# Investigating the association between prior history of asthma and later diagnosis of COPD: an analysis of British Columbia administrative health database in Canada

By

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# Abstract

Adult asthma patients are at an increased likelihood of being diagnosed with chronic obstructive pulmonary diseases (COPD) later in life. The main aim of this dissertation is to examine the factors associated with asthma patients that lead to COPD diagnosis later in life. The study was motivated by the dearth of research explaining the complex relationship between prior history of asthma and a later diagnosis of COPD. Similarly, there is a lack of academic literature and clinical research that examines the association between sub-optimal medication adherence (MA) in asthma patients and their subsequent risk of COPD. Additionally, there exists no gold standard with a clinical or pharmacological rationale for measuring optimal MA in asthma patients using pharmacy-based databases. In examining these critical research areas, meta-analysis and a retrospective observational cohort design were employed. Four linked databases obtained from the Population Data BC, spanning from January 1, 1998, to December 31, 2018, were used for data analysis. The meta-analysis showed that patients with a previous history of asthma were 7.87 times more likely to develop COPD in the future than were non-asthmatics. In addition, an analysis of the Population Data BC found that the following risk factors predicted COPD in asthma patients: "being an older adult (40 years and older)", "being male and obese", "a history of tobacco use", "comorbidity burden", "length of hospital stay", "asthma severity levels", "asthma exacerbations", and overuse of Short-Acting Beta-2 Agonist (SABA).

Also, the study identified medication possession ratio (MPR) and proportion of days covered (PDC) as the most commonly used methods for measuring medication adherence with higher sensitivity. The study identified an adherence threshold of at least 0.80 as optimal in categorizing adherent and non-adherent adult asthma patients. Further, patients who achieved a sub-optimal level of MA were at a significantly increased risk for developing COPD over time after adjusting for relevant confounders. Levels of asthma severity modified

the MA effect. Additionally, overuse of short-acting beta-2 agonist (SABA) was significantly associated with an increased risk of COPD after adjusting for relevant confounders and covariates. This study's findings provide important insights into the lifestyle and behavioural risk factors associated with COPD risk. Healthcare providers and policymakers should highlight the need for smoking cessation programs, weight management, and medication compliance interventions, particularly in difficult-to-control adult asthma patients who are at an elevated risk of developing COPD.

**Keywords**: Asthma, COPD, risk factors, medication adherence, adherence thresholds, asthma medications

## General summary

Asthma and COPD are two respiratory diseases that affect the airways of humans, making it difficult for patients with these conditions to breathe. Evidence shows that some patients with asthma are more likely to develop COPD later in life. However, the factors likely to increase asthma patients' risk of developing COPD have not been largely investigated, especially using a large sample of adult asthma patients in Canada. The primary purpose of this study was first 1) to estimate the degree of asthma patients' overall risk of developing COPD; and 2) to identify the factors related to asthma patients that lead to the development of COPD. I used adult asthma patient records in British Columbia, Canada, to answer these questions. Further, I combined the estimates of the existing published studies to calculate the overall COPD risk in asthma patients.

Overall, my research found several modifiable risk factors that contribute to COPD incidence in asthma patients. Some of the risk factors included "smoking tobacco", "obesity", "having existing chronic medical conditions", "being 40 years and older", "those who overused their reliever inhalers more than expected", "male sex at birth," and "asthma exacerbations or worsening". In addition, my study identified two main methods (namely PDC and MPR) and an appropriate cut-off of (0.80 or more) for distinguishing between adult asthma patients who properly complied and did not comply with their medications. Also, asthma patients who complied with their prescribed medicines over an 18-year observation period were less likely to develop COPD. However, severe asthma patients who did not correctly adhere to their prescribed drugs were not protected from future incidence of COPD.

My study finding provides an understanding of some lifestyle and behavioral factors resulting in COPD incidence in asthma patients. Healthcare providers should highlight critical approaches directed at reducing COPD risk in asthma patients.

# Co-authorship statement

The research findings presented in this dissertation comprise a collection of six manuscripts that have been either published (Chapters **3**, **4**, **5**, and **6**) or are currently under review (Chapters **7** and **8**) in reputable peer-reviewed journals. The primary study findings are presented in the six manuscripts, the details of which are given below:

**Chapter 3**: Asamoah-Boaheng M, Acheampong L, Tenkorang EY, Farrell J, Oyet A, Midodzi WK**. Association between the early history of asthma and COPD diagnosis in later life: a systematic review and meta-analysis**. Published in *International Journal of Epidemiology*. 2018; volume 47(6):1865-1876. https://doi.org/10.1093/ije/dyy207

**Chapter 4**: Asamoah-Boaheng M, Farrell J, Osei Bonsu K, Midodzi WK. **Examining risk factors accelerating time-to-chronic obstructive pulmonary disease (COPD) diagnosis among asthma patients.** Published in *COPD: Journal of Chronic Obstructive, Pulmonary Disease*, 2021, vol 19 (1): 1-10. https://doi.org/10.1080/15412555.2021.2024159

**Chapter 5**: Asamoah-Boaheng M, Osei Bonsu K, Farrell J, Oyet A, Midodzi WK. **Measuring medication adherence in a population-based asthma administrative pharmacy database: A systematic review and meta-analysis**. Published in *Clinical Epidemiology*, 2021; 13:981-1010. https://doi.org/10.2147/CLEP.S333534

**Chapter 6**: Asamoah-Boaheng M, Farrell J, Osei Bonsu K, Midodzi WK. **Determining the optimal threshold for medication adherence in adult asthma patients: An analysis of British Columbia administrative health database in Canada**. Published in *Journal of Asthma*, 2021,1-12. https://doi.org/10.1080/02770903.2021.2014862

**Chapter 7**: Asamoah-Boaheng M, Farrell J, Osei Bonsu K, Oyet A, Midodzi WK. **Association between medication adherence and risk of COPD diagnosis in patients with asthma: a retrospective cohort study in Canada**. (Accepted at *Clinical Epidemiology*, 2022)

**Chapter 8**: Asamoah-Boaheng M, Farrell J, Osei Bonsu K, Midodzi WK. **Association of short-Acting β-2 Agonist (SABA) overuse and risk of COPD among adult Asthma patients** (under review at *Journal of Asthma*)

I, at this moment, declare that this doctoral dissertation is the findings of my research and that all six manuscripts were written under the supervision of my dissertation supervisor, supervisory committee, and other authors named above. I, therefore, declare that none of the study findings presented in this dissertation have been used elsewhere for an award at any university in Canada or any other part of the world. Additionally, I certify that I have conducted original research involving the description of study rationale, identification of research questions, literature and systematic reviews, study design, data programming and analysis, and overall manuscript preparation. Furthermore, I declare that this research represents a true copy of my dissertation, including revisions approved by my dissertation supervisory committee. I also certify that I have received permission from the copyright owners of my published papers to be included in this dissertation. All published documents, materials, and websites cited in this study have been fully acknowledged in accordance with standard referencing procedures.

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# Dedication

To my dear late sister

**Miss Linda Theresa Boahemaah,**

Whose untimely death came as a shock to me.
She supported me in diverse ways when she was alive.
(May her soul rest in peace)

and to my late father

**Mr. John Joseph Boaheng**

## Disclaimer

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) or Population data BC.

# Table of Contents

# List of Tables

# List of Figures

# List of Abbreviations

| | |
|---|---|
| AATD | Alpha-1 Antitrypsin Deficiency |
| ACO | Asthma COPD overlap |
| AFT | Accelerated Failure Time |
| AHR | Airway Hyper-Responsiveness |
| AMR | Asthma Medication Ratio |
| BC | British Columbia |
| BMI | Body Mass Index |
| BTS | British Thoracic Society |
| CAD | Canadian Dollar |
| CCDSS | Canadian Chronic Disease Surveillance System |
| CCI | Charlson Commodity Index |
| CMA | Continuous Medication Availability |
| CMAq | Continuous Measure of Medication Acquisition |
| CMG | Multiple Interval Measure of Medication Gaps |
| CTS | Canadian Thoracic Society |
| DAD | Discharge abstract database |
| ECRHS | European Community Respiratory Health Survey |
| ED | Emergency Department |
| $FEV_1$ | Forced Expiratory Volume in 1 second |
| FTR | Failure Time Ratio (FTR) |
| FVC | Forced Vital Capacity |
| GEE | Generalize Estimating Equation |
| GINA | Global Initiative for Asthma |
| GOLD | Global Initiative for Chronic Obstructive Lung Disease |
| GRADE | Grading of Recommendations, Assessment, Development, and Evaluations |
| HCP | Healthcare Providers |
| HR | Hazard Ratio |
| HREB | Health Research Ethics Board |
| ICD-9 | International Classification of Diseases-$9^{th}$ edition |
| ICD-10 | International Classification of Diseases-$10^{th}$ edition |

| | |
|---|---|
| ICES | Institute for Clinical Evaluative Sciences |
| ICS | Inhaled Corticosteroids |
| IPTW | Inverse Probability Treatment weighting |
| ISPOR | Pharmacoeconomics and Outcome Research |
| RRS | Japanese Respiratory Society |
| LABA | Long-Acting Beta-2 Agonist |
| LASMA | Long-Acting Muscarinic Antagonists |
| LLN | Lower Limit of Normal |
| LTRA | Leukotriene Receptor Antagonists |
| MA | Medication Adherence |
| MeSH | Medical Subject Heading |
| MOOSE | Meta-analyses of Observational Studies in Epidemiology |
| MPR | Medication Possession Ratio |
| MSC | Marginal Structural Cox |
| MSP | Medical Service Plan |
| MRA | Medication Refill Adherence |
| NHANES III | the third National Health and Nutrition Examination Survey |
| OASIS | Ontario Asthma Surveillance Information System Database |
| OLIN | Obstructive Lung Disease in Northern Sweden |
| PDC | Proportion of Days Covered |
| PEF | Peak Expiratory Flow |
| PFT | Pulmonary Function Test |
| PHAC | Public Health Agency of Canada |
| PH | Proportional Hazard |
| PPR | Prescription Possession Ratio |
| PPDC | Proportion of Prescribed Days Covered |
| PS | Propensity Scores |
| PoPData, BC | Population Data BC |
| PRIS | Preferred Reporting Item for Systematic Review and Meta-analysis |
| PY | Person's Years |
| POR | Pharmacoeconomics and Outcome Research |
| OADs | Obstructive Airway Diseases |

| | |
|---|---|
| OR | Odds Ratio |
| QALYs | Quality-Adjusted Life-Years |
| ROC | Receiver Operating Characteristics |
| SABA | Short-Acting Beta-2-Agonist |
| SAMA | Short-Acting Muscarinic Antagonist |
| SDM | Shared Decision-Making |
| UK | United Kingdom |
| USA | United States of America |
| USPSTF | US Preventive Services Task Force |
| WHO | World Health Organization |
| 95% CI | 95% Confidence Interval |

## List of Appendices

| | |
|---|---|
| Appendix 1 | Ethics approval letter/certificate |
| Appendix 2 | Supplementary Material for Chapter 3 |
| Appendix 3 | Supplementary Material for Chapter 4 |
| Appendix 4 | Supplementary Material for Chapter 5 |
| Appendix 5 | Supplementary Material for Chapter 6 |
| Appendix 6 | My curriculum vitae (CV) |

# Chapter 1: Introduction

## 1.1 Obstructive airways diseases

Obstructive airway diseases (OADs) consist of chronic lung diseases, including asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis, and cystic fibrosis [1]. These conditions affect millions of people worldwide. OADs are characterized by chronic inflammation of the airways resulting in airflow obstruction and successive airflow limitation with different levels of severities and clinical presentations [1]. Asthma and COPD are the two most prevalent OADs that cause substantial morbidity and mortality associated with increased healthcare resource utilization and cost [2]. There exist striking similarities and differences between asthma and COPD. For instance, COPD attacks the airways and the parenchyma, while asthma only affects the airways [3]. Whereas most asthma patients have mild to moderate disease that can easily be controlled with medications, a small cluster of asthma patients have their disease not well-controlled. It has been well established that a significant proportion of asthma patients develop irreversible airflow obstruction, or COPD, despite optimal therapy[4,5]. Recently, Asthma-COPD overlap (ACO) has become a common phenomenon diagnosed among individuals with clinical features of asthma and COPD with overlapping symptoms.

### 1.1.1. Asthma

Asthma is a chronic respiratory condition characterized by reversible bronchoconstriction and airway inflammation that varies over time and in intensity [6]. The Global Initiative for Asthma, or GINA [5], defines asthma as a heterogeneous disease characterized by chronic airway inflammation. The condition has a variety of phenotypes that affect both children and adults with varying severities. Globally, asthma affects an estimated 334 million people [7, 8] and accounts for 250,000 deaths annually [9]. According to the World

Health Organisation (WHO), asthma is projected to affect about 400 million people worldwide by 2025 [10,11]. Most patients with asthma have a controllable disease. While millions of people worldwide suffer from the disease, there is evidence that the prevalence of asthma in Canada is increasing. Canada's share of the global burden of asthma is substantial, given that 2.4 million (or 8.4% of) people in Canada aged 12 years and older suffer from the condition [12–14].

***Prevalence and incidence of adult asthma***

Breathing can be a challenge for Canadians who live with asthma. Currently, asthma affects over 3.8 million people in Canada [15], including approximately 850,000 children under 14 years [16]. The disease accounts for about 80% of chronic respiratory diseases in Canada, with 317 Canadians diagnosed every day [17,18]. In 2016, asthma was considered the third-most common chronic disease in Canada [19]. As a result, asthma patients in Canada were more likely to live with other comorbid conditions such as diabetes, hypertension, and anxiety disorders, than were non-asthmatic patients [20].

In a study investigating the prevalence of asthma among adult Canadians aged between 18 to 80 years, overall adult asthma prevalence increased from 5% in 1994/1995 to 11% in 2010/2011. During the same period, asthma prevalence decreased by 12% among individuals aged 20 years and younger and 6% in the 50–60-year-old age group. However, the prevalence rate among the older adults (80 and older) increased from 5% to 8% (i.e., from 1994/1995 to 2010/2011). Also, the overall prevalence of active adult asthma rose from 5% to 8% between 1994/1995 and 2010/2011 [21]. Similarly, in the 2011-2012 fiscal year, the Canadian Chronic Disease Surveillance System (CCDSS) documented disparities in adult asthma prevalence by age. For instance, during the 2011-2012 fiscal year, asthma prevalence was 15% in individuals aged 20-24 years, 8.3% in 35-44-year-olds, and less than 9% in the 45-64-year-old group, and a slight increase in prevalence from 9.2% in 65-69-year-olds to

10.6% in older adults (80-84 years) [15]. Bosonea et al. (2020) [6] investigated the province-wide asthma prevalence, incidence, and mortality in Alberta from 1995 to 2015 using Alberta Health's administrative database. The study found an increasing trend in asthma prevalence (from 2.4% in 1995 to 13.2% in 2015) among males aged 15 to 39 years. Within the same study period, there was a growing prevalence rate among males aged 40 to 69 years, with rates increasing from 2.1% to 8.1% and an increase in prevalence from 4.6 to 10.7% among males 70 years and older. Likewise, asthma prevalence among females within the age groups '15-39', '40-69', and '70 years and above' increased from 3.3-4.1% in 1995 to 12.6-13.3% in 2015. Nonetheless, the overall age-adjusted asthma incidence decreased from 1.5% in 1995 to 0.7% in 2015.

In a related study that employed Ontario Asthma Surveillance Information System Database (OASIS), the overall province-wide prevalence rate from 2002 to 2006 was 12.93% [22]. Among adults aged 20-29 years, the prevalence rate within the study period was 10.79% in males and 13.50% in females, with a sharp decrease of 7.27% in males aged 30-39 years. Further, the study recorded a single-digit prevalence rate among male older adults within the age groups: '30-39', '40-49', '50-59', and '60-69', but not for the 70+ age group. For instance, the prevalence rates among males within the year groups '30-39', '40-49', '50-59', and '60-69' years were 7.27%, 7.15%, 6.99%, and 8.17%, respectively. Conversely, the prevalence rates increased among females within the same adult year group [22]. Within the same jurisdiction, the incidence rate of asthma from the 1994/95 to 2001/2002 fiscal years remained stable, with rates ranging from 10-12 per 1000 population [23].

In the province of Prince Edward Island, the lifetime prevalence of asthma increased from 7.9% in 2001 to 11.2% in 2011. The proportion of active asthma cases in the province remained relatively stable within the same period, from 2.5% to 2.8%. Regarding asthma incidence, the number of new asthma cases among Islanders declined from 964 in 2001 to

657 in 2011. The incidence of asthma prevalence among adult Islanders (aged 20 years and older) was less than five new cases per 1000 individuals between 2001 and 2011 [24]. In the province of British Columbia (BC), the cumulative incidence rate of asthma was 13.1 cases per 1000 workers between 1999 and 2013 [25].

Asthma prevalence and incidence among some populations of interest, including indigenous people and immigrants, have been investigated in the literature over the past decade. For instance, a study that examined the prevalence and risk factors of asthma in off-reserve indigenous population (specifically Aboriginals) found the prevalence of asthma among adult Aboriginals to be 14% [26]. Also, the overall prevalence of ACO among Aboriginals in Canada was 2.7% from February to July 2012 [27].

***Economic burden of asthma in Canada***

The growing prevalence of asthma is associated with increased healthcare use and costs [28]. In a recent study, Zafari et al. (2018)[29] projected the undiscounted 20-year (from 2014-2033) direct cost and quality-adjusted life-years (QALYs) lost attributable to uncontrolled asthma to be CAD 24 billion and CAD 1.82 million, respectively. After applying a 3% discount, the projected discounted healthcare cost and QALYs lost from suboptimal asthma control were CAD 18.54 billion and CAD 1.38 million, respectively. The projected undiscounted and discounted indirect costs for the 20 years were CAD 280.49 billion and CAD 213.10 billion, respectively [29]. A study conducted on 341,457 asthma cohorts in a population-based study in British Columbia (BC) found the excess cost of asthma patients to be CAD 1,028 per patient-year. During the study period (from 2002 to 2011), medications contributed to the highest share of the excess cost of CAD 471.7 per patient-year in BC [30]. A systematic review conducted in 2013 on the economic burden of asthma in Canada found the average annual cost between CAD 366 and CAD 647 per patient. The annual population-level direct cost of asthma management ranged from approximately CAD

46 million in BC to roughly CAD 141 million in Ontario [28]. A population-based study conducted between 2002 and 2007 in BC estimated the direct asthma-related healthcare cost to be CAD 315.9 million. Of this amount, medication costs accounted for 68.2%, and hospitalization and physician visits accounted for 16% and 15.7%, respectively. The cost of asthma treatment increased from CAD 49.4 million in 2002 to CAD 54.7 million in 2007 [31].

***Clinical presentation and diagnosis of adult asthma***

Adults diagnosed with asthma present various signs and symptoms, with a range in disease severity from one patient to another or within the same patient over time. Therefore, the different clinical practice guidelines [32–35] recommend that physicians assess all patients who present to the hospital with common respiratory conditions such as wheezing, shortness of breath, chest tightness, and coughing. These symptoms often: a) occur variably over time or vary in intensity; b) mainly worsen at night or early morning or on waking from sleep; c) are triggered by exercise, laughter, allergies, or cold air; and d) appear or worsen with exposure to viral infections. Healthcare providers (HCPs) are expected to take the medical and family history of the patient and follow it up with a physical examination to find out if the respiratory symptoms experienced by the patient support an adult asthma diagnosis. In summary, the guidelines recommend that the diagnosis of asthma be based on the historical pattern of the common respiratory symptoms and supported by objective evidence using spirometry to determine the presence of variable airflow obstruction [32,33].

***Spirometry: Objective test for diagnosis of asthma***

Asthma is characterized by variable expiratory airflow limitation. In diagnosing patients with asthma, patients who present with common respiratory symptoms are assessed by spirometry. Spirometry (pre- and post-bronchodilator) is mainly used to test for evidence of variable airflow obstruction in patients with suspected asthma. The 2021 GINA guidelines

[33] recommend lung function tests by spirometry be carried out by a well-trained operator. A decreased ratio of Forced Expiratory Volume in 1 second ($FEV_1$) to Forced Vital Capacity (FVC) [$FEV_1$/FVC] compared with the lower limit of normal (LLN) indicates the presence of expiratory airflow limitation [33]. The presence of an airflow limitation in patients requires an administration of a post-bronchodilator. Thus, an $FEV_1$/FVC post-bronchodilator measurement is taken to evaluate the extent or level of reversibility of airflow limitation. Usually, spirometry is performed at baseline on patients, after which an inhaled bronchodilator (such as 200-400mcg salbutamol) is administered. As indicated in the 2021 GINA guidelines, an adult who experiences respiratory symptoms typical of asthma and records an increase or a reduction in $FEV_1$ of >12% and >200mL from baseline (or, if spirometry is not accessible: a change in peak expiratory flow (PEF) of $\geq$ 20%), 15 minutes after use of an inhaled short-acting beta-2 agonist (SABA), is an indication for a diagnosis of asthma [32,33].

***Methacholine challenge test***

If spirometry results are near normal or negative (i.e., $FEV_1$ of >0.75-0.80 in adults) and there is a high suspicion of asthma, repeat spirometry when the patient is symptomatic, or refer the patient to a specialist to perform further bronco-provocation testing, such as methacholine, histamine, cold air, or exercise challenges [32], [33].

***Other tests***

To exclude other conditions that behave like asthma (i.e., that have similar symptoms and clinical presentations), the guidelines recommend alternative diagnostic tests, such as chest x-ray and allergy testing (specific to allergic asthma), be performed to rule out such conditions [32,33].

***Pharmacological management of adult asthma***

The clinical practice guidelines recommend pharmaceutical therapies through a stepwise approach for managing patients diagnosed with asthma. The three pharmacological options for long-term treatment of asthma include:

a) Controller medications that contain inhaled corticosteroids (ICS). These are used primarily to reduce airway inflammation, attain optimal asthma control, and, subsequently, reduce future exacerbations.

b) Reliever medications (medications used as and when needed to provide as-needed relief of breakthrough symptoms; and

c) Add-on therapies for patients with severe asthma (for controlling persistent symptoms despite optimized treatment with high dose ICS plus long-acting beta-2 agonist (LABA)).

As indicated in the updated 2021 GINA guidelines [33], treatments for adults and adolescents 12 years and older with a diagnosis of asthma have been grouped into track 1 (preferred INITIAL treatment) and track 2 (alternative INITIAL treatment ). In *track 1*, the prescribed reliever is as-needed low dose ICS-formoterol. GINA recommends low-dose ICS-formoterol as the preferred reliever medication, rather than SABA reliever since it reduces the risk of severe exacerbations in patients with similar symptom control. Therefore, if a patient exhibits asthma symptoms at any treatment step, low-dose ICS-formoterol in a single inhaler is recommended for symptom relief. In *track 2*, the reliever medication is as-needed SABA, and this is an alternative approach when *track 1* is not possible or not preferred by a patient with no exacerbations. If an adult or adolescent with a confirmed diagnosis of asthma is likely to be poorly adherent with daily controller ICS-containing therapy, *track 1* is recommended, even if the symptoms are not frequent.

In *steps 1-2*, if symptoms occur less than 4-5 days a week, the preferred recommendation is the use of as-needed low dose ICS-formoterol. In *step 3*, use low dose

maintenance ICS-formoterol when symptoms occur most days, or if the patient is waking from sleep with asthma once a week or more. In *step 4*, prescribe medium-dose maintenance ICS-formoterol when symptoms occur daily, or asthma symptoms wake the patient from sleep once a week or more with evidence of low lung function. In *step* 5, prescribe add-on Long-Acting Muscarinic Antagonists (LAMA) and refer the patient for phenotypic assessment when presenting with severely uncontrolled asthma.

The *track 2* approach is an alternative to *track 1* and is mainly adopted in response to checking whether a patient is likely to be adherent to daily controller therapy. In *step 1*, it is recommended that patients take ICS whenever SABA is taken as an "as-needed" reliever when symptoms occur less than twice a month. *Step 2*: If symptoms occur twice a month or more (but less than 4-5 days a week), prescribe low dose maintenance ICS. *Step 3*: When the patient experiences symptoms most days, or wakes from sleep with asthma once a week or more, recommend low dose maintenance ICS-LABA. Step 4 recommends medium/high dose maintenance ICS-LABA when symptoms occur daily or when a patient wakes with asthma once a week or more. In *step 5*, prescribe add-on LAMA and refer the patient for phenotypic assessment if the patient presents with severely uncontrolled asthma [33].

### 1.1.2. Chronic obstructive pulmonary disease (COPD)

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD as "*a common*, *preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases*" [36]. The disease is characterized by shortness of breath, cough, and sputum production and is an umbrella term for the occurrence of chronic bronchitis and emphysema. The airflow limitations in patients with COPD are usually progressive and not fully reversible [36,37]. Tobacco smoking remains

the primary cause of COPD, followed by exposure to other environmental factors, such as biomass fuel and air pollution. 75% of COPD mortality in high-income countries is attributable to smoking, while 40% of COPD deaths are linked to smoking in low- and middle-income countries [38].

***The burden of COPD (prevalence, incidence, and economic burden)***

Chronic obstructive pulmonary disease (COPD) is the leading cause of morbidity and mortality worldwide [36, 37], and is associated with significant economic and social burdens. COPD prevalence varies due to differences in diagnostic criteria and the analytical and survey approaches employed in various studies [39]. The global burden of disease study estimated COPD prevalence to be more than 300 million [40]. An earlier study estimated the overall prevalence of stage II or higher COPD as 10.1% (prevalence among men and women was 11.8% and 8.5%, respectively) [41]. Among European adults (aged 40 years and older), the prevalence of COPD ranged from 15-20% [42–44]. Regarding incidence, the overall incidence rate of COPD has been estimated in recent studies as 8.9 per 1000 *person-years* (PY) with a 95% confidence interval (CI) of 8.4 to 9.4% in a cohort of 14,619 participants. Similarly, the Rotterdam study estimated the overall prevalence of COPD as 9 per 1000 PY, with an increased incidence in the male sex [45].

In Canada, an appreciable number of the population are burdened with the disease, with a population prevalence rate of 16.2% (95% CI: 14.5 to 17.8) defined by a *fixed ratio* (FR) of $FEV_1/FVC<0.7$ and 11.2% (95% CI: 9.7-12.6) by the lower limit of normal [LLN] ($FEV_1/FVC < 5^{th}$ percentile) [46]. In the same study, the highest population prevalence of COPD, based on the airflow limitation defined by LLN and FR, was 14.7% and 19.0% in Montreal, LLN: 13.9%, FR:19.9% in Kingston, and LLN:13.4%, FR:19.3% in Vancouver [46]. According to the Canadian initiative for the burden of chronic pulmonary disease (BOLD) study, COPD afflicts more than 15% and 7.5% of Canadians in the early and advanced stages

(GOLD II or higher) of the disease, respectively [47]. Other population-based studies using Canadian administrative health databases estimated COPD prevalence to be 9.5% [48].

Economic analysis from previous studies in 2003 demonstrated an annual direct cost of CAD 1997.81 per patient, where over half of this amount was attributable to inpatient hospitalization. In the same study, COPD impacted the economy with an indirect cost of CAD 1198.18 [49]. A recent study investigated the excess economic burden of COPD using an administrative health database from BC. The study found an excess generated cost of CAD 5196 per patient-year (95% CI of CAD 3540 to 8529), of which 26% of the amount was attributable to the care of COPD and 51% to comorbidities [50].

***Diagnosis of COPD***

As is clearly indicated in the GOLD 2021 guidelines, COPD should be considered in any patient who shows symptoms of dyspnea, chronic cough or sputum, and recurrent lower respiratory tract infections, and who has a history of exposure to risk factors such as *host factors* (genetic, congenital/developmental abnormalities), tobacco smoke, smoke from home and occupational dust, fumes, gases, and other chemicals, as well as a family history of COPD. Spirometry is required to make a clinical diagnosis of COPD. The presence of persistent airflow limitation given by a post-bronchodilator $FEV_1/FVC<0.70$ confirms COPD diagnosis in patients with appropriate symptoms and significant history of exposure to noxious stimuli [36]. Even though the airflow limitation defined by a post-bronchodilator of a fixed ratio of $FEV_1/FVC< 0.70$, the use of the fixed ratio ($FEV_1/FVC$) is more likely to result in overdiagnosis of COPD in the elderly than in adults less than 45 years [51,52]. The lower limit of normal (LLN) addresses the over-diagnosis of COPD and minimizes potential misclassification. Therefore, a threshold based on the LLN values for $FEV_1/FVC$ is also recommended to complement the fixed ratio in COPD diagnosis. The persistent airflow

limitation determined by the spirometry can be classified into four categories of COPD diagnosis based on a post-bronchodilator $FEV_1$. These categories include: GOLD 1: Mild ($FEV_1 \geq 80\%$); GOLD 2: Moderate ($50\% \leq FEV_1 < 80\%$ predicted); GOLD 3: Severe ($30\% \leq FEV_1 < 50\%$ predicted), and GOLD 4: Very severe ($FEV_1 < 30\%$ predicted) [36].

To rule out any other disease with characteristics similar to COPD, the *World Health Organization* (WHO) has recommended that all patients diagnosed with COPD be screened for the *Alpha-1 antitrypsin deficiency* (AATD), particularly in areas with a high prevalence of AATD [36]. Also, a chest x-ray test may help exclude alternative diagnoses that resemble COPD. Other objective tests include "lung volume and diffusing capacity," "oximetry and arterial blood gas measurement," exercise testing, and assessment of physical activity and composite scores [36].

***Pharmacological management of COPD***

To reduce symptoms, minimize asthma exacerbations, and improve the quality of life in patients diagnosed with COPD, pharmacological therapy is advised. Some of the pharmacological therapies used for treating COPD include bronchodilators (such as beta-2 agonists); short-acting antimuscarinics (SAMA); and long-acting muscarinic antagonists (LAMAs) such as tiotropium, aclidinium, and others; methylxanthines; combined bronchodilator therapies (such as LABA +LAMA); anti-inflammatory agents; inhaled corticosteroids; and triple therapies (LABA/LAMA/ICS). The use of bronchodilators in patients with COPD alters the smooth airway muscle tone and improves expiratory flow. The use of antimuscarinic drugs in COPD patients blocks the effects of bronchoconstriction expressed on the smooth airway muscle [36, 53].

Commonly used maintenance medication in the management of COPD includes beta-2-agonists, anticholinergics, a combination of short-acting beta-2 agonist (SABA) plus anticholinergic in one device (SABA/SAMA), a combination of long-acting beta-2 agonist

plus anticholinergic in one device (LABA/LABA), methylxanthines, a combination of long-acting beta-2 agonist plus corticosteroid in one device (LABA/ICS), triple combination in one device (LABA/LAMA/ICS), phosphodiesterase-4 inhibitors, and Mucolytic agents [36].

### 1.1.3. Asthma-COPD overlap (ACO)

It has been widely established that asthma and COPD coexist in patients with similar clinical features of both diseases. The descriptive term given to this phenomenon is *asthma-COPD overlap* (ACO). A joint project of GINA and GOLD guidelines in 2017 described ACO as a "*persistent airflow limitation with several features usually associated with asthma and several features typically associated with COPD*" [54,55].

***The burden of ACO (prevalence, incidence, economic)***

A recent meta-analysis estimated the global prevalence of ACO as 2% with a 95% CI: 1.4%-2.6% [56]. In the United States of America, the age-adjusted prevalence of ACO was estimated as 1.05% between 2009 and 2012, representing 0.94 (95% CI: 0.62-1.26) million Americans [57]. In the same jurisdiction, the prevalence of ACO was estimated as 3.2% among Americans aged 35 years and older who participated in the Behavioral Risk Factor Surveillance System survey [58]. The recent increase in prevalence in the US has been associated with the increased use of healthcare resources. Individuals with ACO recorded 1.5 times higher healthcare expenditure than patients with asthma or COPD alone. For instance, the total average expenditure for older adults with ACO was higher than expenditures for asthma or COPD alone, with an estimated cost of USD 45,532 [59].

In the United Kingdom (UK), the overall prevalence of ACO was 20% (95% confidence interval: 18-23%) in a study that included 2,165 individuals aged 40 years and older and looked at outpatient primary care visits in the UK Optimum Patient Care Research Database [60]. With regard to the incidence of ACO in the general population, an overall

incidence of 0.64 per 1000 person-years was recorded among 662 participants, with women having the highest incidence (0.73 per 1000 person-years) compared to men (0.54 per 1000 person-years) [61].

A substantial number of Canadians are also diagnosed with ACO, with a recently estimated prevalence rate of 1.59% found in a study that employed a population-based cross-sectional survey of the *Canadian Health Measures Survey* (CHMS) [62].

***Diagnosis of ACO***

Spirometry is recommended to assess patients with suspected ACO. The Japanese Respiratory Society (JRS) recommends the following diagnostic criteria for evaluating patients with suspected ACO: *Step 1*: Individuals aged 40 years and older who visit a physician with symptoms such as cough, sputum production, and dyspnea or with a documented history of airflow obstruction ($FEV_1/FVC<0.70$), should have a chest radiograph to rule out other diseases likely to cause airflow obstruction. After that, if the measurement of a post-bronchodilator of $FEV_1/FVC$ is less than 0.7, then the patient is potentially diagnosed as an ACO. In *step 2* of the diagnostic process in the JRS, a confirmation of features of COPD or asthma should be made by taking history and performing clinical investigations [54], [63].

As indicated in the GINA-GOLD 2017 guidelines, a standard pre- or post-bronchodilator $FEV_1/FVC$ is not compatible in patients with ACO. If the post-bronchodilator $FEV_1/FVC<0.7$ (indicating airflow limitation in asthma and required for a diagnosis of COPD), then there could be a potential confirmation of ACO. Also, if the post-bronchodilator $FEV_1 \geq 80\%$ (i.e., compatible with asthma and COPD diagnosis), this confirms compatibility with ACO. Additionally, if there is an increase in post-bronchodilator of $FEV_1 > 12\%$ and 400ml from baseline (indicating a high probability of asthma and unusual in COPD), this confirms the compatibility of ACO [55].

***Pharmacological management of ACO***

The GINA-GOLD guidelines recommend that if the syndromic assessment suggests ACO, initial therapy of ICS and LABA or LAMA should be recommended to the patient. COPD drugs can also be prescribed to ACO patients at the initial stage with no LABA monotherapy [55]. A recent systematic review evaluated the stepwise pharmacological management of ACO [64]. That study recommended using advanced therapies, including phosphodiesterase inhibitors, macrolides, N-acetylcysteine, and statin therapy, for ACO patients after the use of inhalers. Further, the authors recommended prescribing advanced asthma therapies (leukotriene receptor antagonists and synthesis blocking agents) to patients with atopic ACO. However, ACO patients with high blood eosinophils should be considered for immunotherapy [64].

## 1.2 Epidemiological evidence on the association between prior asthma diagnosis and risk of COPD

Chronic obstructive pulmonary disease is characterized by chronic inflammation and irreversible airflow obstruction resulting in the destruction of both small airways and parenchyma. The primary causes of COPD diagnosis are exposure to noxious particles (tobacco smoke) and genetics[65]. However, 10-12% of COPD patients have never smoked[66,67]. Thus, COPD diagnosis is linked to other non-smoking factors, including occupational exposures and early childhood respiratory events. Epidemiological evidence indicates that early childhood events influence lung function growth (resulting in an inability to attain maximal lung function growth) and contribute to an increased risk of irreversible airflow obstruction or COPD during adulthood. Existing studies have identified some childhood risk factor profiles and their adverse effect on lung function decline and risk of COPD in later life[65,68,69,70,71]. For instance, in 2018, Bui and colleagues[70] identified parental smoking,

allergy, frequent asthma & bronchitis, infrequent asthma & bronchitis, and frequent asthma, bronchitis & allergy as the significant childhood risk profiles associated with impaired lung function and increased risk of COPD (odds ratio [OR]: 4.9; 95% confidence interval [CI]: 2.1 to 11) at age 53[70]. Data from the Tucson Epidemiologic Study of Airway Obstructive Diseases (TESAOD) indicated that individuals with active asthma were 12.5 times more likely to develop COPD over the 20 years of follow-up compared to the non-asthma patients after controlling for smoking history and other relevant confounders[68]. In a study investigating the early life origins of COPD, adult participants aged 20-45 years were randomly selected from the European Community Respiratory Health Survey (ECRHS) to participate in the study. Individuals with childhood asthma had a 10.5-fold (95% CI: 6.10, 18.03) increased likelihood of developing COPD compared to individuals with no childhood asthma. Similarly, childhood asthma was significantly associated with lung function decline (decline in $FEV_1$: coefficient ($\beta$) = -5.9, 95% CI: -10.7, -1.2)[69]. A case-control study conducted in Japan also found a significant association between childhood asthma and COPD risk. . The study found a higher prevalence (6.3%) of childhood asthma among physician-diagnosed COPD [72]. Additionally, in a population-based study, children who had asthma-like symptoms at ages 1, 3, and 6 years were followed until age 50 to measure the risk of COPD. Children with asthma-like symptoms were at an increased risk of developing COPD (OR: 1.96, 95% CI: 1.13, 3.34) and reduced lung function ($FEV_1$/FVC: $\beta$= -1.23, 95% CI: -2.17, -0.38) at age 50 years[73].

Studies that included adult participants have demonstrated the association between the interaction between “asthma and smoking history” and airway obstruction. Individuals with early and late-onset asthma were 10 to 20 times more likely to develop airway obstruction. Similarly, subjects who developed asthma after ten (10) years and had a current smoking history were at an increased risk of adult airway obstruction[74].

### 1.3 Risk factors for diagnosis of COPD in asthma patients

Several epidemiological studies have established a strong positive association between early history of asthma and subsequent risk of COPD in a large population-based cohort study[65,68,69,75]. However, the risk factors linking asthma progression to COPD diagnosis are unclear. Very few related studies have been conducted to identify the risk factors progressing asthma to later onset of COPD. For instance, a predictive modeling study (Bayesian network model) identified patient age, sex, race, smoking status, and eight comorbid variables as the predictors of COPD in asthma patients. These risk factors were able to predict COPD in asthma patients with an accuracy rate of 83.3% [76]. A population-based study in Ontario, Canada, investigated the association between exposure to higher levels of air pollution and the risk of COPD among asthma patients[77]. Of the 6,040 adult asthma patients sampled from the Canadian Community Health Survey (CCHS), 630 were identified with a diagnosis of COPD. The study found that asthma patients exposed to higher levels of particulate matter ($PM_{2.5}$ per 10μg/$m^3$) and $O_3$ (per 10ppb) were 2.78 and 1.31 times more likely to develop COPD. Thus, individuals exposed to increased levels of air pollution had a greater risk of developing COPD[77]. In a large cohort study of 4,051 women with prevalent asthma, low education, high body mass index, rurality, and increased levels of tobacco smoking were the factors that progressed asthma to the risk of COPD. However, exposure to high levels of air pollution was not a significant risk factor for COPD development in asthma patients[78]. This finding contradicted the earlier results published by To et al. (2016)[77] on the association between the independent effect of air pollution and the risk of COPD. Also, findings from this study were limited to women, thus making the results less generalizable. Although some studies have been conducted to identify the factors linking asthma progression to later onset of COPD, the existing pieces of evidence are mixed, scanty, less generalizable, and largely inconclusive.

### 1.4 Asthma medication adherence

Medication adherence (MA) is defined as the extent to which patients use their medications as prescribed by their health care providers [79,80]. Optimal adherence to asthma medications leads to reasonable asthma control and improved quality of life. Whereas adherence to asthma medications contributes to good asthma control and minimizes disease severity, non-adherence is linked to poor clinical outcomes, increased disease exacerbation, increased healthcare costs, and reduced quality of life [81–85]. Adherence to asthma medications tends to be poor, with rates ranging from 30-to 70%. It differs by country, age, sex, and ethnicity, primarily due to differences in the definition of adherence in different settings [86–88]. For instance, in a study conducted in Canada among 349 asthma patients (between 12 and 45 years), correct use of asthma medications was self-reported by 12% of the participants [89]. Also, a study that employed an administrative population-based survey in BC estimated a two-year adherence rate ranging between 16% and 32% using the percentage of days covered by definition [90]. Additionally, asthma patients' MA tends to decline over time, making long-term disease management a significant challenge for healthcare providers [91]. Consequently, economic studies have documented increased costs associated with poorly controlled adult asthma management compared to well-controlled patients with the same disease severity [80].

***Determinants of nonadherence to asthma medications***

Several medication-related and unrelated factors increase medication nonadherence rates in asthma patients. Such factors include difficulties in using inhaler devices, use of multiple medications, hospitalizations, complications, treatment failure, failure to discuss concerns about the medication, poor supervision and follow-up, underestimation of disease severity, and religious and cultural beliefs [91]. Additional factors attributable to poor adherence to asthma controller medications include patient concerns about the medication prescribed [92], poor patient-physician relationships, and fear of medication side effects. For

example, in a study that recruited 238 asthma patients prescribed inhaled corticosteroids (ICS), 44% of the participants reported that they worry about a possible long-term side effect associated with the use of their inhalers [93]. Other patient-level factors that may serve as a barrier to optimal adherence include forgetfulness [94]; the complex nature of the treatment regimen [95]; patient experience; and subjective perceptions about the medication, such as "having a bad taste" [89, 95, 96]. System-level factors contributing to the increased prevalence of non-adherence include access to healthcare and asthma specialists [97] and high medication costs [95].

***Asthma database adherence measures***

The use of pharmacy claims databases for assessing asthma medication use and adherence has gained importance in recent population-based studies due to electronic health records. A wide variety of adherence methods and thresholds exist in measuring asthma medication adherence using pharmacy claim database[98,99]. Some of the database measures include the medication possession ratio (MPR), proportion of days covered (PDC), continuous measure of medication acquisition, proportion of prescribed days covered (PPDC), concordance for days' supply, refill rate, and group-based trajectory modeling (GBTM)[98–102]. The two most commonly used database adherence measures are MPR and the PDC[99]. These measures assess medication adherence in adult asthma patients based on their prescribed filled and refilled medications and days of medications supplied or covered. The two measures evaluate the time a patient has medication at hand[99]. However, these measures do not determine whether patients took their prescribed medications or not. The database adherence measures serve as a proxy for measuring the degree of medication adherence and thus reflect the actual medication use. Although a wide variety of adherence measures exists, researchers and clinicians are unsure about the choice of appropriate adherence measures.

Also, the up-to-date measures for asthma medication adherence and potential limitations have not been recently documented, especially in the adult asthma population.

Additionally, the adherence cut-off values for these measures vary from study to study and differ across different medication classes. Although studies have consistently used the 0.80 cut-offs as optimal, the 0.80 cut-offs are chosen arbitrarily with no pharmacological or clinical basis. Therefore, there is the need to systematically synthesize the available evidence in the various bibliographic databases to produce the highest level of clinical research in determining the most recent measures for adherence in the adult asthma database and determine the best threshold for optimal medication compliance.

***Interventions for enhancing medication adherence in asthma patients***

One of the essential interventions for improving patient adherence to asthma medication is using a multi-component digital health intervention. Some digital health interventions include mobile health apps (securely connected to a desktop application for monitoring disease control), electronic trackers, text messages, and medication reminder alarms to prevent forgetfulness [103,104]. Other interventions known to improve adherence to asthma medications include educational adherence support interventions, including one-to-one and group face-to-face adherence education sessions; motivational interviewing; family-based problems solving interventions; teamwork interventions; nurse-led psychoeducation; telephone interventions; and interactive voice recognition systems [104,105]

## 1.5 Study rationale

Worldwide, asthma affects millions of individuals, and is associated with significant morbidity[7,106] and increased healthcare use and costs[107,108]. Recently, the burden of asthma in Canada has increased substantially, with a growing prevalence rate of 8.1% among individuals 12 years and older[109]. Whereas most asthma patients have mild to moderate

disease that can easily be controlled with medications, a small cluster of asthma patients have disease that is not well-controlled. It has been well established that a substantial fraction of asthma patients develop persistent airflow obstruction, despite optimal therapy[4,5]. Over time, the persistent obstruction in these patients becomes indistinguishable from the chronic airflow limitation seen in patients with chronic obstructive pulmonary diseases (COPD).

Current evidence documents an early history of asthma as an independent risk factor for COPD onset [65,74,110]. Existing epidemiological studies have demonstrated a strong positive association between prior history of asthma and risk of COPD regardless of tobacco smoking and other adjusted confounders.[65,69,74,75,110] However, no study has been conducted that quantitatively summarizes the available evidence to describe the extent of the association. Although the existing literature shows a robust positive association between prior history of asthma and COPD diagnosis, the risk factors linking asthma progression to COPD remain unknown and unresolved. Currently, determinants of COPD diagnosis in adult asthmatic patients have not been well addressed, especially using a large population cohort study. In particular, the association of patient factors with progressive lung function decline in asthma patients and subsequent risk of COPD is unclear.

One crucial factor that could explain asthma progression to COPD development is suboptimal adherence to medications for long-term asthma treatment, especially in patients with severe exacerbations. It has been well established that poor asthma medication adherence is linked to several clinical events, such as poor control, increased exacerbation, persistent eosinophilic inflammation, increased oral corticosteroid use, and mortality [83–85]. In the long term, suboptimal use of asthma medication and non-adherence to the various prescribed asthma medications could increase the risk of asthma patients developing COPD. There exists a significant gap in current literature to assess the role of this critical factor, and this knowledge could play a mediating role in medication adherence, thereby reducing the

number of asthma patients' who progress to COPD. Understanding and investigating the modifiable risk factors driving asthma progression to COPD diagnosis will enable specific strategies to be targeted to reduce the burden of COPD diagnosis in asthma patients.

Also, the use of an appropriate adherence method and adherence thresholds to assess and classify adherent and non-adherent adult asthma patients has become a problem for researchers and clinicians due to the existence of various adherence measures in current research. The non-existence of an ideal adherence threshold for the database adherence measures has contributed to an increased variety of adherence thresholds adopted by researchers with no clinical rationale. This study also intends to address this knowledge gap by identifying the best cut-off point for differentiating between optimal and suboptimal medication adherence in the adult asthma population.

Additionally, existing evidence suggests that a substantial cluster of asthma patients overuse SABA despite recent clinical practice guidelines against this practice[111,112]. Patients with suboptimal adherence to their asthma controller medications tend to over-rely on SABA alone to lessen their symptoms[113]. Regular or excessive SABA use is associated with poor asthma control and asthma-related deaths [112]. Nonetheless, evidence on the potential risk of COPD among adult asthma patients who overuse their SABA and other bronchodilators is unclear and yet to be uncovered.

To address these knowledge gaps, I conducted the research for this dissertation using four existing administrative health databases from Population Data BC. This dissertation was mainly focused on investigating the link between asthma medication use, asthma medication adherence levels over time, other modifiable risk factors, and subsequent risk of COPD. Thus, the use of the four linked databases ("Discharge Abstract Database", "Medical Service Plan", "PharmaNet", and "demographic & registration database") from the Population Data BC were appropriate and feasible for answering all the objectives of this dissertation since it

includes a database (*PharmaNet*) that captures a complete coverage of all prescribed medications to all residents of British Columbia (BC) since 1985. Other databases in other jurisdictions, including the Ontario Drug Benefit claims at (Institute of Clinical and Evaluative Sciences [ICES]), New Brunswick Prescription Drug Program [NBPDP]) were limited to medication coverage for residents 65 years and older and those under social assistant programs. Also, other databases in other provinces (including Newfoundland and Labrador pharmacy network at the Newfoundland Centre for Health Information [NLCHI]) were limited to less than 20 years of medication coverage for residents. Secondly, databases from the "Population Data BC" were used because it was free for students enrolled in any University in Canada who did not receive grant funding for their research project.

## 1.6 Research objectives

Based on the research gaps identified, this dissertation aimed to investigate the modifiable risk factors associated with asthma patients and their progression to early COPD diagnosis in a large population-based study, with a particular focus on the role of suboptimal medication adherence.

***Specific objectives of the studies***

The following specific objectives guided the investigation leading to this dissertation:

1. To systematically review the literature to synthesize the existing evidence on the association between prior history of asthma and subsequent risk of COPD (Chapter 3).
2. To estimate the risk factors responsible for early diagnosis of COPD in patients with asthma (Chapter 4).
3. To determine the optimal threshold for measuring medication adherence in adult asthma patients (Chapters 5 and 6).

4. To investigate the association between asthma medication adherence levels and the risk of COPD diagnosis in asthma patients (Chapter 7).
5. To investigate the association between overuse of Short-Acting Beta-2 Agonist (SABA) in asthma patients and the risk of COPD (Chapter 8).

## 1.7 Overview of dissertation

The dissertation is organized into nine chapters. The first chapter provides the background and a brief literature review on asthma and COPD outcomes and the study rationale. The *second chapter* briefly describes the study methodology, outlining the data used and the various statistical methods employed in deriving the effect estimates. The *third chapter* addresses the first objective of the study by examining and systematically reviewing the existing literature on the association between an early history of asthma and COPD diagnosis in later life. This chapter informs the subsequent chapters. *Chapter Four* examines the risk factors predicting COPD diagnosis among asthma patients. *Chapter Five* summarizes and describes the various adherence measures and thresholds used to assess medication adherence (MA) in a systematic review and meta-analysis. The study presents the most substantial evidence on the subject matter. The results of this review informed the subsequent stages of this dissertation in determining an appropriate method and threshold for assessing MA. *Chapter Six* of the dissertation investigates the optimal cut-off point for measuring medication adherence in adult asthma patients. The study linked the varying cut-offs of two adherence methods (identified in *Chapter Five*) to important clinical events (asthma exacerbations). The threshold with the most significant reduction in asthma exacerbation compared to the lowest cut-off point was adjudged optimal in classifying adherent and non-adherent patients. The optimal adherence threshold documented in this chapter is used in the

subsequent chapters (Chapters 7 and 8) to categorize adherent and non-adherent asthma patient groups.

*Chapter Seven* of the dissertation focuses on the effects of medication adherence levels over time, asthma severity levels, and the risk of developing COPD in asthma patients during an 18-year follow-up. The final manuscript (*Chapter Eight*) assesses the association between excessive SABA use among asthma patients and COPD incidence. Finally, in the last chapter of this dissertation (*Chapter Nine*), discussions and conclusions are drawn based on the findings reported in the six manuscripts described in Chapters 3 to 8.

# Chapter 2: Data Source and the statistical methods employed

## 2.1 Introduction

This chapter describes the various methods employed in the dissertation. Each of the six manuscripts applied specific methodologies to achieve the overall study objective. Thus, this chapter describes the study setting (the location of the population studied), the statistical methods, and the administrative health databases used for data analysis.

## 2.2 Profile of British Columbia (BC) province in Canada

Among Canada's ten (10) provinces, British Columbia (BC) is the westernmost. The province shares boundaries with the Yukon and Northwest Territories to the north and Alberta's province to the east. The province is also bounded to the south by Montana, Idaho, and Washington in the United States of America (USA) and to the west by the Pacific Ocean. In the second half of the 20$^{th}$ century, BC emerged as one of the prominent provinces in Canada in terms of population and economic wealth/growth. The main cities in the province include Victoria (the provincial capital) and Vancouver (one of the largest ports in Canada). The province covers an area of 944,735km$^2$ (equivalent to 364,764 square miles). As of 2019, the entire province's population was estimated as 5,071,336. The province is one of the most ethnically diverse in Canada [114].

### *BC health & drug coverage*

BC's health care system is publicly funded. It ensures that all eligible residents of BC have access to all health care services that are medically necessary via the Medical Services Plan and to eligible prescription medications via the PharmaCare program [115].

## 2.3 Description of the Population Data BC

The Population Data BC or PopData BC "is a multi-university, data, and education resource that facilitates interdisciplinary research on the determinants of human health, well-being, and development" [116]. Population Data BC provides the following services: data access, data linkage, secure data storage, and education and training. In addition, the facility offers access to comprehensive data on healthcare, health services, and population health. Further, PopData BC provides longitudinal, person-specific, and de-identified data on a population of 5 million BC residents in Canada, spanning from 1985 to the present. The various databases managed by PopData BC are linkable to each other and other datasets outside the jurisdiction of the data provider, including data collected by any researcher. The data provider must approve all external databases before they can be linked to any of the databases provided by PopData BC.

The study obtained approval from the Data Stewardship Committee (DSC) and the BC Ministry of Health (MoH) to use their data for this research project. The study employed four approved primary databases from PopData BC, for the years spanning January 1, 1998, to December 31, 2018. The four databases used were the Discharge Abstract Database (DAD), Medical Services Plan data set (MSP), PharmaNet database, and the demographic and registration (consolidated) database. The DAD provided data on hospital separations from January 1, 1998, to December 31, 2018. The MSP database captured data on physician visits from January 1, 1998, to December 31, 2018. The PharmaNet database provided patient records of all medications dispensed to residents of BC from January 1, 1998, to December 31, 2018. The consolidated data provided demographic information and longitudinal registration status in the healthcare system of BC from January 1, 1998, to December 31, 2018. The study linked the four databases using a patient common identification number.

## 2.4 Statistical methods applied

The study applied the following statistical approaches in addressing the study objectives:

***Inverse variance approach to meta-analysis***

For an inverse variance approach, the weight assigned to each study is estimated as the inverse of the variance of the effect estimates (expressed mathematically as "one divided by the standard error"). That is, larger studies with smaller standard errors were assigned more weights compared to smaller studies. The assignment of weights minimizes imprecision of the pooled effect estimate. The inverse variance approach adjusts the study weights based on the extent of study heterogeneity among varying intervention/exposure effects. This is because smaller studies provide more information about the distribution of effects across different studies[117].

***Random-effects meta-analysis model***

The random-effects meta-analysis (REM) model is preferred when heterogeneity cannot be readily explained across the effects estimates of different primary studies retrieved from the various bibliographic research databases. A variation on the inverse-variance method produces a random-effects meta-analysis. The REM model assumes that "different studies are estimating different, yet related intervention effects". In other words, the REM model assumes that the effects estimated from different studies are un-identical but follow some particular distribution. The center of the distribution explains the average of the effects, while its width describes the extent of study heterogeneity. The normal distribution is conventionally chosen as the distribution of the model. One major limitation of the REM model is the difficulty of establishing any distributional assumptions' validity [117].

These methods have been applied in the study presented in Chapters 3 and 5.

***Survival analysis***

Survival analysis is used to describe data analysis from a well-defined time origin to the occurrence of a particular event. Therefore, the outcome variable of interest is the time until an event occurs. In most cases, the term "failure" is used to define the occurrence of an event of interest. The primary feature of survival data that makes the standard methods inappropriate for analyzing time-to-event data is that survival times are censored. The censoring of survival times indicates that the event of interest has not been observed for a particular individual. The occurrence of censoring can be attributable to individuals lost to follow-up. If censoring occurs after an individual has already been recruited into the study, this is termed *right censoring*[118]. The identified asthma cohort used for this study was typical survival data. The primary endpoint of interest or the "failure" was time-to-COPD diagnosis among asthma patients. An individual in this study cohort was censored if they left the study without observing the event, died, or lost track (unreachable) on the last follow-up day.

***Some non-parametric survival procedures***

Survival and hazard functions are normally estimated to summarize survival data. The methods for estimating these functions from a single sample of survival data include the empirical survivor function (estimated as the ratio of the total number of participants who survive at time "***t***" to the total number of participants in the study) and standard error of the estimated survivor functions. Also, there exist some formal statistical methods (log-rank and Wilcoxon tests) for comparing two or more groups of survival times. Other non-parametric estimates of survivor function which can be used in the presence of censored survival times include the Kaplan-Meier estimate of the survivor function and the life table estimate of the survivor function [118]. In the study presented in Chapters 7 and 8, I described the survival data and compared the survival times for levels of asthma medication adherence, overuse of

SABA, and other important patient factors using the Kaplan-Meier survival curve. The log-rank test was further used to test the significant difference between the survival curves.

***Cox proportional hazard model***

I employed the Cox proportional hazard (PH) model or the Cox PH model to investigate the effect of overuse of SABA at baseline and the risk of COPD (during the observation period) in Chapter 8 of this dissertation. The Cox PH model is regression model, proposed by Cox in 1972. The model is based on an assumption of proportional hazards (i.e., the hazard of an event occurring at any given time for an individual in one group is proportional to the risk at the same time for a similar individual in a different group). However, despite the proportional hazard assumption, there exists no assumption for the probability distribution of the survival times. Therefore, the model is referred to as a semi-parametric model.

Suppose the hazard of an event occurring at a particular time depends on $x_1, x_2, \ldots, x_k$ of *K* predictor variables, $X_1, X_2, \ldots, X_k$. Assuming that values $(x_1, x_2, \ldots, x_k)$ of the variables have been recorded at the same time origin of the study, then the set of the explanatory variable in the PH model is denoted by a vector "**x**", such that $\mathbf{x} = (x_1, x_2, \ldots, x_k)'$.

Let "$h_0$" denote the hazard function for an individual in which the values of all the predictor variables that constitute the vector **x** are zero. The resulting function "$h_0(t)$" is called the baseline hazard function. Hence the hazard function of the ***i***th individual can be expressed mathematically as:

$$h_i(t) = \emptyset(x_i)h_0(t)$$

where $\emptyset(x_i)$ represents the function of the values of the vector of the predictor variables for the ***i***th individual. The expression $\emptyset(.)$ can be explained as the hazard at time ***t*** for an individual whose vector of explanatory variables is $\boldsymbol{x_i}$, compared to the hazard for an

individual for whom $\boldsymbol{x = 0}$. Since the expression $\emptyset(\boldsymbol{x_i})$, called the relative hazard, is nonnegative, the function can be re-written as $exp(\theta)$ where $\theta$ represents the linear combination of the $\boldsymbol{k}$ predictor variables in $\boldsymbol{x_i}$. Therefore

$$\theta = \beta_1 x_{1i} + \beta_2 x_{2i} + \cdots + \beta_k x_{ki}$$

which can be re-expressed as $\theta_i = \sum_{j=1}^{k} \beta_j x_{ji}$ where $\boldsymbol{\beta}$ is the vector of coefficient of the predictor variables (which estimates the effect of the explanatory variable) $\boldsymbol{x_1, x_2, \ldots x_k}$ in the model. The expression $\boldsymbol{\theta_i}$ forms the linear component of the model, and it is also termed the risk score or prognostic index for the $\boldsymbol{ith}$ individual.

The general proportional hazard model can be re-expressed as

$$\boldsymbol{h_i(t) = exp(\beta_1 x_{1i} + \beta_2 x_{2i} + \cdots + \beta_k x_{ki}) h_0(t)}$$

[118].

***Accelerated failure time model***

To investigate the effects of covariates predicting time-to-COPD incidence in patients with asthma, it was expedient to adopt an appropriate approach to analyze this longitudinal survival data to incorporate all explanatory variables into the accelerated failure time (AFT) model. Therefore, the study employed the log-logistic AFT model with random effects to investigate this phenomenon. The AFT model is one of the parametric models for survival data where a set of explanatory variables or covariates acts multiplicatively on the time scale. Thus, the AFT model describes a direct linear relationship between the log of the failure time and sets of explanatory variables. The exposure variables or the covariates accelerate or decelerate the expected failure time (median failure time). When the proportional hazard assumption is violated, the AFT model is an alternative to the widely used Cox Proportional Hazard (PH) model. This model can investigate the speed of disease progression [118, 119].

Given a survival time $\boldsymbol{T_{ij}}$ of the $\boldsymbol{J^{th}}$ individual in the $\boldsymbol{i^{th}}$ cluster and a vector of covariates $\boldsymbol{X}$ (which belong to a set of real numbers), with $\boldsymbol{\beta}$ representing a vector of the

estimated parameter (unknown regression coefficients of the covariate vector $\boldsymbol{X}$), the AFT model can be expressed mathematically on a log-scale as:

$$log\left(T_{ij}\right) = \beta_0 + \beta' X + \varepsilon_{ij}$$

An additional parameter "$\boldsymbol{\sigma}$ "is added to the model when the distribution of the survival times yields to the Weibull distribution. The parameter ***σ scales*** the "$\varepsilon_{ij}$". The above equation can be re-written as:

$$log\left(T_{ij}\right) = \beta_0 + \beta' X + \varepsilon_{ij}$$

where $\boldsymbol{\beta_0}$ is the intercept, $\boldsymbol{\varepsilon_{ij}}$ is the random error term with density function $\boldsymbol{f_0(\varepsilon)}$ and baseline survivor function $\boldsymbol{S_0(\varepsilon)}$ that is assumed to follow some parametric distribution. The survival times of this model are considered to follow a known distribution that is notable for consistency with theoretical survival, time-varying predictions, and simplicity [120], [121]. Some distributions primarily used to model survival time in an AFT model include Weibull, log-logistic, log-log-normal, and gamma. In this study, I used the *log-logistic* as the appropriate distribution of the survival times based on the AIC values compared to other parametric models.

***The log-logistic accelerated failure time model***

The survival times for the data used followed a log-logistic distribution after comparing AFT models for Weibull, log-normal, log-logistic, and gamma distributions based on their AIC and BIC values. Thus, the lifetime survival times $\boldsymbol{T}$ follows a log-logistic distribution when $\boldsymbol{\varepsilon}$ is log-logistically distributed with the survival function:

$$S_\varepsilon(h) = \frac{1}{(1+e^h)}$$

The survival function of the log-logistic AFT model becomes $S_{T|X}(t|x) = \frac{1}{1+(\lambda t)^\alpha}$ where $\frac{1}{\lambda} = exp(\beta_0 + \beta' x), \alpha = 1/\sigma$

***Log-logistic AFT model with random effects***

For clustered data, individuals are usually correlated within a cluster. Mixed-effects log-logistic AFT models account for dependencies of repeated responses on one individual over time by incorporating a random component to the equation. The equation can be re-written on a log scale as: $log\left(T_{ij}\right) = \beta_0 + \beta' X + \varepsilon_{ij} + z'_{ij} b_i$

where $\Omega = z'_{ij} b_i$ is the random component distributed across the "individual patient clusters". The random part also accounts for all the effects on all relevant unmeasured covariates in the model. From the above equation, $\boldsymbol{\beta}$ is the regression coefficient for the fixed effects of covariate vector $\boldsymbol{X}$, and $\boldsymbol{b_i}$ represents the vector of random effects with a set of random covariate vector, $\boldsymbol{z_{ij}}$. The coefficients of the random covariates $\boldsymbol{b_i}$ are distributed with zero (0) mean and variance-covariance matrix $\Sigma = \Sigma(\Theta)$ where $\boldsymbol{\Theta}$ is an unknown vector parameter [119].

***Interpretation of the mixed-effects log-logistics AFT model***

The effects of the covariates determined by the regression coefficients are interpreted as accelerating or decelerating the time-to-COPD incidence in asthma patients after controlling for random covariates in the model over time. The adjusted Failure Time Ratio (aFTR) is estimated as the acceleration factor. The acceleration factor or the aFTR for a given risk factor is estimated as the exponent of the corresponding regression coefficient. An **aFTR >1** implies the effect of the covariate or risk factor that increases the survival time and delays the time to COPD onset in asthma patients over time. However, **aFTR<1** signifies that the factor is associated with an earlier time to COPD onset, or the covariate is at an increased risk of developing COPD in asthma patients over time. If **aFTR=1**, then there exists no effect of the covariate on COPD incidence [121].

***Generalized estimating equation (GEE) logistic regression***

The generalized estimating equation (GEE) is a statistical approach for fitting marginal models for longitudinal data analysis. The GEE approach was first introduced by Liang and Zeger (1986) [122] to produce more efficient and unbiased model estimates for longitudinal/repeated measures analyses. The method has since been widely applied in analyzing medical, biomedical, and life sciences data such as epidemiology, biology, and gerontology. The longitudinal nature of the data (linked PopData BC databases) with repeated outcome measures (asthma exacerbations) and other patient factors necessitated using the GEE logistic regression to analyze the study in Chapter Six. The GEE approach extends the generalized linear models and is useful for analyzing longitudinal data with discrete response variables (i.e., binary, ordinal, or count). Therefore, using linear models is less appropriate for investigating the changes in the mean response of the covariates over time [123].

Further, applying a generalized linear model to longitudinal data is inappropriate since there is no independence among the repeated measures on the same individual over time [123]. Hence, the GEE allows for the adjustment of correlation between observations. One significant advantage of using GEE is it does not require correct specification of the multivariate distribution but instead focuses only on the mean structure [124].

The GEE approach allows for the extension of the quasi-likelihood equations (otherwise called estimating equations) in a multivariate setting. The regression parameters $\boldsymbol{\beta}$ in a *generalized linear model* (GLM) can be estimated by solving the quasi-likelihood equation given as

$$\sum_{i=1}^{N} \left(\frac{\delta \mu_i}{\delta \beta}\right)' V_i^{-1}\{Y_i - \mu_i(\beta)\} = 0$$

where $\boldsymbol{Y_i}$ is the response variable related to $\boldsymbol{p}$-covariates, $\boldsymbol{X_{i1}, \ldots, X_{ip}}$, and $\boldsymbol{V_i}$ represented any choice of weights. In general, the assumed covariance matrix can be written as

$$V_i = \emptyset A_i^{\frac{1}{2}} R_i(\alpha) A_i^{\frac{1}{2}} \quad ;$$

where $\boldsymbol{A_i} = diag\{v(\mu_{ij})\}$ is a diagonal matrix with elements $\boldsymbol{v}(\mu_{\boldsymbol{ij}})$, $\boldsymbol{R_i}(\boldsymbol{\alpha})$ is an $n_i \times n_i$ correlation matrix with $\emptyset$ being the dispersion parameter. The $\boldsymbol{V_i}$ is typically referred to as the "working covariance" in GEE. The $\boldsymbol{V_i}$ is an approximation of the true covariance [$\Sigma_i = Cov(Y_i)$], hence the term "working".

***Properties of GEE***

- The GEE provides an alternative to the maximum likelihood (ML) estimation of the regression coefficients in the marginal models in longitudinal data. The GEE estimator is almost as efficient as the ML estimator in several longitudinal designs.
- The GEE estimator is robust and yields a consistent regression parameter estimator, even when the within-subject correlations among the repeated measures are misspecified. However, the GEE approach only requires the model for the mean response to be correctly specified. Whereas the GEE provides a consistent estimator for the regression parameters when the within-subject correlation is misspecified, the associated standard errors (estimated under the misspecified model of the within-subject correlation) are invalid. This Sandwich variance estimator is usually used to address this problem and estimate valid standard errors for regression parameter estimators. The sandwich estimator is robust and provides accurate standard errors when the assumed model for the covariance among the repeated measures is incorrect [123].

***Interpretation***

The GEE logistic regression model estimation is similar to the standard logistic regression (when the outcome variable is dichotomous with sets of explanatory variables).

The GEE accounts for dependence within subjects over time. The GEE estimates the average population average over time.

Given that the outcome variable (asthma exacerbation) is dichotomous (0=no exacerbation, 1=exacerbation), an Odds ratio (OR) >1 signifies that patients who belonged to a particular group of adherence thresholds were more likely to experience asthma exacerbation over the 18-year follow-up period. If an OR<1, asthma patients who obtained optimal adherence compared to suboptimal were less likely to experience exacerbations. An OR=1 indicates no change in the effect of varying adherence thresholds on asthma exacerbation.

***Propensity score analysis***

A propensity score analysis is a statistical method medical researchers employ to minimize selection bias and known confounding factors, such as confounding by indication in an observational study. The adoption of propensity scores also improves interval validity. Rosenbaum and Rubin described propensity analysis in 1983. They defined it as the probability of an individual being assigned a particular treatment given a set of observed baseline characteristics [125]. The conditional probabilities can be estimated using the treatment group as the outcome variable in multivariate logistic regression. The baseline factors are the set of explanatory variables/covariates. The predicted probabilities of a given treatment group obtained from the multivariate logistic regression are the propensity scores ranging from 0 through to 1 for each individual [126].

After generating the propensity scores, four methods, namely, matching, stratification, inverse probability of treatment weighting, and covariate adjustment, are usually employed to incorporate the propensity scores into the data analysis and design [126].

***Marginal Structural Cox Model (MSC)***

The *Marginal Structural Cox* (MSC) model is a statistical approach that provides a powerful tool for controlling for confounding caused by time-dependent covariates. When the time-varying confounders act as mediating variables or unmeasured confounders, the standard multivariate Cox proportional hazard model yields biased estimators of the total causal effects of the exposure variable of interest [127]. To address this problem, Marginal structural models have been developed to adjust for time-dependent confounding covariates [128]. The *Marginal Structural Cox* (MSC) model for survival data analysis was introduced by Henan et al., 2000 and Henan et al. 2001[129,130]. In an MSC model, the *inverse-probability-of-treatment weighting* (IPTW) is usually employed to consistently estimate the effect of the time-dependent exposure/treatment of interest on the hazard instead of adjusting for time-varying confounder in the MSC model.

First and foremost, the weights for each sample at each time interval are calculated to employ the MSC model in analyzing survival data. These weights should be related to the patients' probability of receiving a particular treatment or being exposed to one specific event. These weights are time-dependent and are estimated as the inverse of the probability of receiving a particular treatment/observed exposure of interest conditional on the previous history of confounding factors, exposure or treatment history, and sets of baseline covariates. The next step is to fit a weighted time-varying logistic regression model by estimating the contribution of each patient participant to a specified risk set at a given time which is weighted by their corresponding weights [127,128]. The MSC model was applied to investigate the association between time-varying asthma medication adherence and risk of COPD in Chapter 7.

# Chapter 3: Association between the early history of asthma and COPD diagnosis in later life: a systematic review and meta-analysis

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## 3.1 Overview

This study forms the basis of my entire doctoral work, and subsequent stages of my research will be based on this paper. This chapter reports the findings of a systematic review and meta-analysis, which sums up the best evidence on the association between prior history of asthma and risk of COPD in later life, published in the *International Journal of Epidemiology.* The study further employs a meta-analysis to synthesize the available evidence quantitatively. In this paper, individuals diagnosed with asthma compared to non-asthmatics were 7.87 times more likely to develop COPD in later life after controlling for important confounders. Thus, this study's findings confirm a clinical suspicion of asthma progression to COPD over time. In addition, the study identified essential gaps in the literature about the determinants of COPD diagnosis among patients with asthma.

## 3.2 Abstract

*Background*: While most studies have reported prior history/diagnosis of asthma as an independent risk factor for COPD development in later life, no systematic review and meta-analysis have been conducted to synthesize these observational studies. This review aims to investigate associations between prior history of asthma and later development of COPD.

*Methods*: I conducted a comprehensive search in PubMed, Cinahl, and Embase for studies related to prior history of asthma and COPD diagnosis. Articles were screened for relevance

by two independent reviewers. Methodological quality was independently assessed, and data was extracted for qualitative and quantitative review. The review explored heterogeneity and performed a publication bias check.

*Results*: From the 1260 articles retrieved, nine (9) were included in the qualitative review and 7 in the meta-analysis. History of asthma was associated with developing COPD in later life (Inverse Variance Random-effects model, OR: 7.87, 95% CI: 5.40-11.45, p<0.00001).

*Conclusions*: Studies with the high methodological quality provided sufficient evidence to suggest that individuals with a previous history of asthma have an increased likelihood of developing COPD in later life.

*Keywords*: Chronic Obstructive Pulmonary Disease, prior asthma, risk factor, meta-analysis, random effect model.

## 3.3 Introduction

*Chronic Obstructive Pulmonary Disease* (COPD) is a progressive lung disease that limits normal airflow in the bronchial tubes, resulting in chronic cough, breathlessness, and exercise intolerance. [131,132]. The condition was projected to be the third leading cause of death worldwide by 2020. [133,134]. Tobacco smoking is widely accepted as the leading cause of COPD. It has been linked to the gradual damage to the parenchymal cells of the lungs over time, leading directly to poor quality of life in people with the disease [135,136]. Evidence suggests that 25-45% of patients with COPD have never smoked, and a proportion of smokers (10-20%) develop it [137,138]. These figures raise questions of other possible factors driving COPD cases. It has been reported that early childhood experiences may influence the normal growth and development of lungs and subsequently pose a risk for COPD in later adult life [139]. Impaired lung development during childhood and adolescence resulting from recurrent infections, premature gestation, atopy, bronchial hyper-responsiveness, and asthma has been associated with failure to attain maximum lung function in adult life [139]. There is

recent evidence of the prior or existing history of early asthma in the subsequent development of COPD. Many epidemiological studies have demonstrated that asthma diagnosis in early life could be a risk factor of COPD regardless of smoking history or status [140–142]. However, there have been no systematic reviews and meta-analyses of studies in this important area to the best of our knowledge. Accordingly, this study was conducted to review the evidence of the association between prior asthma and later COPD diagnosis.

The purpose of this review was to systematically identify, select and summarize the literature linking the prior history of asthma and subsequent development of COPD. To this end, we analyzed the results from independent studies quantitatively and produced a single and more precise estimate of the extent of the association using meta-analysis. In addition, the review addressed the following question: for a general population of individuals aged five years and older, does a prior history of asthma compared to no previous history of asthma increase the risk of developing COPD in later life?

## 3.4 Methods

The study used systematic and explicit methods to review the existing literature to identify, select, and critically appraise potentially relevant studies related to the question of interest. I used the recommended Preferred Reporting Item for *Systematic Review and Meta-analysis* (PRISMA) and *Meta-analyses of Observational Studies in Epidemiology* (MOOSE) checklists to conduct and report the systematic review and meta-analysis of the selected studies [143]. The methods are summarized below.

### 3.4.1 Literature search

The literature search was conducted using MEDLINE (PubMed), EMBASE, CINAHL. The search included articles and review articles published from inception to

September 2017. The search criteria included keywords and MeSH terms, and a combination of the two. MeSH terms had “Pulmonary Disease, Chronic Obstructive”, “asthma”, and “risk factors”; keywords included “chronic obstructive pulmonary disease”, “asthma”, “child”, “history”, “previous” and “risk factors”. The search focused on studies conducted on humans with no restriction on language. The reference lists of articles were screened to identify additional studies. Some experts and study authors were contacted and asked about any additional studies (both published and unpublished). The comprehensive search started on 10 September and ended on 2 October 2017. The final search string used in PubMed, Embase, and Cinahl is shown in Table S3.1 in the supplementary material.

The initial literature search included cohort, case-control, and cross-sectional studies. Studies investigating patients with and without previous history of asthma (whether childhood or adult-onset) as the exposure of interest were included. Likewise, studies and reviews were included if COPD was mentioned as one of the outcomes (preferably the primary outcome). The exclusion criteria included case series and case reports, studies that did not have asthma as one of the exposure variables, and studies that did not include COPD as one of the outcomes. Studies were included in the quantitative synthesis (meta-analysis) if they investigated the association between the previous history of asthma and COPD diagnosis, were cohort and case-control studies, published measures of association such as *hazard ratios* (HR), *odds ratio* (OR), and had a 95% *confidence interval* (CI) for their estimates.

### 3.4.2 Study selection and quality assessment

Two reviewers (MAB, LA) independently provided a quality assessment of the articles at all stages. The titles and abstracts yielded by the databases in the initial search were read or scanned. After their relevance was assessed, selected articles were further screened. Nine (9) were extracted from the final screening (4 cohort studies, four case-control studies,

and one cross-sectional study). The quality of the studies was assessed using the US Preventive Services Task Force (USPSTF) Quality Rating Criteria assessment of bias for cohort and case-control studies. Using the USPSTF assessment of bias tool, each author independently assessed and graded the nine (9) studies as good, fair, or poor. Before evaluating the individual studies, an independent reviewer was called to blackout the authors' names, study titles, and institution of affiliation to ensure blinding. Any disagreement in assessing the articles was resolved by reaching a consensus.

### 2.4.3 Data extraction

I developed a standardized form using generic items to assist in the data extraction process. Two (2) independent reviewers concurrently performed the entire data extraction process; any recognized differences, such as the definition of cases, were reconciled by mutual agreement. The form was piloted on three (3) selected studies before its incorporation. Using the standardized form as a guide, the two (2) reviewers extracted the following information from the selected studies: authors' surnames and year of publication, participants, COPD diagnosis in the exposed and unexposed group, exposure variables, outcomes, results, and adjusted confounders (see Table 3.1). I estimated the relative association measure (ORs) and corresponding 95% confidence interval, p-values, and the adjusted results.

### 3.4.4 Statistical analysis

The principal summary measure for the seven studies included in the meta-analysis was the odds ratio (OR). The Review Manager (RevMan version 5.3) and Comprehensive Meta-Analysis (CMA) software were used for data analysis at the quantitative synthesis stage. I employed a random-effects model with a generic inverse variance method, as I suspected heterogeneity across the studies because of differences in asthma diagnosis, study

type, and patient population. I used a funnel plot to determine the presence or absence of publication bias in the review through visual inspection; more specifically, I conducted Egger's and Begg's tests to look for funnel plot asymmetry/ small study effect to assess the publication bias quantitatively. Finally, I conducted a sensitivity analysis to determine the robustness of the meta-analysis results in the presence of differences in the studies' results.

## 3.5 Result

***Summary of included studies***

Using the three electronic databases, the initial literature search yielded 1258 articles (PubMed=422, Embase=765, Cinahl=71). Two (2) papers were obtained from other sources (scanning reference lists of articles =2). After removing duplicates using the referenced manager software, we were left with 1200 articles. The titles and abstracts of 1200 articles were screened for relevance by Two (2) reviewers (MAB, LA); after the screening, 27 articles were retrieved and downloaded for full-text review. When all 27 full-text articles had been assessed, articles were excluded because they did not meet the inclusion/exclusion criteria, leaving nine (9) articles for the qualitative assessment (see Figure 3.1). The nine (9) selected articles comprised four (4) cohort studies, four case-control studies, and one cross-sectional study. The year of publication for the selected studies ranged from 2004 to 2016. The studies were conducted in several European countries as well as Japan, New Zealand, Australia, China, and the United States (i.e. the *European Community Respiratory Health Survey* (ECRHS) study includes several centres, of which only one is from Norway). The length of follow-up ranged from 20 to 50 years. The primary measure of association reported in the studies was odds ratios (ORs). The majority provided tables of patient characteristics at the levels of baseline and multivariate analysis. Most adjusted for important confounders, such as age, sex, smoking status, maternal smoking, and exposure to

air pollution. We reviewed all nine studies qualitatively and seven studies quantitatively.

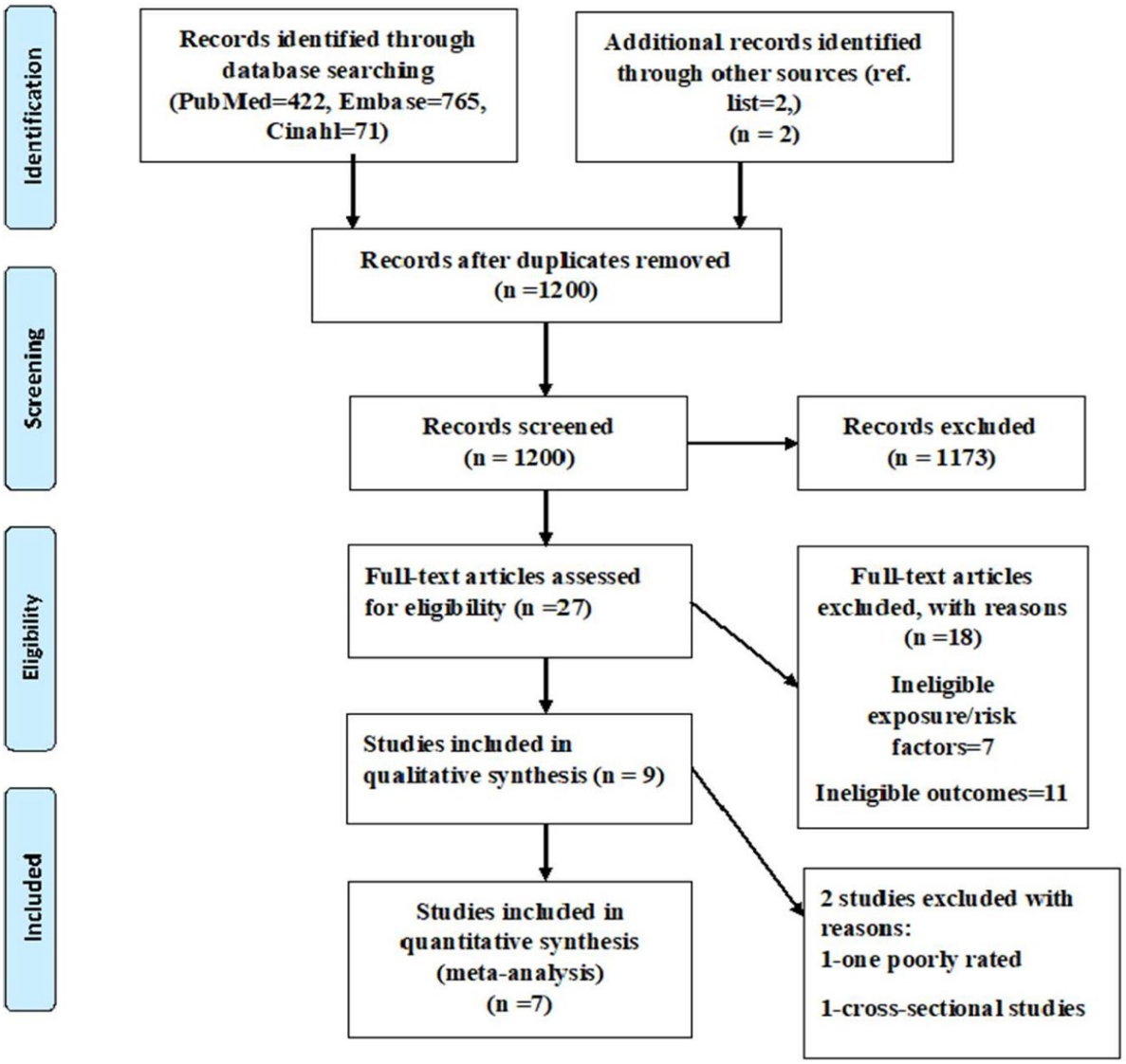


**Figure 3.1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of search strategy and article selection**

***Qualitative review/Narrative synthesis***

The total quality score for each paper is reported in Table 3.2. Overall, those selected for review were of "fair" quality. Only 1 out of the 9 selected papers was graded as "poor", and this was due to very high drop-out rates (>50%) which were not accounted for [144]. For longitudinal studies, the domain "maintenance of comparable groups" was generally assessed as "fair" across studies. Retrospective studies (case-control and cross-sectional) mostly had a "fair assessment" for one particular USPSTF domain: "measurement of exposure accurate and applied equally to each group". The fair assessment here was due to the recall nature of exposure measurement (history of asthma). The criteria and the study type made it impossible for these studies to objectively measure the exposure variable since it was entirely based on recall. Overall, the risk of bias was minimal across studies, as potential confounding factors (smoking status and history, age, maternal smoking, and exposure to air pollution) were identified and adjusted for in all selected papers.

In all studies COPD was ascertained with spirometry using the 2001 version of the Global Obstructive Lung Disease (GOLD) criteria defined by spirometric data of post-bronchodilator $FEV_1/FVC < 0.7$ as well as $FEV_1 < 80\%$ predicted[145]. The longitudinal studies used medical records and the retrospective studies used self-reports. In all studies, the outcome was measured as the development of COPD but they differed slightly in their definition of COPD in terms of the use of post and pre-bronchodilator. Seven defined COPD using the GOLD approved definition of a spirometric finding of $FEV_1/FVC < 0.7$ after the use of a bronchodilator while two other studies used a pre-bronchodilator value of $FEV_1/FVC < 0.7$, rather than the post-bronchodilator value used by most studies[74,75]. However, the 2014 GOLD criteria report that the degree of airflow limitation (which measures $FEV_1$ before and after bronchodilator or corticosteroids) is no longer recommended[146]. In all, 9 studies

provided an objective measure of COPD diagnosis using spirometry and based on the GOLD standard before and after the use of a bronchodilator.

Studies found some evidence of a positive association between prior history of asthma and the development of COPD in later life. Although the extent of the association was significant, the precision of their estimates was unclear, as confidence intervals were very wide. This could be attributed to the smaller sample sizes for both the exposed and unexposed groups. Studies with smaller sample sizes tend to provide very large effects estimates and are less powered. Therefore, the prediction of the true effects in these studies could have been overestimated.

**Table 3.1: Summary of findings of studies included in the review for investigating the association between prior history of asthma and COPD**

| Article | Study type/design | Patient/population | Exposed group | Non-exposed group | Outcomes assessed | Results | Adjusted variables |
|---|---|---|---|---|---|---|---|
| Omori et al (2017) [147] | Prospective study | A total of 9896 participants within the age range 35-60 years were included. | Remitted asthma (n=287, adult-onset asthma (n=354), childhood-adulthood asthma (n=101) | Healthy controls (without asthma, n=9154) | Airflow obstruction objectively measured as: (FEV1/FVC < 0.7) and FEV1. | Remitted asthma was independently associated with airflow obstruction, OR: 2.87(95% CI: 1.66-4.96), **β**:-2.4)-3.09, -1.71) | Adjusted for age, sex, current smoking & pack years (per 10). |
| Aanerud et al (2015) [74] | Prospective cohort study | Randomly selected adults aged 20-44 years from the European Community Respiratory Health Survey (ECRHS) I (1991-1993) surveys in 25 countries. | Early asthma independent of smoke (< 10 years), late asthma independent of smoking (> 10 years) | Never smokers without diagnosis of asthma. | Airway obstruction objectively measured as FEV1/FVC<0.7 | Early asthma independent of smoking was associated with airway obstruction (AO): (OR: 21.0, 95% CI: 12.7-35.0). Late asthma was also associated with AO (OR: 11.2, 95% CI: 6.8-18.6). | Adjusted for potential confounders such as age, sex, country, education, BMI, height, smoking and sample design. |
| Hirayama & Lee (2015) [72] | Case Control study | 300 COPD patients aged 50 to 75 and 400 controls/adults residing in the same communities as the cases were recruited | 278 patients (244 men, 34 women) | 340(272 men, 68 women) | Diagnosis of COPD confirmed by spirometry after bronchodilation with FEV1/FVC<0.7 | Childhood asthma was significantly associated with the risk of COPD adj. OR, 95% CI as 3.32 (1.05-10.45). | Adjusted for age, gender, cumulative smoking exposure, education level, body mass index, alcohol drinking status, lifelong physical fitness, residential location and marital status. |
| Chan-Yeung et al (2007) [144] | Case-control study | 289 patients with COPD were recruited from out-patient clinic. | Patients with COPD | Healthy controls from two sources. | COPD | Several risk factors were assessed and smoking was found to be associated with COPD. | |
| Tai et al (2014) [65] | Longitudinal prospective cohort study | 401 patients recruited from the | 113 children with asthma, 83 with severe asthma | Children without the symptoms of wheeze at age 7 | Outcomes assessed includes: asthma | Children with severe asthma were at 32 times higher risk of | Adjusted for sex, childhood wheezy bronchitis groups, |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | 1957 birth cohort at age 7 years and | and 178 with intermittent asthma. | years (105-non-asthmatics), | remission, current asthma and COPD. | developing severe asthma after adjusting for important covariates. OR: 32 (95% CI: 3.4– 269) | childhood hay fever or eczema, smoking status. |
| Tsuda et al. (2009) [148] | Case–control study | 9493 patients older than 65 years registered in the hospital database were recruited | Never smokers with COPD (n= 49) | Smokers with COPD (n = 98) | Clinically relevant COPD | Patients with history of asthma were significantly associated with COPD, OR: 29.4 (95% CI: 10.1–85.4) | Adjusted for female sex, age, body mass index, age at initial diagnosis, smoking history, extrinsic allergy, second-hand smoke |
| Svanes et al. (2010) [149] | Mixed design (cross-sectional study and cohort study) | Participants aged 20–44 years from general population of study in the European Community Respiratory Health Survey (ECRHS) | Childhood disadvantage factors: maternal and paternal asthma, childhood asthma and childhood respiratory infections childhood asthma | Subjects without any of the childhood disadvantage factors | FEV1 and COPD | COPD increased with increasing childhood disadvantage 3 factors, men: OR 6.3 (95% CI: 2.4–17), women: OR 7.2 (95% CI: 2.8–19) | Adjusted for age, height, smoking, education, social class and country |
| Shirtcliffe et al. (2012) [150] | Cross-sectional study | A total of 3500 subjects were gathered from the Wellington Respiratory Survey and divided between the ages of 25 and 75 years | Childhood asthma | Non-asthmatics | GOLD lung function criteria for defining COPD | Childhood asthma was strongly associated with GOLD-defined COPD | Adjusted for age, atopy, hospitalized under age 2 years, sex, Maori and pack years (per 10) |
| Tagiyeva et al. (2016) [110] | Prospective cohort study | A cohort of children aged 10–15 years recruited and followed up to age 60–65 years | Childhood asthma=38, 53 with childhood wheezy bronchitis | 239 control subjects | FEV1, FVC, COPD | Childhood asthma was associated with an increased risk of COPD, OR 6.37 (95% CI: 3.73–10.94) and childhood wheezy bronchitis, OR 1.81 (95% CI: 1.12–2.91) | Adjusted for sex, age, history of ever smoking and Scottish Index of Multiple Deprivation |

**Table 3.2: Assessment of potential bias of studies for inclusion in the synthesis using USPSTF Quality criteria for cohort studies and case control studies**

| Article | Assembly of comparable group | Maintenance of comparable groups | No important differential loss to follow-up or overall high loss to follow-up | Measurements: equal reliable, valid (includes masking of outcome assessment) | Clear definition of intervention | All-important outcomes considered | Analysis: Adjustment for potential confounders | Overall assessed quality |
|---|---|---|---|---|---|---|---|---|
| Aanerud et al. (2015) [74] | Good | Good | Good | Good | Good | Good | Good | Good |
| Tai et al. (2014) [65] | Good | Fair | Fair | Good | Good | Good | Good | Good |
| Tagiyeva et al. (2016) [110] | Good | Fair | Fair | Good | Good | Good | Good | Good |
| Svanes et al. (2010) [149] | Fair | Unclear | Good | Good | Good | Good | Fair | Fair |
| | | | | | | | | |
| **Assessment of potential bias of studies for inclusion in the synthesis using USPSTF Quality criteria for case control studies** | | | | | | | | |
| Article | Accurate ascertainment of cases | Non-biased selection of cases/controls | Response Rate | Diagnostic testing procedures applied equally to each group | Measurement of exposure accurate and applied equally to each group | Appropriate attention to potential confounding variable | Overall assessed quality | |
| Hirayama and Lee (2015) [72] | Good | Good | Good | Good | Fair | Good | Good | |
| Tsuda et al. (2009) [148] | Fair | Unclear | Fair | Good | Fair | Fair | Fair | |
| Omori et al. (2017) [147] | Good | Good | Fair | Good | Fair | Fair | Fair | |
| Chan-Yeung et al. (2007) [144] | Good | Unclear | Poor | Unclear | Fair | Fair | Poor | |
| Shirtcliffe et al. (2012) [150] | Good | Fair | Fair | Unclear | Unclear | Good | Fair | |

***Quantitative review/Meta-analysis***

I performed a meta-analysis on 7 studies comprising 4 cohort studies and 3 case-control studies after we assessed their quality using the USPSTF quality assessment of bias tool. These 7 studies were generally rated as "fair" and "good". All 7 studies used the odds ratio (OR) as the main summary measure for the effects estimate. The study used a generic inverse variance method to estimate the contribution of each study (expressed in weights) to the pooled effect. The log (OR) for all studies was transformed back, and the effects estimate of all studies was calculated as an odds ratio. Table S3.2 (in the supplementary material) presents the summary of the studies in the quantitative review. Although 7 studies were included, slightly different exposure variables were extracted and considered as separate studies resulting in a total of 10 studies.

### 3.5.1 Effect of prior history of asthma on patients' likelihood of developing COPD

Figure 3.2 shows the forest plot of the 10 studies summarizing the effect of prior history of asthma on the likelihood of developing COPD. The forest plot indicated that patients with a prior history of asthma (such as childhood asthma, adult-onset asthma) were 7.23 times more likely to develop COPD, with a 95% confidence interval (CI) of 5.05 to 10.33 and p- 45 46 value <0.00001. This means early diagnosis of asthma could be a significant risk factor for developing COPD. However, the average summary effect was not consistent across studies, and there was substantial heterogeneity ($I^2$= 66%, $p$ = 0.001) among the 10 studies. This suggests that results were not similar from study to study. The studies might have differed by study type, methodological quality, and other sources of heterogeneity. To identify the source(s) of the heterogeneity, we conducted a subgroup meta-analysis stratified by the study-quality ratings of "fair" and "good"

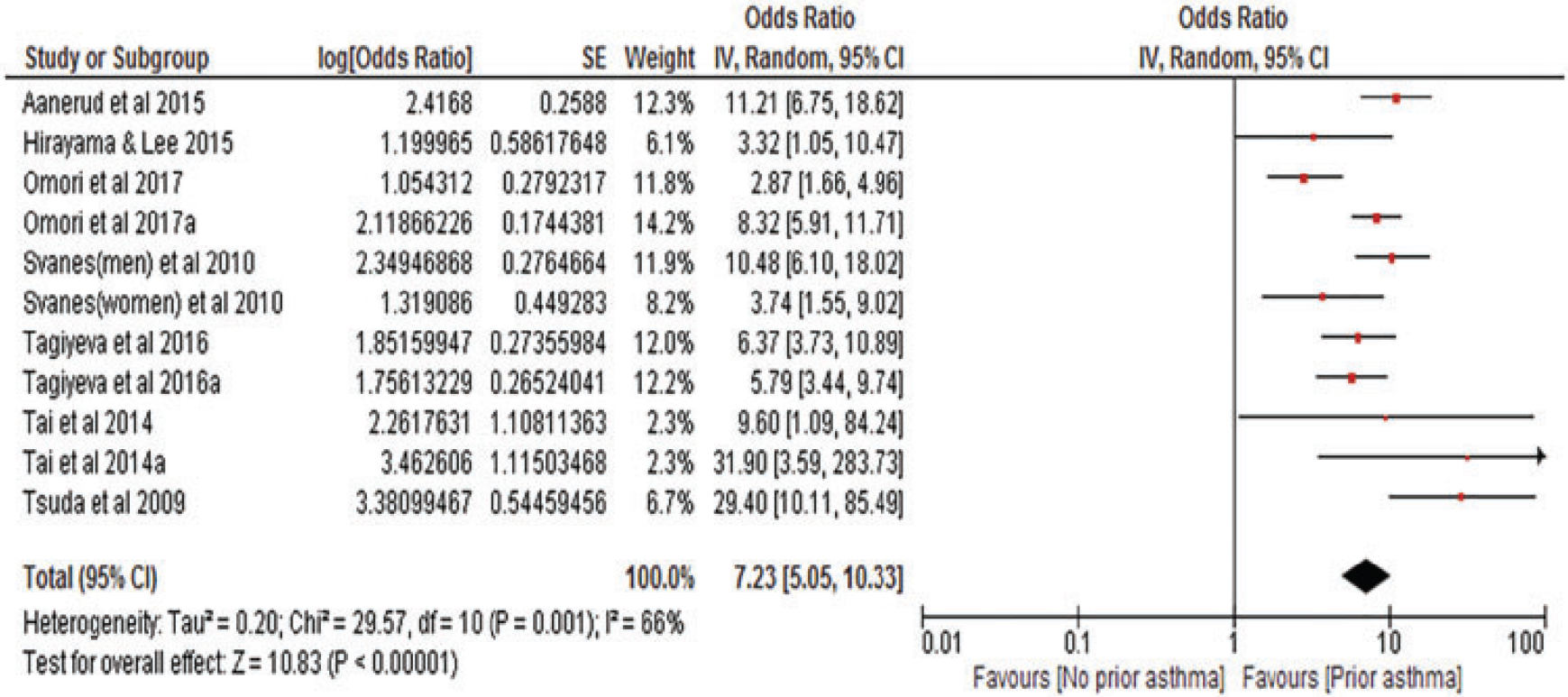


**Figure 3.2. Forest plot of assessing whether a prior history of asthma increases the likelihood of developing COPD.**

***Subgroup analysis***

Via subgroup analysis, the study was able to identify the source or cause of heterogeneity. Figure 3.3 shows the subgroup analysis by quality assessment grading. The first subgroup consisted of studies graded as "good," followed by the second subgroup "fair." The studies graded and classified as "good" had a pooled OR of 7.87 with a 95% confidence interval of 5.40 to 11.45 and $p<0.00001$. The meta-analysis of the first subgroup indicated that individuals with a prior history of asthma had an increased likelihood of developing COPD compared to individuals without any history of asthma (7.87 times more likely to develop COPD). Studies in this subgroup were generally homogeneous ($I^2= 26\%$, p=0.25), and their results were similar. The pooled effects estimate was consistent across studies graded "good".

The second subgroup synthesized studies graded as "fair". The forest plot gave a pooled effect estimate/average estimate (OR) of 6.62 with a 95% CI of 3.7-11.86 and $p<0.00001$. Meta-analysis of this combined effect also showed individuals with a prior history of asthma had an increased likelihood of developing COPD. Nonetheless, results in this subgroup were not similar, making the pooled effects inconsistent across studies (highly heterogeneous at $I^2=79\%$, $p=0.0002$). The combined effects estimate for studies with "fair" methodological quality cannot be used, as these studies are entirely different from each other; the wider confidence interval and higher heterogeneity render the precision of the effects estimate uncertain.

Figure 3.3 shows the test of subgroup differences between the two subgroups. The forest plot revealed that the two subgroups were similar, hence, their pooled effects estimates were similar with no substantial heterogeneity ($I^2=0\%$, $p=0.63$). The combined effect for the association between prior history of asthma and development of COPD was OR: 7.23 (95% CI: 5.05-10.33, $p<0.00001$).

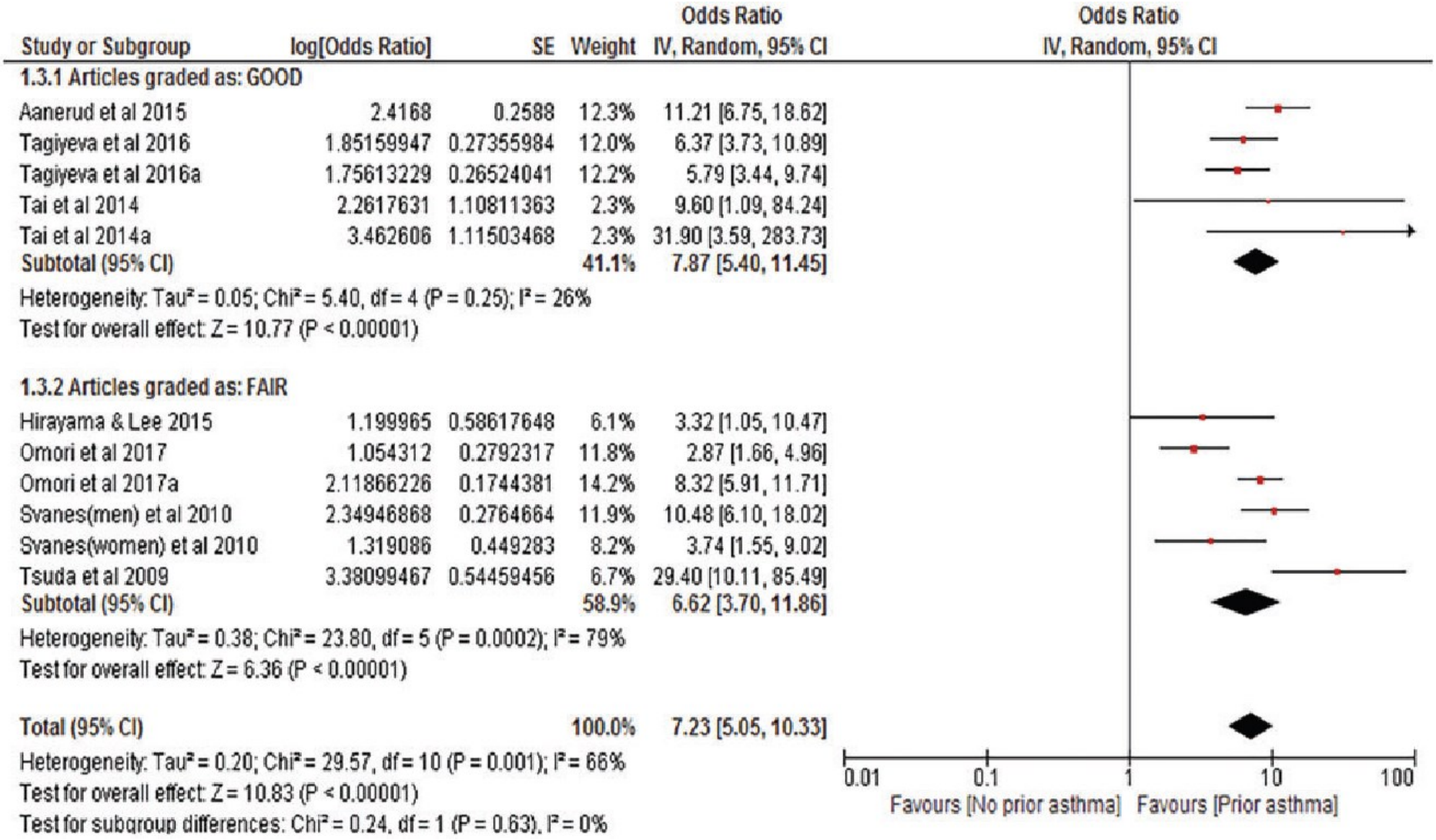


**Figure 3.3. Forest plot assessing whether a prior history of asthma increases the likelihood of developing COPD (subgroup analysis by study quality).**

***Publication bias***

The funnel plots shown in Figures 3.4 and S3.2 were employed to visually assess and detect publication bias. A visual inspection of the two funnel plots showed some level of symmetry, indicating no possibility of publication bias.

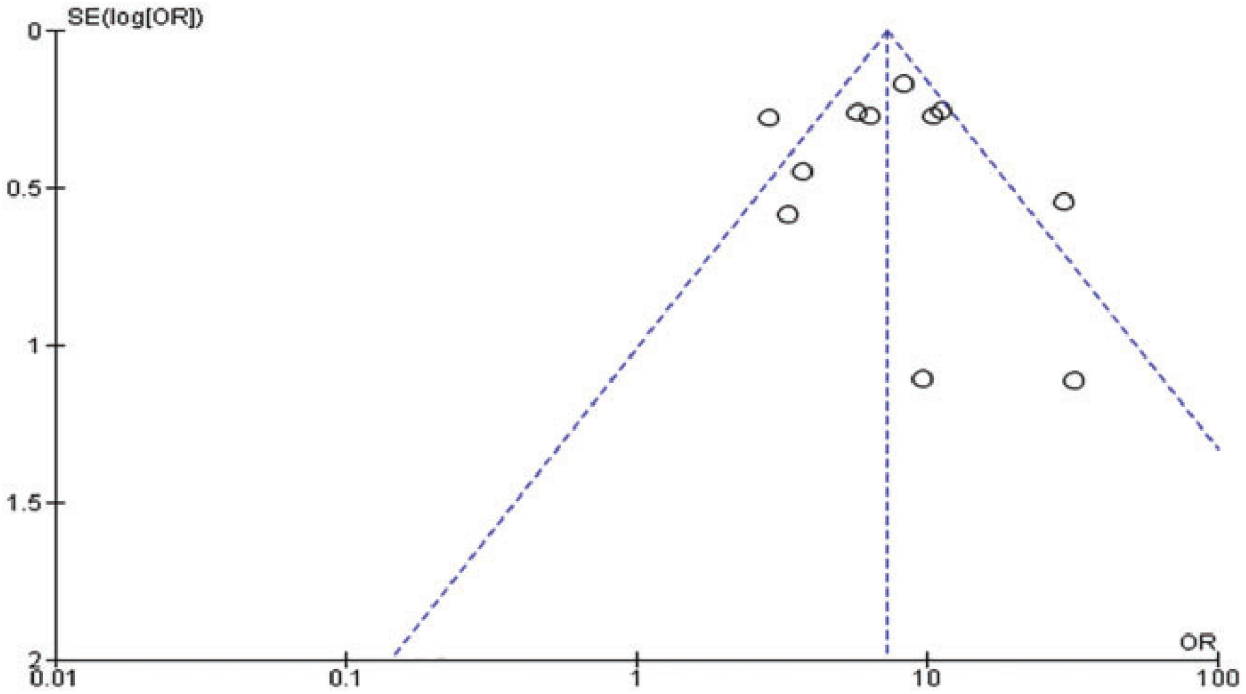


**Figure 3.4. Publication bias check for assessing whether a prior history of asthma increases the likelihood of developing COPD.**

***Egger's and Begg's tests for checking publication bias***

Egger suggests that we assess publication bias or small study effect by using precision (the inverse of the standard error) to predict the standardized effect (effect size divided by the standard error). From Table S3.3 (in the supplementary material), the intercept ($\beta_0$) is 0.28688, 95% confidence interval (-2.50302, 3.07678), with $t$=0.23261, df = 9. The one-tailed p-value is 0.41063, and the two-tailed p-value is 0.82127. Results from Egger's test indicate no substantial publication bias. Similarly, the Begg and Mazumdar rank correlation recorded a one-tailed *p*-value of 0.50, indicating no publication bias in this review.

***Sensitivity analysis***

The considerable heterogeneity identified in the "fair" study quality subgroup was explained by sensitivity analysis. I performed a meta-analysis by excluding some studies in the subgroup with larger effects estimates (OR greater than 8.00). The studies excluded were "Omori et al (2016a)", "Svanes (men) et al. (2009)", and "Tsuda et al. 2009". Results from the remaining studies were similar from study to study ($I^2$=0%, p=0.88), with very precise effects estimates (OR: 3.12, 95% CI: 2.03-4.80, p<0.00001) (see Figure S3.1 in supplementary material).

## 3.6 Discussions

The purpose of this study was to systematically summarize the available literature on the association between prior history of asthma and subsequent development of COPD. To the authors' knowledge, this is the first comprehensive systematic review and meta-analysis of this topic. In a population aged 5 years and older, prior history of asthma was found to be

significantly associated with the development of COPD in later life. I adhered to strict priori inclusion and exclusion criteria for all studies. The study excluded cross-sectional studies at the quantitative synthesis stage, as they do not present the best evidence compared to other higher levels of evidence such as case-control and cohort studies to answer the question of interest. A priori, COPD was chosen as the outcome measure, and further excluded studies not reporting COPD as an outcome. The USPSTF Quality Rating Criteria assessment of bias tool confirmed that the selected studies had low a risk of bias. The evidence obtained from this study was of good strength, had a low risk of bias, and was considered sufficient to draw broad conclusions on the association between asthma history and COPD development in later life. As COPD continues to be a global burden, efforts are being made to identify all risk factors and the necessary interventions to reduce the disease burden. In the past decade, an increasing number of epidemiological studies have noted the growing prevalence of COPD among non-smokers in developed countries. The risk of acquiring COPD from smoking was assessed as 45% and 44% in the Swedish OLIN and the US NHANES III studies, respectively; in other words, more than half of all COPD cases are unrelated to smoking[137]. The findings provide good evidence that having asthma at some point in an individual's life, regardless of the person's age, smoking status, and occupational exposure puts them at risk of developing COPD about seven times more likely than someone who has never had asthma. The study findings agree with the narrative review by Tai et al (2015)[151] and are stronger than this previous work because of our comprehensive search for studies and the use of quantitative syntheses. Poorly controlled asthma is thought to be a progressive disease that can advance from a fully reversible bronchospasm to permanent airflow obstruction of the airways. Airway inflammation and remodeling have been seen in some young children and adolescents with asthma and have been hypothesized to be linked to the development of irreversible airflow obstruction and a Forced Expiratory Volume in 1 second ($FEV_1$) decline,

a characteristic of COPD. To date, this hypothesis has not been verified, and more research is needed to unravel the complex relationship between asthma and COPD. This review highlights the need for research investigating whether asthma medication might reduce the risk of developing COPD. Patients with asthma should also be educated on the need to avoid other risk factors for COPD, such as smoking. The results of this systematic review imply that despite improved availability of therapeutic options, asthma still contribute to significant morbidity, resulting in increased healthcare use and cost and subsequently lead to a greater burden on the society. Strategies that involves pharmacists, primary care physicians, and respirologists have contributed to improved important asthma events. Thus, programs and interventions including pharmacy led strategies for improving patient's medication adherence, patient-physician education on the disease (through communication of changes in patient's health status and needs), and patient self-monitoring approaches should be implemented and intensified to improve important patient clinical and economic outcomes.

***Strength and limitations***

One of the strengths of this study was the fact that studies of good methodological quality provided ample evidence of the association between prior history of asthma and later development of COPD. Any differences could be attributed to chance or random error. In addition, the study included articles adjusted for potential confounders, and I obtained adjusted estimates of the effects. Finally, COPD as the primary outcome was objectively measured in all studies in the quantitative synthesis. Limitations of this study were: (1) studies with slightly different exposures were not included; (2) the inclusion of studies of "fair" methodological quality with substantial heterogeneity made pooling of a common-effects estimate impossible. The study attributed this latter limitation to the inability of most studies to objectively measure asthma from infancy to adulthood; most were based on recall.

Differences in study type introduced heterogeneity across studies in the synthesis stage. Some retrospective and prospective studies also differed in the duration of their follow-up.

### *Conclusions*

The study findings demonstrated evidence of a positive association between prior history of asthma and COPD. Studies with high methodological quality (operationalized here as “good”) provided considerable evidence that prior history of asthma, independent of tobacco smoking and other factors, is associated with the development of COPD in the life course. Future work should include more studies with a low risk of bias, which would present the best evidence to improve the precision of the effects estimates.

# Chapter 4: Examining risk factors accelerating time-to-chronic obstructive pulmonary disease (COPD) diagnosis among asthma patients

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## 4.1 Overview

Chapter 3 provides the foundation for the study presented here. This chapter presents the first result from the analysis of the administrative databases obtained from PopData BC. Here, the study examines the risk factors accelerating early COPD diagnosis in patients with asthma over an 18-year follow-up. The motivation for this study arose from the dearth of information about the factors` linking asthma progression to COPD over a long period, which was identified by our systematic review in Chapter 3. This study identified increased burden of comorbidities, history of tobacco smoking, obesity, asthma severity, and medication non-adherence, among others, as the possible risk factors predicting COPD incidence in asthma patients.

## 4.2 Abstract

*Background*: Asthma patients may have an increased risk for a diagnosis of chronic obstructive pulmonary disease (COPD). However, risk factors accelerating time-to-COPD diagnosis are unclear. This study aims to estimate risk factors associated with the incidence of COPD diagnosis in asthma patients.

*Methods*: Four linked databases from the PopData BC were used to identify asthma patients without prior COPD diagnosis between January 1, 1998, to December 31, 1999. Patients were assessed for time-to-incidence of COPD diagnosis from January 1, 2000, to December 31, 2018. The study estimated the effects of several risk factors in predicting the incidence of COPD in asthma patients during the 18-year follow-up period. An important patient factor, Medication Adherence (MA), was assessed by using the proportion of days covered (PDC) and the medication possession ratio (MPR). The log-logistic mixed-effects accelerated failure time model was used to estimate the adjusted *failure time ratios* (aFTR) and 95% Confidence Interval (95% CI) for factors predicting time-to-COPD diagnosis among asthma patients.
*Results*: The study identified 68,211 asthma patients with a mean age of 48.2 years included in the analysis. Risk factors accelerating time-to-COPD diagnosis included: male sex (aFTR: 0.62, 95% CI:0.56-0.68), older age (age>40 years) [aFTR: 0.03, 95% CI: 0.02-0.04], history of tobacco smoking (aFTR: 0.29, 95% CI: 0.13-0.68), asthma exacerbations (aFTR: 0.81, 95%CI: 0.70, 0.94), frequent emergency admissions (aFTR:0.21, 95% CI: 0.17-0.25), longer hospital stay (aFTR:0.07, 95% CI: 0.06-0.09), comorbidities (aFTR:0.28, 95% CI: 0.22-0.34), obese male sex (aFTR:0.38, 95% CI: 0.15-0.99), SABA overuse (aFTR: 0.61, 95% CI: 0.44-0.84), moderate asthma (aFTR:0.23, 95% CI: 0.21-0.26), and severe asthma (aFTR:0.10, 95% CI: 0.08-0.12). After adjustment, MA ≥0.80 was significantly associated with 83% delayed time-to-COPD diagnosis [i.e. aFTR =1.83, 95% CI: 1.54- 2.17 for PDC]. However, asthma severity significantly modifies the effect of MA independent of tobacco smoking history.
*Conclusion*: Targeted intervention aimed to mitigate early diagnosis of COPD should prioritize enhancing medication adherence among asthma patients to prevent frequent exacerbation during follow-up.

**Keywords:** Asthma, Cohort study, COPD, Risk factors, Accelerated Failure Time model

## 4.3 Background

Asthma affects millions of people worldwide and is associated with significant morbidity, resulting in high health care utilization [107,108,152,153]. Recent epidemiological studies have speculated that patients with asthma may have increased risk for COPD development regardless of tobacco smoking history [65,74,110, 141,147,149]. In a recent meta-analysis, [154] patients with prior history of asthma were 7.87 times more likely to develop COPD in later life after controlling for relevant confounders.

Despite the strong association between prior history of asthma and subsequent COPD development, patient factors accelerating or delaying the progressive lung function decline in asthma patients and subsequent risk of COPD are unclear. Very few related studies have attempted to explain the factors progressing asthma to COPD incidence over time. For instance, in a study by To et al (2016) [77], air pollution was a strong predictor for the development of COPD in asthma patients or *asthma-COPD overlap* (ACO). ACO has shown a strong association with increased disease severity and poorer quality of life compared with patients with asthma or COPD alone [78]. Other individual risk factors associated with an increased risk of COPD among women with asthma included low education, high body mass index, rurality, and cigarette smoking, while air pollution (fine particulate matter) was not a predictor [78]. While there exists mixed evidence on the risk factors responsible for COPD development in asthma patients, the existing literature on the subject matter is very limited.

In the general population, the risk factors that speed up asthma progression to COPD diagnosis in later life have not been widely explored in the current literature. Understanding and investigating the modifiable risk factors driving the acceleration or deceleration of asthma to COPD diagnosis will enable specific interventions and prevention strategies to be targeted to reduce the burden of COPD diagnosis in asthma patients. This study aims to

estimate the risk factors for the diagnosis of COPD in patients with asthma in a 20-year observational cohort study in Canada.

## 4.4 Subject, materials, and methods

The study used a cohort design that links four health administrative claim databases obtained from the PopData BC. The PopData BC covers health records of all residents of BC in the province's insurance program and facilitates interdisciplinary research on the risk factors of human health, well-being, and development [31,152]. The dataset includes longitudinal de-identified electronic medical data from the following sources: **a)** the *Discharge Abstract Databases* (DAD) [containing patients' hospitalization and discharge records][155], **b)** the *Medical Service Plan* (MSP) capturing data on patients visits to physicians [156], **c)** the PharmaNet database (contains records of all dispensed medications) [157], and **d)** the demographic and registration database (consolidated file) capturing demographic records of patients [158,159].

Health records captured in all four databases spanned from January 1, 1998, to December 31, 2018. The study cohort was identified during the index period (between January 1, 1998, and December 31, 1999) as patients with physician-diagnosed asthma with no prior history of COPD diagnosis. The two-year index period defined between January 1, 1998, and December 31, 1999, was used as the *wash-in* period to increase the incident asthma cases at baseline.

### 4.4.1 Cohort definition, exposure, and outcome variables

I employed a validated case definition to identify all physician-diagnosed adult asthma patients from three databases (DAD, MSP, and PharmaNet) [31,160]. Patients were included in the source population if they met at least one of the following criteria:

a) Patients who had at least one record of asthma-related hospitalizations in the DAD database based on the international classification of diseases-9th edition (ICD-9): 493.x, ICD-10th edition: J45, J46 within a calendar year, or

b) Patients having records of at least 2 physician visits for asthma, based on diagnostic codes (ICD-9 codes: 493.x), during a calendar year. The identified asthma patients in the MSP and DAD databases were further validated in the PharmaNet database if they filled prescriptions for at least four asthma-related medications within the same calendar year *(*see attached asthma-related drug lists in the supplementary material in Table S4.2).

Based on the case definitions specified above, adult asthma patients aged 18 years and older with no prior history or diagnosis of COPD between January 1, 1998, and December 31, 1999, were included in the study cohort. The study followed the identified asthma cohort from January 1, 2000, to December 31, 2018, to measure the risk factors and the outcome of interest over time.

***COPD outcomes measure***

The primary outcome was time to the first diagnosis of COPD during the study follow-up period. Using a validated case definition by Chen et al. (2017) [50], COPD was defined based on at least one of the following criteria:

1. Patients with records of at least one hospitalization with COPD as the most responsible diagnosis using ICD-9 diagnostic codes: 491.xx, 492.xx, 493.2x, 496.xx, and ICD-10 diagnostics codes: J43.xx, J44.xx.
2. Patients having records of at least one outpatient visit with COPD as the main responsible diagnosis based on ICD-9 diagnostic codes: 491.xx, 492.xx, 493.2x, 496.xx, and ICD-10 diagnostic codes J43.xx, J44.xx.

***Risk factor measures***

Socio-demographic information was examined for each patient, and included a year of the index (January 01, 1998, to December 31, 1999); *patient sex* (male or female); obesity (body mass index > 30kg/$m^2$); patient's age (categorized as '< 30 years', '30-40 years', and '40 years and older'); and lifestyle variables, such as tobacco use/nicotine dependence. Asthma medication adherence (MA) was assessed by two proxy variables on a scale of '0 to 1' and defined as the *proportion of days covered* (PDC) and the *medication possession ratio* (MPR). I estimated the PDC as the ratio of the sum of days of medication covered to the sum of days between the first and the last refill [161,162]. Further, we estimated the MPR measure as the ratio of the sum of days of medication supplied to the sum of days between the first, and the last fill dates [161,162]. The study used the 0.80 cut-off value to classify patients into high-adherent (≥0.80) and low-adherent (<0.80) groups, as consistently reported in the literature [99,163].

Another factor considered in this study was the *Charlson comorbidity index* (CCI), responsible for measuring the burden of comorbid conditions among the identified asthma patients after excluding asthma from the score. The CCI scores were grouped into three classes (CCI score 0; CCI score 1; CCI score ≥ 2) as documented in a study by Nunez et al., (2004) [164]. Additionally, I extracted some specific asthma-related comorbidities using ICD codes at baseline (namely sinusitis and upper respiratory diseases). The authors included asthma-related comorbidities because they have been widely documented as a contributing factor for asthma exacerbation and subsequent persistent airflow limitations [165,166].

Healthcare utilization variables include all emergency hospital admissions, specifically intensive care unit [ICU] (asthma and non-asthma related), asthma hospitalizations (yes=1, vs no=0), emergency department visits (yes=1, vs no=0), and length of hospital stay (categorized as '0', '1 day', '2 days', and '≥ 3 days') were also considered.

*Asthma exacerbation* was defined as the occurrence of one or more asthma-related hospitalizations, asthma-related emergency department visits, and episodes of asthma that required the prescription of oral corticosteroids (OCS) [112,167].

*Asthma severity* levels (categorized as mild, moderate, and severe) were also considered. Patients who had records of prescribed dosages of *inhaled corticosteroids* (ICS) (such as budesonide, ciclesonide, fluticasone furoate, and beclomethasone dipropriate) of 0-500µg/day without the additional intake of other asthma controller drugs were classified as '*mild*'. Patients having records of prescribed ICS doses of '0-250µg/day' and taking additional controller therapies were also defined as *mild* asthmatic patients. In addition, mild asthma patients must not have a marker of moderate to severe asthma exacerbation or should not have used at least 3 doses of SABA every week within a 12-month period. *Moderate* asthma patients had records of at least 500µg/day doses of ICS with no additional intake of other controller therapies or had a prescription of more than 250µg/day doses of ICS plus additional inhalation of other controller therapy. *Severe* asthma patients were identified as having records of more than 1000µg/day of ICS doses plus inhalation of more than 10 doses of *short-acting beta-2 agonist* (SABA) per week [168].

Lastly, the SABA overuse variable was extracted from the PharmaNet database using *drug identification numbers* (DINs). SABA overuse was defined as patients having a prescription of at least 3 SABA canisters within a year (12 month period) [112]. The SABA overuse variable was dichotomized as overuse (> 2 SABA canisters) =1, and appropriate (≤ 2 SABA canisters).

### 4.4.2 Statistical methods and analysis

The study used the 'SAS version 9.4' and 'STATA version 16' software for performing data analyses. Standard descriptive statistics (specifically: frequency table,

measures of central tendencies, and measures of dispersion) were used to present baseline characteristics.

Further, I performed bivariate analyses between the individual covariates and the risk of COPD. For the bivariate and multivariate analyses, the study used the mixed-effects log-logistic accelerated failure time (AFT) regression to model the correlated (multiple observations recorded on the same individual) survival data with possible censoring. Therefore, traditional methods of estimation that consider observations as independent are inappropriate for this database [119]. The AFT model was considered over the Cox proportional hazard (PH) model, since the data violated the proportional hazard assumption. The violation of the PH assumption in a Cox PH model can lead to misinterpreting the estimation results as well as decreasing the power of the statistical tests [169]. The AFT regression models survival times directly and assumes a multiplicative effect of covariates on survival time [119,170]. The mixed-effects log-logistic AFT model incorporates random effects with dependence structures to account for within-cluster association [119]. The study used the AFT regression methods to estimate an unadjusted and adjusted failure time ratio (FTR) and 95% confidence interval (2-sided *p*-values) and to check for model assumptions.

***Mixed-effects log-logistic AFT regression model***

The AFT model describes a direct linear relationship between the log of the failure time and sets of explanatory variables. The exposure variables or the covariates accelerate or slow down the expected failure time (median failure time). For clustered data, individuals are normally correlated within a cluster. Mixed-effects log-logistic AFT models account for dependencies of repeated responses on one individual over time by incorporating a random component to the model. The equation/model can be written on a log-scale as:

$$log\left(T_{ij}\right) = \beta_0 + \beta' X + \varepsilon_{ij} + z'_{ij} b_i$$

where $\Omega = z'_{ij} b_i$ is the random component that is distributed across the individual patient clusters. The random component also accounts for the effects of all relevant unmeasured covariates in the model. From the equation, $\beta$ is the regression coefficient for the fixed effects of covariate vector $\boldsymbol{X}$, and $b_i$ represents the vector of random effects with a set of random covariate vector $z_{ij}$. The coefficients of the random covariates $b_i$ are distributed with zero (0) mean and variance – covariance matrix $\Sigma = \Sigma(\Theta)$ where $\Theta$ is an unknown vector parameter [119].

***Interpretation of the mixed – effects log-logistics AFT model***

The effects of the covariates determined by the regression coefficients are interpreted as accelerating or decelerating the time-to-COPD incidence in asthma patients after controlling for random covariates in the model over time. The adjusted Failure Time Ratio (aFTR) is estimated as the acceleration factor. The acceleration factor or the aFTR for a given risk factor is estimated as the exponent of the corresponding regression coefficient. An **aFTR >1** implies the effect of the covariate or risk factor increases the survival time and delays their time to COPD onset in asthma patients over time. However, **aFTR<1** signifies that a covariate is at an increased risk of developing COPD in asthma patients over time, or the factor is associated with an earlier time to COPD onset. If **aFTR=1**, then there exists no change in the effect of the covariate on COPD incidence [121].

***Sample size calculations***

Power and sample size calculation was conducted in STATA using the command (stpower cox). The command was used to compute sample size, power, and effect size using the standard Cox proportional hazard model. Assuming a 10% increase in MA for the asthma patient cohort exposed to only short acting beta-2 agonist [SABA] (including those taking very little ICS) and a COPD diagnosis in asthma patient rate of 20%, with power (1-β) of

80% and type 1 error (α) of 5%, a minimum of 13,028 asthma patients are required to detect a 20% relative risk reduction of COPD diagnosis. (i.e., hazard ratio of 0.80) in 20 years.

***Ethics approval***

Our study protocol was approved by the Health Research Ethics Board (HREB) at Memorial University of Newfoundland (reference number: 2019.216).

## 4.4 Results

Table 4.1 reports the baseline characteristics of the 68,211 patients with physician-diagnosed asthma at baseline identified from the four linked databases between January 01, 1998, and December 31, 1999. The incidence of COPD diagnosis was determined in the 18-year follow-up period from January 01, 2000, to December 31, 2018. After 1,036,811 years of person-time of follow-up, a total of 10,170 (15% of 68,211) were diagnosed with COPD. The incidence of COPD diagnosed among the *mild asthma* patients was 0.85 per 1000 person-years (n=886), among *moderate asthma* patients it was 2.82 per 1000 person-year (n=2924) and among *severe asthma* patients it was 6.13 per 1000 person-year (n=6360).

**Table 4.1: Characteristics of physician-diagnosed asthma patients (N=68,211)**

| Study variables | n (% of N) or Mean ±SD |
|---|---|
| *Index Year (Baseline)* | |
| January 1, 1998, to December 31, 1998 | 49,685 (72.84) |
| January 1, 1999, to December 31, 1999 | 18,526 (27.16) |
| *Age, (mean years ± SD)* | 48.20 ± 18.63 |
| < 30 years | 12,908 (18.92) |
| 30-39 years | 13060 (19.15) |
| ≥ 40 years | 42,243 (61.93) |
| Sex | |
| Male | 27,756 (40.69) |
| Female | 40,455(59.31) |
| Obesity (BMI>30kg/$m^2$) | 205 (0.30) |
| Tobacco use/nicotine dependence | 96 (0.14) |
| *Charlson Comorbidity Index* (CCI) | |
| CCI score 0 | 66,766 (97.88) |
| CCI score 1 | 1,226 (1.80) |
| CCI score ≥ 2 | 219 (0.32) |
| Sinusitis | 108 (0.16) |
| Upper respiratory infection | 284 (0.42) |
| *Healthcare utilization* | |
| Emergency admission (yes) | 1,023 (1.50) |
| Asthma-related hospitalization (yes) | 2,701 (3.96) |
| Emergency hospitalization (yes) | 2,427 (3.56) |
| Emergency visits (yes) | 3,158 (4.63) |
| Length of hospital stay (Days) | |
| 0 | 65526(96.06) |
| 1 | 1876(2.75) |
| 2 | 559(0.82) |
| ≥ 3 | 250(0.37) |
| *Asthma medications (dispensed)* | |
| Inhaled Corticosteroids (ICS) | 24,428 (35.81) |
| Short-Acting Beta-2 Agonist | 26,034 (38.17) |
| Long-Acting Beta-2 Agonist (LABA) | 2,636 (3.86) |
| ICS/LABA combination | 90 (0.13) |
| Leukotriene receptor antagonists | 1,046 (1.53) |
| Inhaled mast cell stabilizers | 201 (0.29) |
| Theophylline | 2,145 (3.14) |
| Short-acting muscarinic antagonist | 633 (0.93) |
| Inhaled anticholinergics | 2,139 (3.14) |
| Other beta-agonists | 58 (0.09) |
| Other corticosteroids | 8,551 (12.54) |
| Other Xanthines | 78 (0.11) |
| Other anti-allergic agents | 172 (0.25) |
| *Asthma severity* | |
| Severe | 3,461 (5.07) |
| Moderate | 15,595 (22.87) |
| Mild | 49155(72.06) |
| SABA use (> 2 canisters) | 4811(7.05) |

| | |
|---|---|
| *Medication adherence levels (MAL)* | |
| MPR scale (mean ± SD) | 0.41± 0.35 |
| PDC scale (mean ± SD) | 0.39 ± 0.32 |
| High adherence level (PDC≥0.80) | 11988(17.57) |
| High adherence level (MPR≥0.80) | 13,754 (20.16) |

SD = Standard Deviation, IQR= interquartile range, CCI=Charlson Comorbidity Index; PDC=Proportion of days covered, MPR=Medication Possession Ratio.

The mean age of the study cohort was 48.20 years, with the majority aged 40 years and older and of male sex (n=27,756, 40.69%). Regarding the burden of comorbid conditions associated with asthma patients at baseline, 97.88% of the patients constituting the majority had no comorbid condition (CCI score 0), while 1226(1.80%) had 'CCI score of 1', and 219 (0.32) had a CCI score of at least 2. Additionally, two asthma-related comorbid conditions, namely sinusitis (108, 0.16%) and upper respiratory infections (284, 0.42%), were identified at baseline.

A total of 1023(1.50%) patients had records of emergency admissions (both asthma-related and non-asthma related), 2427(3.56%) had emergency asthma hospitalizations, and 3158(4.63%) had emergency department visits. The median length of hospital stay was estimated as 3.00 days with an interquartile range of 4.00 days. The majority of the asthma patients were prescribed ICS (n=26034, 38.17%) and SABA (n=24428, 35.81%) respectively. A total of 2636(3.86%) collected *long-acting beta-2 agonist* (LABA), 90(0.13%) were prescribed with the combined ICS/LABA at baseline, and 1046(1.53%) had *Leukotriene receptor antagonists* (LTRA). Additional medications prescribed to the study cohort included inhaled mast cell stabilizers, theophylline, *short-acting muscarinic antagonist* (SAMA), and others.

***Bivariate analysis***

Table 4.2 summarizes the unadjusted failure time ratio (uFTR) output in the bivariate analysis and associated 95% confidence interval (95% CI) and *p-values*. In selecting patient factors related to the time-to-COPD diagnosis from baseline patient's characteristics, I set the maximum significance level of 'at most 0.20' to include as many covariates as possible into the multivariate model. Based on the results, any covariates that were significantly related to time-to-COPD onset with significant levels ranging from '0.00-0.20' were included in the multivariate model. Significant factors identified in the bivariate analysis were male sex, patient's age group (< 30 years, 30-40 years, 40 + years), length of hospital stay (days), emergency admissions, asthma exacerbation, Charlson comorbidity index, history of tobacco use/nicotine dependence, asthma-related comorbidities, asthma severity levels (mild, moderate, and severe), SABA overuse, and medication adherence levels ('high', 'low'). For instance, male patients were at an increased risk of developing COPD, with a shortened time to COPD onset with an unadjusted time ratio of 0.52; 95 % CI: (0.47-0.58). Also, compared to patients aged less than 30 years, individuals who were 40 years and older were 98% more likely to develop COPD faster (i.e., uFTR: 0.02, 95% CI: 0.01-0.03).

The patient's history of tobacco use/nicotine dependence at baseline was statistically and clinically relevant at the bivariate level with an increased risk of COPD diagnosis (uFTR: 0.21, 95% CI: 0.08-0.52). That is, asthma patients who frequently smoke tobacco compared to non-smokers accelerate their risk of COPD incidence by 79%. The patient-level effect of asthma exacerbation, Charlson's comorbidity index, PDC and MPR varies significantly over the follow-up period in the mixed effect AFT analysis.

**Table 4.2: Bivariate analysis* of the association between patient factors predicting risk of COPD**

| Covariates** | Patient-level variance (SE) | uFTR | 95% CI | P-value |
|---|---|---|---|---|
| Male Sex | n/a | 0.52 | (0.47, 0.58) | <0.0001 |
| *Age (years)*[at baseline] | | | | |
| ≥ 40 years | | 0.02 | (0.01, 0.03) | <0.0001 |
| 31-39 years | n/a | 0.38 | (0.26, 0.55) | <0.0001 |
| <30 years | | Ref | Ref | Ref |
| *Length of stay(days)*[*at baseline*] | | | | |
| 1 | | 0.11 | (0.09, 0.13) | <0.0001 |
| 2 | n/a | 0.04 | (0.03, 0.05) | <0.0001 |
| ≥3 | | 0.05 | (0.04, 0.05) | <0.0001 |
| 0 | | Ref | Ref | Ref |
| Emergency admission | n/a | 0.09 | (0.07, 0.11) | <0.0001 |
| Asthma exacerbation | 7.28(0.66) | 0.78 | (0.69, 0.90) | <0.0001 |
| Tobacco use (*at baseline*) | n/a | 0.21 | (0.08, 0.52) | 0.001 |
| Obesity, BMI≥30kg/$m^2$ (*at baseline*) | n/a | 1.34 | (0.52, 3.49) | 0.546 |
| Charlson Comorbidity Index | | | | |
| CCI score 1 | | 0.52 | (0.23, 1.16) | 0.112 |
| CCI score ≥ 2 | n/a | 0.12 | (0.10, 0.16) | <0.0001 |
| CCI score 0 | | Ref | Ref | Ref |
| Sinusitis(*baseline*) | n/a | 0.47 | (0.18, 1.22) | 0.120 |
| Upper respiratory infection(*baseline*) | n/a | 0.38 | (0.19, 0.76) | 0.006 |
| *Asthma severity (at baseline)* | | | | |
| Severe | | 0.06 | (0.05, 0.07) | <0.0001 |
| Moderate | n/a | 0.13 | (0.12, 0.15) | <0.0001 |
| Mild | | Ref | Ref | Ref |
| SABA overuse ( > 2 SABA canisters) (*at baseline*) | n/a | 0.37 | (0.26, 0.54) | <0.0001 |
| MAL: (PDC ≥ 0.80) | 1.95(0.53) | 1.85 | (1.59, 2.15) | <0.0001 |
| MAL: (MPR ≥ 0.80) | 2.42(0.47) | 1.88 | (1.64, 2.15) | <0.0001 |

*Unadjusted Failure –Time-Ratio (uFTR) in the accelerated analysis of Time-to-COPD diagnosis from baseline.
**Covariates that were significant at 0.20.; ED=Emergency department; CCI= Charlson comorbidity index; SABA=Short Acting Beta Agonist; PDC= Proportion of Days Covered MPR= Medication Possession Ratio (MPR) MAL=Medication Adherence Level, BMI=Body Mass Index, N/A:=non-applicable.

***Multivariate Analysis***

The results of the multivariate analysis are summarized in Tables 5 and S4 (supplementary material) with adjusted failure time ratios (aFTR) and their corresponding 95% confidence interval (95% CI). Patient demographic factors associated with increased risk of COPD diagnosis with a faster time to COPD incidence from baseline were male sex (aFTR: 0.62, 95% CI: 0.56-0.68) and patients aged '≥40 years' (0.03; 95% CI: 0.02-0.04,

$p$<0.0001) So, male patients have a 38% shorter time to COPD onset compared to female patients. Also, the time-to-incidence of COPD was 97% shorter among older adults (40 years and older) than it was for individuals below the age of 30 years.

With regard to healthcare utilization patient factors, an admission for asthma and staying in the hospital for at least a day were significantly associated with increased risk of time-to-COPD diagnosis (aFTR: 0.13, 95% CI: 0.12-0.15 for 1 day; and 0.07, 95% CI: 0.06-0.09 for ≥ 2 days) compared to no hospitalizations. In other words, asthma patients who were hospitalized for more than a day were 93% more likely to develop COPD faster than patients who were not hospitalized. Similarly, patients with a history of asthma emergency admission (aFTR: 0.21, 95% CI: 0.17-0.25), asthma exacerbation (aFTR: 0.81, 95%CI: 0.70-0.94), or tobacco use or nicotine dependence (aFTR: 0.29, 95%CI: 0.13, 0.68) have an increased risk of early COPD diagnosis. Individuals who were exposed to tobacco smoking were 71% more likely to develop COPD faster than non-tobacco smokers. Also, compared to asthma patients who did not experience exacerbations, patients who experienced asthma exacerbations over time were 19% more likely to accelerate their risk of future COPD incidence.

Likewise, patients with greater comorbid conditions measured by CCI showed a greater risk of COPD diagnosis. That is, individuals with increased comorbidity burden were 72% more likely to have a faster diagnosis of COPD compared to patients with fewer or no pre-existing conditions. A history of *severe asthma* was associated with a greater risk of COPD diagnosis, with a 90% shorter time to COPD incidence (aFTR: 0.10, 95% CI: 0.08-0.12) compared to those with *mild asthma* after controlling for relevant covariates, confounders, and the random components. Patients with optimal medication, adherence assessed by PDC≥0.80 over time were significantly less likely to develop COPD, with a prolonged time to the disease onset (aFTR: 1.83, 95% CI: 1.54, 2.17) compared to the non-adherent patients. That is, patients who optimally adhered to their prescribed medications

over time were 83% more likely to slow down or delay the future incidence of COPD. Furthermore, the use of more than 2 SABA canisters within a year (12 months) compared to the appropriate use (≤ 2 canisters) was a significant predictor for COPD incidence. The identified risk factors accelerating time-to-COPD incidence have been summarized in Figure S6.2 in the supplementary material.

**Table 4.3: Multivariate analysis of risk factors for time-to-COPD incidence-PDC model***

| Variables | aFTR | 95% CI | P-value |
|---|---|---|---|
| Male Sex | 0.62 | (0.56, 0.68) | <0.0001 |
| Age (years) | | | |
| ≥ 40 years | 0.03 | (0.02, 0.04) | <0.0001 |
| 30-39 years | 0.34 | (0.23, 0.50) | <0.0001 |
| <30 years | Ref | | |
| Length of stay (days) | | | |
| ≥3 | 0.08 | (0.07, 0.10) | <0.0001 |
| 2 | 0.07 | (0.06, 0.09) | <0.0001 |
| 1 | 0.13 | (0.12, 0.15) | <0.0001 |
| 0 | Ref | | |
| Emergency admissions | 0.21 | (0.17, 0.25) | 0.000 |
| Asthma exacerbation | 0.81 | (0.70, 0.94) | 0.007 |
| Tobacco use/nicotine dependence | 0.29 | (0.13, 0.68) | 0.004 |
| Obesity (BMI≥30kg/$m^2$) | 1.01 | (0.54, 1.89) | 0.977 |
| Charlson Comorbidity Index | | | |
| CCI score ≥ 2 | 0.28 | (0.22, 0.34) | <0.0001 |
| CCI score 1 | 0.70 | (0.39, 1.26) | 0.239 |
| CCI score 0 | Ref | | |
| Sinusitis (yes) | 4.66 | (1.45, 15.02) | 0.010 |
| Upper respiratory infection (yes) | 0.49 | (0.30, 0.82) | 0.006 |
| Asthma severity | | | |
| Severe | 0.10 | (0.08, 0.12) | 0.000 |
| Moderate | 0.23 | (0.21, 0.26) | 0.000 |
| Mild | Ref. | | |
| SABA overuse (> 2 SABA canisters) | 0.61 | (0.44, 0.84) | 0.003 |
| Medication adherence (PDC≥80%) | 1.83 | (1.54, 2.17) | <0.0001 |
| Random effects | | | |
| Patient cluster | | | |
| Variance (constant) | 2.31(0.33) | | |
| Variance [PDC Medication adherence effect (se)] | 6.87e-5(0.53) | | |
| /logs | 0.41(0.02) | | |

Where 95% CI=95% confidence interval; SABA=Short acting beta-2 agonist. Only the PDC variable (proxy for medication adherence) was included in the random effect component. BMI=Body Mass Index

Figure 4.1 presents the effect modification of medication adherence by asthma severity, sex, obesity, and SABA overuse by ICS adherence and risk of time to COPD diagnosis. Medication adherence ≥ 0.80 assessed by both PDC and MPR in mild asthma was associated with the greatest likelihood of delayed COPD diagnosis in asthma patients. History of obesity in male asthma patients was a significant risk factor for early diagnosis of COPD.

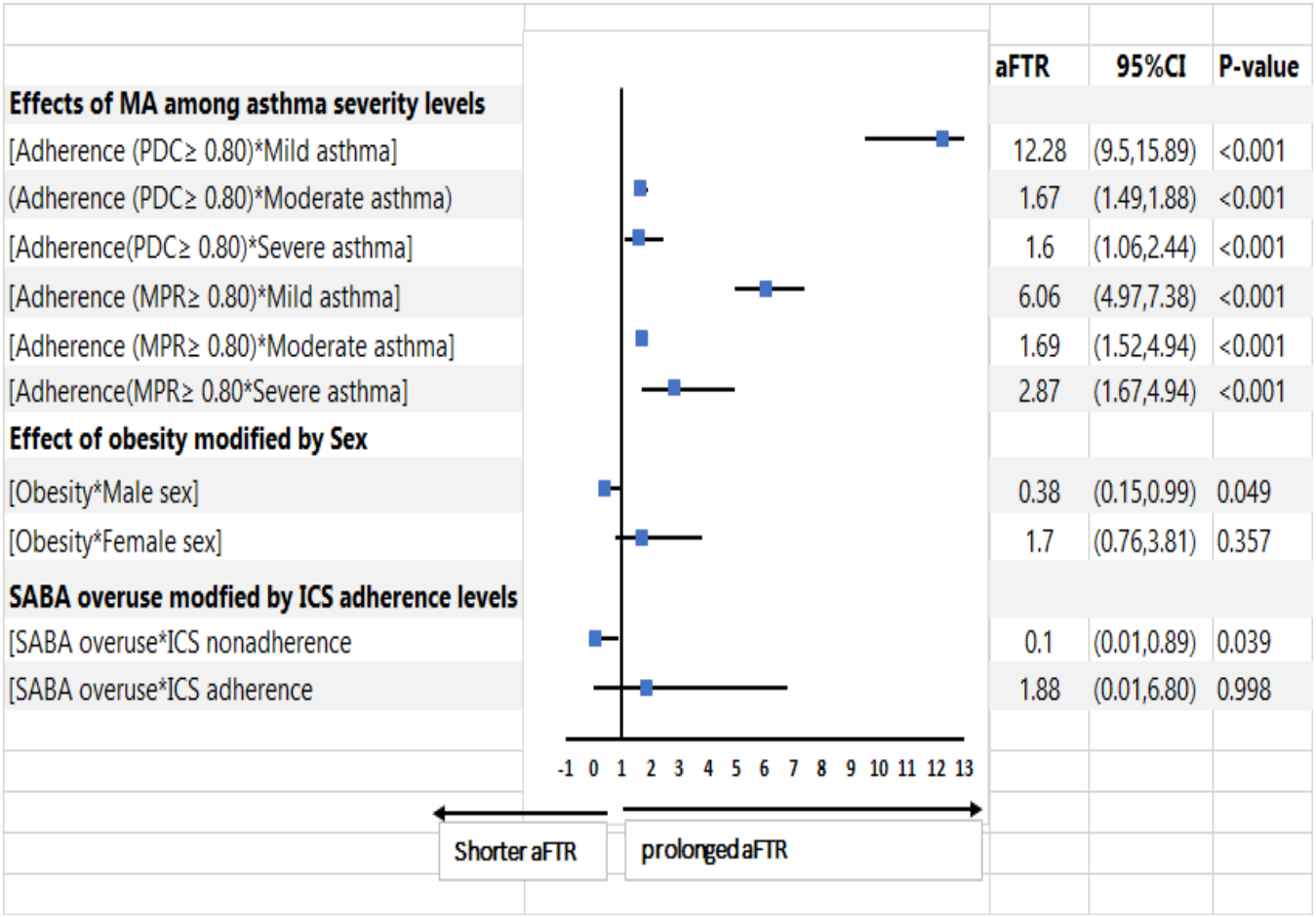


**Figure 4.1: Plot of association between the effect of patient factors and time to COPD diagnosis.**

The model was *adjusted for sex, age, emergency admissions, tobacco use/nicotine dependence, obesity; Charlson Comorbidity Index, asthma-related comorbidities, sinusitis, and upper respiratory infection*

Where ICS=Inhaled corticosteroids; MA=Medication adherence; PDC=Proportion of Days Covered; MPR=Medication Possession Ratio; SABA=Short acting beta-2 agonist

## 4.5 Discussion

In this study, I examined the role of asthma patients' demographic factors, lifestyle factors, healthcare utilization factors, medication adherence, SABA usage, and other risk factors on the progression to a diagnosis of COPD. Significant risk factors found to accelerate time to COPD incidence in patients with asthma included male sex; older age (40 years and older); history of tobacco use; having had an increased length of hospital stay; asthma exacerbation, including asthma-related hospitalization; increased comorbidity burden (CCI score ≥1); moderate and severe asthma; SABA overuse, obesity in males; and medication non-adherence among asthma patients over time.

Of note, the risk factors linking asthma and its progression to COPD have not been thoroughly investigated. Whereas most asthma patients have mild to moderate disease that can easily be controlled with medications, a small cluster of asthma patients are not well controlled [171]. It has been well established that a significant proportion (representing 5-10%) of asthma patients develop persistent airflow obstruction despite optimal therapy [172,173]. Such patients are more likely to have a poorer prognosis [174]. The persistent obstruction in severe asthma patients over time becomes indistinguishable from the chronic airflow limitation seen in patients with physician-diagnosed COPD.

This is one of the few epidemiological cohort studies to investigate and identify individual risk factors associated with increased risk of COPD in patients with asthma using a large population-based cohort study. The longitudinal nature of the database (clustered survival data) necessitated the use of the mixed-effects log-logistic AFT model to account for time-dependent covariates, clustered components, and unobserved covariates in the model. The findings of this study are partly consistent with the limited existing studies. For instance, a previous cohort study by To and colleagues (2016) [77], found cigarette smoking, 'BMI ≥ 30', and higher exposure to particulate matter ($PM_{2.5}$) to be significant risk factors for the

development of COPD in asthma patients. Also, in a study to quantify the risk of developing COPD in Ontario women with asthma, low level of education, high BMI, rurality, and increased levels of cigarette smoking were associated with increased risk of COPD incidence. However, exposure to fine particulate matter was not significantly associated with the risk of COPD in asthma patients [78]. Indeed, the results of the latter study, which was restricted to women, suffered from the limitation that the estimates may not have accurately represented lifelong exposure to air pollutants. To date, limited epidemiological studies have examined the risk factors for developing COPD in asthma patients using a large population-based study.

The findings contribute to the existing knowledge that male sex, exposure to tobacco smoking, older age (≥ 40), asthma exacerbations, obesity in male patients, asthma severity, SABA overuse, medication non-adherence, and increased burden of comorbidities increase the likelihood of the diagnosis of COPD in asthma patients. Sex-related differences exist in patients with COPD and other related obstructive airway diseases, such as ACO [175–178]. Emerging evidence indicates that females are more susceptible to COPD, and this could be attributed to increased tobacco use in women [175–178]. However, the mechanism explaining this phenomenon is largely unknown.

Whereas previous studies found SABA overuse to be a major risk factor for severe asthma exacerbations [112,179], this study further found that it also contribute to an increased risk of COPD among asthma patients. Additionally, the effect of SABA overuse among asthma patients who did not adhere to prescribed ICS was a significant risk factor for COPD development, with a 90% shorter time to COPD onset (aFTR: 0.1, 95% CI:0.01-0.89; see Figure 3.1). Current clinical practice guidelines, such as those provided by the *Global Initiative for Asthma* (GINA) [5], *British Thoracic Society* (BTS) [35], and *Canadian Thoracic Society* (CTS) [180] recommend against the use of SABA as monotherapy, and increasingly endorse the use of ICS as the first-line controller therapy for all ages. Recently, documented

evidence shows that replacing SABA with fast-acting LABA/ICS therapy reduces patients' risk of severe exacerbations by one-third [181]. Therefore, *healthcare providers* (HCPs), particularly clinicians who treat patients with asthma, are encouraged to adhere to the recommendations in the treatment guidelines to improve the best practice of the management of the disease. Consequently, interventions such as decision support tools, feedback and audits, and clinical pharmacy support [182] are encouraged to improve HCPs compliance to the treatment guidelines recommendations.

Also, patients who had a greater percent of medication adherence over time were significantly less likely to receive an early diagnosis of COPD when compared to non-adherent patients. The association between medication adherence and risk of COPD was modified by the various levels of asthma severity, as mild asthma patients had a prolonged time to developing COPD compared to the moderate and severe patients.

***Limitations***

Despite the strength of this study, some limitations that could have influenced it to some extent are worth noting. First is the completeness of the list of patients' factors identified from the PopData BC administrative databases. There is a potential for unmeasured confounding variables; that is, the database used was limited to some important clinical data, such as laboratory findings, pulmonary function tests, environmental factors, and some lifestyle variables. Unmeasured variables could have introduced residual confounding into the model. However, the study adopted a robust statistical approach and proxy variables to account for these unmeasured confounders.

Second, the study have used prescription data as a proxy for measuring medication adherence in asthma patients, with the risk that we may have under- or overestimated the exposure due to the occurrence of primary non-adherence (patients never filling a

prescription written by their provider) or secondary non-adherence (filling a prescription but partially or never consuming the medication). The third potential limitation relates to the potential ascertainment bias or misclassification associated with asthma and COPD diagnosis from the DAD, MSP, and the PharmaNet databases. However, previous studies have demonstrated that these databases are highly valid for confirmed asthma in obstructive airway diseases, especially for COPD diagnosis [31,50].

## 4.6 Conclusion

In conclusion, the present large population-based study with an 18-year follow-up period highlights some important risk factors that are likely to accelerate asthma patients' progression to COPD diagnosis. Of note, some individual factors, such as adherence to asthma medications over time (PDC ≥0.80), delay and decelerate a patient's risk of developing COPD over time. Healthcare providers and policymakers should emphasize greater medication adherence as a preventive intervention capable of reducing the risk of COPD in asthma patients. Patient-specific education and counseling should be intensified to increase awareness of the importance of adhering to prescribed medications over time and of minimizing unhealthy lifestyles, such as cigarette smoking and sedentary lifestyles leading to obesity, particularly in male patients.

# Chapter 5: Measuring medication adherence in a population-based asthma administrative pharmacy database: a systematic review and meta-analysis

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## 5.1 Overview

The previous chapter (chapter 4) identified medication non-adherence and other patient factors as potential factors linking the association between asthma and COPD onset. To properly define medication adherence/non-adherence, I conducted a systematic review and meta-analysis to identify the current, up-to-date methods for measuring adherence in asthma administrative health databases. There are several medication adherence methods and a wide variety of adherence thresholds in the literature for measuring medication adherence in an asthma administrative population-based database. In this chapter, the study report on a systematic review and meta-analysis conducted to synthesize evidence on common methods for measuring compliance in asthma databases and identify the strengths and weaknesses of the methods. The study quantitatively synthesized the available evidence to determine an optimal adherence threshold for assessing adherence to asthma medications using meta-analysis. The identified adherence methods and thresholds in this study will be used in subsequent chapters to define the degree of adherence to medication.

## 5.2 Abstract

*Background*: Limited studies have systematically reviewed the literature to identify and compare the various database methods and optimal thresholds for measuring medication adherence in adolescents and adults with asthma. The present study aims to identify the methods and optimal thresholds for measuring medication adherence by using population-based pharmacy databases.

*Methods*: The search was conducted in PubMed, Embase, International Pharmaceutical Abstracts (IPA), Web of Science, Google Scholar, and grey literature from January 1, 1998, to March 16, 2021. Two independent reviewers screened the studies, extracted the data, and assessed the quality of the studies. A quantitative knowledge synthesis was employed.

*Results*: Thirty-eight (38) retrospective cohort studies were eligible. This review identified 20 methods for measuring medication adherence in adolescent and adult asthma administrative health records. Two measures, namely the Medication Possession Ratio (MPR) and Proportion of days Covered (PDC), were commonly reported in 87% of the literature included in this study. From the meta-analysis, asthma patients who achieved an adherence threshold of "**0.75-1.00**" [OR: 0.56, 95% CI: 0.41 to 0.77] and "**> 0.5**" [OR: 0.71, 95% CI: 0.54 to 0.94] were less likely to experience asthma exacerbation.

*Conclusion*: Despite their limitations, the PDC and the MPR remain the most common measures for assessing adherence in asthma pharmacy claim databases. The evidence synthesis showed that an adherence threshold of at least 0.75 is optimal for classifying adherent and non-adherent asthma patients

**Keywords:** Medication Adherence; Adherence Measures; Asthma; Adherence Thresholds; Meta-analysis; Administrative Health Databases; Review.

## 5.3 Background

Achieving targeted clinical outcomes–asthma control, reduced asthma exacerbation, and improved lung function–in asthma patients requires a certain degree of medication use. Medication adherence (MA) evaluates the degree to which patients use their medications as prescribed by their health care providers [79,183]. While treatment adherence is essential to optimize the benefits of therapy, nonadherence has been associated with poor clinical outcomes, increased healthcare costs, and low quality of life [83–85]. MA in adult asthma patients ranges from 30–70% [86–88], with these estimates differing by country, age, sex, and ethnicity [184].

Several methods have been developed to measure MA, and the use of records on prescribed medications to indirectly estimate adherence has gained prominence, due to the increasing availability of electronic health records and administrative data [98,99]. The accurate evaluation of MA in large populations using administrative data is important for assessing medication effectiveness and identifying risk factors associated with suboptimal adherence, as well as for introducing effective interventions for improving adherence [81,185]. However, the use of administrative and pharmacy claim databases have several shortcomings, including incomplete or missing data and the inability to confirm whether patients ingested the medication acquired [167,186]. Nonetheless, these adherence measures could reflect real-life settings [186] and improve clinical outcomes if the database captures complete coverage of prescribed medications and history of refills [81].

Using administrative data, researchers and clinicians are often faced with the dilemma of choosing an appropriate adherence measure from a wide range of measures and approaches in the literature [187]. In particular, the availability of different adherence measures and their variations commonly used in estimating adherence to asthma medications presents a challenge for researchers in this area. While some investigators have consistently reported

common methods for measuring adherence, a wide variety of threshold classifications exist [99,188,189]. Two of the most widely used adherence measures are the *medication possession ratio* (MPR) and the proportion of days covered (PDC), which estimates the proportion of the time a patient has medication available [99]. The PDC and MPR adherence rate data can be reported as continuous or converted to a dichotomous measure when a patient attains a certain degree of compliance. To identify patients who are adherent to their medication using these measures, a threshold of '≥ 0.80' is conventionally used regardless of the clinical contexts; nonetheless, the threshold may differ across medication therapeutic classes or disease conditions [99,190]. There is no ideal threshold for measuring adherence to prescribed medications, and the selection of arbitrary cut-off values or thresholds is of great concern to researchers, since there is no pharmacological basis underlying the choice of cut-off values [99,191]. In addition, several studies have proposed and used disease-specific measures to assess adherence to medications among patients with various conditions including asthma [190,192]. Therefore, it remains unclear which adherence measure would be most appropriate to assess adherence to asthma medications in a patient population already known to have high non-adherence rates.

To our knowledge, few studies have systematically summarized the evidence around adherence measures to identify an appropriate measure for patients with adolescent and adult asthma. In addition, there is a dearth of studies that have identified an optimal adherence threshold for the appropriate adherence measure and its association with clinical outcomes in adolescents and adults with asthma. Given this, the study aim to systematically review the evidence in extant literature to identify and compare various methods for measuring medication adherence and optimal thresholds for assessing adherence to medications, and their association to targeted clinical outcomes in adolescents and adults with asthma.

## 5.4 Material and methods

The study followed the recommended checklist, the *Preferred Reporting Item of Systematic Reviews and Meta-Analyses* (PRISMA) [193], to conduct and report the comprehensive systematic review of the selected studies. The protocol of this review was registered in PROSPERO with registration number CRD42020168922.

### Literature search and search strategy

The search strategy was developed by the author (MA-B) in consultation with a Health Sciences Librarian at the Faculty of Medicine, Memorial University of Newfoundland. I performed a comprehensive search in PubMed, Embase, and International Pharmaceutical Abstracts (IPA), and manually searched Google Scholar, Web of Science, grey literature, ResearchGate, and other research platforms. The authors started the exhaustive search on February 1, 2020, and ended on February 5, 2020, which was subsequently updated up to March 16, 2021. The search included articles published from January 1, 1998, to March 16, 2021. The search criteria comprised 'MeSH' terms in PubMed, 'Emtree' in Embase, keywords and a combination of 'MeSH' terms and Keywords, and, finally, 'Emtree' and Keywords. MeSH terms used for the search were ("medication adherence"[Mesh]), and ("Asthma"[Mesh]). Keywords used included (prescription[tiab] OR medication[tiab] OR puffer[tiab] OR "inhaled corticosteroid"[tiab]) AND (adherence[tiab] OR compliance[tiab] OR filling[tiab] OR dispensing[tiab] OR dispensed[tiab] OR filled[tiab]) AND ("Asthma"[Mesh] OR asthma[tiab]). Our search focused on human studies and was limited to studies involving asthma patients aged 12 years and older. Additionally, only studies published in the English language were included in this review. I manually screened the reference lists of the relevant studies to identify additional articles. Also, content

experts were contacted to inquire about other, related, studies. The final search strategy for the research databases is summarized in the supplementary material in Table S5.1.

### 5.4.1 Study Eligibility and Selection

Two reviewers (MA-B, KOB) independently screened the titles and abstracts yielded by the three bibliographic databases for eligibility at the initial stage. The Rayyan software (a free web and mobile app reference manager) [194] was used to expedite the initial screening of the abstracts and titles. Further, Rayyan was used to remove duplicates and sort inclusions and exclusions of the retrieved abstracts. Any disagreement in the selection of the studies was resolved by consensus or arbitration by an independent researcher. After their relevance was assessed, selected articles were further screened. Studies were eligible for inclusion if they met the following criteria: (a) included individuals 12 years and older with a physician diagnosis of asthma, with physician diagnosis of asthma defined as any diagnosis based on ICD codes for asthma in claim/administrative databases, as well as prescribed asthma-related medications; b) used population-based administrative claim databases; c) reported claim databases medication adherence measures for asthma; d) were published from January 1, 1998 to March 2021; e) written in English; and f) discussed studies only on humans.

#### *Quality assessment and risk of bias*

The reviewers independently assessed the risk of bias and quality assessment of the included studies. The study adopted the Joanna Briggs Institute checklist [195] to evaluate the risk of bias of the cohort studies. Using the checklist, I assessed the quality of the individual studies based on 10 domains (see Table S5.2 in the supplementary material). Any disagreement that arose from the assessment of the risk of bias of the studies was resolved by an arbitrator (third reviewer). Further, I determined the confidence in the evidence of studies

included in the meta-analysis using the *Grading of Recommendations, Assessment, Development, and Evaluations* (GRADE) [196].

***Data Extraction***

The reviewers used a standardized spreadsheet based on some generic items and relevant information to independently extract the following data: (a) study ID or author's name, (b) study population, (c) study design, (d) name of the administrative database, (e) location, (f) outcome assessed/study objectives, (g) medication adherence measures/related measures, (h) definition of the measure, (i) strength and weaknesses/limitations of the measures, and (j) estimated rate of adherence measured/study results. The data extraction process was simultaneously performed by the reviewers (MA-B & KOB). The study resolved disagreements in the data extraction by mutual agreement.

***Evidence synthesis***

The study anticipated significant variations, particularly in the design and objectives of studies included for review. This could introduce heterogeneity and impact conclusions drawn from our synthesis of the evidence. To mitigate the impact of heterogeneity on the evidence synthesized, two separate approaches–quantitative and narrative–were used to synthesize evidence from retrieved studies. Specifically, I presented outcome data that were practicable to quantitatively combine in a meta-analysis. I used narrative/qualitative synthesis for data with significant heterogeneity and that were impracticable to combine in the quantitative synthesis. This was done to ensure that solid conclusions could be drawn from the evidence gleaned from the various studies included in our systematic review.

***Qualitative/narrative data synthesis***

I conducted a narrative synthesis of studies meeting the inclusion criteria. A narrative synthesis is an approach to the systematic review and synthesis of findings from multiple

sources that primarily uses text to summarize and explain the findings of the synthesis [197]. It is used when statistical meta-analysis is not feasible, particularly due to substantial methodological and clinical heterogeneity between studies identified [197]. This study sought to find appropriate adherence measures and further determine the optimal adherence threshold for adults with asthma using administrative data. Thus, this narrative synthesis focused on adherence measures reported in the various claims/administrative databases, and study findings were grouped by type, definition/equation, cut-off values, or threshold determination of medication adherence measures.

### *Quantitative data synthesis*

The main summary measure for the quantitative synthesis was the *odds ratio* (OR). Review Manager, version 5.4, and *Comprehensive Meta-analysis* (CMA) software were used to analyze data for the quantitative synthesis. I employed the random effects model to synthesize the available evidence due to the suspicion of between-study heterogeneity. The effects estimates were synthesized using the generic inverse variance method to estimate the contribution of each study (expressed in weights) to the pooled effect. Meta-regression was conducted to investigate the source of the between-study heterogeneity. The authors performed a publication bias check by using the 'Orwin's fail-safe Ns', Egger's regression test, and Funnel plot.

## 5.5 Results

### *Identification of studies*

The database search generated a total of 7268 citations (PubMed =2456, Embase = 4479, IPA = 321, and additional searches from other sources =12) [see Figure 5.1]. The Rayyan web app reference manager removed duplicate studies, leaving 2756 records. The titles and

abstracts of the 2756 records were screened for relevance. After the screening, I retrieved and downloaded 70 articles for full text review and finally excluded 32 studies based on the study's inclusion and exclusion criteria. The remaining 38 retrospective/prospective cohort studies met the inclusion criteria for this review. The flow diagram in Figure 5.1 summarizes studies identified and excluded at each stage of the review.

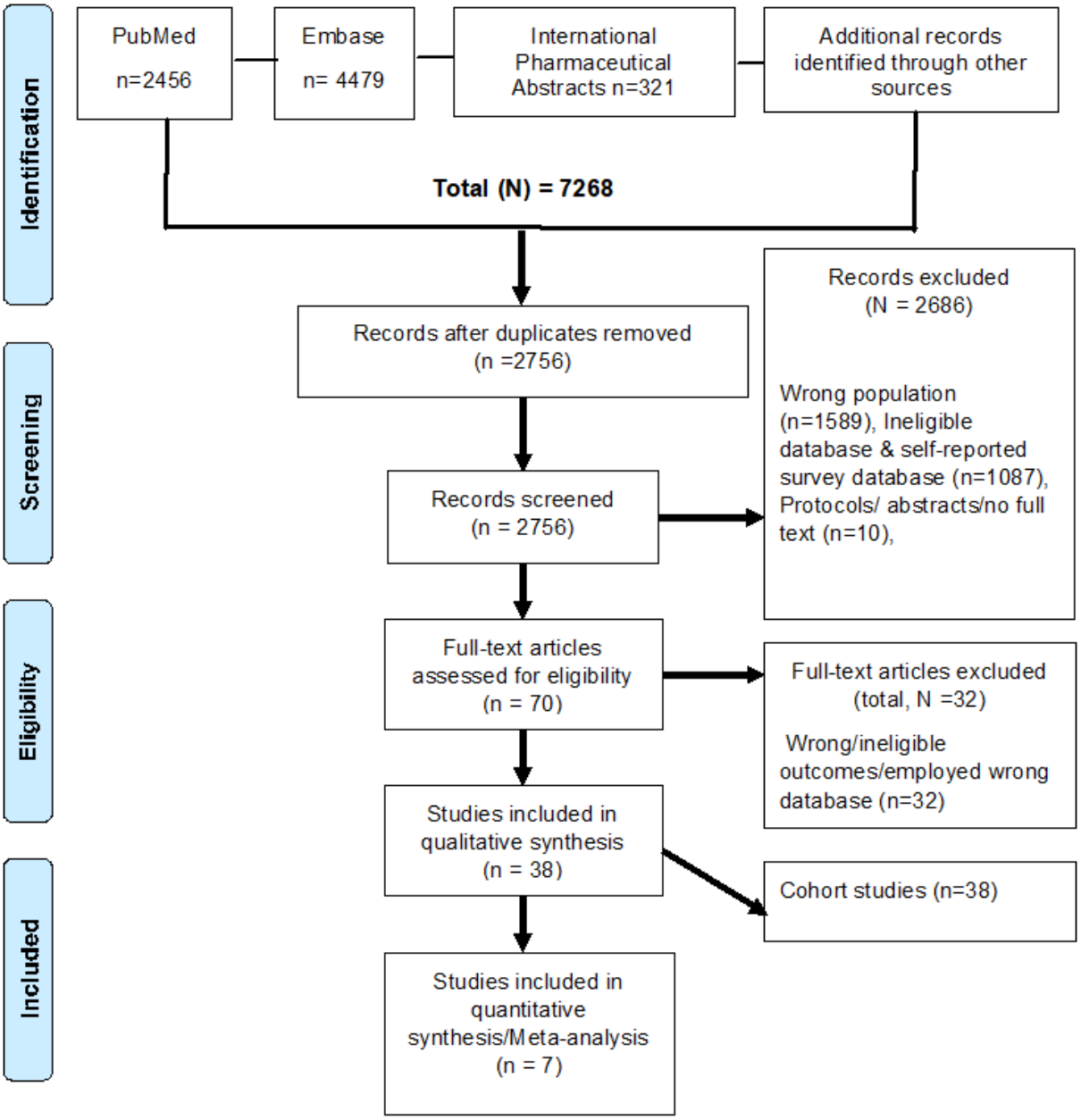


**Figure 5.1: Flow diagram depicting article inclusion and exclusion along with reasons**

### 5.5.1 Study characteristics

The general characteristics of the 38 included articles are presented in Table 5.1. Most of the studies (n = 33) were retrospective cohort studies with pharmacy claims data [167,186], [189,192], [82,100,101,198–223]. Three studies employed a retrospective design with prospective assessment [208,215,224], and two other studies conducted by Bidwal et al [190] and Vaidya et al [225]

were retrospective in design with cross-sectional assessment of medication adherence without follow up. All 38 articles were published between 2010 and 2020. More than half of the studies were conducted in North America (USA =23, Canada =5) [82,163,167,186,190,192,197,198,201,205,207–210,212–214,216–220,222–227]. The remaining articles were mostly performed in Europe (Netherlands =1, Denmark =1, Spain =2, United Kingdom (UK) = 8, Germany =1 and France =1), and one study was conducted in each of South Korea (n=1) and Australia (n=1) [101,102,189,201,203,205,209,213,216,217,223,224,228,229]. The study population consisted of 1,001,662 adolescents and adults with physician diagnosis of asthma in any population-based administrative database. More than one third (n=13) of studies observed adherence and clinical outcomes (i.e., asthma exacerbation, emergency room visits) simultaneously [82,167,186,188,189,198,200,204,208,218,220,221,224], while three studies assessed the association between medication adherence and cost of asthma [207,211,225]. The occurrence of the targeted clinical outcome was assessed from 12 months to 10 years.

Given this, the various asthma databases employed were of great interest in this review. As reported in Table 5.1, the majority of the administrative databases used were pharmacy claim databases capturing patients' medical records, prescription refills, and records of drugs dispensed. Notable among them were the pharmacy claim databases from the IQVIA™ Health Plan Claims Data, Danish Registry of Medicinal Product Statistics, HMO-claim records/database, Quebec Provincial Health Insurance administrative databases, *Maintenance et exploitation des données pour l'étude de la clientele hospitalière* (MED-ECHO), Québec prescription claims databases, *Optimum Patient Care Research Database* (OPCRD), Administrative insurance claims database, Medstat MarketScan database, and *Clinical Practice Research Datalink* (CPRD).

### 5.5.2 Measures of medication adherence

The assessment of medication adherence varied across studies. This review identified 20 different metrics used in measuring medication adherence in asthma patients. Some of the reported measures were MPR, PDC, *Continuous Measure of Medication Acquisition* (CMAq), *Proportion of Prescribed Days Covered* (PPDC); persistence with inhaled therapies; *Continuous Medication Availability* (CMA), refill Rate, annual *Prescription Possession Ratio* (PPR); *Group-Based Trajectory Modelling* (GBTM), and others (see Tables 6 and 7). The MPR and PDC were commonly reported as the primary measures of medication adherence. That is, approximately 87% of the included studies reported the use of both PDC and MPR as the main/primary metrics for asthma patients' medication adherence in the long term. Specifically, 20 studies (53 %) employed MPR, and 13 (34 %) used PDC as a measure of MA. The majority of studies chose a fixed time-frame for the refill interval rather than using the last refill as the endpoint for the refill interval and did not exclude the last refill in the estimation of MPR. Additionally, some studies [167,192,210,214,216,219] adopted multiple asthma adherence metrics (specifically: Med-Total & MPR; MPR & persistence; PDC & MPR; Prescription fills and PDC;. Refilling and PDC; and MPR & persistence metric). Modifications of the two commonly reported measures (MPR and PDC) were also reported. Blais et al., 2011 [100] developed the annual proportion of prescribed days covered (PPDC) method as a modification of the PDC measure. The PPDC can account for prescribing patterns used in the administrative databases. Several studies reported the continuous measure of availability as an adherence metric, which is an MPR calculated across multiple refills [200,230]. Hardstock et al., 2019 [223] and Visaria et al., 2012 [231] compared the weighted average MPR and adjusted MPR to other measures in identifying non-adherent asthma patients.

***Definition/equation of the adherence measures***

There was variation in the definition and calculation of the two commonly reported adherence measures, MPR and PDC. With regard to the MPR related measures, the denominator of the MPR formula varied from study to study. For instance, the majority of the studies estimated MPR as the sum of the days' supply for medication fills divided by the time from the first supply fill until the end of the measurement period [190,204,217,221]. Similarly, MPR was calculated in other studies as the sum of days of medication supply divided by the total time treated or evaluated [216,225]. Other adherence calculations of MPR adopted a fixed denominator within the year representing the days between the first and last refill. In a study by Martin et al. in 2013 [227], MPR was computed as the sum of the number of days' supply of inhaled corticosteroids (ICS) divided by 365 days and multiplying the overall expression by 100% to provide an adherence percentage value. Measures such as the Med-Total, *Medication Refill Adherence* (MRA), and *Continuous* (Multiple Interval Measures of) *Medication Availability* (CMA 4 and 7) used formulae similar to MPR definitions.

The MPR fixed interval is generally applied for assessing seasonal use of medication as well as for assessing medication use in patients with allergies [232]. The MPR takes a range of positive values from 0 inclusive through to "at least 1". A zero MPR denotes no adherence, while an MPR value of 1 measures optimal adherence. In some extreme cases, an MPR above one shows that the patient took more of the medication than was prescribed, while an MPR value below 1 indicates less than the prescribed amount of medication was taken within a specified period [233].

Similar to MPR, there were variations in the calculation of PDC-related measures in the majority of studies estimating the PDC as a quotient value of the days covered divided by the days in the measurement period. It was also estimated as the percentage of days a patient had access to medication depending on the amount of medication obtained. A fixed interval

PDC was calculated as the ratio of the number of days a patient had medication on hand to the total number of post-index days (i.e., 365 days) [163,186,192,199,202,206,210,212,213,215,219,220,223].

Three studies assessed medication adherence using the CMA measure with slight variations in formulae [188,203,208]. The CMA was calculated as the cumulative days' supply obtained over a series of intervals divided by the total days from the beginning to the end of the time period in the study. The overall average of all participants' CMA provided the adherence value of the entire period of the study and evaluates the relationship of adherence and drug effect. It has been suggested that the CMA and MPR as well as *Medication Refill Adherence* (MRA), provide identical adherence measuring power [188,203,208].

The AMR was calculated as the ratio of units of controller medication to the sum of units of controller medication and rescue medication. Two studies–Bidwal et al., 2017 [190] and Standford et al., 2019 [192] assessed medication adherence with the AMR metric and further evaluated the impact of treatment groups on adherence among adults with persistent asthma.

Six studies assessed persistence as another measure of medication adherence which was estimated as the total time between index treatment/date and time to discontinuation of the therapy [192,206,210,216]. Several variations in calculation of persistence were reported among included studies [167,192,203,206,210,216]. While drug persistence was calculated based on prescriptions filled within 30 days and between 31 and 180 days after the provision of prescription in some studies [203,206,216], others estimated persistence based on the absence of treatment gap '≥30' days [167]. Table 5.1 has a detailed description of the formulae and equations for the remaining adherence methods.

The Continuous, Multiple Interval Measure of Medication Gaps (CMG) measures were used in only one study [208] to assess the level of adherence and the impact of treatment on adherence. According to William and Colleagues, the CMG was obtained by dividing the total number of days in treatment gaps by the duration of the period of interest in order to

recognize any time intervals without drug exposure. Any negative value was set to 0. The CMG essentially calculates nonadherence values for cumulative periods without considering the possibility of early refill or overfill [188].

**Table 5.1: Summary of study findings**

| Author | Population (adolescent or adult asthma) | Study type | Name of administrative health database | Location | Outcome assessed/study objectives | Medication adherence/related measures | Definition of the measure/method | Strength and weaknesses/limitations of the measures | Estimated rate of adherence measured/study results |
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| Averell et al [212] | Patients with diagnosis of asthma 18 years and older initiating ICS/LABA therapy with FF/VI, B/F, or FP/SAL between January 1, 2014 and June 30, 2016. (n=3764+3339 = 7103). | Retrospective cohort study | Medical and Pharmacy claims data, and enrollment information from IQVIA™ Health Plan Claims Data | United States | The primary outcome was medication adherence. Secondary outcome included proportion of patients achieving PDC ≥0.5 and PDC ≥0.8 and persistence with index medication | PDC | PDC calculated based on dispensing data. Defined as the ratio of covered days of asthma medications to days in the measurement period. | 1) The use of claim for a filled prescription does not indicate confirmation of usage of the medication.<br>2) Also, the PDC does not include medication usage during inpatient visits. | The study found significantly higher mean PDC for FF/VI versus B/F (0.453 vs 0.345; adjusted p<0.001) and FP/SAL (0.446 vs 0.341; adjusted p<0.001). |

| Author | Population (adolescent or adult asthma) | Study type | Name of administrative health database | Location | Outcome assessed/study objectives | Medication adherence/related measures | Definition of the measure/method | Strength and weaknesses/limitations of the measures | Estimated rate of adherence measured/study results |
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| Backer et al [213] | Medical records of 300 patients referred with a suspected asthma during a one-year period. A total of 171 verified | Retrospective register-based study | Danish Registry of Medicinal Product Statistics (Collected one-year data on dispensed medicine). | Respiratory Outpatient Clinic at Bispebjerg Hospital, Copenhagen, Denmark. | Medication adherence/redemption. | Two measures were used.<br>1): Defined as a minimum of 2 redeemed prescriptions of controller medications prescribed by | PDC defined as the percentage of days a patient had access to medication based on the amount of medication collected, assuming daily use of medication was prescribed. The | Drug adherence could have been overestimated since dispensed medications used for PDC calculation does not necessarily indicate actual use of medication. | Using PDC, the study found a higher rate of adherence to ICS in the verified asthma group compared to the unverified asthma group |

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| | asthma cases were identified. | | | | | the outpatient clinic.<br>2): PDC | defined daily doses (DDDs) for each redemption was used for the calculation. | | (88% vs 30%, p=0.004). |
| Balkrishnan and Christensen [214] | The study included a total of 1595 older adults aged 65 years and older with chronic respiratory diseases including asthma with usage of inhaled corticosteroids for a period of 2 years. | Retrospective study | HMO-claim records/database (containing prescription refill records) | Seven states in the USA. | Long-term inhaled corticosteroid adherence | Three (3) Medication possession indexes; and a refill regularity measure namely:<br>1): Med-Total (proposed by Steiner et al<br>2): Med-Out<br>3): Suissa et al measure of regularity of inhaler refills<br>4) MPR | 1): Med-Total = (total number of days of drug supply dispensed) / (365-number of days hospitalized).<br>2): Med-Out = (Number of days without medication in the year) / (365−days hospitalized).<br>3): The third index was defined as the monthly cumulative proportion of canisters dispensed during that 12-month period for each subject. | 1): The Med-Total may be may not be sensitive to episodic variations in obtaining medications.<br>2): Studies has documented that Med-Out index is more strongly associated with therapeutic outcomes. | |
| **Author** | **Population (adolescent or adult asthma)** | **Study type** | **Name of administrative health database** | **Location** | **Outcome assessed/study objectives** | **Medication adherence/related measures** | **Definition of the measure/method** | **Strength and weaknesses/limitations of the measures** | **Estimated rate of adherence measured/study results** |
| Bidwal et al [190] | A total of 121 adult persistent asthma patients receiving medication refills were included. | Retrospective study from cross-sectional data. | Electronic chart review was adopted to extract patients' data who obtained asthma medication from Community | USA | Medication adherence rates: strategies to improve adherence. | 1): MPR for asthma controller medications. MPR threshold used were: Medium-high (MPR>=0.5), Low | 1): MPR = calculated as the sum of the days' supply for medication fills divided by the time from first supply fill until the end of the measurement | The MPR which is a secondary measure of adherence cannot be used to confirm whether patients actually used their prescribed inhalers | The study found full adherence rate among individuals as 8.3%. Nonadherence rate was 66.1%. |

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| | | | Health Clinic Ole. | | | (MPR<0.5). Full or optimal medication adherence (MPR>=0.8). 2): Asthma medication ratio (AMR). If an AMR >=0.5, then it means that there is an indication of a therapeutic effect and adequate control in asthma patients. | period. The Medication day supply= calculated for each medication based on dispensed quantity and prescription directions. The authors used SAS software to compute MPR. 2): AMR= sum of controller medications dispensed divided by the sum of the controller medications and short-acting beta-2 agonists dispensed. | with precise technique. | |
| **Author** | **Population (adolescent or adult asthma)** | **Study type** | **Name of administrative health database** | **Location** | **Outcome assessed/study objectives** | **Medication adherence/related measures** | **Definition of the measure/method** | **Strength and weaknesses/limitations of the measures** | **Estimated rate of adherence measured/study results** |
| Blais et al [100] | A cohort of 4190 ICS-naive patients with diagnosis of asthma aged 18-45 years were eligible. | Retrospective cohort study. | Two administrative health databases of Quebec (the Regiedel'Assurance Maladie du Quebec (RAMQ) and the Maintenance et Exploitation des Donnees pour l'Etude de la Clientele | Canada | To develop a new measure of patients' adherence | Proportion of prescribed days covered (PPDC). PPDC is a modification of PDC. | PPDC defined as the ratio of the total days' supply dispensed to the total days' supply prescribed during the study period. | 1): The PPDC could be used to account for the non-adherence attributed to patients when measured with PDC which could be as a result of non-prescribing of ICSs for daily use. The PPDC also account of differing | During a one-year study, the mean PPDC and PDC were 52.6% and 18.1% respectively. |

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| | | | Hospitaliere (MED-ECHO) | | | | | prescribing patterns.<br>In other words, the PPDC adjust for prescribing patterns used in administrative databases.<br>2): Using PDC to measure adherence has been documented to be very low among patients with asthma (low as 30%). | |
| **Author** | **Population (adolescent or adult asthma)** | **Study type** | **Name of administrative health database** | **Location** | **Outcome assessed/study objectives** | **Medication adherence/related measures** | **Definition of the measure/method** | **Strength and weaknesses/limitations of the measures** | **Estimated rate of adherence measured/study results** |
| Blais et al [226] | Data for 1108 ICS original prescription stored in the 40 pharmacies and a second sample of 2676 ICS prescriptions from reMed (medication registry) were collected. | Retrospective study. | Québec prescription claims databases for inhaled corticosteroids. | 40 community pharmacies in Québec, Canada. | To evaluate the accuracy of the days' supply & number of refills allowed, develop correction factors and used in medication adherence calculation. | Concordance for days' supply, concordance for the refills allowed. | | NR | There was a moderate accuracy in terms of the days of supply among those aged 0-11 years, while a substantial accuracy was recorded among those aged within 12-64 years. |
| Blais et al [215] | Included both 198 children and 208 | Retrospective and prospective study. | Registre de données en Santé Pulmonaire or | Québec, Canada. | Assessing adherence to | 1): Primary adherence metric | Primary adherence = filling the ICS prescription at a | The use of PDC as a unique measure could lead to | Using PDC adherence in adults was |

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| | adults with one ICS prescription in their medical chart between 2010 and 2012. Focus will be on the 208 adults. | | RESP), the BioBank (PADB), the Régie de l'assurance-maladie du Québec (RAMQ) Medication Prescriptions database, and the reMed (Registre de données sur les médicaments) database. | | inhaled corticosteroids | 2): Secondary adherence metric was based on PDC in subjects who filled at least one prescription. | pharmacy within 12 months. | substantial overestimation in adults. An integrated measure of primary and secondary are recommended. | found to be 36.6% compared to adherence rate of 52.8% when a primary adherence metric is used. |
| **Author** | **Population (adolescent or adult asthma)** | **Study type** | **Name of administrative health database** | **Location** | **Outcome assessed/study objectives** | **Medication adherence/related measures** | **Definition of the measure/method** | **Strength and weaknesses/limitations of the measures** | **Estimated rate of adherence measured/study results** |
| Covvey et al [216] | The study included Patients with physician Diagnosed asthma or COPD who received inhaled therapy (10,177 patients with asthma were included). | A retrospective study | A prescribing database from the National Health Service (NHS) Forth Valley Airways Managed Clinical Network in coordination with the E-PRS clinical recording tool program (Campbell Software Solutions©, Irvine, UK) | NHS Forth Valley Scotland, UK | Compare adherence and persistence with inhaled therapies in patients with asthma and COPD | MPR; Persistence with inhaled therapies. | 1): MPR = the sum of the days of medication supply provided divided by the total time treated. Mathematically, MPR= (*total days of medication supply*) ÷ (*Days between first and last fills*) ×100%. 2): Persistence was determined by employing the Kaplan-Meier survival analysis for | NR | Overall median TTD was 90 days (IQR: 50-184 days) for patients with asthma and 115 days (58-258 days, comparison $p<0.001$) for patients with COPD |

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| | | | | | | | time to discontinuation. | | |
| Darba' et al [217] | The authors reviewed the medical registries of asthma patients treated with ICS/LABA totaling (n=2213) | A retrospective and multicenter study | Medical registries of asthmatic patients (Pharmacy administrative database and clinical visit data from electronic asthma patient records) | Badalona Serveis Assitencials, Barcelona, Spain | Asthma medication compliance | MPR | MPR was defined as the ratio of the number of days supplied for a given medication to that of the number of days in the study and persistence data. | MPR has been documented to be biased upwards (Price 2013; WHO 2003). The authors tried to correct the bias by elevating the cut-off point so that few patients will be seen as compliant with their medication. | |

| **Author** | **Population (adolescent or adult asthma)** | **Study type** | **Name of administrative health database** | **Location** | **Outcome assessed/study objectives** | **Medication adherence/related measures** | **Definition of the measure/method** | **Strength and weaknesses/limitations of the measures** | **Estimated rate of adherence measured/study results** |
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| D'Anconna et al [224] | Ninety-one (91) severe eosinophilic asthma (SEA) patients [with mean age of 53.7] were included. | Retrospective assessment, & prospective follow-up. | NHS sources including Summary Care Records, Local Care Records, GP recording system, and hospital pharmacy dispensing system. | UK | ICS adherence and clinical outcomes in SEA patients | MPR | MPR = the number of doses of ICS issued on prescription divided by expected number. Good adherence was defined as MPR>0.75, Intermediate adherence (MPR: 0.74-0.51) and poor adherence <MPR=0.5 | MPR is expressed as a function of prescription issued and hence it does not measure directly whether the medication was use or not. This is likely to overestimate ICS use. The adherence cut-off rate adopted was arbitrary although consistent with other studies. | The study found 68% of the patients with good ICS adherence use and 18% with poor ICS adherence. There was a greater reduction in oral corticosteroids (OCS) dose among patients with good adherence. |

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| Delea et al [218] | The study included 12907 patients (mean age=40 years) with two prescriptions of FSC and diagnosis of asthma. | Retrospective longitudinal analysis | PharMetrics Patient Centric Database | USA | Assessing the association between adherence with fluticasone propionate/salmeterol combination (FSC) | MPR | MPR was estimated as the ratio of the total number of 'covered days' during the 'treatment period' to the number of days in the treatment period. | NR | Achieving each 25% improvement in adherence was associated with a 10% reduction in the odds of asthma-related ED visit after adjusting for baseline factors. |
| Feehan et al [219] | The study examined 2193 patients who received controller medications for managing asthma in a 12-month duration including their refill data. | Prospective cohort study | Community pharmacy dispensing database | Utah, USA | Level of adherence to controller asthma medications | PDC, MPR (standard cut-offs of ≥80% medication availability) | PDC, MPR | | Approximately 14-16% of the patients had satisfactory adherence over the 6-month follow-up after employing the standard cut-offs of ≥ 80%. |
| Friedman et al [186] | The study analyzed and included 692 eligible adults and young adults aged 12-25 years with diagnosis of mild asthma from the database and | A retrospective claims analysis | Administrative insurance claims database | United States | Adherence and asthma control | 1): Adherence measured by prescription fills and PDC. Refilling prescription on or before the scheduled medication to run out records PDC =1. Inability to | 1): Prescription fills: The total number of prescriptions fills during the post-index period. *PDC*: was calculated by dividing the number of days patients had medication on hand by the total number of post-index days, | In calculating Medication Adherence using medical pharmacy records, it is difficult to verify whether or not medication was taken by the patient as prescribed. | During the post index period, compared to the Fluticasone propionate (FP), adherence was significantly higher in the Mometasone furoate delivered |

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| | assigned an index date based on their first prescription fill. | | | | | refill prescription as scheduled records PDC<1. 2): Asthma control was measured by exacerbations short-acting β2-agonist (SABA) canister claims. | which in this case was 365 days. 2): Asthma exacerbations*:* an asthma episode that required hospitalization, treatment in an emergency room, or an outpatient visit in which patients received nebulized medication or a prescription for oral corticosteroids 3): Asthma control: the study measured this by evaluating exacerbations and SABA canister claims. | However, this approach of adherence using the claim approach is objective and could be more representative of the "real-world" than other measures. | through a dry powder inhaler (MF-DPI) cohort ((23.5% vs. 14.5%; p < .0001) and prescription fills (2.70 vs. 1.91; p < .0001). |
| **Author** | **Population (adolescent or adult asthma)** | **Study type** | **Name of administrative health database** | **Location** | **Outcome assessed/study objectives** | **Medication adherence/related measures** | **Definition of the measure/method** | **Strength and weaknesses/limitations of the measures** | **Estimated rate of adherence measured/study results** |
| Gelzer et al [220] | The study included 3589 Medicaid members claims that have a primary diagnosis of asthma (ICD-9, 493.xx) and prescription | Two arm retrospective cohort study with one year follow-up. | Database of Medicaid members with primary diagnosis of asthma. | Two Pennsylvania-based AmeriHealth Caritas MCOs (SEPA and Lehigh-Capital/New West Pennsylvania [LCNWPA]) | Effect of interventions on medication adherence and hospitalization rates. | Proportion of days covered (PDC) | PDC is the quotient value of the covered days of asthma medication divided by the days in the measurement period. PDC, with low adherence threshold was (0.20-0.67). | PDC report a more conservative estimate of MA than other measures such as MPR in cases where concomitant multiple medications are used. 2) Avoidance of double counting of | Significant improvement in mean PDC rate in both cohorts (+4.9% and +7.2%; p=0.01and p=0.03, respectively. |

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| | fills for asthma controllers. | | | | | | | days of medication coverage. | |
| Guo et al [221] | The authors selected a total of 299,917 patients with moderate or severe asthma. | A retrospective study | MarketScan Multistate Medicaid database from 2002 to 2007 | USA | ICS/LABA medication compliance | ICS-and-LABA MPR | ICS-and-LABA MPR: The sum of day' supply for ICS and LABA drugs divided by the number of follow-up days during the first year after the patient's asthma index date | NR | Average MPRs were 0.23 (median 0.14) for ICSs and LABAs and 0.66 (median 0.46) across all asthma medications within 12 months after asthma index date. |
| Hagiwara et al [222] | The study included eligible 18283 patients with an asthma using the ICD-9-CM diagnostic code and 2 or more fluticasone propionate100µg and salmeterol 50µgvia Diskus (FSC) or mometasonefuroate (MF). | A retrospective cohort study | IHCIS National Managed Care Benchmark Database (Large health insurance claims dataset from January 2004 to December 2008). | USA | Risk of asthma exacerbation; asthma-related health care utilization and costs; adherence to controller therapy. | MPR and refill rates were used to measure adherence to controller therapy. | 1): MPR: calculated as the sum of the number of therapy-days supplied on all FSC 100/50, MF110 or MF220 dispensed from the index date to the end the follow-up period divided by the sum of the number of days between the first and last such prescription during follow-up and the number of days on the last such prescription.<br>2): The refill rate: the number of prescriptions for | Estimate of MPR could be bias (downwardly or upwardly bias) if the patients were instructed to use their medications at a different dosage than implied by the days and quantity supplied information on each claim. | For adherence to ICS therapy, using MPR, the adherence rate for FSC was 27.2% compared to 21.1% in MF. For adherence using the refill rate per year, the adherence rate for FSC was 2.9% compared to 3.1% in MF. |

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| | | | | | | | FSC 100/50, MF 110, or MF 220 dispensed from the index date to the end of the follow-up period divided by the duration of follow-up. | | |
| Hardstock et al [223] | A total of 406 patients with asthma were included in the study with mean age pf 55.48 years | A secondary data analysis/retrospective study. | Primary data collected over 12 months linked to patient-specific claims data (AOK PLUS database). | Germany | The impact of a specific method for measure patients' non-adherence. | Non-adherence (NA) was measured by:<br>1): MPR<br>2): Weighted average MPR across different agents.<br>3): PDC (PDC: day covered if at least one medication was available). | MPR, PDC | NR | The selection or the use of a particular method to measure adherence based on prescription data has a significant effect on the study results. |
| **Author** | **Population (adolescent or adult asthma)** | **Study type** | **Name of administrative health database** | **Location** | **Outcome assessed/study objectives** | **Medication adherence/related measures** | **Definition of the measure/method** | **Strength and weaknesses/limitations of the measures** | **Estimated rate of adherence measured/study results** |
| Ismaila et al [167] | A total of 19,126 patients, age 12 years with diagnosis of asthma between 2001 and 2010. | Observational single cohort study | Quebec Provincial Health Insurance administrative databases (Re ´gie de l'Assurance Maladie du Que ´bec, RAMQ). | Quebec, Canada | Assessing long term association between adherence and risk of exacerbations. | Adherence measured by: MPR, with cut-off ≥0.80; and persistence (absence of treatment gap ≥ 30 days). | 1): MPR: calculated as the percentage of days covered by the medication during the follow up period. Compliance was defined as MPR ≥ 80% and non-compliance as MPR <0.80.<br>2): Persistence was defined as having | The use of the MPR and persistence measures does not guarantee whether patients actually took their medications. | There was significant reduction in the adjusted odds of exacerbation for the compliant patients and persistent patients. |

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| | | | | | | | prescriptions of the ongoing therapy continuously renewed without a gap of more than 30 days. | | |
| Kang et al [189] | A total of 22130 adult asthma patients were eligible for inclusion. | Nationwide population-based observational study | Korean National Sample Cohort database | South Korea | Asthma exacerbation, associated with many risks' factors | MPR | MPR used in the study | NR | High MPR (MPR ≥ 0.50), compared to low MPR (<0.20) showed adjusted ORs of 0.828 (95% CI 0.707 to 0.971) and 0.362 (0.185 to 0.708) in moderate and severe asthma, respectively. |
| Kellow ay et al [198] | The study included 59 patients with mean age 46.7, with diagnosis of asthma. | A retrospective medical chart and pharmacy claims record review | Pharmacy claims data | Minnesota, USA | Effects of addition of salmeterol to a medication regimen on patient adherence. | The rate of adherence for inhaled corticosteroids alone, salmeterol alone, and both salmeterol and ICS were calculated as using % adherence method. | % Adherence = (Medication refilled /Medication prescribed) ×100% | NR | The addition of salmeterol to the ICS did not affect adherence rates to prescription refills for prescribed ICS therapy. There was a higher rate of adherence to salmeterol than ICS at baseline (58.7%±28.3%) |

| Author | Population (adolescent or adult asthma) | Study type | Name of administrative health database | Location | Outcome assessed/study objectives | Medication adherence/related measures | Definition of the measure/method | Strength and weaknesses/limitations of the measures | Estimated rate of adherence measured/study results |
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| Makhinova et al [202] | A total of 32172 patients with a primary diagnosis of asthma. | A retrospective study | Texas Medicaid claims data | Texas, USA | Adherence to asthma controller medication, risk of exacerbation, and use of rescue agents. | PDC | PDC to asthma long-term controller medication. PDC cut-off used (PDC≥0.80, PDC≥0.70, PDC≥0.60, PDC≥0.50). | NR | Compared to the non-adherent patients (PDC<0.50), patients who were adherent to the medications (PDC≥0.50) were 1.967 times more likely to have ≥ SABA claims. |
| Navaratnam et al [199] | 16,063 asthma patients (aged 12-65 years) who initiated treatment with Mometasone furoate (MF) or fluticasone propionate (FP) formed the study population. | A retrospective study | Pharmacy claims database from a commercial insurance database | USA | Adherence to MF or FP, mean number of exacerbations, and asthma exacerbation incidence | PDC was used to measure adherence during post-index. | PDC | NR | NR |
| **Author** | **Population (adolescent or adult asthma)** | **Study type** | **Name of administrative health database** | **Location** | **Outcome assessed/study objectives** | **Medication adherence/related measures** | **Definition of the measure/method** | **Strength and weaknesses/limitations of the measures** | **Estimated rate of adherence measured/study results** |

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| Papi et al[200] | Asthma patients (n=7195) aged 18 years and older with 2 or more ICS prescriptions were identified from the OPCR database. | Historical cohort study | Optimum Patient Care Research (OPCR) Database and the initiative Helping Asthma in Real People (iHARP) database. | UK (England, Scotland, Wales, and Northern Ireland). | Relationship between ICS nonadherence and asthma exacerbation. | MPR | MPR: the number of ICS prescriptions issued divided by the expected number of ICS prescriptions (based on prescribed ICS dose), MPR>0.80 is considered adherence to ICS therapy. | These researchers have demonstrated that a wide variety of cut-off values for definition of medication adherence have been employed, the cut-off of MPR>80% has been employed as an arbitrary standard threshold in the respiratory literature. | Patients who adhered to ICS therapy was not associated with decrease exacerbations of asthma. |
| Sicras-Mainar et al [201] | 2303 confirmed diagnosed asthma patients 15 years and older who initiated ICS treatment. | An observational, retrospective study | Electronic medical records of the Badalona Health Service provider | Barcelona, Spain | To estimate adherence to asthma treatment with inhaled corticosteroid. | MPR, MPR ≥80%, = adherent MPR, MPR<80% = MPR nonadherence | MPR ≥0.80, = adherent MPR, MPR<0.80 = MPR nonadherence | NR | 51.0% of patients adhered to treatment. |
| Souverein et al [203] | Individuals with physician diagnosed asthma who had initiated ICS therapy. In all, a total of 13,922 eligible patients (mean age, 39.9 years) | A historical cohort study | Optimum Patient Care Research Database (OPCRD) | UK | ICS adherence pattern. The primary outcome was EMR-based ICS adherence estimated by continuous medication availability (CMA). | Treatment episode length (persistence) and Continuous Medication Availability (CMA1) implementation . The threshold for CMA1 for adherence was CMAI ≥ 0.80, | 1): Treatment episode: defined as a series of successive ICS prescriptions irrespective of switching between different products and changes in dose. 2): CMA implementation: CMA1 (the first method) is also called the PDC | NR | Results not specifically related to rate of adherence or non-adherence. |

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| | were identified | | | | | and CMA II ≥0.80. | which does not take into account the period between the start of the window to the first dispensing or prescription within the window. The CMA II, the second method considers the effect into the observation window as well as carryover within the window and the remaining surplus at the end. | | |
| **Author** | **Population (adolescent or adult asthma)** | **Study type** | **Name of administrative health database** | **Location** | **Outcome assessed/study objectives** | **Medication adherence/related measures** | **Definition of the measure/method** | **Strength and weaknesses/limitations of the measures** | **Estimated rate of adherence measured/study results** |
| Standford et al [192] | A total 9951 adult asthma patients 18 years and older with at least 15-month continuous enrollment were identified. | A retrospective cohort study | Optum Research Database, a proprietary research database containing enrollment, medical, and pharmacy claims data | USA | Comparing asthma patients' measures of adherence, persistence, and the asthma medication ratio (AMR). | 1): PDC-adherence measure (mean PDC≥0.5; PDC≥0.8<br><br>2): Persistence and AMR. | 1): PDC = (total number of days of medication availability based on filled prescription) ÷ (Length of each subject's observation period).<br><br>2): Persistence: The total time between the index treatment/date and the time to discontinuation of the therapy. | NR | A significant proportion of patients on FF/VI achieved a PDC ≥0.5 |

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| | | | | | | | PDC: used a proxy measure to measure adherence. | | |
| Stern et al [204] | A total of 97743 asthma patients and with controller medication prescriptions with mean age of 32.8 years were identified and included. Number of patients in the adult age category (18-64) years was n=61,238 and the elderly (65 +) was n=3316. | A retrospective cohort study analysis | PharMetrics database (contains a nationally representative health and billing information) | USA | Examining the association between medication compliance and exacerbation in asthmatic patients | MPR (using the 75$^{th}$ percentile of MPR as the cut-off for adherence), and number of prescriptions for each index medication. MPR was used as a proxy for compliance.<br><br>Additional cut-off points: patients with at least 2 prescriptions were classified as more compliant than compared to patients with only 1 prescription. | MPR = (the number of days supplied for a particular medication) ÷ the number of days in the study. For maximum MPR, MPR=1 or 100%.<br><br>This measure provides information whether the patient is using the right number of medications in a specified time frame. | Researchers indicated that the use of MPR and refill rates as a measure for adherence may reflect appropriate use of inhaler medications.<br><br>A limitation with the use of MPR is that it makes it impossible to be able to determine with certainty whether the patients were taking their medications as prescribed in the appropriate timely fashion. | The study found more compliant patients as having lesser likelihood of experiencing exacerbation. |
| Svedsater et al [206] | A total of 4327 adult asthma patients initiating FF/VI and BDP/FM were eligible for inclusion | A retrospective cohort study | Health Improvement Network (THIN) database | UK | Primary objective was to compare persistence of ICS/LABAs. Secondary objectives were: PDC and proportion of patients with | PDC and persistence | PDC and persistence | NR | Median (interquartile range) PDC was 89.2 (61.6–100.0) for FF/VI and 75.9 (50.5–98.0) for BDP/FM ($p<0.0001$) |

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| | into the study population. | | | | PDC ≥0.50 and ≥0.80 | | | | |
| Taylor et al [205] | The study included 292,738 asthma patients aged between 12 and 65 years from the period 1997 to 2010. | A retrospective cohort study | Clinical Practice Research Datalink (CPRD) database | UK | Developing annual measure of asthma patients' adherence to ICS use | Adherence to ICS was measured by the annual prescription possession ratio (PPR) | PPR = (Number of days prescribed during calendar year) ÷ (Number of days in the interval) × 100 | The PPR employed the prescribing data which makes it difficult to interpret the accuracy of the measure. However, the precision of this metric appeared to be good. The authors concluded that the PPR should be used with caution to determine the actual levels of medication adherence in asthma patients. | The PPR is useful in measuring changes in adherence over time. |

| **Author** | **Population (adolescent or adult asthma)** | **Study type** | **Name of administrative health database** | **Location** | **Outcome assessed/study objectives** | **Medication adherence/related measures** | **Definition of the measure/method** | **Strength and weaknesses/limitations of the measures** | **Estimated rate of adherence measured/study results** |
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| Vaidya et al [225] | The study included 277 patients, 18 years and older with persistent asthma | A retrospective, cross-sectional study | Medical Expenditure Panel Survey (MEPS) 2013–2014 data | USA | Determining racial and ethnic disparities with the adherence to inhaled corticosteroids (ICSs) in adults with persistent asthma | Median MPR was used to dichotomize adherence levels | MPR was defined for each patient as the total number of supply divided by the total number of days evaluated. The median MPR was used to categorize adherence into two levels. Asthma patients with adherence levels | Using this metric, researchers were unsure or not able to confirm whether patients used their prescribed medication received as expected. There could be instances where patients filled their | The study showed average MPR level as 0.33 among the white race, 0.37 among the African Americans, and the rate among the minorities was 0.35. |

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| | | | | | | | below the median MPR cut-off were non-adherent to ICS, MPR levels above the median MPR were considered adherent to ICS. The median MPR was 0.25. | medications but did not take them as recommended by their health care provider. | |
| Vaidya et al [207] | A total of 1447 asthma patients with mean age of 32.27 years were included | A retrospective cohort study (with follow-up) | Medstat MarketScan databases (containing paid medical and prescription drug claims for privately insured patients) | USA | Adherence to controller drugs | MPR | MPR calculated as the number of days of a given medications supplied divided by the number of days in a specified time frame. The authors computed the MPR for dual-controller medications by finding the average MPR values for individual controller medications (ICS and LABA or LTRA). The median MPR was set as the cut-off point to categorize patients into either more adherent group or less adherent group.<br><br>This study computed MPR by dividing the number of the number of days of medication | There is no ideal threshold for measuring adherence to prescription medications in the literature. An arbitrary threshold of MPR (0.7 or 0.80) has been used by many researchers in the literature. Using the median as the cut-off point could avoid variation in the results when different thresholds are used. | A significant association was observed between increasing risk of non-adherence to medications and increased level of cost sharing among asthma patients on dual-controller medications. |

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| | | | | | | | supply during the 6-month follow-up period by 180. | | |
| **Author** | **Population (adolescent or adult asthma)** | **Study type** | **Name of administrative health database** | **Location** | **Outcome assessed/study objectives** | **Medication adherence/related measures** | **Definition of the measure/method** | **Strength and weaknesses/limitations of the measures** | **Estimated rate of adherence measured/study results** |
| Van Boven et al [101] | A total of 3062 new users of ICS/LABA FDC with diagnosis of asthma were identified. | A retrospective cohort study | Australia subsidized via the national Pharmaceutical Benefits Scheme (PBS) database | Australia | Trajectory analyses of adherence patterns in asthma patients | Group-based trajectory modeling (GBTM) | Patients' adherence to ICS/LABA FDC was estimated using the GBTM over 1 year duration from index-date. The GBTM first identifies clusters/groups of asthma individuals with similar trajectories (e.g., Dispensing patterns) using maximum likelihood method. | The GBTM is an alternative method to PDC, and it overcome the limitations of PDC of being unable to provide information about the longitudinal course of adherence to treatment over time. | For adherence trajectories, the rate of non-persistent use was 20%, seasonal use was 8%, poor adherence was 58% and good adherence was recorded as 13%. |

| **Author** | **Population (adolescent or adult asthma)** | **Study type** | **Name of administrative health database** | **Location** | **Outcome assessed/study objectives** | **Medication adherence/related measures** | **Definition of the measure/method** | **Strength and weaknesses/limitations of the measures** | **Estimated rate of adherence measured/study results** |
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| Vervloet et al [209] | A total of 10472 asthma patients were included | A retrospective study | Optimum Patient Care Research Database (OPCRD) | UK | investigating the relationship between ICS implementation and asthma-related outcomes over 2 years | ICS implementation /adherence | ICS implementation defined as the percentage of days covered by the prescription on the basis of quantity, dosage and duration | ICS implementation ranges from 1% to 99% | ICS implementation in the preceding interval was not predictive of risk domain asthma control. |
| Williams et al [208] | A total of (9706 BFC and 27975 FSC) asthma | A retrospective analysis | HealthCare Integrated Research Database | USA | Evaluating the association between patients' adherence to prior | MPR (the study assessed MPR for monotherapies | A composite weighted MPR measure was computed ranging | | Adherence to previous use of controller therapy was |

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| | patients aged 12-64 years with 1 or more pharmacy claim for ICS/LABA were included. | | | | asthma controller medication and choice of therapy initiation. | such as ICS, LABA, leukotriene receptor antagonist [LTRA], theophylline, omalizumab), and combination therapies (ICS+LABA, ICS+LTRA, and LABA+LTRA) | from 0 to 1 based on the percentage of time each medication was used. MPR>0.80 indicated patients' adherence to the therapy, | | similar between the two groups. |
| **Author** | **Population (adolescent or adult asthma)** | **Study type** | **Name of administrative health database** | **Location** | **Outcome assessed/study objectives** | **Medication adherence/related measures** | **Definition or formulae of the measure** | **Strength and weaknesses/limitations of the measures** | **Estimated rate of adherence measured/study results** |
| William [230] | 298 participants aged 12-56 years (mean age=34.5) in the Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race ethnicity (SAPPHIRE). | A prospective asthma cohort study/retrospective study | Data from SAPPHIRE study linked with Pharmacy claim data | USA | Measuring changes (ICS) adherence over time | MPR related measure. More than (MPR>0.75) was associated with reduction in exacerbation. | Estimated as the cumulative days' supply divided by the number of days of observation (i.e., a moving 6-month observation period for the current study). | Their method accounted for (prorated) prescription refills. This is because prescription refills partially overlapped with the beginning and end of each observation period and incorporated when a medication was discontinued by a physician. | Achieving more than 75% adherence was associated with reduction in exacerbation. An estimated 24% of asthma exacerbations were attributable to ICS medication non-adherence. |

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| Woodcroft et al [82] | The study identified and included 5256, with persistent asthma patients with mean age of 30.4. | A retrospective study | Integrated Healthcare system database | Detroit, USA | Assessing adherence to ICS±LABA and rate of exacerbations | PDC; Exacerbation: defined as oral corticosteroids fill dispensed within 2 weeks after primary diagnosis of asthma. | PDC | NR | The study found adherence rate to ICS ±LABA to be low with high rate of exacerbations. |
| Wu et al [210] | The study included 69652 patients with persistent asthma with mean age of 37 years. | A retrospective cohort study | Population Based Effectiveness in Asthma and Lung Diseases (PEAL) Network | USA | Comparing adherence to controller medications for asthma | Four (4) measures of adherence on each of ICS, LTRA, ICS/LABA were studied.<br>1): Primary adherence<br>2): early-stage persistence<br>3): adjusted PDC (dichotomized as PDC<0.75, and PDC ≥0.75)<br>4): Mean adjusted PDC | 1): Primary adherence: Was determined whether or not the prescription was filled within 30 days.<br>2): Prescriptions filled within 30 days and between 31 and 180 days after provision of prescription.<br>3) Adjusted PDC which employed the use of an index date based on the date of the first prescription than the date of the fill. | 1): The authors employed a combined data on prescriptions from providers and fills to determine what they claim as a more accurate measure of adherence rather than using only medication dispensing data.<br><br>2): One common limitation was the fact that all the adherence metrics were based on an electronic and hence makes it difficult to determine whether individuals took their dispensed medications. | Using PDC as a measure, the study recorded improved adherence for LTRAs and ICS/LABAs than using ICSs. |
| Zhang et al [211] | The study population | Observation cohort study | Quebec Health Insurance | Quebec, Canada | Impact of adherence and | Overall MPR (MPR ≥0.80) | Overall MPR | NR | For every year, the non- |

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| included 9716 patients 12 years and older (mean age =47.09 years) with diagnosis of asthma and severe asthma. | administrative databases | exacerbation frequency on health care utilization and direct cost | adherent patients' healthcare was more costly than the adherent patients. |

**Table 5.2: Distribution of the adherence metric reported by the included studies**

| ID | Adherence metric & related measures | Number of studies | Reference |
|---|---|---|---|
| 1 | Medication Possession Ratio [MPR] (weighted average MPR, adjusted MPR, MPR using CMAq4 & CMAq 7) | 22 | 167,189,190,200,201,204,207,208,211,214,216,217,219,221,223–225,227–229,231 |
| 2 | Proportion of days covered [PDC]- (mean adjusted PDC, adjusted PDC) | 14 | 82,163,186,192,199,202,206,210,212,213,215,219,220,223 |
| 3 | Medication total [Med-Total] (proposed by Steiner et al) | 1 | 214 |
| 4 | Medication Out [Med-Out] | 1 | 214 |
| 5 | Suissa et al measure of regularity of inhaler refills | 1 | 214 |
| 6 | Continuous Measure of Medication Acquisition (CMAq7), CMAq4], [CMAq7] | 1 | 102 |
| 7 | Asthma medication ratio (AMR) | 2 | 190,192 |
| 8 | Proportion of prescribed days covered [PPDC] | 1 | 100 |
| 9 | Concordance for days' supply | 1 | 226 |
| 10 | Concordance for the refills allowed | 1 | 226 |
| 11 | Monthly cumulative proportion of canisters dispensed | 1 | (196) |
| 12 | Persistence with inhaled therapies/ Early-stage persistence (i.e., Length of treatment episode) | 6 | 167,192,203,206,210,216 |
| 13 | Refill rate | 1 | 222 |
| 14 | Percentage (%) adherence method | 1 | 198 |
| 15 | Continuous Medication Availability [CMA] | 1 | 203 |
| 16 | Annual prescription possession ratio (PPR) | 1 | 205 |
| 17 | Group-based trajectory modeling [GBTM] | 1 | 101 |
| 18 | ICS implementation/adherence | 1 | 209 |
| 19 | Primary adherence metric | 2 | 210,215 |
| 20 | Prescription fills | 1 | 186 |

***Adherence measures and cut-off value (threshold)***

In this review, studies used various cut-off values or thresholds to estimate the level of medication adherence among adolescents and adults. For MPR, the cut-off values or thresholds for good/high medication adherence ranged from '> 0.75 to >1.00' (See Table S5.9 in the supplementary material). Adherence metrics identified in this review were commonly categorized into two or more levels during assessment and for testing associations with study outcomes. The cut-offs or thresholds distinguishes adherence from suboptimal adherence. Categorizing adherence metrics into two distinct levels (adherence vs. non-adherence) was observed in most of the studies. Among studies that dichotomized adherence score, ten (10) assessed adherence using MPR, seven (7) with PDC, two (2) assessed adherence with AMR and one (1) employed the CMA measure. An arbitrary cut-off value or threshold of '≥ 0.80' was commonly employed in most of the studies for both MPR and PDC [167,190,200,201,208,211]. The adherence cut-off value for the AMR measure reported in this review was >0.50 [190,192]. Four studies categorized adherence metrics into three or more categories. They were either categorized based on arbitrary cut-offs/thresholds or around suitable quintiles of the adherence scores. A study by Bidwal et al., 2017 [190] set the cut-off point for good adherence at MPR ≥ 0.80, medium at MPR ≥ (0.5-0.80), and low at MPR <0.5, whereas D'Ancona et al.'s 2020 [224] study used the following adherence levels: good adherence (MPR > 0.75), intermediate (MPR: 0.74-0.51), and poor (MPR ≤ 0.5). Good adherence cut-off value for the PDC ranged from at least 0.50 to 0.80 and considered any value < 0.5 as non-adherent. Three studies estimated adherence thresholds by computing median and 75$^{th}$ percentile of the adherence scores [204,207,225], and the values above the medians denoted good or high adherence cut-off value. In the same vein, adherence scores ≥ 1 denoted optimal and excess adherence (see Tables S5.4, S5.9 and S5.10 in appendix 4). Only two studies assessed

adherence and the impact of treatment groups or covariates on it as a continuous variable [208,220]. Therefore, researchers did not set an adherence cut-off.

***Adherence threshold determination***

Several methods were used to model or link clinical outcomes and adherence rates or determine adherence rates and their determinants in the retrieved articles. Seven studies used descriptive and unadjusted analytical methods to link the various clinical outcomes and adherence rates [100,213,215,219,222,224,226]. The remaining studies employed a wide range of statistical methods to determine the adherence cut-offs, as well as to link the adherence rates to targeted clinical outcomes. The statistical methods ranged from simple to more advanced adjusted regressions. Logistic regression analyses (binary and multivariate) were used to assess the association between adherence and a range of clinical outcomes, including asthma hospitalizations, emergency department (ED) visits, and asthma exacerbation in some of the studies [190,200,202,204,216,221].

Studies using logistic regression compared the odds ratio of different adherence rate groups for asthma related ED visits, asthma-related hospitalization [167,221], intubation, all-cause hospitalization [167], short – acting beta 2 agonist (SABA) use [167,200], or asthma exacerbation [204]. A combination of advanced statistical approaches, such as propensity score with various survival analyses and multivariate generalized linear models, were used in examining the association between adherence thresholds and various targeted outcomes (see Table S5.10).

For propensity score with survival analysis, log – rank statistics generated two adherence groups that separated most significantly either by shifting the threshold and comparing the resulting dichotomized adherence groups or risk of discontinuation [192,212].

Adjusted Poisson regressions were employed to determine adherence thresholds or cut-offs and their associations with targeted clinical outcomes in two studies [208,211].

### 5.5.3 Meta-analysis result for threshold determination

In addition to the narrative/qualitative synthesis, I performed meta-analyses to quantitatively summarize the effect estimates [odds ratios (OR)] for asthma exacerbation associated with specific adherence thresholds. The meta-analysis (Figure 5.2) focused on the MPR adherence thresholds and asthma exacerbation. The forest plot was sub-grouped into 3 MPR adherence thresholds ("0.75-1.00", "0.5", and "mean/median/75$^{th}$ percentile of MPR value"). Using an inverse variance random effects model, I found a significant association between achieving a '0.75-1.00' range of MPR adherence thresholds and reduction in asthma exacerbations with pooled effects estimate [odds ratio (OR): 0.56; 95% confidence interval (CI): 0.41-0.77]. The pooled effect size was heterogeneous across the included studies with $I^2$ = 74%. Similarly, achieving an MPR adherence threshold of "0.50 or more" was associated with a lower risk of asthma exacerbations ['OR= 0.71, 95% CI= (0.54-0.94)] with $I^2$ = 65%. In summary, patients who achieved an adherence threshold between '0.75 and 1.00' reduced their risk of exacerbation by 44% compared to those with a cut-off value less than 0.75.

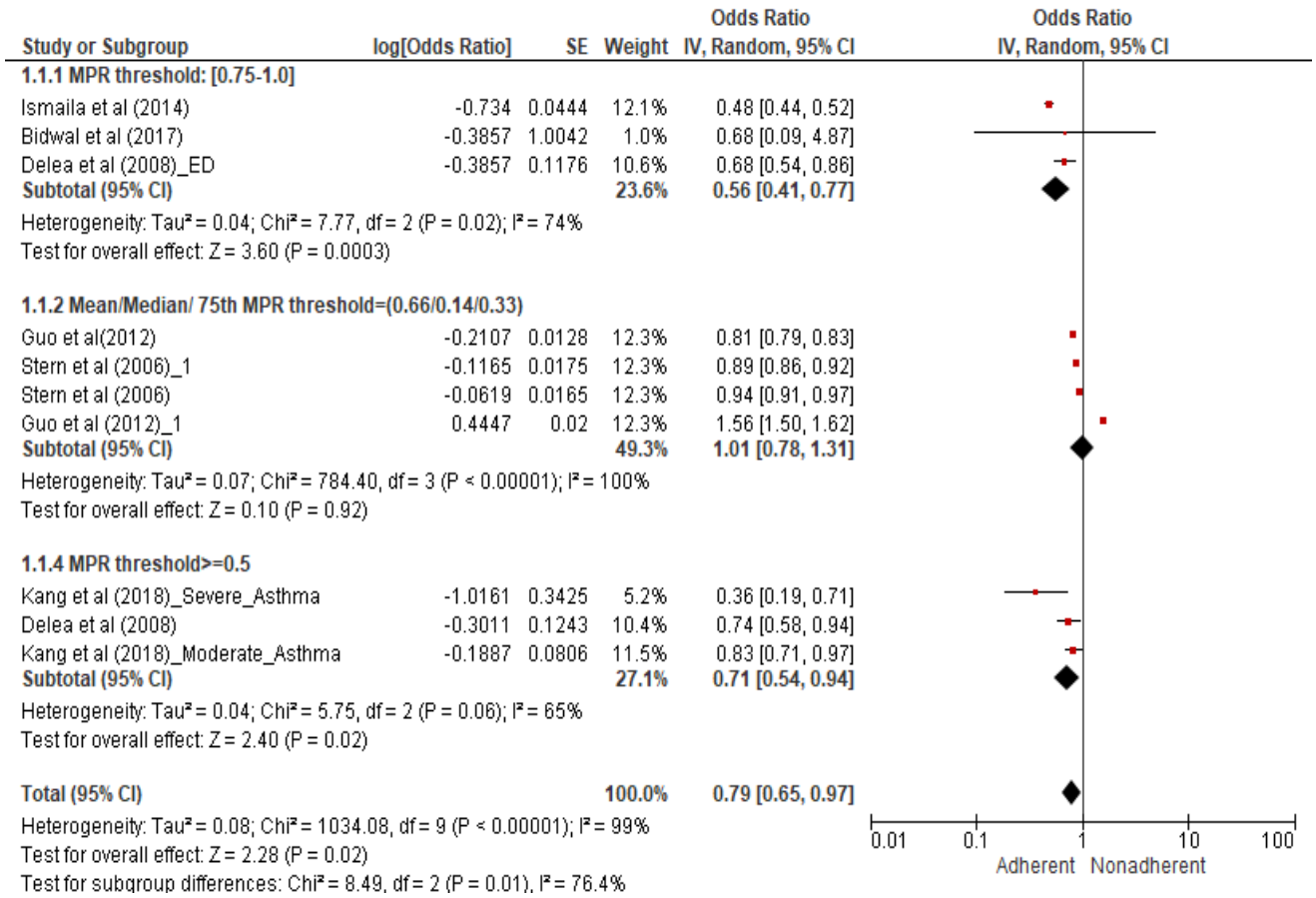


**Figure 5.2. Forest plot of the association between achieving specific MPR adherence thresholds and risk of asthma exacerbations**

Additionally, I employed a meta- regression to identify the source of the between-study heterogeneity. I identified 'differences in adherence thresholds', 'different study locations', and 'varied study durations' as the main sources of the study heterogeneity in the meta-summary analysis. (See Tables S5.5 and S5.6 in appendix 4.)

### *Publication bias*

The Eggers test recorded a T – statistics of 0.0096, Egger's regression intercept of 0.051 with 95% confidence limits of (-12.04 to 12.15), indicating no substantial publication bias in this review (See Tables S5.7, and S58). The study was limited to the smaller number of studies included in the meta-analysis for estimating the pooled effect of asthma exacerbation

among adherent and non-adherent asthma patients, resulting in a wider confidence interval with an unprecise estimate for the Eggers test intercept. Also, the Fail- safe N test and the funnel plot showed no substantial publication bias. (See Table S5.8 and Figure S5.1 in the supplementary material.)

***Outcomes and adherence cut-off/threshold***

The prevalence of nonadherence to asthma medications varied with adherence cut-offs/thresholds set by retrieved studies. Seven (7) studies reported data on adherence prevalence or reported some data that enabled estimation of medication adherence prevalence. With an AMR cut-off of > 0.50, non-adherence prevalence was the least and ranged from 10.7% - 34.6%. (See Table S5.5 for detailed estimates of adherence prevalence on all 7 studies in the supplementary material.) While some lower thresholds were associated with improved targeted outcomes of asthma [189,200,205,216,219,230], there appears to be a trend that exhibits adherence thresholds of at least 0.50 for MPR, PDC, CMA, and AMR could result in a significant reduction in asthma-related ED visits, asthma-related hospitalization, and SABA use.

***Quality assessment***

Using the Joana Brigs checklist for cohort studies, I performed a quality assessment on all 38 studies included in the review. Overall, studies were evaluated as having a low to medium risk of bias with good methodological quality (see Table S5.2 in the supplementary material). Overall, confidence in the evidence from the reviews of the quantitative research ratings of the included studies was moderate (see Table S5.3 in the supplementary material).

## 5.6 Discussion

This review uses administrative health databases to provide evidence of medication adherence measures in adolescent and adult asthma patients. A total of 38 retrospective cohort studies were eligible for inclusion in this review using a stringent criterion. I observed low to medium overall risk of bias across the included studies with a substantially good methodological quality. Overall, a total of 1,001,662 adolescents and adults with a physician diagnosis of asthma were included in this review. The authors identified 20 medication adherence measures from the various asthma databases. The measures were calculated using pharmacy claims databases comprising dispensed medications and refill records.

Data on prescription refills provides information about the possession of medication but does not necessarily provide details of the actual use of the drug. Hence, information on prescription refills provides a rough estimate of the adherence and thereby provides a probable overestimation of patients' adherence [98]. The use of administrative data for the assessment of medication adherence has limitations that include the inability of researchers to confirm whether or not the patients have actually ingested their prescribed medications. Also, the administrative health databases do not always capture detailed patient data, such as their physical examinations, clinical outcomes, and laboratory tests [167]. In spite of these limitations, adherence measured from administrative data has widely been demonstrated to correlate well with objective adherence measures and with clinical outcomes in various disease conditions. There is also documented evidence demonstrating concordance between healthcare database adherence rates and rates estimated from objective measures of adherence such as pill counting and electronic monitoring [234,235]. In particular, adherence measured from administrative data has been shown to improve clinical outcomes such as asthma exacerbation, is highly sensitive in predicting improved asthma outcomes, and reflects real-life medication use [99]. Additionally, the *International Society for Pharmacoeconomics and*

*Outcome Research* (ISPOR) working group has proposed both the MPR and the PDC for measuring medication compliance in claim databases, while the *Pharmacy Quality Alliance* (PQA) has recommended the PDC as the preferred method for assessing adherence for use in their Medicare Star Ratings [236]. Moreover, the administrative electronic health databases are easy to use, linkable to other health databases, and inexpensive in assessing adherence to prescribed medications in patients with asthma [237].

The MPR and PDC were the two commonly reported methods (representing 87% of the included studies). I found some evidence of subtle distinctions in the operationalization of the MPR and PDC measures. For instance, the PDC numerator measured the sum of days of medication covered, while the MPR numerator measured the sum of days of medication supplied. A cut-off value is advised for the adherence measures in classifying patients' as being adherent or non-adherent [238,239] . A majority of the studies reported threshold for good adherence for the MPR-related measures as '≥ 0.8', while the PDC-related measures ranged from at least '0.5 to (≥ 0.80)' [See Table S3.3]. To identify the optimal threshold capable of reducing important clinical events in asthma patients, I linked the varying thresholds ("0.5", "0.75-0.80" and "median/75 percentile" MPR thresholds) to a clinical outcome of interest (asthma exacerbation). I found a significant association between achieving the MPR threshold of "0.5-1.00" and reduced risk of asthma exacerbation. The use or choice of thresholds between "0.75-1.00" and "≥0.50 was capable of ensuring good asthma control with a reduced asthma exacerbation (OR: 0.56, 95% CI: 0.41-0.77) and (OR: 0.71; 95CI: 0.54-0.94) respectively. The choice of the optimal adherence threshold was based on the cut-off value that reduced asthma exacerbation to a larger extent. Here, patients who achieved a threshold from 0.75-1.00 were 44% less likely to experience asthma exacerbation, compared to those with adherence rates less than 0.50. Also, individuals who attained an adherence value of at least 0.5 reduced subsequent exacerbations by 29% compared to less than 0.5.

Therefore, achieving an adherence threshold within "0.75-1.00" is optimal in reducing important clinical events in asthma patients.

The PDC is known to provide a more conservative estimate of medication adherence compared to other measures in cases of concomitant multiple medication usage [220]. It is recommended for assessing medication adherence of patients on multiple therapies as compared to the MPR measure. This measure is also capable of avoiding double counting of days of medication coverage when two refills overlap. Additionally, the PDC provides a more accurate representation of medication adherence because it eliminates the possibility of being unreasonably elevated by omitting the possibility of overlapping days, such as when a patient refills a medication early. Major groups and institutions, including the Pharmacy Quality Alliance, recommend the use of the PDC measure for assessing medication adherence of patients on multiple therapies at the same time.

On the other hand, the MPR is unable to cover multiple therapies, and is mainly used for measuring single-medication use. One of the strengths of the MPR measure is its ease of accessibility and low-cost [240]. Even though the MPR is widely used in assessing adherence in most chronic disease medication intake, there exist some limitations associated with it. The MPR is estimated as a function of a prescription issued and does not directly measure patients' usage of the prescribed drug or medications. The MPR measures the total days of supply of medications from all medication records over a period for adherence calculations. As a result, it leads to double-counting the days patients refill their medications before the previous prescription runs out. This drawback is likely to overestimate the usage of some maintenance medications such as ICS. Also, the MPR is likely to cause a downward or upward bias [80] if patients had been instructed to use their medications at a different dosage than implied by the days and quantity of information supplied on each claim [222].

A common limitation of using administrative filled-claim databases for adherence calculation was the inability to determine whether the medication was ingested by the patient. Also, the definitions of the common methods (namely MPR and PDC) reported by some studies differed slightly from each other. Notwithstanding, most of the studies reportedly used almost the same definition for the calculation of MPR and PDC measures.

Also, adherence measures do not include medication usage during inpatient visits and hospitalizations, due to limitations such as incomplete coverage of some databases. When patients pay out-of-pocket to obtain refills from multiple pharmacies and do not submit an insurance claim, administrative claim databases could be incomplete and limited [237]. I believe that, if the patient records in an administrative database are complete (by accounting for patients' likelihood of obtaining medications from pharmacies not captured in the database), the derived methods can be considered to have a high sensitivity.

In choosing an adherence measure using asthma databases, some general issues should be considered and addressed. The measurement of adherence over a short period of time is likely to be imprecise due to unplanned circumstances–hospitalizations–that may be unrelated to adherence. Andrade et al. (2006) [81] recommended adjusting for the measure of adherence for the hospitalized patients after determining the number of days they were hospitalized.

***Conclusion***

This review identified two commonly reported measures–MPR and PDC–for measuring medication adherence in adolescents and adults with a diagnosis of asthma. Other measures identified for measuring the various divisions of adherence included: persistence, Multiple Interval Measure of Medication Gaps (CMG), medication implementation/adherence, and prescription fills. Using meta-analysis, I identified an

adherence threshold of at least 0.75 as optimal for achieving targeted clinical outcomes such as the reduced risk of asthma exacerbation. These measures were found to be consistently used in assessing adherence among asthma patients in administrative claim databases. While I admit that adherence measures assess medication acquisition rather than ingestion, the identified measures were highly sensitive, with complete coverage of patients' medication records in the database. Despite their limitations, the two database adherence measures are objective and reflect medication use in a real-world setting. Future studies should conduct detailed investigation of medication adherence thresholds (considering varying thresholds) concerning asthma clinical outcomes using administrative health databases.

# Chapter 6: Determining the optimal threshold for medication adherence in adult asthma patients: An analysis of British Columbia administrative health database in Canada

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## 6.1 Overview

The use of an administrative health database for measuring medication adherence in adult asthma patients has gained prominence in recent years. The previous chapter identified PDC and MPR as the most commonly reported methods recommended for measuring adherence to single and multiple asthma medications in an administrative database. The study in Chapter Five identified important gaps in the literature about the non-existence of a gold-standard threshold for measuring adherence in a pharmacy administrative health database with clinical and pharmacological rationale. This study aims to determine an optimal adherence threshold for assessing medication adherence in adult asthma patients by linking varying medication adherence thresholds to relevant clinical events in asthma patients. This study identified an adherence threshold of "at least 0.80 and 0.90" as optimal in categorizing fully adherent and sub-optimal adherent adult asthma patients. The definition of medication adherence and thresholds in the subsequent chapters will be based on this study.

## 6.2 Abstract

*Objective***:** This study investigated the association between varying cut-offs for Medication Adherence (MA) among physician-diagnosed asthma patients and subsequent association with asthma exacerbation.

*Methods*: The study linked four administrative health databases obtained from the Population Data BC. Index cases were physician-diagnosed asthma patients between January 1, 1998, to December 31, 1999, aged 18 years and older. Patients were prospectively assessed in the follow-up period from January 1, 2000, to December 31, 2018, to identify asthma exacerbation. Two proxy measures were used to assess MA: the *proportion of days covered* (PDC) and the *medication possession ratio* (MPR). Using the generalized estimating equation (GEE) logistic regression adjusted for patient covariates, the outcome of "asthma exacerbation" was modeled against varying MA cut-offs; *excellent* '≥ 0.90'; *very good* '0.80-0.89'; good '0.70-0.799'; *moderate* '0.6-0.699'; *mild* '0.50-0.599' compared to *poor* '<0.50' for both PDC and MPR.

*Results***:** The sample included 68,211 physician-diagnosed asthma patients with a mean age of 48.2 years, 59.3% of whom were female. The adjusted odds ratios (OR) and 95% confidence interval (CI) at the various cut-off for PDC-levels predicting asthma exacerbation events were: *Excellent* MA [OR=0.84, 95 % (0.82-0.86), *very good* MA [OR: 0.86, (0.83, 0.89), *good* MA [0.91, (0.88-0.94)], *moderate* MA [0.93, (0.90-0.96)], *mild* MA [0.95, (0.92-0.98)], compared to *poor* MA level. Threshold levels for both the PDC and MPR measure greater than 0.80 provided optimal threshold associated with over 15% reduced likelihood of experiencing asthma exacerbations.

*Conclusion***:** Interventions aimed at preventing or minimizing asthma exacerbation events in adult asthma patients should encourage increased medication adherence, with a threshold level greater than 0.80.

**Keywords:** Asthma, Adherence thresholds, Medication Adherence, PopData BC

## 6.3 Background

The primary purpose of asthma management is to achieve good asthma control and minimize future disease exacerbations. Recent evidence documents poor asthma control among all age groups, which is linked to decreased quality of life [241], increased use of bronchodilators [95], increased healthcare utilization [242], and increased costs [243]. To achieve optimal control of asthma and improve the health outcomes of patients, adherence to prescribed medications is essential[242,244,245]. Increased *medication adherence* (MA) among patients is known to be associated with improved clinical outcomes and patient prognosis. Administrative claim databases represent a vital source of information for assessing asthma medication adherence among community patients with physician-diagnosed asthma [100]. Currently, there is no standardized or ideal threshold for measuring optimal MA for asthma patients.

Recently, pharmacy administrative databases have emerged as an essential resource for calculating MA [246]. Measuring MA in a pharmacy claim database presents several benefits, including identifying a substantial number of asthma medication users promptly in the community and providing access to data on prescription claims and quantity of dispensed medications over time [100,247].

Several measures of asthma MA have been reported for measuring adherence to single and multiple prescribed asthma medications in pharmacy claim databases [99,220], [248]. The Medication Possession Ratio (MPR) and Proportion of Days Covered (PDC) were the two commonly reported methods for measuring medication adherence in adolescent and adult asthma patients [99 167248]. These two adherence metrics were valid, sensitive, and reflected the real-life situation of medication usage [81].

While MPR and PDC have been widely applied, medical researchers and clinicians face a dilemma concerning the optimum degree of adherence expected to achieve significant clinical outcomes among asthma patients. Engelkes et al; 2015[99] have reported varying adherence thresholds (MPR or PDC < 0.5, ≥0.75, ≥0.80, 75 percentile, and median) for classifying adherent and non-adherent asthma groups. Notable among them was adopting the '≥0.80' thresholds for classifying adherent and non-adherent patients, which has been conventionally used regardless of the clinical context [224]. The choice of '≥0.80' adherence thresholds has been suggested in most studies as the optimum adherence level [99,167,190,211]. However, the threshold may differ across medication therapeutic classes or disease conditions [246,249]. While previous studies have estimated disease-specific adherence cut-offs, several gaps remain. First, existing studies used healthcare utilization, such as hospitalization [220,221], as surrogate outcome measures, rather than using clinical outcomes that reflect disease control. Clinical outcomes that reflect disease control, such as asthma exacerbation, would more accurately reflect medication adherence for adult patients with asthma.

In addition, some researchers have raised concerns about this cut-off point lacking a clinical rationale for the chosen threshold value [99,188]. Also, the actual impact of varying adherence thresholds on asthma control remains unclear. The nonexistence of a gold-standard threshold for assessing the 0.80 cut-off presents an opportunity to investigate this vital research area, with a particular focus on determining the optimal threshold to achieve significant clinical endpoints, such as asthma exacerbation (asthma hospitalization, emergency department visits, and oral corticosteroids' (OC) claims).

I believe that attaining a certain adherence level will positively improve important clinical outcomes in adult asthma patients. To the best of my knowledge, very few studies have investigated the association between using varying MA thresholds and the risk of

asthma exacerbations. This study adds to the literature from the Canadian point of view. The primary objective of this study was to investigate the association between varying adherence thresholds of the PDC and MPR methods among asthma patients and the risk of asthma exacerbation to determine the optimal adherence cut-off value.

## 6.4 Methods

### 6.4.1 Study design and setting

The study conducted an observational cohort study using four Canadian administrative population-based health databases obtained from the PopData BC. The PopData BC includes health records of all BC residents registered in the province's publicly funded universal insurance program [31]. The PopData BC is a multi-university, data, and education resource that facilitates interdisciplinary research on the determinants of human health, well-being, and development [116]. The study obtained the requested databases from the PopData BC for 1998 to 2018 (20 years of observational administrative data). I used the first two years, that is, the period between January 1, 1998, to December 31, 1999, as a '*wash-in*' period, to allow sufficient time for the prevalent cases of physician-diagnosed asthma to be identified. I defined the index period (1998-1999) as the time a patient was first recorded in the database with a history of diagnosis for asthma. As such, subsequent asthma exacerbation outcomes were determined within an 18-year follow-up period spanning from January 1, 2000, to December 31, 2018.

***Data source***

The four administrative health databases used included: **i)** the *Discharge Abstracts Database* (DAD) for hospital separations from 1998 to 2018 [155]; **ii)** the *Medical Service Plan* (MSP), which captures records of physician visits from 1998 to 2018 [156]; **iii)** the PharmaNet

database, which contains records of all medications dispensed in BC community pharmacies from 1998 to 2018 [157]; and **iv)** the Demographic and Registration (consolidated) database, which provides primary demographic data and longitudinal registration status in the healthcare system of the province [158,159].

***Cohort definition***

The study employed a validated case definition of asthma to identify all physician-diagnosed asthma patients in three databases (DAD, MSP, and PharmaNet) [31,160]. According to the validated case definition, patients were considered to have a diagnosis of asthma based on meeting at least one of the following criteria:

i) patients having one or more asthma-related hospitalizations in the DAD database (based on International Classification of Diseases-9th edition (ICD-9): 493.x, ICD-10th edition: J45, J46) during a 12-month rolling window; or

ii) Patients having two or more physician visits for asthma using asthma diagnosis codes (ICD-9 codes: 493.x) in the MSP database. Additionally, asthma patients in the DAD and MSP databases should have records of at least four prescriptions of an asthma-related medication in the PharmaNet database (see asthma-related drug lists in the supplementary Material in Table S4.2).

Using these criteria for case definitions, asthma patients 18 years and older with no history of ever having been diagnosed with chronic obstructive pulmonary disease (COPD) were identified between January 1, 1998, to December 31, 1999, and included in the source population. The identified asthma patients were followed to identify subsequent asthma exacerbation outcomes from January 1, 2000, to December 31, 2018.

***Exposure variable: Assessment of medication adherence measure***

The primary exposure measure for this study was medication adherence. Adherence was assessed using the *Medication Possession Ratio* (MPR) [162] and *Proportion of Days Covered* (PDC) [186] adherence metrics. The authors calculated the PDC adherence measure by dividing the number of days of medication covered (i.e., the number of days with a drug on hand) by the sum of days between the first and last fill dates. The study estimated the MPR measure as the ratio of the sum of days of medication supplied to the sum of days between the first and last fill dates [185,186]. Using the PDC and the MPR methods, the study calculated medication adherence for all prescribed controller medications over time. Thus, all asthma controller medications listed in Table S3.1 in the supplementary material were included in the calculation of medication adherence over time. Specifically, I estimated medication adherence for prescribed inhaled corticosteroids (ICS), Long-acting beta-2 agonist (LABA), ICS/LABA combination, and Leukotriene receptor antagonists (LTRA). Further, I also calculated patients' adherence to prescribed *short-acting beta-2 agonists* (SABA) at the baseline/patient identification stage. During the computation of asthma medication adherence, I adjusted for inpatient (IP) stays by censoring the days a patient was hospitalized. The study calculated patients' adherence to prescribed concomitant medications based on the first approach of Choudhry et al.'s 2009 [250] proposal for the definition of concurrent adherence. Based on this proposal, I first calculated the prescription-based PDC and MPR for each medication class for the individual patients. The study later averaged the estimated PDC and MPR at the patient level. The continuous adherence rates were categorized into five different adherence thresholds levels for both PDC and MPR and coded as follows: *poor* MA ('< 0.5'=0, reference); *mild* MA ('0.50-0.59'=1); *moderate* MA ('0.60-0.69'=2); *good* MA('0.70-0.79'=3); *very good* MA ('0.80-0.89'=4); and *excellent* MA ( '≥ 0.90'=5).

***Outcome measures***

The primary outcome was measured as "*asthma exacerbation"* during the 18-year follow-up/measurement period (2000 - 2018). The study defined asthma exacerbation as the occurrence of at least one of the following three events: i) asthma episodes that required collection of prescribed oral corticosteroids (OCS), ii) emergency room visits, and/or iii) hospitalization due to asthma [112,161,167,251].

***Covariates***

Demographic information captured for each patient included their age and sex (male/female). Charlson's comorbidity index (CCI) was estimated to measure the burden of comorbid conditions associated with asthma patients [252]. The various comorbid conditions were identified based on the diagnostic codes (ICD-9 and ICD-10) recorded as part of inpatient and outpatient hospital care. The CCI was calculated at baseline and subsequently measured at follow-up after excluding asthma from the score [252]. Other asthma-related comorbidities, such as sinusitis and upper respiratory infections, were also identified in this study. Other covariates considered in this study included tobacco use and nicotine dependence (yes=1, vs. no=0), and obesity (body mass index $\geq 30 kg/m^2$) [obese=1, vs. normal=0]. Patients' length of stay in hospital and emergency hospital admissions (asthma and non-asthma related) were also considered important risk factors for asthma exacerbations.

The various categories of asthma severity at diagnosis (mild, moderate, and severe) were identified at baseline (1998-1999) and included in the model. The study defined asthma severity based on an algorithm developed by Firoozi et al. (2007) [168]. The three asthma severity states (mild, moderate, and severe) were defined based on the intensity of prescribed ICS and other controller medications, the use of short-acting beta-2 agonist (SABA), and an

indication of markers of moderate-to-severe asthma exacerbations. Patients were identified as belonging to the *mild asthma* group if they had records of prescription of 0-500µg/day doses of ICS and were not taking any additional controller drugs. *Mild asthma* was also defined as having prescriptions of ICS doses of 0-250µg/day plus additional controller therapy, and the patient must not have had a marker of moderate to severe asthma exacerbation, nor have overused SABA (defined as using an average of at least 3 doses of SABA per week within 12 months). Patients prescribed with >500µg/day doses of ICS with no additional usage of controller therapy or having more than >250µg/day doses of additional therapy were classified as having *moderate asthma*. Finally, patients were defined as having *severe asthma* if they had a prescription of more than 1000µg/day of ICS, except for patients with markers of uncontrolled asthma who ingested additional prescriptions of more than 10 doses of SABA per week for patients with uncontrolled asthma.

### 6.5.2. Statistical methods

The study measured "*asthma exacerbation*" during the follow-up period as the study outcome and investigated the association between the five adherence cut-off values *(poor*, *mild*, *moderate*, *good*, and *excellent*) and the risk of exacerbations over time.

I used SAS version 9.4 and STATA version 16 (SAS Institute Inc. 2013) for data, cleaning, coding, and analyses. Descriptive statistics were presented for baseline characteristics. First, I employed the bivariate generalized estimating equation (GEE) logistic regression to estimate the unadjusted odds ratio, and 95% confidence interval to identify possible risk factors associated with asthma exacerbations [122]. This was done to identify the relevant risk factors to be included in the model by estimating adjusted odds ratios (OR).

I further applied the multivariate GEE logistic regression to examine the association between the five varying adherence thresholds and risk of asthma exacerbation after adjusting

for significant covariates. The GEE logistic regression model was adopted to account for correlation due to the patient's repeated set of measurements on asthma exacerbations and other sets of covariates [122]. A *p-value* of 0.05 was used in all tests of statistical significance. Sensitivity and specificity analysis were further performed. Using the Receiver Operating Characteristics (ROC) curve, I determined the ideal cut-off for both PDC and MPR adherence measures to achieve optimal control of asthma exacerbation using the value with the highest sensitivity.

Ethics approval was sought from the Health Research Ethics Board (HREB) at the Memorial University of Newfoundland (REF #: 2019.216).

## 6.6 Results

### 6.6.1 Patient characteristics at baseline

At baseline, a total of 68,211 patients were identified in the index years spanning January 1, 1998, to December 31, 1999; that is, 49,685 (72.84) asthma patients were identified from January 1, 1998, to December 31, 1998, and 18,526 (27.16) from January 1, 1999, to December 31, 1999. Based on the validated case definition, the study identified 248,086 patients from the PharmaNet database, 101,555 from the MSP database, and 3,666 patients from the DAD database at the initial stage. I linked the three databases together with the consolidated database. After removing duplicate patient records and incident cases of COPD (asthma-COPD), the study included 68,211 unique adult asthma patients (≥ 18 years) as the study population (See Figure 6.1).

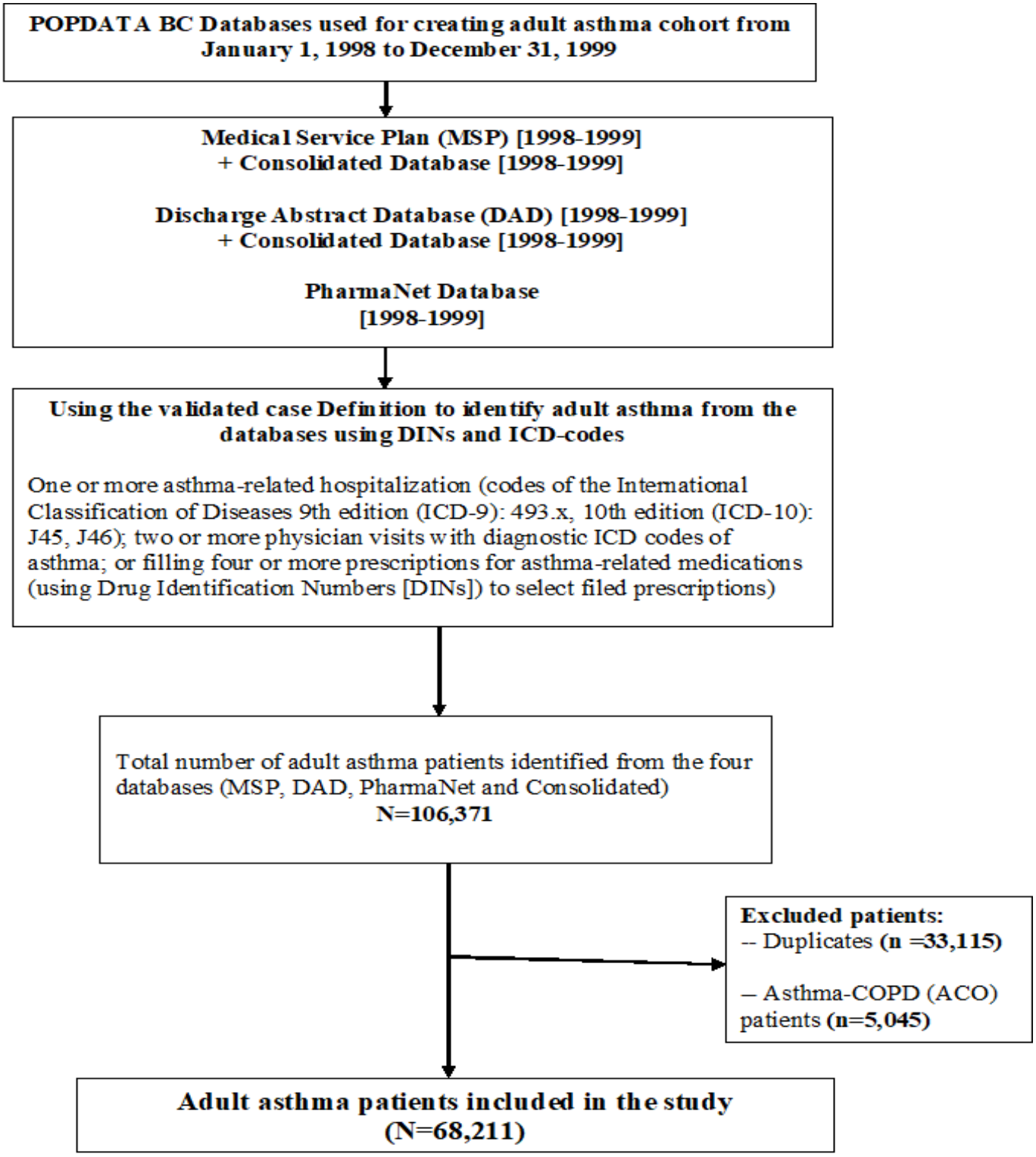


**Figure 6.1. Study flow chart for selecting adult asthma patients from the POPDATA BC databases**

Table 6.1 presents the descriptive statistics of the characteristics of the study population at baseline. The mean age was 48 years, with the majority of patients being 40 years and older. More than half of the study population were female (59.25%, n=40,455). No comorbidity was reported for 97.88% of the patients, and 1.80%, 0.22%, and 0.10 reported 1, 2, and >3 comorbidities, respectively. Additionally, I identified 205 obese patients and 96 patients with a history of tobacco use and nicotine dependence. 49,155(72.06%) were *mild* asthma patients, 15,595(22.87%) *moderate*, and 3,461(5.07%) were *severe* asthma patients.

**Table 6.1: Sample characteristics by medication adherence thresholds***

| Baseline variables | Overall N = 68,211 | Medication Adherence thresholds N (%) or Mean ± SD | | | | | |
|---|---|---|---|---|---|---|---|
| | N (%) | < 0.5 | 0.50-0.59 | 0.60-0.69 | 0.70-0.79 | ≥ 0.80 | P-value |
| PDC, mean (SD) | 0.39(0.32) | 46,666(68.41) | 3,982(5.84) | 3,091(4.53) | 2,484(3.64) | 1,1988(17.54) | 0.00 |
| MPR, mean (SD) | 0.41(0.34) | 45,569(66.81) | 3,818(5.60) | 2,876(4.22) | 2,194(3.22) | 13,754(20.16) | 0.00 |
| Sex (Male), N (%) | 27,756(40.69) | 18,306(65.95) | 1,686(6.07) | 1,346(4.85) | 1,104(3.98) | 5,314(19.15) | 0.00 |
| Sex (Female), N (%) | 40,455 (59.25) | 28,360(70.10) | 2,296(5.68) | 1,745(4.31) | 1,380(3.41) | 6,674(16.50) | |
| Mean Age (SD, years) | 48.20 (18.63) | 46.12(17.99) | 49.89(18.80) | 49.62(18.66) | 52.28(19.03) | 52.22(19.15) | 0.00 |
| Length of hospitalization [days, N (%)] | | | | | | | |
| 0 | 65,526(96.06) | 4,4918(68.54) | 3,811(5.82) | 2,969(4.53) | 2,390(3.65) | 11,438(17.46) | 0.00 |
| 1 | 1,876(2.75) | 1,262(67.27) | 119(6.34) | 77(4.10) | 54(2.89) | 364(19.40) | |
| 2 | 559(0.82) | 353(63.15) | 34(6.08) | 34(6.08) | 21(3.76) | 117(20.93) | |
| ≥ 3 | 250(0.37) | 133(53.20) | 18(7.20) | 11(4.4) | 19(7.6) | 69(27.60) | |
| Emergency admission (Yes), N (%) | 1,023(1.50) | 662(64.71) | 60(5.87) | 49(4.79) | 42(4.10) | 210(20.53) | 0.09 |
| Tobacco use/nicotine dependence (Yes), N (%) | 96(0.14) | 59(61.46) | 6(6.25) | 6(6.25) | 7(7.29) | 18(18.75) | 0.33 |
| Obesity (BMI >30kg/m$^2$), N (%) | 205(0.30) | 134(65.37) | 13(6.34) | 6(2.93) | 6(2.93) | 46(22.43) | 0.33 |
| **Charlson Comorbidity Index (CCI)** | | | | | | | |
| CCI score 0 | 66,766 (97.88) | 45,906(68.76) | 3,878(5.81) | 3,003(4.49) | 2,396(3.59) | 11,583(17.35) | 0.00 |
| CCI score 1 | 1,226 (1.80) | 615(50.16) | 93(7.59) | 80(6.53) | 78(6.36) | 360(29.36) | |
| CCI score 2 | 151(0.22) | 99(65.56) | 11(7.28) | 8(5.30) | 10(6.62) | 23(15.24) | |
| CCI score ≥ 3 | 68(0.10) | 46(0.10) | | | | 22(32.35) | |
| **Asthma related comorbidity** | | | | | | | |
| Sinusitis | 108(0.16) | 74(68.52) | 8(7.40) | 6(5.56) | | 20(18.52) | 0.58 |
| Upper respiratory infection | 284(0.42) | 174(61.27) | 15(5.28) | 15(5.28) | 12(4.23) | 68(23.94) | 0.05 |
| **Asthma severity** | | | | | | | |
| Mild | 49,155(72.06) | 33,503(68.23) | 3,054(6.22) | 2,395(4.88) | 1,841(3.75) | 8,311(16.92) | 0.00 |
| Moderate | 15,595(22.87) | 13,137(68.94) | 928(4.87) | 696(3.65) | 643(3.37) | 3,652(19.17) | |
| Severe | 3,461(5.07) | 1,754(50.70) | -- | 17(0.50) | 90(2.60) | 1,600(46.20) | |

Baseline variables indicate a variable is significant at 0.01. PDC=Proportion of Days Covered; MPR=Medication Possession; BMI=Body mass index, SD=Standard deviation; *Medication adherence thresholds: *Poor* = "< 0.5" *Mild* = "0.50-0.59" *Moderate* ="0.60-0.69" *Good* ="0.70-0.79" *Very good* ="0.80-0.89" *Excellent* ="0.90-1.00"

**Bivariate analysis of patient factors**

The study set the statistical significance level at a maximum of 0.20 for examining all bivariate analyses of the association between varying adherence thresholds and "*asthma exacerbations*" outcomes. Table 6.2 present the covariates, including the varying adherence thresholds that were significant at 0.20 statistical level of association between varying adherence thresholds and "*asthma exacerbations*". For PDC, using the *poor* "< 0.5" as the reference category level, the *mild* MA category, that is "0.50-59", was significantly associated with less likelihood of developing *asthma exacerbations* (OR: 0.93; 95% CI: 0.90, 0.95, $p<0.0001$). Similarly, the categories of PDC cut-off values at *moderate* MA "0.60-0.69", *good* MA "0.70-0.79", *very good* MA "0.80-0.89" and *excellent* "≥ 0.90" were significantly associated with less likelihood of asthma exacerbation over time.

A similar trend was observed for the bivariate analysis comparing MPR thresholds with "*asthma exacerbation*" over the study period. Additionally, the following patient covariates were significantly associated with "*asthma exacerbations*". They included patients' sex, age (years), length of stay, tobacco use/nicotine dependence, obesity, CCI, asthma-related comorbidities, and asthma severity at baseline.

**Table 6.2: Bivariate association between the patient characteristics and level of medication adherence predicting risk of asthma exacerbations**

| Covariates | Unadjusted odds ratio | 95% Confidence Interval | P-value |
|---|---|---|---|
| ***PDC threshold*** | | | |
| Poor "< 0.5" | Ref | | |
| Mild "0.50-0.59" | 0.93 | (0.90, 0.95) | <0.0001 |
| Moderate "0.60-0.69" | 0.93 | (0.90, 0.96) | <0.0001 |
| Good "0.70-0.79" | 0.92 | (0.89, 0.94) | <0.0001 |
| Very good "0.80-0.89" | 0.88 | (0.86, 0.91) | <0.0001 |
| Excellent "0.90-1.00" | 0.87 | (0.86, 0.89) | <0.0001 |
| ***MPR threshold*** | | | |
| Poor "< 0.5" | Ref | | |
| Mild "0.50-0.59" | 0.93 | (0.90, 0.95) | <0.0001 |
| Moderate "0.60-0.69" | 0.93 | (0.90, 0.96) | <0.0001 |
| Good "0.70-0.79" | 0.93 | (0.91, 0.97) | <0.0001 |
| Very good "0.80-090" | 0.90 | (0.87, 0.93) | <0.0001 |
| Excellent "090-1.00" | 0.88 | (0.87, 0.90) | <0.0001 |
| | | | |
| Sex (Male) | 0.67 | (0.66, 0.68) | <0.0001 |
| Age (years) | 0.94 | (0.94, 0.95) | <0.0001 |
| Length of stay (days) | | | |
| 0 | Ref | | |
| 1 | 4.09 | (3.98, 4.17) | <0.0001 |
| 2 | 2.34 | (2.28, 2.40) | <0.0001 |
| ≥3 | 1.32 | (1.28 1.36) | <0.0001 |
| Tobacco use/nicotine dependence (yes) | 3.05 | (2.79, 3.33) | <0.0001 |
| Obesity [BMI ≥ 30kg/$m^2$] (yes) | 1.46 | (1.35, 1.59) | <0.0001 |
| Charlson Comorbidity Index | 0.62 | (0.60, 0.65) | <0.0001 |
| CCI score 0 | Ref | | |
| CCI score 1 | 0.05 | (0.06, 0.07) | <0.0001 |
| CCI score 2 | 0.01 | (0.01, 0.02) | <0.0001 |
| CCI score ≥ 3 | 0.01 | (0, 0.02) | <0.0001 |
| Asthma related comorbidities | | | |
| Sinusitis (yes) | 3.49 | (3.19, 3.83) | <0.0001 |
| Upper respiratory infection (yes) | 4.96 | (4.72, 5.22) | <0.0001 |
| Asthma severity | | | |
| Mild | Ref | | |
| Moderate | 1.08 | (1.07, 1.10) | <0.0001 |
| Severe | 1.28 | (1.24, 1.31) | <0.0001 |

PDC=Proportion of days covered; MPR=Medication possession ratio

### 6.6.2 Multivariate analysis of the association between varying adherence thresholds and asthma exacerbations

In the multivariate analysis presented in Table 6.3, I examined the association between varying adherence thresholds and "*asthma exacerbations*". The significant patient baseline characteristics and variables in the bivariate analysis were adjusted in the GEE model. In Table 6.3, the study obtained the adjusted odds ratio for measuring the strength of the association between PDC thresholds and asthma exacerbations. Compared to the reference category of 'PDC level < 0.5', patients who achieved *mild* MA (PDC level=0.50-0.60) were significantly less likely to develop asthma exacerbations (OR: 0.95, 95% CI: 0.92-0.98) after controlling for patient factors at baseline. Similar significance (OR, 95% CI) was achieved for the effect of "*moderate* MA" (OR: 0.93, 95% CI: 0.90-0.96), "*good* MA" (OR: 0.91, 95% CI: 0.88-0.94), "*very good"* MA (OR: 0.86, 95% CI: 0.83-0.89) and "*excellent* MA" (OR: 0.84, 95%CI: 0.82, 0.86) categories after adjusting for important significant covariates. The adjusted relative likelihood of a reduction in asthma exacerbation outcomes using the PDC cut-offs were 5%, 7%, 9%, 14%, and 16% for *mild* MA, *moderate* MA, *good* MA, *very good* MA, and *excellent* MA categories when compared to the *poor* MA category as the reference.

**Table 6.3: Multivariate analysis of the association between varying PDC adherence thresholds and risk of asthma exacerbation**

| **PDC thresholds** | **Asthma hospitalization** | **Emergency department visit** | **Asthma exacerbation** (Combined asthma hospitalization & ED visits) |
|---|---|---|---|
| | **Adjusted OR (95% CI)** | **Adjusted OR (95% CI)** | **Adjusted OR (95% CI)** |
| Poor "< 0.5" | Ref | Ref | Ref |
| Mild "0.50-0.59" | 0.96(0.92, 1.00) | 0.96(0.93, 1.01) | 0.95(0.92, 0.98) *** |
| Moderate "0.60-0.69" | 0.96(0.93, 1.01) | 0.93(0.90, 0.98) | 0.93(0.90, 0.96) *** |
| Good "0.70-0.79" | 0.93(0.90, 0.97) *** | 0.90(0.86, 0.94) *** | 0.91(0.88, 0.94) *** |
| Very good "0.80-0.89" | 0.90(0.87, 0.94) *** | 0.86(0.83, 0.89) *** | 0.86(0.83, 0.89) *** |
| Excellent "0.90-1.00" | 0.89(0.87, 0.92) *** | 0.85(0.83, 0.88) *** | 0.84(0.82, 0.86) *** |

Adjusted for patient sex, age (years), length of hospital stays, tobacco use, Charlson comorbidity index (CCI), asthma-related comorbidities (sinusitis, upper respiratory diseases), obesity, and asthma severity; *** indicates a variable is significant at 0.05.

**Table 6.4: Multivariate analysis of the association between varying MPR adherence thresholds and asthma exacerbation**

| MPR thresholds | Asthma hospitalization | Emergency department visit | Asthma exacerbation (Combined asthma hospitalization and ED visits) |
|---|---|---|---|
| | **Adjusted OR (95% CI)** | **Adjusted OR (95% CI)** | **Adjusted OR (95% CI)** |
| Poor "< 0.5" | Ref | Ref | Ref |
| Mild "0.50-0.59" | 0.94(0.90, 1.00) | 0.98(0.93, 1.03) | 0.95 (0.92, 0.98) *** |
| Moderate "0.60-0.69" | 0.94(0.89, 1.00) | 0.96(0.92, 1.00) | 0.94 (0.91, 0.97) *** |
| Good "0.70-0.79" | 0.94(0.89, 1.01) | 0.92(0.89, 0.97) *** | 0.93 (0.90, 0.96) *** |
| Very good "0.80-0.89" | 0.91(0.87, 0.95) *** | 0.88(0.84, 0.92) *** | 0.88 (0.85, 0.92) *** |
| Excellent "0.90-1.00" | 0.90(0.88, 0.93) *** | 0.86(0.84, 0.88) *** | 0.85 (0.84, 0.87) *** |

Adjusted for patient sex, age (years), length of hospital stays, tobacco use, Charlson comorbidity index (CCI), asthma-related comorbidities (sinusitis, upper respiratory diseases), obesity, and asthma severity; *** indicates a variable is significant at 0.05.

A similar multivariate analysis was performed for the MPR adherence measure presented in Table 6.4. After I adjusted for male sex, age, length of stay, history of tobacco use/nicotine dependence, obesity, asthma-related comorbidities, CCI, and asthma severity in the multivariate model, the data was consistent with that observed using the PDC score presented in Table 6.3. The relative likelihood of a reduction in asthma exacerbation outcomes using the MPR cut-offs were 5%, 6%, 7%, 12%, and 15% for mild, moderate, good, very good, and excellent, compared to the poor MA category as the reference.

Further, I performed subgroup analysis by investigating the association between varying thresholds of PDC and MPR and asthma exacerbation over time among users of ICS and ICS/LABA controller medications. Figure 6.2 summarizes the effects of varying ICS and ICS/LABA adherence thresholds and the risk of asthma exacerbation. From Figure 6.2, the optimal PDC and MPR adherence thresholds '0.80-1.00' reduced asthma exacerbation by 21% among users of ICS medication. Using the PDC adherence thresholds, patients who achieved an adherence threshold of at least 0.90 among ICS/LABA users improved their asthma control by 30%, while those who attained adherence within 0.80-090 reduced their

exacerbations by 17%. Similarly, higher levels of MPR adherence (>0.90) among ICS/LABA users were significantly associated with a reduced burden of the disease over time.

| Subgroups | aOR | 95% CI | P-value |
|---|---|---|---|
| **Adherence to ICS (PDC thresholds)** | | | |
| 0.5-0.59 | 0.87 | (0.82-0.92) | <0.001 |
| 0.60-0.69 | 0.86 | (0.81-0.91) | <0.001 |
| 0.70-0.79 | 0.82 | (0.77-0.84) | <0.001 |
| 0.80-0.89 | 0.79 | (0.74-0.84) | <0.001 |
| 0.90-1.00 | 0.79 | (0.76-0.83) | <0.001 |
| **Adherence to ICS (MPR thresholds)** | | | |
| 0.5-0.59 | 0.87 | (0.82-0.93) | <0.001 |
| 0.60-0.69 | 0.86 | (0.8-0.91) | <0.001 |
| 0.70-0.79 | 0.86 | (0.81-0.92) | <0.001 |
| 0.80-0.89 | 0.79 | (0.74-0.85) | <0.001 |
| 0.90-1.00 | 0.78 | (0.75-0.82) | <0.001 |
| **ICS/LABA adherence (PDC theresholds)** | | | |
| 0.5-0.59 | 1.02 | (0.96-1.08) | 0.509 |
| 0.60-0.69 | 0.98 | (0.92-1.04) | 0.557 |
| 0.70-0.79 | 0.95 | (0.89-1.01) | 0.107 |
| 0.80-0.89 | 0.83 | (0.78-0.88) | <0.001 |
| 0.90-1.00 | 0.7 | (0.67-0.74) | <0.001 |
| **ICS/LABA adherence (MPR thresholds)** | | | |
| 0.5-0.59 | 1.02 | (0.95-1.08) | 0.498 |
| 0.60-0.69 | 1.01 | (0.94-1.07) | 0.711 |
| 0.70-0.79 | 1.01 | (0.94-1.08) | 0.709 |
| 0.80-0.89 | 0.93 | (0.87-0.99) | 0.04 |
| 0.90-1.00 | 0.75 | (0.72-0.79) | <0.001 |

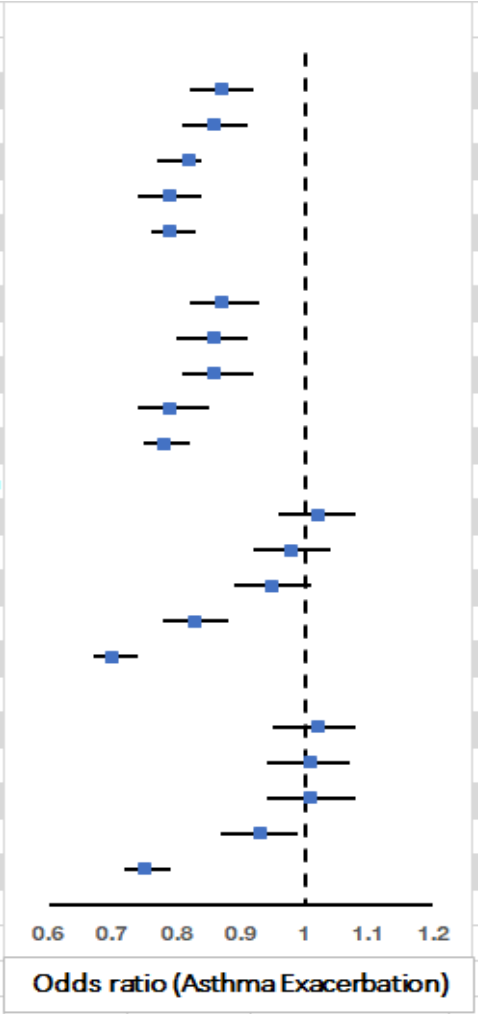


**Figure 6.2: Forest plot of association between varying PDC and MPR thresholds among patients with ICS and ICS/LABA usage and risk of asthma exacerbation.**

***ICS**=Inhaled corticosteroids; **ICS/LABA**=Inhaled corticosteroids/Long-acting beta-2 agonist; **aOR**=Adjusted odds ratio; **PDC**=Proportion of days covered; **MPR**=Medication Possession Ratio. The model was adjusted for sex, age, comorbidity burden (CCI), asthma related comorbidities, history of tobacco smoking/nicotine dependence, obesity, and length of hospital stay.*

### Sensitivity analysis

Figures S6.1 and S6.2 present *Receiver Operating Curve* (ROC) curve analysis for PDC and MPR. This was performed to investigate the overall predictive ability of the estimated adherence rates for each of the PDC and MPR adherence cut-off values. The *Area*

*under the curves* (AUC) were 0.7697 and 0.7684 for the PDC and MPR variables, respectively, which were statistically greater than the chance (0.50). As shown in Table S6.1 in the supplementary material, the higher PDC and the MPR adherence scores (≥ 0.70; ≥ 0.80) were highly sensitive in predicting the risk of exacerbation among adult asthma patients.

## 6.7 Discussion

In this study, I conducted an observational cohort study to determine the optimal adherence threshold for classifying adherent and non-adherent asthma groups. To the best of our knowledge, very few studies have examined varying PDC and MPR adherence thresholds and their association with clinical outcomes in the adult asthma population. This study aimed at determining an optimal adherence threshold for achieving important clinical outcomes, such as reduced asthma exacerbations, asthma hospitalization, emergency department (ED) visits, and oral corticosteroids claims.

Our results show that patients who attained a PDC or MPR adherence rate of at least 0.5 were significantly less likely to experience asthma exacerbation compared to the MA cut-off value of less than 0.5. The selection of the most predictive adherence cut-off value was based on the strength of the odds ratio (i.e., the higher the adherence scores, the lower the odds ratio in predicting exacerbations). Six adherence thresholds were adopted and were subsequently examined for the risk of asthma exacerbations. Compared to PDC or MPR values <0.5, all the remaining adherence thresholds (*mild* MA '0.5-0.59'; *moderate* MA '0.60-0.69', *good* MA '0.70-0.79' *very good* MA '0.80-0.89' and, *excellent* MA ≥ 0.90) were significantly associated with reduced asthma exacerbations over time.

However, higher compliance rates such as *excellent*, *very good*, and *good* MA levels significantly reduced the risk of asthma exacerbation to a larger extent than the *moderate* and

*mild* adherence rates. In particular, patients who achieved an *excellent adherence* (PDC ≥ 0.90) demonstrated better asthma control with a greater reduction in asthma exacerbations (16%). In contrast, patients who achieved a cut-off higher than 0.50 demonstrated some improvement in their clinical events. For instance, patients who attained a *mild adherence* (PDC: 0.50-0.59) compared to *poor* adherence (PDC<0.5) reduced their future exacerbations by 5%. That is, higher levels of adherence scores were significantly more effective in improving asthma exacerbations than the moderate compliance scores. These findings have significant implications for managing patients with a diagnosis of asthma. Given that poor/sub-optimal medication adherence contributes to increased asthma exacerbations, it is expedient for healthcare providers to distinguish between poorly adherent asthma patients and those who need additional therapies as stipulated in the GINA guidelines to achieve maximum symptom control.

This study generally corroborates existing studies that found reduced asthma exacerbations among adherent patients [99,167,189,218,221,230]. For instance, in a study by Ismaila et al. (2014) [167], users of fluticasone-propionate/salmeterol who achieved an MPR adherence threshold of ≥0.80 were significantly associated with a 52% reduction in exacerbation. Guo et al., 2012 [221] found an achievement of ICS-and-LABA MPR ≥ 0.80 associated with a 29% reduced likelihood of emergency department visits (OR: 0.81 95% CI:0.79-0.84) but a higher risk of asthma – related hospitalization (OR: 1.56, 1.50-1.62). Similarly, high ICS adherence (MPR ≥ 0.50) compared to low (MPR <0.20) was significantly associated with less likelihood of asthma exacerbation (adjusted OR: 0.83, 95% CI: 0.71 to 0.97) [189]. The findings of this study, therefore, suggests that a greater achievement of adherence (>0.90) combined with treatment persistence reduces the likelihood of relevant clinical events (such as asthma-related hospitalization and emergency department visits), and subsequently reduces future complications.

Of note, the findings in the literature partially corroborate our current study with regard to the effects of specific categories of adherence cut-off values and reduced risk of asthma exacerbation. However, previous studies did not provide a broader threshold categorization to determine the cut-off that ensures that patients are fully compliant with their medications. Our study shows that a higher threshold of over 0.90 provides better asthma control than the conventional 0.80 thresholds. This suggests that it would be valuable for healthcare providers who treat patients with asthma to incorporate routine assessment to ensure optimization of adherence to prescribed treatments. Therefore, clinicians should include educating asthma patients about the importance of adherence to prescribed medications and asthma control at every physician visit. Further, the introduction of effective interventions aimed at facilitating and improving asthma medication adherence may be beneficial in minimizing asthma morbidity and subsequent exacerbations.

Furthermore, the assessment of the long-term effect of changes in adherence with treatments using specific thresholds has not been fully addressed. This study was built on these existing studies and further addressed the knowledge gaps. The study investigated the association between six varying adherence thresholds and asthma exacerbation to provide a clinical basis for the choice of a threshold. This study adds further evidence to the literature with regard to the selection of appropriate thresholds capable of achieving important clinical outcomes. Further, whereas both MPR and PDC have been widely documented for assessing medication adherence in asthma administrative databases, our study recommends the use of the PDC over the MPR method. This is because the PDC provides a more conservative estimate of medication adherence compared to MPR, and it is appropriate for calculating adherence to multiple prescribed medications. The PDC avoids double counting of medication coverage when two refills overlap. Also, the Pharmacy Quality Alliance recommends PDC be used to calculate medication adherence for prescribed multiple

therapies. Although the PDC adherence measure is highly recommended for measuring adherence by adult asthma patients, the estimation of adherence could have been affected by certain factors. For instance, incorrect inhaler techniques might have influenced the optimal delivery of therapies, since certain inhalers require different approaches in their administration. Other factors that might have affected optimal adherence rates included fear of side effects and unintentional patient-centered barriers such as forgetfulness.

### *Strength and limitations*

In this study, a large population cohort of physician-diagnosed asthma patients was used to determine the association between six varying scores of medication adherence and the risk of asthma exacerbation. Due to the longitudinal nature of the data, we employed the GEE logistic regression model to account for possible correlation due to the patient's repeated set of measurements on asthma exacerbations and other covariates [34]. This study was limited by incomplete patient records on clinical and laboratory data, such as pulmonary function test (PFT), laboratory findings, systolic and diastolic blood pressures. However, despite the omission of these variables in the administrative databases, the variables used provided robust estimates of the model parameters after adjusting for relevant confounders and covariates such as the changes in asthma severities over time, tobacco use and nicotine dependence, obesity, and asthma-related comorbidities.

### *Conclusion*

This study aimed at determining optimal adherence threshold(s) capable of improving important clinical endpoints in adult asthma patients. Our results suggest that attaining compliance of '0.80-0.89' reduced patients' risk of asthma exacerbations by 12% compared to compliance < 0.50. Further, a higher compliance rate of ≥ 0.90 reduced patients'

exacerbations by over 15%. Also, patients who adhered to their prescribed ICS and ICS/LABA based on the PDC improved their asthma control by 21% and 30%, respectively. I noted that achieving '≥ 0.80' adherence is optimal in improving asthma control and characterizing adherent and non-adherent adult asthma patients. This information could serve as the basis for selecting an appropriate adherence threshold with clinical rationale for assessing patient compliance. Additionally, the findings provide policymakers with information to effect change within the healthcare system and ultimately improve patient outcomes.

# Chapter 7: Association between medication adherence and risk of COPD in patients with asthma: a retrospective cohort study in Canada

**Under Review**

**@**

***Clinical Epidemiology***

## 7.1 Overview

Findings from the previous study in Chapter 4 indicated that asthma patients who optimally adhered to their medications were protected from developing chronic obstructive pulmonary disease (COPD). One of the potentially modifiable risk factors that is most important to clinicians is the role of optimal or suboptimal adherence in explaining the relationship between prior asthma diagnosis and COPD onset. The extant literature has not investigated the role of medication adherence levels over time, nor whether there is a potential effect modification of the various asthma severity levels and subsequent risk of COPD. To properly define medication adherence levels, findings from Chapters 4 and 5 have established the choice of appropriate adherence methods and thresholds for assessing medication adherence in asthma patients. The study presented in this chapter is aimed primarily at investigating the long-term effects of asthma medication adherence over time and subsequent risk of COPD. This study is currently under review in *Clinical epidemiology* journal.

## 7.2 Abstract

*Background*: Patients with asthma may be subsequently diagnosed with chronic obstructive pulmonary disease (COPD). Factors determining the incidence of COPD in asthma patients have not been well addressed, especially using a large population-based cohort study. This study investigated the independent effect of medication adherence (MA) and severity of physician-diagnosis of asthma on the risk of COPD.

*Methods*: Four linked databases from the PopData BC in Canada were used to identify asthma patients aged 18 years and older between 1998 and 1999. The primary event was time-to-COPD diagnosis during the follow-up period (2000 to 2018). The proportion of days covered (PDC) was used as a surrogate measure for medication adherence (MA) assessed at optimal-level (≥ 0.80), intermediate-level (0.50-0.79), and low-level (< 0.5) of adherence. A propensity adjusted analysis with Marginal Structural Cox (MSC) model was employed to estimate the adjusted hazard ratios (aHR) and 95% confidence intervals (95% CI) for the effect of medication adherence and asthma severity over time.

*Results***:** At cohort entry, the sample included 68,211 asthma patients with an overall mean age of 48.2 years. The 18-year incidence of COPD in asthma patients was 9.8 per 1000 persons per year. In an inverse weighted propensity adjusted analysis of the MSC model, higher MA levels were significantly associated with decreased risk of COPD as follows: optimal-level (aHR: 0.19, 95% CI: 0.17-0.24) and intermediate-level (aHR: 0.20, 95% CI: 0.18, 0.23) compared to the low-level adherence group. A significant increase in COPD risk was observed in severe asthma patients with low medication adherence (aHR: 1.72, 95% CI: 1.52-1.93), independent of other patient factors.

*Conclusion***:** Compared to low adherence, optimal (≥ 80%) and intermediate (0.50 to 0.79) adherence levels were associated with a reduced risk of COPD incidence over time. Interventions aimed at improving adherence to prescribed medications in adult asthma patients should be intensified to reduce their risk of COPD.

**Keywords:** Asthma, COPD, medication adherence, severe asthma, propensity analysis

## 7.3 Introduction

Asthma is highly prevalent disease with substantial health and economic burden. In Canada, appreciable number of the population (12 years and older) are burdened with the condition with a growing prevalence rate of 8.4%[109]. Asthma results in increased morbidity, and it is a major cause of disability, increased hospitalizations, and low quality of life[253]. Fortunately, good asthma control through optimal medication adherence can help avoid costly asthma complications and exacerbations. To minimize asthma complications and exacerbations, treatment should be adjusted stepwise as recommended by the Global Initiative for asthma (GINA) guidelines and other guidelines [254,255,256]. Adhering to the recommended treatment is essential to optimize the benefit of the drug. Treatment adherence has been recognized as an important determinant influencing the effectiveness of the medications. Current clinical practice guidelines including the 2020 and 2019 GINA guideline recommend the use of low-dose inhaled corticosteroids (ICS)-formoterol (Symbicort) use as needed and for maintenance therapy [254,257]. Despite the known benefits of asthma medications, adherence remains suboptimal among adults, with rates ranging from 30-50% [255,258,259].

Poor adherence is linked to several clinical events including poor asthma control, asthma exacerbation, asthma-related emergency visits and hospitalizations, persistent eosinophilic inflammation, oral corticosteroids (OCS) use[260,188] and mortality[261]. In a meta-analysis by Engelkes et al (2015) [99], poor adherence to asthma medications was significantly associated with severe asthma exacerbations. Several researchers have also documented similar findings [259,251,262–265]. Also, approximately 5% of severe asthmatics are not optimally controlled with standard therapy and are classified as “difficult to control” [266] and subsequently develop airway remodeling that causes chronic irreversible airflow obstruction [267,268]. A recent meta-analysis has identified a significant association between early history of

asthma and later risk of COPD or asthma-COPD overlap (ACO) diagnosis with (odds ratio= 7.9; 95% Confidence Interval: 5.4-11.5) [154]. ACO is a clinical phenomenon characterized by the coexistence of asthma and COPD features in an individual. Individuals with ACO have increase disease exacerbation (increased emergency department visits and hospitalizations), poorer quality of life compared to asthma or COPD alone [269–271].

Although there exists a strong positive association between prior history of asthma and COPD diagnosis, the factors linking progression from asthma diagnosis to COPD over time remain largely unresolved. Currently, factors determining COPD incidence in asthma patients have not been well addressed, especially using a large population cohort study. Poor adherence to the various prescribed asthma and concomitant medications could be a contributing factor to this phenomenon. This important factor could play a mediating role in reducing the number of asthma patients who develop COPD.

Sub-optimal use of asthma medication and non-adherence to the various prescribed asthma medications could be a contributing factor to later development of COPD. There exists a significant gap in current research assessing the role of this important factor. Since achieving optimal asthma medication adherence (MA) has the potential of minimizing asthma exacerbations [99,248], our study investigated the effect of MA levels on the risk of developing COPD in later life. We hypothesize that improved adherence to asthma medications over time is likely to reduce asthma patients' risk of developing COPD in later life. The unique contribution of this study is based on investigating the long-term effects of asthma medication adherence levels over time and subsequent risk of COPD using a large population-based cohort with long-term follow-up.

## 7.4 Methods

### *Study design and data sources*

I employed a retrospective cohort study that utilized four linked administrative claims databases obtained from the PopData BC. The PopData BC captures health records of all BC residents registered in the province's universal insurance program [31]. The PopData BC includes longitudinal de-identified electronic medical data from primary care visits, general practitioners, and specialist consultants. These data are linkable both to each other and to other externally managed datasets [116]. This study was approved by the Health Research Ethics Board (HREB) at Memorial University in Newfoundland, Canada (REF #: 2019.216). The DSC and the BC MoH approved the following four patient databases to be assessed for this study:

**i**) The *Discharge Abstract Databases* (DAD) [155] for hospital separations, which captures data on discharges and hospitalizations of in-patients and day surgery patients from acute care hospitals in BC;

**ii**) The *Medical Service Plan* (MSP) database [158], which captures records of physician visits;

**iii**) the *PharmaNet database* [157], which contains records of all medications prescribed and medical supplies dispensed from community pharmacies in BC; and

**iv**) the *registration and demographic* (consolidation file) database, which provided data on the demographic and longitudinal registration status of patients in the healthcare system of BC [159].

I obtained all health records captured in the four databases from January 1, 1998, to December 31, 2018. I defined the index period (January 1, 1998, to December 31, 1999) as the date in which patients were first identified in the database with a diagnosis of asthma. Thus, the 2-year index period was used as the '*wash-in'* period to allow sufficient time for

prevalent asthma to be identified. The follow-up period for this study spanned from January 1, 2000, to December 31, 2018.

***Case identification – Index cohort at baseline***

The study selected patients with a physician diagnosis of asthma (January 1, 1998 to December 31, 1999) using a validated case definition [31,116]. Based on the case definition, asthma patients were identified from three databases (DAD, MSP, and PharmaNet) based on at least one of the following criteria:

i) Patients having one or more asthma-related hospitalizations based on International Classification of Diseases-9th edition (ICD-9): 493.x, ICD-10th edition: J45, J46) during a 12-month rolling window.

ii) Patients with two or more records of physician visits with asthma diagnostic codes (ICD-9 codes: 493.x).

Patients identified with either criteria 1, 2, or both, were also checked for records of filled prescriptions for at least four asthma-related medications within 1 year in the PharmaNet database (See Table 4.2 for medication lists). I applied the case definition criteria to identify asthma patients 18 years and older with no diagnosis of COPD from January 1, 1998 to December 31, 1999. I further excluded incident cases of COPD among the identified asthma patients at baseline during cohort identification. The identified cohorts were followed from January 1, 2000, to December 31, 2018, for the diagnostic outcome of COPD.

***Primary exposure variable of interest – medication adherence***

The primary exposure variable was *medication adherence* (MA). I employed the *proportion of days covered* (PDC) as a proxy for assessing the level of adherence to prescribed medications [212,202,272]. The PDC was calculated as the ratio of the number of days

of medication covered, or drug-on-hand, to the sum of days within the treatment period [186,212,202,272]. The PDC was estimated from the PharmaNet database using the 'days of medication supply', 'fill/refill date', and 'drug identification number' variables. Using the 'SAS Macro' by Chang et al (2015) [273], I calculated the PDC rates and adjusted for inpatient stays by censoring the number of hospitalized days during the measurement period. The study estimated medication adherence for all prescribed single and multiple controller medications [*inhaled corticosteroids* (ICS), *Long-acting beta-2 agonist* (LABA), ICS/LABA combination, and *Leukotriene receptor antagonist* (LTRA)] and short-acting beta-2 agonist (SABA). Choudhry et al. (2009) [250] outlined three proposals for computing adherence among patients with concomitant medication prescriptions. Based on the first approach by Choudhry et al. (2009) [250], I averaged the estimated adherence rates for each medication class at the patient level. That is, if more than one medication was prescribed for a patient, mean adherence was calculated at the patient level. The adherence rates were categorized into the optimal-adherence ($\geq 0.80$), intermediate-adherence (0.50-0.799), and low-adherence ($< 0.5$) levels. The study used the 0.80 cut-off value for assessing the optimal adherence, as it has been documented as the optimal threshold for achieving important clinical outcomes in adult asthma patients [99,167].

***Secondary variable-asthma severity***

Asthma severity level was defined based on the criteria specified in the Canadian Asthma Consensus Guidelines for assessing the severity and control of patients with asthma. Based on the algorithm developed by Firoozi and colleagues (2007) [168], I defined asthma severity levels based on the degree of prescribed ICS/other controller medications, prescription of short-acting-beta 2 agonist, and whether there is an indication of markers of moderate-to-severe asthma exacerbations (asthma-related hospitalization or emergency

department visits due to asthma) or not. Thus, asthma severity levels were defined as follows: a) *mild asthma* group corresponds to having a prescription of 0-500µg/day doses of inhaled corticosteroids (ICS) [including budesonide, fluticasone, beclometasone, ciclesonide] and not receiving additional controller therapy or having ICS doses of 0-250µg/day for patients receiving additional controller therapy. Also, patients were classified into the *mild asthma* category if they did not have a marker for a moderate to severe exacerbation or had taken at least an average of three short-acting beta-2 agonists (SABA) doses per week for a 12 -month period. Patients were classified into the *moderate asthma* category if they were prescribed with >500µg/day doses of ICS with no additional usage of controller therapy or had a prescription of >250µg/day doses of additional controller therapy, except for those with high SABA usage and moderate to severe asthma exacerbations. Patients were classified as *severe* if they had records of a prescription of >1000µg/day ICS doses, except for patients with markers of uncontrolled asthma (i.e., taking > 10 doses of SABA per week).

***Study outcome: Time-to-incidence of COPD***

The primary study outcome was the time-to risk of COPD diagnosis in asthma patients. The study defined COPD during the follow-up period (January 1, 2000, to December 31, 2018) using a validated case definition. I used the Chen et al.'s (2017) [50] case definition, which has been validated against chart reviews with high sensitivity and specificity. Thus, the study identified COPD patients based on the presence of at least one hospitalization or two or more outpatient visits on different dates with COPD as the most responsible diagnosis (using ICD-9 codes: 491.xx, 492.xx, 493.2x, 496.xx; and ICD-10-codes: J43.xx, J43.xx, J44.xx).

### 7.4.1 Propensity adjusted covariates

At baseline, several covariates were identified based on the literature and the availability of complete information on variables in the database to be controlled for as confounders. The limited extant literature, although mixed, listed variables such as obesity, history of cigarette smoking, air pollution, particulate matter, and sex as potential risk factors for incidence of COPD in the Canadian population [77,78]. Additionally, various socio-demographic characteristics, such as patient sex and age, were selected for analysis. I scanned the diagnosis codes in medical claims during the baseline and the post-index period (follow-up) to identify various comorbidities. Using the identified comorbid conditions, I estimated the Charlson comorbidity index (CCI) as a marker for the comorbidity burden of patients by excluding asthma from the score [252]. Comorbidity burden was classified into three categories based on a documented cut-off point by Nunez et al. (2004) [164] : -CCI score 0; CCI score 1; CCI score ≥ 2; where higher score accounted for greater comorbidity burden in the adjusted analysis. Asthma-related comorbidities, such as sinusitis and upper respiratory diseases, were also identified at baseline and examined. Asthma exacerbations were considered as one of the covariates and defined as either oral corticosteroid (OCS) claims, emergency room visits, and/or asthma hospitalizations [186,189112]. I further scanned the medical claims database to identify patients' use of tobacco and nicotine dependence, categorized as presence =1 or absence=0. A study by Wiley et al. (2013) [274] supports the use of ICD-codes for identifying smokers or smoking status in a clinical population. Also, I included obesity (coded as 1 for body mass index (BMI)>30kg/$m^2$ and 0 otherwise) as one of the risk factors extracted from the database. In addition, emergency hospital admission and length of hospital stay were considered as possible risk factors.

### 7.4.2 Statistical methods

Standard descriptive statistics were used to describe the baseline characteristics. I performed all the statistical analyses in both SAS version 9.4 and STATA version 16. I estimated the mean, median, standard deviation, and interquartile range (IQR) of the continuous variables, and constructed frequency and relative frequency tables for categorical variables. The study employed the Pearson chi-square test to test the association between categorical covariates and adherence levels at baseline. Also, the authors performed the one-way *analysis of variance* (ANOVA) and Kruskal-Wallis test to test significant differences between the means and medians of the continuous variables among the three MA levels.

***Propensity-score derivation***

Using multinomial logistic regression, propensity scores, estimated as the probability of adherence conditional on baseline covariates associated with COPD, were generated and adjusted for in the primary analysis. The model included the predicted probability of predefined levels of MA; that is, optimal, intermediate, and low levels of medication adherence. Significant covariates for COPD included in the propensity score included the patient's age, sex, Charlson comorbidity index, asthma-related comorbidities (such as upper respiratory diseases & sinusitis), asthma-related hospitalizations, emergency department visits, asthma exacerbation, length of hospital stay, tobacco use/nicotine dependence, and asthma severity at baseline. These factors were independently and significantly associated with COPD outcome in a bivariate logistic regression model. Obesity was not significantly related to the risk of COPD, but was included in the propensity score model since earlier studies have documented obesity as a risk factor for COPD in asthma patients [78].

***Primary analysis-assessment of MA to all prescribed medications***

The primary analysis was to assess the independent effects of medication adherence (MA) and asthma severity (physician-diagnosed) on the risk of COPD, adjusting for other relevant patient covariates and confounders using the inverse probability treatment weighted (IPTW) estimates and propensity cores generated at baseline.

I used multivariate *marginal structural Cox's* (MSC) model with *Inverse Probability Treatment Weighting* (IPTW) that included time-varying medication adherence level, asthma exacerbation, and asthma severity, in addition to all baseline covariates adjusted for potential confounders using propensity scores. Due to the presence of time-varying exposure (medication adherence), time-varying asthma exacerbation, and asthma severity, using any of the forms of standard Cox proportional hazard models (i.e., standard Cox and time-dependent Cox models) could lead to biased estimates. Also, the longitudinal nature of the database with the inclusion of repeated measurements in the presence of time-dependent covariates violates the proportional hazard assumption and makes the standard Cox's model inappropriate for the analysis of this dataset. Moreover, the time-dependent Cox model is unlikely to properly adjust for time-varying confounders, resulting in biased estimates. The Marginal Structural Cox model addresses the limitations of both the standard Cox's proportional and time-dependent Cox's models by employing inverse probability of exposure weighting to provide consistent and unbiased estimates of the effect of the main exposure of interest [130275]. Time-varying/dependent confounders and covariates included in the multivariate structural Cox's model were time-dependent medication adherence levels (*low*, *intermediate*, and *optimal*), asthma severity levels (*mild*, *moderate*, *severe*), and asthma exacerbations over time. Each analysis was evaluated at 5-year, 10-year, and 18-year (overall) follow-up periods.

***Secondary analysis-assessment of MA to specific medication classes***

The secondary analysis was performed to assess the specific effect of adherence to various individual and combined asthma medications, including short-acting beta-2 agonist (SABA), long-acting beta-2 agonist (LABA), and inhaled corticosteroids (ICS), adjusting for other relevant patient covariates and confounders using the propensity scores generated. Effect modification using interaction terms was performed for both primary and secondary analysis to assess the differential effect of medication adherence by the severity of asthma.

## 7.5 Results

### 7.5.1 Patient characteristics at baseline

A total of 68,211 adult asthma patients were identified from the four linked databases obtained from the PopData BC (see Figure 6.1 in the supplementary material). Overall, the distribution of the sample by medication adherence levels at baseline were low-level (n=46, 666, 68.4%), moderate-level (9,557, 14.0%), and optimal-level (11,988, 17.6%). At the cohort entry, there were 49,155(72.06%) patients diagnosed with *mild asthma*, 15,595(22.87%) *moderate,* and 3,461(5.07 %) *severe,* with an overall mean age of 48.2 years. The patients' baseline characteristics are presented in Table 7.1 stratified by medication adherence (MA) levels.

**Table 7.1: Cohort characteristics by asthma medication adherence levels for the patient at baseline**

| Variables | Overall | Medication Adherence (MA) levels | | | |
|---|---|---|---|---|---|
| | | Low-level (PDC<0.50) | Intermediate (PDC=0.5-0.79) | Optimal (PDC: ≥80%) | P-Value |
| N | 68,211 | 46,666 (68.4%) | 9,557 (14.0 %) | 11,988 (17.6%) | |
| *Socio-demographic* | | | | | |
| Mean age, (SD in years) | 48.20 (18.63) | 46.50 ±18.12 | 50.89 ±18.09 | 52.71 ±19.29 | <0.0001 |
| Male Sex | 27,756(40.69) | 18306(39.23) | 4136(43.28) | 5314(44.33) | <0.0001 |
| Obesity (BMI>30kg/$m^2$) | 205(0.30) | 134(0.29) | 25(0.30) | 46(0.40) | 0.171 |
| Tobacco/nicotine use | 96(0.14) | 59(0.10) | 18(0.20) | 19(0.20) | 0.288 |
| *Charlson comorbidity index* | | | | | |
| Score=0 | 66,766 (97.90) | 45906(98.37) | 9277(97.07) | 11583(96.62) | <0.0001 |
| Score=1 | 1,226 (1.80) | 615(1.32) | 251(2.63) | 360(3.00) | |
| Score ≥2 | 219(0.30) | 145(0.31) | 29(0.30) | 45(0.38) | |
| *Clinical variables/outcomes* | | | | | |
| Sinusitis | 108(0.16) | 74(0.16) | 15(0.16) | 19(0.16) | 0.999 |
| URI | 284(0.42) | 174(0.37) | 42(0.44) | 68(0.57) | 0.012 |
| Asthma hospitalization | 2,701(3.96) | 1760(3.77) | 389(4.07) | 552(4.60) | <0.0001 |
| Emergency department visit | 3,158(4.63) | 2295(4.92) | 354(3.7) | 509(4.25) | <0.0001 |
| Asthma exacerbation | 5,585(8.19) | 3871(8.30) | 705(7.4) | 1009(8.42) | 0.007 |
| Hospital stay [median (IQR)] | 3.0(2-6) | 3.0(2-6) | 4(2-7)) | 4(2-7) | 0.009 |
| *Asthma severity at baseline* | | | | | |
| Mild asthma | 49,155(72.06) | 33730(72.28) | 7205(75.39) | 8220(68.57) | |
| Moderate asthma | 15,595(22.87) | 10776(23.09) | 1851(19.37) | 2968(24.76) | <0.0001 |
| Severe asthma | 3,461(5.07) | 2160(4.63) | 501(5.24) | 800(6.67) | |
| *Asthma medications prescribed* | | | | | |
| SABA only | 14037(20.58) | 10718(22.97) | 1464(15.32) | 1855(15.47) | <0.0001 |
| ICS only | 5842(20.58) | 4220(9.04) | 751(7.86) | 871(7.27) | <0.0001 |
| ICS/LABA combination | 90(0.13) | 57(0.12) | 12(0.13) | 21(0.18) | 0.355 |
| ICS+SABA only | 39451(57.84) | 26354(56.47) | 5870(61.42) | 7227(60.29) | <0.0001 |
| ICS+LABA only | 6639(9.73) | 4003(8.58) | 1148(12.01) | 1488(12.41) | <0.0001 |
| Others | 2152(3.15) | 1281(2.75) | 324(3.39) | 547(4.56) | <0.0001 |

BMI= Body Mass Index, URI=Upper Respiratory Infections, SABA= Short acting beta-2 agonist, LABA=Long-acting beta-2 agonist, ICS/LABA=Inhaled corticosteroids/Long-acting beta-2 agonist; other medications included leukotriene receptor antagonists (LTRA) and theophylline, IQR=interquartile range, SD=standard deviation.

The prevalence of patients' clinical variables at baseline included asthma hospitalizations (n=2701, 3.96%), emergency department visits (n=3158, 4.63%), and median (interquartile range) length of hospital stay as 3.00 (2-6) days. The patients collected a number of prescribed asthma-related medications. Prevalence of prescription medication includes inhaled corticosteroids (ICS) only (n=5842, 20.58%); short-acting beta-2 agonist or SABA only (n=14037, 20.58%), ICS/LABA combinations (n=90, 0.13%). Also, a total of (6639, 9.73%) were prescribed with both ICS and LABA separately at the same time, and 39451(57.84%) prescribed with ICS and SABA separately at the same time.

### 7.5.2 Survival trend within the 18-year follow-up period

The 18-year incidence of COPD in the overall cohort was 9.81 per 1000-person years. Figures 7.1 and 7.2 present the survival curves for the overall 18-year follow-up for COPD stratified by medication adherence and severity of asthma obtained from Cox's survival model. Asthma patients with sub-optimal (or low) levels (MA< 0.5) and a history of severe asthma are at increased risk of COPD diagnosis later in life.

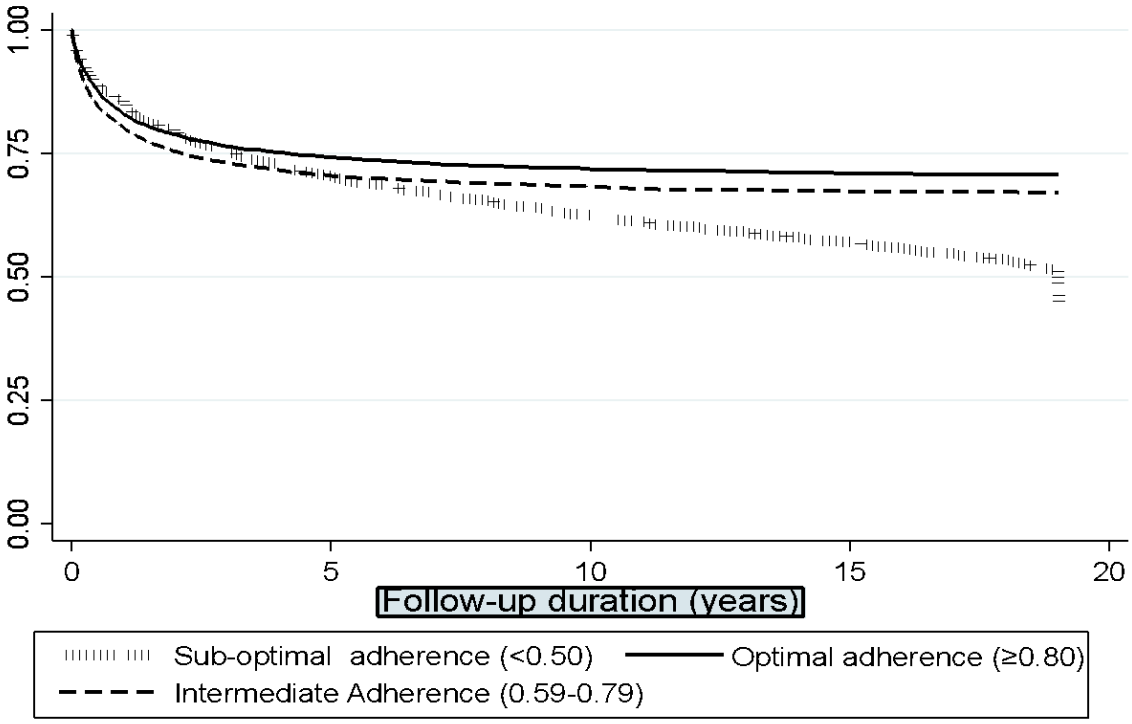


**Figure 7.1**. Adjusted survival curves for time-to incidence of COPD stratified by medication adherence

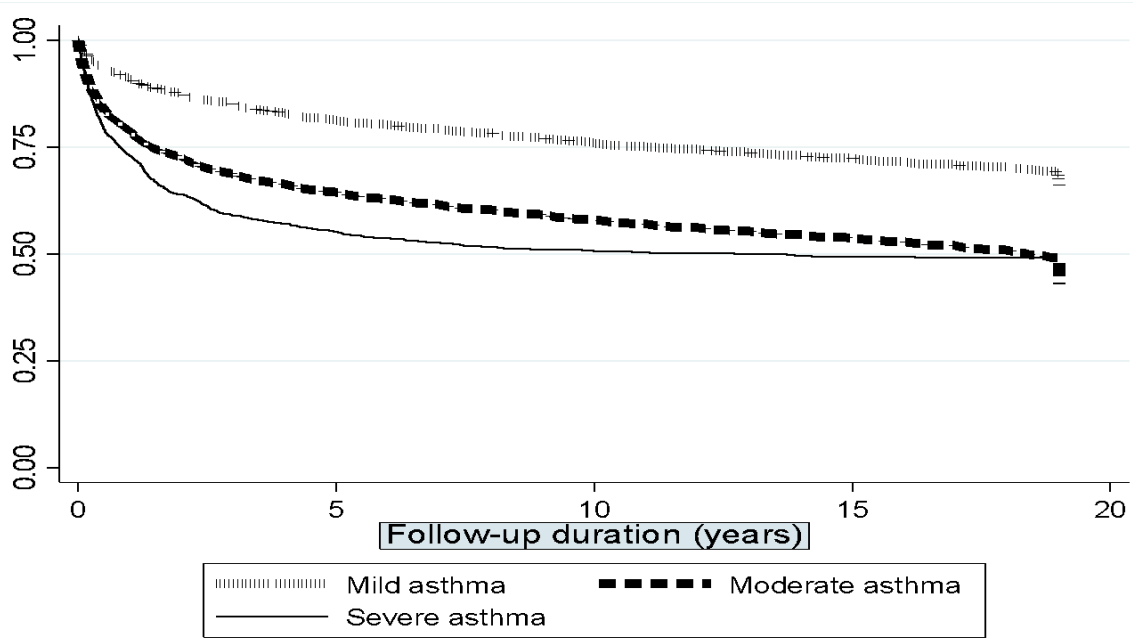


**Figure 7.2**. Adjusted survival curves for time-to incidence of COPD stratified by asthma severity

***Bivariate analysis of baseline factors and risk of COPD***

Table 7.2 present the bivariate association between the various baseline factors and risk of COPD in asthma patients. All significant covariates presented at baseline were included in the derivation of the propensity score used in the multivariate analysis for assessment of the effect of medication adherence and severity of asthma over time. Obesity was not significantly related to the risk of COPD, but was included in the propensity model, since earlier studies have documented obesity as a risk factor for COPD in asthma patients [46].

**Table 7.2: Patient baseline factors associated with the risk of COPD in bivariate analysis (18-year follow-up).**

| Patient factors | Hazard ratio | 95% CI | *p*-value |
|---|---|---|---|
| Age (years) | 1.03 | (1.031, 1.04) | <0.0001 |
| Male sex | 1.27 | (1.23, 1.33) | <0.0001 |
| Charlson Comorbidity Index | 1.45 | (1.37, 1.54) | <0.0001 |
| *Asthma-related comorbidity* | | | |
| Sinusitis | 0.53 | (0.30, 0.94) | 0.029 |
| Upper respiratory diseases | 1.41 | (1.16, 1.73) | 0.001 |
| Asthma-related hospitalization | 1.18 | (1.09, 1.28) | <0.0001 |
| Emergency department visit | 0.94 | (0.85, 1.03) | 0.203 |
| Asthma exacerbation | 1.08 | (1.01, 1.15) | 0.019 |
| Length of stay (days) | 1.38 | (1.35, 1.40) | <0.0001 |
| Tobacco use/nicotine dependence | 1.78 | (1.28, 2.46) | 0.001 |
| Obesity (BMI>30) | 0.97 | (0.75, 1.27) | 0.846 |

### 7.5.3 Propensity weighted analysis of MA effect on COPD

From Table 7.3, the adjusted hazard ratios (aHR) for each of the primary and secondary analyses were estimated, comparing the effect of MA on COPD incidence at 5-year, 10-year, and 18-year (overall) follow-up.

Compared to the low (or sub-optimal) adherent patients, individuals who attained intermediate and optimal adherence levels in the 18-year follow-up period were 80% (aHR: 0.20, 95% CI: 0.18-0.23) and 81% (aHR: 0.19, 95%CI: 0.17-0.24) less likely to develop

COPD respectively after adjusting for asthma severity levels and the potential confounders in the propensity score for all prescribed asthma-related drugs. Similar trends were observed at 5-year and 10-year follow-up periods in the *primary analysis.*

Further, when compared to the mild asthma patients, severe and moderate asthma patients were at an increased risk of developing COPD with (aHR: 3.73, 95%CI: 2.74, 5.09) and (aHR: 1.68, 95% CI: 1.49, 1.89), respectively. The risk of COPD in severe asthma patients increased by more than threefold, while that of the moderate asthma group increased by a factor of 1.68.

**Table 7.3: Propensity-adjusted association between medication adherence, the severity of asthma and incidence of COPD**

| | 5-year | | 10-year | | Overall (18-year) | |
|---|---|---|---|---|---|---|
| Study factors | aHR(95%CI) | *p*-value | aHR(95%CI) | *p*-value | aHR(95%CI) | *p*-value |
| **(A) Primary analysis:** Adherence levels to all prescribed asthma medications combined | | | | | | |
| *Adherence measured by PDC* | | | | | | |
| Optimal-level | 0.33(0.31, 0.35) | <0.0001 | 0.25(0.23, 0.28) | <0.0001 | 0.19(0.17, 0.24) | <0.0001 |
| Intermediate | 0.35(0.33, 0.37) | <0.0001 | 0.27(0.25, 0.30) | <0.0001 | 0.20(0.18, 0.23) | <0.0001 |
| Low-level (or suboptimal) | ref | n/a | ref | n/a | ref | n/a |
| *Asthma Status* | | | | | | |
| Severe | 3.07(2.81, 3.35) | <0.0001 | 3.10(2.81, 3.44) | <0.0001 | 3.73(2.74, 5.09) | <0.0001 |
| Moderate | 1.65(1.57, 1.74) | <0.0001 | 1.53(1.43, 1.63) | <0.0001 | 1.68(1.49, 1.89) | <0.0001 |
| Mild | ref | n/a | ref | n/a | ref | n/a |
| **(B) Secondary analysis*:** Adherence asthma specific-medications | | | | | | |
| *Adherence to ICS only* | | | | | | |
| Optimal-level | 0.32(0.29, 0.37) | <0.0001 | 0.32(0.28, 0.37) | <0.0001 | 0.33(0.27, 0.41) | <0.0001 |
| Intermediate | 0.39(0.35, 0.44) | <0.0001 | 0.39(0.35, 0.44) | <0.0001 | 0.39(0.32, 0.47) | <0.0001 |
| Low-level | ref | n/a | ref | n/a | ref | n/a |
| *Adherence to combinations (ICS/LABA)* | | | | | | |
| Optimal-level | 0.29(0.25, 0.32) | <0.0001 | 0.26(0.22, 0.30) | <0.0001 | 0.25(0.20, 0.31) | <0.0001 |
| Intermediate | 0.40(0.35, 0.45) | <0.0001 | 0.37(0.33, 0.42) | <0.0001 | 0.30(0.26, 0.35) | <0.0001 |
| Low-level | ref | n/a | ref | n/a | ref | n/a |

Table include *adjusted hazard ratios* (aHR) and 95% *Confidence Interval* (95% CI). Propensity adjusted analysis using Marginal Structural Cox model (inverse probability weighted cox model) which adjusted for both baseline covariates and time varying covariates and confounders. ICS=*Inhaled corticosteroids*, LABA=Long-acting beta-2 agonist; MA=*Medication adherence*; PDC=*Proportion of Days Covered*. *Optimal level* = [PDC ≥ 0.80], *Intermediate level*= [0.50 ≤ PDC ≤ 0.79], *low-level (or suboptimal)* = [PDC <0.5]; ref=reference group; n/a= not applicable.
*Analysis are adjusted for severity of asthma.

***Drug-specific effect in secondary analysis***

Adherence to specific asthma medications such as ICS and ICS/LABA combinations and risk of COPD over 5-year, 10-year, and 18-year follow-up periods were also assessed. As shown in Table 7.3, patients who attained optimal adherence to their prescribed ICS over time were significantly less likely to develop COPD [aHR: 0.33, 95% CI: 0.27, 0.41] using inverse probability weighted estimates (stabilized weights), and after adjusting for propensity scores at baseline and asthma severity compared to the sub-optimal (low) ICS users. Similarly, patients with optimal adherence to prescribed combined ICS/LABA over the 18-year follow-up period were 75% less likely to develop COPD, 74% less likely to develop COPD in the 10-year follow-up, and 71% less likely to develop COPD in the 5-year follow-up compared to the non-adherent patients.

***Effect modification of MA by the severity of asthma***

Figure 7.3 presents an additional subgroup analysis of effect-modification of MA by asthma severity levels on COPD diagnosis in asthma patients. There was a significant effect modification of MA by asthma severity over time. For instance, individuals who attained optimal adherence in the mild asthma group, compared to low adherence patients, achieved the greatest protection from COPD risk with an adjusted hazard ratio and 95 % confidence interval of (0.18, 0.14-0.80, $p<0.0001$). Also, severe asthma patients who achieved optimal adherence (that is, PDC$\geq$ 0.80) over time, compared to low adherence in mild asthma patients, were not protected to a greater extent, with a 14% reduced risk of developing COPD (aHR: 0.86, 95% CI: 0.76-0.98). However, patients with low adherence (<0.5) and a history of severe asthma were 1.72 times more likely to be diagnosed with COPD.

| Subgroups | aHR | 95% CI | *p* -value |
|---|---|---|---|
| **1.1: Medication adherence modified by asthma severity** | | | |
| Adherence(Intermediate)*Moderate asthma | 0.32 | 0.29-0.35 | <0.0001 |
| Adherence(Optimal)*Moderate asthma | 0.27 | 0.24-0.32 | <0.0001 |
| Adherence(Low)*Moderate asthma | 0.75 | 0.50-1.13 | 0.1676 |
| Adherence(Intermediate)*Severe asthma | 0.62 | 0.51-0.75 | <0.0001 |
| Adherence(Optimal)*Severe asthma | 0.86 | 0.76-0.98 | 0.0239 |
| Adherence(Low)*Severe asthma | 1.72 | 1.52-1.93 | <0.0001 |
| Adherence(Intermediate)*Mild asthma | 0.22 | 0.19-0.26 | <0.0001 |
| Adherence(Optimal)*Mild asthma | 0.18 | 0.14-0.87 | <0.0001 |
| | | | |
| **1.2: Adherence to specific medications** | | | |
| **ICS** | | | |
| ICS adherence (Intermediate) | 0.39 | 0.32-0.47 | <0.0001 |
| ICS adherence (Optimal) | 0.33 | 0.27-0.41 | <0.0001 |
| **ICS/LABA** | | | |
| ICS/LABA Adherence (Intermediate) | 0.30 | 0.26-0.35 | <0.0001 |
| ICS/LABA Adherene (Optimal) | 0.25 | 0.20-0.31 | <0.0001 |

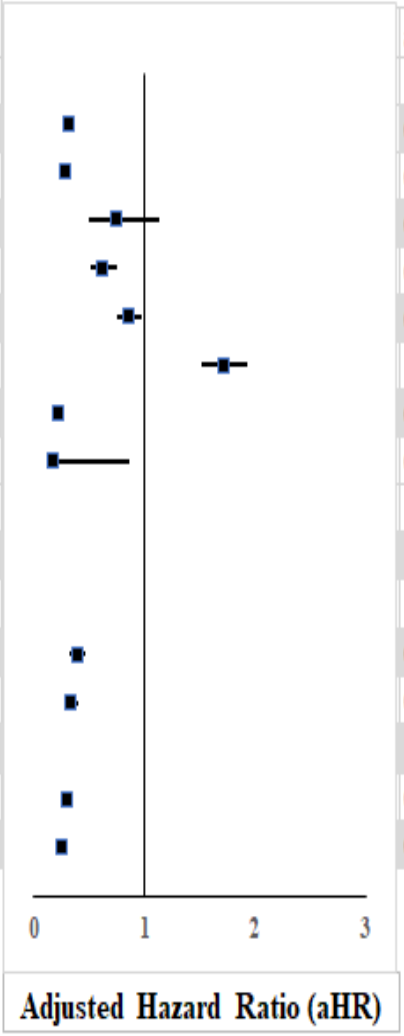


**Figure 7.3**. Association between medication adherence and risk of COPD modified by severity of asthma severity levels.

All analysis adjusted for Inverse probability weighted at baseline and time-varying covariates/confounders in the structural Cox Model; aHR= adjusted hazard ratio, 95%CI=95% confidence interval. *Reference category for subgroup 1.1 is "*low adherence*mild asthma*" *Reference category for subgroup 1.2 is "*low adherence*"

## 7.6 Discussion

*Medication adherence* (MA) has been recognized as an important determinant influencing treatment outcomes of asthma patients. Previous studies have shown a significant association between sub-optimal MA and several clinical events including poor control, increased exacerbation with related emergency visits and hospitalizations, persistent

eosinophilic inflammation, increased oral corticosteroids use [188260] and mortality [261] among asthma patients [99,167,190,218,221,230]. Current clinical practice guidelines recommend a stepwise treatment approach and the use of potent maintenance therapy for managing the disease [5,33]. Despite the known benefits of asthma medications, adherence remains suboptimal among adult asthma patients, with rates ranging from 30-50% [86,88,190]. The current study built on the previous literature and added global evidence for the association between medication adherence and incidence of COPD among patients diagnosed with asthma and followed up for an 18-year period. This study assessed the impact of medication adherence on the risk of COPD by using administrative data from the Province of British Columbia, Canada.

In this large observational cohort of asthma patients, I found poor (low) MA as a significant determinant of developing COPD in asthma patients. The 18-year incidence of COPD in the overall cohort of asthma patients (n=68,211) was 9.8 per 1000-persons year. Following adjustment for potential confounding factors using propensity analysis and IPTW estimates, I found a significant association between asthma MA and risk of incidence of COPD. *Suboptimal* level of MA was associated with increased risk of COPD incidence as early as 5-years after asthma diagnosis. Numerous sensitivity analyses using asthma-specific medications (ICS alone and ICS/LABA combinations) performed in this study demonstrated consistent findings of increased risk of COPD diagnosis associated with low or suboptimal adherence to medications in asthma patients, even after adjusting for time-dependent asthma severity. *Severe asthma* patients were 3-fold times more likely to be diagnosed with COPD later in life, independent of other confounding factors that were controlled for in the propensity analysis. However, the association of MA with COPD incidence was modified by asthma severity levels, with poorly adherent severe asthma patients bearing the greatest burden of early diagnosis of COPD. That is, poorly adherent severe asthma patients were

1.72 times more likely to develop COPD over the 18-year follow-up period compared to mild asthma patients.

This study provides some important clinical insight into the risk profile of suboptimal adherence to asthma medications and subsequent disease exacerbations. The results corroborate our recent meta-analysis of seven observational studies, which indicated an overall increased risk of the early history of asthma significantly associated with later risk of COPD diagnosis in adulthood [154]. Also, the results of the present study are partly consistent with previously conducted studies that investigated optimal adherence and reduced risk of asthma exacerbations [99,167,189,221]. However, the previous studies did not investigate the further association between *optimal*, *intermediate,* or *low* adherence levels of MA and the risk of COPD diagnosis in a long-term follow-up. In addition, previous studies did not evaluate the impact of time-varying adherence to asthma medications on the risk of COPD. Moreover, the long-term effect of compliance and non-compliance to the various treatment regimens and risk of developing COPD in asthma patients have not been fully investigated in a large population-based study. This study fills these gaps in the literature through the adoption of a large administrative database with an 18-year follow-up period. Since asthma is a chronic disease with no cure, it is important to understand the long-term effects of changes in medication adherence levels on the risk of COPD over time.

Our study also adds to the evidence in the current literature [99,167,189,218,221] that improved adherence to asthma medications over a long period improves asthma control, and so may delay the risk of COPD diagnosis. Additionally, the reduced risk of COPD onset may plausibly be attributed to the healthcare provider's adherence to updated clinical practice guidelines such as the Global Initiative for Asthma [33], British Thoracic Society [35], and Canadian practice guidelines [180]. The guidelines recommend potent and effective long-term anti-inflammatory medications that help maintain asthma-control over time.

This observational population-based analysis contributes to the growing body of knowledge that provides evidence for the role of MA in the outcomes of asthma patients. The major strength of this study is that I have examined the association between changes in medication adherence levels, asthma severity over time, and risk of COPD among asthma patients. The results indicate that mild, moderate, and severe asthma patients who achieved optimal adherence, or mostly comply with the guideline-directed treatments, are less susceptible to asthma exacerbations and COPD diagnosis. Health care providers (HCPs) should adopt an innovative and cost-effective intervention to achieve optimal medication adherence in patients with severe asthma. For instance, an effective multi-component mobile health intervention has recently been developed for improving adherence to asthma controller medications [103]. In addition, HCPs can help improve inhaler techniques as one of the possible solutions to nonadherence to asthma inhaler medications. This could be done through both HCP and patient education on inhaler techniques to promote the proper usage of inhalers, and thereby achieve optimal adherence [276].

***Limitations***

The use of an administrative claim database for population-based studies presents some limitations that might have affected the study. First and foremost, the PDC measure used as a proxy for medication adherence was calculated based on filled/refilled claims and the sum of days covered, and so does not guarantee that patients actually ingested the medications. However, healthcare database adherence rates have been documented to demonstrate concordance with adherence rates estimated from some objective methods, such as pill counting and electronic monitoring [277,278]. Also, I adjusted for inpatient stays or days hospitalized from the calculation of the medication adherence, and thus, the estimates derived reflected actual medication use.

Furthermore, the linked database had limited data on physical examination variables, laboratory tests, and some patient lifestyle factors. Therefore, some of these unmeasured and limited variables in the data could have possibly resulted in residual confounding in the model. Also, there were limited records on the history of tobacco use and obesity in the administrative database used. However, these limitations were accounted for to a larger extent since I included and adjusted for some important baseline and time-varying confounders and covariates, such as obesity, asthma severity levels, tobacco use history, and asthma exacerbation using the Marginal Structural Cox model, which provides a robust adjusted estimate for making inferences. Although the data used lacked detailed clinical information, the use of a large administrative population database added relevant information that reflected the real-world setting. Therefore, the results of this study can be generalized to other populations with similar demographics in other provinces or territories in Canada and to other parts of North America.

***Conclusion***

This study investigated the association between changes in medication adherence levels (optimal, moderate, and low/poor) and risk of COPD diagnosis among patients in an 18-year follow-up period that spanned from January 1, 2000, to December 31, 2018. From the Marginal Structural Cox model, optimal adherence to medication in adult asthma patients over time was significantly associated with reduced risk of COPD diagnosis in later life. Specifically, patients who optimally adhered to asthma controller medications such as ICS and ICS/LABA were significantly protected from the risk of COPD onset after adjusting for important patient factors. Additionally, severe and moderate asthma patients were at an increased risk of COPD incidence compared to mild asthma patients over time, with severe asthma patients having the greatest risk. However, the association was modified by asthma

severity levels, with poorly adherent severe asthma patients 1.72 times more likely to develop COPD over the 18-year follow-up period compared to mild asthma patients. Healthcare providers and policymakers should intensify programs aimed at improving ongoing adherence to all prescribed asthma medications, specifically ICS and ICS/LABA, in severe asthma patients to minimize their risk of COPD diagnosis.

# Chapter 8: Association of Short-Acting-β-2 Agonist (SABA) overuse and risk of COPD among adult asthma patients

**Under Review @ Journal of Asthma**

## 8.1 Overview

The existing evidence has established a significant association between overuse of *short-acting beta 2 agonists* (SABA) and higher risk of future asthma exacerbations, mortality, and increased asthma-related hospitalization. Despite recent clinical practice guidelines recommending against the prescription of SABA as a monotherapy, excessive SABA use and suboptimal adherence to maintenance medications persist. Studies are yet to investigate a potential association between overuse of SABA and subsequent risk of COPD. The findings in Chapter 4 identified SABA overuse as one determinant that predicts COPD risk in asthma patients. Therefore, the independent effect of excessive SABA use and subsequent risk of COPD is unclear. This study aims to investigate the association between SABA overuse and subsequent risk of COPD using a large population cohort study.

## 8.2 Abstract

*Background*: Despite the well-known availability of treatment guidelines on the proper use of asthma medications, excessive SABA and suboptimal adherence to controller medications persist. However, the link between overuse of inhaler bronchodilators among asthma patients and the risk of COPD diagnosis remains unknown.

*Methods*: I conducted a retrospective observational study using four linked population-based administrative claim databases from the PopData BC. The study included adult asthma patients aged 18 years and older during the index period from January 1, 1998, to December 31, 1999, using ICD codes and *drug identification numbers* (DINs). The identified patients were followed to measure COPD incidence and asthma exacerbations from January 1, 2000,

to December 31, 2018. The primary exposure variable "*short-acting beta-2 agonist* (SABA) overuse" was defined as the collection of more than two (2) SABA canisters in a calendar year. The standard Cox proportional hazard model was employed to examine the association.
*Results***:** A total of 14,036 adult asthma patients with prescription of SABA only between January 1, 1998, to December 31, 1999, and with a mean age of 48.2 years met the study's inclusion criteria based on a validated case definition. In the multivariate Cox proportional hazard model, overuse of SABA only at baseline was significantly associated with increased risk of COPD compared to appropriate SABA users at the 5-year follow-up period [adjusted Hazard Ratio (aHR): 2.35, 95% CI:1.92-2.87), (aHR: 2.38, 95% CI: 2.0-2.83) at the 10-year follow-up period, and (aHR: 2.38, 95% CI: 2.03, 2.78) at the 18-year follow-up duration after controlling for all relevant covariates and confounders.
*Conclusion*: Regular use of inhaler bronchodilators such as SABA was significantly associated with increased risk of COPD incidence in as early as 5-years of follow-up and subsequent 10 and 18-year follow-ups. Interventions aimed at improving healthcare providers' adherence to the updated asthma clinical practice guidelines should be prioritized to minimize excess prescription of short-acting bronchodilators.

**Keywords**: Short-acting beta-agonists, SABA, bronchodilators, asthma, COPD, asthma medications

## 8.3 Background

Asthma is a common obstructive airway disease that increases morbidity and disability-adjusted life years. Worldwide, asthma affects an estimated 334 million people, and it is projected to affect about 400 million people by 2025 [153, 279]. Common asthma symptoms, such as dyspnea, wheezing, chest tightness, and coughing, reduce patients' quality of life and cause increased healthcare utilization costs [243],[108,280]. International and Canadian clinical practice guidelines recommend a stepwise approach for treating asthma patients [5,33, 180]. Inhaled bronchodilators, such as short-acting beta-2 agonists (SABA), temporarily relieve the symptoms associated with bronchoconstriction[5].

Earlier guidelines recommended SABAs for treating mild intermittent asthma as and when needed. In contrast, inhaled corticosteroids (ICS), alone or in combination with long-acting beta-agonists (ICS/LABA), are recommended for moderate to severe asthma patients. The changes in recent clinical practice guidelines have resulted in the use of ICS/LABA as the first-line medication for the treatment of asthma. Previous evidence highlights a history of safety concerns associated with excessive use of SABA as a monotherapy and /or with inappropriate maintenance drug use [179, 281]. Increased SABA use quickly relieves patient symptoms and masks underlying airway inflammation from being treated [281]. For instance, overuse of SABAs is linked to asthma-related deaths and a higher risk of severe exacerbations [112179], hospitalization [282], and increased levels of airway inflammation [283,284].

To treat the underlying airway inflammation and achieve asthma control, treatment guidelines recommend ICS-containing medications as the first-line controller therapy for patients of all ages. Additional therapies, including LABA and leukotriene receptor antagonists (LTRAs), are subsequently considered when asthma is not well controlled with low doses of ICS [5,180]. A meta-analysis conducted by Sobieraj et al. (2018) [181] concluded that

substituting SABA with fast-acting LABA/ICS therapy reduces patients' risk of severe exacerbations by one-third.

Despite the effectiveness of ICS, adherence is poor, particularly in patients with a low symptom burden [10]. Such patients over-rely on SABA alone to relieve symptoms. Administration of low doses of ICS and other maintenance therapies eliminates patients' exposure to SABA overuse [285]. The updated 2021 GINA guidelines recommend against using SABA as a monotherapy for treating asthma in adults and adolescents. Nonetheless, overuse of SABAs and poor adherence to maintenance therapies persist among asthma patients [286].

The association between SABA overuse and increased risk of asthma exacerbation and mortality has been well established. However, no study has investigated the relationship between the overuse of SABAs among asthma patients and the subsequent risk of COPD development. The factors linking excessive SABA use, poor adherence to controller medications, and susceptibility to severe exacerbations leading to COPD are unclear and yet to be uncovered. To the best of my knowledge, this study is the first to investigate the effect of SABA overuse on the risk of developing COPD diagnosis among asthma patients in a 20-year observational cohort study.

## 8.4 Methods

### 8.4.1. Study design and data source

This observational study used four administrative claims databases from the PopData BC. The PopData BC provides access to comprehensive healthcare, health services, and population health data for 4.7 million BC residents from 1985 onwards. The databases are longitudinal, person-specific, and de-identified (PopData BC, 2021). I used four approved databases from the PopData BC for this study. The approved databases included: i) the Discharge Abstract Database (DAD), which captures hospital separations[155]; ii) the Medical

Service Plan (MSP), which captured records of physician visits[156]; iii) the PharmaNet database, which provided records of dispensed medications[157]; and iv) the demographic and registration database [31,116]. I used the year interval "January 1, 1998, to December 31, 1999" as the study's index period to increase the prevalence of asthma cases. The index period in this study was defined as the period in which patients were first identified in the database as having received a diagnosis of asthma. All health records captured in the databases spanned January 1, 1998, to December 31, 2018. The study obtained ethics approval from the Health Research Ethics Board (HREB) at Memorial University of Newfoundland (REF #: 2019.216).

***Cohort definition***

The authors defined and extracted the study cohort from three databases (DAD, MSP, and PharmaNet) based on a validated case definition [31,160]. With reference to the case definition, asthma patients were identified based on meeting at least one of the following criteria:

i. Patients having at least one asthma-related hospitalization based on the International Classification of Diseases-9$^{th}$ edition (ICD-9): 493.x, ICD-10$^{th}$ edition: J45, J46) during a 12-month period.
ii. During a 12-month period, patients had at least two or more records of physician visits using asthma diagnostic ICD-9 codes: 493.x in the MSP database.
iii. Asthma patients identified (using ICD codes) from the MSP and DAD databases should have records of filled prescriptions for at least four-asthma-related medications within a 12-month period. (See the attached the asthma-related drug lists in the supplementary material in Table S4.2.)

After adopting the above previously validated case definition criteria, the study identified adult asthma patients aged 18 years and over with no record or history of COPD diagnosis from January 1, 1998, to December 31, 1999. The identified asthma patients were followed to measure study outcomes of interest from January 1, 2000, to December 31, 2018.

***Exposure measure***

The primary exposure variable was SABA use ('overuse' vs. 'appropriate use'). I quantified SABA use as the number of canisters collected within a calendar year, with a standardized SABA canister unit defined as 200 doses [112]. According to Bateman et al. (2008)[255], a well-controlled asthma patient will not use their SABA reliever more than twice a week (equivalent to at most two SABA canisters per year). SABA overuse was defined in this study as prescriptions filled for more than 2 SABA canisters annually (a 12-month period). Overuse of SABA was dichotomized as [appropriate use (≤ 2 SABA canisters], and Overuse (>2 SABA canisters). SABA exposure was restricted to only SABA prescriptions over the study period. Patients who were prescribed other asthma medications alone or in combination with SABA were excluded from the comparative analysis of appropriate use versus SABA overuse.

***Outcome measure***

The authors measured COPD diagnosis as the primary study outcome in the follow-up period (January 1, 2000, to December 31, 2018). Using a validated case definition for COPD with higher sensitivity and specificity, COPD was measured by the following criteria: i) patients with one or more hospitalizations or ii) patients with outpatient visits on different dates with COPD as the most responsible diagnosis (using ICD-9 diagnostic codes: 491.xx, 492.xx, 493.2x, 496.xx; and ICD-10-codes: J43.xx, J43.xx, J44.xx) [50]. The secondary

outcome was asthma exacerbation, defined as asthma-related hospitalizations or emergency room visits due to asthma. An individual was censored once they discontinued the inhaler medication, left the MSP, PharmaNet, and the DAD databases, or died or lost on the last follow-up day.

***Covariates***

Patient factors and covariates used in this study were based on evidence from the literature (risk factors of asthma and COPD) [77,78], and on the availability of relevant variables in the database used. Patients' demographic characteristics considered in this study were age and sex. Additionally, a recent study published in the "*COPD: Journal of Chronic Obstructive Pulmonary Disease*" by Asamoah-Boaheng et al. (2021)[287] identified asthma exacerbations, increased comorbidity index, a longer length of hospital stays, tobacco use, obesity and male sex, older age, male sex, and medication nonadherence as the significant risk factors for developing COPD in asthma patients. Thus, the Charlson comorbidity index (CCI) was estimated to measure the burden of comorbid conditions among adult asthma patients by excluding asthma from the score. The estimated CCI was further grouped into three categories based on Nunez et al.'s (2004)[164] CCI classification. Other relevant covariates included were asthma exacerbation (defined as asthma-related hospitalizations and/or emergency room visits or oral corticosteroids clams); history of tobacco use and nicotine dependence (coded as 1=yes, 0=no), obesity (1=obese, 0=normal weight); total length of hospital stay, asthma severity classifications (coded as 1=mild, 2=moderate, 3=severe); and medication adherence levels, defined as the proportion of days covered greater or equal to 0.80.

### 8.4.2 Statistical methods

The study used descriptive statistics to describe the baseline patient characteristics. All statistical analyses were performed using SAS version 9.4 and STATA version 16. The study used two measures of central tendencies (mean and median) and measures of dispersion (standard deviation, interquartile range) to describe the continuous patient variables at baseline. Further, frequency tables and proportions were employed to describe the categorical patient factors. Differences between any of the categorical variables and SABA overuse variables were tested using the Pearson Chi-square test. An independent sample t-test was used to test the difference between the mean ages of patients who *overused* and *appropriately* used their SABA medications. Wilcoxon signed-rank test was used to test the differences between the median days of hospital stay between individuals who overused and appropriately used their SABA. At the bivariate and multivariate analysis stage, the study employed the Cox proportional hazard model to examine the association between SABA use (*appropriate use* versus *overuse*) and risk of COPD diagnosis.

## 8.5 Results

### 8.5.1 Sample characteristics at baseline

A total of 14,036 adult asthma patients prescribed with only SABA satisfied the study's eligibility criteria (based on the case definition). The description of patient factors at baseline was stratified by SABA use levels (*overuse* and *appropriate use* ([≤2 SABA canisters]). Out of the 14,036 patients that received only SABA prescriptions at baseline, 7,011 patients overused their prescribed SABA at baseline (that is collecting more than 2 SABA canisters within a calendar year). Among individuals who overused their prescribed SABA, a total of 492 (7.02%) experienced asthma exacerbation. Length of hospital stay for

individuals who were over-relying on SABA was 2.0 days with interquartile range (IQR) of (1.0 to 5.0). Similarly, the median length of hospital stay among *appropriate SABA* users was 2.0 days with IQR: (1.0 to 4.5). Patient age, sex, and CCI differed significantly between individuals who overused their prescribed SABA and appropriate SABA users. Furthermore, history of tobacco use and nicotine dependence, obesity, asthma-related comorbidities (sinusitis and upper respiratory infections), and median length of hospital stay were similar across the two SABA groups at baseline (see Table 8.1). Additionally, Figure 8.1 shows the survival curves of the effects of SABA overuse at baseline and COPD risk over the 18-year follow-up period.

**Table 8.1: Univariate analysis of baseline patient variables by SABA use levels**

| **Baseline variables** | **SABA use** | | |
|---|---|---|---|
| | **SABA use (≤ 2 SABA Canisters) n=7025** | **SABA overuse (> 2 SABA canisters) n =7011** | ***P*-value** |
| N | | | |
| Mean age (SD) | 39.42(15.71) | 42.19(18.09) | <0.0001 |
| Age category | | | |
| < 30 years | 2207(31.42) | 2150(30.67) | |
| 30-39 years | 1810(25.77) | 1589(22.66) | <0.0001 |
| ≥ 40 years | 3008(42.82) | 3272(46.67) | |
| *Sex* | | | |
| Male, n (%) | 2602(37.04) | 3352(47.81) | |
| Female n (%) | 4423(62.96) | 3659(52.19) | <0.0001 |
| Obesity (BMI>30kg/$m^2$) | 11(0.16) | 10(0.14) | 0.831 |
| Tobacco/nicotine use, n (%) | 5(0.07) | 10(0.14) | 0.108 |
| *Charlson comorbidity index* | | | |
| Score 0, n (%) | 6974(99.27) | 6918(98.67) | |
| Score 1, n (%) | 40(0.57) | 78(1.11) | 0.003 |
| Score ≥ 2, n (%) | 11(0.16) | 15(0.21) | |
| Asthma exacerbation, n (%) | 381(5.42) | 492(7.02) | |
| Length of hospital stay [*median days (IQR*)] | 2.0(1.0-4.5) | 2.0(1.0-5.0) | 0.726 |
| Medication adherence (PDC≥0.80) | 669(9.52) | 1409(20.10) | <0.0001 |

IQR=Interquartile range, SD=standard deviation, SABA=short acting beta-2 agonist, ICS=inhaled corticosteroids, LTRA=Leukotriene receptor antagonists, LABA=Long-acting beta-2 agonist, PDC=proportion of days covered.

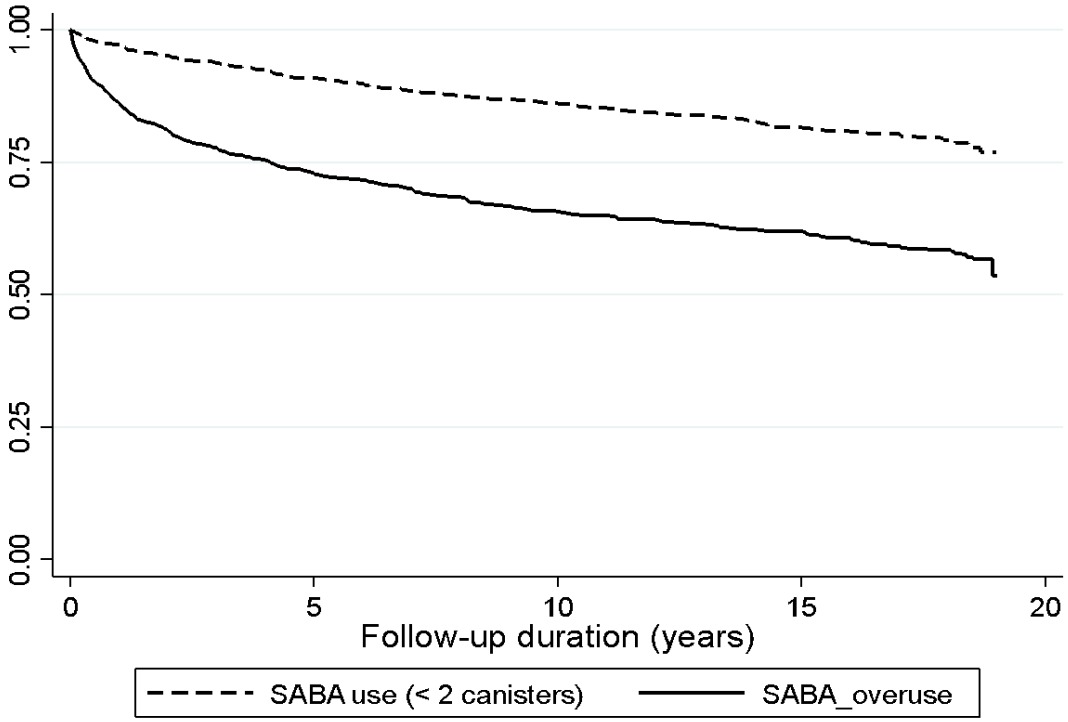


**Figure 8.1. Survival curve for incidence of COPD stratified by SABA overuse levels**

### 8.5.3 Multivariate analysis

The authors conducted a multivariate Cox proportional hazard model to examine the effects of excessive use of SABA at baseline and risk of development of COPD in the follow-up period. The primary exposure variable of interest was SABA use, dichotomized as SABA overuse (> 2 SABA canisters) and appropriate use (≤ 2 SABA canisters). The study adjusted for the following baseline factors in the model: patient's sex, history of tobacco use and nicotine dependence, obesity, CCI, asthma-related comorbidities, asthma exacerbation, length of stay, and medication adherence levels. After controlling for all the relevant covariates and confounders, patients who overused their prescribed SABA compared to appropriate SABA users were significantly associated with an increased risk of developing COPD during the 18-year follow-up period with an adjusted hazard ratio and confidence interval of aHR: 2.38, 95% CI: 2.03-2.78. Furthermore, during the 10-year follow-up period, overuse of SABA was significantly associated with an increased risk of COPD (aHR: 2.38, 95% CI: 2.00-2.83)

compared to appropriate use (≥2 SABA canisters). Likewise, compared to proper SABA users, individuals who over-relied on SABA and excessively used SABA were 2.35 times more likely to develop COPD over a 5-year follow-up period after controlling for relevant covariates [aHR; 2.35(1.92, 2.87)].

Further, the study analyzed the link between SABA overuse and the risk of asthma exacerbations during the observation period. From Table 8.2, patients who used more than two SABA canisters were at an increased risk of experiencing asthma exacerbations. For instance, patients who used more than 2 SABA canisters increased their risk of future exacerbations by 1.19 folds compared to those who used less than 2 canisters during the 18-year follow-up. Similar results were found when patients were followed for 5 and 10 years.

Lastly, the study investigated the effects of the interaction between overuse of SABA and some patient factors and subsequent risk of COPD. For example, from Figure 8.2, after controlling for other relevant covariates, female and male patients who overused their SABA were 2.3 and 3.18 times more likely to develop COPD than the appropriate SABA users. Similarly, SABA overuse among obese older adults, increased comorbidity burden, and a history of tobacco use/nicotine dependence led to an increased risk of developing COPD after adjusting for relevant baseline covariates and confounders.

| Subgroups | aHR | 95% CI | *p* -value |
|---|---|---|---|
| **SABA overuse*Sex** | | | |
| SABA overuse*Female | 2.3 | 1.88-2.81 | <0.0001 |
| SABA overuse*Male | 3.18 | 2.61-3.88 | <0.0001 |
| | | | |
| **SABA overuse*Tobacco use** | | | |
| SABA overuse*no tobacco use | 2.54 | 2.18-2.96 | <0.0001 |
| SABA overuse* tobacco use | 4.44 | 1.42-13.88 | 0.01 |
| | | | |
| **SABA overuse*Obesity** | | | |
| SABA overuse*normal weight | 1.14 | 2.17-2.95 | 0.895 |
| SABA overuse*Obesity | 2.53 | 2.17-2.95 | <0.0001 |
| | | | |
| **SABA overuse*Age (years)** | | | |
| < 30 years | 2.37 | 0.49-11.41 | 0.282 |
| 30-39 years | 2.18 | 0.51-9.35 | 0.295 |
| ≥ 40 years | 9.3 | 2.32-20 | 0.002 |
| | | | |
| **SABA overuse*CCI** | | | |
| CCI score 0 | 2.53 | 2.17-2.96 | <0.0001 |
| CCI score 1 | 3.08 | 0.99-9.64 | 0.053 |
| CCI score ≥ 2 | 4.79 | 3.08-7.43 | <0.0001 |

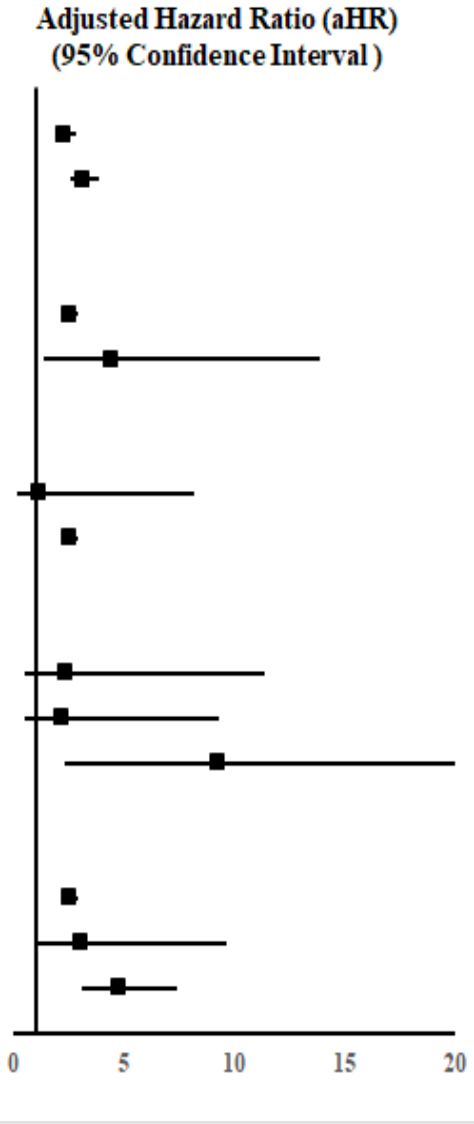


**Figure 8.2**. Association between the interaction between patient factors and SABA overuse and risk of COPD in the 18-year follow-up period.

The various models presented in Figure 3.2 were adjusted for relevant baseline factors. aHR: Adjusted Hazard Ratio; 95% CI: 95% confidence interval; CCI: Charlson comorbidity index; SABA: Short-acting beta-2 agonist.

**Table 8.2: Multivariate analysis of the association between SABA overuse and risk of COPD; and asthma exacerbations**

| | Model 1 | | Model 2 | |
|---|---|---|---|---|
| **Variables** | **aHR (95% CI)** | ***P*-value** | **aHR (95% CI)** | ***P*-value** |
| **5-year follow-up** | | | | |
| *SABA use* | | | | |
| Appropriate use | reference | | reference | |
| SABA overuse | 2.35(1.92, 2.87) | <0.0001 | 1.17(1.04, 1.31) | 0.010 |
| **10-year follow-up** | | | | |
| *SABA use* | | | reference | |
| Appropriate use | reference | | 1.18(1.07, 1.31) | <0.0001 |
| SABA overuse | 2.38(2.00-2.83) | <0.0001 | | |
| **18-year follow-up** | | | | |
| *SABA use* | | | | |
| Appropriate use | reference | | reference | |
| SABA overuse | 2.38 (2.03, 2.78) | <0.0001 | 1.19(1.09, 1.30) | <0.0001 |

The outcome variable for *Model 1* is time to COPD diagnosis; the Outcome for *Model 2* is time to asthma exacerbations

All models were adjusted for age(years), sex, obesity, tobacco use/nicotine dependence, Charlson comorbidity index, asthma exacerbation, length of hospital stays (days), aHR=adjusted Hazard ratio, 95% CI= 95% Confidence interval.

**Indicates the exposure variable is significant at 0.005

## 8.6 Discussions

This study investigated the association between overuse of inhaled bronchodilators (SABA) and risk of COPD at 5-year, 10-year, and 18-year follow-up periods. The study employed four linked administrative databases from the PopData BC to define the study cohort. Overall, 14,036 patients were included in the study cohort. I defined regular use or overuse of SABA as collecting > 2 SABA canisters in a calendar year (12 months). The study investigated the effect of SABA use at baseline and subsequent risk of COPD in the follow-up period among patients with a physician diagnosis of asthma. Overall, individuals who did not adhere to their prescribed short-acting bronchodilators and overused their SABA were 2.38-fold more likely to develop COPD in the 18-year follow-up period compared to appropriate SABA users (≤ 2 canisters per year). Similarly, patients who overused their SABA were at an increased risk of developing future asthma exacerbations.

Due to its repetitive use, regular and prolonged use of short-acting beta-2 agonists (SABA) lead to progressive reduction in response to the SABA doses. This phenomenon is known as tachyphylaxis or refractoriness [288]. Also, excessive usage of beta-2 agonists can contribute to increased tolerance to their bronchoprotective effect. This can contribute to reducing the bronchodilator's sensitivity to beta-2 agonists [289]. Liao and colleagues (2010) [290] have also established that increased tolerance to SABA therapies leads to enhanced sensitivity to bronchospasm stimuli, contributing to poor asthma control requiring hospitalization. It is, therefore, noteworthy that stepping down or reducing the prescription of SABA and adhering to asthma controller medications is optimal for achieving good asthma control. The updated 2021 GINA guidelines and various Canadian asthma clinical practices guidelines recommend against SABA monotherapy because it can lead to poor adherence to maintenance medications. Therefore, it is essential that physicians who manage patients with asthma adhere to the recommendations in the updated clinical practice guidelines to achieve

reasonable asthma control and maintain a good clinical practice. Also, interventions aimed at improving healthcare providers' adherence to clinical practice guidelines and other related interventions involving patients' participation should be intensified and prioritized.

This current study partially corroborates documented studies that have established an association between over-or regular SABA use and increased risk of future asthma exacerbations [112,281], increased hospitalizations [282], and asthma mortality [112]. However, studies have yet to establish a further association between excessive SABA usage among patients with prior history of asthma and subsequent risk of COPD. This study was designed to remedy this knowledge gap and has contributed to the limitations in the literature.

### *Strengths & limitations*

One of the strengths of the present study is the use of a large population-based adult asthma cohort with a long-term follow-up. The findings for the large asthma cohorts included in this study can be generalized to other populations with similar demographics in Canada and other parts of the world. The linked administrative database used was limited to data on some clinical events and laboratory tests. Hence some of these unmeasured variables could have resulted in a potential residual confounding in the model. However, the study adjusted for available covariates and confounders in the data, with some variables serving as a proxy for some of the unmeasured variables. This, to a considerable extent, minimized the effect of residual confounding on the overall effects estimates of the model.

### *Conclusions*

In conclusion, this study found that an appreciable number of the adult asthmatic population were overusing SABA. The multivariate Cox regression model showed that overuse or regular use of SABA was significantly associated with an increased risk of COPD

development during a 5-year, 10-year, and 18-year follow-up duration. The findings suggest that SABA use among patients should be monitored regularly and doing so should be adopted as one of the critical strategies in improving adult asthma management. Additionally, interventions that enhance healthcare providers' adherence to the updated clinical practice guidelines and patient involvement should be prioritized to increase HCPs' uptake of the recommendations in the guidelines.

# Chapter 9: Summary, Conclusions, and Recommendations

The overarching aim of this dissertation was to investigate patient factors associated with asthma progression to COPD diagnosis in later life. To achieve these objectives, an observational cohort study design was employed using four linked population-based administrative health databases from PopData BC. This chapter provides an overview of the preceding chapters, followed by the study contributions and their clinical implications for practice and policy. Finally, the main limitations of this research are discussed. Based on the study limitations, recommendations for future research are provided.

## 9.1 Thesis overview

In this present study, a quantitative knowledge synthesis (meta-analyses) and a retrospective cohort study design using four linked administrative databases were employed to investigate the association between prior history of asthma and COPD risk; and the factors linking asthma progression to COPD diagnosis. Chapter 1 introduced the entire dissertation by providing background information on obstructive airway diseases, specifically asthma, COPD, and ACO. Additionally, this chapter provided the main rationale of the thesis—examining the modifiable risk factors linking asthma progression to COPD diagnosis over 20 years. Asthma and COPD affect an increasing number of Canadians annually, with a substantial burden on healthcare use and cost. While there are many studies investigating the association between previous history of asthma and later diagnosis of COPD, the overall effect estimate explaining the extent of the association is unknown. The existing primary studies have reported varying effects estimates; thus, the exact effect estimate measuring asthma as an independent risk factor for COPD is unknown. Also, the factors that progress asthma patients to early diagnosis of COPD remain unknown and inconclusive. One major

factor that accounts for poor asthma control is sub-optimal medication adherence. Despite increasing research on medication adherence levels and risk of asthma exacerbations over time, the effects of asthma medication adherence levels and later risk of COPD remain unknown and unexplored in current clinical research. Finally, research on using appropriate pharmacy database adherence methods and optimal threshold for defining and differentiating adherent and poorly adherent adult asthma patients are unclear.

In Chapter 2, I described the four linked administrative databases used and further outlined the statistical methods for this thesis. It was explained that the four linked administrative databases were obtained from the PopData BC spanning from January 1, 1998, to December 31, 2018. Different statistical methods and the reason for the choice of the methods used in answering specific research questions were extensively discussed in this chapter. Specifically, the inverse variance random-effects models were employed to pool the various effects estimates explaining the association between asthma and risk of COPD together. Further, the GEE logistic regression, log-logistic AFT, MSC, and Cox proportional hazard models were subsequently discussed.

In Chapter 3, the first manuscript of the thesis was presented. The main aim was to systematically synthesize the existing varying effects estimates explaining the association between asthma and later development of COPD using meta-analysis. The meta-analysis showed the highest level of clinical evidence in deriving the exact estimate explaining the association between the two diseases. The results obtained in this part of the research revealed that previous diagnosis of asthma (childhood or adult-onset asthma) was a significant risk factor for future development of COPD. Thus, patients with previous diagnosis of COPD compared to no asthma were 7.87 times more likely to develop COPD over time. In addition, the synthesis of the 7 included cohort studies were of good

methodological quality with a low risk of bias. Thus, the overall effect estimate is reliable for explaining the association between the two diseases.

The manuscript presented in Chapter 4 examined the risk factors linking asthma progression to COPD diagnosis after establishing a strong positive association between the two diseases in Chapter 3. The findings of this study suggest that "male sex", "older adults (40 years and older)", "history of tobacco smoking and nicotine dependence", "increased length of hospital stay", "asthma exacerbation", "obesity in male sex", "increased burden of comorbidities", "moderate asthma", and "severe asthma" increases asthma patients' risk to early COPD diagnosis.

In Chapter 5, I systematically reviewed the existing literature to identify the update-to-date "pharmacy claim database" adherence measures and adherence thresholds for defining adherent and sub-optimal adherent asthma patients. The findings of this chapter indicated that the PDC and MPR were the common methods used for defining adult asthma patients' adherence. The meta-analysis identified the optimal adherence threshold as "0.75 or more".

The manuscript presented in Chapter 6 investigated the association between five varying adherence thresholds and risk of asthma exacerbation to determine the optimal adherence measures for the PDC or MPR methods. The following findings were obtained for this study: Compared to the poor adherent group, patients who achieved a higher PDC adherence threshold of '0.80-0.89' and '≥ 0.90' reduced their asthma exacerbation by 14% and 16%, respectively. Therefore, achieving a threshold of at least 0.80 for patients with prescribed multiple medications was optimal in attaining good asthma control compared to other lower cut-off points. Further, a sensitivity analysis found that individuals who achieved a higher ICS adherence (≥0.90) using PDC and MPR measures reduced their risk of exacerbation by 21% and 22%, respectively. Similarly, a higher adherence proportion (at

least 0.90) to prescribed ICS/LABA combination therapy reduced future asthma exacerbation events by 30% and 25% for PDC and MPR measures, respectively.

Chapter 7 investigated the independent effect of medication adherence levels (*optimal*, *intermediate*, *low*/*poor*) and asthma severity levels on risks of COPD, adjusting for relevant patient covariates and confounders to fill in the knowledge gap. Compared to the *low*-adherent adult asthma patients, individuals who attained *optimal* and *intermediate* adherence during the 18-year follow-up period were respectively 80% and 81% less likely to develop COPD after adjusting for potential confounders. Further, individuals who optimally adhered to prescribed ICS during the 18-year follow-up period were significantly less likely to experience COPD. Similarly, optimal adherence to prescribed ICS/LABA compared to poor ICS/LABA compliance for long-term treatment during the 18 years reduced asthma patients' risk of COPD by 74% after adjusting for potential confounders. Further, severe asthma patients with poor compliance to their prescribed medications were 72% more likely to be diagnosed with COPD during an 18-year follow-up duration.

The last manuscript presented in Chapter 8 examined the association between overuse of SABA and risk of COPD after controlling for baseline patient factors. The analysis of the four linked administrative data from the PopData BC revealed that patients who overused their prescribed SABA medications compared to the appropriate SABA users were at an increased risk of developing COPD after controlling for relevant covariates and confounders.

### 9.2. Contributions of this study

This present study made several contributions to the existing clinical evidence on the complex relationship between early history of asthma and later diagnosis of COPD.

***Measuring the association between previous asthma and risk of COPD***

Limited studies have investigated the association between prior history of asthma diagnosis and later risk of COPD; no "systematic review and meta-analysis" has been performed to determine the extent and strength of the association that persists. This review was the first to document the highest level of evidence of knowledge synthesis in studying the relationship between asthma progressions to COPD in later life. Compared to individuals with no history of asthma diagnosis, patients with prior history of asthma were 7.87 (95% CI: 5.40-11.45, *p*-value<0.0001) fold more likely to develop COPD in later life after controlling for relevant covariates and confounders. Thus, the findings from this review provide strong evidence that patients diagnosed previously with asthma are at an increased likelihood of developing COPD later in their lifespan regardless of their age, sex, smoking status, or exposure to occupational hazards.

***Risk factors linking asthma progression to COPD diagnosis***

Current research has not significantly explored evidence on modifiable risk factors explaining asthma progression to COPD diagnosis. This study contributed to knowledge by identifying increased comorbidity burden, increased length of hospital stays, history of tobacco use, male sex, obesity and male sex, and age of 40 years and older as the risk factors accelerating early COPD diagnosis in asthma patients. This study is one of the few studies that investigated the factors linking asthma progression to COPD using a large administrative population-based study with a long-term follow-up in the Canadian population.

***Determining the optimal adherence threshold for PDC and MPR measures***

This study has provided an optimal cut-off value for categorizing optimal and sub-optimal adherence for patients prescribed multiple or single medications over time with a clinical or pharmacological basis. The optimal adherence threshold for asthma patients prescribed multiple medications over time was "≥0.80". The optimal adherence threshold for

patients prescribed with long-term ICS was "≥0.90". The optimal adherence threshold for patient's prescribed long-term ICS/LABA combination therapy was "≥0.90".

***Association between medication adherence levels and risk of COPD***

This study investigated the role of medication adherence levels (*optimal*, *intermediate*, *low*) and risk of COPD during an 18-year follow-up duration. Individuals with optimal adherence to prescribed multiple medications were 80% less likely to develop COPD over time. Adult asthma patients who optimally adhered to ICS and ICS/LABA compared to poor ICS and ICS/LABA compliance were 77% and 74% less likely to develop COPD or ACO over an 18-year assessment period. The study found significant effect modification of MA by the various asthma classifications and risk of COPD, as mild asthma patients who optimally adhered to prescribed medications achieved the greatest protection from COPD risk. Meanwhile, poorly adherent severe asthma patients were more prone to future risk of COPD diagnosis.

***SABA overuse and risk of COPD in asthma patients***

Existing evidence documents the link between overuse of SABA and subsequent risk of asthma exacerbations and asthma-related deaths. However, evidence examining excessive use of SABA and subsequent risk of irreversible airway obstruction or COPD is unknown. This study was the first to investigate this phenomenon and has contributed clinical evidence on the association between over-reliance of SABA and risk of COPD. The study found that compared to patients who use less than 2 SABA canisters a year, patients who overuse SABA (inhaling more than 2 SABA canisters a year) were 2.38 times more likely to develop COPD during the 18 years of observation time.

### 9.2.1. Implications for clinical practice and policy

This research has implications for clinical practice and policies concerning interventions for minimizing the risk of COPD among asthma patients. The result of the study suggests the need for a more proactive prevention strategy. Thus, health promotion approaches and interventions including a) interventions for improving patients' adherence to prescribed medications, b) improving healthcare providers (HCPs) adherence to clinical practice guidelines**,** c) improving the overall quality of life, d) optimizing lifestyle interventions, and e) smoking cessation programs, could contribute to reducing the number of asthma patients that develop COPD in later life.

***Interventions for improving patient's adherence to prescribed medications***

A substantial number of the adult asthma cohort identified for this research poorly adhered to their prescribed asthma medications. As a result, adult asthma patients who achieved *optimal* and *intermediate* adherence over time subsequently reduced their risk of COPD over time. Since asthma is a chronic disease with no cure, patients are encouraged to optimally adhere to their medications to achieve good asthma control. Several factors and barriers such as forgetfulness, lack of belief in the medication, poor inhaler techniques, and complex asthma treatment regimens contribute to increased non-adherence rates. In response to these challenges, several interventions involving both patients and HCPs have been documented to enhance patients' adherence to their prescribed medications. "Adherence educational interventions" such as "one-to-one" and group "face-to-face education sessions", "motivational interviewing", "family-based problem-solving interventions", "nurse-led psychoeducation", and "interactive voice recognition system interventions" have demonstrated improved adherence to inhaled corticosteroids[104]. Also, to address the need for optimized adherence to controller medications in adult patients with long-standing asthma, several multi-component digital/mobile health interventions have been developed. The

existing interventions include text-message reminders, interactive voice response telephone calls, audio-visual reminders, computerized intervention authoring software, electronic inhalers, and mobile applications to record and monitor symptoms and patient lung function[104,291,292]. These strategies have been supported by strong evidence of clinical effectiveness that reflects the needs of asthma patients and HCPs[291]. For instance, digital technologies have been established as effective in enhancing asthma patients' medication compliance and overall asthma control[292,293]. Health care providers who manage adult asthma patients should ensure that they routinely monitor and assess patients' adherence to their prescribed medications using the multicomponent digital/mobile health interventions to ensure they attain maximal thresholds of at least 0.80.

Although the existing technologies have been useful and demonstrated clinical relevance, there has been a rapid advancement in these digital technologies with additional features to better monitor and enhance adherence and address the limitations of earlier versions. One of the improved features includes developing smart inhalers used to send data on patient inhaler usage to mobile apps or websites. The patient information gathered from this platform helps visualize and measure the degree of inhaler usage for adherence monitoring purposes[294,295]. Some advanced technologies are specifically designed to measure patients' peak flow and exhaled nitric oxide (FeNO)[296,297]. Thus, using these digital strategies, patient adherence data collected over time can help provide reliable information on patients' adherence patterns and overall disease control. Digitally collected information on adherence and future exacerbations assist HCPs to determine changes in lung function decline attributable to poor/low adherence. Also, using these digital smart devices can assist HCPs to identify patients who did not achieve optimal adherence and suggest new strategies to improve adherence. Such strategies may include offering additional training on inhaler techniques.

Policy makers and HCPs should ensure that more cost-effective, clinically relevant multi-component digital adherence interventions are incorporated into the clinical guidelines to help improve and maintain adherence levels to at least 80%.

***Improving HCPs adherence to Clinical practice guidelines***

Several clinical practice guidelines (both internationally and Canada-specific) have been documented to guide asthma management. Despite the availability of these existing guidelines, HCPs adherence to the recommendations in the guidelines is suboptimal and varies across different HCPs[298,299]. The low adherence to the clinical guidelines is linked to poor clinical events and low quality of life in asthma patients[299]. A variety of strategies have been introduced to improve the standard of care among adult asthma patients through improved providers' adherence to asthma guidelines. Interventions including decision support tools, feedback and audit, and clinical pharmacy support provide moderate evidence for improving HCPs prescriptions of controller medications to their patients as recommended by the guidelines[182]. Policy makers and stakeholders involved in managing adult asthma patients should ensure healthcare providers comply with the disease's guideline-directed pharmacological and non-pharmacological management. Policy makers should recommend strategies such as decision support (designed to facilitate HCPs decision making), feedback, and adult (provides data on performance to HCPs about their quality of care) as well as clinical pharmacy support interventions (targets pharmacists delivery of care) to help increase HCPs adherence to the recommendations in the guidelines.

***Improving the overall quality of life of asthma patients***

This research found that adult asthmatic patients with comorbid conditions such as diabetes, cardiovascular diseases, hypertension, and upper respiratory infections can increase COPD risk. As a result, HCPs should continuously monitor their patients' overall quality of

life by assessing the management of other non-asthma comorbid factors through patient engagement and consultation with other healthcare providers.

***Optimizing lifestyle (physical activity and weight management) interventions***

This study's findings also provide important insights into the lifestyle and behavioural risk factors for COPD, such as obesity in asthma patients. Obesity has been associated with an increased risk of asthma and asthma exacerbations[300,301]. To address obesity in asthma patients, lifestyle strategies targeting obesity control have been developed to address exercise, diet, and stress management. These interventions include a multi-component lifestyle intervention including dietary or exercise components, stress reduction, and behaviour modification. Evidence shows that improved dietary quality improves asthma patients' response to prescribed rescue medications[300,302]. As physical inactivity contributes to the development of obesity and subsequently worsens asthma control, interventions addressing physical inactivity should be prioritized. Effects of exercise training strategies have shown to improve airway hyperresponsiveness resulting in improved asthma symptoms, quality of life, and exercise capacity[303].

Additionally, findings from several randomized controlled trials (RCT) demonstrated the effectiveness of the weight reduction programmes (consisting of low caloric intake, and use of sibutramine; weight-loss program paired with exercise intervention) in improving asthma control in obese patients with moderate or severe asthma[304–306]. Thus, intensifying lifestyle multicomponent interventions such as weight-loss programs paired with exercise and quality dietary practices may be beneficial in minimizing risk of COPD diagnosis in obese asthma patients. Also, weight loss programs should be incorporated into the adult asthma clinical practice guidelines for non-pharmacological management of the disease.

***Smoking cessation programs***

Healthcare providers and policymakers should highlight the need for smoking cessation programs (programs specific to the patient's province of residence), particularly in difficult-to-control adult asthma patients who are at an elevated risk of developing COPD. Also, HCPs should critically educate asthma patients about the harmful effects of exposure to tobacco smoking to minimize their risk of future COPD onset.

## 9.3 Study limitations

Despite the strength of this study, this research has some limitations that must be acknowledged. First, the data used was administrative health data, which was not specifically designed for research. As such, the database did not capture some clinical information such as pulmonary function tests (PFTs), laboratory findings, environmental factors, and some lifestyle variables. Also, socio-economic status, housing and family history of asthma were missing from the data. These unmeasured factors could have contributed to some level of residual confounding in the various models.

Secondly, the administrative databases used were limited to health records of residents of British Columbia province in Canada. Although the results can be generalized to other jurisdictions with similar demographic characteristics due to the large cohort of asthma used, care should be taken since the characteristics of asthma patients might differ across different provinces in Canada. Also, due to financial and time constraints, the study could not link the databases used to external databases within the province of BC and Canada in general to include available relevant clinical data.

Thirdly, the database adherence methods used as a proxy for medication adherence were based on patients' prescription records and thus measured patients' possession of medication. The method is unable to determine whether patients ingested their medications or

not. This could have resulted in overestimation or underestimation of the adherence rates. However, clinical evidence has demonstrated concordance of the PDC or MPR measures with the gold standard (pill count) with high sensitivity in measuring actual medication use.

## 9.4 Overall conclusion

Overall, the findings of this study contribute to the existing scientific evidence and provide novel insights into potentially modifiable risk factors that increase COPD risk in patients with long-standing asthma. Further, this study contributed to knowledge by being the first to examine a cohort of over 68,000 adult asthma patients in a large population-based study with long-term follow-up in Canada. This Dissertation demonstrated evidence of a strong positive association between prior history of asthma and future risk of COPD. Further, the study identified "male sex", "older adults (40 years and older)", "asthma severity levels/exacerbations", "male sex and obesity", "increased comorbidity burden", "increased hospital stay", and "excessive SABA use", as the potential risk factors for predicting COPD in asthma patients. More importantly, one of the major takeaways from this Dissertation was examining the role of medication adherence levels and subsequent COPD risk. This research found that patients who optimally adhered to their prescribed medications were protected from future exacerbations and risk of COPD. However, the study found significant effect modification of medication adherence and various levels/classifications of asthma severity and development of COPD. Thus, mild asthma patients who adhered to their prescribed medications over time were less likely to experience COPD. Meanwhile, the severe asthma patients were at an increased risk of developing COPD over an 18-year follow-period.

Additionally, I systematically reviewed the literature published in the past 21 years (1998 to 2021) to identify the most up-to-date adherence methods and thresholds for assessing asthma patients' medication compliance in a population-based pharmacy database.

The PDC and MPR were commonly reported as the recommended measures with higher sensitivity. Results from the meta-analysis found optimal adherence thresholds to be "≥0.75". Using the four linked-population databases from PopData BC, I found the optimal threshold to be "0.90" in classifying fully adherent adult asthma patients from suboptimal adherent patients.

### 9.5 Recommendations for future studies

While the findings of this study have added to the existing clinical knowledge about the complex relationship between previous asthma and future development of COPD, many research areas remain unresolved. For example, future studies should consider linking a large number of population-based administrative data to clinical data in the various hospital and possibly merge data across different provinces in Canada and include the unmeasured clinical and laboratory data in their analysis.

More research is needed to elucidate the complex association between early asthma and the risk of COPD. For instance, some sections of this research investigated the association between overuse of only SABA and subsequent risk of COPD without focussing on the long-acting bronchodilators. Hence, future studies should investigate the long-term effect of LABA prescribed as monotherapy among adherent and non-adherent asthma patients and the future risk of COPD.

Finally, this study recommended using the various multi-component digital health interventions for improving patient adherence to maintenance asthma medications. However, evidence shows that no economic analysis has been conducted to recommend the most cost-effective intervention for improving patients' medication compliance. Future studies should focus on performing a comprehensive cost-effectiveness analysis to aid policymakers in

recommending the appropriate intervention to be implemented in the various healthcare settings in the province of BC and Canada.

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# Appendices

## Appendix 1: Ethics approval letter/certificate


**Research Ethics Office**
**Suite 200, Eastern Trust Building**
**95 Bonaventure Avenue**
**St. John's, NL A1B 2X5**

December 03, 2019

Dear Mr. Asamoah-Boaheng:

Researcher Portal File #
20200949 Reference # 2019.216

RE: Investigating factors related to the association between early history of asthma and later diagnosis of COPD

Your application was reviewed by a subcommittee under the direction of the HREB and the following decision was rendered:

| | |
|---|---|
| X | Approval |
| | Approval subject to changes |
| | Rejection |

Ethics approval is granted for one-year effective December 3, 2019. This ethics approval will be reported to the board at the next scheduled HREB meeting.

This is to confirm that the HREB reviewed and approved or acknowledged the following documents (as indicated):

- Application, approved
- Research proposal, approved
- Signed variable list from data custodian, approved
- Chart review,

approved

Please note the

following:

- This ethics approval will lapse on December 3, 2020. It is your responsibility to ensure that the Ethics Renewal form is submitted prior to the renewal date.

- This is your ethics approval only. Organizational approval may also be required. It is your responsibility to seek the necessary organizational approvals.
- Modifications of the study are not permitted without prior approval from the HREB. Request for modification to the study must be outlined on the relevant Event Form available on the Researcher Portal website.
- Though this research has received HREB approval, you are responsible for the ethical conduct of this research.
- If you have any questions please contact info@hrea.ca or 709 777 6974.

The HREB operates according to the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS2), ICH Guidance E6: Good Clinical Practice Guidelines (GCP), the Health Research Ethics Authority Act (HREA Act) and applicable laws and regulations.

We wish you every success with your study.

Sincerely,

Joy Maddigan

Dr Joy Maddigan, Co-Chair, Non-Clinical Trials
Health Research Ethics Board

# Appendix 2: Supplementary materials for Chapter 3

**Table S3.1- Search string in the three databases**

| Database | Search string |
|---|---|
| **PubMed** | ("Pulmonary Disease, Chronic Obstructive"[Mesh] OR COPD [tiab] OR "chronic obstructive pulmonary disease"[tiab]) AND ("Asthma"[Mesh] OR asthma*[tiab]) AND (child*[tiab] OR history[tiab]) AND (relationship[tiab] OR association[tiab] OR "Risk Factors"[Mesh] OR "risk factor"[tiab] OR "risk factors"[tiab]) |
| **Embase** | ('chronic obstructive lung disease'/de OR copd:ab,ti OR 'chronic obstructive pulmonary disease':ab,ti) AND ('asthma'/exp OR asthma*:ab,ti) AND (child*:ab,ti OR history:ab,ti OR previous*:ab,ti) AND ('risk factor'/exp OR 'risk factor':ab,ti OR 'risk factors':ab,ti) |
| **Cinahl** | (MH "Pulmonary Disease, Chronic Obstructive+" OR TI COPD OR AB COPD OR TI "chronic obstructive pulmonary disease" OR AB "chronic obstructive pulmonary disease") AND (MH "Asthma+" OR TI asthma OR AB asthma) AND (TI child* OR AB child* OR TI history OR AB history OR TI previous* OR AB previous*) AND (MH "Risk Factors" OR TI "risk factor" OR AB "risk factor" OR TI "risk factors" OR AB "risk factors") |

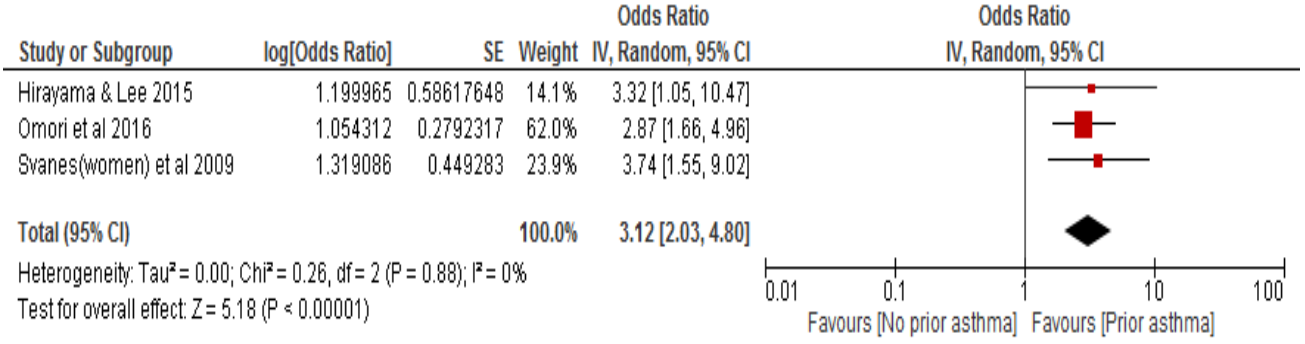



**Figure S3.1- Forest plot of sensitivity analysis after removing studies with odds ratio greater than 8.00**

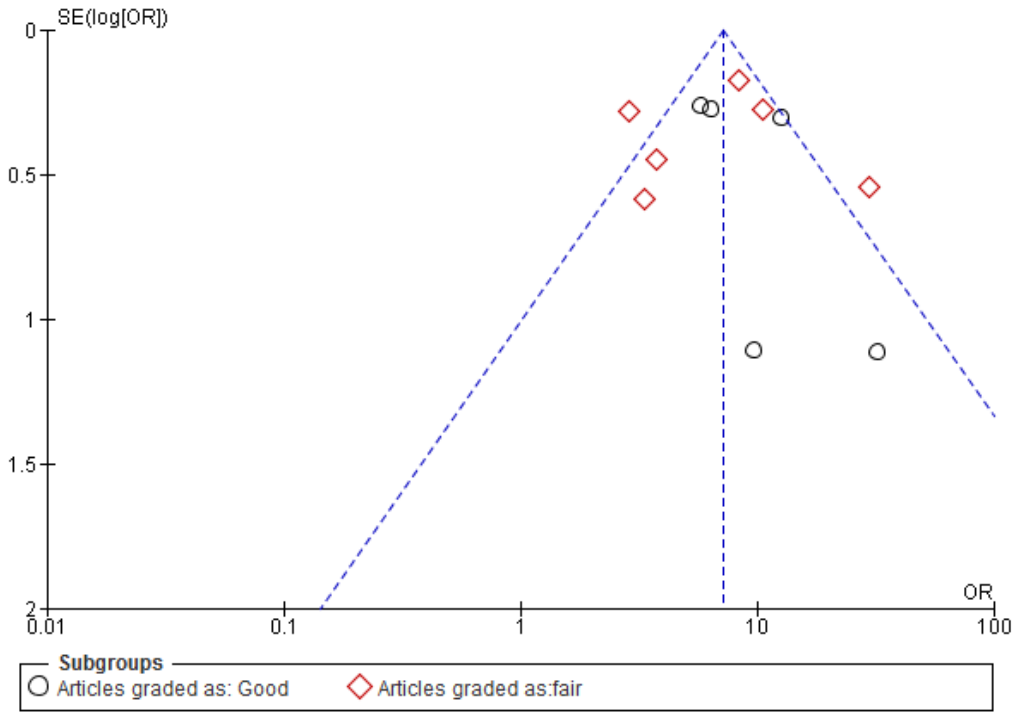



**Figure S3.2- Publication bias check for assessing whether a prior history of asthma increases the likelihood of developing COPD (Subgroup analysis by Study Quality Grading)**

**Table S3.2: Summary studies included in meta-analysis**

| Article | Exposure variable | Study type | Exposed group | | Unexposed group | | Results |
|---|---|---|---|---|---|---|---|
| | | | Events | Total | Events | Total | |
| Aanerud et al (2015) | Late-onset asthma (>10 years, never-smokers) | Cohort | 118 | 425 | 192 | 425 | OR: 11.21, 95% CI (6.75-18.60) |
| Tai et al (2014)a | Severe asthma | Cohort | 15 | 34 | 1 | 48 | OR: 31.9,95%CI(3.4-269) |
| Tai et al (2014) | Asthma | | 8 | 49 | 1 | 48 | OR: 9.6,95%CI(1.0-77) |
| Tagiyeva et al (2016)a | Childhood asthma(1964 wheeze group) | Cohort | | 135 | | 820 | OR: 5.79,95%CI(3.44-9.73) |
| Tagiyeva et al (2016) | Childhood asthma(2001 wheeze group) | Cohort | | 135 | | 637 | OR: 6.37,95%CI(3.73-10.9) |
| Hirayama and Lee, 2015 | Childhood asthma | Case control | 17 | 268 | 8 | 336 | OR:3.32, 95%CI(1.05, 10.45), p=0.04 |
| Tsuda et al (2009) | History of asthma | Case control | 30 | 49 | 5 | 98 | OR:29.4, 95%CI(10.1, 85.4) |
| Omori et al (2016) | Remitted Childhood asthma | Case control | 15 | 287 | 199 | 9154 | OR:2.87, 95%CI(1.66, 4.96), p=<0.001 |
| Omori et al (2016)a | Adult-onset asthma | Case control | 51 | 354 | 199 | 9154 | OR: 8.32, 95% CI(5.91,11.71), p=<0.001 |
| Svanes(men) et al (2009) | Childhood asthma | Mixed(cross sectional &cohort | | 0 | | 0 | OR: 10.48, 95% CI: (6.10 to 18.03), p=<0.001 |
| Svanes(women) et al (2010) | Childhood asthma | Mixed(cross sectional &cohort | | 0 | | 0 | OR: 3.74, 95% CI: (1.55 to 9.02),P=0.003 |

**Table S3.3: Test for funnel plot asymmetry**

| **Egger's regression** | |
|---|---|
| Intercept | 0.28688 |
| Standard error | 1.23329 |
| 95% lower limit (2-tailed) | -2.50302 |
| 95% upper limit (2-tailed) | 3.07678 |
| t-value | 0.23261 |
| df | 9.00000 |
| P-value (1-tailed) | 0.41063 |
| P-value (2-tailed) | 0.82127 |
| | |
| **Begg and Mazumdar rank correlation** | |
| Kendall's S statistics (P-Q) | -1.00000 |
| Kendall's tau without continuity correction | |
| Tau | -0.01818 |
| z-value for tau | 0.07785 |

| | |
|---|---|
| P-value (1 tailed) | 0.46897 |
| P-value (2-tailed) | 0.93795 |
| *Kendall's tau with continuity correction* | |
| Tau | 0.00000 |
| z-value for tau | 0.00000 |
| P-value (1 tailed) | 0.50000 |
| P-value (2-tailed) | 1.00000 |

# Appendix 3: Supplementary materials for Chapter 4

**Table S4.1: Multivariate analysis of risk factors for time-to-COPD incidence---MPR model***

| Covariates | aFTR | 95% CI | P-value |
|---|---|---|---|
| Male Sex | 0.60 | (0.55, 0.66) | <0.0001 |
| *Age(years)* [*at baseline*] | | | |
| ≥ 40 years | 0.03 | (0.02, 0.04) | <0.0001 |
| 30-39 years | 0.36 | (0.25, 0.51) | <0.0001 |
| < 30 years | Ref | | |
| *Length of stay* (days) [at baseline] | | | |
| ≥3 | 0.08 | (0.07, 0.09) | <0.0001 |
| 2 | 0.07 | (0.06, 0.08) | <0.0001 |
| 1 | 0.13 | (0.11, 0.15) | <0.0001 |
| 0 | Ref | | |
| Emergency admission | 0.20 | (0.17, 0.24) | <0.0001 |
| Asthma exacerbation | 0.79 | (0.68, 0.92) | 0.002 |
| Tobacco use (*at baseline*) | 0.28 | (0.12, 0.65) | 0.003 |
| Obesity (*at baseline*) | 0.99 | (0.54, 1.85) | 0.993 |
| *Charlson Comorbidity Index (CCI)* [*at baseline*] | | | |
| CCI score ≥ 2 | 0.27 | (0.22, 0.34) | <0.0001 |
| CCI score 1 | 0.69 | (0.39, 1.23) | 0.214 |
| CCI score 0 | Ref | | |
| Sinusitis (baseline) | 5.02 | (1.58, 16.05) | 0.006 |
| Upper respiratory infection (baseline) | 0.48 | (0.29, 0.78) | 0.003 |
| *Asthma severity (at baseline*) | | | |
| Severe asthma | 0.15 | (0.12, 0.17) | <0.0001 |
| Moderate asthma | 0.32 | (0.29, 0.35) | <0.0001 |
| Mild asthma | Ref | | |
| SABA overuse (>2 canisters) [*at baseline*] | 0.56 | (0.40, 0.76) | <0.0001 |
| Medication adherence (MPR ≥ 0.80) | 2.46 | (2.18, 2.77) | <0.0001 |
| Patient cluster (MPR model) | | | |
| Variance (constant) | 5.91(0.24) | | |
| Variance [Medication adherence effect) | 0.65(0.32) | | |
| /logs | -0.05 | | |

Where 95% CI=95% confidence interval; SABA=Short acting beta-2 agonist. Only the MPR variable (proxy for medication adherence) was included in the random effect component.

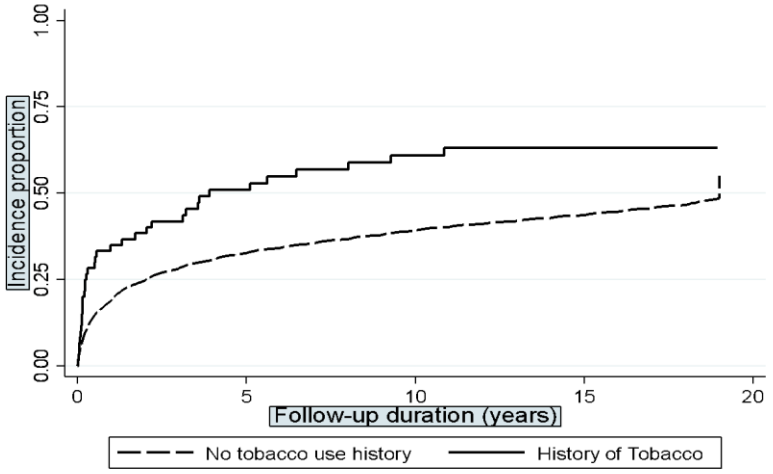
**Table S4.2: Lists of Asthma-related medications with Active ingredients, and Drug Identification Numbers (DINs) selected from the PharmaNet database**

| Medication categories | Active ingredients | Used for case definition | Drug Identification Number (DIN) |
|---|---|---|---|
| Inhaled corticosteroids (ICS) | Beclometasone | Yes | 2242030, 2242029, 374407, 828521, 828548, 872334, 893633, 897353, 1949993, 1950002, 2079976, 2213710, 2213729, 2215039, 2215047, 2215055, 2216531 |
| | Budesonide | Yes | 2229099, 1978918, 1978926, 852074, 851752, 851760 |
| | Fluticasone | Yes | 2237247, 2237246, 2237245, 2237244, 2244293, 2244292, 2244291, 2174731, 2174758, 2174766, 2174774, 2213583, 2213591, 2213605, 2213613 |
| | Ciclesonide | Yes | 2285614, 2285606, 2303671 |
| Short-acting beta-agonists (SABA) | Salbutamol | Yes | 790419, 812463, 832758, 832766, 851841, 860808, 867179, 897345, 1926934, 1938851, 1938878, 1945203, 1947222, 1986864, 2022125, 2046741, 2048760, 2069571, 2084333, 2148617, 2154412, 2173360, 2208229, 2208237, 2208245 2212315, 2212323, 2213400, 2213419, 2213427, 2213478, 2213486, 2214997, 2215004, 2215616, 2215624, 2215632, 2216949, 2231430, 2231488, 2231678, 2231783, 2231784, 2232570, 2232987, 2236931, 2236932, 2236933, 2239365, 2239366, 2241497, 2243115, 2243828, 2244914, 2245669, 2259583, 2326450 |
| | | Yes | 620955, 620963, 874086, 894249, 894257, 1932691, 2035421, 2063689, 2091186, 2146843, 2146851, 2164434, 2164442, 2165368, 2165376, 2212390, 2213435, 2213443, 2213451, 2261324 |
| | Terbutaline | Yes | 786616 |
| | Orciprenaline | Yes | 249920, 3891, 2236783, 2229862, 2152568, 2192675 |
| Long-acting beta-agonists (LABA) | Salmeterol | Yes | 2211742, 2214261, 2231129, 2136139, 2136147 |
| | Formoterol | Yes | 2230898, 2237224, 2237225 |
| ICS and LABA in combination (ICS/LABA) | Budesonide, formoterol | Yes | 2245385, 2245386 |
| | Fluticasone, salmeterol | Yes | 2240835, 2245126, 2245127, 2240836, 2240837 |
| Leukotriene receptor antagonists (LTRA) | Montelukast | Yes | 2247997, 2238217, 2243602, 2238216 |
| | Zafirlukast | Yes | 2236606 |
| Anti-immunoglobulin E monoclonal antibody | Omalizumab | Yes | 2260565 |
| Inhaled mast cell stabilizers | Cromoglicic acid | Yes | 2231431, 2231671, 2046113, 534609, 555649, 261238, 638641, 2049082, 2219468 |
| Theophylline | Choline theophyllinate | No | 346071, 405310, 441724, 441732, 451282, 458708, 458716, 476366, 476390, 476412, 503436, 511692, 536709, 565377, 589942, 589950, 792934 |
| | Theophylline | No | 156701, 261203, 460982, 460990, 461008, 466409, 488070, 532223, 556742, 575151, 599905, 627410, 631698, 631701, 692689, 692697, 692700, 722065, 1926586, 1926594, 1926608, 1926616, 1926640, 1966219, 1966227, 1966235, 1966243, 1966251, 1966278, 1966286, 2014165, 2014181, 2230085, 2230086, 2230087 |

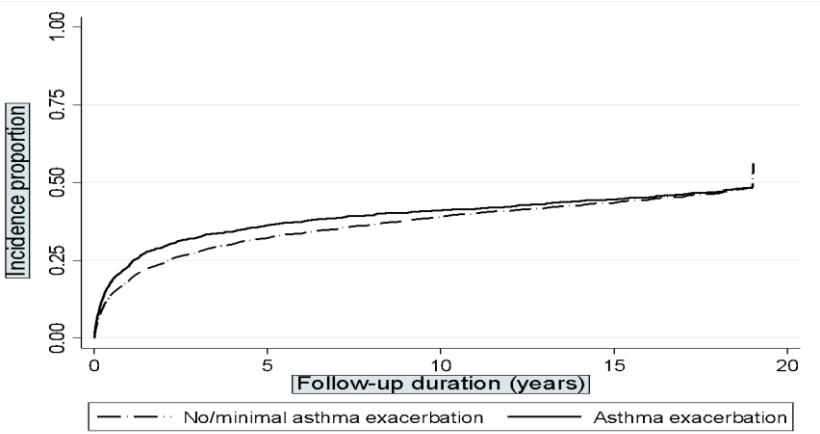
| | | | |
|---|---|---|---|
| | Aminophylline | No | 14923, 178497, 497193, 497193, 497207, 582654, 582662, 868450, 2014270, 2014289 |
| Inhaled anticholinergics | Ipratropium bromide | No | 2246084, 2246083, 2163705, 2163713, 2240508, 2240072 |
| | | No | 2126222, 2243827, 2231494, 731439, 576158, 2247686, 824216, 2026759, 1950681, 2239131, 2216221, 2210479, 2231785, 2236934, 2236935, 2237134, 2237135, 2239627, 2231135, 2231136, 2231245, 2231244, 2097141, 2097176, 2097168 |
| | Ipratropium bromide, fenoterol | No | 02148633 |
| | Tiotropium bromide | No | 02246793 |
| Other beta-agonists | Epinephrine | No | 2017555, 466417, 525103, 1927582 |
| | Ephedrine | No | 2237085, 2229698, 2100231, 2100258, 2243148, 2236722, 2229678, 2219743, 2012111, 2229711, 38121, 2242961, 876534, 893323, 893331, 438847, 2242639, 2126419, 2126400 |
| | Isoprenaline | No | 2017652 |
| | Orciprenaline | No | 1923870, 1928449, 2017660, 254134, 3859 |
| Other corticosteroids | Cortisone | No | 280437, 16241, 16446, 16438 |
| | Triamcinolone | No | 2194090, 15016, 15024, 2194082 |
| | Prednisone | No | 610623, 598194, 550957, 312770, 252417, 210188, 868426, 868434, 868442, 21695, 232378, 607517, 508586, 156876, 271373, 271381 |
| | Prednisolone | No | 21679, 2230619, 2152541, 2245532 |
| | Methylprednisolone | No | 1934325, 1934333, 1934341, 30759, 30767, 36129, 30988, 2245406, 2245400, 2245408, 2245407, 2241229, 2231893, 2231894, 2231895, 2232750, 2232748, 2063727, 2063697, 2063719, 2063700, 36137, 2230210, 2230211, 30678, 30651, 30643 |
| | Betamathasone | No | 2237835, 36366, 2063190, 176834, 28096, 28185 |
| | Hydrocortisone | No | 888222, 888230, 888206, 888214, 30910, 30929, 872520, 872539, 878618, 878626, 30635, 30600, 30619, 30627 |
| | Dexamethasone | N0 | 2261081, 2250055, 213624, 16462, 354309, 716715, 874582, 1977547, 664227, 2204274, 2204266, 295094, 285471, 489158, 2239534, 732893, 732885, 2260301, 2237044, 2260298, 2237046, 2237045, 1946897, 1964976, 1964968, 1964070, 2279363, 783900, 751863, 2311267, 2240687, 2240685, 2240684 |
| Other xanthines | Theophylline, combination | No | 545090, 476374, 334510, 356123, 792942, 721301, 317225, 828718, 640093, 828726, 828742, 307548 |
| Other anti-allergic agents | Levocabastine | No | 2020017 |
| | Ketotifen | No | 2221330, 2176084, 2230730, 2218305, 2231680, 2231679, 600784, 577308 |

***NB: Lists of medications used for case definition were indicated in the third column as "Yes"***

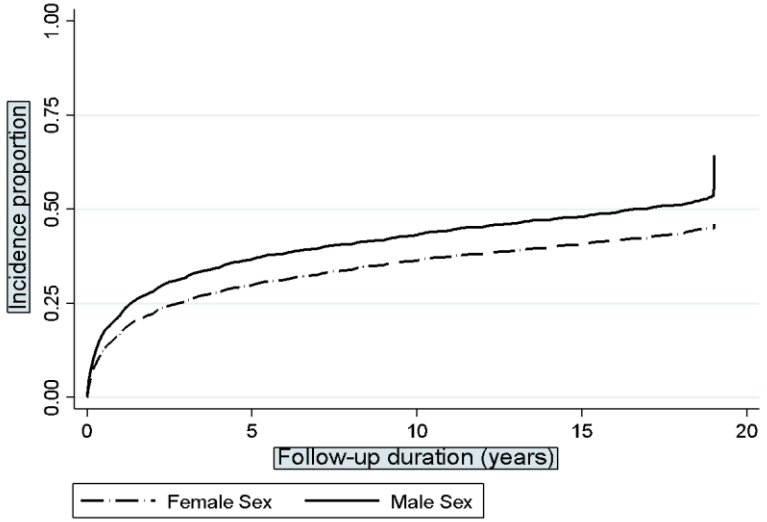
**A**


Incidence proportion
0.00
0.25
0.50
0.75
1.00
0
5
10
15
20
Follow-up duration (years)
No tobacco use history
History of Tobacco

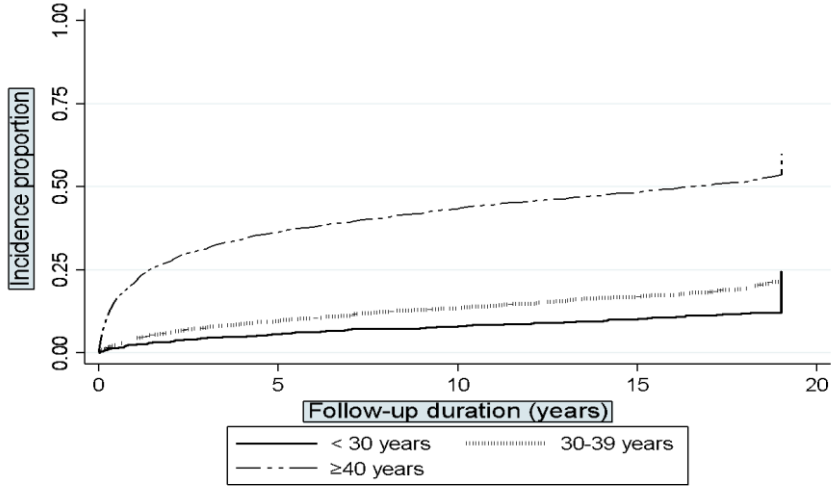
**B**


Incidence proportion
0.00
0.25
0.50
0.75
1.00
0
5
10
15
20
Follow-up duration (years)
No/minimal asthma exacerbation
Asthma exacerbation

**C**


Incidence proportion
0.00
0.25
0.50
0.75
1.00
0
5
10
15
20
Follow-up duration (years)
Female Sex
Male Sex

**D**


Incidence proportion
0.00
0.25
0.50
0.75
1.00
0
5
10
15
20
Follow-up duration (years)
< 30 years
30-39 years
≥40 years

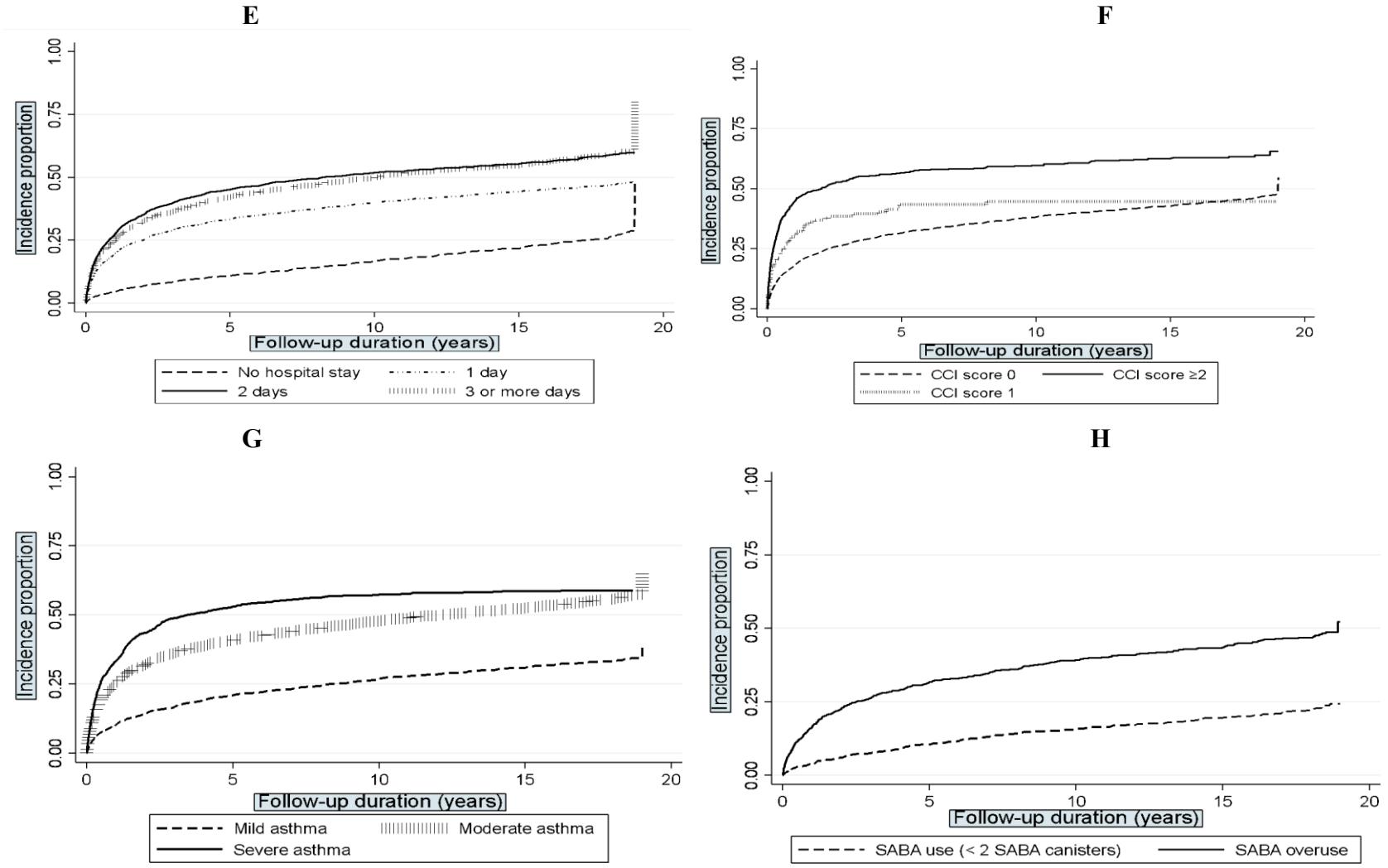



**Figure S4.1**: Time to incidence of COPD in asthma patients stratified by: A) history of tobacco use; B) Asthma exacerbations; C) Sex; D) Age (years); E) length of hospitalization ; F) Charlson comorbidity index (CCI); G) Asthma severity ; H) SABA overuse

# Appendix 4: Supplementary materials for Chapter 5

**Table S5.1: Search strings and articles yielded**

| Databases | Search strings/terms | Results |
|---|---|---|
| PubMed (**From 1998-2020**) | Search (("medication adherence"[Mesh] OR ((prescription[tiab] OR medication[tiab] OR puffer[tiab] OR "inhaled corticosteroid"[tiab]) AND (adherence[tiab] OR compliance[tiab] OR filling[tiab] OR dispensing[tiab] OR dispensed[tiab] OR filled[tiab]))) AND ("Asthma"[Mesh] OR asthma[tiab])) Filters: Publication date from 1998/01/01 to 2020/12/31; Humans | 1967 studies/articles |
| Updated PubMed Search (**from 1998 to 2021**) | (("medication adherence"[MeSH Terms] OR (("prescription"[Title/Abstract] OR "medication"[Title/Abstract] OR "puffer"[Title/Abstract] OR "inhaled corticosteroid"[Title/Abstract]) AND ("adherence"[Title/Abstract] OR "compliance"[Title/Abstract] OR "filling"[Title/Abstract] OR "dispensing"[Title/Abstract] OR "dispensed"[Title/Abstract] OR "filled"[Title/Abstract]))) AND ("Asthma"[MeSH Terms] OR "Asthma"[Title/Abstract])) AND ((1998/1/1:2021/3/16[pdat]) AND (english[Filter])) | 2456<br><br>Found additional **489** studies |
| Embase (from **1998 to 2020**) | ('medication compliance'/exp OR ((prescription:ti,ab OR medication:ti,ab OR puffer:ti,ab OR 'inhaled corticosteroid':ti,ab) AND (adherence:ti,ab OR compliance:ti,ab OR filling:ti,ab OR dispensing:ti,ab OR dispensed:ti,ab OR filled:ti,ab))) AND ('asthma'/exp OR asthma:ti,ab) AND [humans]/lim AND [1998-2020]/py | 4148 studies |
| Updated Embase (From **1998 to 2021**) | ('medication compliance'/exp OR ((prescription:ti,ab OR medication:ti,ab OR puffer:ti,ab OR 'inhaled corticosteroid':ti,ab) AND (adherence:ti,ab OR compliance:ti,ab OR filling:ti,ab OR dispensing:ti,ab OR dispensed:ti,ab OR filled:ti,ab))) AND ('asthma'/exp OR asthma:ti,ab) AND (1998:py OR 1999:py OR 2000:py OR 2001:py OR 2002:py OR 2003:py OR 2004:py OR 2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py OR 2020:py OR 2021:py) AND 'human'/de AND ('allergic asthma'/dm OR 'asthma'/dm OR 'mild persistent asthma'/dm OR 'severe persistent asthma'/dm) | 4479 studies<br><br>Found additional **331 studies** |
| International Pharmaceutical Abstracts (IPA) | (prescription OR medication OR puffer OR "inhaled corticosteroid") AND (adherence OR compliance OR filling OR dispensing OR dispensed OR filled) AND asthma | 321 studies |

**Table S5.2: Risk of Bias Ratings for Cohort Studies (Yes, No, Unclear)**

| First author (year) | Was the intervention delivered in a standardized manner? | Was exposure measured in reliable and valid manner? | Were confounding factors identified? | Were strategies to deal with confounds stated? | Were participants free of outcome at start of study? | Were outcomes measured in reliable and valid way? | Was follow-up time reported and sufficient for outcomes to occur? | Was follow-up completed? If not, were reasons for attrition stated and explored? | Were strategies used to address incomplete follow-up? | Were appropriate statistical analyses used? |
|---|---|---|---|---|---|---|---|---|---|---|
| Averell et al (2019) | N/A | Yes | Yes | Yes | Yes | Yes | Yes | N/A | N/A | Yes |
| Backer et al (2018) | N/A | Yes | unclear | unclear | Yes | Yes | unclear | unclear | unclear | Yes |
| Balkrishnan and Christensen (2001) | N/A | Yes | No | unclear | Yes | Yes | unclear | unclear | unclear | Yes |
| Bidwal et al (2017) | N/A | Yes | unclear | unclear | Yes | Yes | No | N/A | N/A | Yes |
| Blais et al (2011) | N/A | Yes | N/A | N/A | Yes | Yes | N/A | N/A | N/A | Yes |
| Blais et al (2014) | N/A | Yes | unclear | No | Yes | Yes | Unclear | N/A | N/A | Yes |
| Blais et al (2017) | N/A | Yes | No | No | Yes | Yes | N/A | N/A | No | Yes |
| Covvey et al (2014) | N/A | Yes | Yes | Yes | Yes | Yes | N/A | N/A | N/A | Yes |
| Darba' et al (2016) | N/A | Yes | Yes | Yes | Yes | Yes | N/A | N/A | Yes | Yes |
| Feehan et al (2015) | N/A | Yes | No | No | Yes | Yes | No | No | No | Yes |
| Friedman et al (2010) | N/A | Yes | Yes | Yes | Yes | Yes | N/A | N/A | unclear | Yes |
| Gelzer et al (2019) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | unclear | Yes |
| Guo et al (2012) | N/A | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Hagiwara et al (2013) | N/A | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Unclear | Yes |
| Hardstock et al (2019) | N/A | Yes | Unclear | Unclear | Yes | Unclear | Unclear | Unclear | Unclear | Yes |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Ismaila et al (2014) | N/A | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Kang et al (2017) | N/A | Yes | Yes | Yes | Yes | Yes | Unclear | Unclear | Unclear | Yes |
| Kellowa y et al (2000) | N/A | Yes | Unclear | Unclear | Yes | Yes | Probably yes | Unclear | Unclear | No |
| Makhin ova et al (2015) | N/A | Yes | Yes | Yes | Yes | Yes | Unclear | Unclear | Unclear | Yes |
| Navarat nam et al (2011) | N/A | Yes | Yes | Yes | Yes | Yes | Unclear | Unclear | Unclear | Yes |
| Papi et al (2018) | N/A | Yes | Yes | Yes | Yes | Yes | Unclear | Unclear | Unclear | Yes |
| Sicras-Mainar et al (2017) | N/A | Yes | Unclear | Unclear | Yes | Yes | Yes | Yes | Unclear | Yes |
| Souvere in et al (2016) | N/A | Yes | Unclear | Unclear | Yes | Yes | Yes | Yes | Yes | Yes |
| Standfor d et al (2019) | N/A | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Stern et al (2006) | N/A | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Svedsat er et al (2019) | N/A | Yes | Unclear | Unclear | Yes | Yes | Unclear | Unclear | Unclear | Yes |
| Taylor et al (2014) | N/A | Yes | Yes | Yes | Yes | Yes | Unclear | Unclear | Unclear | Yes |
| Vaidya et al (2019) | N/A | Yes | Yes | Yes | Yes | Yes | Unclear | Unclear | Unclear | Yes |
| Vaidya et al (2013) | N/A | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Van Boven et al (2020) | N/A | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Vervloe t et al (2020) | N/A | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| William s et al (2012) | N/A | Yes | Unclear | Unclear | Yes | Yes | Yes | Probably yes | No | Yes |
| Woodcr oft et al (2016) | N/A | Yes | Unclear | Unclear | Yes | Yes | Yes | Probably yes | Unclear | Yes |
| Wu et al (2015) | N/A | Yes | Yes | Yes | Yes | Yes | Unclear | Unclear | Unclear | Yes |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Zhang et al (2016) | N/A | Yes | Yes | Yes | Yes | Yes | No | No | No | Yes |

**Table S5.3: Confidence in the Evidence from reviews of quantitative research ratings of studies included in the meta-analysis using GRADE**

| No of studies | Exposure | Outcome | Limitations | Inconsistency | Indirectness | Imprecision | Publication bias | Estimate of effect of result | Confidence in evidence |
|---|---|---|---|---|---|---|---|---|---|
| 3 cohort studies | Adherence rate (MPR: 0.75-1.00) | Asthma exacerbation | Concerns unlikely to alter outcome | Not serious | Not serious | Not serious | Probably serious | Pooled effect was OR: 0.56, 95%CI: 0.41-0.77 | Moderate |
| 4 cohort studies | Average MPR (mean/Median/75$^{th}$ percentile) | Asthma exacerbation | Concerns unlikely to alter outcome | Not serious | Not serious | Not serious | Not serious | Pooled estimate: OR: 1.01, 95% CI:0.78-1.31 | Moderate |
| 3 cohort studies | Adherence rates (MPR >=0.50) | Asthma exacerbation | Concerns unlikely to alter outcome | serious | Not serious | Not serious | Not serious | Pooled estimate- OR: 0.71, 95% CI:0.54-0.94 | Moderate |

OR=odds ratio, 95%CI: 95% confidence interval, MPR=Medication possession ratio

**Table S5.4: Adherence Thresholds and Clinical Outcomes**

| Study | Medication adherence rate ± Standard Deviation | Medication adherence rate cut-off value | Likelihood to reach the targeted clinical outcome with the medication adherence threshold (OR, HR, RR and confidence interval [CI]) | Percentage of patients below medication adherence threshold |
|---|---|---|---|---|
| Bidwal et al (2017) | MPR 0.55. Average MPR in (medium-high) group was 0.66 compared to 0.13 in low adherence group. | 0.80 | Patients with low adherence (66.1%) had fewer medication refills (2.3 vs. 5.3; *P<0.0001*), fewer primary care provider visit (3.4 vs 5.0; *p*<0.001); and lower asthma control test (ACT) scores (13.1 vs 17.3; *p*<0.001), lower AMR (0.7 vs 0.9; *p*<0.001). | 66.1% |
| D'Ancona et al (2020) | MPR 0.81 ± 0.32 | 0.75 | Good adherence resulted in reduction in OCS dose [(median percentage OCS reduction 100(IQR 74–100) *versus* 60(IQR 27–100); *p*=0.031)]; reduced exacerbation [(AER change -2.1±3.1 versus 0.3±2.5; *p*=0.011); and (adjusted OR 3.19; 95%CI 1.02–9.94; *p*=0.045) for likelihood of stopping maintenance OCS. | 18% |
| Ismaila et al (2014) | MPR | 0.80 | Patients achieving adherence at 0.80 recorded reduced adjusted odds of exacerbations (OR=0.48; 95% CI: 0.44–0.54) and lower rate of healthcare utilization [ER visits: 0.48 (0.36-0.64), hospitalizations: 0.49 (0.42-0.57), ICU admissions: 0.62(0.39-0.98). | 57.3% |
| Martin et al (2013) | MPR | 1.00 | Severe exacerbations were more common in patients who achieved an adherence at MPR>100%. Conversely, risk domain asthma control (RDAC) was lower in patients with MPR>100%. Exacerbations were likely to be uncommon among those with MPR≤100%. | 99.93% |
| Papi et al (2018) | MPR | 0.80 | Compared to the non-adherent patients, the study found an increasing proportion of adherent patients in the elevated blood eosinophil group having 2 or more exacerbations (14.0% vs 7.2%, p=0.0003) and uncontrolled asthma (73% vs 60.8%; *p=0.004*). | 81% |
| Stern et al (2006) | MPR 0.24±0.25 | Median MPR (0.14) or 75$^{th}$ percentile of MPR (0.33) | Compared to less compliant patients, more compliant patients were less likely to experience exacerbations (odds ratio, 0.94; 95% confidence interval, 0.91–0.97; P < .001) using Median MPR as threshold. The study further recorded reduced exacerbation for compliant patients when the 75$^{th}$ percentile of MPR values was used as the threshold. (Odds ratio, 0.89; 95% | 49.1% for median MPR, and 74.9% for 75$^{th}$ percentile MPR. |

| | | | | |
|---|---|---|---|---|
| | | | confidence interval, 0.86–0.92; P < .001). | |
| Sicras-Mainar et al (2017) | MPR | 0.80 | 63.4% of the non-adherent patients suffered at least one exacerbation. In other words, achieving adherence at MPR>0.8 was associated with reduced risk of asthma exacerbation. | 49% |
| Zhang et al (2016) | MPR | 0.80 | Non adherent patients experienced increased in disease severity (having more than 2 exacerbations was associated with upward healthcare cost. | |
| Kang et al (2018) | MPR | 0.50 | Achieving MPR ≥ 0.5 compared with low MPR (<0.2) was associated with reduced asthma exacerbations in moderate asthma patients with OR: 0.828, 95% CI: (0.707-0.971), severe asthma: OR 0.362, 0.185-0.708. | |
| Guo et al (2012) | Average MPR : 0.23 (mean 0.14) for ICS & LABAs; 0.66(median 0.46) across all medications | Average: 0.66 (median 0.46) across all medications | The odds ratios of an asthma related emergency department (ED) visit was 0.81 (0.79-0.84) for a higher ICS-and LABA MPR, but the odds ratio of asthma-related hospitalization or intubation was 1.56(1.50-1.62). | |
| Delea et al (2008) | Mean MPR: +0.25 | Mean MPR: +0.25 | OCS initiation and ED visits□0.97 (0.94, 0.996) for OCS; 0.90 (0.89-0.92) for ED visit or hospitalization. | |
| William (2012) | MPR: >0.75 versus <0.25 | MPR: >0.75 versus <0.25 | Combined asthma exacerbations (ED/hosp/OCS )□ HR: 0.89 (0.81–0.97), equivalent to OR: 0.58 | |
| Gelzer et al (2019) | PDC | 0.68 | Resulted in reduction in emergency department (ED) visits. | |
| Averell et al (2019) | PDC 0.453±0.300 | 0.5, 0.8 | Better adherence and lower risk of discontinuing treatment | |
| Korgaonkar et al (2018) | PDC | 0.80 | Asthma patients with depression had had a greater risk of asthma-related ED visits (Risk Ratio [RR] 1.33, 95% Confidence Interval [CI]: 1.20 – 1.46, p < 0.001) and asthma related hospitalizations (RR 2.79, 95% CI: 1.75 – 4.44, p < 0.001) as compared to those without depression | |
| Makhinova et al (2015) | PDC 0.322 ± 0.197 | 0.50 | Excessive SABA use was associated with patients who were adherent to controller therapy. Excessive SABA use was also associated with increased risk of asthma exacerbation. | |
| Wu et al (2015) | PDC Mean PDC for ICS=0.19, mean PDC for LTRA= 0.30; mean PDC for ICS/LABA =0.25. | 0.75 | Evidence of asthma patients' adherence to their prescribed controller medications was poor. | |

**Table S5.5: Meta-regression analyses (Dependent variable: log of odds ratio for asthma exacerbation/ED visits)**

| Variable | Model 1 (univariate) | | | | Model 2 (multivariate) | | |
|---|---|---|---|---|---|---|---|
| | exp(b) | 95% CI | *p*-value | | exp(b) | 95% CI | *p*-value |
| **MPR (continuous** | 0.85 | 0.24 – 3.02 | 0.77 | | 5.37 | 2.77 -10.38 | 0.002 |
| | Adjusted $R^2$ = 1.35% | | | | | | |
| **Age (years)** | 0.99 | 0.98 – 1.00 | 0.31 | | 0.99 | 0.99 – 1.00 | 0.183 |
| | Adjusted $R^2$ = 15.63% | | | | | | |
| **Study Duration (months)** | 1.00 | 0.99 – 1.01 | 0.77 | | 1.01 | 1.01 - 1.01 | 0.001 |
| | Adjusted $R^2$ = 0.8% | | | | | | |
| Country | | | | | | | |
| **Canada** | (ref) | | | | (ref) | | |
| **South Korea** | 1.15 | 0.50 - 2.65 | 0.71 | | 4.85 | 2.30 - 10.23 | 0.004 |
| **USA** | 1.62 | 0.79 – 3.34 | 0.16 | | 5.15 | 2.93 - 9.06 | 0.001 |
| | Adjusted $R^2$ = 36.45% | | | | | | |
| | | | | | | | |
| Adjusted $R^2$ | | | | | 99.9% | | |
| K | | | | | 10 | | |

*K* is the number of studies involved in the meta-analysis

**Table S5.6: Meta regression analysis (Dependent variable: log of ORs for asthma exacerbation/ED visits**

| Variable | Model 1 (univariate) | | | | Model 2 (multivariate) | | |
|---|---|---|---|---|---|---|---|
| | exp(b) | 95% CI | *p*-value | | exp(b) | 95%CI | *p*-value |
| **MPR (category)** | | | | | | | |
| ≤ 0.33 | (ref) | | | | (ref) | | |
| ≤0.50 | 0.74 | 0.34 – 1.60 | 0.38 | | 1.66 | 1.01 - 2.76 | 0.049 |
| ≤0.75 | 1.08 | 0.57 – 2.05 | 0.78 | | 2.31 | 1.62 – 3.29 | 0.009 |
| ≥0.80 | 0.65 | 0.27 – 1.59 | 0.29 | | 0.44 | 0.32 – 0.61 | 0.002 |
| | Adjusted $R^2$ = 37.60% | | | | | | |
| **Age (years)** | 0.99 | 0.98 – 1.00 | 0.31 | | 1.00 | 0.99 -1.01 | 0.753 |
| | Adjusted $R^2$ = 15.63% | | | | | | |
| **Study Duration (m)** | 1.00 | 0.99 – 1.01 | 0.77 | | 1.01 | 1.00-1.02 | 0.004 |
| | Adjusted $R^2$ = 0.80% | | | | | | |
| | | | | | | | |
| Adjusted $R^2$ | | | | | 99.88% | | |
| K | | | | | 10 | | |

**Table S5.7: Egger's regression intercept**

| | |
|---|---|
| Intercept | 0.051 |
| Standard error | 5.245 |
| 95% lower limit (2-tailed) | -12.044 |
| 95% upper limit (2-tailed) | 12.145 |
| t-value | 0.0096 |
| df | 8.000 |
| P-value (1-tailed) | 0.496 |
| P-value (2-tailed) | 0.993 |

**Table S5.8: Fail-safe N tests**

**Classic fail-safe N**

| | |
|---|---|
| Z-value for observed studies | 94.258 |
| P-value for observed studies | 0.000 |
| Alpha | 0.050 |
| Tails | 2.000 |
| Z for alpha | 1.959 |
| Number of observed studies | 10.000 |
| Number of missing studies that would bring p-value to > alpha | 3118.000 |

**Orwin's fail-safe N**

| | |
|---|---|
| Point (log) in observed studies | 0.876 |
| Criterion for a 'trivial' point (log) | 0.2000 |
| Mean point (log) in missing studies | 0.000 |
| Number missing studies needed to bring point (log) under 0.2 | 34.000 |

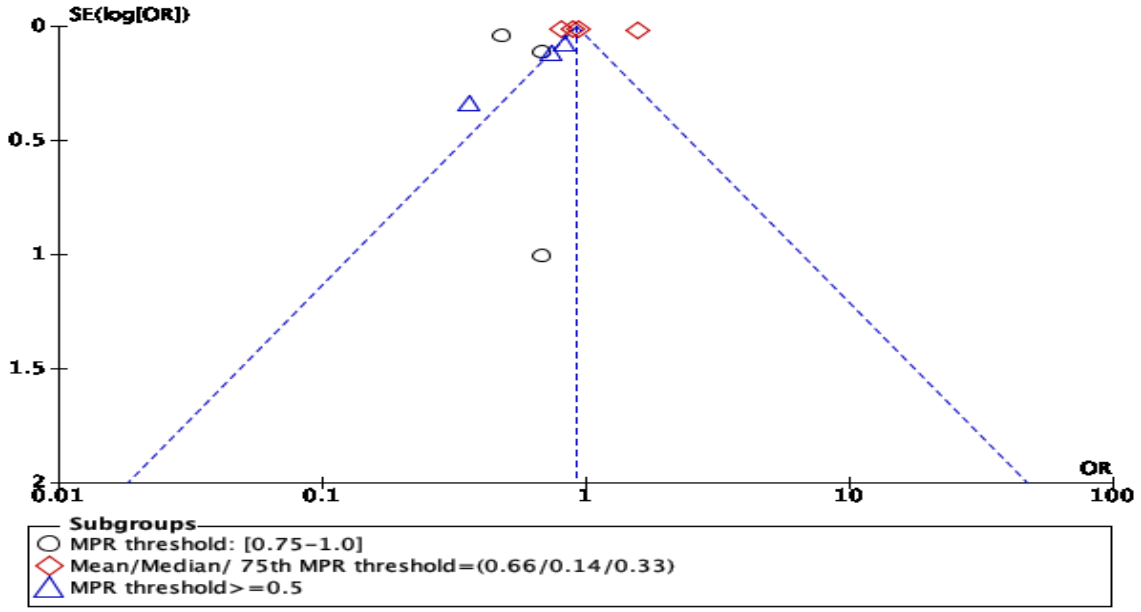



**Figure S5.1: Funnel plot**

**Table S5.9: Adherence measures and cut-off points/threshold**

| **Adherence metric & related measures** | **Adherence cut-off/threshold** | | **Reference** |
|---|---|---|---|
| | **Adherence** (*good or high-medium*) | **Non-adherence** (*Poor or low*) | |
| PDC | 20%-67% | | (154) |
| | PDC ≥ 0.5; PDC ≥ 0.8 | | (173) |
| | PDC =100% | PDC <100% | (139) |
| | PDC≥80 adherent, | PDC <80 as non-adherent. | (111) |
| | PDC≥80%, PDC≥70%, PDC≥60%, PDC≥50%. | | (160) |
| | mean PDC≥0.5; PDC≥0.8 | | (145) |
| | PDC ≥50% and ≥80% | | (166) |
| Adjusted PDC | PDC ≥75%) | PDC < 75%, | (171) |
| MPR | Medium-high = MPR ≥0.5, MPR ≥ 0.8 | Low = MPR<0.5 | (143) |
| | Good = MPR > 0.75, intermediate =MPR: 0.74-0.51, poor <0.5. | MPR ≤ 0.5 | (179) |
| | MPR ≥ 80%, | MPR <80% | (117) |
| | Excess adherence (MPR >100%. | MPR≤100% | (182) |
| | Values above the median MPR | Values below the median MPR | (180) |
| | Values above the median MPR | Values below the median MPR | (167) |

| | | | |
|---|---|---|---|
| | MPR >80%; patients with at least 2 prescriptions | MPR <80%; patients with only 1 prescription | (161) |
| | 75$^{th}$ Percentile of MPR values; MPR=1 or 100%. | | (164) |
| | MPR ≥ 80%, | MPR< 80% | (162) |
| | MPR>0.80 | MPR < 0.80 | (169) |
| | MPR ≥80% | MPR < 80% | (172) |
| Continuous Medication Availability (CMA I), CMA II) | CMAI ≥ 80%, and CMA II ≥80%. | | (163) |
| Persistence | Absence of treatment gap ≥30 days. | | (145) |
| AMR | AMR ≥ 0.5 | | (143) |

**Table S5.10: Additional summary of study characteristic**

| Author | Definition/Diagnosis of asthma | Mean Medication Adherence Rate± Standard deviation | Medication Adherence rate Threshold | Probability to reach the targeted clinical /surrogate outcome with Medication Adherence Threshold (Odds ratios [OR], Hazards ratios [HR] and Confidence Interval [CI]) | Methods of Threshold Determination | Nonadherence Prevalence |
|---|---|---|---|---|---|---|
| Averell et al (173) | The study used ICD-9/ICD-10 codes (493.xx, J43.x) to identify asthma patients. Additionally, patents were included if they had records of at least 1 prescription fill of furoate/vilanterol (FF/VI) or fluticasone propionate/salmeterol (FP/SAL). | PDC 0.34–0.45 | ≥0.5 or ≥0.8 | **Medication Adherence** Adjusted odds of FF/VI initiators achieving PDC ≥0.5 was 2.14 (95% CI: 1.95–2.36) compared with BF initiators Adjusted odds of FF/VI versus BF initiators achieving PDC ≥ 0.8 was 2.84 (95% CI: 2.46–3.26)<br><br>Adjusted odds of FF/VI vs FF/SAL achieving PDC ≥0.5 was 2.11 (95% CI: 1.90–2.35) and PDC≥0.80 was 2.49 (95% CI: 2.16–2.88) **Medication discontinuation** (adjusted HR = 0.70; 95% CI: 0.66–0.74) FF/VI versus BF and (adjusted HR = 0.73; 95% CI: 0.68–0.77) for FF/VI versus and FP/SAL | Propensity score matching (PSM), Inverse Probability weighting (IPWT) and multivariable regressions Survival analysis; Log rank | **PDC ≥0.5** FF/VI vs B/F 74.0% FF/VI vs FP/SAL 74.5% PDC ≥0.8 FF/VI vs B/F 90.2% FF/VI vs FP/SAL 89.5% |
| | | | | | | |
| **Author** | | **Mean Medication Adherence Rate± Standard deviation** | **Medication Adherence rate Threshold** | **Probability to reach the targeted clinical outcome with Medication Adherence Threshold (Odds ratios [OR], Hazards ratios [HR] and Confidence Interval [CI])** | **Methods of Threshold Determination** | **Nonadherence Prevalence** |
| Backer et al (174) | Asthma diagnosis was objectively verified by having | --- | Min two prescriptions redeemed | **Medication Adherence** Prescription redemption PDC | Descriptive statistics with unadjusted analysis | Prescription redemption 46.0% |

| | | | | | | |
|---|---|---|---|---|---|---|
| | positive asthma test through either a beta-2-agonist reversibility test, a bronchial challenge test with methacholine or using mannitol. | | PDC ~ unknown threshold | | | |
| | | | | | | |
| Balkrishnan and Christensen (175) | Patients were identified with asthma using ICD codes and with prescription of prophylactic inhaled corticosteroids (ICS) | ---- | Med-Total | **Medication Adherence**<br>Long-term ICS adherence | | |
| **Author** | | **Mean Medication Adherence Rate± Standard deviation** | **Medication Adherence rate Threshold** | **Probability to reach the targeted clinical outcome with Medication Adherence Threshold (Odds ratios [OR], Hazards ratios [HR] and Confidence Interval [CI])** | **Methods of Threshold Determination** | **Nonadherence Prevalence** |
| Bidwal et al (143) | Adults (18 +) with current diagnosis of persistent asthma with records of asthma medication refills obtained from the clinic. | ----- | MPR<br>≤0.5<br>≥0.5<br>AMR<br>≥0.5 | Medication Adherence | Multivariate logistic regression analysis | MPR<br>66.1% (≥ 0.5)<br>91.7% (fully adherent ≥0.8)<br>AMR<br>10.7% ((≥ 0.5) |
| | | | | | | |
| **Author** | | **Mean Medication Adherence Rate± Standard deviation** | **Medication Adherence rate Threshold** | **Probability to reach the targeted clinical outcome with Medication Adherence Threshold (Odds ratios [OR], Hazards ratios [HR] and Confidence Interval [CI])** | **Methods for Threshold Determination** | **Nonadherence Prevalence** |

| | | | | | | |
|---|---|---|---|---|---|---|
| Blais et al (177) | Patients who were new users of ICS monotherapy, aged 18-45 years with asthma diagnostic ICD code 493.x who have used at least 3 doses of SABA per week. | 52.6±33.0<br>19.1±16.5 | PPDC-<br>PDC- | Medication Adherence | Descriptive statistics | 41.0%<br>estimated using PDC |
| **Author** | | **Mean Medication Adherence Rate± Standard deviation** | **Medication Adherence rate Threshold** | **Probability to reach the targeted clinical outcome with Medication Adherence Threshold (Odds ratios [OR], Hazards ratios [HR] and Confidence Interval [CI])** | **Methods of Threshold Determination** | **Nonadherence Prevalence** |
| | | | | Medication adherence | Descriptive statistics | Not reported |
| Blais et al (181) | Asthma patients with filled new ICS prescription in the Quebec prescription claims databases were identified as the study cohort. | --- | --- | Days' supply<br>Number of refills | | |
| Blais et al (176) | | PDC<br>Children 30.3 ± 25.9<br>Adults 36.6 ± 36.0 | ≥ 1 refill in 12 months | Adherence to ICS | Descriptive statistics | Children; 10.6%<br>Adults;<br>30.6% |
| **Author** | | **Mean Medication Adherence Rate± Standard deviation** | **Medication Adherence rate Threshold** | **Probability to reach the targeted clinical outcome with Medication Adherence Threshold (Odds ratios [OR], Hazards ratios [HR] and Confidence Interval [CI])** | **Methods of Threshold Determination** | **Nonadherence Prevalence** |
| Covvey et al (178) | Patients with physician diagnosed (GP recorded diagnosis) asthma | ---- | MPR ≥0.80<br>MPR<0.80 | Adherence to inhaled therapies<br>Persistence to inhaled therapies | Binary logistic regression analysis<br>Kaplan–Meier Survival analysis | 88% (non-persistence) |

| | | | | | | |
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| | and COPD, having records of at least one prescription | | | | | |
| | | | | | | |
| Darba' et al (151) | All asthmatic patients who used ICS/LABA in the database. | ---- | MPR≥0.80 | ----- | Logistic regression | ----- |
| **Author** | | **Mean Medication Adherence Rate± Standard deviation** | **Medication Adherence rate Threshold** | **Probability to reach the targeted clinical outcome with Medication Adherence Threshold (Odds ratios [OR], Hazards ratios [HR] and Confidence Interval [CI])** | **Methods of Threshold Determination** | **Nonadherence Prevalence** |
| D'Ancona et al | Patients with confirmed severe asthma requiring at least 5mg prednisolone daily for at least 6months and having peripheral blood eosinophil count of at least 300 cells.$\mu L^{-1}$ . | 0.82±0.32 | MPR <0.5 (poor)<br>0.5 – 0.74 (intermediate)<br>⩾0.75 (good) | OCS dose reductions (100 vs 60, p=0.031)<br>AER change (−2.1 ± 3.1 vs 0.3 ± 2.5; p = 0.011)<br>Stopping maintenance OCS (Adjusted OR 3.19, 95% CI 1.02–9.94; *p*=0.045). | Descriptive statistics<br>Linear regression analysis | 32% (suboptimal adherence)<br>16% (poor adherence) |
| | | | | | | |
| Delea et al | All individuals in the database with at least one medical claim during the period of the study with asthma diagnostic ICD09-CM code of 493.xx in addition to at least 2 outpatient pharmacy claims of asthma medications | MPR (54%) | MPR<br><25%<br>25 - <50%<br>50% - <75%<br>≥75% | Each 25% improvement in adherence was associated with a 10% reduction in the odds of asthma-related ED visit or hospitalization (p<0.001), a 10% reduction in the odds of receiving SABA (p<0.001), a 3% reduction in the odds of receiving a corticosteroid (p=0.027) | Multivariate general linear model (GLM) regression analysis | 79.8% (estimated by MPR ≥75%) |
| | | | | | | |
| Feehan et al | Asthma patients dispensed with at | PDC 42±2.7<br>MPR 43±2.9 | PDC ≥ 80%<br>MPR ≥ 80% | Adherence to controller medications | Descriptive statistics | 86% (estimated using PDC) |

| | | | | | | |
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| | least one controller asthma medication for chronic use were included in the study cohort. | | | | | 84% (estimated using MPR) |
| Friedman et al | All patients enrolled in the health plan, 12-25 years with no history of other chronic pulmonary condition but only identified as asthma using the asthma diagnostic codes: 493.0X, 493.1X, or 493.9X | ---- | ---- | Adherence in MF-DPI vs FP using PDC (23.5% vs. 14.5%; $p<$ 0.0001) and prescription fills (2.70 vs. 1.91; $p < 0.0001$)<br>Mean SABA canister claims in MF-DPI vs FP (1.04 vs. 1.40; $p <$ 0.0001)<br>Mean exacerbations in MFDPI vs FP(0.12 vs. 0.14; $p = .5335$) | Propensity Score Analysis<br>Multivariate generalized linear model analyses | ---- |
| **Author** | | **Mean Medication Adherence Rate± Standard deviation** | **Medication Adherence rate Threshold** | **Probability to reach the targeted clinical outcome with Medication Adherence Threshold (Odds ratios [OR], Hazards ratios [HR] and Confidence Interval [CI])** | **Methods of Threshold Determination** | **Nonadherence Prevalence** |
| Gelzer et al | Patients were identified as having primary diagnosis of asthma (ICD-9, 493.xx and prescription fills for asthma controllers. | ---- | PDC 20-67% | Mean PDC rate in managed care-led interventions between two groups (+4.9% and +7.2%; $p =$ 0.01 and $p = 0.03$, respectively)<br>Reductions in ED visits (asthma-related: −23.0% and −17.5%, respectively; $p < 0.01$), and IP admissions (asthma-related: −37.1% and −40.0%, respectively; $p < 0.01$) between two groups on managed care-led interventions | Paired t-tests<br>Repeated analysis of variance | --- |
| | | | | | | |
| Guo et al | Patients identified as moderate to severe asthma with | MPR [0.23 (median 0.14)] for ICSs | --- | odds ratios of an asthma related emergency department (ED) visit was 0.81 (0.79-0.84) for a higher ICS-and-LABA MPR, but the | Logistic Regression Analysis | --- |

| | | | | | | |
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| | prescription of ICS- and -LABA. | [0.66 (median 0.46)] for all asthma medications | | odds ratio of asthma-related hospitalization or intubation was 1.56 (1.50-1.62) | | |
| Hagiwara et al (156) | Asthma cohort identified using ICD-9 codes and prescription of asthma related medications | MPR<br>MF [57.2 (27.2)]<br>FSC 100/50 [59.3 (27.1)] | undefined | Compared to MF patients, patients who received FSC 100/ 50 had lower ICS MPR for MF vs FSC100/50 patients (57.2 vs. 59.3, p < .001) and refill rate (4.1 vs. 4.4, p < .001) | Propensity score analysis<br>Descriptive statistics | ---- |
| Hardstock et al (157) | Patients with asthma using ICD-codes with long term usage of asthma medications | MPR (80.6)<br>PDC (83.2) | MPR and PDC ≥80% | Adherence in prescription-based and interval-based analysis | Not reported | 38.42% estimated by MPR<br>32.52% estimated by PDC |
| **Author** | | **Mean Medication Adherence Rate± Standard deviation** | **Medication Adherence rate Threshold** | **Probability to reach the targeted clinical outcome with Medication Adherence Threshold (Odds ratios [OR], Hazards ratios [HR] and Confidence Interval [CI])** | **Methods of Threshold Determination** | **Nonadherence Prevalence** |
| Ismaila et al (117) | Patients identified from the database using ICD-9 CM codes 493.xx, in addition to prescription of asthma medications. | ---- | MPR ≥ 80%<br>Persistence (absence of treatment gap ≥30 days) | MPR <80% ≥ 80%. Persistence (absence of treatment gap ≥30 <30 days) Exacerbations<br>OR; 0.48 (0.44-0.54) p=0.001<br>OR; 0.42 (0.38-0.48) p=0.001<br>SABA Use<br>OR; 1.00 (0.91-1.11) p=0.972<br>OR; 0.68 (0.61-0.76) p=0.001<br>OCS Use<br>OR; 0.46 (0.42-0.52) p=0.001<br>OR; 0.36 (0.32-0.40) p=0.001<br>ER Visits<br>OR; 0.48 (0.36- 0.64) p=0.001<br>OR; 0.31 (0.21- 0.46) p=0.001<br>Hospitalizations<br>OR; 0.49 (0.42-0.57) p=0.001<br>OR; 0.41 (0.35-0.49) p=0.001<br>ICU Admission | Multivariate logistic regression | 57.3% estimated using MPR<br>70.7% (non-persistence) |

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| | | | | OR; 0.62 (0.39-0.98) p=0.041<br>OR; 0.14 (0.07-0.28) p=0.001<br>Intubation<br>OR; 0.72 (0.31-1.64) p=0.427<br>OR; 0.05 (0.01-0.26) p=0.001<br>Respirologist Visit<br>OR; 0.88 (0.79-0.99) p=0.032<br>OR; 0.43 (0.38-0.50) p=0.001<br>GP Visit<br>OR; 0.63 (0.56-0.71) p=0.001<br>OR; 0.45 (0.39-0.52) p=0.001 | | |
| Kang et al (142) | Patients identified using ICD-10 codes for asthma (J45, J46) and one prescription of asthma medications. | --- | MPR<20%<br>20%≤MPR<50%<br>MPR≥50% | MPR≥50% compared with MPR (<20%) showed ORs of 0.828 (95% CI 0.707-0.971) and 0.362 (0.185-0.708) in moderate and severe asthma, respectively. | Multivariate logistic regression analysis | 91.4% |
| Kelloway et al (158) | | 56.5% ± 28.6 | Not reported | Adherence with ICS before (49.7% vs 29.3%) and after (56.5% ±28.6%) salmeterol introduction ($p$=0.0785, pre vs post) | Multivariate linear regression | Not reported |
| **Author** | | **Mean Medication Adherence Rate± Standard deviation** | **Medication Adherence rate Threshold** | **Probability to reach the targeted clinical outcome with Medication Adherence Threshold (Odds ratios [OR], Hazards ratios [HR] and Confidence Interval [CI])** | **Methods of Threshold Determination** | **Nonadherence Prevalence** |
| Makhinova et al (160) | Patients identified as having charted diagnosis of asthma and had records prescribed in haled corticosteroids (ICS) | PDC 32.2% ± 19.7% | PDC < 50<br>PDC ≥ 50 | Patients with PDC ≥ 50% is 97% more likely to have ≥ 6 SABA claims when compared to patients with PDC < 50% patients (OR = 1.967; 95% CI = 1.826-2.120; $p$ < 0.001). As for OCS use, adherent patients had 0.11 fewer claims compared with non-adherent patients ($p$ < 0.001) | Multivariate logistic and linear regression analyses | Adherence to asthma controller medication, risk of exacerbation, and use of rescue agents. |

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| Navaratnam et al (159) | Cohort identified using ICD-9 codes for asthma: 493.xx and records of filled asthma medications. | ---- | PDC | *Category A*: 24% adherence to mometasone furoate (MF); 15% adherence to fluticasone propionate (FP).<br>*Category B*: 27% adherence to mometasone furoate (MF), 15% adherence to FP. | Multivariate Generalized Linear Model (GLM) with Poisson distribution | --- |
| **Author** | | **Mean Medication Adherence Rate± Standard deviation** | **Medication Adherence rate Threshold** | **Probability to reach the targeted clinical outcome with Medication Adherence Threshold (Odds ratios [OR], Hazards ratios [HR] and Confidence Interval [CI])** | **Methods of Threshold Determination** | **Nonadherence Prevalence** |
| Papi et al (161) | Patients identified as asthma using Read codes indicating physician-diagnosed asthma. Records of prescribed medication was also added as a selection criterion. | | MPR >80%<br>MPR ≤ 80% | Patients with MPR >80% in the elevated blood eosinophil group had 2 or more asthma exacerbations (14.0% vs 7.2%; $p = 0.003$) and uncontrolled asthma (73% vs 60.8%; $p = 0.004$) compared to those with MPR ≤ 80% | Multinomial and binomial logistic regression analysis | 80.65% |
| Sicras-Mainar et al (162) | Based on ICD codes and asthma medications | ---- | MPR ≥ 80%<br>MPR < 80% | --- | --- | --- |
| Souverein et al (163) | Patients who had received one or more ICS prescription and had recorded physician diagnosis of asthma. | 60% ± 0.31% and 35.26% | CMA (I&II) ≥ 80%<br>CMA < 80% | Medication adherence (persistence and implementation) | Chi-square tests<br>Independent *t* tests<br>Mann Whitney *U* tests | 64.74% |
| **Author** | | **Mean Medication Adherence Rate± Standard deviation** | **Medication Adherence rate Threshold** | **Probability to reach the targeted clinical outcome with Medication Adherence Threshold (Odds ratios [OR], Hazards ratios [HR] and Confidence Interval [CI])** | **Methods of Threshold Determination** | **Nonadherence Prevalence** |

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| Standford et al (145) | Patients with prescription of asthma medications, 18 years and older with diagnosis of asthma | ---- | PDC ≥ 80%<br>PDC < 80%<br><br>AMR ≥ 50%<br>AMR < 50% | Patients initiating treatment with FF/VI had 72% greater odds (OR; 1.72; 95% CI, 1.48-2.00; P < .001) of achieving a PDC ≥ 0.5 and 86% greater odds of achieving a PDC ≥ 0.8 (OR; 1.86; 95% CI, 1.51-2.30; P < .001) compared with those on BUD/F<br>Patients initiating treatment with FF/VI had 26% lower risk of discontinuation (HR; 0.74; 95% CI, 0.69-0.79), and 36% greater odds of an AMR ≥0.50 (OR; 1.36; 95% CI, 1.23-1.50) compared with BUD/F. | Propensity-score matching, logistic regression and Cox-proportional hazard models | 67.55% (estimated by PDC ≥50%)<br>88.23% (estimated by PDC ≥80%)<br>34.55% (estimated by AMR ≥50%) |
| Stern et al (164) | Patients identified with asthma diagnosis (ICD-9: 493.xx and with at least one prescription of asthma medication | MPR 0.24 ±0.25 | < Median cut off point<br>≥ Median cut off point<br>≥ 75% cut off point<br>< 75% cut off point | **Median MPR:** Compliant vs less complaint patients (OR; 0.94; 95% CI, 0.91– 0.97; *p*=0.001) for risk of exacerbation.<br>**75% MPR cut off:** Risk of exacerbation was further reduced (OR, 0.89; 95% CI, 0.86–0.92; 20.0% vs 21.8%; *p*= 0.001)<br>**All cut offs:** Compliance showed significantly less exacerbations in compliant vs non-compliant | Multivariate logistic regression analysis | 49.1% (using median cut off point)<br>74.9% (using median cut off point) |
| Svedsater et al (166) | Patients with records of prescription of any ICS/LABA with physician diagnosis of asthma using ICD codes. | ---- | PDC ≥50%<br>PDC ≥ 80% | Medication Adherence by PDC Persistence of ICS/LABAs Median PDC was 89.2 (61.6–100.0) for FF/VI and 75.9 (50.5–98.0) for BDP/FM (p<0.0001), with significantly higher odds of achieving _50% and _80% PDC for FF/VI versus BDP/FM (747/893 [83.7%] vs 2600/3433 [75.7%]; odds | Multivariate logistic regression, Cox-proportional hazard models | |

| | | | | | | |
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| | | | | ratio=1.50; 95% CI 1.23–1.83; p<0.001 and 526/893 [58.9%] vs 1571/3433 [45.8%]; odds ratio=1.57; 95% CI 1.35–1.83; p<0.001, respectively; per-protocol analyses) | | |
| Taylor et al (165) | Patients with physician diagnosis of asthma in the database and with ICS prescription. | ---- | | Adherence to ICS measured by PPR | | |
| **Author** | | **Mean Medication Adherence Rate± Standard deviation** | **Medication Adherence rate Threshold** | **Probability to reach the targeted clinical outcome with Medication Adherence Threshold (Odds ratios [OR], Hazards ratios [HR] and Confidence Interval [CI])** | **Methods of Threshold Determination** | **Nonadherence Prevalence** |
| Vaidya et al (180) | Patients identified using asthma diagnostic ICD-9 codes, and records of prescribed asthma medications | MPR 0.34 | Median MPR<br>≥0.25<br><0.25 | Higher adherence to ICS is associated with significantly higher total health expenditure than lower adherence ($19,223 vs. $12,840 p<.0001) | Multivariate regression analysis (generalized linear model with a log link function and gamma distribution) | --- |
| Vaidya et al (167) | Cohort identified using ICD-9-CM codes to identify physician diagnosed asthma and having records of prescribed asthma medications. | MPR 0.45 | Median MPR<br>≥0.45<br><0.45 | Compared with patients on US$0–15 cost-sharing level, patients on US$16–30 (OR; 0.449, 95% CI; 0.312–0.616), US$31–45 (OR; 0.246, 95% CI; 0.168–0.358) and US$46 or higher (OR; 0.131, 95% CI; 0.084–0.206) levels all had lower odds of acceptable medication adherence. | Logistic regression analysis | --- |
| **Author** | | **Mean Medication Adherence Rate±** | **Medication Adherence rate Threshold** | **Probability to reach the targeted clinical outcome with Medication Adherence** | **Methods of Threshold Determination** | **Nonadherence Prevalence** |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | **Standard deviation** | | **Threshold (Odds ratios [OR], Hazards ratios [HR] and Confidence Interval [CI])** | | |
| Van Boven et al (168) | Physician diagnosed asthma and with records of prescribed asthma medications | ---- | Group-based trajectory modeling (GBTM): - categorized into non-persistent, seasonal use, poor adherence and good adherence. | Poor adherence (58%), nonpersistent use (20%), seasonal use (8%), and good adherence (13%). Poor adherence was associated with longer time to additional GINA-5 (adjusted HR: 0.58; 95% CI: 0.35-0.95. | Multivariable Cox proportional hazards models | Poor adherence rate was 58% |
| **Author** | | **Mean Medication Adherence Rate± Standard deviation** | **Medication Adherence rate Threshold** | **Probability to reach the targeted clinical outcome with Medication Adherence Threshold (Odds ratios [OR], Hazards ratios [HR] and Confidence Interval [CI])** | **Methods of Threshold Determination** | **Nonadherence Prevalence** |
| Vervloet et al (170) | Physician diagnosed asthma and with records of prescribed asthma medications | ---- | ICS implementation (1 - 99%) | ICS implementation (percentage of days covered by the prescription on the basis of quantity, dosage, and duration and computed for each prescription interval) vs RDAC (composite outcome) ICS was weakly positively associated with simultaneous RDAC. | Multilevel analysis | ---- |
| Williams et al (169) | | CMA (0.50 ± 0.37) CMG (0.54 ± 0.27) | ----- | Adherence to ICS correlated negatively with the number of ED visits ([R] = 20.159), the number of fills of OCS (R = 20.179), and the total days' supply of OCS (R = 20.154). Each 25% increase in the proportion of time without ICS resulted in doubling of the rate of asthma-related hospitalization (relative rate, 2.01; 95% CI, 1.06-3.79) | Poisson regressions | ----- |

| Author | | Mean Medication Adherence Rate± Standard deviation | Medication Adherence rate Threshold | Probability to reach the targeted clinical outcome with Medication Adherence Threshold (Odds ratios [OR], Hazards ratios [HR] and Confidence Interval [CI]) | Methods of Threshold Determination | Nonadherence Prevalence |
|---|---|---|---|---|---|---|
| William [50] | | CMA (23.6%) | ------ | Adherence was associated with a reduction in exacerbations but was only statistically significant among individuals whose adherence was >75% of the prescribed dose (HR; 0.61; 95% CI; 0.41–0.90) compared with individuals whose adherence was ≤25%. About 24% of exacerbations attributable to ICS non-adherence. | Proportional hazard models | ----- |
| Woodcroft et al (68) | | Adherence to ICS/LABA: mean ± SD PDC: 47.4 ± 28.8%; Adherence to ICS: - 40.8 ± 29.1% | | The rate of inpatient admissions among persistent asthmatic patients who filed ICS was 1.75 (1.48, 2.05) per 100 persons-years, rate for ED was 13.55 (12.77, 14.35) per 100 person-years, and urgent care visits for asthma was 2.71 (2.37, 3.09) per 100 person-years. Similarly, the rate for inpatient admissions, ED and urgent care visits among asthma patients who filled ICS/LABA were 1.97 (1.67, 2.3), 12.79 (12.01, 13.6), and 2.76 (2.41, 3.15), respectively. | --- | --- |
| Wu et al (171) | | ----- | PDC ≥ 75% | LTR less likely to be primary adherent than those on ICS (OR; 0.82; 95% CI, 0.74–0.92) or ICS/LABA (OR; 0.88; 95% CI; 0.80–0.97)<br>LTRA more likely to be early-stage persistent than those on ICS | Multivariate logistic regression analysis | 96.74% (Estimated with PDC ≥75%) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | (OR, 1.82; 95% CI, 1.64–2.04). LTRA or ICS/LABA more likely to be adherent as measured by adjusted PDC≥75% than those prescribed ICS (OR, 6.21 [95% CI, 5.41–7.19] and 2.13 [95% CI, 1.82–2.48], respectively). | | |
| Zhang et al (172) | Patients with incident diagnosis of asthma based on the Global Initiative of Asthma (GINA) steps 4-5 recommendations. | ----- | MPR ≥80% | Average direct healthcare cost per year of severe asthmatic who are adherent vs non adherent patients ($1,937 vs. $1,596, P<0.001) | Poisson regression and Generalized Linear Models | ---- |

## Appendix 5: Supplementary materials for Chapter 6

Sensitivity and specificity analysis for the various adherence thresholds

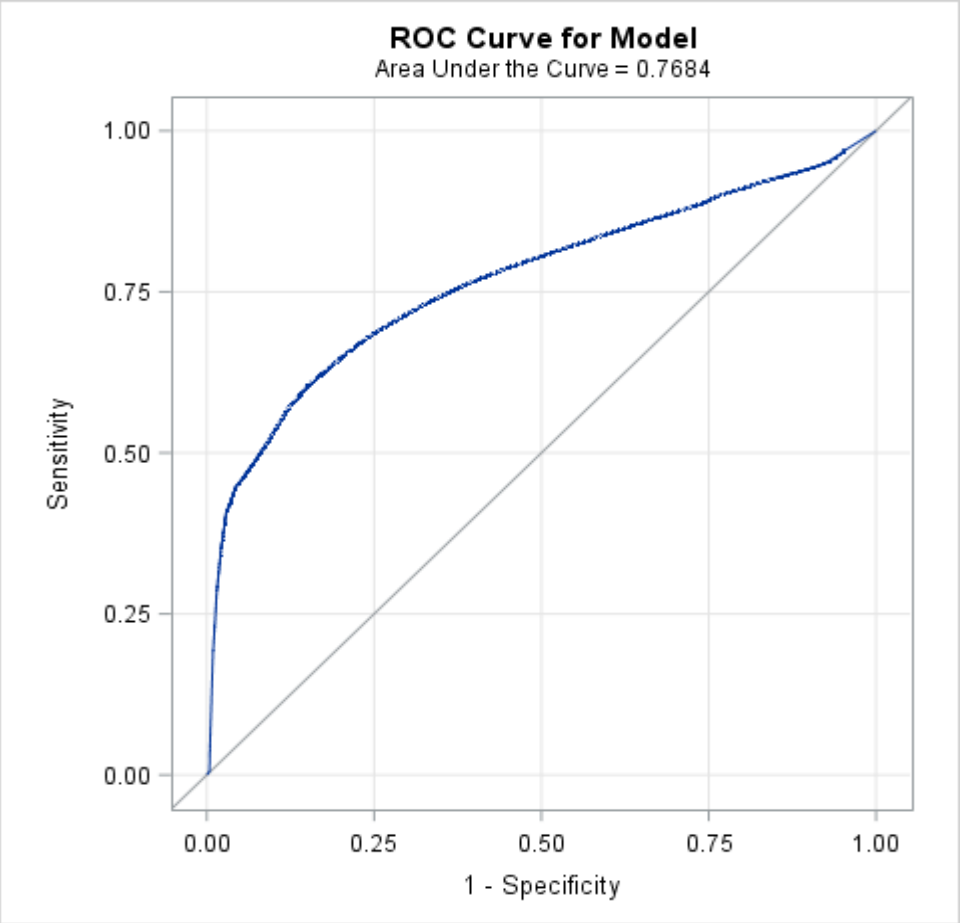


**Figure S6.1**: Receiver operating characteristics (ROC) curve for PDC adherence method

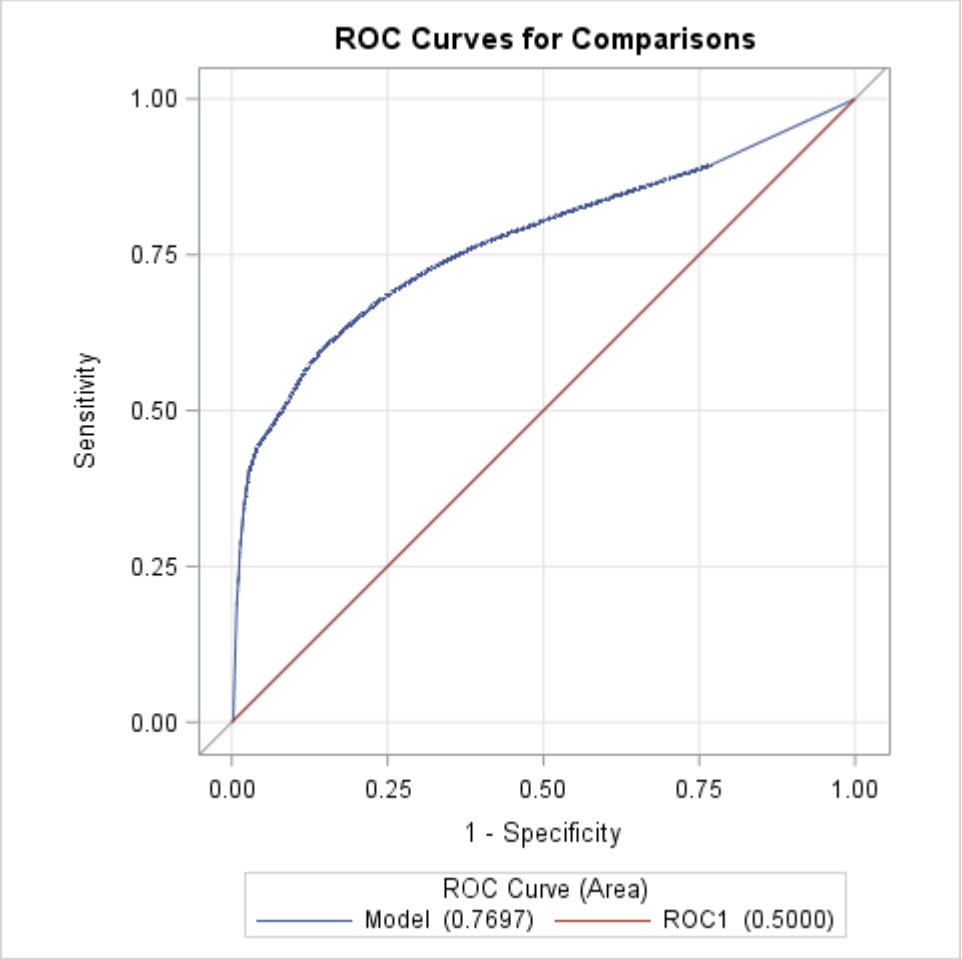


**Figure S6.2: Receiver operating characteristics (ROC) curve for MPR adherence method**

**Table S6.1**: Sensitivity and specificity analysis of PDC and MPR adherence thresholds

| **PDC adherence measure** | | | | | **MPR adherence measure** | | | |
|---|---|---|---|---|---|---|---|---|
| Cut-off values | Sensitivity | Specificity | Youden's Index | | Cut-off values | Sensitivity | Specificity | Youden's Index |
| 0.50 | 0.80 | 0.53 | 0.32 | | 0.50 | 0.79 | 0.55 | 0.34 |
| 0.60 | 0.82 | 0.45 | 0.27 | | 0.60 | 0.81 | 0.48 | 0.29 |
| 0.70 | 0.85 | 0.37 | 0.22 | | 0.70 | 0.83 | 0.41 | 0.25 |
| 0.80 | 0.88 | 0.30 | 0.17 | | 0.80 | 0.85 | 0.35 | 0.21 |
| 0.90 | 0.91 | 0.22 | 0.12 | | 0.90 | 0.87 | 0.29 | 0.17 |
| 1.00 | 1.00 | 0.00 | 0.00 | | 1.00 | 1.00 | 0.00 | 0.00 |