Abstract word count: 248

Word count: 2491 (without abstract, references, tables, and figure captions)

Running title: Costs of misdiagnosed asthma

The costs of misdiagnosed asthma in a longitudinal study of the general population

Bryan Ng[1]; Mohsen Sadatsafavi, MD, PhD[1,2,3]; Abdollah Safari, PhD[1,2]; J. Mark FitzGerald, MD[2]; Kate M. Johnson, MSc[1]

Affiliations:

1. 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, the University of British Columbia, Vancouver, Canada
3. Centre for Clinical Epidemiology and Evaluation, Vancouver Coastal Health Research Institute, 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
Email: kate.johnson@alumni.ubc.ca

Conflicts of Interest: BN, AS, JMF, and KMJ have no conflicts to declare. MS has received honorarium for unrelated consultancy work from GSK Canada and GSK global.

Funding: The Economic Burden of Asthma study was funded by Collaborative Innovative Research Fund, an arm's length, investigator initiated, peer-reviewed grant from GSK Canada. The funders had no role in study design, data collection and analysis, or preparation of the manuscript, and was unaware of the contents of this work before publication.

ABBREVIATIONS:

BC: British Columbia

CI: Confidence Interval

FEV_1: Forced Expiratory Volume in 1 second

MPR: Medication Possession Ratio

SD: Standard Deviation

ABSTRACT

Background: An estimated one third of asthma patients are misdiagnosed. Evaluating the difference in healthcare resource use and costs between misdiagnosed and confirmed cases of asthma can inform assessments of the burden of asthma overdiagnosis.

Methods: Participants with a self-reported physician diagnosis of asthma were recruited through random-digit dialing and followed for 1-year. The diagnosis of asthma was reassessed using bronchodilator reversibility and methacholine challenge tests. We assessed self-reported asthma-related direct healthcare costs (2017 Canadian dollars), outpatient physician visits, and medication use. We used separate regression models to measure the association between each outcome and verified asthma status, adjusting for potential confounders.

Results: The final sample included 345 individuals (61.4% female, mean age 48.9). Asthma was ruled out in 86 (24.9%) participants. Average annual direct healthcare costs for participants with confirmed asthma were $497.9 (SD $677.9), and $307.7 (SD $424.1) for participants who had asthma ruled out. In the adjusted analyses, a confirmed diagnosis was associated with higher direct healthcare costs (Relative Ratio [RR]=1.60, 95%CI 1.14-2.22), rate of specialist visits (RR=2.42, 95%CI 1.06-5.42), and reliever medication use (RR=1.62, 95%CI 1.09-2.34), but not with primary care physician visits (p=0.08), and controller medication use (p=0.12).

Conclusions: A quarter of individuals did not have asthma after objective re-evaluation. Although direct costs were higher in participants with a confirmed diagnosis of asthma, the costs of misdiagnosed asthma remained substantial. Given the high prevalence of asthma and high rate of overdiagnosis, the economic burden of overdiagnosed asthma at the population level is substantial.

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

1.0 INTRODUCTION

Over 300 million people worldwide have been diagnosed with asthma[1]. Patients with asthma experience symptoms of wheezing, shortness of breath, chest tightness, and cough[2]. Due to these symptoms, asthma imposes a significant burden on patients, including increased morbidity, mortality, and reduced quality of life[3]. Patients with asthma use more medications, and have higher rates of hospitalization and physician visits than subjects without asthma[4]. The excess direct medical costs of asthma are estimated to be $1,058 (2013 Canadian dollars) per person-year in British Columbia (BC)[5]. Thirteen percent of these costs were directly attributable to asthma, and the majority (74%) of attributable costs were due to asthma-related medication use[5].

Multiple evidence-based guidelines, including from the Global Initiative for Asthma, recommend the diagnosis of asthma be confirmed by objective tests demonstrating either reversible airflow limitation or increased airway hyperresponsiveness[2,6]. Despite these recommendations, studies suggest that asthma is diagnosed solely based on symptom history in over half of physician-diagnosed cases[7,8]. A recent population-based study in Canada found that one in three patients with physician-diagnosed asthma did not meet the guideline-recommended criteria for asthma diagnosis and could have their medications safely stopped[9]. These 'misdiagnosed' patients are likely imposing costs to the healthcare system due to treatment for a condition that does not exist, and due to untreated underlying illnesses, which in some cases are very serious[9]. By some estimates, there are over 785,000 misdiagnosed patients in Canada alone[10].

In response to these findings, some authors have called for population-based screening to re-evaluate previous diagnoses of asthma[9,10]. Assessing the value of these programs requires precise estimates of the burden of misdiagnosed asthma on the healthcare system. However,

estimates of the cost differences between misdiagnosed and confirmed cases of asthma currently do not exist. Characterizing the patterns of healthcare resource use among patients with misdiagnosed asthma can help identify opportunities for re-evaluation and develop initiatives to improve asthma diagnosis in the community.

We used a longitudinal population-based cohort of individuals with physician-diagnosed asthma to compare total direct asthma-related healthcare costs in patients with a confirmed diagnosis of asthma versus patients in whom a diagnosis of asthma was ruled out using objective tests. Secondary objectives were to characterize differences in healthcare resource use in terms of the 1) number of outpatient physician visits, and 2) type and amount of asthma medication use.

2.0 METHODS

Study Design and Sample

We used longitudinal data from the Economic Burden of Asthma study (University of British Columbia Human Ethics #H10-01542), which has been previously described[11,12]. In summary, individuals with a self-reported physician diagnosis of asthma and at least one asthma-related healthcare encounter in the past 5 years were eligible for study inclusion. Participants were recruited through random-digit dialing of both landlines and mobile phones in the census subdivisions of Vancouver and Central Okanagan (populations of 603,502 and 179,839 in 2011, respectively) of BC, Canada[13]. 618 participants were recruited, evaluated at baseline, and followed for 12 months with visits at 3-month intervals. We included 345 participants ≥12 years of age who successfully completed a bronchodilator reversibility or methacholine challenge test at the end of follow-up.

Outcomes

Participants reported their asthma-related primary care and specialist physician visits, hospitalizations, emergency department visits, and current medications at each study visit with a recall period of 3 months. The primary outcome was total direct asthma-related healthcare costs over the one-year follow-up period. Total direct healthcare costs were comprised of all outpatient and inpatient encounters, as well as medication costs. The methods used for calculating costs are detailed elsewhere[14,15]. Briefly, costs for each patient were determined by multiplying self-reported resource use quantities by unit cost of each resource. We determined the average cost of an asthma-related physician visit (specialist vs. primary care) and hospitalization for the years 2008-2012 using International Classification of Diseases codes from provincial healthcare administrative data[15]. Medication costs were determined by linking Drug Identification Numbers of participant-reported asthma medications to the Provincial Drug Master Plan database[16]. Cost per dose was estimated using the lowest price equivalent of the medication. All costs were adjusted to 2017 Canadian Dollars[17].

Secondary outcomes were the number of asthma-related outpatient physician visits and use of asthma medications. We did not evaluate asthma-related emergency department visits and hospitalizations as a separate outcome due to the low frequency of these events (N=14). The number of outpatient physician visits over one-year of follow-up was assessed separately by physician type (primary care or specialist). Medication use was captured using the questionnaire shown in ***e-Appendix 1***, and medications were classified into controller or reliever using a reference list (***e-Table 1***). Medication use was determined by calculating the Medication Possession Ratio (MPR) separately for controller and reliever medications. MPR represents the

proportion of days in which medications were available to the participant over the follow-up period[18].

Exposure

Participants underwent an objective assessment of asthma at the final visit. The diagnostic algorithm for asthma is shown in ***Figure 1*** and consisted of both bronchodilator reversibility and methacholine challenge tests implemented in a stepwise fashion. Spirometry was performed by a trained technician using a regularly calibrated spirometer. Reversible airflow obstruction was defined as a ≥12% increase in Forced Expiratory Volume in 1 second (FEV_1) 15 minutes after administration of 200mcg of salbutamol via pressurized metered dose inhaler and a spacer device[19]. Participants who did not meet the criteria for reversible airflow obstruction returned within a week to undergo a methacholine challenge test. Participants who did not meet the criteria for asthma diagnosis at the first methacholine challenge test had their controller medications tapered and discontinued by a respirologist before returning for a second methacholine challenge test. A diagnosis of asthma was ruled out if FEV_1 decreased by <20% following administration of 16mg/mL of methacholine[20] in both methacholine challenge tests. Participants had a 'confirmed asthma diagnosis' if they met the criteria for asthma at the bronchodilator reversibility test or either methacholine challenge test.

<<Figure 1>>

Statistical Analysis

All statistical analysis were performed in R version 3.5.0[21]. We considered a two-tailed p-value of <0.05 as statistically significant.

We constructed separate generalized linear regression models (negative binomial distribution, log link) for the primary and secondary outcomes. This resulted in five separate models for the following outcomes: annual (1) total direct healthcare costs, (2) number of primary care physician visits, (3) number of specialist physician visits, (4) controller MPR, and (5) reliever MPR. All models included the objective diagnosis of asthma (confirmed vs. ruled out) as the exposure. Costs and percent MPR values were rounded to the nearest integer value. Models were adjusted for participant age, sex, ethnicity (Caucasian vs. non-Caucasian), education (postsecondary vs. no), income (annual household income ≥$70,000 vs. less), and third-party insurance coverage for medications (coverage vs. no), all self-reported at baseline with a 12-month recall period. The resulting regression coefficients were exponentiated to create effect estimates on the relative scale (rate ratio [RR]).

3.0 RESULTS

Sample Characteristics

The cohort selection procedure is illustrated in ***Figure 2***. From the Economic Burden of Asthma cohort (618 participants), we excluded 86 who were <12 years of age, 153 in whom a methacholine challenge was contraindicated (N=29), refused (N=112), or could not be completed for other reasons (N=14), and 34 participants who were lost to follow-up. The final study cohort included 345 adults who underwent an objective diagnostic test for asthma at their final visit. Their characteristics are shown in ***Table 1***. 212 (61.4%) participants were female, and the mean age at baseline was 48.9 (standard deviation [SD] 17.8) years. A diagnosis of asthma was confirmed in 259 (75.1%) participants: 138 (53.3%) by bronchodilator reversibility test, 98

(37.8%) following the first methacholine challenge test, and 23 (8.9%) following the second methacholine challenge test. Asthma was ruled out in 86 (24.9%) participants following negative results on all bronchodilator reversibility and methacholine challenge tests.

<<Figure 2>>

<<Table 1>>

Total Direct Healthcare Costs

Average annual direct healthcare costs over one year was $497.9 (SD $677.9) in participants with confirmed asthma and $307.7 (SD $424.1) in those with asthma ruled out. The difference in average annual direct healthcare costs ($190.2) between exposure groups was significant in the unadjusted analysis (p<0.01, ***Table 1***). Average annual direct healthcare costs were 1.6 times (95%CI 1.14–2.22, p=0.01) higher in participants with confirmed asthma after adjustment for participant sex, age, ethnicity, income, insurance coverage, and education (***Figure 3***).

<<Figure 3>>

Outpatient Physician Visits

Total number of primary care physician visits over one year was similar between participants with confirmed asthma and those with asthma ruled out (2.1 vs. 2.7 visits, p=0.85, ***Table 1***). However, participants with confirmed asthma visited specialist physicians more often than those who had asthma ruled out (0.6 vs 0.2 visits per year, p=0.02). The adjusted analysis also indicated no significant difference in the number of primary care physician visits between participants with confirmed asthma and those with asthma ruled out (p=0.08, ***Figure 3***).

Confirmed asthma was associated with 2.42 times (95%CI 1.06–5.42, p=0.03) more specialist visits than when asthma diagnosis was ruled out.

Medication Usage

Participants with a confirmed diagnosis of asthma used controller medications for a greater proportion of follow-up time than those with asthma ruled out (MPR of 74.9% vs. 54.0%, p=0.02), and similarly for reliever medications (31.3% vs. 19.5%, p<0.01, ***Table 1***). This difference persisted in the adjusted analysis for reliever medications but not for controller medications (p=0.12, ***Figure 3***). MPR for reliever medications was 1.62 times higher (95%CI 1.09–2.34, p=0.01) among participants with confirmed asthma than those with asthma ruled out.

4.0 DISCUSSION

In this study, we used objective tests to confirm the diagnosis of asthma in a random sample of the general population with a self-reported physician diagnosis of asthma. We found that asthma could be ruled out in 25% of cases. This proportion is in line with previous studies, which estimated a 28-33% rate of overdiagnosis in the general Canadian population[9,10]. We compared direct asthma-related 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 misdiagnosed asthma remained substantial. The average direct healthcare costs for a participant with misdiagnosed asthma was $308 over 12 months; $190 lower than for participants with a confirmed diagnosis.

Participants with misdiagnosed asthma visited specialists less frequently than those with confirmed asthma, and primary care physicians as frequently. These misdiagnosed participants may have scheduled a similar number of annual primary care visits for routine monitoring of 'asthma' activity or to fill new prescriptions. Alternatively, they may have had underlying diseases that caused respiratory symptoms and required management by their primary care physician. However, participants with confirmed asthma tended to visit respiratory specialist physicians more frequently. These participants may have had exacerbations of their asthma symptoms requiring referral to a specialist physician to improve asthma control[22]. 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. Due to this high frequency, re-evaluation of a previous asthma diagnosis during primary care physician visits may be an effective method for detecting misdiagnosed asthma.

On average, misdiagnosed participants possessed controller medications for over half of follow-up time, and reliever medications for 20 percent of follow-up time. In comparison to participants with confirmed asthma, and after adjusting for potential confounders, participants with asthma ruled out tended to use similar levels of controller medications and less reliever medications. This difference may be due to a lower symptom burden in misdiagnosed participants, which led to self-adjustment of reliever medication use[24]. In contrast to reliever medications, which are typically used as needed, controller medications are used daily[2,6]. Under the assumption of treating asthma, misdiagnosed individuals may have used controller medications as prescribed. Although inhaled medications for asthma are generally safe, misdiagnosed asthma patients remain at risk of net harm due to medication side effects[23], and may be incurring healthcare expenditure without therapeutic benefit. Further, asthma

medications may have masked symptoms of a serious underlying illness and resulted in a delay in diagnosis and treatment of the correct disease. We did not evaluate the true underlying condition in this sample, but as an example, two patients in a study by Aaron et al.[9] had subglottic stenosis, which was treated as asthma for a number of years before the correct diagnosis was identified during the study.

To our knowledge, this is the first study examining the costs associated with misdiagnosed asthma. Our findings have important population-level consequences. Given an estimate of approximately 785,000 individuals with asthma misdiagnosed in Canada[10], and direct healthcare costs of $308 per patient-year, the estimated cost of misdiagnosed asthma in Canada is $242 million per year (2017 Canadian dollars). A previous study reported average costs of $263 per patient (2009 Canadian dollars) for additional physician visits to reassess an asthma diagnosis[10]. This suggests that additional assessment to correct a misdiagnosis of asthma would be cost saving in the first year, with asthma-related healthcare savings compounding in subsequent years. Savings could be reallocated to the management of individuals with a true diagnosis of asthma, especially those with severe asthma who could pursue novel but expensive treatments, or to treat the underlying diseases of misdiagnosed patients[25]. Given the prevalence and associated costs of misdiagnosis, our findings highlight the need for objective testing to accompany all new diagnoses of asthma[2,6].

Strengths of this study include a random sample of the general population, which means our results are likely to be representative of routine healthcare use. We evaluated airway reversibility using objective tests recommended by international guidelines[2,6], which allowed us to evaluate the costs of evidence-based practices. Limitations of our study should be recognized. First, our algorithm for ruling out asthma was less rigorous than some previous studies[9,10,26]

because it involved one fewer methacholine challenge test. It is possible that this led to a higher rate of misdiagnosis in our study. Second, we excluded participants in whom an objective diagnostic test was contraindicated due to asthma-related reasons, which may have resulted in lower representation of participants with high resource utilization due to more severe disease. Finally, we did not assess other health conditions that might have been responsible for the misdiagnosis and therefore could not evaluate their cost implications. If ruling out an asthma diagnosis results in the correct alternative diagnosis, the proper management of the underlying condition could confer further benefit; this aspect was not evaluated in our study.

5.0 CONCLUSIONS

In this population-based sample, one in four participants with a physician diagnosis of asthma had their diagnosis ruled out upon objective airflow reversibility testing. Patients with misdiagnosed asthma consume a substantial amount of asthma-related healthcare resources, albeit less resources than those with confirmed asthma. Given the extent of misdiagnosed asthma in Canada and its associated healthcare resource burden, our results suggest that a nationwide screening or case detection initiative for re-evaluating previous diagnoses of asthma may be an efficient use of resources. Formal evaluation of the cost-effectiveness of such a program is needed.

Acknowledgements

JMF and MS conceived, designed, and conducted the Economic Burden of Asthma study. MS formulated the current study idea and MS, KMJ and BN designed the study. BN performed all

data analyses and wrote the first draft of the manuscript. AS and KMJ provided guidance on the statistical analysis. All authors critically commented on the manuscript and approved the final version. KMJ is the guarantor of the manuscript.

BN, AS, JMF, and KMJ have no conflicts to declare. MS has received honorarium for unrelated consultancy work from GSK Canada and GAK global.

We would like to thank all members of the Economic Burden of Asthma study team. This study was funded by Collaborative Innovative Research Fund, an arm's length, investigator initiated, peer-reviewed grant from GSK Canada. The funders had no role in study design, data collection and analysis, or preparation of the manuscript.

REFERENCES

1. Braman SS. The Global Burden of Asthma. *Chest* 2006;130(1):4S–12S.

2. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2018. 2018.

3. Bousquet J, Bousquet PJ, Godard P, Daures J-P. The public health implications of asthma. *Bull World Health Organ* 2005;83(7):548–554.

4. Jacob C, Bechtel B, Engel S, et al. Healthcare costs and resource utilization of asthma in Germany: a claims data analysis. *Eur J Health Econ* 2016;17(2):195–201.

5. Chen W, Lynd LD, FitzGerald JM, et al. Excess medical costs in patients with asthma and the role of comorbidity. *Eur Respir J* 2016;48(6):1584–1592.

6. National Institutes of Health. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma Full Report 2007. *Natl Hear Lung, Blood Inst* 2007.

7. Jin R, Choi BC, Chan BT, et al. Physician asthma management practices in Canada. *Can Respir J* 2000;7(6):456–465.

8. Sharpe HM, Sin DD, Andrews EM, Cowie RL, Man P. Alberta Strategy to Help Manage Asthma (ASTHMA): a provincial initiative to improve outcomes for individuals with asthma. *Healthc Q* 2004;7(3):4,55-60.

9. Aaron SD, Vandemheen KL, FitzGerald JM, et al. Reevaluation of diagnosis in adults with physician-diagnosed asthma. *JAMA - J Am Med Assoc* 2017;317(3):269–279.

10. Pakhale S, Sumner A, Coyle D, Vandemheen K, Aaron S. (Correcting) misdiagnoses of asthma: a cost effectiveness analysis. *BMC Pulm Med* 2011;11:27.

11. Chen W, FitzGerald JM, Rousseau R, Lynd LD, Tan WC, Sadatsafavi M. Complementary and alternative asthma treatments and their association with asthma control: a population-based study. *BMJ Open* 2013;3(9).

12. Sadatsafavi M, Rousseau R, Chen W, Zhang W, Lynd L, FitzGerald JM. The Preventable Burden of Productivity Loss Due to Suboptimal Asthma Control: A Population-Based Study. *Chest* 2014;145(4):787–793.

13. [dataset] British Columbia Statistics. Open Data from the Census - BC Stats [Internet]. Census Div. (Regional Dist. Census Subdiv. (Municipalities, RDEAs, Indian Reserv. 2011 [cited 2018 May 15];Available from: http://www.bcstats.gov.bc.ca/StatisticsBySubject/Census/OpenData.aspx.

14. 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(12):e50949.

15. Sadatsafavi M, Chen W, Tavakoli H, Rolf JD, Rousseau R, FitzGerald JM. Saving in medical costs by achieving guideline-based asthma symptom control: A population-based study. *Allergy Eur J Allergy Clin Immunol* 2016; 71: 371–377

16. [dataset] British Columbia Ministry of Health. PharmaCare Downloadable Data File [Internet]. 2013 [cited 2018 Jul 19];Available from: https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/pharmacare/health-industry-professionals/downloadable-drug-data-files.

17. [dataset] Statistics Canada. Table 18-10-0005-01 Consumer Price Index, annual average, not seasonally adjusted [Internet]. 2018;Available from: https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1810000501.

18. Andrade SE, Kahler KH, Frech F, Chan KA. Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiol Drug Saf* 2006;15(8):565–567.

19. Boulet LP, Becker A, Berube D, Beveridge R, Ernst P. Canadian Asthma Consensus Report, 1999. Canadian Asthma Consensus Group. *CMAJ* 1999;161(11 Suppl):S1-61.

20. Guidelines for Methacholine and Exercise Challenge Testing—1999. *Am J Respir Crit Care Med* 2000;161(1):309–329.

21. R Core Team. R: A Language and Environment for Statistical Computing. 2018.

22. Schatz M, Rachelefsky G, Krishnan JA. Follow-up after acute asthma episodes: what improves future outcomes? *Proc Am Thorac Soc* 2009;6(4):386–393.

23. BJ L. Systemic adverse effects of inhaled corticosteroid therapy: A systematic review and meta-analysis. *Arch Intern Med* 1999;159(9):941–955.

24. Horne R, Weinman J. Self-regulation and Self-management in Asthma: Exploring The Role of Illness Perceptions and Treatment Beliefs in Explaining Non-adherence to Preventer Medication. *Psychol Health* 2002;17(1):17–32.

25. Corrigan SP, Cecillon DL, Sin DD, et al. The costs of implementing the 1999 Canadian Asthma Consensus Guidelines recommendation of asthma education and spirometry for the family physician. *Can Respir J* 2004;11(5):349–353.

26. Aaron SD, Vandemheen KL, Boulet L-P, et al. Overdiagnosis of asthma in obese and nonobese adults. *C Can Med Assoc J* 2008;179(11):1121–1131.

Table 1. Sample characteristics

Characteristic	Total (n = 345)	Asthma confirmed (n = 259)	Asthma ruled out (n = 86)	*p*-value[e]
Female, n (%)	212 (61.4)	156 (60.2)	56 (65.1)	0.50
Age[b], mean (SD)	48.9 (17.8)	49.3 (18.1)	47.7 (17.2)	0.46
Caucasian (vs. non-Caucasian), n (%)	267 (77.4)	206 (79.5)	61 (70.9)	0.13
High income (vs. low income)[bc], n (%)	183 (53.0)	137 (52.9)	46 (53.5)	>0.99
Health insurance (full coverage vs. not full coverage)[bd], n (%)	69 (20.0)	52 (20.1)	17 (19.8)	>0.99
Higher education (postsecondary vs. no postsecondary)[b], 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[a]
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[a]
MPR of controller medications, mean (SD)	69.7% (74.4)	74.9% (76.4)	54.0% (65.8)	0.02[a]
MPR of reliever medications, mean (SD)	28.4% (33.2)	31.3% (34.3)	19.5% (28.0)	<0.01[a]

MPR: Medication Possession Ratio

[a] Significant at 0.05 level

[b] Measured at the baseline visit

[c] High income defined as household income ≥ $70,000

[d] Full coverage defined as all drug and physician services paid for through third-party coverage

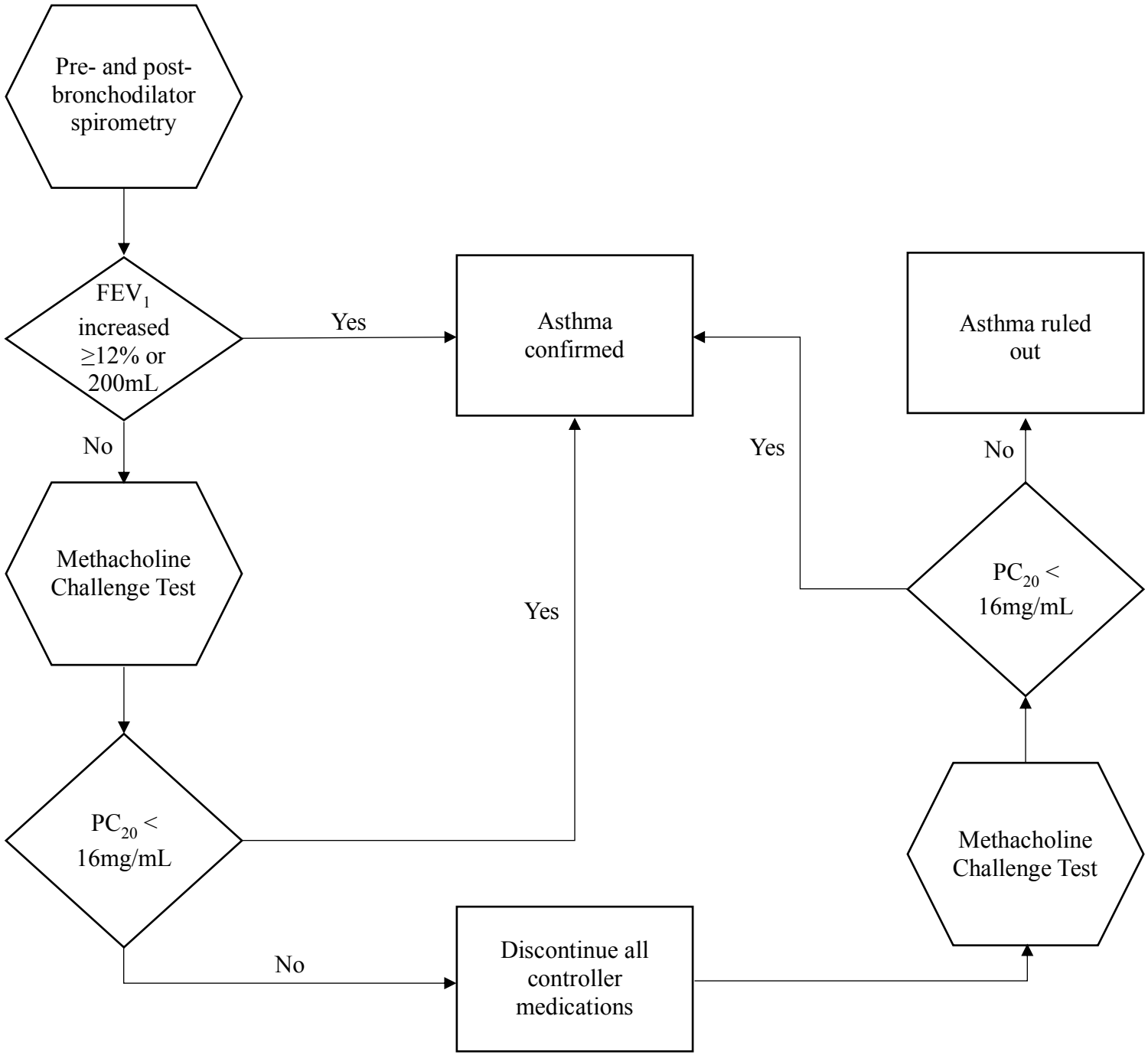
[e] p-values for the absolute difference between the 'asthma confirmed' and 'asthma ruled out' groups were determined using a Student t-test for continuous variables and Chi-squared test for categorical variables

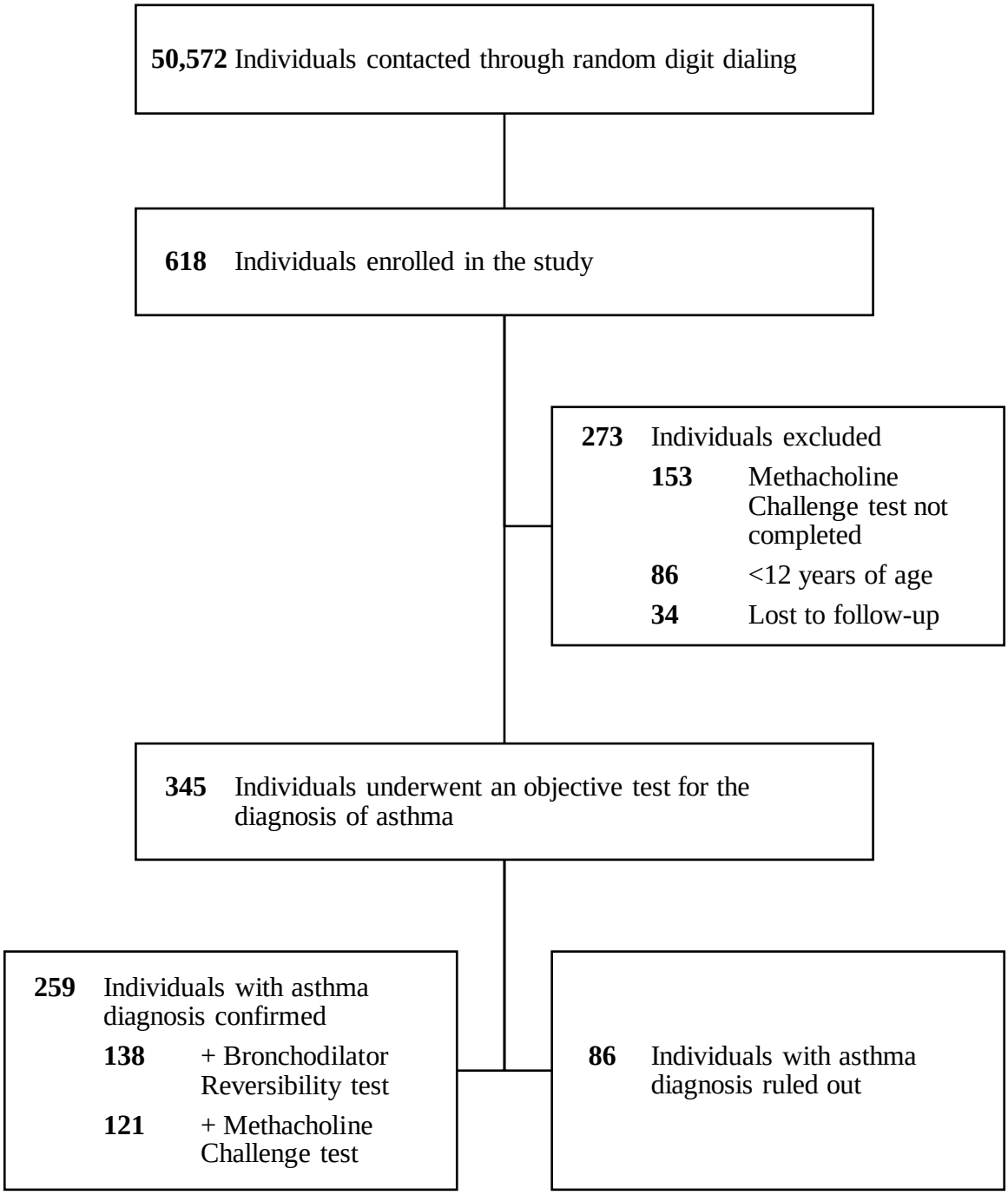
FIGURE LEGENDS

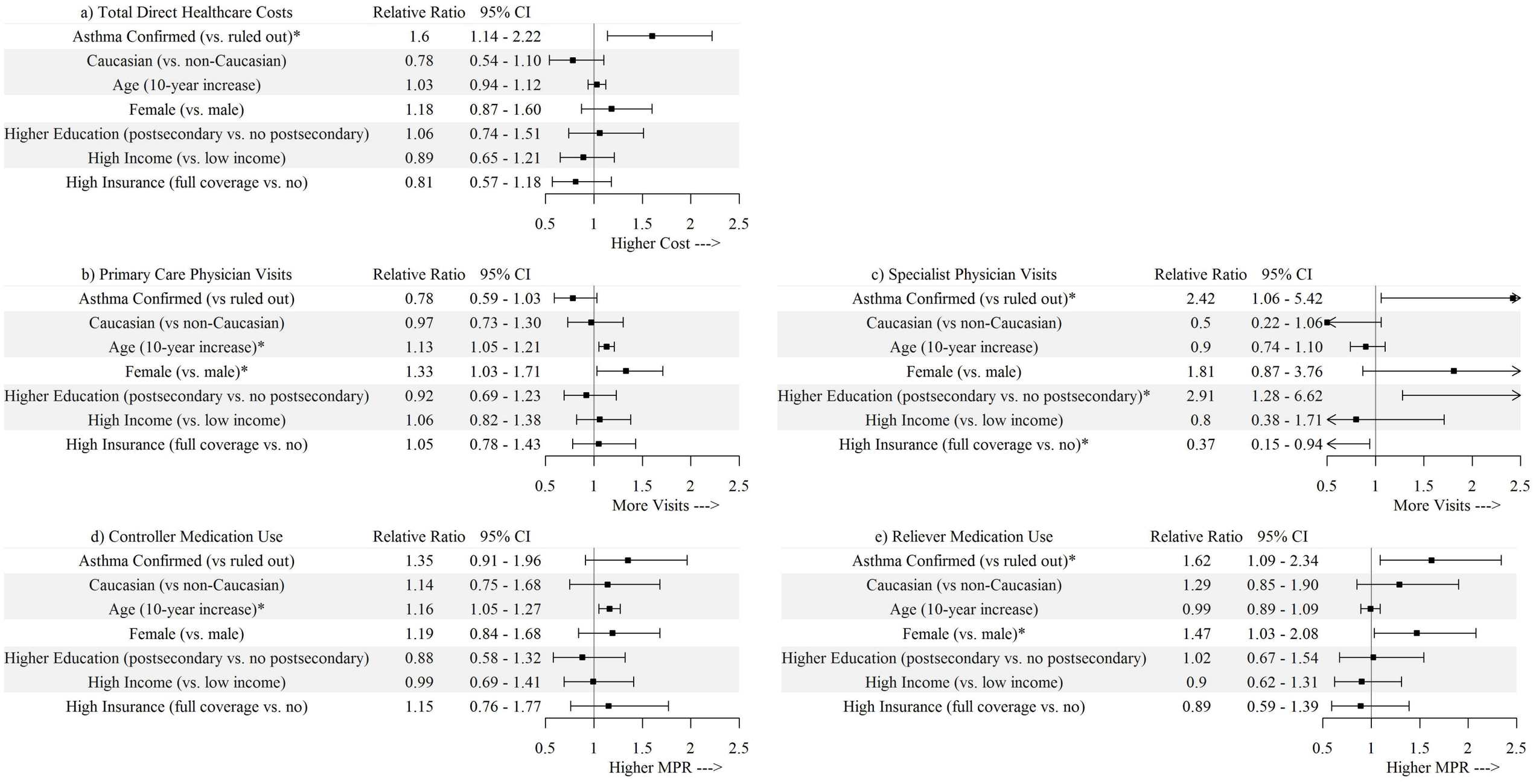
Figure 1. Algorithm for confirming or ruling out a diagnosis of asthma.

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.


Pre- and post-bronchodilator spirometry
FEV1 increased ≥12% or 200mL
Yes
Asthma confirmed
No
Methacholine Challenge Test
PC20 < 16mg/mL
Yes
No
Discontinue all controller medications
Methacholine Challenge Test
PC20 < 16mg/mL
Yes
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 diagnosis confirmed
138 + Bronchodilator Reversibility test
121 + Methacholine Challenge test
86 Individuals with asthma diagnosis ruled out


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
0.5 1 1.5 2 2.5
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
0.5 1 1.5 2 2.5
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
0.5 1 1.5 2 2.5
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
0.5 1 1.5 2 2.5
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
0.5 1 1.5 2 2.5
Higher MPR --->