safely stopped.[11] We refer to this group of patients as 'overdiagnosed'.[12] These

63 overdiagnosed patients are likely to be imposing costs on the healthcare system due to treatment

64 for a condition that does not exist, and may be experiencing symptoms of an underlying illnesses

65 that is not being treated.[11] By some estimates, there are over 785,000 overdiagnosed asthma

66 patients in Canada alone.[13]

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68 In response to these findings, some authors have called for population-based screening or case

69 finding to re-evaluate previous diagnoses of asthma.[11,13] Assessing the value of these

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70   programs requires precise estimates of the burden of overdiagnosed asthma. To the best of our

71   knowledge, estimates of the cost differences between overdiagnosed and confirmed cases of

72   asthma currently do not exist. A previous study of the costs of overdiagnosed asthma was limited

73   to assessing the potential asthma-related cost savings that a secondary screening program could

74   provide.[13] Characterizing the patterns of healthcare resource use among patients in whom

75   asthma can be ruled out can help identify opportunities for re-evaluation and inform initiatives to

76   improve asthma diagnosis in the community.

77

78   We used a longitudinal population-based cohort of individuals with physician-diagnosed asthma

79   to address this important evidence gap. Our primary objective was to compare total direct

80   asthma-related healthcare costs in patients with a confirmed diagnosis of asthma versus patients

81   in whom a diagnosis of asthma was ruled out using objective testing. Our secondary objectives

82   were to characterize differences in healthcare resource use in terms of the 1) number of

83   outpatient physician visits, and the 2) type and amount of asthma medication use.

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85

86   **METHODS**

87   **Study Design and Sample**

88   We used longitudinal data from the Economic Burden of Asthma study (University of British

89   Columbia Human Ethics #H10-01542), which has been previously described.[14,15] In

90   summary, individuals with a self-reported physician diagnosis of asthma and at least one asthma-

91   related healthcare encounter in the past 5 years were eligible. Participants were recruited through

92   random-digit dialling of both landlines and mobile phones in the census subdivisions of

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93   Vancouver and Central Okanagan (populations of 603,502 and 179,839 in 2011, respectively) of

94   BC, Canada.[16] Between 2010 and 2012, 618 participants were recruited, evaluated at baseline,

95   and followed for 12 months with visits at 3-month intervals. We included 345 participants who

96   were ≥12 years of age at baseline and successfully completed a bronchodilator reversibility or

97   methacholine challenge test at the end of follow-up.

98

99   **Outcomes**

100 Participants reported their asthma-related primary care and specialist physician visits,

101 hospitalizations, emergency department visits, and current medication use at each study visit

102 with a recall period of 3 months. The primary outcome was total asthma-related direct healthcare

103 costs per patient over the one-year follow-up period. Total direct healthcare costs were

104 comprised of all outpatient and inpatient encounters, and medication costs incurred by the

105 patient. Cost categories were described by calculating the percentage of total average cost

106 constituted by each category. The methods used for calculating costs are detailed

107 elsewhere.[17,18] Briefly, costs for each patient were determined by multiplying self-reported

108 resource use quantities by unit cost of each resource. We determined the average unit cost of an

109 asthma-related physician visit (specialist vs. primary care) and hospitalization for the years 2008-

110 2012 using International Classification of Diseases codes from provincial healthcare

111 administrative data.[18] Medication unit costs were determined by linking Drug Identification

112 Numbers of participant-reported asthma medications to the Provincial Drug Master Plan

113 database.[19] Cost per dose was estimated using the lowest price equivalent of the medication.

114 All costs were adjusted to 2017 Canadian Dollars[20] and the analysis was conducted from the

115 perspective of the Canadian healthcare system.

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117   Secondary outcomes were the number of asthma-related outpatient physician visits and use of

118   asthma medications. We did not evaluate asthma-related emergency department visits or

119   hospitalizations as a separate outcome due to the low frequency of these events (N=14). The

120   number of outpatient physician visits over one-year of follow-up was assessed separately by

121   physician type (primary care or specialist). Medication use was captured using the questionnaire

122   shown in *Figure E1*, and medications were classified into controller or reliever using a reference

123   list (*Table E1*). In general, controller medications are those with anti-inflammatory effects

124   (namely inhaled corticosteroids and leukotriene receptor antagonists), while reliever medications

125   are those that are used on as-needed basis for temporary symptom relief (namely short-acting

126   beta agonists). Medication use was determined by calculating the Medication Possession Ratio

127   (MPR) separately for controller and reliever medications. MPR represents the proportion of days

128   in which medications were available to the participant over the follow-up period.[21]

129

130   **Exposure: Objective confirmation of asthma**

131   Participants underwent an objective assessment of asthma at the final visit. The diagnostic

132   algorithm for asthma is shown in *Figure 1* and consisted of both bronchodilator reversibility and

133   methacholine challenge tests implemented in a stepwise fashion. Spirometry was performed by a

134   trained technician using a regularly calibrated spirometer. Reversible airflow obstruction was

135   defined as a $\geq 12\%$ increase in Forced Expiratory Volume in 1 second (FEV_1) 15 minutes after

136   administration of 200mcg of salbutamol via pressurized metered dose inhaler and a spacer

137   device.[22] Participants who did not meet the criteria for reversible airflow obstruction returned

138   within one week to undergo a methacholine challenge test. Participants who did not meet the

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139   criteria for asthma diagnosis at the first methacholine challenge test had their controller

140   medications tapered and discontinued by a respirologist before returning for a second

141   methacholine challenge test. A diagnosis of asthma was ruled out if FEV_1 decreased by <20%

142   following the administration of 16mg/mL of methacholine[23] in both methacholine challenge

143   tests. Participants had a 'confirmed asthma diagnosis' if they met the criteria for asthma at the

144   bronchodilator reversibility test or either methacholine challenge test.

145

146   <<Figure 1>>

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148   **Statistical Analysis**

149   All statistical analyses were performed in R version 3.5.0.[24] We considered a two-tailed p-

150   value of <0.05 as statistically significant.

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152   We constructed separate generalized linear regression models (negative binomial distribution,

153   log link) for the primary and secondary outcomes. This resulted in five separate models for the

154   following outcomes: annual asthma-related (1) direct healthcare costs, (2) number of primary

155   care physician visits, (3) number of specialist physician visits, (4) controller MPR, and (5)

156   reliever MPR. All models included the objective diagnosis of asthma (confirmed vs. ruled out) as

157   the exposure. Costs and MPR values (as a percentage) were rounded to the nearest integer value.

158   Models were adjusted for participant tobacco smoking history (ever smoked vs. never smoked),

159   ethnicity (Caucasian vs. non-Caucasian), age, sex, education (postsecondary vs. no), income

160   (annual household income ≥$70,000 vs. less), and third-party insurance coverage for medications

161   (coverage vs. no), all self-reported at baseline with a 12-month recall period. The resulting

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162   regression coefficients were exponentiated to create effect estimates on the relative scale (rate

163   ratio [RR]). Asthma severity was not adjusted for due to the high likelihood that there is a causal

164   relationship between severe asthma and a confirmed diagnosis of asthma.[11]

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167   **RESULTS**

168   **Sample Characteristics**

169   The cohort selection procedure is illustrated in *Figure 2*. From the Economic Burden of Asthma

170   cohort (618 participants), we excluded 86 participants who were <12 years of age, 153 in whom

171   a methacholine challenge was contraindicated (N=29), refused (N=112), or could not be

172   completed for other reasons (N=14), and 34 participants who were lost to follow-up. The final

173   study cohort included 345 participants who underwent an objective diagnostic test for asthma at

174   the final visit (12 months after baseline). Their characteristics are shown in *Table 1*. 212 (61.4%)

175   participants were female, and the mean age at baseline was 48.9 (standard deviation [SD] 17.8)

176   years. A diagnosis of asthma was confirmed in 259 (75.1%) participants: 138 (53.3%) by

177   bronchodilator reversibility test, 98 (37.8%) following the first methacholine challenge test, and

178   23 (8.9%) following the second methacholine challenge test. Asthma was ruled out in 86

179   (24.9%) participants following negative results on all bronchodilator reversibility and

180   methacholine challenge tests.

181

182   <<Figure 2>>

183

184   **Table 1.** Sample characteristics

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Characteristic	Total (n = 345)	Asthma confirmed (n = 259)	Asthma ruled out (n = 86)	p-value§
Variables evaluated at baseline				
Female, n (%)	212 (61.4)	156 (60.2)	56 (65.1)	0.50
Age, mean (SD)	48.9 (17.8)	49.3 (18.1)	47.7 (17.2)	0.46
Ever smoked (vs. never smoked), n (%)	93 (27.0)	71 (27.4)	22 (25.6)	0.85
Caucasian (vs. non-Caucasian), n (%)	267 (77.4)	206 (79.5)	61 (70.9)	0.13
High income (vs. low income) †, n (%)	183 (53.0)	137 (52.9)	46 (53.5)	>0.99
Health insurance (full coverage vs. not full coverage) ‡, n (%)	69 (20.0)	52 (20.1)	17 (19.8)	>0.99
Higher education (postsecondary vs. no postsecondary), n (%)	242 (70.1)	178 (68.7)	64 (74.4)	0.39
Variables evaluated during follow-up				
Total direct healthcare costs, mean (SD)	$450.5 ($629.2)	$497.9 ($677.9)	$307.7 ($424.1)	<0.01*
Primary care physician visits, mean (SD)	2.2 (4.1)	2.1 (2.8)	2.7 (6.6)	0.85
Specialist physician visits, mean (SD)	0.5 (1.9)	0.6 (2.2)	0.2 (0.8)	0.02*
MPR of controller medications, mean (SD)	69.7% (74.4)	74.9% (76.4)	54.0% (65.8)	0.02*
MPR of reliever medications, mean (SD)	28.4% (33.2)	31.3% (34.3)	19.5% (28.0)	<0.01*

MPR: Medication Possession Ratio

* Significant at 0.05 level

† High income defined as household income ≥ $70,000

‡ Full coverage defined as all drug and physician services paid for through third-party coverage

§ p-values for the absolute difference between the 'asthma confirmed' and 'asthma ruled out' groups were determined using a Student t-test for continuous variables and Chi-squared test for categorical variables

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187 **Total Direct Healthcare Costs**

188 Average annual direct healthcare costs over one year was $497.9 (SD $677.9) in participants

189 with confirmed asthma, and $307.7 (SD $424.1) in those with asthma ruled out. There was a

190 significant difference in average annual direct healthcare costs ($190.2) between exposure

191 groups in the unadjusted analysis (p<0.01, *Table 1*). Average annual direct healthcare costs were

192 1.6 times (95%CI 1.14–2.22, p<0.01) higher in participants with confirmed asthma after

193 adjustment for participant smoking history, ethnicity, age, sex, education, income, and insurance

194 coverage (*Figure 3*). Medications comprised the greatest proportion of total costs in both

195 correctly diagnosed and overdiagnosed individuals (56.4% and 47.6%, respectively, *Table 2*).

196

197 <<Figure 3>>

198

199 **Table 2.** Asthma-related healthcare cost categories over one year of follow-up.

Cost Category	Cost per patient mean (SD)	Percentage of total cost per patient
Asthma ruled out		
Medications	$146.39 ($239.94)	47.6%
Primary care physician visits	$118.24 ($292.64)	38.4%
Specialist physician visits	$27.87 ($101.37)	9.1%
Hospitalization	$0 ($0)	0.0%
Emergency visits	$15.23 ($69.07)	4.9%
TOTAL	$307.70 ($422.23)	100.0%
Asthma confirmed		
Medications	$280.74 ($404.17)	56.4%
Primary care physician visits	$90.98 ($125.66)	18.3%
Specialist physician visits	$73.11($257.61)	14.7%
Hospitalization	$39.24 ($362.65)	7.9%
Emergency visits	$13.91 ($72.07)	2.8%
TOTAL	$497.90 ($676.89)	100.0%

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202 **Outpatient Physician Visits**

203 The total number of annual primary care physician visits was similar between participants with

204 confirmed asthma and those with asthma ruled out (2.1 vs. 2.7 visits, p=0.85, *Table 1*). However,

205 participants with confirmed asthma visited specialist physicians more often than those who had

206 asthma ruled out (0.6 vs. 0.2 visits per year, p=0.02). The adjusted analysis also indicated no

207 significant difference in the number of primary care physician visits between participants with

208 confirmed asthma and those with asthma ruled out (p=0.10, *Figure 3*). Confirmed asthma was

209 associated with 2.41 times (95%CI 1.05–5.40, p=0.03) more specialist visits than when an

210 asthma diagnosis could be ruled out.

211

212 **Medication Usage**

213 Participants with a confirmed diagnosis of asthma used controller medications for a greater

214 proportion of follow-up time than those with asthma ruled out (MPR of 74.9% vs. 54.0%,

215 p=0.02), and similarly for reliever medications (31.3% vs. 19.5%, p<0.01, *Table 1*). This

216 difference persisted in the adjusted analysis for reliever medications but not for controller

217 medications (p=0.11, *Figure 3*). The MPR for reliever medications was 1.62 times higher

218 (95%CI 1.09–2.35, p=0.01) among participants with confirmed asthma than those with asthma

219 ruled out.

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DISCUSSION

In this study, we used objective testing to confirm the diagnosis of asthma in a population-based sample of patients with a self-reported physician diagnosis of asthma. We found that asthma could be ruled out in 25% of cases after negative spirometry and two negative methacholine challenge tests. This proportion is in line with the 28-33% rate of overdiagnosis reported in previous Canadian studies.[11,13,25] We compared asthma-related direct healthcare costs between participants with confirmed asthma versus those with asthma ruled out. Although total direct costs were higher in participants with a confirmed diagnosis of asthma, the costs of overdiagnosed asthma remained substantial. The average direct asthma-related healthcare costs for a participant with overdiagnosed asthma was $308 over 12 months, which was $190 lower than for participants with a confirmed diagnosis. This difference in costs remained statistically significant after controlling for confounding variables that could affect both the exposure and outcomes but are likely not on the causal pathway between them.

Participants with overdiagnosed asthma visited specialists less frequently than those with confirmed asthma, but they visited primary care physicians as frequently. These participants may have scheduled a similar number of annual primary care visits for routine monitoring of 'asthma' activity or to fill new prescriptions. Conversely, participants with confirmed asthma may have had exacerbations of their asthma symptoms that required referral to a specialist physician to improve asthma control.[26] Across both groups, participants visited primary care physicians more frequently than specialist physicians; 79% of our sample visited a primary care physician at least once during follow-up. The high frequency of these visits, and their low cost compared to specialist consultations,[13] suggests that primary care visits may provide effective opportunities

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245   for re-evaluating previous asthma diagnoses.

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247   On average, overdiagnosed participants possessed controller medications for over half of follow-

248   up time, and reliever medications for 20 percent of follow-up time. Reliever medications are

249   typically used as needed while controller medications are used daily.[2,5] In comparison to

250   participants with confirmed asthma, and after adjusting for potential confounders, participants

251   with asthma ruled out tended to use similar levels of controller medications and less reliever

252   medications. This difference may be due to a lower symptom burden in overdiagnosed

253   participants, which led to self-adjustment of reliever medication use.[27] Conversely,

254   overdiagnosed individuals may have used controller medications as prescribed.

255

256   Although inhaled medications for asthma are generally safe, the use of asthma medications

257   among overdiagnosed patients puts them at risk of net harm due to medication side effects.[28]

258   These patients are also incurring additional healthcare expenditure without therapeutic benefit.

259   Further, asthma medications may have masked symptoms of a serious underlying illness and

260   resulted in a delay in the diagnosis and treatment of the correct disease. We did not evaluate the

261   true underlying condition in this sample, but a similar study by Aaron et al.[11] found that two

262   out of 213 patients had subglottic stenosis, which was treated as asthma for a number of years

263   before the correct diagnosis was identified during the study. If other health conditions were

264   responsible for the overdiagnosis of asthma, their costs have implications for the burden of

265   overdiagnosed asthma. For example, if ruling out an asthma diagnosis results in the correct

266   alternative diagnosis, the proper management of the underlying condition could confer further

267   cost benefits.

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269   To our knowledge, this is the first study to examine the costs associated with overdiagnosed

270   asthma. Our findings have important population-level implications. Given an estimate of

271   approximately 785,000 individuals with overdiagnosed asthma in Canada,[13] and an annual

272   direct healthcare cost of $308 per patient, the estimated cost of overdiagnosed asthma in Canada

273   is $242 million per year (2017 Canadian dollars). A previous study reported an average cost of

274    $263 per patient (2009 Canadian dollars) for additional physician visits to reassess an asthma

275   diagnosis. This resulted in an average lifetime cost savings of $351 per patient screened,[13]

276   primarily due to the avoided costs of asthma medications. Our results suggest that additional

277   screening to correct an overdiagnosis of asthma would save asthma-related costs in the first year,

278   with savings compounding in subsequent years. Savings could be reallocated to the management

279   of individuals with a true diagnosis of asthma, especially those with severe asthma who could

280   pursue novel but expensive treatments, or to identify and treat the underlying diseases of

281   overdiagnosed patients.[29] Given the prevalence and costs of overdiagnosis, our findings

282   highlight the need for routine objective testing to confirm all new and existing diagnoses of

283   asthma.[2,5]

284

285   There are several strengths to this study. We used a population-based random sample of patients

286   with a physician diagnosis of asthma, meaning our results are likely to be representative of

287   routine healthcare use in the general asthma population. We used longitudinal healthcare

288   utilization data, which compared to cross-sectional data, likely provides a less-biased estimate of

289   the average costs accrued by an individual. Finally, we evaluated airway reversibility using

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290   objective testing following the recommendations of international guidelines.[2,5] This allowed

291   us to evaluate the costs of evidence-based best practices.

292

293   Our study has several limitations. We did not include indirect costs in our analysis, and we were

294   therefore unable to consider the societal costs of overdiagnosis. Previous studies suggest that the

295   cost of productivity loss in this sample is substantial.[15] Physician visits and medication use

296   were self-reported with a recall period of 3 months. It is possible that recall bias reduced the

297   accuracy of our measurements. Our algorithm for ruling out asthma involved one less

298   methacholine challenge test than in some previous studies,[11,13,30] which makes it slightly less

299   rigorous. It is possible that this led to a higher rate of overdiagnosis in our study, however, over

300   90% of diagnoses were confirmed by the second visit in previous studies.[13,25] We excluded

301   participants in whom an objective diagnostic test was contraindicated due to asthma-related

302   reasons, which may have resulted in lower representation of participants with more severe

303   disease and therefore higher resource utilization. Finally, we only assessed asthma-related costs;

304   we were unable to determine the costs of the true underlying condition or the benefit of

305   correcting the diagnosis.

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307

308   **CONCLUSIONS**

309   In this population-based sample, one in four participants with a physician diagnosis of asthma

310   had their diagnosis ruled out upon objective airflow reversibility testing. Patients with

311   overdiagnosed asthma consumed a substantial amount of asthma-related healthcare resources,

312   although less than those with confirmed asthma. The extent of overdiagnosed asthma in Canada

313 and other countries, and its associated healthcare resource costs, suggests that the population-

314 level burden of overdiagnosed asthma is high. Future studies should evaluate the cost-

315 effectiveness of systematic screening or case detection initiatives for re-evaluating previous

316 diagnoses of asthma.

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FIGURE LEGENDS

Figure 1. Algorithm for confirming or ruling out a diagnosis of asthma.

FEV_1; Forced Expiratory Volume in 1 second, PC_{20}; Provocative concentration of methacholine needed to produce a 20% fall in FEV_1 from baseline

Figure 2. Sample selection procedure.

Figure 3. Relative Ratios for the adjusted differences in asthma-related a) total direct healthcare costs, b) primary care physician visits, c) specialist physician visits, d) controller medication use, and e) reliever medication use over one year of follow-up between patients with confirmed asthma and those with asthma ruled out.

* Significant at 0.05 level

```
┌─────────────────┐
│   Pre- and post- │
│   bronchodilator │
│    spirometry    │
└─────────────────┘
         │
         ▼
      ╱FEV₁╲
     ╱increased╲  ── Yes ──▶  ┌──────────────┐        ┌──────────────┐
    ╱ ≥12% or  ╲              │    Asthma    │        │ Asthma ruled │
    ╲  200mL   ╱              │  confirmed   │ ◀──     │     out      │
     ╲        ╱               └──────────────┘        └──────────────┘
         │ No
         ▼
┌─────────────────┐
│   Methacholine  │
│  Challenge Test │
└─────────────────┘
         │
         ▼
      ╱PC₂₀ <╲ ──── Yes ──────────────▶ (Asthma confirmed)
     ╱16mg/mL ╲
      ╲      ╱
         │ No
         ▼
┌──────────────┐        ┌─────────────────┐
│ Discontinue all│ ────▶ │   Methacholine  │
│   controller  │        │  Challenge Test │
│  medications  │        └─────────────────┘
└──────────────┘                │
                                ▼
                             ╱PC₂₀ <╲
                            ╱16mg/mL ╲
                             ╲      ╱
```

Pre- and post-bronchodilator spirometry

FEV$_1$ increased ≥12% or 200mL

Yes → Asthma confirmed

No → Methacholine Challenge Test

PC$_{20}$ < 16mg/mL

Yes → Asthma confirmed

No → Discontinue all controller medications → Methacholine Challenge Test

PC$_{20}$ < 16mg/mL

Yes → Asthma confirmed

No → Asthma ruled out

```
┌────────────────────────────────────────────────────────────┐
│  50,572 Individuals contacted through random digit dialing   │
└────────────────────────────────────────────────────────────┘
                              │
┌────────────────────────────────────────────────────────────┐
│  618    Individuals enrolled in the study                    │
└────────────────────────────────────────────────────────────┘
                              │
                              │        ┌──────────────────────────────┐
                              │        │  273   Individuals excluded   │
                              │        │    153   Methacholine         │
                              │        │          Challenge test not   │
                              │        │          completed            │
                              │        │    86    <12 years of age     │
                              │        │    34    Lost to follow-up    │
                              │        └──────────────────────────────┘
                              │
┌────────────────────────────────────────────────────────────┐
│  345   Individuals underwent an objective test for the       │
│        diagnosis of asthma                                    │
└────────────────────────────────────────────────────────────┘
                              │
        ┌─────────────────────┴──────────────────┐
┌──────────────────────────────┐   ┌──────────────────────────────┐
│  259  Individuals with asthma │   │  86   Individuals with asthma │
│       diagnosis confirmed     │   │       diagnosis ruled out     │
│    138   + Bronchodilator     │   │                              │
│          Reversibility test   │   │                              │
│    121   + Methacholine       │   │                              │
│          Challenge test       │   │                              │
└──────────────────────────────┘   └──────────────────────────────┘
```

a) Total Direct Healthcare Costs

	Relative Ratio	95% CI
Asthma Confirmed (vs. ruled out)*	1.6	1.14 - 2.22
Caucasian (vs. non-Caucasian)	0.78	0.54 - 1.10
Age (10-year increase)	1.03	0.94 - 1.12
Female (vs. male)	1.18	0.87 - 1.60
Higher Education (postsecondary vs. no postsecondary)	1.06	0.74 - 1.51
High Income (vs. low income)	0.89	0.65 - 1.21
High Insurance (full coverage vs. no)	0.81	0.57 - 1.18

Higher Cost --->

b) Primary Care Physician Visits

	Relative Ratio	95% CI
Asthma Confirmed (vs ruled out)	0.78	0.59 - 1.03
Caucasian (vs non-Caucasian)	0.97	0.73 - 1.30
Age (10-year increase)*	1.13	1.05 - 1.21
Female (vs. male)*	1.33	1.03 - 1.71
Higher Education (postsecondary vs. no postsecondary)	0.92	0.69 - 1.23
High Income (vs. low income)	1.06	0.82 - 1.38
High Insurance (full coverage vs. no)	1.05	0.78 - 1.43

More Visits --->

c) Specialist Physician Visits

	Relative Ratio	95% CI
Asthma Confirmed (vs ruled out)*	2.42	1.06 - 5.42
Caucasian (vs non-Caucasian)	0.5	0.22 - 1.06
Age (10-year increase)	0.9	0.74 - 1.10
Female (vs. male)	1.81	0.87 - 3.76
Higher Education (postsecondary vs. no postsecondary)*	2.91	1.28 - 6.62
High Income (vs. low income)	0.8	0.38 - 1.71
High Insurance (full coverage vs. no)*	0.37	0.15 - 0.94

More Visits --->

d) Controller Medication Use

	Relative Ratio	95% CI
Asthma Confirmed (vs ruled out)	1.35	0.91 - 1.96
Caucasian (vs non-Caucasian)	1.14	0.75 - 1.68
Age (10-year increase)*	1.16	1.05 - 1.27
Female (vs. male)	1.19	0.84 - 1.68
Higher Education (postsecondary vs. no postsecondary)	0.88	0.58 - 1.32
High Income (vs. low income)	0.99	0.69 - 1.41
High Insurance (full coverage vs. no)	1.15	0.76 - 1.77

Higher MPR --->

e) Reliever Medication Use

	Relative Ratio	95% CI
Asthma Confirmed (vs ruled out)*	1.62	1.09 - 2.34
Caucasian (vs non-Caucasian)	1.29	0.85 - 1.90
Age (10-year increase)	0.99	0.89 - 1.09
Female (vs. male)*	1.47	1.03 - 2.08
Higher Education (postsecondary vs. no postsecondary)	1.02	0.67 - 1.54
High Income (vs. low income)	0.9	0.62 - 1.31
High Insurance (full coverage vs. no)	0.89	0.59 - 1.39

Higher MPR --->