A POPULATION-BASED COHORT STUDY EVALUATING THE ASSOCIATION BETWEEN INHALED CORTICOSTEROID USE AND STATIN USE WITH LUNG CANCER RISK IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS

by

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Abstract

Background: Lung cancer incidence is elevated in patients with chronic obstructive pulmonary disease (COPD), often due to smoking, but potentially also resulting from inflammation. COPD patients are also often diagnosed with comorbidities, the most prominent being cardiovascular disease (CVD). Statins, due to the increased prevalence of CVD, and inhaled corticosteroids (ICS), are two commonly prescribed medications for COPD patients that may reduce lung cancer risk.

Objective: To evaluate the association between lung cancer risk with ICS and statin use in COPD patients. A *priori*, the hypothesis of this study was that use of these medications would be associated with a reduction in lung cancer risk.

Methods: This study used population-based data for the province of British Columbia to identify a cohort COPD patients. To be included, patients were to have filled three prescriptions for COPD-related medications within a twelve-month period. To evaluate the association between statin and ICS use with lung cancer risk, an array of methods of defining medication exposure were used, including a novel recency-weighed approach.

Results: In the analysis evaluating the association between ICS use and lung cancer diagnosis, time-dependent ICS exposure was associated with a 30% reduction in lung cancer risk. The recency-weighted duration of use exposure metric also demonstrated a

protective effect from ICS exposure (HR: 0.74 (95% CI: 0.66-0.82). This protective effect was consistent over all exposure metrics. Evaluation of the association between statin use and lung cancer risk produced less consistent results. However, the best-fitting model which incorporated the recency-weighted duration of use exposure metric indicated a protective effect from statin exposure (HR: 0.85 (95% CI: 0.77-0.93). Statin exposure in patients 65 or over was protective against lung cancer diagnosis consistently for all exposure metrics. An interaction term between ICS and statin use was also explored, but was not found to be statistically significant.

Conclusions: These results suggest that the benefits of ICS and statin use might extend beyond their primary indication. The results also underscore the importance of using appropriate methods for measuring medication exposure in observational studies, particularly those using administrative data. Finally, this work highlights the importance of 'real-world' evidence.

Lay Summary

Chronic obstructive pulmonary disease (COPD) is a debilitating disease that is associated with increased patient morbidity and mortality. The disease is also associated with several comorbidities, with one of the most common being cardiovascular disease (CVD). Patients with COPD face a higher risk of lung cancer, partially due to a history of smoking. However, the evidence also suggests that the increased risk of lung cancer extends beyond what can be attributed to smoking. Patients with COPD are often prescribed inhaled corticosteroids (ICS). Many COPD patients also receive statins, due to the presence, or risk of, CVD. Evidence suggests that ICS and statins might be associated with reduced lung cancer risk, but this evidence is limited in its generalizability. Therefore, this study aims to evaluate whether ICS and statin use in COPD patients is associated with a reduced risk of lung cancer, using data for the province of British Columbia.

Preface

This dissertation comprises my research in the evaluation of the association between inhaled corticosteroid and statin use with lung cancer risk in a population-based cohort of chronic obstructive pulmonary disease patients. I was chiefly responsible for all data cleaning and setup, data analysis, compiling, interpretation, and presentation of results. Advice and suggestions on data cleaning and the analytic approach was provided from Drs Larry Lynd, Huiqing (Kathy) Li, Mohsen Sadatsafavi, and Ms Maja Grubisic. Ethical approval was granted for this study (certificate number H08-00241).

Chapter 1: Introduction. This chapter was completed by Adam Raymakers with comments and revisions from Drs Larry Lynd, and Mark FitzGerald.

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Chapter 4: Adam Raymakers was responsible for the design, analysis, and writing of this study. Dr Mohsen Sadatsafavi provided an important contribution to the development of this chapter. In addition, Dr Mary De Vera and Dr Larry Lynd provided valuable insight and contributions to develop this chapter. Dr Don Sin provided important clinical insight. Two referees from the journal *Chest* also provided critical peer-review to this chapter.

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Chapter 7: Adam Raymakers was responsible for the writing of compiling the results of the previous chapters and integrating them into this final chapter, complete with limitations, and future avenues of research. Drs Larry Lynd, Mark FitzGerald, and Mohsen Sadatsafavi offered helpful feedback in the development and completion of this chapter.

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List of Abbreviations

AECOPD: Acute Exacerbation of Chronic Obstructive Pulmonary Disease

AIC: Akaike Information Criterion

CI: Confidence Interval

CCB: Calcium Channel Blocker

CCI: Charlson Comorbidity Index

COPD: Chronic Obstructive Pulmonary Disease

CVD: Cardiovascular Disease

EMBASE: Excerpta Medica Database

FEV1: Forced Expiratory Volume in 1 Second

HR: Hazard Ratio

ICD (9 and 10): International Statistical Classification of Diseases and Related Health Problems

ICS: Inhaled Corticosteroid

IQR: Interquartile Range

MPR: Medication Possession Ratio

MSP: Medical Services Plan

HR: Hazard Ratio

MEDLINE: Medical Literature Analysis and Retrieval System Online

MI: Myocardial Infarction

OR: Odds Ratio

PRISMA: Preferred Reporting Standards for Systematic Reviews and Meta-Analyses

RCT: Randomized Control Trial

RR: Relative Risk

SABA: Short-Acting Beta Agonist

SD: Standard Deviation

STATCOPE: Simvastatin for the Prevention of Exacerbations in Moderate to Severe COPD

TORCH: Towards a Revolution in COPD Health

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I would like to thank Drs Carlo Marra and Mark FitzGerald for initially hiring me for a staff position at the Collaboration for Outcomes Research and Evaluation (CORE). They gave me a great opportunity to gain experience in fields of health economics and outcomes research, and were both instrumental in helping make the decision to move on to embarking on a PhD. I also want to thank both of them for their continued interest in my development by agreeing to serve as members of my PhD Supervisory Committee. I would also like to thank Drs Mohsen Sadatsafavi and Don Sin for their support and guidance as part of my PhD Committee, your insights into the methodological and clinical issues associated with the work that comprised my dissertation were invaluable to completing this work. I would also like to thank Dr Huiqing (Kathy) Li for her support in completing the statistical analysis conducted in this dissertation, particularly in the latter stages.

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Dedication

I would like to dedicate this dissertation to my parents, Arno and Kim Raymakers, my aunt, Gail Rudderham, and my partner, Angelina Woof; you have all been instrumental to the completion of this work. Your support, patience, criticisms, inspiration, and patience, is all very much appreciated. This endeavor, and any future endeavors, are possible because of you all. Thank you.

Chapter 1: Introduction

1.1 Background

Chronic obstructive pulmonary disease (COPD) is a progressive and mostly irreversible disease comprising emphysema and chronic bronchitis, and is associated with considerable morbidity and mortality (1). The prevalence of COPD is approximately 10.1% worldwide, with males having a higher prevalence than females (11.7% versus 8.5%) (2). In Canada, the estimates of prevalence are similar, with studies reporting a prevalence of 9.3% for males, and 7.3% for females (2). These numbers have recently been rising, with a shift in the prevalence toward females from males (3). Increasing numbers of COPD patients will pose increasingly difficult problems to health systems worldwide with projections estimating that the number of cases of COPD will increase to approximately 5.8 million in the next 20 years (4). The societal economic burden of this disease, which is already substantial, has been commensurately projected to increase from $4.5 to $7.3 billion ($CAD) in Canada (4).

COPD is diagnosed according to a post-bronchodilator ratio of forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) of less than 0.70. Forced expiratory volume is further utilized to provide a stage of the disease according to the degree of airflow limitation. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (5,6) state that Stage 1 (mild) disease patients have post-bronchodilator FEV1 of ≥ 80% of

predicted. Stage 2 (moderate) disease patients have FEV1 less than 80% and above 50%. Stage 3 (severe) disease patients have FEV1 greater than 30% and less than 50% of predicted. Stage 4 (very severe) patients have FEV1 of less than 30% of predicted (5,6). These stages are summarized in Table 1.1 below.

Table 1.1. GOLD stages of disease.

GOLD Stage	Description	FEV1*
1	Mild	FEV1 ≥ 80% predicted
2	Moderate	FEV1 < 80% and ≥ 50% predicted
3	Severe	FEV1 < 50% and ≥ 30% predicted
4	Very Severe	FEV1 < 30% predicted

* Post-bronchodilator. GOLD: Global Initiative for Chronic Obstructive Lung Disease; FEV1: Forced Expiratory Volume in 1 second.

The treatment of COPD is largely based on the aforementioned disease staging, and often also considers the risk and history of acute exacerbations associated with the disease. Pharmacologic treatment for patients with Stage 1 disease typically comprises short-acting anticholinergics and short-acting beta-agonists (SABAs). Patients with Stage 2 disease can be prescribed long-acting anticholinergics or long-acting beta-agonists (LABA) (6) while

Stage 3 and 4 disease call for inhaled corticosteroids (ICS) in combination with a long-acting beta-agonist or a long-acting anticholinergic (6).

While these criteria help to classify COPD patients, it should be noted that COPD patients are heterogeneous and the disease may have several likely phenotypes (7). Han *et al.* (7) reported that FEV1, as a measure of lung function, does not comprehensively describe this heterogeneity. The authors suggest that (frequent) acute exacerbations can be considered as an outcome of COPD but also that exacerbations may be a manifestation of a specific phenotype of COPD patients. This phenotype may also be linked to systemic inflammation, discussed in Section 1.2 below.

Chronic obstructive pulmonary disease, similar to many chronic diseases, typically progresses in severity with the duration of disease (8). As a result, it is expected that lung function will decline and patients' outcomes will worsen as they become older. Mannino *et al.* (9) showed that declining lung function is a component of the natural history of COPD and is associated with increased morbidity and mortality. As noted above, severe acute exacerbations are a major concern for patients with COPD. These acute exacerbations of COPD (AECOPD) also become increasingly likely as lung function declines and previous AECOPD tend to be the best predictor of future exacerbations (10). Patients who experience acute exacerbations, particularly repeat/frequent acute exacerbations, are often hospitalized and have an increased risk of mortality. As such, Suissa *et al.* (10) state that repeated acute exacerbations are associated with a rapid decline in health status and that considerable effort should be directed toward alleviating the potential for exacerbations to

improve survival. Similarly, Najafzadeh *et al*. (4) used a dynamic simulation model, populated with data from Canada, to estimate the impact of several (hypothetical) interventions on the future economic burden of COPD in Canada over a 25-year time horizon and found that strategies to reduce acute exacerbations of COPD would have the greatest effect in reducing this burden over this period of time. Recently, model-based projections have estimated that inpatient hospitalizations among COPD patients, typically resulting from AECOPD, will increase from 150-185% by 2030 (11), thereby highlighting the impact of AECOPD, not only in terms of patients' outcomes, but also to health systems and/or payers.

1.2 The role of local and systemic inflammation

A COPD diagnosis is characterized by reduced lung function due to localized inflammation which is often a result of a patients' current smoking status or previous smoking history. The negative aspects of smoking behaviour, however, extend beyond this localized inflammation as levels of systemic inflammation are also increased in subjects with a history of smoking (12). However, smoking history does not account entirely for the increased levels of systemic inflammation in COPD patients, as evidence suggests that levels of systemic inflammation observed in COPD patients are greater than that attributable to patients' smoking history or current status (13).

While airflow limitation might be intuitively thought of as affected by localized inflammation in the airway, moderate and severe airflow limitation has further been

associated with increased levels of systemic inflammation. For example, Sin *et al.* (14) found that those with severe airflow limitation (defined as FEV1 ≤ 50%) were two times more likely to have elevated levels of systemic inflammation, measured by levels of circulating C-reactive protein (CRP) levels (OR: 2.18 (95% CI: 1.46-3.27)) than subjects with no airflow obstruction. However, the heterogeneity of COPD (as noted previously) means that systemic inflammation is variable in COPD patients (depending on the marker that is chosen) and there is no clear relationship between any particular aspect of COPD and systemic inflammation (7). However, in those COPD patients with increased levels of systemic inflammation, this is an important issue due to an observed association with reduced survival (15).

The presence of increased levels systemic inflammation in COPD patients has, in recent years, brought forth a new conceptualization of COPD whereby a specific phenotype of COPD may exist that might be characterized by systemic inflammation (16). Whether this is a specific phenotype or simply a more severe disease state remains uncertain but markers for systemic inflammation appear to be more present in patients that experience acute exacerbations and with later stage (more severe) disease (13). Fabbri *et al.* (17) suggest that adding the term 'chronic systemic inflammatory syndrome' to COPD a diagnosis may help convey the strong association between inflammation and the relationship to comorbidities in patients with COPD. Agusti *et al.* (18) report that in a subgroup of COPD patients with persistent systemic inflammation, there was an association with poor clinical outcomes compared to those with no evidence of systemic inflammation, despite similar

lung function[1]. Further, Wouters *et al.* (19) suggest that understanding the role of systemic inflammation, and not simply focusing on respiratory symptoms, is important in understanding the aetiology of acute exacerbations in COPD patients.

There are differing views of where systemic inflammation fits in the disease course in COPD. The question has been asked, does COPD result in systemic inflammation or is COPD a manifestation of systemic inflammation (13)? This may have implications for how the disease is managed and treated.

While the relationship between elevated levels of inflammation and lung cancer has been recognized, the exact mechanism by which inflammation increases lung cancer risk is less well understood. There are several possible links that have been put forward which might explain the association between inflammation in the lungs of COPD patients and increased lung cancer risk. Two potential causes of increased lung cancer risk resulting from inflammation associated with COPD are increased oxidative stress and surfactant dysregulation in the lungs, which are associated with markers of elevated systemic inflammation (12,20–22). In particular, increased oxidative stress has been associated with a reduction in apoptosis (20) while surfactant dysregulation reduces the ability of pulmonary surfactant protein to attenuate inflammation in the lungs. Additional hypotheses have been put forth that inflammation in the airway and in the lungs might

[1] In this study, systemic inflammation was quantified using six different biomarkers: white blood cell, C-reactive protein, interleukin-6, interleukin-8, fibrinogen, and TNF-alpha levels measured in peripheral blood.

stimulate recurring injury and repair of cells in the lungs, leading to uncontrolled cell growth (18), or that inflammation in the lungs may induce the activation of proteins that promote oncogenesis (23). In terms of genetic factors, research suggests that the regulation of anti-oxidant genes in patients with COPD is impaired, thereby increasing oxidative stress, and increasing the risk of lung cancer (13). Therefore, there are several potential explanations for how local and systemic inflammation might make the lungs susceptible to processes that increase lung cancer risk, but the exact mechanism remains an area for future study (18,23).

1.3 Comorbidities of COPD

There are several comorbidities common among COPD patients, including: ischemic heart disease, osteoporosis, depression, lung cancer, and diabetes mellitus (13). For example, Mapel *et al*. (24) estimated that COPD patients had a higher average prevalence of additional medical conditions (3.7) compared to age and sex matched controls (1.7, $p<0.001$) and that only 6% of COPD patients reported no additional medical condition. The role of comorbidities in COPD is an important consideration for patients' health and as such, all-cause mortality has largely become the preferred metric for outcomes in COPD patients (25).

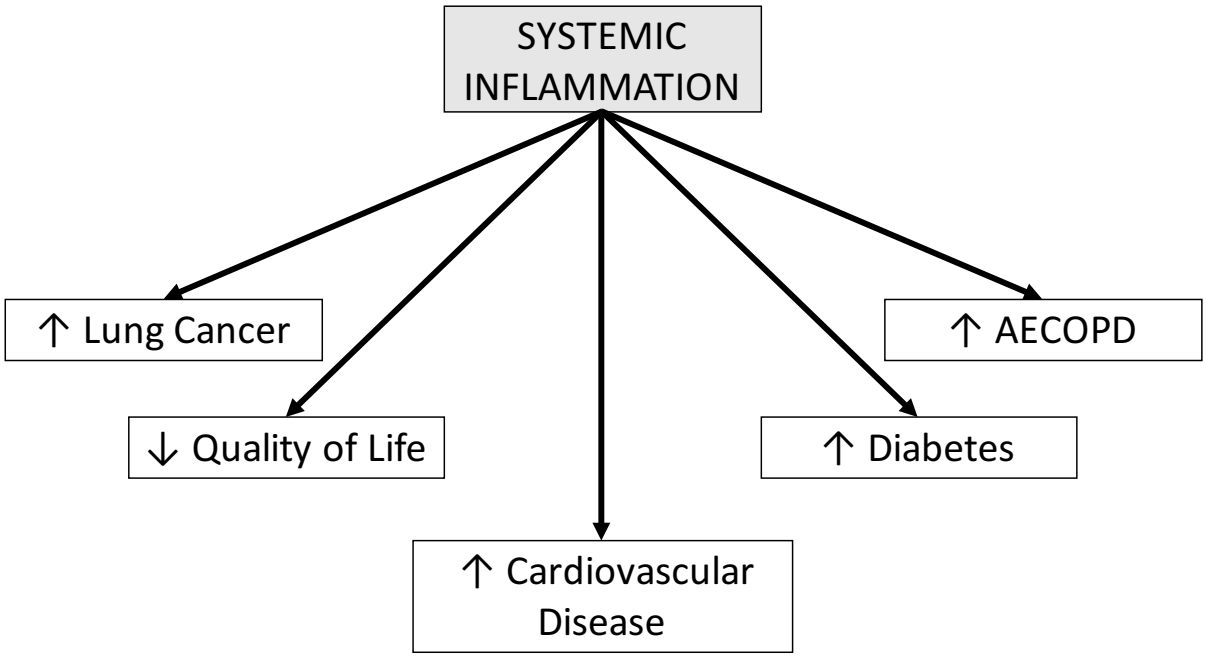


Figure 1.1. Systemic inflammation is associated with several conditions in COPD patients, as well as a decreased quality of life.

Cardiovascular disease (CVD) is among the most common comorbidities present in COPD patients. The prevalence of cardiovascular disease in patients with COPD is elevated compared to the general population of similar age and sex (14,26,27). Mannino *et al.* (27) estimated that the prevalence of CVD in a cohort of COPD patients was 15.2% in the United States. A meta-analysis by Chen *et al.* (28) reported that subjects with COPD were more than two times more likely to have CVD compared to subjects without COPD (OR: 2.46 (95% CI 2.02–3.00)). Similar results were reported by Curkendall *et al.* (26) who found comparable increased odds for several cardiovascular diseases in COPD patients using a population-based cohort study design in Saskatchewan, Canada. In that study, the estimated adjusted odds ratios for subjects with COPD compared to subjects without COPD

ranged from 1.11 (95% CI: 1.02–1.21) for stroke to 5.46 (95% CI: 4.25–7.02) for pulmonary embolism (26). The presence of CVD in these patients may largely be due to their smoking history but there is also a suggestion of a relationship between lung inflammation, systemic inflammation, and vascular inflammation (29). The additional risk of CVD results in patients with COPD often being prescribed an HMG-CoA reductase inhibitor (statins). Statins may be prescribed for primary or secondary prevention of CVD. Secondary prevention is typically delineated by a patient having had a cardiac event prior to their first statin prescription, whereas primary prevention patients are those at risk for such events and are prescribed statins, typically based on levels of low-density lipoprotein levels (30).

1.4 Lung cancer in COPD patients

Lung cancer is the second most common diagnosed cancer among men and women and the most common cause of cancer-related mortality (31). Although smoking is a risk factor for both COPD and lung cancer, evidence suggests that COPD itself is an additional risk factor for lung cancer development, independent of smoking status or history (32–35). For example, Wasswa-Kintu *et al.* (36) conducted a meta-analysis that showed reduced lung function is strongly associated with lung cancer development. One hypothesis for the underlying mechanism of this association that has been postulated is that reduced lung function may result in an inability to clear carcinogens from the airway (37). Elevated markers for inflammation also appear to be associated with lung cancer development. Young *et al.* (32) reported a six-fold greater prevalence of COPD in lung cancer subjects versus smoking-status, sex, and age-matched controls. Using data collected from 5402

participants in the First National Health and Nutrition Examination Survey in the United States, Mannino *et al.* (33) found that moderate or severe COPD was associated with an increased risk of lung cancer diagnosis (HR: 2.8 (95% CI: 1.8-4.4)), even after adjustment for age, sex, smoking status, duration of smoking, and smoking intensity. A longitudinal study of 176,997 men yielded similar results, with both mild and moderate/severe COPD associated with increased smoking-adjusted rates of lung cancer (RR: 1.5 (95% CI: 1.2-1.9) and RR: 2.2 (95% CI: 1.8-2.7), respectively) (38). A longitudinal study by Skillrud *et al.* (34) reported the smoking-adjusted probability of developing lung cancer was 10.8% in COPD patients and 2.5% in controls (p=0.023). Turner *et al.* (35), in a study of 448,600 lifelong non-smokers in the US, found that lung cancer mortality was significantly associated with combined emphysema/chronic bronchitis (HR: 2.44 (95% CI: 1.22-4.90)), over a twenty-year follow-up period (35).

The evidence from these studies suggests that the association between COPD and lung cancer is strong and while smoking is a known risk factor for both diseases, this common factor alone is not sufficient to explain all lung cancer cases (39). Several studies have linked increased markers of systemic inflammation (specifically CRP) to lung cancer development (see Table 1.2). Chaturvedi *et al.* (40) showed that, using data from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, that subjects in the highest quartile of CRP levels had an approximately two times greater risk of lung cancer than those in the lowest quartile, even after adjusting for smoking status (OR: 1.98 (95% CI: 1.35-2.89)). A study by Pine *et al.* (41), used serum IL-6 and IL-8 as biomarkers for

inflammation in two separate patient populations[2]. The results of their analysis suggest that both biomarkers were significantly associated with an increased odds of lung cancer. In the first analysis, patients in the highest quartile of IL-6 levels had three times greater risk than those in the lowest quartile and a two times greater risk for IL-8. In the second analysis, patients in the highest quartile of both IL-6 and IL-8 had 50% increased odds of lung cancer diagnosis compared to patients in the lowest quartile (41). Therefore, if it is true that there is a phenotype of COPD that is more prone to systemic inflammation, that phenotype might also be more likely to develop lung cancer. Identification of this phenotype, and delivering corresponding treatment to reduce levels of systemic inflammation might be useful to reduce lung cancer risk in COPD patients.

The evidence presented above asserts that, after adjusting for smoking status, COPD is associated with higher levels of systematic inflammation. Moreover, further evidence demonstrates that a link exists between systemic inflammation and lung cancer risk.

1.5 Inhaled corticosteroids

The appropriate use of inhaled corticosteroids as therapy by COPD patients has been debated (42,43), particularly for early stage disease; however, the GOLD guidelines suggest that an ICS should be used (as combination therapy) in treating COPD Stage 3 and 4 disease patients (5). The debate stems from evidence that suggests that ICS may not provide

[2] Pine *et al.* (41) used two different study populations: the National Cancer Institute Maryland study (NCI-MD) and the Prostate, Lung, Cancer, Ovarian (PLCO) screening trial.

benefits in terms of improved lung function or a reduction in all-cause or COPD-related mortality (44), but ICS have been shown to reduce AECOPD (45) and also to improve health-related quality of life[3] (46,47). For example, a meta-analysis of 24 studies by Gartlehner *et al.* (45) reported that patients using ICS compared to placebo experienced fewer exacerbations (RR: 0.67 (95% CI: 0.59-0.77)), but that ICS use had no significant risk on overall mortality (RR: 0.81 (95% CI: 0.60-1.08)). However, Sin *et al.* (48) found that patients prescribed an ICS after hospital discharge had a reduced risk of all-cause mortality (RR: 0.75 (95% CI :0.68-0.82)) and that the effect was more pronounced as the dosage increased (low dose (≤ 500 μg): RR: 0.77 (95% CI: 0.69–0.86); medium dose (501-1000 μg): RR: 0.48 (95% CI: 0.37–0.63); and high dose (≥1000 μg): RR: 0.55 (95% CI: 0.44–0.69)).

In addition to the lack of potential benefit conferred by ICS use in COPD patients, there has also been concern about potential adverse effects from ICS use. A study by Suissa *et al.* (10) showed that current ICS increased the risk of serious pneumonia (RR: 1.69 (95% CI: 1.63-1.75)). Similarly, a population based study by Eurich *et al*. (49) used a nested-case control design to evaluate the risk of pneumonia in ICS patients. Patients were classified as 'current', 'past', or 'never' ICS users. The results of the analysis showed a statistically significant increase in the risk of pneumonia from 'current' ICS use compared to 'never' use (OR: 1.90 (95% CI: 1.45-2.50)).

[3] In terms of the St. George's Respiratory Questionnaire (SGRQ).

Table 1.2. Lung cancer risk and associated levels of systemic inflammation.

Study	Study Participants	Biomarker	Smoking Adjusted	Estimated Effect
Chaturvedi *et al.* (40) *	PLCO trial	CRP	Yes	OR: 1.98 (95% CI: 1.35-2.98)
Pine *et al.* (41) *	PLCO trial	IL-6	Yes	OR: 1.48 (95% CI: 1.04-2.10)
	PLCO trial	IL-8	Yes	OR: 1.57 (95% CI: 1.10-2.24)
	NCI-MD	IL-6	Yes	OR: 3.29 (95% CI: 1.88-5.77)
	NCI-MD	IL-8	Yes	OR: 2.06 (95% CI: 1.19-3.57)
Allin *et al.* (50)ϕ	Danish General Population	CRP	Yes	HR: 2.1 (95% CI: 1.2-3.8)
Trichopoulos *et al.* (51)†	EPIC (Greece)	CRP	Yes	OR: 1.31 (95% CI: 1.11-1.53)
Siemes *et al.* (52) ‡	Rotterdam Study	CRP	Yes	HR: 2.78 (95% CI: 1.59-4.85)

* The highest quartile of inflammation level compared to the lowest quartile. ϕ The highest quintile compared to the lowest quintile. † For every 1 SD increment. ‡ For patients with levels > 3mg/L compared to those with ≤ 3 mg/L. EPIC: European Prospective Investigation into Cancer and Nutrition. NCI-MD: National Cancer Institute-Maryland.

The benefit conferred by ICS use in terms of reduced risk of AECOPD is likely achieved thorough a reduction in airway/localized inflammation. The use of ICS to reduce localized inflammation in the airway and lungs, both as monotherapy and combination therapy, is well-established (53–55). More importantly for the purposes of this dissertation, evidence further suggests that ICS use reduces systemic inflammation (Table 1.3). A proof-of-concept study by Sin *et al.* (56), using a final sample of 41 patients showed that ICS

Table 1.3. Studies reporting associations between inhaled corticosteroid use and systemic inflammation.

Study	Patients	Systemic Inflammation Biomarker	Estimated Effect
Pinto-Plata *et al.* (57)	COPD patients	CRP	Non-users: 6.3 mg/l; ICS users: 3.7 mg/l ($p<0.05$)*
Sin *et al.* (56)	COPD patients	CRP	Non-users: -7.6% (-36.6 to 34.8); ICS[a]: -50.3% (-72.9 to -9.0)*
	COPD patients	IL-6	Non-users: 5.0% (-31.6 to 61.0); ICS[a]: -26.1% (-43.6 to -3.2)*
Sin *et al.* (47)	COPD patients	CRP	Non-users: -0.145 (-1.923 to 1.732); ICS[a]: -0.168 (-1.385 to 0.691)
	COPD patients	IL-6	Non-users: -0.2 (-1.3 to 0.5); ICS[a]: 0.1 (-0.6 to 0.9)

* Statistically significant. [a] Fluticasone. IL-6: Interleukin-6; CRP: C-reactive protein; Mg/l: Milligrams per litre.

treatment resulted in lower CRP and IL-6 levels compared to controls. Similarly, Pinto-Plata *et al.* (57) found that CRP levels were elevated in COPD patients relative to non-COPD controls, but that these levels were lower in COPD patients treated with ICS, compared to no ICS use (57).

1.6 Statins

HMG-CoA reductase inhibitors (statins) are lipid lowering agents commonly prescribed as primary or secondary prevention for cardiovascular disease. Patients with COPD are often prescribed statins because these patients may face an increased risk of comorbid cardiovascular disease (CVD) (27). For example, Curkendall *et al.* (26) estimated that the proportion of statin use in a population-based cohort in COPD patients was 11.4% (26). Statins have been shown to be effective in reducing all-cause mortality in patients with risk factors for CVD[4] (58,59) and a recent report released by the United States Preventative Services Task Force (USPSTF) suggests that statin use is of benefit to patients 40 to 75 years of age with at least one risk factor[5] for CVD (60). In addition, and importantly for COPD patients, statins may reduce the risk of acute exacerbations (61) and the risk of all-cause mortality (62,63). Miyata *et al.* (64) suggest that statins may reduce lung inflammation by facilitating the clearance of particulate matter (PM_{10}) by limiting the activation of alveolar macrophages and polymorphonuclear leukocytes in the lungs. Lahousse *et al.* (65) report that sustained statin use (> two years) was associated with decreased risk of all-cause mortality, particularly in patients with higher levels of systemic inflammation (CRP). However, the evidence of the beneficial properties of statins is not undisputed. The recently completed Placebo-Controlled Trial of Simvastatin in the Prevention of COPD Exacerbations (STATCOPE) trial reported that a daily dose of 40 mg of simvastatin was not associated with the rate of acute exacerbations per year or time to an

[4] Without a prior diagnosis of CVD.
[5] These risk factors are: dyslipidemia, diabetes, hypertension, and smoking.

acute exacerbation in patients with COPD (66). This result is not, however, unchallenged (62,63), and perhaps merely increases the debate around the usefulness of statins in COPD patients. The STATCOPE trial had several significant limitations, particularly its inclusion/exclusion criteria (67). These criteria were designed to only allow patients without any indication for a statin[6], to be included in the study. The motivation for these very restrictive criteria was to ensure that benefits would be observed in patients without any reason to use a statin, thus ensuring that the effect was as specific to COPD as possible. However, this reduces the generalizability of the results, by potentially removing those patients in who statins might be of benefit. This lack of generalizability may reveal the usefulness of observational studies to generate real-world evidence in evaluating outcomes for COPD patients that use statins.

The hypothesized link between health outcomes in COPD patients and the impact of statins is the potential reduction of systemic inflammation provided by statin treatment. Table 1.2 (above) reports on the increased likelihood of lung cancer diagnosis in patients with higher levels of systemic inflammation. Existing evidence does support the hypothesis that statins do reduce levels of systemic inflammation. For example, the Pravastatin Inflammation/CRP Evaluation (PRINCE) trial found that statin use, for both primary prevention and secondary prevention for CVD patients, resulted in a decrease in CRP levels by 16.9% (primary prevention) and 13.1% (secondary prevention) at 24 weeks compared to a placebo group

[6] Patients were excluded if they met criteria for statin treatment according to United States Adult Treatment Panel III risk assessment from the National Heart, Lung, and Blood Institute, if they had a previous diagnosis of diabetes, or were already receiving statins.

($p<0.001$ and $p<0.005$, respectively) (69). While the PRINCE trial demonstrated short term effects of pravastatin to reduce levels of CRP, longer term reductions were observed in a randomly selected sample of patients from a trial of patients with previous history of myocardial infarction (i.e. secondary prevention patients) (70). After five years of follow-up there were statistically significant reduction in the mean levels of CRP (-18.4%) in the statin treated group compared to an increase in the CRP levels in the placebo group (+19.4%) (70). Similar findings were reported in the JUPITER trial[7], which also showed that statins were effective as primary prevention therapy (71). The trial results showed that statin treatment resulted in a 37% reduction of CRP levels after twelve months of use compared to subjects in the placebo group (71). The results of these studies suggest that statin use is associated with decreases in the levels of systemic inflammation (typically measured over time), both over short periods (i.e. 24 weeks) and longer periods of time (five years).

[7] Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER).

Table 1.4. Studies reporting associations between statin use and systemic inflammation.

Study	Patients	Systemic Inflammation Biomarker	Estimated Effect
Albert *et al.* (64)	PRINCE trial	CRP	Statin users[a]: -16.9% (baseline level: 0.20 mg/dl, 24 week level: 0.16 mg/dl)[b]; -13.1% (baseline level: 0.27 mg/dl, 24 week level: 0.24 mg/dl)[c]*
Bickel *et al*. (67)	Patients with coronary artery disease	CRP	Statin users: 4.3 mg/l; Non-users: 7.6 mg/l*
		IL-6	Statin users: 9.5 pg/ml; Non-users: 14.4 pg/ml*
Ridker *et al.* (65)	Secondary prevention CVD patients	CRP	Statin users[d]: -18.4% (baseline level: 0.38 mg/l, 5-year level: 0.31 mg/l); Non-users: +19.4% (baseline level: 0.36 mg/l, 5-year level: 0.43 mg/l)*
Ridker *et al.* (66)	JUPITER trial	CRP	Statin users[d]: -37.4% compared to placebo (median CRP level, statin users: 1.8 mg/l; non-users: 3.3 mg/L after 48 months)*
Shishehbor *et al.* (67)	Primary prevention patients	CRP	Statin users[e]: -2% (baseline level: 2.6 mg/l, 12 week level: 2.3 mg/l)

* Results are statistically significant. [a] Rosuvastatin; [b] Primary prevention patients; [c] Secondary prevention patients; d Pravastatin; [e] Atorvastatin. CRP: C-reactive protein; IL-6: Interleukin-6; g: gram; mg: milligram; pg: picogram; l: litre; dl: decilitre; ml: millilitre.

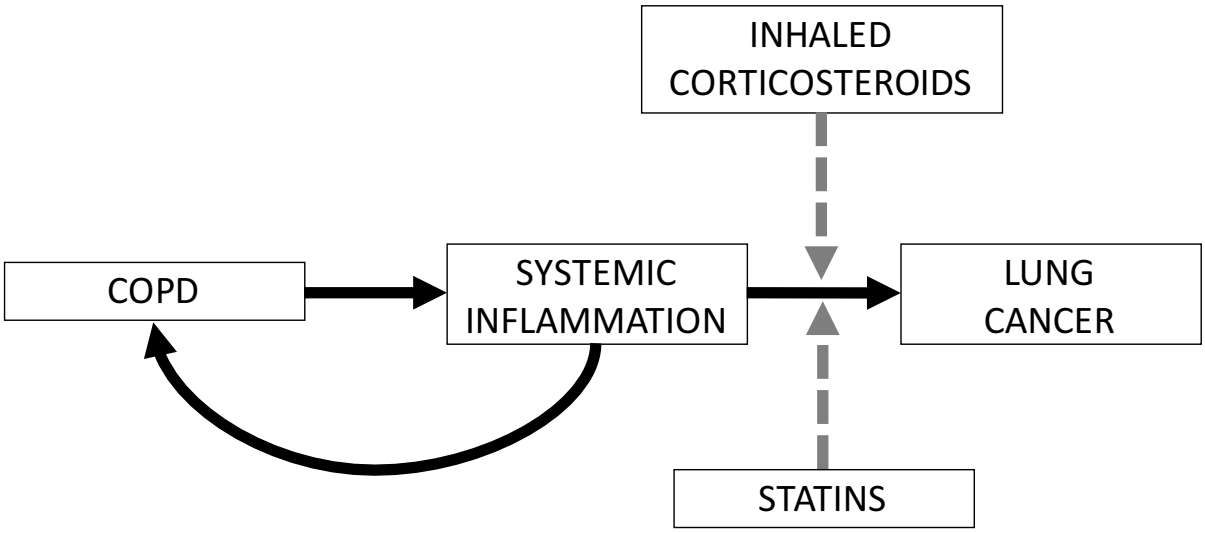


Figure 1.2. COPD is associated with systemic inflammation and systemic inflammation is associated with increased lung cancer risk. Inhaled corticosteroids and statins have anti-inflammatory properties and, thus, have the potential to reduce lung cancer risk.

1.7 Knowledge gaps

The studies that comprise this dissertation will serve to address several gaps that require further evidence regarding the treatment of COPD patients. First, it remains unclear, in the wake of evidence from the STATCOPE trial (66), if statin treatment in COPD patients is of benefit. To this end, I will evaluate the association between statin exposure, using a novel method to define exposure in this area, and mortality. Second, there is limited evidence for

whether ICS use in COPD patients might reduce lung cancer risk. Given that lung cancer risk is elevated among COPD patients, further evidence is required in order to determine if ICS use among COPD patients might provide a protective effect. To address this gap, a systematic review of the evidence will be presented, followed by a population-based cohort study using administrative data for the province of British Columbia (BC) linked to the BC Cancer Registry will be conducted. Similarly, the evidence for the use of statins and lung cancer risk has been inconclusive. While evidence suggests that statin use might reduce levels of systemic inflammation, and systemic inflammation has been linked to lung cancer risk, very little evidence exists for statin use and lung cancer risk, particularly in COPD patients. Therefore, I will conduct a population-based study evaluating statin use with lung cancer risk in a cohort of COPD patients to improve the evidence-base in this area. As well as adding to the evidence-base for treatments for COPD patients outlined above, this dissertation will also improve knowledge in methods employed to answer these research questions.

1.8 Specific objectives and overview of this dissertation

The objectives of this dissertation that will be addressed in the following chapters, are as follows:

1. to critically evaluate methods of defining exposure to medications, particularly in the context of administrative data and chronic diseases;
2. to systematically appraise the evidence regarding ICS use in COPD patients, and to identify improvements for future studies.

3. to evaluate if there is an association between statin use and health outcomes, in terms of mortality, in COPD patients;

4. to evaluate the use of inhaled corticosteroid and statin use in COPD patients in terms of lung cancer risk;

To address the objectives, below is an overview of each of these chapters:

Chapter 2: This chapter provides an overview and critical appraisal of methods of defining medication exposure that can be used in observational studies, particularly in the context of administrative data and chronic diseases. This chapter will provide a foundation for the methods used in the subsequent chapters of this dissertation.

Chapter 3: This chapter is a systematic review that explores the evidence relating to ICS use in COPD patients and lung cancer risk. It discusses the results, and, more importantly, the methodological issues that arise from both observational and trial-based studies with respect to ICS and lung cancer. It identifies significant gaps that exist in the current evidence base, which will be addressed specifically in Chapter 5 of this dissertation.

Chapter 4: One of the two main objectives of this dissertation is to evaluate the association between statin exposure and lung cancer risk in COPD patients. As a precursor to that analysis, this chapter evaluates the association between pulmonary and all-cause mortality and statin use, to provide insight as to whether statins may be of benefit in COPD patients. The analysis employs a novel study design that has not previously been used in this area.

Chapter 5: This chapter addresses the first component of the general research question of this dissertation: is there an association between ICS exposure and lung cancer risk in COPD patients? To answer this question, I use several different methods of quantifying medication exposure, building on the narrative review of these methods in Chapter 2, and the existing evidence presented in Chapter 3. In addition to using methods of defining exposure to medications that are novel in this area of research, this chapter also employs a latency period for lung cancer diagnosis that is seldom used in observational studies, and also accounts for lung cancer histology in the analysis, which is also a novel contribution.

Chapter 6: This chapter addresses the second component of the overall research question of this thesis: is there a relationship between statin exposure and lung cancer risk in COPD patients? Similar to the study presented in Chapter 5, this study builds on the exploration of exposure metrics presented in Chapter 2 and also builds upon the results of the analysis of statin exposure and all-cause mortality presented in Chapter 4.

1.9 Closing remarks

COPD patients have a considerable risk of morbidity and mortality. This is largely due to the increased risk of severe AECOPD and significant comorbidities associated with the disease. These acute exacerbations and comorbidities may be the result of, an often undetected, increased level systemic inflammation that is common in COPD patients. Inhaled corticosteroids and statins have anti-inflammatory properties and, as such, may

reduce the risk of exacerbations and poor outcomes associated with these common comorbidities. Further, the effects of inhaled corticosteroids and statins may reduce lung cancer risk, which evidence also suggests is associated with systemic inflammation. The high incidence and mortality rates associated with lung cancer mean that is it a worthwhile endeavour to identify any therapies that may reduce the incidence of lung cancer.

Chapter 2: A review of methods for defining medication exposure in observational studies

Summary

The definition of exposure to a medication and the relationship with the outcome of interest in observational studies can be complex. Compared to clinical trials which typically offer controlled exposure environments, observational studies may more accurately reflect patients' behaviour and physician practices in reality. However, observational studies still pose analytical problems when attempting to define exposure to prescribed medications; patients' medication dose may fluctuate, the length of time using the medication may vary, patients may discontinue taking their medications, or may not adhere properly to the instructions given by their physician or pharmacist. This narrative review presents several metrics for quantifying medication exposure in observational studies, and critically evaluates their advantages and disadvantages. This chapter will also inform the analytical approach used in subsequent chapters of this dissertation.

2.1 Introduction

The prevalence of chronic diseases has been steadily increasing (74) with a concurrent increase in the number of available medications and the commensurate use of these medications (75,76). The treatment of chronic disease and the evaluation of the effectiveness of these medications represents a different scenario than evaluating

medications for safety and efficacy in randomized controlled trials (RCTs). For medications used in the treatment of chronic diseases, where the effectiveness of a medication must be evaluated over an extended duration of time, the complexity of defining medication exposure is increased. Moreover, the length of time that a patient uses a medication increases the potential for variability in the usage of the medication (77). This variability may influence the ability of the medication to be effective in a real-world setting.

In observational studies, the classification of a patient as exposed or unexposed to a medication can be complex. There are a myriad of factors to consider, particularly in longitudinal studies when the duration of follow-up and exposure may extend over a period of several years (78). For example, the initial medication prescription, drug dosage, and the duration of the prescription all need to be considered. Further, patients may switch between medications or dosages can be altered by physicians. Patients' behaviour also plays an important role as they may choose to discontinue their medication, or use it irregularly for a variety of reasons such as cost, confidence in effectiveness of the medication, or the perceived ability to self-treat (74,75).

Chronic diseases may have other associated complexities. The latency periods and induction periods (see Figure 2.1) that are characteristic of chronic diseases make the relationship between medication exposure and disease even more complex (81). The induction period is defined as the time between the exposure to the agent which causes the disease and subsequent disease initiation. The latency period is the time from disease initiation until the disease becomes clinically detectable (82). For medication exposure that

may provide a beneficial (or a detrimental) effect, understanding these two periods, and how they relate to medication exposure definitions, is important. For example, consider a disease that has a latency period of six months. A patient that receives a medication (the exposure), thought to be protective for the disease, at three months before the disease has become clinically detectable could be classified as exposed. Although the patient has received the medication thought to prevent the disease, in reality, the disease process has already begun and there is little, if any, chance for the medication to have an effect on the disease process. Thus, appropriately defining a window of exposure which acknowledges the latency period of a particular disease, is important in analyzing the effects of medications in chronic diseases or, indeed, any disease with long induction and/or latency periods (i.e. cancers). Analyses must also consider the time that is required for a medication to be effective and the time period for which it remains effective. For example, a patient that received their first prescription of a statin for the primary prevention of cardiovascular disease and experienced a myocardial infarction the following day likely did not experience any benefit from that statin prescription. In such an instance, the patient should not be classified as being exposed to the medication. Similarly, for a study that has a follow-up time of several years, a patient that received their only statin prescription of 30 days in first year of follow-up and experienced an event (i.e. death) in the fifth year is likely not have received any sustained benefit from that initial statin prescription, which should be accounted for by the exposure definition.

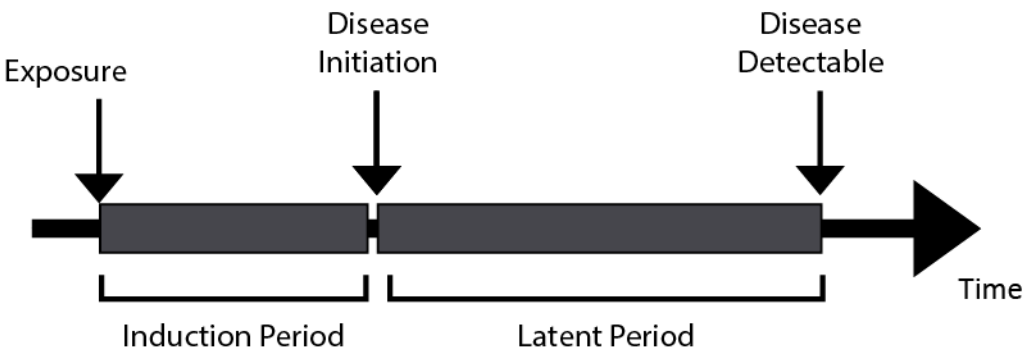


Figure 2.1. Induction and latency periods associated with the onset of a particular disease. In this example, the 'exposure' is that which begins the disease process.

Another relevant consideration in quantifying exposure for patients with chronic disease is patients' adherence to medications, and discontinuation or interruptions, in their medication. Non-adherence is sufficiently common and problematic that it has become a frequently employed exposure metric (78,79). As mentioned above, there are a myriad of reasons why patients take their medication irregularly or cease to take their medication, ranging from perceptions (for example, confidence in the expertise of the prescribing physician (79)) to negative effects of the medication (pain associated with statin use (80)) and these reasons are often not captured in study data.

Randomized controlled trials (RCTs) may be better equipped to control medication usage, dosage, and sustained use by enforcing the protocol of the study. However, observational studies better reflect real-world conditions for post-marketing surveillance of medication effectiveness, particularly in the case for chronic diseases and cancer when the length of

study follow-up or the number of events may be prohibitive to carry within the context of an RCT.

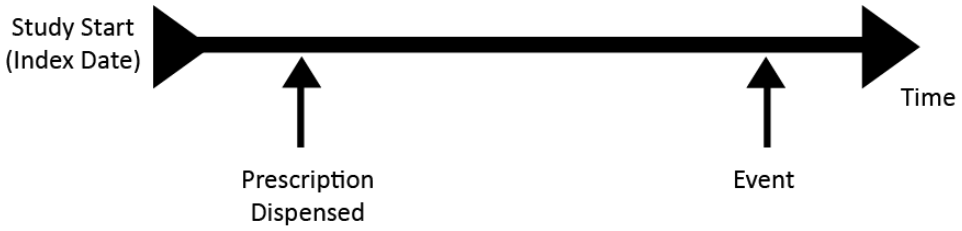
There is an assortment of methods that can be used to define medication exposure including: ever/never use, duration of use, adherence, discontinuation, or cumulative or current dose, among others. Simultaneously quantifying the components of medication exposure (timing, duration, dose, etc.) poses analytic challenges and may significantly affect study results. Therefore, this chapter will provide an overview of several different measures of defining exposure to medications and critically evaluate the implications that each definition will have on the analysis of data and study results. To do so, this review will use the context of an observational cohort study that uses population-based administrative data to evaluate the association between medication use and lung cancer risk, in addition to drawing on published examples from the literature. Moreover, it will provide the foundation and context for the decisions on exposure metrics used in analyses presented in subsequent chapters of this dissertation.

2.2 Measures of medication exposure

2.2.1 Ever/never use

The most basic method of quantifying medication exposure is simply to classify patients as exposed if they have ever received a prescription or were dispensed the medication, in the context of administrative data. The advantage of this method lays in its simplicity, both conceptually and computationally. However, there are several key issues that limit the

appropriateness of this definition of exposure. For example, if the follow-up period in a cohort study is long, and exposure status if fixed, 'exposed' patients that have contributed very little time would be treated equally to 'exposed' patients with much longer follow-up times. This can be problematic, as the length of a patients' follow-up time might not only increase their probability of experiencing the outcome of interest, but also their probability of being exposed to the medication. Since this method of defining exposure is fixed, it also does not take into account improper use, interruptions in use, or discontinuation of medication use. Moreover, dose-response relationships are not considered. This method is often used as a basis for comparison within a study where several other metrics of medication exposure are used (80,81). Using this method of exposure classification, a patient that receives a prescription or is dispensed the medication will always be classified as 'exposed' in the study follow-up period. This static or fixed exposure classification has the potential to bias the study results, particularly for studies with longer follow-up times.



For the ever/never defintion of exposure status, a patient that receives the medication at any point during the study period (prior to the event of interest) is considered exposed. Exposure status is often fixed over the duration of follow-up.

Figure 2.2. Using a fixed, 'ever/never' exposure definition, a patient can be considered exposed if ever having been dispensed the medication in the follow-up period.

This method of quantifying medication exposure can be improved by applying specific exposure windows in the analysis. In doing so, exposure is still fixed, but the period for exposure assessment can be shortened to create a more plausible link between exposure status and the probability of experiencing the outcome of interest. In Chapter 4, the analysis presented explores the association between statin exposure and patient outcomes (all-cause mortality as the primary analysis and pulmonary-related mortality as a secondary analysis). To do so, an exposure ascertainment window was defined (one year from the index date: the diagnosis of COPD) was used in conjunction with a one-year outcome ascertainment window. Thus, the period in which exposure status was defined did not overlap with the period during which the association between exposure and the outcome of interest was explored (82,83). This analytical approach limits the chance of misclassification bias and immortal time bias. The potential for misclassification bias is reduced by defining a specific time period during which patients could be exposed and, also, by limiting the time period during which they could experience the outcome of interest. The potential for immortal time bias is mitigated by creating the non-overlapping exposure ascertainment and outcome ascertainment periods.

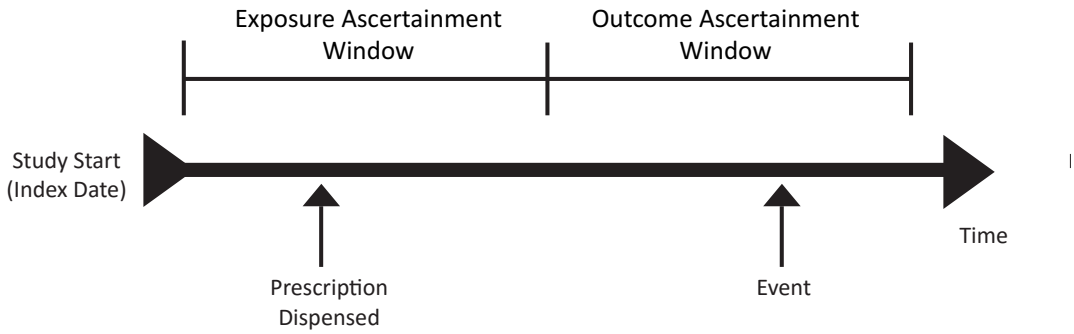
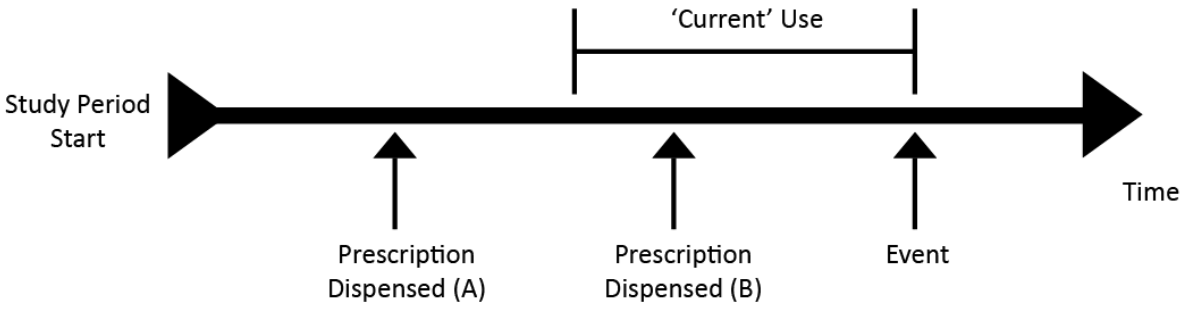


Figure 2.3. Exposure and outcome ascertainment windows.

2.2.2 'Current' medication use

Exposure may also be defined as 'current' use, that is, a specific period defined prior to the event of interest. This method is commonly used in case-control studies (86) and classifies a patient as exposed if the medication was dispensed in a specified time period preceding the event of interest. This method may be most appropriate for certain medications that are used to prevent acute events. However, for diseases that develop slowly and that may have poorly defined start times, it becomes less likely that it is an appropriate measure. The limitations of this approach are that it does not appreciate dose-response relationships or

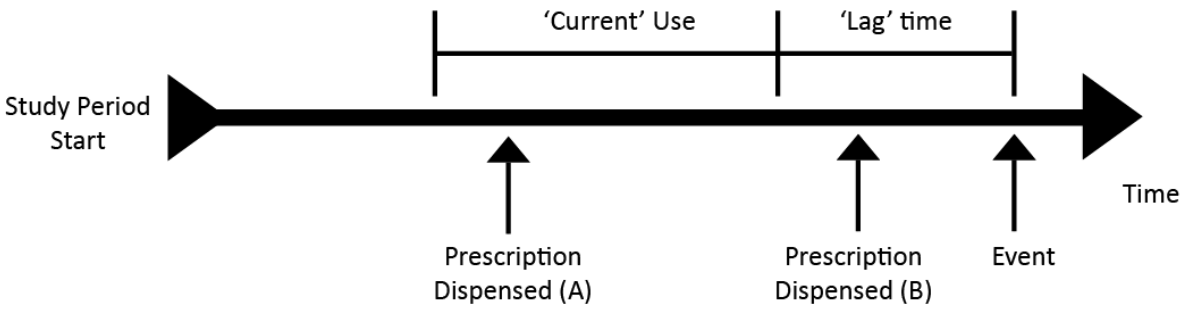
the aggregate duration of medication use. These two factors are important for chronic diseases where medication usage may span several years and where dosages may also vary over time. The intuition, however, behind this method is simple: that exposure in a defined time-window immediately prior to the outcome/event of interest is the most important. Control patients, obviously will include those patients that never received the mediation but may also include patients that received the medication outside the defined exposure window (see Figure 2.4). The result will be that some patients that received the medication, but outside of the exposure window, will be counted as unexposed, which has the potential to bias results towards the null, if past usage affects the outcome.



In this example, the prescription dispensed 'A' does not meet the definition for exposure because it falls outside the defined time-window of 'current' use. Conversely, prescription 'B' was dispensed within the defined time-window meaning that this patient will be classifed as exposed.

Figure 2.4. 'Current' medication use.

An example of this definition used in practice is presented in Tournier *et al.* (89) where the authors used three different measures of exposure to assess the effect of antipsychotic medications prior to a metabolic event. Among these measures, a categorical variable for 'current use' was explored, along with ever/never use, and cumulative duration of medication use. Current use was defined using three levels: (i) current use (using the medication at same time as metabolic event occurred), (ii) recent use (within six months of the event), and, (iii) no use. These three definitions rendered conflicting results: ever-use resulted in a protective hazard ratio, current use showed an increased risk of a metabolic event, and cumulative duration of use did not show a statistically significant effect. One plausible explanation of this discrepancy in results suggests that patients prescribed an antipsychotic who exhibit signs of an impending metabolic event and discontinue use of the antipsychotic prior to the event occurring (89). As such, because the exposure classification in the ever/never use scenario is fixed, these patients would remain considered as exposed in the analysis despite discontinuing their medication use. The authors' use of the current use measure of exposure classification remedies this problem by introducing a specific time-window of exposure related to the event.



As a variation on the previous example, the prescription dispensed 'A' now meets the criteria to define the patient as exposed. However, if the patient had only received the prescription 'B' (dispensed during the 'lag' time period) this would not meet the definition of exposed.

Figure 2.5. Addition of a 'lag' time as a variation on 'current' use.

Lee *et al.* (90) used current and past exposure of inhaled corticosteroids (ICS) to explore their relationship with the development of lung and laryngeal cancer. This nested-case control study used current (within 90 days of the index date, the diagnosis of cancer) and past use (91-365 days from the index date) to define exposure to ICS. Patients with less than a 30-day prescription for ICS were classified as non-users. Dividing current and past users in this way is a strength of the study, however, it omits an important characteristic of lung cancer. That is, a dose of ICS immediately preceding a lung cancer diagnosis should not be considered as a treatment failure because the ICS exposure would have occurred when the initiation of lung cancer had already started (within the latency period). Lung cancer is often diagnosed at an advanced stage, which is why lung cancer screening programs have been the subject of intense research and the role of such programs in potentially reducing the high morbidity and mortality is increasingly recognized. Therefore, when lung cancer is diagnosed, it is likely that the patient has had lung cancer for a period of time and simply

had not received a diagnosis. In this context, current use is likely inadequate in evaluating an association between lung cancer development and ICS use. A strength of this study, however, was that two different 'lag' periods were assigned in sensitivity analysis (three and six months). Application of these lag periods resulted in statistically significant odds ratios that demonstrated a slightly reduced effect (OR: 0.86 (95%CI: 0.80-0.93) and OR: 0.86 (0.80-0.95), respectively) compared to the overall odds ratio (OR: 0.79 (95% CI: 0.69-0.90) (90). The latency period of lung cancer is poorly understood; however, it is likely that a six month period may still be too short for ICS to have an effect on lung cancer risk (39). Moreover, to be considered exposed, patients needed a minimum of a 30-day prescription for ICS, but given the proposed mechanism of action for ICS reducing lung cancer risk, this length of prescription time may also be insufficient (90). In this example, the authors did, in fact, show that ICS provided a protective effect on lung cancer risk (OR: 0.79 (95% CI: 0.69-0.80)). While this result aligns with the *a priori* study hypothesis, further validation of the effect would be confirmed if this result persisted with the duration of ICS use, or with longer definitions of a 'lag' period (i.e. twelve months). Thus, patients might be misclassified as being exposed when they have not had a sufficiently long duration of use of the medication for it to confer benefit. This misclassification would likely result in a conservative bias; that is, it would be expected that because lung cancer patients would be defined as being exposed, the results would be biased toward the null.

2.2.3 Cumulative dose

Medication exposure can also be defined using cumulative dose, that is, the total quantity of medication times the dosage of a medication received during a certain time period. This

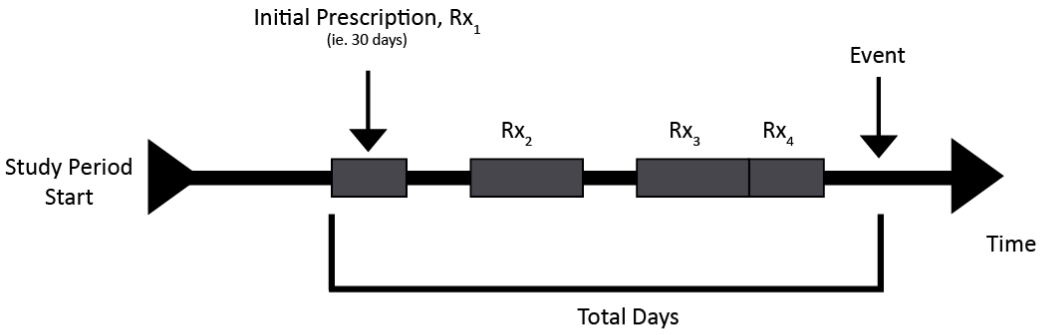
measure is also computationally and conceptually simple. To calculate exposure in this way requires the aggregation of the doses received by the specific patient over the follow-up period. The most complicated issue arises when a patient might switch between medications, that have different strengths, within a specific class of drugs (i.e. between budesonide and fluticasone for inhaled corticosteroids) and dosages need to be transformed into a comparable equivalent dose (86,87). The strength of this method is that it appreciates differences in doses and quantities of medications received by each patient, and that associations may exist for cumulative amounts of the medication used by patients (i.e. dose-response relationships). As an extension, one could calculate the mean daily dose over a specified time period and, potentially account for time-dependency over specific time windows. The drawback of this approach is that it gives no weight to when, during follow-up, the actual exposure occurs. For example, a patient may use a medication in high doses, but very sporadically. The calculation of cumulative dose for this patient would not differ for a patient that used their medication continuously (as directed) over the same period of time, at a lower dose. Similarly, it does not distinguish between a patient that used a low-dose, over a longer period of time, and a patient that used a high dose for a shorter period of time. Finally, it does not appreciate when, during the follow-up period, the medication was received in relation to the outcome. Therefore, to improve this method, it would be advantageous to use an approach that appreciates the cumulative dose of medication received and also when it was received during the follow-up period. One way to accomplish this is to use a series of time-windows during the follow-up period to calculate the cumulative dose of medication received in each window as they relate to the outcome

of interest. Additional methods that incorporate cumulative dose into a more robust metric of exposure are discussed in Section 2.2.5 below.

2.2.4 Medication adherence and discontinuation

Adherence to medication can be a useful metric for quantifying medication exposure. This method appreciates that patients do not always use medications as directed by physicians. In observational studies, particularly studies using administrative datasets, the medication possession ratio (MPR) or proportion of days covered (PDC) are commonly used methods of capturing medication adherence (93). These two methods essentially take the aggregate of the prescribed duration of medication divided by the follow-up time of the patient. The difference in the two measures is reflected in how over-lapping prescriptions are handled; the MPR can be greater than one, no adjustment is typically made for prescriptions that may overlap, whereas, with the PDC, prescriptions cannot overlap, therefore the range of possible values is limited between '0' and '1'. A threshold can then be applied to classify the patients categorically as 'adherent' or 'non-adherent'. For example, Blackburn *et al*. (94) used a threshold for a medication user to be considered adherent of 60% whereas Suissa *et al.* (83) used a threshold of 80%. The threshold for adherence that is chosen will depend on the medication under investigation, but should undoubtedly be subject to sensitivity analyses to determine if the level chosen is adequate to offer therapeutic benefit. A categorical measure of medication adherence might also be useful to determine if a gradient exists for each level of adherence.

A study by Ho *et al.* (95) evaluated the association between adherence (using the PDC method) to cardio-protective medications (statins, beta-blockers, angiotensin receptor blockers) and all-cause mortality. The study found that cardio-protective medications reduced all-cause mortality and, importantly, adherent users[8] had a more pronounced reduction in all-cause mortality. Interestingly, this study found that there was no difference in the risk of mortality between non-adherent medication users and 'never' users. This result highlights the importance of using a threshold of adherent versus non-adherent users as the benefit of medications might only be conferred at a certain level of adherence. Therefore, this metric of exposure can properly classify patients as exposed or unexposed and reduce the chance of bias.



In this case, all of the prescriptions recevied (Rx_1, Rx_2, Rx_3, Rx_4) are non-overlapping. Each prescription comes with an associated supply in days. The medication possession ratio (MPR) for example, would be calculated as the days supply of each medication divided by the 'Total Days' for this patient (the time from the initial dispensation of the prescription to the 'event').

Figure 2.6. Calculation of medication adherence using the medication possession ratio (MPR).

[8] Adherent patients had a PDC ≥ 0.80. Patients with a PDC less than 0.8 were considered to be non-adherent.

Patients' discontinuation of medication can also be used as a metric of 'exposure'. Suissa *et al.* (83) showed that treatment discontinuation from inhaled corticosteroids (ICS) was associated with a reduction in the risk of serious pneumonia. Patients could 'discontinue' their medications at any point in time by not refilling their prescriptions.

Teichart *et al.* (84) provides another example of discontinuation whereby the authors examined the association between discontinuation of beta-blockers and the risk of MI using several windows of discontinuation (<30 days, 30 days to 180 days, >180 days). The study results suggested that the relative risk of MI was increased (less than 30 days, RR: 2.70 (95% CI: 1.06-6.89); 30 days to 180 days, RR: 2.44 (95% CI: 1.07-5.59) for the first two categories of beta-blocker discontinuation but that there was no significant risk increase for discontinuation of greater than 180 days. Again, this result emphasizes the impact that exposure definition might have on study results.

The foremost problem with this approach, when using administrative data, is that the dispensation of the medication is recorded, but it is unknown whether the patient has actually taken the medication. It is necessary, therefore, to make an assumption that prescriptions dispensed are actually used by the patient.

2.2.5 Recency-weighted exposure measures

Recency-weighted exposure definitions such as the recency-weighted cumulative dose method is an attractive method of defining exposure that can incorporate the duration of time a patient has used a medication and weights those medications received proximal to

the event of interest more heavily than those received earlier in the follow-up period. A study by Abrahamowicz *et al.* (96) is the original investigation using this method. The analysis builds on previous work done by the authors' regarding benzodiazepine use and adverse events. The focus of the study was to accurately model the cumulative effects of the duration and dose of exposure. While this study, and subsequent studies employing this methodology, focused primarily on acute events, this methodology can be applied more generally. The original use of the methodology in the context of acute events was by design, as the methodology was developed to explore associations between medication usage and adverse events. Specifically, the authors' motivation for this study was to find a measure that would be sensitive enough to capture weak associations between medication exposure and adverse events (96).

Avina *et al.* (97) used the recency-weighted method to explore whether it would result in a better model fit, compared to common exposure metrics, in predicting cerebrovascular accidents (CVA) after exposure to oral glucocorticoids in patients with rheumatoid arthritis (RA). The results of the study suggested, across all measures of exposure, that there was no statistically significant association between glucocorticoid (GC) exposure and CVA, nor did their results support the incorporation of the recency-weighted exposure metric to improve model fit[9]. A later study by the same author (85) used a similar approach (as a sensitivity analysis) to estimate the risk of acute myocardial infarction (AMI) after

[9] In this study, model fit was assessed by comparing the Akaike Information Criterion (AIC) value for each model.

exposure to glucocorticoids in RA patients. In this study, again, the weighted cumulative exposure method of quantifying medication exposure did not improve the model fit (85).

Dixon *et al*. (86) conducted a study assessing the risk of infection after oral glucocorticoids (86) using eleven different models with various metrics for exposure to highlight the complexity of the relationship between medication exposure and adverse events. All multivariable models were then compared to the model incorporating the weighted cumulative dose exposure metric (using Akiake information criterion (AIC)). The AIC of the weighted cumulative dose model was subtracted from the AIC of the conventional models to evaluate the difference between the respective AIC values where a positive value would indicate that the model incorporating the weighted cumulative dose exposure definition had a greater AIC, and thus was inferior to the conventional models. In every instance, the AIC for the weighted cumulative dose model was lower than that of the conventional models (86) indicating that the models containing the weighted metric for exposure provided better estimates of the association between the exposure and outcome.

A method that attempts to similarly account for variation in medication usage over the exposure period was proposed by Phadnis *et al*. (98). The authors suggest that using just one covariate (even if the covariate was time-dependent) was insufficient to measure variation in medication exposure over time. As a proposed solution, the authors developed a method that used three time-dependent covariates simultaneously in their regression model: (i) current medication usage status (yes/no), (ii) the proportion of cumulative exposure to drug at a given point in time, and (iii) patients' switching between taking and

not taking the medication (98). A study by Shireman *et al*. (99)[10] applied this method to evaluate the association between antihypertensive medications and cardiovascular outcomes in hemodialysis patients. Their finding was that the '...effectiveness [of the drug] depends not only on having a drug available but is tempered by duration and stability of use, likely reflecting variation in clinical stability and patient behaviour' (94, p.113). However, while this approach may be attractive because it seems to offer a comprehensive account of medication exposure, the interpretation of the results becomes less clear. Instead of one result, several hazard ratios and interactions are generated by the analysis and results are presented in a series of three-dimensional graphs that are difficult to comprehend. Therefore, it appears that the method proposed by Abrahamowicz *et al*. (96) may be superior because it appears to accomplish similar comprehensiveness, and is also intuitively attractive because it assigns different weights to past exposures, weighting those medications received recently more heavily than those received in earlier in the study period. However, the method by which weights are assigned needs to be carefully considered in the context of the medication and disease under study when using this approach. The exposure weights and the window of relevant exposure will be different for acute events versus chronic diseases. The overall motivation for both of these methods is that definition of medication exposure, due to differences in duration and time, and the temporal link with the outcome being studied, is complex. These two analytical methods

[10] Phadnis *et al.* (98) reported the development of the method and the Shireman *et al.* (99) study was the application of the method for antihypertensive medication exposure in haemodialysis patients.

attempt to appreciate the relationship between medication dose, duration of use, and proximity of exposure relative to the study outcome.

2.3 Discussion

The objective of this review was to critically evaluate methods used to define exposure to medication in observational studies. The evaluation of these methods presented above should reveal that there may be choice of methods that can be employed in epidemiologic analysis, but these methods must be carefully considered, in the context of the medication and outcome, in a particular study. The assertion of this review is that basic metrics may be appealing due to the ease of calculation and their simplicity, but they may not capture the true effects of medications, and have the potential to misclassify medication exposure, thus biasing results, particularly in periods of sustained and/or interrupted use.

Common definitions of exposure, as described above, such as ever/never use, cumulative dose, or current use, do not take into account variability over time. The longer the study follow-up time, the less appropriate these methods may be as the potential for variability in medication usage will increase over time. While these methods of defining exposure may be adequate for short exposure windows, where the outcome is always proximal to the exposure, very seldom will they appropriately quantify medication exposure, particularly over a longer period of time.

As mentioned, adherence to medications may be an important consideration, but certain methods to calculate adherence may be too coarse, particularly over longer periods of follow-up time. Aggregating days of filled prescriptions over the period of follow-up time for longer studies may not reveal when patients have significant interruptions in medication usage. To illustrate, in a study where a patient received two 30-day prescriptions for a medication and had a follow-up time of one year, the resulting MPR would be 17%. This specific patient used the prescribed medication for only two months of the potential twelve months[11]. However, if, for the same patient, the follow-up period was two years and the patient missed this same eight months of therapy in the first year, but was perfectly adherent in the second year (i.e. filled the full remaining twelve months of prescriptions), the calculated MPR would be approximately 58%. However, this does not capture the fact that the patient went eight months in the first year without using their medication. This aspect of exposure can be improved by evaluating adherence over specific exposure windows. In the example presented above, using the two-year follow-up time, a better approach would be to calculate medication adherence in the first year (17%) and the second year (100%). However, this improvement still does not account for potential dose-response relationships.

Discontinuation is another possible way to define medication exposure that differs from non-adherence. Non-adherence may simply refer to a ratio of medication adherence less than a pre-defined threshold. For example, a threshold of medication adherence of 80%

[11] This assumes that the patient did, in fact, use their medication, which may not be the case, and is a drawback of all studies using administrative pharmacy dispensing databases.

(83) has been used to define adherent users of a medication. Therefore, patients with a value of 70% will be considered non-adherent. Discontinuation reflects a scenario whereby the patient has stopped taking the medication as it was prescribed. These would be periods where no medication was used by the patient as opposed to sporadic usage for patients classified as non-adherent.

The exposure definitions presented in this chapter represent different methods that might be used to quantify exposure in an observational study. Certainly, there have many approaches to attempt quantification of medication exposure and the choice of approach will largely depend on the available data and study objective. The objective of this review was to critically evaluate the methods of defining medication exposure in observational studies, particularly in the context of administrative data and chronic diseases.

2.4 Concluding remarks

Defining medication exposure in observational studies of chronic diseases requires careful attention to the nuances of the specific exposure-outcome associations under investigation. This review chapter sought to critically appraise methods that have been used in defining medication exposure in previous studies and bring forth the potential biases that may result from these various approaches. The review also emphasized the advantages to the use of defined time-windows to enhance exposure assessment, the use of latency periods for diseases such as cancer, and the advantages of using a recency-weighted cumulative dose or duration of exposure definition to simultaneously capture current and previous

exposures to a particular medication. Several of the methods that were discussed in this chapter will be used in the analyses presented in subsequent chapters of this dissertation.

Chapter 3: Do inhaled corticosteroids (ICS) protect against lung cancer in patients with chronic obstructive pulmonary disease? A systematic review[12]

Summary

Chapter 3 systematically reviews the literature that evaluates the association between ICS use and lung cancer risk in chronic obstructive pulmonary disease (COPD) patients. The search strategy allowed for the inclusion of both observational and trial-based studies. This chapter provides another component, along with Chapter 2, for the work that will be presented in Chapter 5 of this thesis.

3.1 Background

Chronic obstructive pulmonary disease (COPD) is a term that includes subjects with chronic bronchitis and/or emphysema and is typically associated with fixed airflow obstruction that is progressive and seldom reversible (100). The primary risk factor for COPD is cigarette smoking, which is associated with approximately 85% of cases (32,101–103). The economic burden associated with COPD is substantial and is expected to increase

[12] A version of this chapter has been accepted for publication: Raymakers AJN, McCormick N, Marra CA, FitzGerald JM, Sin DD, Lynd LD. Do inhaled corticosteroids (ICS) protect against lung cancer in patients with chronic obstructive pulmonary disease? A systematic review. Respirology. (Electronically published: September 2016).

in coming years. Total direct medical costs attributable to COPD and its associated comorbidities in the United States are expected to increase from $32 billion in 2010 to $49 billion in 2020 (104). By 2020, COPD is expected to be the third-leading cause of death worldwide (105).

Chronic obstructive pulmonary disease is strongly associated with the development of lung cancer, which is the leading cause of cancer mortality in males and females in developed countries (106). In 2012, there were an estimated 1.5 million lung cancer deaths worldwide (106). Lung cancer is often only detected at an advanced stage and is typically associated with a poor prognosis (107). While smoking is the most significant risk factor for lung cancer, approximately 10% of individuals who develop lung cancer are lifetime non-smokers (108).

Although smoking is a risk factor for both COPD and lung cancer, evidence suggests that COPD itself is an additional risk factor for lung cancer development, independent of smoking status or history (32,33,35,38). For example, Young *et al.* (32) reported a six-fold greater prevalence of COPD in lung cancer subjects versus smoking-status, sex, and age-matched controls. Mannino *et al.* (33) found that moderate to severe COPD was associated with an increased risk of lung cancer diagnosis (HR: 2.8 (95% CI: 1.8-4.4)), even after adjustment for age, sex, and smoking status. Purdue *et al.* (38) showed in a longitudinal study of men (n=176,997) rendered similar results, with both mild and moderate/severe COPD associated with increased smoking-adjusted rates of lung cancer (RR: 1.5 (95% CI: 1.2-1.9) and RR: 2.2 (95% CI: 1.8-2.7), respectively). A longitudinal study by Skillrud *et al*.

(34) reported the smoking-adjusted probability of developing lung cancer was 10.8% in COPD patients and 2.5% in controls (p=0.023). Turner *et al*. (35), in a study of 448,600 lifelong non-smokers in the US, found that lung cancer mortality was significantly associated with combined emphysema/chronic bronchitis (HR: 2.44 (95% CI: 1.22-4.90)), over a follow-up period of twenty years. Given the evidence presented above, it seems apparent that the evidence strongly suggests, after accounting for smoking history, COPD remains an independent risk factor for lung cancer.

The association between lung cancer and COPD may be well established, but the specific mechanism for the link between COPD and lung cancer is not, although several hypotheses have been postulated. One such hypothesis is that airway inflammation associated with COPD can cause phenotypic alterations in lung cells. For example, in those COPD patients with a history of smoking, Skillrud *et al*. (34) have suggested a mechanism whereby COPD enables carcinogens to reside in the lungs for longer due to decreased mucociliary clearance resulting from COPD-related inflammation, and these substances tend to sit in areas where lung tumours occur most often (34). Additional literature suggests that COPD severity is positively associated with the development of lung cancer (32). For example, van Eeden *et al*. (29) showed that markers of systemic inflammation such as the level of C-reactive protein (CRP), which are associated with lung cancer development (see Table 1.2), fluctuate with an individual's FEV1; that is, as CRP levels increase, lung function declines. A meta-analysis by Wasswa-Kintu *et al.* (36) also reported that reduced FEV1 is strongly associated with lung cancer development, independent of smoking status, particularly in women. Therefore, it would appear that the association between COPD and lung cancer is

potentially enhanced by the severity or degree of systemic and local inflammation that accompanies COPD.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommend inhaled corticosteroids (ICS) as treatment for severe and very severe COPD patients especially in those with a history of exacerbations (5). These patients typically have a post-bronchodilator forced expiratory volume in 1 second (FEV1) of < 50% of predicted and experience one or more acute exacerbations per year (5,6). However, the evidence on the benefit conferred from ICS in COPD patients is not unanimous.

Inhaled corticosteroid use in COPD patients appears to provide benefits for some aspects of the disease, but not for all. For example, ICS use has been shown to improve patients' quality of life measured as an improvement on the St George's Respiratory Questionnaire (109). Treatment with ICS has also been shown to reduce the risk of acute exacerbations of COPD (AECOPD) (44,45). However, the evidence is mixed as to whether ICS use is associated with appreciable gains in lung function. The TORCH trial (44) showed that there was a small improvement in lung function, but a meta-analysis by Yang *et al*. (110) showed mixed results depending on the analytical approach. In terms of whether there is benefit for reduced all-cause mortality in COPD patients, Sin *et al.* (111) showed that ICS use reduces the risk of all-cause mortality. However, the results of the TORCH trial (44) failed

to show a statistically significant association between ICS use and reduced mortality[13]. Gartlehner *et al*. (45) showed a similar result, reporting no statistically significant reduction in mortality associated with ICS use. Finally, evidence suggests that ICS use reduces markers of systemic inflammation, which are often present in COPD patients, and which are also associated with increased lung cancer risk (56). The consequence of this conflicting evidence is contentiousness as to the most appropriate use of ICS in COPD patients.

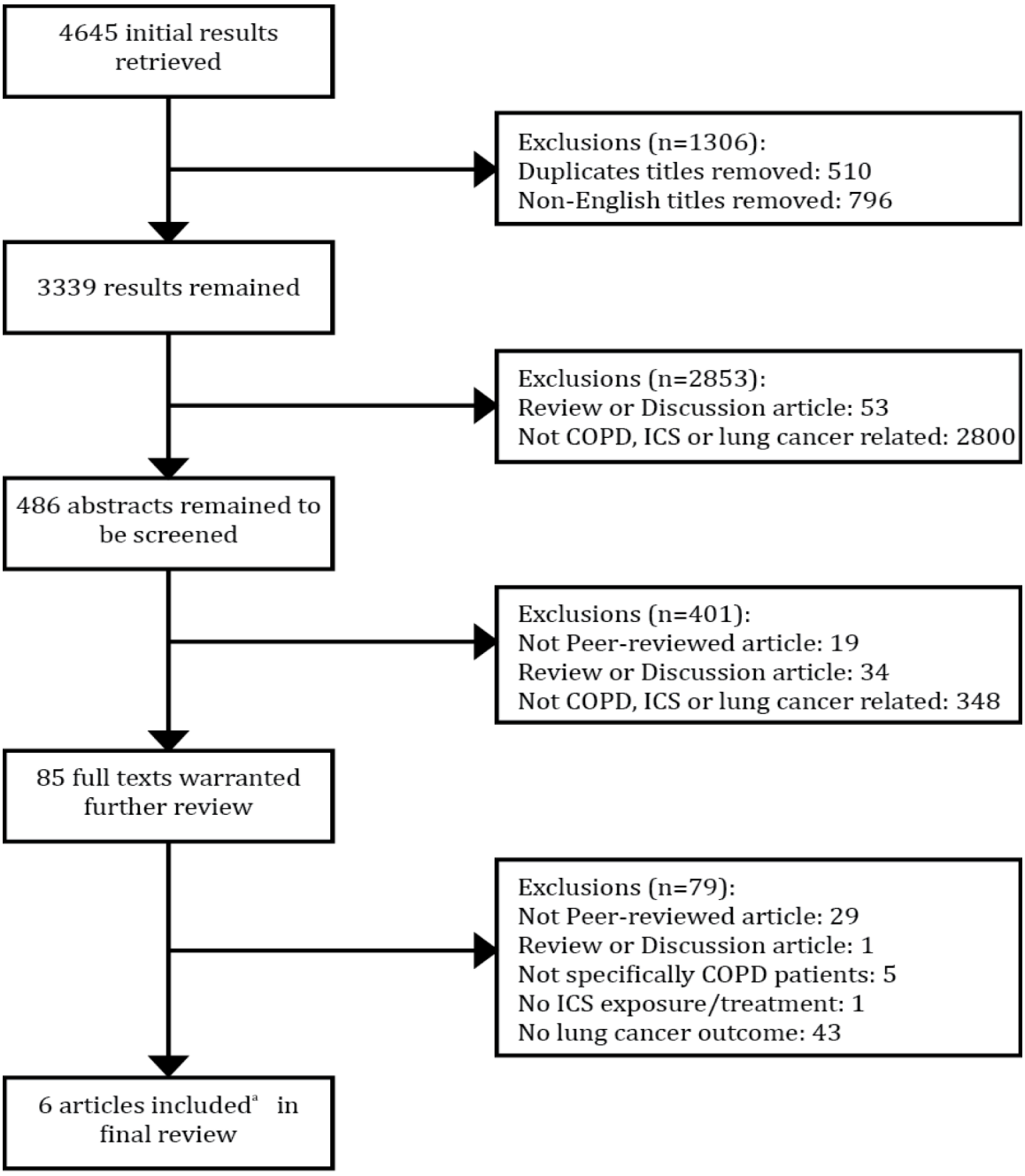
As the global prevalence of COPD increases, it can be anticipated that lung cancer incidence will commensurately increase. A possible protective effect of ICS for lung cancer in COPD patients could help add to the evidence for the prescription of ICS in COPD, which could potentially help to improve both COPD-related outcomes and lung cancer-associated mortality. The objective of this study was, therefore, to identify and critically appraise studies that have sought to answer this research question, and identify avenues for future research.

[13] The estimated p-value for the association between ICS use and mortality was very near statistical significance, p=0.052.

3.2 Methods

3.2.1 Search strategy

A systematic literature search was conducted in the following Ovid databases: MEDLINE (1950 to November 2015), EMBASE, EBM Reviews - Cochrane Central Register of Controlled Trials (CENTRAL), and International Pharmaceutical Abstracts, Web of Science, and BIOSIS Previews. Database searches were conducted using both subject headings (MeSH headings in MEDLINE and CENTRAL, Emtree in EMBASE) and keywords. Four domains were incorporated in the search: 1) COPD (including emphysema and chronic bronchitis), 2) lung cancer (including subtypes), 3) inhaled corticosteroids (including individual drug names), and 4) chemoprevention. Filters selecting for only RCTs and observational study designs were added to some searches. In MEDLINE and CENTRAL all the MeSH headings and most of the keywords applicable to the different lung cancer subtypes were included. A list of MeSH headings pertaining to generic drug name was compiled from background literature searches and those listed under the broader MeSH heading of glucocorticoid drugs. References of identified studies were also searched for relevant publications. The search strategy is provided in Appendix A.



[a] One study (44) was included based on the authors' prior knowledge that the desired data was available from supplemental material provided by the manufacturer and sponsor of the clinical trial.

Figure 3.1. Study selection process.

3.2.2 Study selection criteria

To be included in this systematic review, a study was required to have subjects with a diagnosis of COPD with some proportion of subjects treated with ICS. In an effort to exclude COPD cohorts, which may have included misclassified asthma cases, COPD patients needed to be greater than 40 years of age. We retrieved both RCTs and observational studies. A search method was employed where RCTs examining the efficacy and other long-term outcomes of ICS use (comparing ICS therapy alone with another therapy, such as β-agonists, or combination therapy) were sought since they often included secondary data on the causes of subject withdrawal and death, both within the study period, and over the longer term. Studies needed to include lung cancer diagnosis or lung cancer-related mortality as a primary or secondary outcome. Where possible, online appendices and openly available RCT data were searched to determine whether there was information reported on lung cancer cases or mortality. Study inclusion was based on independent assessment by two reviewers (AR and NM). Where necessary, disagreement between selections was resolved through discussion with the other authors.

3.2.3 Data extraction

General study details (including title, authors, year of publication and data collection, country of origin, study type, and study duration) were extracted from each study using a pre-determined data abstraction form. The main outcome of interest was a lung cancer diagnosis (Table 3.2), though data were also collected on lung cancer deaths (Table 3.4). With regard to ICS exposure, details were collected on the generic name of each drug, dose (quantity per inhalation and number of inhalations per use), names and doses of other

medications given, and frequency and duration of use. A decision was made not to pool results due to both methodological and clinical heterogeneity between studies (112,113). Studies varied substantially in patient populations, follow-up time, ICS prescribed and how lung cancer diagnoses were reported. A risk of bias assessment was completed in accordance with the established guidelines and is presented in Appendix B (114). A checklist completed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (115) is presented in Appendix C.

Table 3.1. Characteristics of included studies.

	Calverley *et al.* (44)	Kiri *et al.* (116)	Lung Health Study Research Group (117)	Parimon *et al.* (92)	Pauwels *et al.* (118)	Tashkin *et al.* (119)
Study Design	RCT	Observational; nested case-control	RCT	Observational; cohort	RCT	RCT
Country	42 countries	United Kingdom	United States, Canada	United States	Belgium, Denmark, Finland, Italy, Netherlands, Norway, Spain, Sweden, United Kingdom	United States, Czech Republic, Netherlands, Poland, South Africa
Years of Data Collection	2000-2005	1989-2003	1994-1999	1996-2004	1992-1996	NR
Follow-Up Period	3 years	≤ 16 years	4.5 years	34 months	3 years	6 months
Sample Size	Placebo: 1545; Salmeterol: 1542; Fluticasone: 1551; Fluticasone+ Salmeterol: 1546 = 6184	127 cases + 1,470 controls=1,597	559 treated + 557 ICS-controls=1,116	517 ICS-exposed + 9957 ICS-unexposed=10,474	634 treated + 643 ICS-controls=1,277	1120 treated + 584 ICS-controls=1,704
Age Parameters	>=40 years of age	≥50 years at diagnosis	40-69 years	≥40 years at study entry	30-65 years at start of follow-up	≥40 years at study entry
% Male	Placebo: 76%; Salmeterol: 76%; Fluticasone: 75%; Fluticasone+ Salmeterol: 75%	Lung cancer cases=64%; Controls=65%	ICS-exposed=64%; ICS-unexposed=64%	ICS-exposed=97%; ICS-unexposed=97%	ICS-exposed=74%; ICS-unexposed=72%	ICS-exposed=69%; ICS-unexposed=67%

Table 3.1: Characteristics of included studies *(…continued)*.

	Calverley *et al.* (44)	Kiri *et al.* (116)	Lung Health Study Research Group (117)	Parimon *et al.* (92)	Pauwels *et al.* (118)	Tashkin *et al.* (119)
Mean Age	Placebo: 65.0 (8.2); Salmeterol: 65.1 (SD: 8.2); Fluticasone: 65.0 (8.4); Fluticasone+ Salmeterol: 65.0 (8.3)	Lung cancer cases=70.7 years, Controls=70.8 years	ICS-exposed=56.2, ICS-unexposed=56.4	ICS-exposed=66, mean ICS-unexposed=64	ICS-exposed=52.5; ICS-unexposed mean=52.4	ICS-exposed=63.4; ICS-unexposed=63.35
Subjects' Smoking Status	Placebo: 48.6 (26.9); Salmeterol: 49.3 (27.7); Fluticasone: 49.2 (28.6); Fluticasone+ Salmeterol: 47.0 (26.5)	Former smokers (cases for mean 2.5 years, controls for mean 2.9 years)	Current (ICS=90.5%, placebo=89.8%) or quit within past two years	ICS-exposed=9% never, 68% former, 23% current. ICS-unexposed=12% never, 53% former, 35% current.	Current or former	Current (ICS mean=43.4%, non-ICS mean=40.8%) or former
Subjects' Smoking History/ Quantity	≥ 10 pack-years	n/a	Current ICS=22.9 cigarettes/day; Current placebo=24.2/day	Exposed=11% <10/day, 13% 11-15/day, 22% 16-20/day, 22% 21-30/day, 14% 31-40/day, 9% >40/day. Non-exposed=14% <10/day, 12% 11-15/day, 22% 16-20/day, 18% 21-30/day, 11% 31-40/day, 10% >40/day	ICS mean pack-years=39.4, placebo mean pack-years=39.2	ICS median pack-years=40.75, non-ICS median pack-years=40

3.3 Results

The systematic literature search identified 4645 initial records. After removing duplicates and non-English language studies, 3339 results remained. At this stage, studies that either explicitly stated a different patient population or that made no reference to a COPD patient population or an ICS exposure or treatment were removed (n=2800). Four-hundred eighty-six abstracts remained to be reviewed, of which 85 full-text studies warranted further review. At this stage, the most common reason for exclusion was studies that did not contain lung cancer as study outcome (n=43). Six articles met the criteria to ultimately be included in this systematic review: four RCTs and two observational studies (40,87,110–113)). The RCTs, which examined the efficacy of ICS, included COPD patients (n=1116 to n=6184 per study) of different severities enrolled at multiple centers throughout the United States, Canada, and Europe. The observational studies used administrative health databases from the United States (n=10,474 COPD patients ≥40 years of age followed up for up to 4.6 years) and the United Kingdom (n=7079 ex-smokers ≥50 years of age with incident COPD followed up for up to sixteen years) to assess the impact of ICS prescriptions on lung cancer development. Characteristics of the included studies are presented in Table 3.1. Details of ICS use, including the specific ICS, dose, and frequency of administration in each study, are presented in Table 3.2. A flow chart illustrating the study selection process is presented in Figure 3.1. The design of each study was assessed for potential risk of bias based on six different criteria (114). The majority of identified studies demonstrated a 'low risk' of bias. None of the identified studies demonstrated a 'high risk' of bias. Further details of the risk of bias assessment are available in Appendix B.

3.3.1 Randomized controlled trials

The primary objective of each identified RCT was to examine the efficacy of ICS use in COPD. The Lung Health Study Research Group (117) studied the effect of triamcinolone on COPD progression. The primary outcome was the rate of decline in FEV1, but cause-specific morbidity and mortality were included as secondary outcomes. Five subjects in the ICS group (n=559) and four subjects in the placebo group (n=557) died of lung cancer, producing a RR of 1.25 (95% CI: 0.34-4.61) (Table 3.2). The mean follow-up time in this study was 40 months, however, the authors report that adherence to triamcinolone may have been as low as 53.7%in the treatment arm (and 58.5% in the placebo arm, based on canister weights).

Pauwels *et al.* (118) studied the long-term effects of budesonide in COPD patients with mild disease. The primary outcome was the change in post-bronchodilator FEV1. Seven patients in the ICS group (n=634) and ten in the placebo group (n=643) withdrew due to a diagnosis of lung cancer, resulting in a relative risk of 0.71 (95% CI: 0.27-1.85). In addition to these withdrawals, the authors reported three deaths from lung cancer in the ICS treatment group and three deaths in the controls. The associated relative risk for lung cancer mortality was 1.01 (95% CI: 0.21-5.01).

Tashkin *et al.* (119) studied the efficacy and safety of an ICS (budesonide) and a beta-agonist (formoterol) combination inhaler in COPD patients with moderate to severe disease. The primary outcome was the change in FEV1 before and after receiving the medication. Four treatment groups were exposed to ICS (n=1120), one was treated with

formoterol alone (n=284), and one received a placebo (n=300; total 'unexposed' subjects n=584). The mean exposure duration among those receiving ICS (alone or as combination therapy) was between 157.1 (SD: 51.3) to 168.3 (SD: 37.3) days (depending on the treatment group). There were two diagnoses of squamous cell carcinoma in the ICS exposed groups and none in the unexposed groups, resulting in an RR of 2.61 (0.13-54.24) (adjusted for 0 in the unexposed group). In addition, one person in the ICS exposed group died from lung cancer but none in the unexposed, resulting in a RR of 1.57 (0.06-38.29) (adjusted for 0).

The Towards a Revolution in COPD Health (TORCH) trial (44) investigated the effect of combination therapy (salmeterol and fluticasone propionate, as combination therapy, and each as monotherapy) on survival of COPD patients[14]. This study included subjects with a smoking history of a minimum of ten-pack years (current of former smokers) between 40 and 80 years of age. To meet the inclusion criteria, subjects had to have a clinical diagnosis of COPD and a pre-bronchodilator FEV1 <60% of predicted along with no significant reversibility of airflow obstruction based on post-bronchodilator change of less than 10% in FEV1. Reported numbers for non-fatal serious adverse events show that 63 patients in the control arm and 68 patients in the combination therapy arm received a lung cancer

[14] While the main publication from the TORCH study (44) did not report lung cancer specific diagnoses or mortality, this data was available in supplementary material provided by the manufacturer at the address: https://www.gsk-clinicalstudyregister.com/files2/21083.pdf. The relative risks reported in this paragraph, and presented in Table 3.3, have been calculated by the author. In the case of this study, lung cancer diagnosis or death was neither a primary nor secondary outcome of the study; however, given that the data were available, the numbers have been included.

diagnosis. The calculated relative risk between the two arms for lung cancer diagnosis was non-significant (RR: 1.07 (95% CI: 0.77-1.50)[15]. This study also reported lung cancer deaths, with 34 occurring in the control arm and 35 in the combination therapy arm. The relative risk for lung cancer death was non-significant (RR: 1.02 (95% CI: 0.64-1.63)[3].

The results from these identified RCTs make it difficult to make any inference based on the low numbers of lung cancer diagnoses or deaths. The large width of the confidence intervals, which reflect the uncertainty of the estimated RRs from the RCTs, demonstrates that these studies were likely underpowered to answer the specific research question of this review.

[15] This is a calculation performed by the author, based on secondary trial data.

Table 3.2. Characteristics of ICS use among patients with COPD in individual identified studies.

	Specific ICS	ICS Dose	Frequency	Total ICS/day
Calverley *et al.* (44)	Fluticasone Propionate	500 µg	Twice Daily	1000 µg
Kiri *et al.* (116)	NR	NR[a]	NR	NR
Lung Health Study Research Group (117)	Triamcinolone	6 x 100ug inhalations	Twice per day	1200ug
Parimon *et al.* (92)	Beclomethasone, flunisolide, fluticasone (converted to triamcinolone equivalents)	NR	NR	<1200ug/day, ≥1200ug/day
Pauwels *et al.* (118)	Budesonide	400ug	Twice per day	800ug
Tashkin *et al.* (119)	Budesonide	1=160ug ICS /4.5ug FM, 2=80ug ICS/4.5ug FM, 3=160ug ICS + 4.5ug FM separately, 4=160ug ICS (all x 2 inhalations), 5=FM only, 6=placebo	Twice per day	1=640ug, 2=320ug, 3=640ug, 4=640ug

[a] This study did report on a 'dose-response' relationship between ICS and ICS+LABA use but this was done using the absolute number of prescriptions as opposed to the actual dose of these prescriptions.
FM=formoterol; ICS=inhaled corticosteroid; LABA=long-acting beta-agonist; NR=not reported; RCT=randomized controlled trial.

3.3.2 Observational studies

Kiri *et al.* (116) used a nested case-control study design to investigate whether ICS exposure was associated with a reduced risk of lung cancer in COPD patients. A cohort of 7079 incident COPD patients (all former smokers) was identified from the United Kingdom's General Practice Research Database (GPRD). A COPD patient diagnosed with lung cancer was matched to a COPD patient without lung cancer, with equal follow-up time, and their prescription records were compared. Subjects were categorized as users of a combination of an ICS and a long-acting beta-agonist (LABA), an ICS alone, or short-acting bronchodilator (SABD) alone, though no specific medications or dosages were mentioned.

Of the entire cohort of COPD patients (n=7079) initially identified from the database, 127 developed lung cancer, and they were individually matched to 1470 controls. The mean duration of COPD (from diagnosis) was 1.5 years (1.6 (cases), 2.1 (controls)). The median time to lung cancer diagnosis, from COPD diagnosis, was 2.2 years (IQR: 1.3-4.0). This population of COPD patients (n=1597) was approximately 30% female, was, on average, 71 years of age at the time of COPD diagnosis, and had a mean time since smoking cessation of more than 2.5 years. ICS use was shown to have a protective effect that was enhanced when combined with a LABA: the hazard ratio (HR) for ICS/LABA users was 0.50 (95% CI: 0.27-0.90) and for ICS users alone was 0.64 (95% CI: 0.42-0.98). A subsequent analysis was performed to assess a possible dose-response relationship for this protective effect. While the HR for ICS/LABA users with one or two prescriptions per year (as compared to users of SABD alone) was non-significant at 0.75 (95% CI: 0.33-1.75), there appeared to be a dose-response relationship, as measured by the number of prescriptions per year, at higher

levels of exposure: ICS/LABA users with three or more prescriptions per year had a HR of 0.39 (95% CI: 0.19-0.79), while patients with three or more prescriptions per year of ICS alone (as compared to users of SABD alone) had an HR of 0.51 (95% CI: 0.30-0.84). Therefore, this study found that ICS may protect against lung cancer, but this effect may only exist with more frequent ICS use, and the protective effect may be stronger when ICS was taken in combination with a LABA.

Parimon *et al.* (92) conducted an observational cohort study investigating whether ICS exposure was associated with a decreased risk of lung cancer in COPD patients. This study had a very specific, predominantly male, population (97%) from Veterans Affairs (VA) clinics in the United States. The COPD cohort (n=10,474) consisted of subjects at least 40 years of age who satisfied at least one of the following criteria: (i) a recorded ICD-9 code for COPD; (ii) self-reported chronic lung disease; or (iii) prescriptions for bronchodilators (beta-agonists or anticholinergics) in the twelve months prior to enrolment (the index date). Patients' medical and prescription history were examined for ICS use and subsequent lung cancer diagnosis. Data on comorbidities and tobacco use were collected at baseline using a patient survey. Patients' lung cancer diagnosis had to occur after the date of study enrolment. Within the cohort, 423 (4%) patients received a lung cancer diagnosis at a median time from COPD 'diagnosis' to lung cancer of 1.4 years (IQR: 0.7-2.5). In the base-case analysis, lung cancer diagnosis could occur at any time after cohort inclusion, not allowing for a latency period. Failure to incorporate such a period is a major limitation of this analysis. Cancer latency periods tend be quite long, therefore, it is possible that subjects included in this study could have already had latent cancer when ICS exposure

occurred, limiting the possibility for this treatment to have an effect (in either direction). ICS exposure was defined as being 80% adherent in the 180 days previous to study inclusion. The authors reported that although 20% of the cohort had received an ICS in the period prior to study inclusion, only 5% of those met this adherence criterion.

For the primary analysis, 517 subjects were classified as ICS users and 9,957 non-users. Exposure to ICS as a continuous variable (per 100 μg/d) was not found be significant (adjusted HR: 0.96 (95% CI: 0.93-1.00). For ICS users with mean daily dose of less than 1200 μg/day, there was no association with lung cancer risk (adjusted HR: 1.13 (95% CI: 0.67-1.90) compared to non-users. However, findings indicated that for higher doses of ICS (≥ 1200 ug/day) there was a protective effect (adjusted HR: 0.39 (95% CI: 0.16-0.96)) for ICS use for lung cancer development compared to non-users. All analyses were adjusted for age, smoking status and intensity, history of non-lung and non-skin cancer, comorbidity, and bronchodilator use.

The authors explored whether there was an association between COPD severity and the development of lung cancer. Since lung function (FEV1) values were not available, the number of bronchodilator canisters prescribed each month during the six months prior to study enrolment was used as a proxy of severity (92). Comparisons of the risk of lung cancer in beta-agonist users and non-users, and ipratropium users and non-users, suggested there was a non-significant trend towards an increased risk of lung cancer amongst cases with more severe COPD (heavier users of bronchodilators).

A secondary analysis was performed where patients were stratified according to their smoking status. In this analysis, the HR for ICS use by former smokers at < 1200 μg /day was 1.22 (95% CI: 0.65-2.30), HR for former smokers at ≥ 1200 μg/day was 0.41 (95% CI: 0.13-1.30), HR for current smokers at < 1200 μg/day was 1.01 (95% CI: 0.36-2.81), and a HR for current smokers at ≥ 1200 μg/day was 0.39 (95% CI: 0.10-1.64). These results further suggest the presence of a dose–response relationship between ICS use and lung cancer risk.

To assess the potential impact of confounding by indication (whereby COPD patients who were prescribed ICS are at a higher risk of lung cancer than individuals who were not prescribed ICS) a propensity score, representing an individual's probability of being prescribed ICS, was calculated for each subject. After adjusting for the propensity score, the hazard ratio for the < 1200 μg/day group remained non-significant (HR: 1.35 (95% CI: 0.82-2.23)), while that for the ≥ 1200ug/day group was still indicative of a protective effect but shifted from being statistically significant (HR: 0.39 (95% CI: 0.16-0.96)) to non-significant (HR: 0.57 (95% CI: 0.24-1.38)).

Results from sensitivity analyses regarding the cohort definition included restricting the case definition to those individuals (n=3233) who met all three of the inclusion criteria: a recorded ICD-9 code for COPD, self-reported COPD, and a history of bronchodilator prescriptions (HR, < 1200ug/day: 0.98 (95% CI: 0.54-1.80); HR, ≥ 1200ug/day: 0.44 (95% CI: 0.18-1.09)), or restricting the case definition to only those (n=2493) with an ICD-9 code for COPD and prescriptions for ipratropium (HR, < 1200ug/day: 1.09 (95% CI: 0.55-2.19);

HR, ≥ 1200ug/day: 0.37 (95% CI: 0.13-1.01)). Interestingly, excluding subjects who were diagnosed with lung cancer within one year of the index date resulted in a non-significant association between ICS use and lung cancer development (HR < 1200 μg/day: 0.85 (95% CI: 0.39-1.84); HR, ≥ 1200 μg /day: 0.41 (95% CI: 0.13-1.31)).

Another subgroup analysis examined the risk of lung cancer only amongst the 517 members of the cohort who were users of ICS. Findings from this analysis (HR: 0.90 (95% CI: 0.82-0.99) for every 100 μg increase in dose) provided more evidence for a protective dose-response relationship with ICS. As discussed by the authors, the consistency between the primary analysis and subgroup/sensitivity analyses suggests that the apparent protective effect of ICS is robust to various potential confounders and analytical approaches.

Table 3.3. Results from identified studies for the relative risk of lung cancer diagnosis for ICS exposed/treated and unexposed/untreated patients with COPD.

Study	Exposure/Treatment	Risk Among ICS-Exposed/Treated	Risk Among ICS-Unexposed/Controls	Relative Risk (95% CI)
Calverly *et al.* (44)	-	68/3067=2.22%[a]	63/3045=2.07%	1.07 (0.76-1.50)
Kiri *et al.* (116) †	ICS alone (overall)	61/841=7.3%	46/421=10.9%	0.64 (0.42-0.98)[b]
	ICS alone:≥3 prescriptions/year	NR	NR	0.51 (0.30-0.84)
	ICS alone: 1-2 prescriptions/year	NR	NR	0.88 (0.51-1.52)
	ICS and LABA (overall)	20/335=6.0%	46/421=10.9%	0.50 (0.27-0.90)*[b]
	ICS and LABA: ≥3 prescriptions/year	NR	NR	0.39 (0.19-0.79)
	ICS and LABA: 1-2 prescriptions/year	NR	NR	0.75 (0.33-1.75)
Parimon *et al.* (92) †	<1,200ug/day triamcinolone equivalents (overall)	16/298=5.4%	402/9,957=4.0%	1.13 (0.67-1.90)
	<1,200ug/day triamcinolone equivalents (former smokers)	11/201=5.5%	211/5,188=4.1%	1.22 (0.65-2.30)
	<1,200ug/day triamcinolone equivalents (current smokers)	4/64=6.3%	168/3,349=5.0%	1.00 (0.36-2.81)
	≥1,200ug/day triamcinolone equivalents (overall)	5/219=2.3%	402/9957=4.0%	0.39 (0.16-0.96)*
	≥1,200ug/day triamcinolone equivalents (former smokers)	3/140=2.1%	211/5,188=4.1%	0.41 (0.13-1.30)
	≥1,200ug/day triamcinolone equivalents (current smokers)	2/53=3.8%	168/3,349=5.0%	0.39 (0.10-1.64)
Pauwels *et al.* (118)	-	7/634=1.1%	10/643=1.6%	0.71 (0.27-1.85)
Tashkin *et al.* (119)	-	2/1,120=0.2%	0/584=0%	2.61 (0.13-54.24)[c]

* Statistically significant. [a] This is the number of ICS treated patients, both as monotherapy and combined with salmeterol. [b] Adjusted for use of other respiratory medications, comorbidities, duration of smoking cessation, duration of COPD, and demographic/clinical characteristics. [c] Adjusted for 0 by adding 0.5 to the value of each numerator and denominator. †Observational study.

3.4 Discussion

This systematic review identified studies that evaluated the association between ICS use and lung cancer risk in COPD patients. The results of this review suggest that there are several important methodological considerations that are important in assessing the relationship between ICS use and lung cancer risk. Our search identified four relevant RCTs, which only reported small numbers of lung cancer diagnoses and deaths as secondary data from trials evaluating the efficacy of ICS in COPD. However, two observational studies were identified that directly addressed this research question. ICS exposure in these studies was associated with a significantly lower incidence of lung cancer, in their respective COPD populations. The results of these two studies also suggest there is a dose-response relationship, with the protective effect appearing at ICS doses greater than 1200 ug/day (92), and when patients receive three or more ICS prescriptions per year (116). This evidence, however, should be interpreted cautiously as there are methodological concerns with both studies.

Findings in identified studies were clearly dependent on the study type, with the RCTs suggesting ICS use had no significant effect while the observational studies suggested ICS use might protect against lung cancer. It must be noted, however, that the RCTs reported in this review were not designed or powered for looking at the incidence of rare events so these results are very prone to a Type II error (i.e. failure to detect a significant difference when one exists). It can be argued that the observational studies are more prone to bias because the distribution of potentially confounding factors may not be equally balanced

amongst the exposure groups. However, in the observational cohort study by Parimon *et al*. (92), the two groups that were compared had similar smoking intensity, and the protective effect in both observational studies remained after adjustment for known confounders like COPD duration, comorbidities, age, and smoking status. These studies have the potential for results to be susceptible to confounding by indication whereby patients that are prescribed ICS actually have more severe COPD. In that case, we would expect those receiving ICS would have a higher chance of developing lung cancer. This was not the case in either observational study, both studies showed protective effects of ICS in lung cancer development. Therefore, it could be the case that these results are, in fact, conservative estimates of the benefits of ICS for lung cancer development in COPD patients. In addition, despite the potential for bias, observational studies may be the most adequate design for such a study question.

The latency period associated with lung cancer also means that protopathic bias should be an important consideration. Protopathic bias can occur when medication exposure might be based on manifestations of an undiagnosed (i.e. subclinical) disease (120). Therefore, in this instance, it could be possible that the symptoms of lung cancer in COPD patients lead to ICS being prescribed prior to lung cancer diagnosis. However, in that case we would expect that there would be an increased risk of lung cancer (or at least no significant and protective effect of ICS use), which was not the case in the observational studies. The influence of protopathic bias was discounted in a recently published observational study evaluating the impact of ICS exposure on lung cancer incidence (90). This study, which was not included in this review because the study population included subjects with either

COPD, asthma, or other respiratory conditions, reported a significant protective effect for ICS against lung cancer. Like the two observational studies that were included in this review, this protective effect was dose-dependent. With respect to protopathic bias, those authors performed a sensitivity analysis where exposure to ICS within the three or six months prior to lung cancer diagnosis was excluded, and the protective effect of ICS persisted (90). Neither identified observational study (92,116) used a lagged exposure period to reduce the possibility of protopathic bias in their base-case analysis, however Parimon *et al.* (92) did so in a sensitivity analysis. The authors removed lung cancer cases that occurred in the first year of follow-up, reducing the number of cases from 423 to 254, and found no significant association with ICS exposure (either as a continuous variable or stratified by low and high dose). However, it is possible that the reduced numbers from restricting this analysis did not provide sufficient power to detect an association.

The RCTs included in this review were designed to study the short-term efficacy of ICS therapy but were underpowered, both in terms of the sample size and follow-up period, for detecting a significant effect on lung cancer in either direction. Lung cancer has a latency period that is likely longer than the follow up time most of these RCTs. A patient could feasibly develop lung cancer at day one of the study and may not become symptomatic until after the study was completed. We must also consider the likely duration of time necessary for ICS use to make an impact on lung cancer risk. For example, the six-month follow-up period in Tashkin *et al.* (119), was likely far too short. Also, in these trials lung cancer events were based on adverse event reporting and withdrawals during the follow-up period; therefore, even though the two RCTs had longer follow-up periods (3 years (118)

and 4.5 years (117)), these events may have occurred within a shorter period of time after the start of ICS exposure. Although COPD patients are at an increased risk of lung cancer, the reported incidence rates of lung cancer in this population, 48 to 64 per 10,000 individuals (121), would not result in a substantial number of diagnoses amongst the RCT study populations. While understandable, given the cost and resources required to conduct an RCT, none of those studies included in this review enrolled a sufficient number of subjects in both the exposed and unexposed groups to detect a significant difference (see Table 3.1). For example, to obtain the same 0.56 unadjusted RR for lung cancer diagnosis with ICS exposure reported by Parimon *et al.* (92), (α=0.05 and 80% power), one would need 1599 subjects in each study arm of a RCT. In comparison, the study by the Lung Health Study Research Group (117) had less than half this number of subjects in each exposure group. Even more subjects would be required when taking a more conservative approach and anticipating a smaller relative risk reduction from ICS. Therefore, despite the potential for bias in observational studies, it is likely the ideal design for studying this research question given the extended follow-up period required to detect lung cancer and relatively low event rate.

While observational studies are likely to be superior to RCTs to answer this research question, for reasons such as sample size and feasibility of adequate follow-up periods, the observational studies included in this review have several major limitations. First, the choice of patient populations was questionable in both studies. Parimon *et al.* (92) focused on a patient population that was almost exclusively male (97%). Kiri *et al.* (116) focused only on patients that had quit smoking. A population-based cohort analysis would be better

suited to answer this research question. Second, the follow-up time in both studies was still short, particularly when considered in conjunction with the latency period of lung cancer. Third, the complexity of the exposure-outcome relationship between ICS use and lung cancer as an outcome was not fully explored. It is likely that the duration of ICS use, in addition to its dose, might be crucial to whether or not an effect can be observed. An exploration of the relationship between medication exposure and lung cancer development warrants further investigation, and will be presented in Chapter 5.

3.4.1 Limitations

This review has several limitations. First, a language bias might exist because we were only able to assess studies written in English. However, the majority of studies identified by the search were in written in English, therefore we are confident in the robustness of our results. Second, we did not contact authors of all RCTs evaluating ICS efficacy for additional data on ICS exposure status or lung cancer events. The rationale is that the objective of this study was to appraise methodological approaches to evaluating the association between ICS use and lung cancer risk in COPD patients. Therefore, while we conducted a very sensitive search to reduce the probability of missing relevant studies, the true aim was to discuss the methods in the studies identified, particularly in the observational studies specifically addressing this relationship. In addition, in the case where an RCT does exist that may have secondary data on this relationship, it is likely that it would not have had sufficient power (given the rarity of lung cancer and/or short time horizons), nor would there have been a systematic look for lung cancer. Finally, while often beneficial, we actively elected not to pool study results due to the heterogeneity of studies included in

this review but contend the value of this review is the identification of methodological considerations that are required for future studies attempting to answer this research question.

Table 3.4. Results from identified studies for the relative risk of lung cancer specific death in for ICS treated and untreated patients with COPD.

Study	Risk Among ICS-Exposed/Treated	Risk Among ICS-Unexposed/ Controls	Relative Risk (95% CI)
Calverley *et al.* (44)	35/3067= 1.1%[a]	34/3045=1.1%	1.02 (0.64-1.63)
Lung Health Study Research Group (117)	5/559=0.9%	4/557=0.7%	1.25 (0.34-4.61)
Pauwels *et al.* (118)	3/634=0.5%	3/643=0.5%	1.01 (0.21-5.01)
Tashkin *et al.* (119)	1/1,120=0.1%	0/584=0%	1.57 (0.06-38.29)[b]

[*] Statistically significant. [a] This is the number of ICS treated patients, both as monotherapy and combined with salmeterol. [b] Adjusted for 0 by adding 0.5 to the value of each numerator and denominator

3.5 Closing remarks

In conclusion, this review sought to critically appraise the literature on whether ICS use decreases the risk of lung cancer in patients with COPD. The results from randomized controlled trials and observational studies were conflicting, with the RCTs demonstrating that ICS use does not affect these patients' risk of lung cancer, while observational studies found that ICS use did reduce this risk, particularly at high doses. However, the RCTs identified here were likely underpowered to answer the research question. Given the substantial burden of lung cancer, this question has significant implications and needs to be addressed with more appropriate research methods, using a population-based longitudinal cohort design and proper consideration of the complex exposure relationship between ICS and lung cancer development.

Chapter 4: Mortality in COPD patients that use statins: a population-based cohort study[16]

Summary

This chapter presents an evaluation of the association between statin use and mortality within a cohort of COPD patients. Patients were identified as having COPD if they had received three prescriptions for an anticholinergic medication or a short-acting beta agonist in a 365-day period. For this chapter, statin exposure is defined in the one-year period after this COPD 'diagnosis'. The objective of this study is to evaluate the association between statin use by COPD patients with pulmonary-related and all-cause mortality. Previous observational evidence suggests that statin treatment might offer a protective effect against mortality in COPD patients. However, a recently completed randomized controlled trial studying the efficacy of statin use and acute exacerbations of COPD has casted doubt on the beneficial properties of statin use in COPD patients.

[16] A version of this chapter has been accepted for publication with the journal *Chest*: Raymakers AJN, Sadatsafavi M, Sin DD, De Vera MA, and Lynd LD. The impact of statin use on all-cause mortality in patients with COPD: a population based cohort study. Chest (2017). [Currently in press]. Also, an earlier version of the results of this study were presented (as a poster) at the Canadian Association for Population Therapeutics Conference. Reference: Raymakers AJN, Sadatsafavi M, Lynd LD. One-year survival among statin users in a population-based cohort of COPD patients. Canadian Association for Population Therapeutics (CAPT). Toronto, Ontario (2015, 2 November).

4.1 Introduction

Chronic obstructive pulmonary disease (COPD) affects 380 million people worldwide, representing 12% of adults over 30 years of age (122) and approximately 9-10% of Canadians over 40 (1,2). It is a progressive and mostly irreversible disease associated with airway inflammation and airflow limitation. An important aspect of COPD is that it is often associated with several comorbidities. For example, the estimated prevalence of cardiovascular disease[17] (CVD) in patients with COPD is greater than two times that of the general population (14,27,28). Mannino *et al.* (27) reported that in a cohort of 20,296 subjects with COPD, 3091 (15.2%) had concomitant CVD, significantly higher than general population estimates (123)[18]. Similarly, COPD patients are at increased risk of CVD-related mortality which may increase as the severity of patients' COPD worsens (118,119). The importance of CVD and other comorbidities in COPD is such that all-cause mortality has largely become the most relevant metric for outcomes in these patients (25).

Localized chronic inflammation of the airways has long been observed in COPD patients but there is a growing understanding of systemic inflammation in a subset of patients with COPD. Specifically, high levels of C-reactive protein (CRP) and interleukin-6 (IL6) have been associated with poor outcomes in COPD patients (18,120). Sin *et al.* (14) reported on the association between systemic inflammation and airflow obstruction, showing that

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[17] Cardiovascular disease typically comprises: ischemic heart disease, cerebrovascular disease, peripheral vascular disease, heart failure, rheumatic heart disease, and congenital heart disease.
[18] The Public Health Agency of Canada reports that general population (≥ 20) for 2014 are 6.2% (95% CI: 5.9%-6.5%), with higher prevalence among males (7.2% (95% CI: 6.7%-7.7%) than females (5.2% (95% CI: 4.8%-5.6%) (119).

patients with severe airflow obstruction (FEV ≤ 50% of predicted) were more than two times more likely to have elevated CRP levels and that these individuals were more likely to report previous cardiac injury (14). Agusti *et al.* (18) identified a specific COPD phenotype that is characterized by persistent low-grade systemic inflammation and increased risk of adverse cardiovascular outcomes, which may benefit from targeted therapy aimed at reducing the inflammatory process (18). Young *et al.* (126) also suggest that COPD progression might be the result of systemic inflammation, rather than a 'spillover' from inflammation in the lungs, and that measuring inflammation may provide valuable prognostic information.

Patients with cardiovascular disease, regardless of COPD status, are commonly treated with a HMG-CoA reductase inhibitor (i.e., a statin). These are lipid-lowering agents to treat patients with elevated cholesterol levels (primary prevention) and/or with established cardiovascular disease (secondary prevention). Statins have been shown to be effective in reducing all-cause mortality in patients with risk factors for CVD (58,59). In patients with COPD, observational evidence has shown statin use may reduce the risk of acute exacerbations of COPD (AECOPD) (57,122,123), reduce respiratory-related mortality (129), and reduce all-cause mortality (62,63). The prevailing hypothesis is that the reduction in inflammation provided is the mechanism by which statins can potentially reduce the risk of exacerbations in COPD patients (57,122) and further evidence also suggests that statin use may be associated with a reduced cancer risk. For example, Khurana *et al*. (130) showed that statin use was associated with a 45% reduction

(adjusted) in lung cancer risk and this effect was more pronounced in patients with greater than six months of statin use, where there was a 55% reduction in lung cancer risk (130).

As stated, the retrospective observational evidence for statin use in COPD patients has supported the hypothesis that statin use may improve outcomes for COPD patients, typically by reducing the frequency and severity of AECOPD (127). However, the recently completed Prospective Randomized Placebo-Controlled Trial of Simvastatin in the Prevention of COPD Exacerbations (STATCOPE) trial attempted to answer this same question using a prospective randomized controlled trial design (66). In this study, there were no significant differences in exacerbation rates or time to exacerbation between statin users and controls. While the results of this study may appear to be strong because of the prospective randomized design, the exclusion criteria for study participants may have limited the generalizability of results. Patients in this trial were excluded if they had ever received a statin previously or had any indication for receiving a statin, including pre-existing CVD, which, as stated, is more prevalent in COPD patients. Exclusion of these patients may have represented a scenario whereby patients with characteristic systemic inflammation often believed to be the aetiology of COPD-related comorbidities, were excluded from the trial. Thus, the trial may have only included patients that were unlikely to benefit from statins. A subsequent publication by the study authors reported low levels of CRP, in both study arms, compared to previously published studies of systemic

inflammation in stable COPD patients[19] (131) which may support the hypothesis that those patients with higher levels of systemic inflammation were excluded from the STATCOPE trial and questions the generalizability of the results.

As such, the relationship of statin exposure to pulmonary-related and all-cause mortality in COPD patients in a 'real-world' setting remains unresolved. Therefore, the primary objective of this study was to evaluate the impact of statin use on all-cause and pulmonary-related mortality in COPD patients.

4.2 Methods

This was a retrospective population-based cohort study based on administrative data from the province of British Columbia (BC), Canada, from 1997 to 2007. Population Data BC (PopDataBC) is an extensive data resource that contains health services information from linkable databases (described below) for all residents of British Columbia (approximately 4.7 million residents, December 2015[20]) which provides the opportunity to conduct generalizable, population-based health research.

The PharmaNet prescription data file includes prescriptions filled for the entire population of British Columbia regardless of insurer or payer (132). These data are linked to the data

[19] The comparator is the 'Macrolide Azithromycin to Prevent Rapid Worsening of Symptoms Associated With Chronic Obstructive Pulmonary Disease (MACRO)' trial.
[20] British Columbia Statistics (BCStats), Population Estimates. http://www.bcstats.gov.bc.ca/StatisticsBySubject/Demography/PopulationEstimates.aspx

on hospital separations (the Discharge Abstract Database (DAD) (133), deaths (British Columbia Vital Statistics – Deaths (134)), a registration file containing the regional health authority and census tract neighborhood income data (135), and physician-billing data from the provincially administered universal insurance program (the Medical Services Plan (MSP) data file (136)).

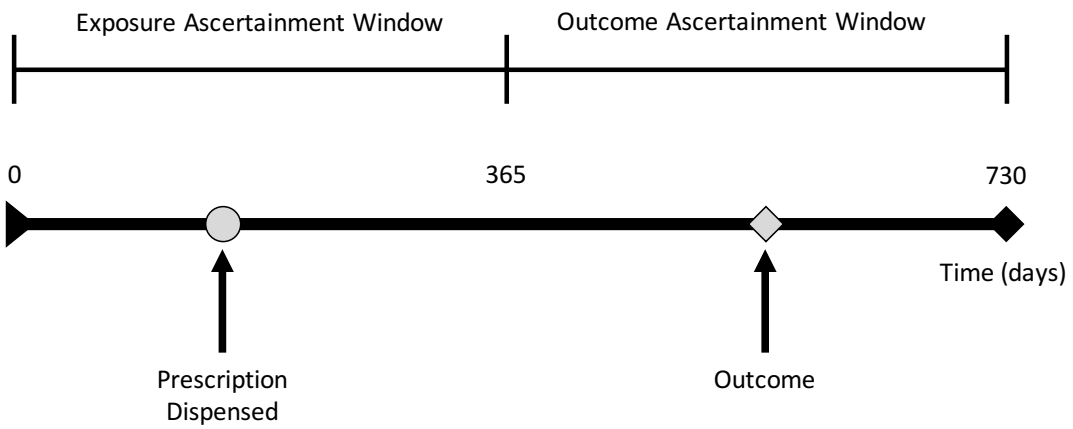
4.2.1 Identification of the COPD cohort

Patients 50 years of age and older were identified who had received at least three prescriptions for an anticholinergic or a short-acting beta agonist (SABA) in a twelve month floating-time window; that is, over twelve continuous months between 1998 and 2007. The index date was defined as the date of receipt of the first of these three prescriptions. A one-year 'wash-in' period for COPD was used to identify incident COPD cases. The 'wash-in' period attempts to exclude prevalent cases of COPD by removing those patients that would satisfy the inclusion criteria in the first year of which data are available.

4.2.2 Identification of statin users

Statin use was identified from PhamaNet records using American Hospital Formulary Service (AHFS) codes (240608; 'HMG-CoA Reductase Inhibitors') (137). The available statins that had ever been prescribed to the population of COPD patients during the study period were: atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin (see Figure 4.2). From the index date, a one-year exposure ascertainment window was constructed to classify COPD patients as exposed or unexposed to statins. Patients that received a statin within 365 days of their study index date were classified as being statin

exposed, and thus, exposure status was fixed over the follow-up period (the outcome ascertainment period, 365 days) (see Figure 4.1). Only statins received after the patients' index date were considered to define exposure status. This makes it possible for patients to have received a prior statin prescription without being classified as 'exposed'. However, misclassification as not statin exposed could only occur if the individual received a prescription prior to the index date and then a subsequent prescription at least 366 days thereafter. In this scenario, it is unlikely that such sporadic statin usage might confer any benefit and although technically misclassified as 'unexposed' this may more accurately represent these patients' exposure status. Further, the advantage of using this defined window of exposure ascertainment in an observational cohort study is that it reduces the probability than an individual in the study is more likely to have been exposed due to longer follow-up time and means that exposure periods and outcome periods are non-overlapping, thus avoiding complex time-dependent biases (82,83,132).



Patients that were dispensed a statin prescription during the 'exposure ascertainment window' are considered exposed. Patients dispensed their *only* statin prescription outside of this window will not be considered exposed.

Figure 4.1. Exposure and outcome ascertainment periods in the primary analysis.

In sensitivity analyses, the length of time used to assess exposure to statins was varied in to determine its effect on the results. In addition, the medication possession ratio (MPR) was calculated to distinguish between statin users that had multiple or longer statin prescriptions compared to those that did not. The MPR was calculated by identifying all the prescriptions received by an individual patient within the exposure ascertainment window and the associated days supplied of each prescription was aggregated and divided by the length of exposure ascertainment window to give a ratio representative of the proportion of days in the exposure window for which the patient had a been dispensed a statin.

4.2.3 Outcome ascertainment

The primary outcome for this analysis was all-cause mortality and the secondary outcome was pulmonary-related mortality. These were evaluated in the period that began 366 days after the index date and lasted until up to 730 days after the index date (i.e. the 365-day period beyond the exposure ascertainment window; see Figure 4.1). This approach prevented the overlap of the exposure and outcome periods (83,132) and has been used previously in evaluating medication exposure and hospital readmissions in asthma patients (87). An advantage to this approach is that it minimizes the potential for immortal time bias by fixing exposure status prior to the outcome ascertainment period (139). Mortality was assessed as time-to-death from the end of the exposure ascertainment window to the date of death or to the end outcome ascertainment period for a maximal total of 365 days for the survivors. The cause of death was identified using the listed ICD-10 code in the Vital Statistics Deaths file (134). Pulmonary-related deaths were those associated using ICD-10 codes: J15 to J44 (65).

4.2.4 Adjustment for potential confounders

Covariates that were considered as potential confounders for the association between statin exposure and mortality were obtained during the exposure ascertainment window. The demographic covariates included: age, sex, neighborhood income quintiles based place of residence, and health authority (regional health service entity) in which the patient resided. In addition, for each patient the number of prescriptions dispensed, the number of hospital encounters, the number of inpatient hospital stays, and the number of physician encounters were calculated. Finally, to account for comorbidities at the beginning of follow-

up, Charlson Comorbidity Index was calculated, excluding COPD and CVD, based on health services use records during the exposure ascertainment period (140,141).

4.2.5 Statistical analyses

A Cox regression model was constructed to model the time from the end of the exposure ascertainment window to the time to the outcome of interest (mortality in the primary analysis) or censoring. Bivariate analyses of potential confounders were conducted with the outcome of interest such that those with a p-value less than 0.20 were considered for inclusion in the multivariable analysis. The multivariable model was chosen by stepwise addition of candidate variables from the bivariate analyses using the aforementioned criterion and compared at each step using Akaike Information Criterion (AIC) (142). All analyses were conducted using SAS Version 9.4 (SAS Institute Inc, Cary, NC, USA). No personal identifying information was made available as part of this study; procedures used were in compliance with British Columbia's Freedom of Information and Privacy Protection Act. Ethics approval was obtained from the University of British Columbia.

4.2.6 Sensitivity analyses

Several sensitivity analyses were performed to test the robustness of our results (presented in Table 4.5). The exposure ascertainment window was varied to six months and to eighteen months. Alternative definitions of exposure were also used to evaluate the effect of the specific definition on study results. The medication possession ratio (MPR) for statins was calculated by summing the days supplied of statins received by an individual patient over the length of exposure ascertainment window. We also dichotomized MPR

using a commonly used threshold of 0.8 (90,135) to compare 'adherent' and 'non-adherent' statin-users, as a binary variable, where the reference category included both non-users and those that did not meet this threshold. Finally, an exposure definition based on the cumulative dose of statins received during the exposure ascertainment window was explored.

4.3 Results

4.3.1 Cohort of COPD patients

The cohort of COPD patients consisted of 39,678 patients which were identified and included in the analysis. The mean age in the cohort of COPD patients on the study index date was 71.0 (SD: 11.6) years and 54.7% were female. There were 1446 (4%) deaths recorded within the COPD cohort in the outcome ascertainment period. Further details of the COPD cohort are available in Table 4.1.

Table 4.1. Patient characteristics, stratified by exposure status to statins.

Patient Characteristic	**Statin Exposed**	**Not Exposed**
N	7566	32112
Age	69.9 (SD: 8.8)	70.5 (SD: 11.4)
% female	46.2%	55.1%
Age Distribution (n (%))		
50<60	1175 (15.5%)	7292 (22.7%)
60<70	2460 (32.5%)	7971 (24.8%)
70<80	3005 (39.7%)	9512 (29.6%)
>80	926 (12.2%)	7337 (22.8%)
Income Quintile (# (%))		
1	1841 (25.8%)	7808 (25.4%)
2	1497 (21.0%)	6324 (20.6%)
3	1393 (19.5%)	5512 (18.0%)
4	1170 (16.4%)	5236 (17.1%)
5	1033 (14.5%)	4633 (15.1%)
Health Authority (# (%))		
Interior	1504 (19.9%)	7099 (22.2%)
Fraser	2370 (31.3%)	8926 (27.9%)
Vancouver Coastal	1341 (17.7%)	6374 (19.9%)
Vancouver Island	1385 (18.3%)	6109 (19.1%)
Northern	512 (6.7%)	1957 (6.1%)
Charlson Comorbidity Index (CCI)	3 (2-5)	2 (1-4)
CCI Category		
0	247 (3.4%)	1621 (5.2%)
1	1141 (15.9%)	8124 (26.2%)
2	1376 (19.2%)	5932 (19.1%)
>=3	4421 (61.5%)	15351 (49.5%)
Any Hospitalization (overnight)	1621 (21.4%)	7513 (18.9%)
Number of Prescriptions Received[a]	39 (26-60)	31 (18-53)
Number of Physician Encounters[a]	14 (8-24)	12 (6-20)

CCI: Charlson Comorbidity Index; SD: standard deviation. Note: Where percentages do not add to 100% the reason is due to rounding. Except where noted, continuous variables are presented as mean and standard deviation. [a] Median and interquartile range.

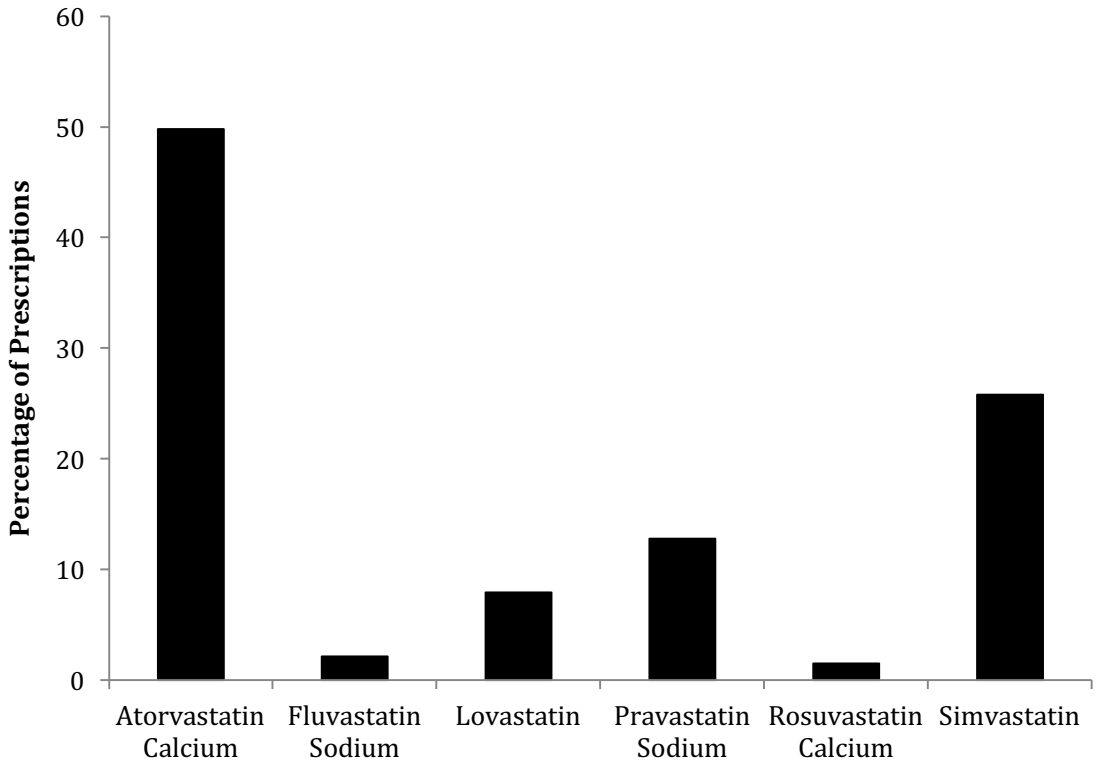


Figure 4.2. Distribution of statins prescribed within the one-year exposure ascertainment window in the cohort of COPD patients.

4.3.2 Statin use in the cohort of COPD patients

Within this cohort of COPD patients, 7775 (19.6%) patients filled at least one statin prescription in the exposure ascertainment window. There were a total of 41,897 statin prescriptions dispensed during this period, with an average of five prescriptions per patient-year, among patients who had filled at least one prescription. The distribution of specific statins dispensed is shown in Figure 4.2. The most prescribed statin was atorvastatin (calcium) (49.1%). Most patients received a 30-day (15%), 90-day (23%), or 100-day (20%) supply of statins.

Table 4.2. Hazard ratios from bivariate regression analysis to assess potential confounders, with time to all-cause mortality as the outcome variable.

Parameter	HR	95% Confidence Interval		p-value
Statin Exposure	0.79	0.69	0.91	0.0012
Age (continuous)	1.06	1.05	1.06	<.0001
Age Category				
Age 50-60		Reference		
Age 60-70	1.69	1.36	2.12	<.0001
Age 70-80	2.97	2.43	3.64	<.0001
Age 80+	5.44	4.46	6.64	<.0001
Sex (Ref=female)	1.35	1.22	1.50	<.0001
Any Physician Encounter (Ref=None)	5.06	2.99	8.56	<.0001
Number of Physician Encounters	1.02	1.02	1.02	<.0001
Any Hospitalization (overnight)	2.52	2.26	2.80	<.0001
Total Length of Hospital Stay Over the Period (days)	1.00	1.00	1.01	<.0001
Number of Hospitalizations	1.46	1.40	1.52	<.0001
Charlson Comorbidity Index (continuous)	1.14	1.13	1.16	<.0001
Charlson Comorbidity Category				
0		Reference		
1	0.81	0.582	1.14	0.2236
2	1.09	0.78	1.56	0.6189
≥3	2.33	1.72	3.16	<.0001
Number of Prescriptions Received	1.00	1.00	1.01	<.0001
Health Authority				
Interior		Reference		
Fraser	0.93	0.80	1.08	0.3247
Vancouver Coastal	1.03	0.88	1.20	0.7266
Vancouver Island	1.00	0.85	1.17	0.9557
Northern	1.04	0.83	1.31	0.7294
Income Quintiles				
5		Reference		
4	1.20	0.98	1.46	0.0715
3	1.16	0.96	1.42	0.1277
2	1.28	1.06	1.55	0.0095
1	1.38	1.15	1.65	0.0005

Table 4.3. Hazard ratios obtained from multivariable regression analysis for association between statin exposure and all-cause mortality (primary analysis).

Parameter	HR	95% Confidence Interval		p-value
Statin Exposure	0.79	0.68	0.92	0.0016
Age (continuous)	1.05	1.04	1.06	<.0001
Sex (Ref=female)	1.36	1.22	1.51	<.0001
Physician Encounter (Ref=None)	0.71	0.41	1.20	0.1986
Any Hospitalization (overnight)	1.72	1.54	1.93	<.0001
Charlson Comorbidity Index				
0		Reference		
1	0.89	0.63	1.26	0.5079
2	0.90	0.64	1.27	0.5453
≥3	1.56	1.13	2.15	0.0068
Number of Prescriptions Received	1.00	1.00	1.01	<.0001
Income Quintiles				
5		Reference		
4	1.20	0.99	1.47	0.0681
3	1.18	0.97	1.43	0.1038
2	1.26	1.04	1.52	0.0174
1	1.32	1.10	1.58	0.0026

4.3.3 All-cause and pulmonary-related mortality

In a bivariate analysis, the hazard ratio for statin use associated with all-cause mortality was 0.79 (95% CI: 0.69-0.91, p=0.0012), indicating a protective effect of statin exposure (see Table 4.2). This significant and protective effect of statin exposure for one-year all-cause mortality was maintained in the multivariable analysis suggesting a 21% reduction

in the risk of mortality (adjusted HR: 0.79 (95% CI: 0.68-0.92, p=0.0016) (Table 4.3). Similar findings were obtained for pulmonary-related mortality with an estimated bivariate hazard ratio of 0.51 (95% CI: 0.31-0.85, p=0.0016) and in multivariable analysis, an adjusted HR of 0.57 (95% CI: 0.34-0.96, p=0.0254) indicating a greater than 40% reduction in the risk of mortality for pulmonary-specific causes (Table 4.4).

4.3.4 Sensitivity analyses

4.3.4.1 Exposure ascertainment window

Several model assumptions were adjusted to determine their effect on the results of our study. First, the length of the exposure ascertainment window was shortened to six months after their COPD index date. In this analysis, there were 3986 statin users identified. This resulted in 134 (3.4%) all-cause deaths among statin users and 1482 (4.5%) among non-statin users in the one-year follow-up period. In multivariable analysis, the estimated HR showed a protective effect from statin exposure on all-cause mortality (HR: 0.80 (95% CI: 0.71-0.90, p=0.0001). Similarly, an analysis was conducted in which the exposure ascertainment window was extended to a period of eighteen months. A protective effect was also exhibited in multivariable analysis with this lengthened exposure ascertainment window, with an estimated HR of 0.66 (95% CI: 0.54-0.80, p=0.0002) for mortality within the one year outcome ascertainment period.

Table 4.4. Multivariable regression analysis for the association between statin exposure and pulmonary-related mortality (secondary analysis).

Parameter	HR	95% Confidence Interval		p-value
Statin Exposure	0.55	0.32	0.93	0.0254
Age (continuous)	1.07	1.05	1.08	<.0001
Sex (Ref=female)	1.14	0.82	1.58	0.4244
Any Physician Encounter (Ref=None)	1.06	0.15	7.65	0.9550
Any Hospitalization (overnight)	2.08	1.49	2.92	<.0001
Charlson Comorbidity Index				
0		Reference		
1	1.85	0.56	6.14	0.3153
2	1.96	0.59	6.44	0.2709
≥3	1.76	0.55	5.63	0.3403
Number of Prescriptions Received	1.01	1.00	1.01	<.0001
Income Quintiles				
5		Reference		
4	0.85	0.46	1.57	0.6028
3	1.19	0.68	2.09	0.5380
2	0.94	0.53	1.66	0.8371
1	1.18	0.70	1.99	0.5295

Table 4.5. Multivariable regression models with time to all-cause mortality as the outcome using alternative specifications for the exposure variable.

Parameter	Hazard Ratio	95% Confidence Interval		p-value
Exposure Definition				
Medication Possession Ratio(MPR)	0.80	0.68	0.94	0.008
Adherent (MPR≥0.80)*	0.85	0.71	1.01	0.0592
Cumulative Dose	0.98	0.96	1.01	0.2231
Exposure Ascertainment Window				
6 Months	0.80	0.71	0.90	0.0001
18 Months	0.74	0.63	0.86	0.0002

* Only patients with an MPR greater than or equal to 0.80 are considered exposed.

**Models are adjusted for covariates listed in Table 4.3.

4.3.4.2 Statin adherence

The medication possession ratio (MPR) was calculated for patients over the course of the exposure ascertainment window. This gave some indication of those patients that would have received multiple prescriptions or longer duration of statin therapy. Using the MPR as a continuous variable, the adjusted HR was 0.80 (95% CI: 0.68-0.94, p=0.008) indicating a protective effect for statin-use and all-cause mortality, similar to the 20% reduction in risk in the primary analysis. An MPR threshold of 0.8 was then used to distinguish between an adherent statin user and a non-adherent statin user (90,135). There were 4582 (58.9%) statin users who met this criterion for being considered adherent. Statin users that did not achieve the adherence level of 0.8 were considered unexposed, reflecting a conservative

estimate of the effect of statin exposure. The HR in this analysis was in a similar direction as previous results but the estimated HR was not statistically significant (adjusted HR: 0.85 (95% CI: 0.71-1.01, p=0.0592).

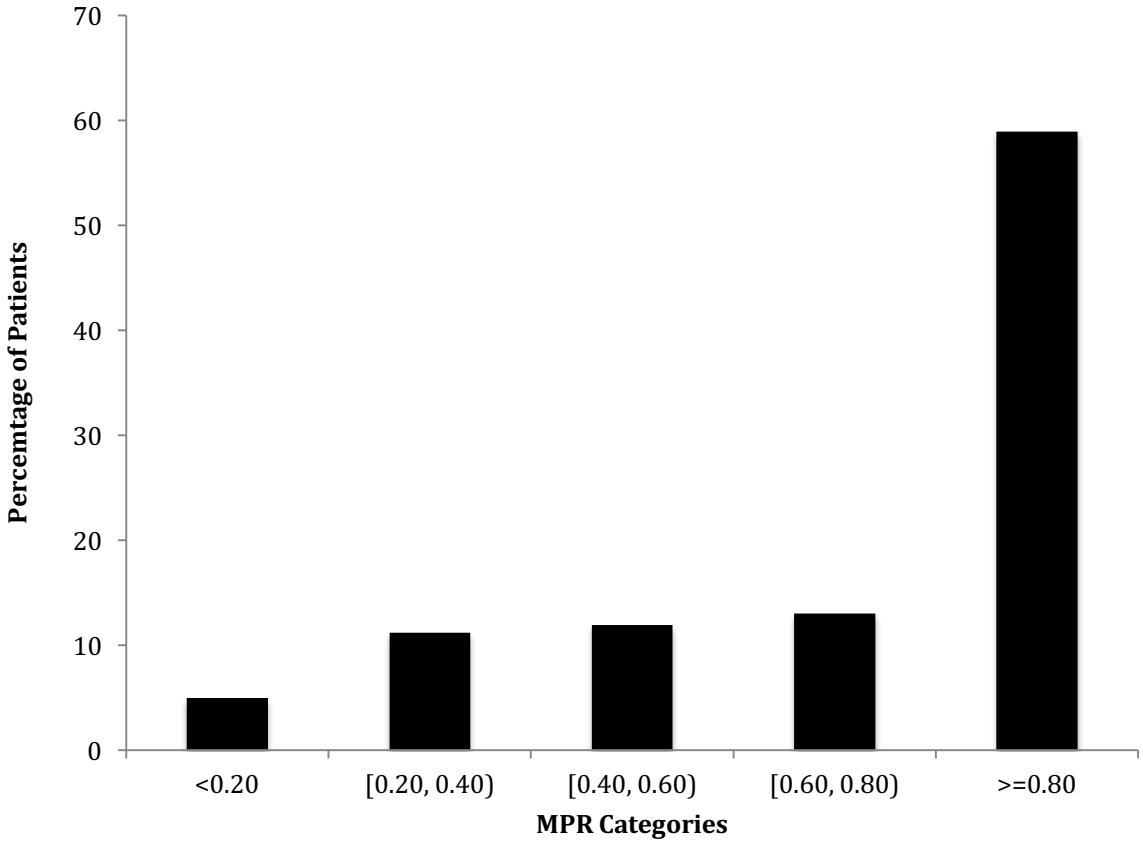


Figure 4.3. Number of statin exposed patients, by MPR category, in the 1-year exposure ascertainment window.

4.3.4.3 Statin cumulative dose

The average cumulative dose (grams) of statins received during the exposure ascertainment window was 3.8 (SD: 3.5). The estimated HR for the association between the risk of all-cause mortality and cumulative dose (grams) in the adjusted analysis was not significant but in the expected direction (HR: 0.98 (95%CI: 0.96-1.01, p=0. 2231)).

4.4 Discussion

This study used population-based administrative data from the province of British Columbia, Canada, to evaluate the association of patients' outcomes with statin use in a cohort of COPD patients. The findings of this study suggest that statin use is associated with reduced pulmonary-related and all-cause mortality in COPD patients. Further, the results were robust across several different definitions of statin exposure.

Statins have been demonstrated to reduce cholesterol levels thereby potentially reducing the risk of cardiovascular disease (59). Previous observational studies have shown that statins might also reduce the frequency of acute exacerbations of COPD (127). However, this evidence has been disputed recently due to the negative results of the STATCOPE trial, which showed no association between statin use (simvastatin, 40mg daily) and acute

exacerbations compared to placebo (66)[21]. The results of that study were contentious, largely due to the study inclusion criteria (68). Specifically, patients in this trial were excluded if they had ever received a statin previously or had any indication for receiving a statin including those who had glycated hemoglobin level beyond 6.5% or mildly elevated blood cholesterol levels. Indeed, nearly one in three patients screened for this trial were excluded owing to these and other factors. Exclusion of these patients may have represented a scenario whereby patients with elevated levels of systemic inflammation were excluded from the trial (67). Thus, the final sample might have been comprised predominantly of patients who would not benefit from statins, casting doubt about the generalizability of results. Indeed, a subsequent publication by the study authors reported low levels of CRP compared to previously published studies of systemic inflammation in stable COPD patients (131). Moreover, STATCOPE did not have sufficient power to assess the effects of statins on mortality of COPD patients. In the study presented in this chapter, the association between statin exposure and acute exacerbations of COPD was not explored, however, a significant effect was found in a reduction in pulmonary-related and all-cause mortality, underscoring the potential benefits of statin use in some COPD patients. Statins have also been linked other benefits, such as reducing the risk of cancer, generally (144), and lung cancer specifically (130), for which COPD patients are known to have an elevated risk, not only because COPD patients are typically current or former smokers, but also because of the increased systemic inflammation associated with COPD.

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[21] This study found no statistically significant difference in the mean number of exacerbations between the statin arm and control arm of the study, 1.36 +/- 1.61 and 1.39 +/- 1.73, respectively (p=0.54). Moreover, the time to first COPD exacerbation was also similar: 223 days (95% CI: 195-275) and 231 days (95% CI: 193-303), respectively (p=0.34).

The proposed mechanism by which statins may improve outcomes for COPD patients is that statin exposure may reduce underlying systemic inflammation either brought on by COPD or, indeed, may be manifested as COPD and its comorbidities. The results of this chapter may lend credence to the idea that systemic inflammation has a negative effect on health outcomes and that statins anti-inflammatory properties may reduce this inflammation and improve health outcomes for COPD patients (145). It has been postulated that there may be a specific phenotype of COPD characterized by persistent low grade systemic inflammation, who may benefit the most from statin therapy (18,146). Several recently completed small exploratory trials have also shown that statin use may be associated with decreases in pulmonary inflammation (147–149) which supports the result that statins may reduce pulmonary-related mortality. It is also possible that while statins may not modify the rate of exacerbations in COPD, they may have beneficial effects on mortality, owing to their pleiotropic effects and their known disease-modifying effects on the cardiovascular comorbidities, which contributes directly and indirectly to the morality of patients with COPD (21,142,143). We extend the previous work by demonstrating the salutary effects of statins on pulmonary and total mortality of COPD patients in the population.

The results of the analysis presented in this chapter also support the idea that randomized controlled trials, while often considered the ideal study design, may not be adequate in certain circumstances where the inclusion/exclusion are not generalizable to the population to which the results would be inferred. COPD patients that may benefit from

statins may reflect heterogeneous patients with multiple comorbidities, systemic inflammation, and with more severe COPD. In Chapter 3 of this thesis, it was highlighted that conducting a randomized controlled trial, where outcomes were rare, can be logistically difficult due to the large number of patients required. In the context of the current chapter, the STATCOPE trial was conducted in response to observational findings, but did not lead to conclusive evidence, as would be hoped, for whether statin use was beneficial in COPD patients. In both of these instances, the results of well-designed observational studies may prove to be better equipped to answer these important research questions.

4.4.1 Strengths and limitations

The most significant strength of this study is the use of population-based administrative data for an entire Canadian province of approximately 4.5 million people, which enhances the generalizability of results. An additional strength of this study is the definition of exposure that has been used. The exposure ascertainment window equates the probability of being exposed within the cohort due to time in the cohort and then evaluates outcomes over the same fixed time period for all patients. Using the intention-to-treat principle in this analysis for the exposure definition means that the results of this study are likely to be conservative (due to the dilution of exposure over time) in that patients may have been exposed to statins, and received benefits from statin therapy, without being classified as such. Reciprocally, patients who were classified as exposed might have discontinued the medication shortly after the start of follow-up.

This study has several limitations: the cohort of COPD patients was defined based on their prescription profiles from an administrative database, not a clinical diagnosis. Similar approaches have been used previously (152) and it is believed to be a reasonable approach to defining a cohort of COPD patients. Administrative data do not indicate how many prescriptions were ordered but never filled, nor how many prescriptions were filled but never taken. Patients having filled but not taken their medication would result in an overestimate of the number of statin exposed patients in our cohort, potentially misclassifying unexposed patients as exposed, and result in a conservative bias. In a sensitivity analysis, the MPR was used as a measure to determine adherence to statin therapy. Patients with a higher MPR were likely to have filled multiple prescriptions and it follows logically that, for most cases, having filled multiple prescriptions means that the previous prescriptions had been exhausted. In addition, the possibility of the 'healthy user' or 'healthy adherer' effect cannot be ignored (153). However, the design of this study and the statistical analysis, for example, by adjusting for the total number of medications patients received and the presence of other comorbid conditions, should minimize this effect. Finally, I did not have access to patients' smoking status or lung function measurements. As such, I could not adjust for these clinical characteristics that are important confounders and contributors to mortality. I did, however, adjust for other important patient characteristics such as income level, which is significantly associated with both smoking status and severity of COPD in the real world.

4.5 Concluding remarks

In conclusion, while recent evidence from a randomized controlled trial suggested that statin use is of little benefit to COPD patients, this population-based analysis showed that statin use reduced pulmonary-related and all-cause mortality among COPD patients. Moreover, this association persisted across several sensitivity analyses. Our findings, in conjunction with previously reported observational evidence, suggests that there may be a specific subtype of COPD patients, characterized by elevated levels of local and/or systemic inflammation, that may benefit from statin use.

Chapter 5: An evaluation of inhaled corticosteroid use and lung cancer risk in chronic obstructive pulmonary disease patients: a population-based cohort study[22]

Summary

This chapter builds on the work presented in Chapter 3 of this dissertation where observational evidence suggested that ICS use may be associated with a reduced risk of lung cancer in COPD patients. However, Chapter 3 also highlighted methodological issues with published studies that addressed this research question. In this chapter, I will attempt to answer this research question and improve on the methods used in previous studies. In doing so, this study makes two valuable contributions to the literature in this area: (i) it uses a number of methods of quantifying medication exposure using patients' prescription profiles obtained from administrative data; and (ii) it uses a latency period in the analysis which is based on the plausible assumption of the existence of a lag time between the exposure to ICS and change in the risk of lung cancer.

[22] A version of this work has been presented previously, as a poster, at the Canadian Institutes for Health Research, Institute for Circulatory and Respiratory Health, Young Investigators Forum in May of 2013 (Toronto, Ontario, Canada).

5.1 Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive and predominantly irreversible disease characterized by airflow obstruction (8). This disease may affect between 4% (self-reported) (154) to 11% (1) of Canadians depending on the method of identifying the disease. Moreover, COPD is one of the leading causes of death worldwide, with approximately 5% of all deaths being attributed to the disease (155), with projections indicating that these numbers will rise in the next decade (11). In addition to the increased risk of mortality, patients with COPD report a lower quality of life than the general population, which decreases as their disease progresses in severity (147,148).

Chronic obstructive pulmonary disease is a heterogeneous disease often associated with comorbidities (13,24,25). While there are several common comorbidities, including cardiovascular disease, diabetes, depression, and osteoporosis, lung cancer is likely the most severe due to the poor prognosis associated with the diagnosis. COPD patients are at an increased risk of lung cancer, which may largely be due to their smoking status or history (149,150), but while smoking is a significant risk factor for lung cancer, evidence also suggests that patients with COPD are, independent of the role of smoking, at an increased risk of lung cancer. For example, Brennar *et al.* (160) showed that patients with COPD were 40% more likely to develop lung cancer after adjustment for patients smoking status (OR: 1.4 (95% CI: 1.1-1.8)). Similarly, a study using a patient population of UK-based COPD patients in a primary care setting estimated a relative risk of 3.33 (95% CI: 2.33-4.75) of lung cancer compared to patients without a COPD diagnosis, again controlling for

patients' smoking status[23] (161). Young *et al.* (32) presented similar results showing that in patients with a history of smoking, those with COPD experienced an increased risk of lung cancer, compared to individuals with a history a smoking without COPD. There is further evidence to suggest that patients with COPD that have no history of smoking are also at increased risk of developing lung cancer compared to individuals without COPD, lending support to the idea that there are factors inherent in COPD that increase the risk of lung cancer beyond smoking status/history. For example, Turner *et al.* (35) conducted a study of 448,600 never smokers and found that over a period of twenty years, patients with emphysema (HR: 1.66 (95% CI: 1.06-2.59)) and combined emphysema/chronic bronchitis (HR: 2.44 (95% CI: 1.22-4.90)) were at an increased risk of lung cancer. Finally, Kosihol *et al.* (162) reported that while the risk of lung cancer is increased in patients with COPD, this increased risk is not solely attributable to smoking. After adjustment for smoking status lung cancer risk was elevated in patients with a history of COPD (adjusted OR: 2.5 (95% CI: 2.0-3.1) (162). Therefore, the current evidence resoundingly suggests that while smoking is an important contributor to an increased risk of lung cancer, there also appears to be an element of COPD that increases lung cancer risk, above what can be attributable to an individuals' smoking status or history.

While the mechanism by which COPD is associated with an increased risk of lung cancer is not well-established, there is evidence to support the hypothesis that systemic

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[23] This study, interestingly, showed that lung cancer incidence was positively associated with less airflow obstruction (GOLD Stages I and II), whereas most evidence would suggest that lung cancer risk increases with greater disease severity.

inflammation may be the primary etiologic factor in the causal pathway (see Table 1.2). Barnes *et al.* (13) report that patients with COPD, and in particular patients with more advanced disease, have higher levels of systemic inflammation, as measured by circulating cytokines (interleukin-6 or IL6). Another study evaluated the association between levels of systemic inflammation using multiple biomarkers (C-reactive protein, (CRP), fibrinogen, and leukocyte count) and the risk of lung cancer in COPD patients (163). The authors found a statistically significant increased risk of lung cancer when two of these three levels were elevated (HR: 2.14 (95% CI: 1.21-3.77)), while controlling for smoking status (among other covariates), which increased to approximately four times greater risk (HR: 4.00 (95% CI: 2.12-7.54)), if all three levels were elevated, compared to those with no elevated levels (163). Overall, the result of this evidence suggests that systemic inflammation is an important consideration in COPD, and needs to be measured and considered when treating patients (126). Indeed, several authors have suggested that there may be different phenotypes of COPD, and that one of these phenotypes may be specifically characterized by increased levels of systemic inflammation (16,139,155,156). If this phenotype exists, it follows that these COPD patients would likely be at an increased risk of lung cancer.

Treatment for COPD is largely based on guidelines established by the Global Initiative for Lung Diseases (GOLD). Inhaled corticosteroid use is common for patients with advanced stages of disease (see Table 1.1), for example, GOLD Stages '3' or '4' and/or for patients at high risk of acute exacerbations associated with COPD (AECOPD); that is, ≥2 per AECOPD per year, or >1 hospitalization (5). While evidence suggests that ICS use might not necessarily be beneficial in terms of lung function and mortality in patients with COPD

(44), ICS use may confer benefits in terms of improving quality of life (46,47) and reducing the rate of AECOPD (45). Moreover, ICS use appears to reduce localized inflammation in the airway and lungs which is typical in COPD patients (43,49,157,158). Inhaled corticosteroid use has also been associated with reducing systemic inflammation which provides an important mechanism by which ICS use might reduce lung cancer risk (see Table 1.3). For example, two studies conducted by Sin *et al.* (47,56) attempted to evaluate the association between ICS use and levels of inflammation. In the 2004 study, ICS use was associated with a 50% reduction in CRP levels and a 26% reduction in IL-6 levels compared to placebo treated controls. In the later study (47), there were lower levels of CRP in those patients treated with ICS, but the observed differences associated with ICS treatment were not statistically significant.

Lung cancer is often diagnosed at an advanced stage and is typically accompanied with a poor prognosis (168). As such, it is important to identify interventions that might reduce the risk of this disease, particularly in a population of patients that face an elevated risk. Therefore, the objective of this study was to examine the association between ICS use and lung cancer risk, using a variety of definitions of medication exposure, in a population-based cohort of COPD patients. A secondary objective was to explore whether ICS exposure has a significant association with specific subtypes of lung cancer.

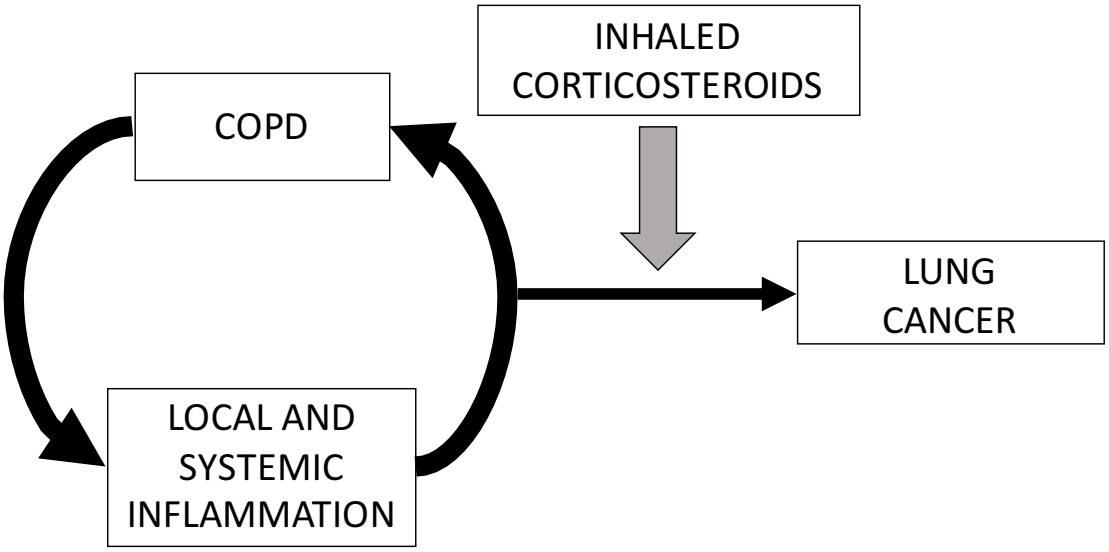


Figure 5.1. The basic conceptual framework for the study presented in Chapter 5. COPD is associated with systemic and local (pulmonary) inflammation which are also associated with lung cancer risk. Therefore, the study hypothesis is that ICS use in COPD patients may reduce levels of inflammation, thereby reducing the risk of lung cancer.

5.2 Methods

This study uses population-based linked administrative data for the province of British Columbia, Canada, to identify a cohort of COPD patients based on patients' prescriptions profile, linked to a registry of cancer patients obtained from the British Columbia Cancer Research Agency.

5.2.1 Database description

The population-based administrative data for this study comprised the following data:

1. Medical Services Plan (MSP) data file: includes fee-for-service physician billings, for every encounter with a physician in the province, under the universal provincial health insurance scheme, including the date of the encounter and the reason for the encounter (ICD9 code) (136).
2. Discharge Abstracts Database (DAD): comprising all hospital separations for the province during the study period. Data includes the date of admission, the date of separation, primary and secondary reasons for admission (ICD9 code), and method of admission (133).
3. PharmaNet datafile: is comprised of all prescriptions dispensed in British Columbia over the study period. This data file provides the medication dispensed (generic name), brand name, the number of days of the medication supplied, American Hospital Formulary Service (AHFS) code, the dosage, the quantity, a unique medication identifier ('DinPin'), and the date that the medication was dispensed (132).
4. British Columbia Cancer Registry file: provides data on lung cancer diagnosis date, death due to cancer, and cancer characteristics (histology and tumour type) (169).

5.2.2 Cohort identification

Patients were included in the cohort if they were 50 years of age or greater and had filled at least three prescriptions for an anticholinergic medication or short-acting beta-agonist (SABA) in a one-year rolling time window (144,160). If the individual met these criteria, the date of the first of these dispensed prescriptions was used as their study index date.

which is considered the date of COPD diagnosis. To reduce some of the heterogeneity among COPD patients, a one-year 'wash-in' period was imposed such that patients were required to have a twelve month period prior to their index where they were not in receipt of a SABA or anticholinergic drug. The rationale for this decision is that for those patients that had already been using one of these medications used to identify the cohort, we would not know for how long they may have had COPD. By applying the 'wash-in' period, we increased the probability of the patients we identified as being incident COPD cases. We removed patients who could not contribute at least two years of follow-up time to ensure that patients would have sufficient time to potentially develop lung cancer.

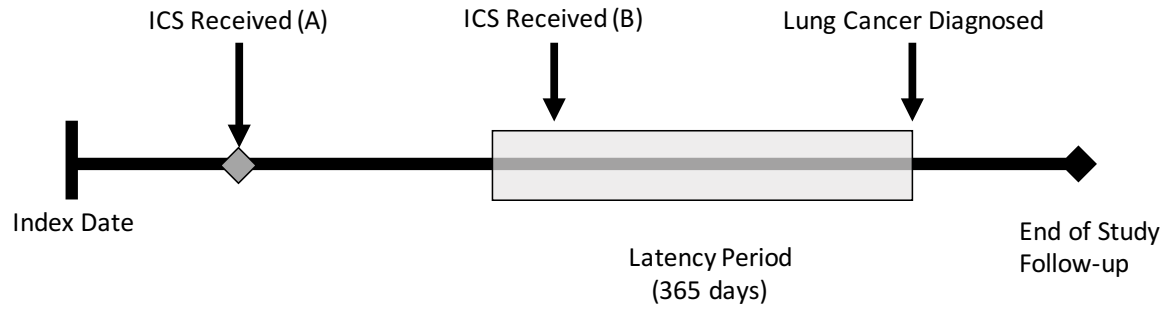
The PharmaNet data file was then linked with physician billings (Medical Services Plan (MSP)), hospital discharges (Discharge Abstract Database), demographic information and mortality (Vital Statistics), and the British Columbia Cancer Agency Registry file using a unique de-identified personal health number (PHN) to conduct the analysis.

5.2.3 Inhaled corticosteroid use

Inhaled corticosteroid users were initially identified according to American Hospital Formulary Service (AHFS) codes 520808, 680400, and 840600 (137). Identified prescriptions meeting this criterion were further scrutinized to ensure that only inhaled medications were considered as potential ICS exposure. For example, within these three AHFS codes, there remained topical and oral formulations; thus, these were not considered as ICS exposure. ICS monotherapy and ICS combination therapy were both considered in this analysis.

5.2.4 Latency period

In an attempt to provide sufficient time for ICS exposure to affect the pathogenesis of lung cancer, a one-year (365 day) latency period (or 'lag' period) was applied in the primary analysis. That is, any medication exposure in the one-year period prior to lung cancer, death, or censoring, was not counted as the pathogenesis of lung cancer was assumed to have already begun. The length of the latency period was chosen based on evidence by Henschke *et al.* (171) and Chaturvedi *et al.* (40) and was subject to several sensitivity analyses. A graphical representation of the latency period associated with lung cancer diagnosis and its relationship to medication exposure is presented in Figure 5.2.



The application of the latency period (365 days) means that prescriptions received during the latency period (B), prior to the diagnosis of lung cancer in this illustration, are not counted as exposures. Prescriptions received after the index date and prior to the latency period are counted as ICS exposures.

Figure 5.2. The latency period associated with medication exposure and lung cancer diagnosis.

5.2.5 Exposure measurement

The method used to measure medication exposure in observational studies using administrative data requires careful consideration. The choice of measure should depend on the medication being considered and the properties of the study outcome (in this case, disease diagnosis). To ensure the robustness of the results of this study, several different methods of quantifying drug exposure were used in the analyses. These methods attempted to appreciate the nuances of medication exposure over longer follow-up periods and a disease, lung cancer, with a substantial induction and latency periods. There were four conventional methods of defining medication exposure in this analysis: (i) time-dependent exposure; (ii) 'current' use; (iii) cumulative years of use; and, (iv) total cumulative dose received. In addition, there were two recency-weighted exposure measures: (v) recency-weighted duration of medication use; and, (vi) recency-weighted cumulative dose. Each of these are described in more detail below:

(i) Time-dependent exposure: The reference case for this analysis was time-dependent exposure, defined as a time-dependent binary variable. For this definition of medication exposure, at any specific time during the follow-up, a patient could be considered as exposed or unexposed to ICS, contingent on whether that patient had filled an ICS prescription prior to that specific time and after the start of follow-up. This calculation was performed using the date that the prescription was filled by the patient and the 'days supply' of that specific dispensed prescription. The use of a time-dependent method of quantifying medication exposure is superior to a fixed 'ever/never' exposure definition whereby a patient receiving an ICS prescription at

any time during follow-up would be considered exposed for the entirety of the follow-up period, and has implications for reducing potential biases that result from using fixed exposure definitions. Immortal-time bias may exist where the time between the index date and the date of first exposure is calculated as exposed time, which is incorrect because during that time, the patient was not actually unexposed to the medication under investigation (139,172). Therefore, using a time-dependent measure of medication exposure correctly classifies the time for which the patient had not filled a prescription as unexposed time, and time for which the patient had filled a prescription as exposed time.

(ii) 'Current Use': In this analysis, current use has been defined as a patient that filled an ICS prescription in a six-month window previous to the latency period and those that did not receive a prescription for ICS during this period as unexposed. This definition of medication exposure implies there is a period during which exposure to the medication previous to the outcome is especially important. This method may be used more frequently in the case of acute events (i.e. myocardial infarction) whereby an exposure immediately preceding an event may be associated with that event (85).

(iii) Cumulative Duration of Use: This definition, the quantity representing medication exposure is calculated by aggregating the length of time for which a patient has taken the medication. In this analysis, the 'days supply' of each individual dispensed prescription were aggregated, for any given point during the study follow-up period, and divided by 365, to get the total years of ICS use.

(iv) Cumulative Dose: Medication exposure is calculated by aggregating the total dose of medication prescribed to a specific patient over the study period. Inhaled corticosteroids have different potencies; therefore, each ICS prescription was converted to fluticasone equivalent dosages to allow for comparison between different type of ICS use (173). This method of capturing medication exposure is based on the assumption that the total amount of medication received (in grams, for this analysis) is associated with the outcome. This is calculated using the dose of the medication prescribed multiplied by the quantity prescribed.

(v) Recency-Weighted Cumulative Duration of Use: The weighted cumulative duration of use approach was used to account for the duration of medication use while also accounting for when, during follow-up, the medication use occurred (96). To accomplish this, a function was constructed that weighted those prescriptions that occurred closer to the date of the event, or end of follow-up, higher than those from earlier in the study period. The assumption behind this method is straightforward: those prescriptions that were dispensed more proximal to the outcome or the end of follow-up are likely to result in a greater risk reduction than those prescriptions that were dispensed earlier in the follow-up period. The assumption of this assigning weights in this way is consistent with how this method has been used previously in the literature (86,96).

(vi) Recency-Weighted Cumulative Dose: The recency-weighted cumulative dose approach was used to simultaneously account for cumulative dose and when during follow-up the dose was received (96). This method implies that doses of medication received across the study period are not equal and that those that occur more recently may have a greater association, and in this case, a greater risk reduction, with the study outcome. Both of the recency-weighted approaches described above also respect the latency period (discussed above). That is, both of these methods weighted ICS exposure until the beginning of the latency period, and after this period began, filled prescriptions for ICS were not counted toward exposure.

5.2.6 Adjustment for potential confounders

Covariates that were thought to be potential confounders of the association between ICS exposure and lung cancer diagnosis were incorporated into a multivariable model described in the next section. The demographic covariates included: age, sex, neighborhood income quintiles based residence, and health authority (regional health service) in which the patient resided. In addition, for each patient the number of prescriptions dispensed, the number of hospital encounters, the number of inpatient hospital stays, and the number of physician encounters were calculated. Finally, to account for comorbidities at the beginning of follow-up, the Charlson Comorbidity Index was calculated based on health services use (140,141). Covariates were assessed in the one year period immediately prior to the latency period.

5.2.7 Statistical analysis

A Cox regression model (174,175) was used to estimate the hazard ratio associated with lung cancer diagnosis based on exposure to ICS, using the aforementioned exposure definitions. In the context of this study, the analytical approach calculates the time from COPD diagnosis (the index date) to lung cancer diagnosis, death, or end of study follow-up. A series of bivariate regression analyses were conducted to determine candidate covariates for the final multivariable model using a threshold of $p<0.20$ to be considered for inclusion. Results from these bivariate regression models are reported in Table 5.3. Each covariate that met this threshold was added to the multivariable model via stepwise selection comparing Akaike Information Criterion (AIC) values (142). The AIC is a method of comparing models which adds a penalty for additional covariates in the model with lower scores being considered superior to higher scores. Comparison of AIC score is a well-established method for determining the most parsimonious and best-fitting model (86,96).

Hazard ratios (HR) and their associated 95% confidence intervals (CI) were reported for each of the exposure metrics quantifying ICS use as: (a) bivariate analyses, (b) multivariable (age and sex adjusted) analyses, and as (c) 'fully' adjusted multivariable analyses, with time to lung cancer diagnosis as the outcome. Akaike Information Criterion values are also presented to show the performance of each exposure metric with a given set of covariates. Statistical significance was achieved for p-values less than alpha of 0.05.

5.2.8 Secondary analysis: medication possession ratio

The medication possession ratio (MPR) is typically used as a measure of adherence as outlined in detail in Chapter 2. It is calculated as the ratio between the time (days, for example) from the initial prescription of the medication (ICS) to the end of follow-up or the outcome of interest, and the estimated total number of days of treatment for which the medication was dispensed (93). Thus, it gives a ratio for the amount of time the patient had a prescription over the course of the study period, and provides an estimate of sustained medication use. Patients using ICS were classified as adherent or non-adherent based on an MPR threshold of 0.8 (78,90). The results of the multivariable regression using the MPR are presented in Table 5.5.

5.2.9 Sub-group analysis: lung cancer histology

The BC Cancer Agency Registry file provided information on the histology of each lung cancer case reported. Therefore, we were able to classify lung cancers according into: (i) non-small cell lung cancer (NSCLC); (ii) small cell lung cancer (SCLC); and (iii) 'other'. The distribution of these cancers within the cohort of COPD patients is reported in Figure 5.5. Using the same analytical approach as described in Section 5.2.6, individual multivariable models were estimated with the outcome variables SCLC and NSCLC.

5.2.10 Sensitivity analyses

Several sensitivity analyses were performed to test the effect of assumptions made on the results of this study. First, as stated above, in the primary analysis a one-year period for lung cancer latency was assumed. In a sensitivity analysis, this period was: (i) reduced to

not being present at all (i.e. zero days), (ii) reduced to 180 days, and (iii) extended to two years, to explore whether study results were robust to this assumption. Second, to be included in the cohort of COPD patients, individuals were required to be 50 years of age or greater. However, lung cancer incidence is quite low under 65 years of age (176,177), therefore, the cohort age restriction was increased to greater than or equal to 65 years to be included.

5.3 Results

A cohort of 39,879 patients was identified that met the inclusion criteria. The mean age of the patients was 70.6 (SD: 11.2) years and 53.5% of COPD patients were female. Mean follow-up time among the cohort was 5.1 years. More information on the cohort of COPD patients is presented in Table 5.1.

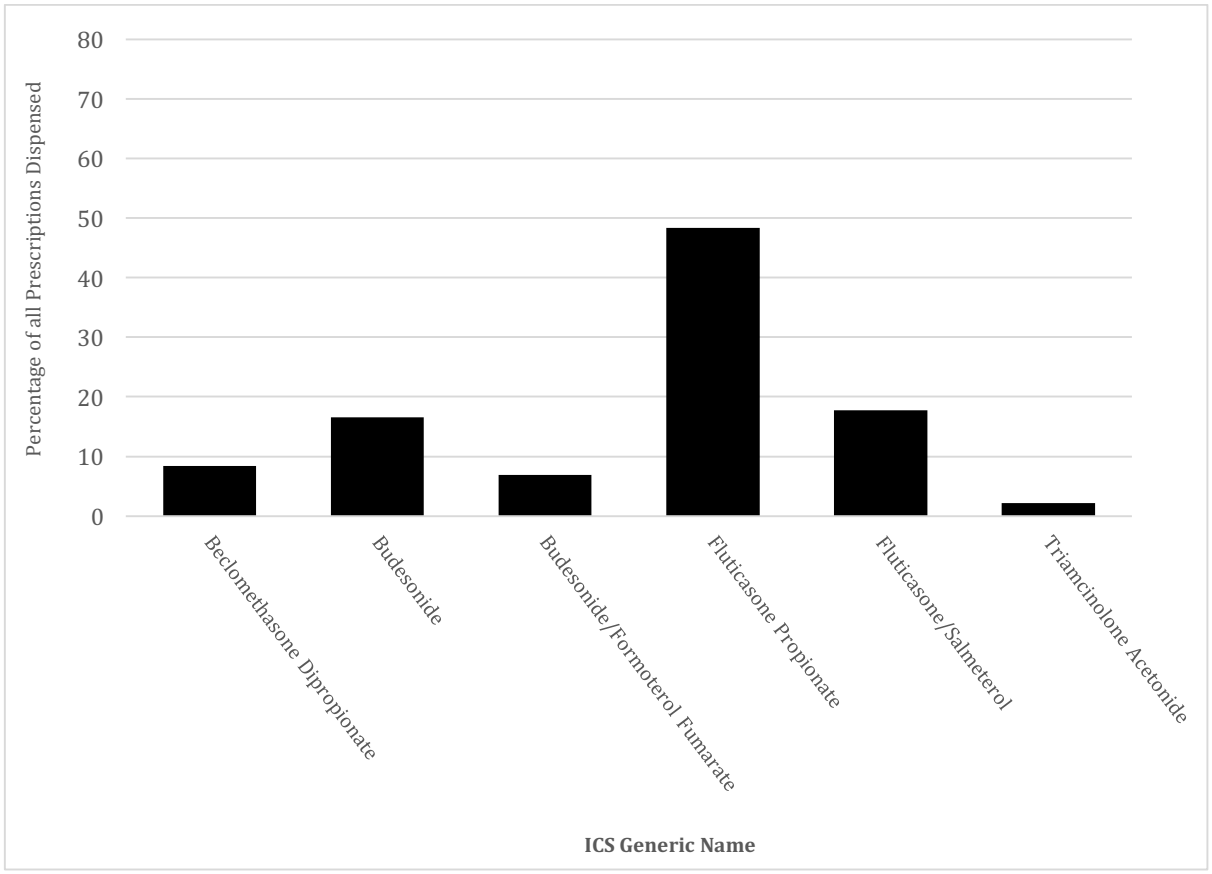


Figure 5.3. Distribution of all ICS prescriptions dispensed to the COPD cohort within the follow-up period.

Table 5.1. Demographics of the COPD cohort (n=39,879).

Patient Characteristic	Value
Age (Mean (SD)	70.6 (SD: 11.2)
Age Distribution	
50<60	8356 (21.0%)
60<70	10,212 (25.7%)
70<80	12,436 (31.2%)
>80	8785 (22.1%)
Female	21,273 (53.5%)
Income Quintile	
1	9701 (25.6%)
2	7864 (20.8%)
3	6854 (18.1%)
4	6381 (16.8%)
5	5696 (15.0%)
Health Authority	
Interior	8569 (21.6%)
Fraser	11,354 (28.6%)
Vancouver Coastal	7740 (19.5%)
Vancouver Island	7522 (18.6%)
Northern	2465 (6.2%)
Hospitalizations	
Any Reason	6651 (16.7%
COPD-related	1084 (2.7%)
CVD-related	512 (1.3%)
Charlson Comorbidity Score[1]	2 (IQR: 1-4)
Charlson Comorbidity Category[2]	
0	31,354 (79.0%)
1	6303 (15.9%)
2	1176 (3.0%)
3	843 (2.1%)
Combination Therapy (ICS/LABA)	6585 (16.5%)
Physician Encounters (any reason)[1]	11 (3-22)
Number of Prescriptions Filled (any reason)[1]	26 (6-56)

Note: Values represent mean (standard deviation) or number (percentage) unless otherwise indicated. Where percentages do not add to 100% the reason is due to rounding.
1 - Median and interquartile range (IQR). 2 - Category 0 is a Charlson Score of 0, Category 1 is (0,2], Category 2 is (2, 3], Category 3 is >3.

5.3.1 ICS use in the COPD cohort

There were 435,991 dispensed prescriptions for an ICS within the cohort of COPD patients. When the one-year latency period was applied and ICS prescriptions filled during this period were excluded, there were 372,075 filled ICS prescriptions that remained for analysis. The resulting number of ICS users was 28,314 (71.2%) within this cohort of COPD patients. Most patients filled more than one prescription for ICS, with a median of eight (IQR: 3-19) ICS prescriptions filled during the follow-up period. The most prescribed ICS among the patients was fluticasone propionate (see Figure 5.3) and the mean dose of ICS filled was 1.4 (SD: 0.7) grams. The median days of ICS supplied was 60 days (IQR: 30-90). Using a threshold to be considered an adherent user of 0.8 (95), only 2.4% of the cohort was considered adherent to ICS. Figure 5.4 shows the distribution of the MPR for ICS users in the COPD cohort.

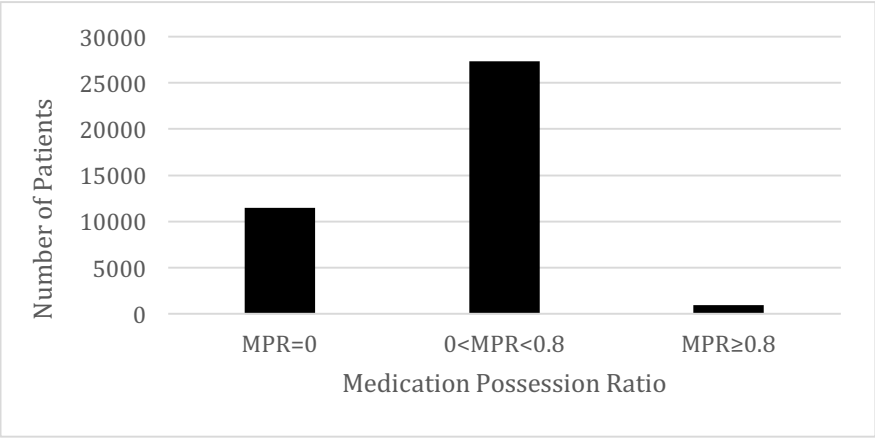


Figure 5.4. Medication Possession Ratio (MPR) for ICS use in the COPD cohort over the study follow-up period, by category.

5.3.2 Lung cancer among COPD patients

Among the cohort of COPD patients, there were initially 1966 cases of lung cancer that occurred within the study follow-up period. Lung cancers that were diagnosed within one year of the index date were removed which resulted in 994 cases of lung cancer that remained. The median age at lung cancer diagnosis was 71.3 (IQR: 65.6-76.4) years and 46.2% of lung cancer diagnoses occurred in females. Consistent with the evidence for lung cancer, diagnosis was associated with a poor prognosis. There were 401 deaths in patients diagnosed with lung cancer and the median time from diagnosis to death from any cause was 112 days (IQR: 24-267). Of the identified lung cancer cases, 854 (85.9%) were classified as non-small cell lung cancer (NSCLC) which is consistent with population estimates (177,178). The distribution of lung cancer histology is presented in Figure 5.5.

5.3.3 Bivariate results: potential confounders

Several covariates showed statistically significant associations with the outcome of interest, time to lung cancer diagnosis (see Table 5.3). As expected, age was significantly associated with lung cancer risk, showing an approximately 1% increased risk per additional year (HR: 1.01 (95% CI: 1.00-1.01, p=0.0011)). Men had a higher risk of lung cancer compared to women (HR: 1.39 (95% CI: 1.24-1.56, p<0.0001)). The number of comorbidities and the COPD-related hospitalizations was also associated with an increased risk of lung cancer (HR: 1.29 (95% CI: 1.27-1.30, p<0.0001) and HR: 2.56 (2.00-3.27, p<0.001), respectively) which also may be indicative of the elevated levels of systemic inflammation or pre-existing lung cancer, or both.

Table 5.2. Bivariate regression results for covariates considered for inclusion in the multivariable model, with time to lung cancer diagnosis as the outcome variable.

Covariate	Hazard Ratio	95% Confidence Interval		p-value
Age	1.01	1.00	1.01	0.0011
Age Categories				
<60	Ref	Ref	Ref	Ref
[60, 70)	2.02	1.67	2.43	<.0001
[70, 80)	2.33	1.95	2.80	<.0001
≥80	1.29	1.03	1.61	0.241
Sex (Male)	1.39	1.24	1.56	<.0001
Health Authority				
Interior	1.29	0.98	1.71	0.0744
Fraser	1.23	0.93	1.62	0.1485
Vancouver Coastal	1.04	0.78	1.40	0.7687
Vancouver Island	1.46	1.10	1.94	0.0084
Northern	Ref	Ref	Ref	Ref
Income Quintile				
5	Ref	Ref	Ref	Ref
4	1.27	1.03	1.57	0.0246
3	1.14	0.92	1.41	0.2152
2	1.23	1.00	1.50	0.0491
1	1.24	1.02	1.51	0.0305
Total Number of Prescriptions	1.00	0.99	1.00	<.0001
Charlson Comorbidity Score (Continuous)	1.06	0.97	1.16	0.1853
Charlson Comorbidity Score (Categorical)				
0	Ref	Ref	Ref	Ref
1	1.15	0.98	1.36	0.0931
2	0.94	0.62	1.40	0.7459
≥3	0.90	0.55	1.48	0.6814
Inpatient Stay	3.57	3.16	4.03	<.0001
Number of hospitalizations	1.66	1.64	1.68	<.0001
COPD-related hospitalization	2.56	2.00	3.27	<.0001
CVD-related hospitalization	1.04	0.58	1.88	0.8958
Combination Therapy (ICS/LABA)	1.27	1.11	1.47	0.007
Number of physician encounters	1.02	1.02	1.02	<.0001
Oral glucocorticoid use	1.09	0.91	1.30	0.3399

HR: Hazard Ratio; AIC: Akaike Information Criterion; CI: Confidence Interval.

5.3.4 Bivariate results: exposure definitions

Table 5.3 presents the results of bivariate analyses, as well as multivariable (age and sex-adjusted) analyses, using each of the aforementioned exposure metrics with the time to lung cancer diagnosis as the outcome. All of the exposure metrics capturing ICS use were significantly associated with lung cancer diagnosis in bivariate and multivariable analyses, in the *a priori* hypothesized direction, showing a protective effect for ICS use on lung cancer risk. No bivariate or multivariable analyses indicated that ICS exposure might increase lung cancer risk. In the reference case (time-dependent exposure), the estimated bivariate HR was 0.70 (95% CI: 0.61-0.80, p<0.0001). The magnitude of the protective effect varied, with largest risk reduction for time-dependent exposure (see above) and the smallest effect size for cumulative duration of ICS use (HR: 0.89 (95 % CI: 0.84-0.95, p=0.0004)) per gram of ICS dispensed. The use of both recency-weighted metrics (cumulative years of use and cumulative dose) in bivariate regression analyses resulted in a lower risk of lung cancer (HR: 0.76 per year of exposure (95% CI: 0.68-0.82, p<0.0001) and HR: 0.62 per gram of fluticasone equivalent dose (95% CI: 0.48-0.80, p=0.0002), respectively).

Table 5.3. Bivariate, and age and sex adjusted, regression results (hazard ratio and 95% CI) for each ICS exposure definition with time to lung cancer diagnosis as the outcome variable.

Exposure Metrics	Bivariate			Age and Sex Adjusted		
	HR	95% CI		HR	95% CI	
Time-Dependent ICS Exposure	0.70	0.61	0.80	0.725	0.63	0.83
Current Use[a]	0.78	0.68	0.88	0.80	0.71	0.91
Cumulative Duration[b]	0.89	0.84	0.95	0. 90	0.84	0.96
Cumulative Dose[b]	0.79	0.66	0.95	0.80	0.67	0.95
Recency-Weighted Duration of Use	0.75	0.68	0.82	0.76	0.68	0.83
Recency-Weighted Cumulative Dose	0.62	0.48	0.80	0.62	0.49	0.80

HR: Hazard Ratio; Ref: Reference Category; CI: Confidence Interval.
[a] Current use is defined as having filled a prescription in the 6- month period immediately prior to the latency period.
[b] Measured as a continuous variable.

5.3.5 Multivariable analysis: main results

In multivariable analyses, after adjustment for potential confounders, there remained a reduction in lung cancer risk from ICS use compared to no ICS use in patients with COPD. Although the magnitude of the effect varied according to the specific exposure metric

employed in the multivariable regression analyses, the protective effect was consistent across all metrics of exposure. In the reference case, classifying ICS exposure using time-dependent ICS exposure metric, the resulting adjusted HR was 0.70 (95% CI: 0.61-0.80, p<0.0001), suggesting a 30% reduction in lung cancer risk associated with ICS use. Based on AIC values, this exposure metric was superior to the other conventional metrics of measuring exposure (current use, cumulative duration of use, and cumulative dose). Exposure to ICS, as measured by the two recency-weighted metrics, were statistically significantly associated with reduced lung cancer risk. The recency-weighted duration of use exposure metric showed an approximately 25% reduction in lung cancer risk from ICS use (HR: 0.74 (95% CI: 0.66-0.87, p<0.0001) per year of exposure, and use of the recency-weighted cumulative dose metric resulted in an HR of 0.57 (95%CI: 0.43-0.74, p<0.0001) indicated a 43% reduction in the risk of lung cancer per gram (fluticasone equivalent) of ICS use.

For each of the multivariable analyses using distinct exposure metrics, AIC values were compared to determine the metric that produced the best model fit. Of the time-dependent exposure metrics presented in Table 5.4 the best (lowest) AIC value was 19116 for recency-weighted duration of use, approximately 15 points lower than the next lowest value (time-dependent exposure). This indicated that the use of the recency-weighted duration of use exposure metric provided the best model fit, given the study data.

Table 5.4. Multivariable results (hazard ratio, 95% CI, p-value) for each ICS exposure metric and associated Akaike Information Criterion values, with time to lung cancer diagnosis as the outcome variable.

Exposure Metrics	Multivariable Regression†				
	HR	95% CI		p-value	AIC
Time-Dependent ICS Exposure	0.70	0.61	0.80	<0.0001	19132
Current Use[a]	0.76	0.67	0.87	<0.0001	19140
Cumulative Years of Use	0.89	0.83	0.95	0.0003	19141
Cumulative Dose[b]	0.83	0.72	0.97	0.0201	19149
Recency-Weighted Duration of Use	0.74	0.66	0.82	<0.0001	19116
Recency-Weighted Cumulative Dose	0.57	0.43	0.74	<0.0001	19133

HR: Hazard Ratio; AIC: Akaike Information Criterion; CI: Confidence Interval.
†Multivariable regression analysis was adjusted for the following covariates: age, sex, region, income quintile, inpatient hospitalization, number of physician encounters, COPD hospitalization, the year of cohort entry, Charlson Comorbidity Score, the total number of prescriptions received, oral glucocorticoid use, and time-dependent statin exposure.
[a] Current use is defined as receiving having received a prescription in the 6-month period immediately prior to the defined latency period. [b] Measured as a continuous variable (grams).

5.3.6 Secondary analysis: medication possession ratio

In multivariable analysis incorporating the MPR to account for exposure to ICS, the resulting HR indicated that a higher MPR resulted in a reduction in lung cancer risk (Table 5.5). Because the effect of MPR measured as a continuous variable was unlikely to be linear, ICS users were categorized as adherent to their medication if their individual MPR was greater than or equal to 0.8. A significant effect was observed in adherent ICS users where there was a greater than 50% reduction in lung cancer risk compared those who did not use any ICS (HR: 0.46 (95% CI: 0.27-0.80, p<0.0001)) after adjustment for potential confounders.

Table 5.5. Multivariable regression analysis using the medication possession ratio to capture exposure to ICS.

Exposure Metrics	**Multivariable Regression**			
	HR	**95% CI LL**	**95%CI UL**	**p-value**
Adherent vs Non-Adherent[a]	0.46	0.27	0.80	0.0057
MPR Category[b]				
1	Reference			
2	0.55	0.48	0.64	<0.0001
3	0.29	0.16	0.50	<0.0001

[a] Adherent users are defined as having a MPR ≥ 0.8. [b] MPR categories are as follows: the reference category is MPR=0 (reference category); MPR category '2' is a MPR > 0 and < 0.8; MPR category '3' is ≥ 0.8.

5.3.7 Lung cancer histology

Two subgroup analyses were conducted with specific lung cancer histology. The results of these analyses also suggested that the protective effect of ICS use occurs in the two main types of lung cancer histology. The results were also consistent for both the reference case exposure metric (time-dependent exposure) and the recency-weighted duration of use metric. In multivariable analysis, ICS use, using the reference case exposure definition, was associated with an almost 30% reduction in the risk of NSCLC (HR: 0.70 (95% CI: 0.60-0.82, p<0.0001)) and for the recency-weighted duration of use metric, there was a 24% reduction in risk associated with ICS use (HR: 0.76 (95% CI: 0.68-0.84, p<0.0001). In the case of SCLC, ICS use, for the reference case, was also associated with a risk reduction, although there was more uncertainty around the estimates (HR: 0.59 (95% CI: 0.40-0.87, p=0.0084) and HR: 0.56 (95% CI: 0.39-0.80, p=0.0018) for the recency-weighted duration of use metric), likely due to the small number of SCLC cases (n=117).

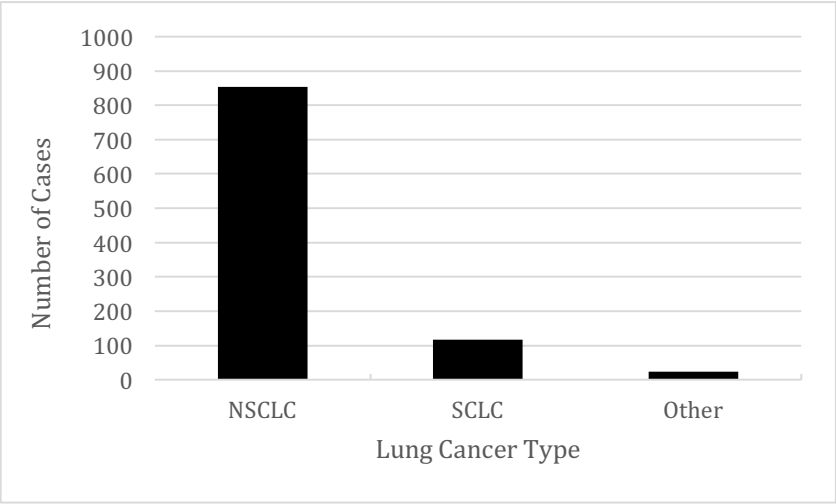


Figure 5.5. Distribution of lung cancer cases, according to histology.

Table 5.6. Sub-group analyses based on lung cancer histology. Multivariable regression analysis with time to NSCLC or SCLC diagnosis as the outcome variables.

	HR	Multivariable Regression 95% Confidence Interval		p-value
NSCLC				
Time-Dependent ICS Exposure[a]	0.70	0.60	0.82	<0.0001
Recency-Weighted Duration of Use[b]	0.76	0.68	0.84	<0.0001
SCLC				
Time-Dependent ICS Exposure	0.59	0.40	0.87	0.0084
Recency-Weighted Duration of Use	0.56	0.39	0.80	0.0018

HR: Hazard Ratio; CI: Confidence Interval; NSCLC: Non-small cell lung cancer; SCLC: Small cell lung cancer. [a] This is the reference-case for the analysis. [b] The recency-weighted duration of use exposure metric is presented because it was selected as the best model based on AIC values (an *a priori* criterion).

5.3.8 Sensitivity analyses

In sensitivity analyses, the length of the latency period associated with lung cancer was varied (Table 5.7) to evaluate whether the assumption of a one-year latency period had an effect on the relationship between ICS exposure and lung cancer risk. Interestingly, when the latency period was removed altogether, using the time-dependent exposure status metric and the recency-weighted duration of use metric, the multivariable hazard ratio was statistically significant and in the opposite direction (HR: 1.12 (95% CI: 1.02-1.40, p=0.0242 and HR: 1.19 (95% CI: 1.11-1.28, p<0.0001), respectively). While this result contrasts with the *a priori* hypothesis of this study and results from the primary analysis, given the latency period associated with lung cancer development, this result may actually illustrate the potential for protopathic bias when a latency period is not incorporated into

the analysis (179). In the next analysis, a 180-day latency period was assumed. The estimated HR for ICS use, using both exposure metrics were in the expected direction, indicating a protective effect of ICS use for lung cancer risk, but the results were not statistically significant. Finally, the latency period was extended to a period of two years, and the resulting adjusted HR for time-dependent ICS use and recency-weighted duration of ICS use both indicated a substantial risk reduction in lung cancer risk from ICS use (HR: 0.32 (95% CI: 0.28-0.37, p<0.0001) and HR: 0.31 (95% CI: 0.26-0.37, p<0.0001), respectively).

5.4 Discussion

This study explored the relationship between ICS exposure and lung cancer risk using a population-based cohort of chronic obstructive pulmonary disease patients. Additionally, to my knowledge, this is the first study that has done so using a variety of medication exposure definitions, with the intention of exploring the relationship by which ICS exposure may be associated to lung cancer risk in COPD patients. *A priori*, and based on the existing literature, the hypothesis of this study was that ICS exposure would be associated with a reduced risk of lung cancer. The results of this study aligned with this hypothesis: ICS use, using all exposure definitions, and adjusted for a wide range of potential confounders, was associated with a reduced risk of lung cancer diagnosis. The results of the analysis suggest that, according to the AIC criterion, the recency-weighted duration of use metric, a method that accounts for the duration of ICS use, while simultaneously accounting

for when during follow-up that use occurred, was the best method for measuring this association, and resulted in a greater than 25% reduced risk of lung cancer.

Table 5.7. Sensitivity analyses of different lengths of the latency period and a cohort age restriction, using the time-dependent ever metric of ICS medication exposure (the reference case).

	Multivariable Regression			
	HR	**95% CI LL**	**95% CI UL**	**p- value**
Latency Period				
(i) None				
Time-Dependent ICS Exposure[a]	1.20	1.02	1.40	0.0242
Recency-Weighted Duration of Use[b]	1.19	1.11	1.28	<0.0001
(ii) 6 months				
Time-Dependent ICS Exposure	0.91	0.78	1.05	0.1974
Recency-Weighted Duration of Use	0.97	0.89	1.05	0.4758
(iii) 1 year[c]				
Time-Dependent ICS Exposure	0.70	0.61	0.80	<0.0001
Recency-Weighted Duration of Use	0.74	0.66	0.82	<0.0001
(iv) 2 years				
Time-Dependent ICS Exposure	0.32	0.28	0.37	<0.0001
Recency-Weighted Duration of Use	0.31	0.26	0.37	<0.0001
Cohort (Age>= 65 years)				
Time-Dependent ICS Exposure	0.66	0.56	0.77	<0.0001
Recency-Weighted Duration of Use	0.70	0.62	0.79	<0.0001

[a] This is the reference-case for the analysis. [b] The recency-weighted duration of use exposure metric is presented because it was selected as the best model based on AIC values (an *a priori* specified criterion). [c] A 1-year latency period was assumed in the primary analysis and is presented here for comparison.

This study presented in this chapter had three main objectives. First, the broadest objective of this analysis was to evaluate the association between ICS use and lung cancer risk using population-based administrative data. Prior observational evidence suggested a protective effect of ICS use (92,116); however, these studies had significant limitations, such as patient populations that were not representative of the COPD population. Moreover, no clinical trial evidence exists that specifically addresses this research question, nor should it be expected given the nature of the research question. Therefore, the use of high quality population-based administrative data that facilitates the accurate classification of both exposure and outcomes at the population level, coupled with sophisticated epidemiologic analyses, can provide the best evidence-base in this area. Second, in addressing this research question, I sought to explore the association between ICS use and lung cancer risk using a variety of medication exposure definitions to ensure the robustness of the study results and to add to the methodological literature regarding medication exposure using administrative data. The third objective was to explore the use of a latency-period, and variations thereof, to add the methodologic literature of observational studies with lung or other cancer as the outcome of interest.

Implementation of a latency period in the primary analysis is a valuable contribution of this study to the literature. The intuition for the use of such a period is simple. Medication received, for example, on the day immediately prior to a lung cancer diagnosis is unlikely to have an impact on whether or not lung cancer develops. Indeed, lung cancer is often diagnosed at an advanced stage and is likely to have been present (sub-clinically or undiagnosed) for quite some period prior to actually being clinically diagnosed. The

sensitivity analyses altering the length of this latency period also produced interesting results (see Table 5.6). Removal of the latency period altogether resulted in a statistically significant association between ICS use and increased lung cancer risk. While this result does not align with the study hypothesis, as stated above, given what is known about the pathogenesis of lung cancer, this is a likely example of protopathic bias (179). However, as the latency period increased, first to six months, then to one year, and then two years, the HR associated with use ICS decreased and became statistically significant. Given the current knowledge about of tumour growth time in lung cancer, the assumption of a one year latency period seems appropriate, but this requires further research.

The recency-weighted approaches were intuitively attractive as they simultaneously accounted for the duration of use, the dosage, and the point in time during follow-up of when the prescription was filled. This method has been used in several previous studies (80,81), but it has been exclusively used for acute medical events, never for a disease such as lung cancer that has induction and latency periods. Both methods of recency-weighting ICS exposure resulted in HRs that indicated a reduction in lung cancer risk and the corresponding AIC value for recency-weighted duration of use model was superior to the other approaches of defining medication exposure. While it is possible that this method of defining medication exposure simply would not be relevant for diseases with long latency periods, the results of this study suggest otherwise. Therefore, the recency-weighted approach may be a valuable method of quantifying medication exposure in studies evaluating cancer risk and medication use. At minimum, the results of this study suggest

that this method should be considered as a sensitivity analysis for evaluating cancer risk associated with medication use.

To illustrate the impact that immortal time bias (180) can have on analysis results, a bivariate regression model was estimated with ever/never use as a fixed covariate. This analysis produced a hazard ratio of 0.56 (95% CI: 0.49-0.64, $p<0.0001$). If this estimated HR is contrasted with the bivariate analysis which used the time-dependent method of exposure (HR: 0.70 (95% CI: 0.68-0.88, $p<0.0001$), the magnitude of the effect from an incorrect specification of the exposure definition becomes immediately apparent, with an overestimate in the risk reduction of approximately 14%. This highlights the importance of using time-dependent covariates in regression analyses.

Medication adherence to inhaled medications is typically poor (181). Thus, providing evidence on the relation between adherence to ICS and lung cancer is an important contribution of this study. Results from this analysis suggests that adherent patients have a lower risk of lung cancer diagnosis than non-adherent patients. Moreover, the study results show that the total cumulative dose of medication received plays an important role in the risk of lung cancer. As such, this should provide evidence and thus, motivation for patients to take their inhaled medication, as prescribed, if doing so can confer benefits that extend to a reduction in lung cancer risk.

The fact that the impact of ICS use on lung cancer risk did not differ between lung cancer histology is unsurprising given the existing literature. If the mechanism by which ICS use

may reduce lung cancer risk in COPD patients is via a reduction in systemic inflammation, then this finding aligns with Chaturvedi *et al.* (40). In that study, increased CRP levels, while significantly associated with lung cancer risk, were not statistically significantly associated with a particular lung cancer histology[24]. Similarly, the results of this study suggest that the mechanism by which ICS might reduce lung cancer risk is not specific to either histology of lung cancer.

5.4.1 Strengths and limitations

This study has several key strengths. First, the population-based nature the data, comprising approximately 4.3 million residents of British Columbia, Canada, is a definite strength as it protects against selection biases that may occur when subjects are recruited. Thus, using these data improves on previously reported studies that used very specific patient populations (87 110). Second, this is the first study that has been able to incorporate specific types of lung cancer, from accurate clinical level data, in evaluating whether ICS use is associated with lung cancer risk in COPD patients. Third, incorporating latency period associated with lung cancer development into the primary analysis is also an important contribution of this study. Including this latency period respects the time during which lung cancer develops, where medication exposures may no longer have an effect. Future observational studies must consider this aspect of (lung) cancer when defining medication exposure. Fourth, to reduce the chance of survivorship bias, a cohort of incident COPD patients was identified using a one-year wash-in period. However, this may have also

[24] Similar to the present study, lung cancer was divided into 3 categories: (1) small cell lung cancer, (2) non-small cell lung cancer, and (3) other.

resulted in a cohort of patients with less severe COPD, and as such, a lower rate of lung cancer diagnosis, particularly if this resulted in a cohort of younger patients. In a sensitivity analysis, however, the age of the cohort was restricted to 65 years and over, and the results of the analysis were consistent with the main analysis of the entire cohort. Finally, this study used an extensive list of methods to define exposure to ICS using pharmacy records from an administrative database. Importantly, the finding that ICS reduced lung cancer risk was consistent across each of these methods of defining exposure. The consistency across each of these methods is important given the inherent limitations of administrative data in measuring medication exposure, variability in use of inhaled medications, and the heterogeneity of COPD patients.

This study has several limitations which must be acknowledged. First, while administrative data is a valuable source of information and can be extremely useful to answer research questions, it is limited in the scope of variables that could inform exposure-outcome associations. For example, while filled prescriptions are recorded, there is no data on whether or not patients actually use their medication. Moreover, in the context of inhaled medications, it is well-established that patients often use an incorrect technique and seldom use their medications as directed (182,183) and administrative data do not provide this type of information. Second, no clinical data were available for these patients and the classification of patients as having COPD is based solely on their prescription profiles. For example, no data on lung function, nor any other clinical marker of disease (or disease severity) was available. However, the definition that has been used to identify these COPD patients has been used previously (144,160) and is likely a sensitive definition rather than

a specific definition. Moreover, the importance of this study is not that these results are applicable for COPD patients, but rather that ICS may offer a protective effect for lung cancer risk in those with poor lung function (or lung inflammation), regardless of whether the patient has diagnosed COPD. Third, this study is subject to the limitations of all observational studies, where unmeasured confounding may be present. It is possible that ICS users may have differed from non-users, in a manner that was unmeasured in the study data, which affected their risk of lung cancer. However, the population-based nature of the study data, the systematic approach to inclusion of potential confounders, and the use of a broad set of exposure metrics, should have minimized the potential for bias. Moreover, the magnitude of the association between ICS exposure and lung cancer risk, and also, the consistency of this association across all of the exposure metrics, enhances the validity of the results of this study. Lastly, no data on patients smoking status was available for this analysis. While an obvious limitation, given the literature on COPD, it can be reasonably assumed that the majority of these patients do have a history of smoking or may indeed be current smokers with likely as little as 15% of the cohort being 'never' smokers (97,98).

5.5 Concluding remarks

In conclusion, this study provides evidence for the protective effect of ICS exposure on lung cancer development in patients with COPD. In doing so, this chapter makes several important contributions to the literature, including: (i) the use of alternative methods of quantifying medication exposure, including the application of the recency-weighted method of quantifying medication exposure, (ii) the incorporation of a latency period in the

analysis to appreciate the characteristics of lung cancer development, and (iii) the inclusion of specific lung cancer histology, which allowed for evaluation of whether medication exposure had differential effects for lung cancer subgroups.

The appropriate use of ICS in COPD patients is often debated and not all patients might benefit from the use of ICS. The clinical benefits and risk of use in an individual patient must be weighed by the physician. This study, however, does indicate that potential benefits may accrue from ICS use in COPD patients and that sustained use may be associated with reduced risk of lung cancer. Moreover, ICS use may also reduce acute exacerbations of COPD and improve quality of life. These results highlight the importance of properly identifying which patients might be at the highest risk of lung cancer, to enhance the therapeutic benefits in COPD patients.

Chapter 6: An evaluation of the association between statin use and lung cancer risk in chronic obstructive pulmonary disease patients: a population-based cohort study[25]

Summary:

In this chapter, I expand on the results of the analysis presented in Chapter 4 of this thesis. In Chapter 4, I showed that statin use appears to be associated with a reduction in the risk of mortality when compared against no statin use in COPD patients. In Chapter 5, the results of the analysis showed that inhaled corticosteroid (ICS) use was associated with a reduction in lung cancer risk in COPD patients, across several definitions of medication exposure. Previously, Nielsen *et al.* (144) have reported that statins may reduce lung cancer risk in COPD patients. In this chapter, I expand on the work presented in Chapter 4 and will evaluate whether the pleiotropic effects of statins extend to reducing the risk of lung cancer in COPD patients, using a similar analytic framework as presented in Chapter 5. In addition, this chapter explores whether or not there may be a synergistic effect for concurrent ICS and statin use, and also employs a negative control exposure to test the robustness of the results presented in Chapters 5 and 6.

[25] A presentation based on this chapter has been accepted as an oral presentation at the Canadian Centre for Applied Research in Cancer Control (ARCC) Conference to be held in Toronto, Ontario, Canada, in May 2017.

6.1 Introduction

Chronic obstructive pulmonary disease (COPD) is a disease that is associated with considerable morbidity and mortality (8). The disease is characterized by pulmonary and systemic inflammation and is typically associated with several comorbidities (24,25). In particular, the prevalence of cardiovascular disease (CVD) is approximately two to three times greater in COPD patients than in the general population (28). As such, HMG-CoA reductase inhibitors, or statins, which are indicated for treatment for hypercholesterolemia in patients with established CVD (184), or thought to be at risk for CVD (185), are a commonly used medication by COPD patients.

Evidence suggests that patients with COPD are also at increased risk of lung cancer (32–35). There may be multiple factors that increase COPD patients' lung cancer risk, one of which is that COPD patients typically have a history of smoking (186). However, it would appear that in a subset of patients, the increased risk of lung cancer extends beyond what can be attributed to their smoking status or history. In these patients, it is thought that the additional risk of lung cancer is due to increased systemic inflammation that may increase their risk of cancer over and above what is attributable to their smoking history or status (see Table 1.2). Patients with concomitant CVD and COPD exhibit even higher levels of systemic inflammation than COPD patients without CVD (187) and, as such, are likely at an even greater risk of lung cancer.

While there are a great deal of studies that evaluate whether statin use is associated with cancer risk (175,176) there are a limited number of studies that have evaluated statin use and lung cancer risk, specifically. For example, Marelli *et al.* (190) conducted an analysis using electronic medical records of 45,857 matched pairs of adult Americans with an average of 4.6 years of follow-up, and found no statistically significant relationship between exposure to statins and risk of any cancer compared with no statin exposure (HR: 1.04 (95% CI: 0.99-1.09)). Van Gestel *et al.* (191) evaluated the association between statin use and cancer mortality, and, more specifically, the association between statin use with lung cancer specific mortality in COPD patients. The authors reported a two-fold greater risk of lung cancer mortality among COPD patients (HR: 2.06 (95% CI: 1.32-3.20)) but found no statistically significant association between statin use and lung cancer mortality in these patients (HR: 0.75 (95% CI: 0.28-2.05))[26]. A meta-analysis by Bonovas *et al.* (192) attempted to evaluate the association between statin use and cancer risk using seven large randomized controlled trials (RCTs) – each with more than 3000 participants. The results of their study showed no significant association between statin use and development of any cancer – nor did their study specifically show any significant association between statin use and the development of respiratory cancer. In their meta-regression analysis, there was some evidence that suggested statin use may decrease cancer incidence in younger patients (192). However, similar to what was reported in Chapter 3 with respect to RCTs for ICS use and lung cancer risk, the analysis presented in this study used RCTs that evaluated statin use for cardiovascular outcomes, not cancer. Therefore, the results of this meta-analysis

[26] For cancer mortality, the results showed borderline significance for a protective effect of statin use versus non-use in COPD patients (HR: 0.57 (95% CI: 0.20-1.01)).

should be interpreted cautiously, as the results may be an instance of Type II error (that is, a failure to detect a significant effect when one exists). A study by Setoguchi *et al.* (193) focusing on an elderly population suggested no statistically significant reduction in lung cancer incidence associated with statin use. Conversely, a meta-analysis of case-control studies produced an overall pooled OR of 0.71 (95% CI: 0.56-0.89) for any cancer and a non-significant result of 0.75 (95% CI: 0.50-1.11) specifically for lung cancer development (194). The authors acknowledged, however, that the studies included in this meta-analysis had short time horizons and were not all sufficiently powered to address outcomes such as lung cancer development and mortality, specifically, thereby rendering the non-significant results questionable. Another study by Khurana *et al.* (130) focused on statin use prior to lung cancer diagnosis in the US (in a VA setting). In this study, statin use was defined as a categorical variable based on years of statin use (either any use or use longer than six months) to account for different effects based on duration of use. The primary analysis presented in the study reported an estimated OR of 0.55 (95% CI: 0.52-0.59) suggesting a significant protective effect for statin use versus no use. The same study found that the duration of statin use also impacted the likelihood of lung cancer development. That is, patients that had used a statin for greater than six months had an OR of 0.45 (95% CI: 0.42-0.48) compared to patients with shorter duration of use. Indeed, the results were similar for smokers who used statins for greater than six months with an OR of 0.47 (95% CI: 0.43-0.51) compared to patients with no statin use. One of the limitations to this study, much like that of Parimon *et al.* (92) study for ICS exposure reported on in Chapters 3 and 5, is that the study population was almost exclusively male (97.9%).

Understanding the association between lung cancer risk and statin use in COPD patients can have important implications for the management of COPD. The significant costs, morbidity, and mortality associated with lung cancer means that any reduction in the number of incident cases will mean a significant gain to patients and for health services provision. Given the potential role of statins in improving outcomes in COPD patients, the evidence base in support of using statins in COPD patients will be stronger if it is shown that statin use also reduces lung cancer risk. The objective of the analysis presented in this chapter, therefore, was to evaluate the association between statin use and lung cancer development in a population-based cohort of COPD patients.

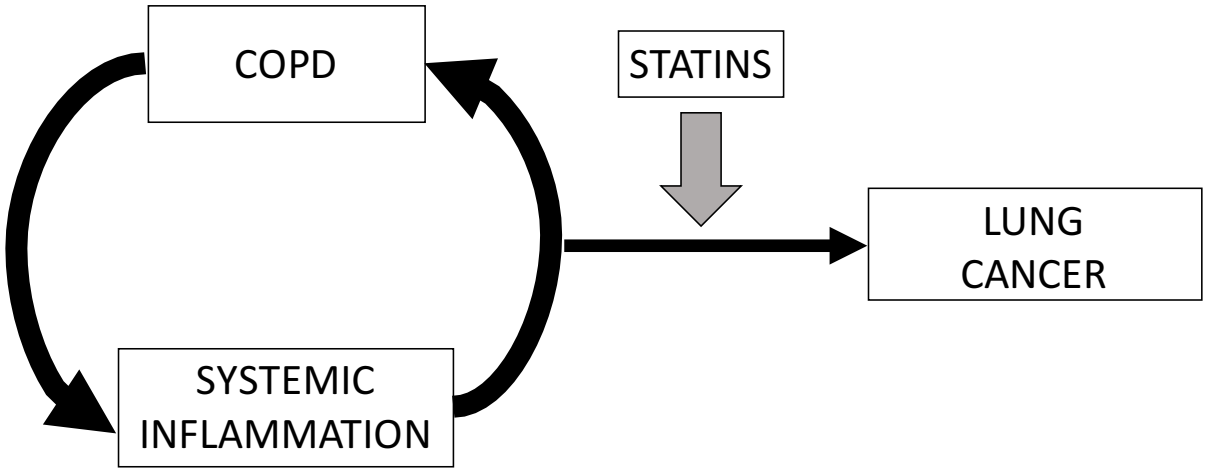


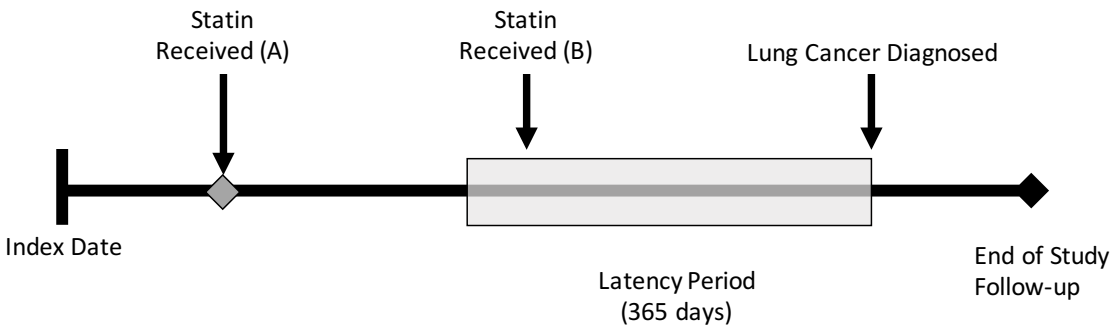
Figure 6.1. Conceptual framework for the analysis presented in Chapter 6. Systemic inflammation resulting from, or as a cause of COPD, is significantly associated with lung cancer risk. The hypothesis of this study is that statin use might reduce levels of systemic inflammation thereby reducing lung cancer risk.

6.2 Methods

This study used population-based administrative data for the province of British Columbia, Canada, to identify a cohort of COPD patients based on individuals' administrative prescription records. The databases used for this study and a description of the criteria to be included in the study cohort are presented in Chapter 5 (Section 5.2.1 and Section 5.2.2, respectively).

6.2.1 Latency period

To attempt to appropriately classify statin exposure with respect to the pathogenesis of lung cancer, a one-year (365 day) latency period (or 'lag' period) was applied in the primary analysis. That is, any dispensed statin prescription that was filled in the one-year period prior to lung cancer diagnosis, death, or censoring, was not considered as an exposure because lung cancer pathogenesis is likely have already been initiated during this period, and any exposure during this period was assumed to not confer an effect on lung cancer development. Each of the approaches to defining medication exposure described below incorporated this latency period, and the assumption of a one-year latency period was subjected to several sensitivity analyses.



The application of the latency period (365 days) means that prescriptions received during the latency period (B), prior to the diagnosis of lung cancer in this illustration, are not counted as exposures. Prescriptions received after the index date and prior to the latency period are counted as statin exposures.

Figure 6.2. A graphical representation of the latency period, and how medication exposure is considered with respect to this latency period.

6.2.2 Exposure measurement

Statin users were initially identified according to American Hospital Formulary Service (AHFS) code '240608': 'HMG-CoA Reductase Inhibitors' (137). The distribution of specific statins prescribed within the cohort of COPD patients is presented in Figure 6.3. While there were several different statins prescribed to the cohort of COPD patients, a class effect was assumed for all statins (195).

Similar to the approach taken in Chapter 5 of this thesis, the analytic approach to evaluate the association between statins and lung cancer employed an array of methods of defining medication exposure. The reason behind taking this approach is to explore whether the effect of statins on lung cancer risk is robust across different methods of defining exposure. Moreover, this approach allows one to see if the results of the analysis are consistent across

all exposure definitions. This analysis used four (i-iv) conventional measures for medication exposure and two recency-weighted approaches (v, vi), as follows: (i) time-dependent exposure; (ii) 'current' use; (iii) cumulative years of use; (iv) cumulative dose received; (v) recency-weighted duration of use; and (vi) recency-weighted cumulative dose. All exposure measures were time-dependent and are described in more detail below:

(i) Time-dependent exposure: This method of defining medication exposure is considered as the reference case for this analysis and classifies those patients who had filled a statin prescription during the follow-up period (after the index date, or COPD 'diagnosis') as 'exposed', and those that did not as 'unexposed'. Importantly, this method was 'time-dependent'; that is, whether or not a patient was considered exposed or not exposed to statins could vary over the course of the follow-up time, depending on whether or not the patient had been dispensed a statin prescription at that time. Allowing for a patients' exposure status to vary over the study follow-up time has important implications for minimizing bias, such as immortal time bias, which is not uncommon in observational studies using administrative data to evaluate the effectiveness of medications (196) and has the potential to render significantly biased results (180). This bias may be present when exposure status is fixed, and the time prior to actual exposure is counted as exposed time, despite the patient not yet being exposed to the medication (139,172).

(ii) 'Current Use': 'Current' use is defined as a patient having filled at least one prescription for a statin in the six month period prior to the beginning of the latency period. This definition of medication exposure implies that there may be a period

during which exposure to the medication, previous to the event, is especially important.

(iii) Cumulative Duration of Use: For this approach, the days supplied of each prescription was aggregated during the follow-up period for each individual patient and divided by 365 to get the total years of statin use. This definition of medication exposure assumes that the length of time for which a patient has taken the medication will be associated with the study outcome.

(iv) Cumulative Dose: This definition of medication exposure is calculated by summing the actual amount of medication prescribed to a specific patient over the study period. This method of capturing medication exposure assumes that the total amount of medication received (in grams, for this analysis) is associated with the outcome. The cumulative dose is calculated using the dose of medication prescribed multiplied by the quantity prescribed. Statins prescriptions were converted to equivalent doses of atorvastatin (the most frequently prescribed statin in the cohort) (197).

(v) Recency-Weighted Cumulative Duration of Use: The weighted cumulative duration of use method was employed to account for the duration of medication use while also accounting for when, during follow-up, the prescription was filled with respect to the outcome (96). To account for when during follow-up the prescription was filled, a function was estimated that weighted prescriptions filled closer to the date of the event, or end of follow-up, greater than those filled earlier in the follow-up period, while also respecting the latency period. This shape of the weighting function is based on previous literature employing this method (80,81,91). This method assumes that while the duration of use is important, the exposures occurring immediately previous

to the event, again respecting the latency period, confer a greater protective effect than exposures that occurred earlier in the follow-up period.

(vi) Recency-Weighted Cumulative Dose: Similar to the approach taken above in (v), the recency-weighted cumulative dose exposure definition was used to simultaneously account for both the cumulative dose and the time point at which the prescription was filled (96). The same weighting function was employed which assigned a greater weight to doses of prescriptions of medications filled more proximal to the outcome, while respecting the latency period. The underlying assumption with this method of defining exposure is that the cumulative dose of the medication is important, but it is also important when that dose is received, relative to the study outcome.

6.2.3 Adjustment for potential confounders

Covariates that were identified as potential confounders of the association between statin exposure and lung cancer diagnosis were incorporated into the multivariable model, based on the procedure described in the next section. Potential confounders were assessed in the one year period preceding the latency period. The demographic covariates considered included: age, sex, neighborhood income quintiles based neighborhood of residence, and the health authority (regional health service) where the patient resided. For each patient, the number of prescriptions dispensed (excluding statins), the number of hospital encounters, the number of inpatient hospital stays, and the number of physician encounters were calculated. Moreover, to account for comorbidities experienced by the patient during the follow-up period, the Charlson Comorbidity Index was calculated based on health services records, excluding COPD, CVD, and cancer (185,186).

6.2.4 Statistical analysis

A Cox regression model was used to estimate the hazard of lung cancer diagnosis based on statin exposure. In the context of this study, the analytical approach calculates the time from COPD 'diagnosis' (the index date) to lung cancer diagnosis, death, or end of study follow-up. To identify potential confounders to be included the multivariable model, a series of bivariate regression analyses were carried out to determine candidate covariates for the final multivariable model using a threshold of $p<0.20$ for consideration. The results of these bivariate regressions with potential covariates are reported in Table 6.3. Each covariate that met this threshold in a bivariate regression was then added to the multivariable model via stepwise selection comparing Akaike Information Criterion (AIC) values, with lower AIC values indicating better model fit (142). Comparison of AIC values is a method of evaluating model fit which incorporates a penalty for the addition of each covariate, thereby favoring more parsimonious models. Hazard ratios and associated 95% confidence intervals are reported for each of the exposure metrics as: (a) bivariate analyses; (b) multivariable age and sex adjusted analyses; and (c) 'fully' adjusted multivariable analyses, with time to lung cancer diagnosis as the outcome. An interaction term for statin and ICS use was also evaluated given the evidence presented both in Chapter 5 as well as the *a priori* hypothesis of this study.

6.2.5 Secondary analysis: medication possession ratio

The medication possession ratio, typically used as a measure of adherence, is the ratio between the time from the initial prescription of a statin to the end of follow-up, or the event of interest, and the number of days supplied of the medication (93). Thus, it gives a

ratio for which the patient had a prescription over the course of the follow-up period, and provides an estimate of medication use. The relationship between MPR and lung cancer risk is unlikely to be linear, therefore the MPR was used to categorize COPD patients as 'adherent' if the value of MPR was greater than or equal to 0.8 (95) over the follow-up period. However, whether or not a patient was 'adherent' to statins is not focus of this study. Rather, the MPR is used as measure which estimates the proportion of follow-up time for which a COPD patient was dispensed a statin, and is simply another method of capturing medication use.

6.2.6 Sub-group analysis: lung cancer histology

The British Columbia Cancer Agency Registry file provided information on each lung cancer case to classify lung cancers as: (i) non-small cell lung cancer (NSCLC); (ii) small cell lung cancer (SCLC); and (iii) 'other'. The distribution of these cancers within the cohort of COPD patients is reported in Figure 6.5. Using the same model developed for the main multivariable analysis, the lung cancer cases were restricted to either SCLC or NSCLC, and the association between statin use and these specific cancer types was evaluated and is presented in Table 6.5 below.

6.2.7 Sensitivity analyses

Several sensitivity analyses were performed to test the importance of assumptions on the results of this study. First, in the primary analysis a one-year period for lung cancer latency was assumed. Therefore, to test this assumption, the latency period was: (i) reduced to not present at all (i.e. zero days); (ii) reduced to six months; and (iii) extended to two years.

Second, lung cancer incidence is low for patients less than 65 years of age (163,164). Therefore, a sensitivity analysis was conducted in which the cohort of COPD patients was restricted to 65 years and over to evaluate whether statin exposure resulted in a similar effect on lung cancer risk under this restriction.

6.2.8 Negative control exposure

To explore whether or not the association between medication exposure and lung cancer risk observed in this study might be due to confounding, a further analysis was conducted employing a negative control as an exposure. In this approach, an alternative medication class was identified for which there was no evidence of an association between exposure to the medication and a reduction in the risk of developing cancer. This approach is similar to using a placebo in a trial-setting; that is, the placebo, similar to the negative control exposure, should have no association with the study outcome (198). Therefore, if an association exists between the negative control exposure, similar to what was found in the primary analysis, it is likely that the original result was due to confounding and provides evidence for the absence of a true association (198–200). To conduct the negative control exposure analysis, calcium channel blockers (CCB) were chosen based on a review of the literature which suggested there was no association between CCB and lung cancer development, nor evidence supporting an association with cancer, generally (201–203). Consistent with existing literature that has employed negative control exposures in observational research, time-dependent CCB exposure was first included in a bivariate Cox regression model, then in the fully-adjusted multivariable model, and then also included in

a multivariable Cox regression model with exposures of the interest, statin and ICS exposure (188,193).

6.3 Results

A cohort of 39,678 COPD patients was identified that met the study inclusion criteria. The mean age of the patients was 70.6 (SD: 11.2) years and 53.5% were female. Mean follow-up time among patients in the COPD cohort was 5.1 years. There were 994 cases of lung cancer identified within the COPD cohort. Further characteristics of the cohort of COPD patients is presented in Table 6.1.

6.3.1 Statin use in the COPD cohort

There were 12,469 COPD patients that received at least one prescription for a statin. Among these statin users, there were 258,458 statins prescriptions dispensed during the study follow-up time, resulting in an average of approximately 21 prescriptions per patient and an average cumulative dose of 11.9 (SD: 9.2) grams. Figure 6.3 shows that the most commonly prescribed statin was atorvastatin (>55%) with simvastatin as the second most prescribed (24%). The MPR for statin users is shown in Figure 6.4; of those prescribed a statin, only 10.3% had an MPR greater than 0.80, which is a common threshold to be considered as adherent (95).

Table 6.1. Demographics of the COPD cohort (n=39,879).

Patient Characteristic	Value
Age	70.6 (SD: 11.2)
Age Distribution	
50<60	8356 (21.0%)
60<70	10,212 (25.7%)
70<80	12,436 (31.2%)
≥80	8785 (22.1%)
Female	21,273 (53.5%)
Income Quintile	
1	9701 (25.6%)
2	7864 (20.8%)
3	6854 (18.1%)
4	6381 (16.8%)
5	5696 (15.0%)
Health Authority	
Interior	8569 (21.6%)
Fraser	11,354 (28.6%)
Vancouver Coastal	7740 (19.5%)
Vancouver Island	7522 (18.6%)
Northern	2465 (6.2%)
Hospitalizations	6651 (16.7%
Any Reason	6651 (16.7%
COPD-related	1084 (2.7%)
CVD-related	512 (1.3%)
Charlson Comorbidity Category[1]	
0	31,354 (79.0%)
1	6303 (15.9%)
2	1176 (3.0%)
≥3	843 (2.1%)
Combination Therapy (ICS/LABA)	6585 (16.5%)
Physician Encounters (any reason)[2]	11 (3-22)
Number of Prescriptions Received (any reason)[2]	21 (7-44)

Note: Values represent mean (standard deviation) or number (percentage) unless otherwise indicated. Where percentages do not add to 100% the reason is due to rounding.
1 – Category 0 is a Charlson Score of 0, Category 1 is (0,2], Category 2 is (2, 3], Category 3 is >3. This calculation excludes COPD, CVD, and cancer. 2 – Median and interquartile ranges.

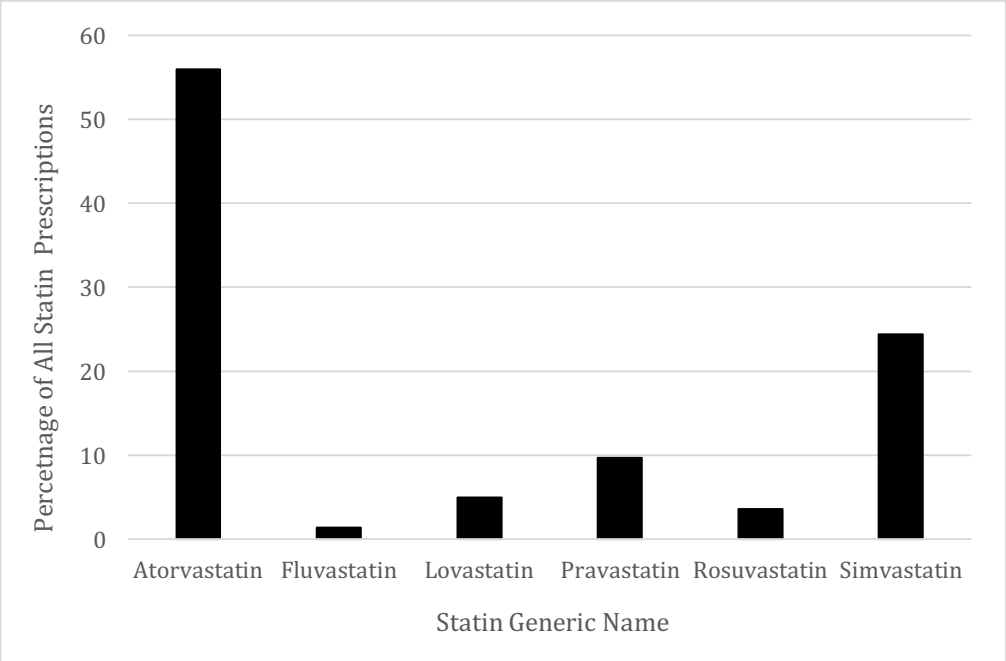


Figure 6.3. Distribution of all statins dispensed among statin users in the COPD cohort.

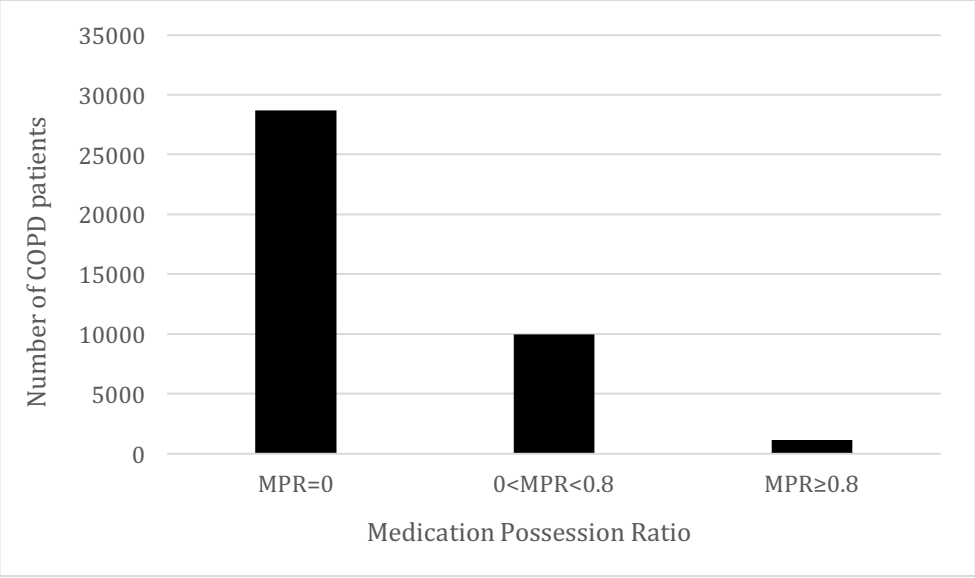


Figure 6.4. Medication possession ratio (MPR) for statin users in the COPD cohort.

6.3.2 Bivariate and age/sex adjusted results: statin exposure definitions

In the bivariate analyses, statin exposure was not significantly associated with lung cancer risk using any of the conventional methods (time-dependent exposure, current use, cumulative years of use, cumulative dose) of defining medication exposure, though the direction of the effect was in the *a priori* expected direction, that is, showing a reduction in the risk of lung cancer associated with statin exposure. The two recency-weighted exposure metrics, however, both resulted in a reduction in the risk of lung cancer by 13% and 2% (recency-weighted duration of use (HR: 0.87 (95% CI: 0.79-0.95)) per year of statin use, and recency-weighted cumulative dose (HR: 0.98 (95% CI: 0.96-0.99)) per gram of statin use, respectively).

The results of the age and sex adjusted analysis were similar to the bivariate results in that none of the conventional time-dependent exposure definitions for statin use exhibited statistical significance, though hazard ratios were all less than one, suggesting a protective effect from statin use, as expected. Similar to the bivariate analysis, both recency-weighted approaches produced statistically significant hazard ratios. For the recency-weighted duration of use metric, statin use was associated with a 13% reduction in lung cancer risk per year of exposure (HR: 0.86 (95% CI: 0.79-0.94) and a 2% reduction in lung cancer risk for each additional gram of statin received (HR: 0.98 (95% CI: 0.96-0.99). Full results of the bivariate and age/sex adjusted analyses are presented in Table 6.2.

Table 6.2. Bivariate, and age/sex adjusted regression results (hazard ratios and 95% confidence intervals) for each exposure definition with time to lung cancer diagnosis as the outcome.

Exposure Metrics	Bivariate			Age and Sex Adjusted		
	HR	95% CI LL	95% CI UL	HR	95% CI LL	95% CI UL
Time-dependent statin exposure	0.88	0.76	1.02	0.87	0.74	1.01
Current Use[a]	0.91	0.78	1.06	0.90	0.77	1.05
Cumulative Years of Use	0.97	0.91	1.02	0.96	0.91	1.02
Cumulative Dose[b]	0.99	0.98	1.00	0.99	0.98	1.00
Recency-Weighted Cumulative Duration of Use	0.87	0.79	0.95	0.86	0.79	0.94
Recency-Weighted Cumulative Dose	0.98	0.96	0.99	0.98	0.96	0.99

HR: Hazard Ratio; Ref: Reference Category; CI: Confidence Interval; LL: Lower Limit; UL: Upper Limit
[a] Current use is defined as having filled a prescription in the 6- month period immediately prior to the latency period.
[b] Measured as a continuous variable (grams).

Table 6.3. Bivariate regression model results, with time to lung cancer diagnosis as the outcome, for covariates to be considered for inclusion in the multivariable model.

Covariate	Hazard Ratio	95% Confidence Interval		p-value
Age	1.01	1.00	1.01	0.0011
Age Categories				
<60	Ref	Ref	Ref	Ref
[60, 70)	2.02	1.67	2.43	<.0001
[70, 80)	2.33	1.95	2.80	<.0001
≥80	1.29	1.03	1.61	0.241
Sex (Male)	1.39	1.24	1.56	<.0001
Health Authority				
Interior	1.29	0.98	1.71	0.0744
Fraser	1.23	0.93	1.62	0.1485
Vancouver Coastal	1.04	0.78	1.40	0.7687
Vancouver Island	1.46	1.10	1.94	0.0084
Northern	Ref	Ref	Ref	Ref
Income Quintile				
5	Ref	Ref	Ref	Ref
4	1.27	1.03	1.57	0.0246
3	1.14	0.92	1.41	0.2152
2	1.23	1.00	1.50	0.0491
1	1.24	1.02	1.51	0.0305
Total Number of Prescriptions	1.00	0.99	1.00	<.0001
Charlson Comorbidity Score (Continuous)	1.06	0.97	1.16	0.1853
Charlson Comorbidity Score (Categorical)				
0	Ref	Ref	Ref	Ref
1	1.15	0.98	1.36	0.0931
2	0.94	0.62	1.40	0.7459
≥3	0.90	0.55	1.48	0.6814
Inpatient Stay	3.57	3.16	4.03	<.0001
Number of hospitalizations	1.66	1.64	1.68	<.0001
COPD-related hospitalization	2.56	2.00	3.27	<.0001
CVD-related hospitalization	1.04	0.58	1.88	0.8958
Combination Therapy (ICS/LABA)	1.27	1.11	1.47	0.007
Number of physician encounters	1.02	1.02	1.02	<.0001
Oral glucocorticoid use	1.09	0.91	1.30	0.3399

HR: Hazard Ratio; AIC: Akaike Information Criterion; CI: Confidence Interval; LL: Lower Limit; UL: Upper Limit.

6.3.3 Multivariable analysis

In multivariable analysis, after adjusting for potential confounders, the hazard ratio for statin exposure was in the expected direction but was not statistically significant for the conventional exposure metrics (metrics (i)-(iv) listed above in Section 6.2.2). For these exposure metrics, the largest reduction of risk resulted from the reference case exposure definition, where time-dependent statin exposure was associated with a 14% decrease in lung cancer risk, but was not statistically significant (HR: 0.85 (95% CI: 0.73-1.00, p=0.050)), at an absolute threshold for statistical significance of alpha equal to 0.05. Although AIC values were similar among these conventional measures of exposure, the model employing time-dependent statin exposure metric produced the smallest AIC value among these metrics (Table 6.4). Exposure classified based on the cumulative dose of statin received had the poorest AIC value, and the estimated HR was not statistically significant for lung cancer risk (HR: 0.99 (95% CI: 0.96-1.00, p=0.128)).

The two recency-weighted approaches had superior AIC values compared to the conventional time-dependent exposure definitions, exhibiting approximately a ten-point difference. The estimated multivariable hazard ratio for the recency-weighted duration of use exposure metric showed a 15% reduction in lung cancer risk from per year of statin use (HR: 0.85 (95% CI: 0.77-0.93, p=0.0006)) and the recency-weighted cumulative dose measure showed a 5% reduction in lung cancer risk per gram of statin (HR: 0.97 (95% CI: 0.96-0.99, p=0.0019)). Of all the models incorporating time-dependent covariates in multivariable analysis, the recency-weighted duration of use exposure definition had the

best AIC value (19122). Full results of multivariable analysis, along with AIC values, are presented in Table 6.4.

Table 6.4. Multivariable regression results for each statin exposure metric with time to lung cancer diagnosis as the outcome variable.

Exposure Metric	Multivariable Regression†				
	HR	**95% CI LL**	**95%CI UL**	**p-value**	**AIC**
Time-Dependent Statin Exposure	0.85	0.73	1.00	0.050	19132
Current Use[a]	0.88	0.75	1.04	0.145	19133
Cumulative Years of Use	0.95	0.90	1.01	0.118	19133
Cumulative Dose[b]	0.99	0.98	1.00	0.128	19133
Recency-Weighted Duration of Use	0.85	0.77	0.93	0.001	19122
Recency-Weighted Cumulative Dose	0.97	0.96	0.99	0.002	19124

HR: Hazard Ratio; AIC: Akaike Information Criterion; CI: Confidence Interval; LL: Lower Limit; UL: Upper Limit
†Multivariable regression analysis was adjusted for the following covariates: age, sex, region, income quintile, inpatient hospitalization, number of physician encounters, COPD hospitalization, the year of cohort entry, Charlson Comorbidity Score, the total number of prescriptions received, oral glucocorticoid use, and time-dependent ICS exposure.
[a] Current use is defined as receiving having received a prescription in the 6-month period immediately prior to the defined latency period. [b] Measured as a continuous variable (grams).

Given the results from Chapter 5, where ICS use was associated with a reduced risk of lung cancer, an interaction term was added to the multivariable model to evaluate whether a synergistic effect between statin and ICS use might reduce the risk of lung cancer. The addition of this term into the multivariable model, however, resulted in a non-significant hazard ratio for the interaction term (HR: 1.01 (95% CI: 0.72-1.42, p=0.9427), therefore not lending to support to the idea of a synergistic effect of concurrent statin and ICS use. Addition of statin use to the multivariable model including ICS use did not alter the significant association of ICS, suggesting an independent protective effect.

Table 6.5. Evaluation of the medication possession ratio to capture exposure to statins over the study follow-up period, and lung cancer risk.

Exposure Metric	**Multivariable Regression**			
	HR	**95% CI LL**	**95% CI UL**	**p-value**
Adherent vs Non-Adherent[a]	0.46	0.29	0.73	0.0011
MPR Category[b]				
1	Reference			
2	0.69	0.58	0.81	<0.0001
3	0.41	0.26	0.66	0.0002

[a] Adherent users are defined as having a MPR ≥ 0.8. [b] MPR categories are as follows: the reference category '1' is MPR = 0; MPR category '2' is a MPR > 0 and < 0.8, and MPR category '3' is ≥0.8.

6.3.4 Lung cancer histology

Of the 994 cases of lung cancer identified within the COPD cohort, 854 were classified as non-small cell lung cancer (NSCLC) and 117 were classified as small cell lung cancer (SCLC). The distribution of these classifications align with estimates from other jurisdictions that report approximately 15% of lung cancer cases are classified as SCLC (177,178). The estimated hazard ratios for the association between statin use the development of NSCLC was 0.83 (95% CI: 0.70-0.99, p=0.0349) for time-dependent exposure and 0.83 (95% CI: 0.75-0.92, p=0.0004) for the recency-weighted duration of use metric. For SCLC, the estimated HRs for each metric of statin exposure were not statistically significant (Table 6.6), however, this result may have been due to the lower number of SCLC cases observed (n=117).

Table 6.6. Evaluation of association between statin exposure and lung cancer histology.

	Multivariable Regression			
	HR	**95% CI LL**	**95%CI UL**	**p value**
NSCLC				
Time-Dependent Statin Exposure[a]	0.83	0.70	0.99	0.0349
Recency-Weighted Duration of Use[b]	0.83	0.75	0.92	0.0004
SCLC				
Time-Dependent Statin Exposure	1.18	0.77	1.80	0.4542
Recency-Weighted Duration of Use	1.04	0.82	1.32	0.7561

HR: Hazard Ratio; CI: Confidence Interval; LL: Lower Limit; UL: Upper Limit; NSCLC: Non-small cell lung cancer; SCLC: Small cell lung cancer. [a] This is the reference-case for the analysis. [b] The recency weighted duration of use exposure metric is presented because it was selected as the best model based on AIC values (an *a priori* criterion).

6.3.5 Sensitivity analyses

Several sensitivity analyses were performed to explore how different specifications of the latency period might affect the results of this study. These results are presented in Table 6.7. When the latency period was eliminated altogether, statin use was not significantly associated with lung cancer risk using the time-dependent statin exposure metric. When a six-month latency period was applied, the estimated HR for each exposure metric was not statistically significant but, again, was in the expected direction. When the latency period was extended to two years, the association between lung cancer risk and statin use was statistically significant, suggesting an almost 40% reduction in lung cancer risk from statin use compared to non-use (HR: 0.62 (95% CI: 0.52-0.73, p<0.0001). For the recency-weighted duration of use exposure metric, the results were similar under this assumption, where the estimated multivariable HR suggested a greater than 40% reduction in lung cancer risk conferred from statin use (HR: 0.57 (95% CI: 0.49-0.66, p<0.0001).

In another analysis, the cohort of COPD patients was then restricted to those 65 years of age and over to reflect the fact the lung cancer has a typically occurs in patients near this age. The estimated HR for time-dependent statin exposure, under the reference latency period, was 0.72 (95% CI: 0.60-0.86, p=0.0004) showing a protective effect from statin use on lung cancer risk. Similarly, using the recency-weighted duration of use exposure metric, statin use was associated with an 22% decrease in lung cancer risk per year of statin use (HR: 0.77 (95% CI: 0.70-0.87, p<0.0001).

A further sensitivity analysis was conducted, using a negative control exposure, to detect whether the results of the primary analysis were inherently biased or confounded. To do so, the association between time-dependent CCB exposure and lung cancer risk was explored in the multivariable model. In the multivariable (without statin and ICS exposure), and in multivariable analysis including time-dependent ICS and statin exposure, no association between the negative control exposure and lung cancer risk was found using any definition of medication exposure (for time-dependent CCB exposure, the estimated HRs were 0.89 (95% CI: 0.75-1.10, p=0.2102) and 0.92 (95% CI: 0.77-1.11, p=0.385) when included with statin and ICS exposure). This result lends further credibility to there being a true association between statin use and a reduction in lung cancer risk.

6.4 Discussion

This study evaluated the association between lung cancer risk and statin exposure in a population-based cohort of COPD patients. The analysis employed an array of metrics for quantifying medication exposure, adding to the pharmacoepidemiologic literature about the use of exposure metrics in studies using administrative data. While statin exposure was not statistically significantly associated with a reduction in lung cancer risk across all exposure metrics, the overall results of this study do suggest that statin use in COPD patients potentially reduces the risk of lung cancer and lends support to the hypothesis that patients with COPD might benefit from statin therapy in this regard. Comparison of AIC values to determine the model that best fit the study data suggested that the recency-weighted cumulative duration of use exposure metric was best. Beyond superior AIC

values, the recency-weighted approach is intuitive as well; it implies that the duration of statin use is important, but also when that use occurs, with respect to the outcome, is also important. The decreasing gradient of risk observed for higher categories of the MPR, and also the magnitude of the protective effect in multivariable analysis using this measure of exposure, strengthen the plausibility of these results. The results of this analysis also suggest that statin use may reduce the risk of lung cancer in COPD patients aged sixty-five or greater, and that the protective effect of statins might be greater for NSCLC.

Table 6.7. Sensitivity analyses: evaluation of different lengths of the latency period and a cohort age restriction, using time-dependent exposure and the recency-weighted duration of exposure metrics, with time to lung cancer as the outcome.

	HR	Multivariable Regression 95% CI LL	95%CI UL	p-value
Latency Period				
None				
Time-Dependent Statin Exposure[a]	1.00	0.87	1.16	0.9698
Recency-Weighted Duration of Use[b]	1.04	0.97	1.12	0.2754
6 months				
Time-Dependent Statin Exposure	0.96	0.82	1.12	0.5808
Recency-Weighted Duration of Use	1.00	0.92	1.08	0.9214
1 year[c]				
Time-Dependent Statin Exposure	0.85	0.73	1.00	0.05
Recency-Weighted Duration of Use	0.85	0.77	0.93	0.0006
2 years				
Time-Dependent ICS Exposure	0.62	0.52	0.73	<0.0001
Recency-Weighted Duration of Use	0.57	0.49	0.66	<0.0001
Cohort (Age ≥ 65 years)				
Time-Dependent Statin Exposure	0.72	0.60	0.86	0.0004
Recency-Weighted Duration of Use	0.78	0.70	0.87	<0.0001

[a] This is the reference-case for the analysis. [b] The recency-weighted duration of use exposure metric is presented because it was selected as the best model based on AIC values. [c] A 1-year latency period was assumed in the primary analysis and is presented here for comparison.

The results of this analysis are strengthened by the existence of a plausible biological mechanism by which statin use might reduce lung cancer risk. Systemic inflammation, which may result from COPD or, indeed, may be a cause of COPD (126), is associated with increased lung cancer risk. Evidence suggests that elevated levels of markers for systemic inflammation are associated with a one to three times greater likelihood of lung cancer, independent of smoking status (see Table 1.2). Previously conducted studies have reported that statin use also appears to be associated with reducing levels of systemic inflammation. There have been several trials conducted which demonstrated that statin use is associated with reduced levels of systemic inflammation (see Table 1.3). For example, in the JUPITER trial, statin use was associated with a 37.4% reduction in systemic inflammation after 48 months relative to placebo (71). In addition to their effect on systemic inflammation, there is recently published evidence from pilot studies that suggest statin use may actually reduce markers for local/pulmonary inflammation (139,141) which has also been associated with increased lung cancer risk.

While the evidence is far from unanimous, previously completed observational studies support the idea that statins might reduce cancer risk (205) but only one study previously found statistically significant reductions in lung cancer risk, specifically associated with statin use (130). The results of this study, however, are not generalizable; the analysis used data from the United States Veterans Health Administration which was almost exclusively male (97.9%). Evidence also suggests statins have been shown to improve survival for those who continued statin therapy after cancer diagnosis (206). Therefore, this study provides an important contribution to the evidence for statin use and lung cancer risk.

In addition to the results of this study showing a robust protective effect of statin use and a reduction in lung cancer risk, the results also suggested that statin use reduced the risk of NSCLC, specifically. The results for SCLC, however, were not statistically significant. The inclusion of lung cancer histology into this analysis is a novel contribution and the results presented in this chapter were also consistent with the results presented in Chapter 5. Prior to this analysis, I had no *a priori* hypothesis as to whether statin exposure would offer differential effects on specific lung cancer histology. However, the absence of a differential effect is supported by the work of Chaturvedi *et al.* (40) which found that elevated levels of systemic inflammation were associated with lung cancer, generally, and there was no statistically significant difference in the levels of systemic inflammation were elevated in patients that developed SCLC or NSCLC. That is, systemic inflammation appeared to be significantly associated with both types of lung cancer. Therefore, if the mechanism by which statins are thought to reduce the risk of lung cancer in COPD patients is via a reduction in systemic inflammation, and elevated levels of systemic inflammation are associated with both SCLC and NSCLC, the results of the analysis suggesting statins reduce the risk of NSCLC are consistent. While the results of the analysis with SCLC and statin use were not statically significant, this is likely due to the low number of observed SCLC cases.

Previously published evidence suggests that statin use in COPD patients is associated with a slowing in the decline in lung function (207), a reduction in the risk of acute exacerbations of COPD (208), and a reduction in the risk of all-cause mortality (61). In this dissertation, the results from the analyses presented in Chapter 4 aligned with previously published observational evidence and demonstrated that statin use might reduce the risk

of all-cause and pulmonary-related mortality. In this chapter, the results presented show a potential additional benefit to statin use in COPD patients, in terms of a reduction in lung cancer risk. Several recently published studies have estimated that the burden associated with COPD will increase substantially in coming years, thereby necessitating the identification of therapies that can reduce this burden (4,11). Therefore, the culmination of this evidence suggests that statins have pleiotropic effects in COPD patients and should be considered as a potential therapy beyond hypercholesterolemia (209). This evidence might also suggest that identification of patients with elevated levels of systemic inflammation might offer prognostic information and allow for targeted statin treatment.

6.4.1 Strengths and limitations

The study has several strengths. First, it uses population-based administrative data for an entire Canadian province which significantly enhances the generalizability of its findings compared to other existing studies. Moreover, it was possible to link this administrative data to high-quality registry data from the British Columbia Cancer Agency to accurately identify the diagnosis date and histology of lung cancer. As such, the data used in this study provides the highest level of real-world effectiveness evidence. Moreover, where previous studies may have lacked adequate power to identify an association between statin exposure and lung cancer risk, this study did not. Second, it is the first study that has used an extensive list of medication exposure definitions to address the question of whether statins might confer benefit, in terms of reduced lung cancer risk, in COPD patients. Statin exposure was statistically significant in several adjusted analyses and for all exposure definitions when the cohort was restricted to patients aged 65 and over, which enhances

the robustness of these results. In addition, the use of recency-weighted approaches, which showed superior model fit to the conventional exposure definitions, is also a key strength, and may provide a useful methodological approach in future studies evaluating cancer risk associated with medication use. This method of defining medication exposure implies that the duration of statin use is important, but also that when the use occurs, proximal to the outcome, is important. Third, the incorporation of a latency period associated with lung cancer, and, therefore, not classifying medication exposures immediately preceding lung cancer diagnosis as relevant exposures, is a strength of this study and should inform future observational studies in cancer research. Finally, the use of a negative control (in this case, CCB exposure) to detect if the results of the analysis were due to bias or confounding is a major strength of this study, which provides support for a true association between statin exposure and lung cancer risk, and significantly enhances the robustness of the results (and also the results presented in Chapter 5 which used the same analytic approach).

There are several limitations to this study which also require acknowledgement. First, the administrative data used in this study did not include any clinical variables that would be useful in the analysis (for example, level of systemic inflammation or lung function). As such, COPD patients were not identified according to spirometry but rather based on their individual prescription records. However, previous studies have used a similar method for identifying COPD patients (144,160) and this is believed to be a sensitive approach to identifying these patients. It is possible that this approach identified some patients as having COPD, when, in reality, they did not. To attempt to provide a more specific definition of COPD, by also adding in the requirement for a physician encounter with an ICD-9 code

(491, 492, and 496) consistent with COPD within one year of the index date. This reduced the size of our cohort by less than approximately 10% and is an approach is similar that used by Curkendall *et al.* (26) and Gershon *et al.* (210). Using a more restrictive approach, for example by requiring a hospitalization for COPD, may have only identified patients with more severe disease. Therefore, this approach should enhance the generalizability of the study results. In addition, the focus of this research was not to study patients with COPD, but rather to evaluate lung cancer risk in patients at high risk for developing the disease. As such, while I attempted to identify a cohort of COPD patients, it is less important that patients have COPD, and more important that patients were at an increased risk of lung cancer in the cohort. Second, smoking status and smoking history were also not captured in our administrative data. However, previous literature does suggest that the majority of the cohort will have a history of smoking (97,98) so it would be expected that the majority of this cohort did, indeed, have a history of smoking. For example, estimates suggest that approximately 85% of COPD patients have a history smoking (211–213); therefore, we could crudely assume that approximately 34,000 patients identified in the cohort of COPD patients had a history of smoking. It might also be the case that smokers may have more severe COPD, and that this group of patients would be more likely to develop lung cancer, which would conservatively bias the results for the effect of statins. Third, while a strong effect was observed for statin use and lung cancer risk, this study is subject to the limitations of all observational studies whereby we cannot be certain that there is an element of unmeasured or residual confounding that explains the study results. In order to mitigate this possibility, a systematic approach to identifying potential confounders to be included in the multivariable analysis was adopted. The magnitude of the effect size also

reduces the likelihood that the protective effect of statin use could be explained by residual confounding. Moreover, the use of a one year latency period reduces the likelihood that the study results could be explained by protopathic bias. Finally, the study results were also consistent for a variety of medication exposure definitions and in several sensitivity analyses.

6.5 Conclusions

This analysis presented in this chapter demonstrated that statin use in COPD patients may reduce the risk of lung cancer. While the association between statin exposure and lung cancer risk was not consistently statistically significant across all specified exposure metrics, the direction of the hazard ratios was consistent with the *a priori* study hypothesis. Using the recency-weighted approaches to capture statin exposure resulted in statistically significant hazard ratios, and these two models were deemed superior based on an *a priori* specified criterion. In sub-group analyses, statin exposure was significantly associated with a reduction in lung cancer risk for patients sixty-five years of age or greater, across all exposure metrics, and also for NSCLC. These results were further strengthened by an analysis incorporating a negative control exposure to detect residual confounding or bias. In combination with the results of Chapter 4, where statins were shown to reduce mortality in COPD patients, on balance, the results presented in this analysis strengthen the hypothesis that there may be a segment of COPD patients, likely characterized by elevated levels systemic inflammation, that could benefit substantially from statin therapy.

Chapter 7: Discussion and conclusions

Summary

In this chapter I summarize and reiterate the results from Chapters 2-6, and discuss both the methodological and empirical implications of these findings in a broader context. I also acknowledge the limitations of my research, identify avenues for future research, and offer final conclusions.

7.1 Research findings and implications

The overall objective of the studies that form this dissertation was to evaluate the association between medication exposure, both to statins and inhaled corticosteroids, with lung cancer development in a population-based cohort of chronic obstructive pulmonary disease patients (Figure 7.1). Under that over-arching objective, there were several specific ancillary objectives.

The first was to present and critically evaluate different measures of medication exposure in observational studies and to illustrate the potential biases that could be created if due consideration was not given to this aspect of the analysis. In doing so, I highlighted methods of defining medication exposure that would be useful in the subsequent analyses presented in this disseration. These measures could be classified in three different general categories: (i) conventional methods of defining medication exposure; (ii) recency-

weighted approaches to defining medication exposure; and (iii) medication adherence approaches to defining exposure. These categories of defining medication exposure are used in Chapters 5 and 6 of this dissertation and have implications for the understanding of the relationship between medication exposure and the study outcome.

The second was to identify and assess the literature that attempted to evaluate whether ICS use in COPD patients was associated with lung cancer risk. Several RCTs were identified that evaluated ICS treatment in COPD patients, but none of these addressed the study question directly. In these studies, lung cancer diagnosis was recorded as a secondary outcome (i.e. adverse events), which made it difficult to assess whether or not ICS use was associated with lung cancer risk. The lack of a trial to answer this important research question is unsurprising; adequately powering a study to detect lung cancer outcomes would require a large number of participants, an extensive follow-up period, and thus substantial costs and resources. As such, it is likely that the best approach to generate the real-world evidence required to answer this research question would be a well-designed observational study. The studies identified in Chapter 3 also showed that existing evidence from observational studies implied that there might be a significant and protective effect between ICS exposure and lung cancer risk (87,110). However, the findings of Chapter 3 also suggested that these results should be interpreted cautiously. Both identified observational studies dealt with specific patient populations and used metrics to capture medication exposure that led to questions about the reliability of the study results. Thus, the question of whether there was an association between ICS use and lung cancer risk, in my opinion, remained unanswered.

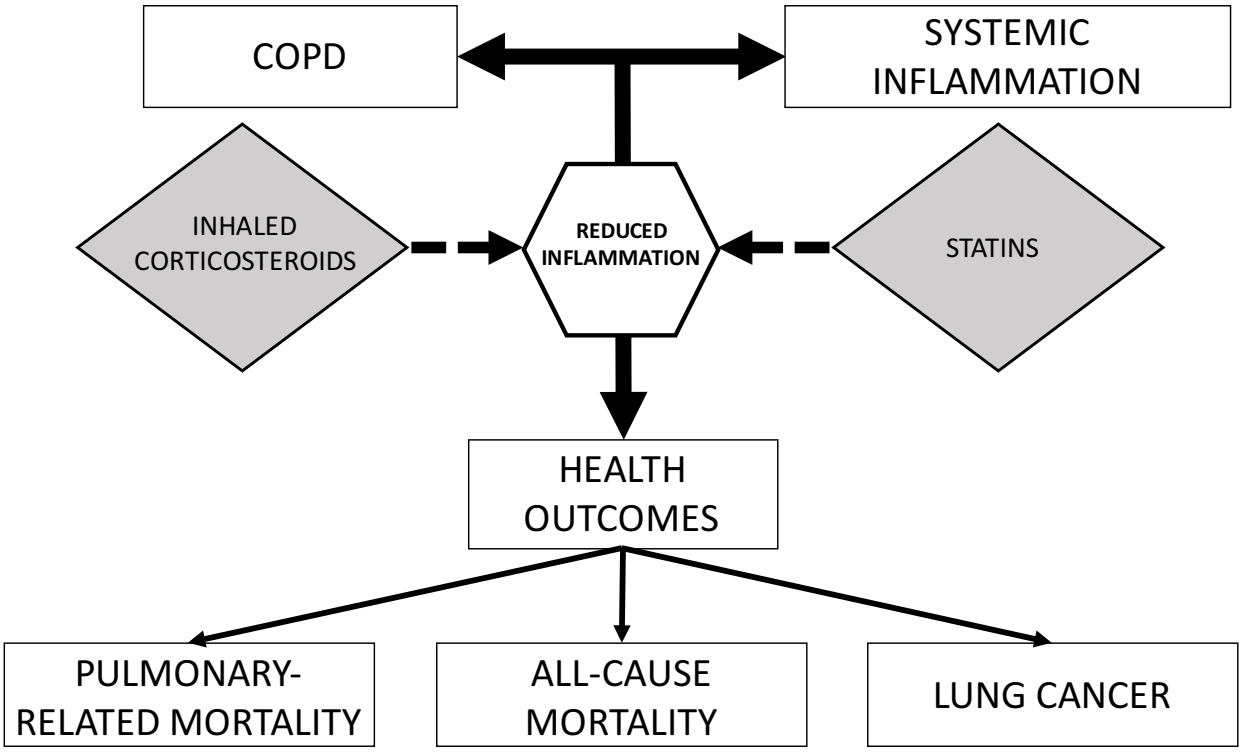


Figure 7.1. The conceptual framework for this thesis. COPD may be the result of and/or a cause of systemic inflammation which has been linked to poor health outcomes. Statin and ICS use have been shown to reduce levels of systemic inflammation and may therefore reduce levels of systemic inflammation and may therefore reduce mortality and lung cancer risk.

Third, it was important to evaluate whether statin use, generally, was of benefit to COPD patients. Therefore, the analysis presented in Chapter 4 evaluated whether there was an association between statin use and health outcomes, specifically both all-cause and pulmonary-related mortality. The impetus for this analysis stemmed from the results presented from the STATCOPE trial (66) which questioned the clinical utility of statins in

treating COPD patients. However, it is my contention that there were several problematic issues with the STATCOPE trial. The inclusion and exclusion criteria used in the STATCOPE trial, I believe, was overly restrictive and therefore rendered the trial unable to generate meaningful answers to the clinical question of whether statins should be prescribed to COPD patients, for benefits beyond improving CVD outcomes. In reality, the STATCOPE trial likely identified a subset of COPD patients that would not benefit from statins. That is, in an attempt to identify a homogeneous group of COPD patients without comorbidity to enroll in the trial, STATCOPE likely excluded patients with elevated levels of systemic inflammation, thereby minimizing the chance of statins showing any clinical utility. The results of the analysis using real-world data presented in Chapter 4, however, did indeed show that statin use confers benefits to COPD patients in terms of a reduction in the risk of all-cause and pulmonary-related mortality, and bolsters the case for statin use in these patients. I believe these findings to be significant, as they demonstrate the importance of real-world evidence in comparison to results obtained from a controlled trial setting. Thus, the results of the study conducted in Chapter 4 provide evidence for the beneficial properties of statins that is much more relevant and informative than the results of the STATCOPE trial.

Finally, the objective of the analyses presented in Chapters 5 and 6 was to answer the overall research questions of this thesis, and also to contribute to the methodological literature as to how such a research question might be addressed. The results presented in these chapters demonstrated the protective effect of statins and ICS in terms of reduced risk of lung cancer, and these results were consistent for a variety of measures of defining

medication exposure. While the results for statin use were less conclusive than the results for ICS use, the magnitude of the estimated protective effect from ICS and statin use on lung cancer diagnosis, coupled with the systemic approach to model construction with a host of potential confounders, also minimized the likelihood of these results being attributable to residual confounding. The use of a negative control exposure to attempt to detect bias or confounding was an additional strength of the analysis presented in these two chapters. Moreover, the population-based administrative data which were linked to a registry of lung cancer patients used in this study was superior to data used in previous studies in this area. The use of cancer registry data limits the possibility of measurement error of the outcome, and also minimizes the possibility of misclassification of lung cancer cases. In addition, the use of population-based administrative data increases the generalizability of my results, minimizes the likelihood of selection bias which is a common concern with observational data, and provided both the power and the length of follow-up time, required to conduct such a study.

The results presented in these chapters have important implications for the treatment of COPD patients. Lung cancer is often diagnosed at a late stage and as such, the diagnosis is accompanied with a poor prognosis of survival (176). For example, the 1-year survival associated with a diagnosis of Stage IV lung cancer is 39.4% (95% CI: 36.2-42.2%) (214). The poor survival, low quality of life, and substantial costs of therapy associated with a lung cancer diagnosis should place a considerable emphasis on the need for interventions to reduce the risk of lung cancer, particularly in patients with COPD who are already at a higher risk of the disease. The results of these studies suggest that statins and ICS may

reduce the risk of lung cancer in COPD patients. Both statins and ICS have a relatively low cost, a low user burden, and appear to provide a reduction in the risk of lung cancer. For COPD patients that already use these medications, the findings reported in Chapter 5 and 6, that the duration of use for both ICS and statins is associated with a reduced risk of lung cancer, should highlight the need for COPD patients to use their medications as prescribed. Moreover, inhaled medications are often used inappropriately by users (215). Therefore, this could also provide motivation for patients to receive proper training from clinicians to maximize the effectiveness of the medication.

The economic burden of COPD is also substantial and this is likely to increase in coming years. Najafzadeh *et al.* (4) reported that the incidence of COPD is due to increase until 2035, and that while smoking cessation might reduce the burden of disease, interventions to reduce acute exacerbations of COPD (AECOPD) would have the most significant impact on reducing this burden. Similarly, Khakban *et al.* (11) reported on the increasing burden of COPD-related hospitalizations, which consumes considerable health care costs and resources, thereby posing a significant problem to health service provision and increased pressures on a limited healthcare budget. With respect to lung cancer, a recent study conducted by Fitzmaurice *et al.* (216) reported that lung cancer was the leading cause of cancer-related mortality in men, and the third leading cause in women, which resulted in an estimated 1.2 million deaths worldwide. These studies highlight the need for evidence to inform interventions to reduce the substantial burden caused by both COPD and lung cancer.

Table 7.1. Key findings for each specific chapter of this dissertation.

Chapter	Key Finding
Chapter 2	Methods to measure medication exposure require careful consideration in observational studies in the context of chronic diseases. Methods that incorporate both the timing and duration of prescriptions have theoretical and practical advantages.
Chapter 3	Observational evidence supports the hypothesis that lung cancer risk might be decreased by inhaled corticosteroid use but there are concerns about the generalizability of the results.
Chapter 4	The use of statins in COPD patients is contentious, but this study shows that statin use might reduce all-cause and pulmonary-related mortality.
Chapter 5	Inhaled corticosteroid use appears to be associated with reduced risk of lung cancer, using a variety of medication exposure definitions. This highlights the role ICS therapy in COPD patients.
Chapter 6	Statin use appears to reduce lung cancer risk in COPD patients, however the results are less conclusive than for ICS. In conjunction with the results of Chapter 4, it appears there is a segment of the COPD population that would benefit substantially from statin use. This chapter also explored if there was a potential synergistic effect of statins and ICS use, and found no synergistic effect.

7.2 Research contributions

This dissertation makes several valuable contributions to the literature. These contributions are both empirical, which will inform the evidence base of the therapeutic benefits that can be obtained in COPD patients from statin and ICS use, and also methodological, in that they will inform future pharmacoepidemiologic analyses using administrative data and non-acute outcomes.

The empirical contributions of this dissertation should improve understanding and management of patients with COPD. The results presented in Chapter 4 showed that statins may confer additional beneficial effects in COPD patients, and reduce the risk of mortality, compared to non-users. As noted above, this is not to argue that statins should be prescribed to all COPD patients, but rather that there may exist a sub-group of COPD patients with significant levels of systemic inflammation, that might benefit in terms of reduced mortality from statin use. Similarly, Chapter 6 further demonstrated the potential pleiotropic effects of statins and showed a significant reduction in lung cancer risk associated with the use of a statin, particularly for patients over 65 and those at risk of developing NSCLC. Moreover, the results were consistent for a number of exposure metrics, and in several sensitivity analyses which reduces the likelihood of the results being explained by residual confounding. Therefore, statin use appears to reduce all-cause and pulmonary-related mortality, in addition to potentially reducing the risk of lung cancer. Finally, the appropriate stage at which ICS should be prescribed in COPD patients is contentious, but this study builds on previous evidence reported in observational studies

that showed ICS use reduces the risk of lung cancer. This evidence would suggest that ICS could potentially be initiated earlier in COPD patients; however, it must also be balanced against and individual patients' risk of adverse effects (10,49).

One further observation from the research presented in this dissertation is the deficiency of randomized controlled trials to answer 'real-world' questions. Suissa (180) stated:

> 'The randomized controlled trial design is essential to evaluate the effectiveness and safety of medications and to obtain regulatory approval for their use in clinical practice. Yet, it rarely provides information on their pragmatic benefit in terms of major disease outcomes.' (180).

Randomized controlled trials are the current 'gold standard' as the highest level of evidence but the design does not always capture the data that is required for real-world decisions. Moreover, RCTs are not always feasible if the outcome in question is rare. For example, no RCT has been conducted to address whether ICS use reduces the risk of lung cancer in COPD patients, despite COPD patients being at an increased risk of lung cancer, ICS use being contentious, and observational evidence to suggest such an association. It is well-established that RCTs are expensive, and may result in additional costs and resource use to health service (217). It is also becoming increasingly well-understood that RCTs might not be able to generate the evidence that is required to improve real-world treatment decisions (206,207). In instances where outcomes are rare and long-term follow-up is required (such as lung cancer diagnoses) or where there are significant

comorbidities resulting in considerable patient heterogeneity (such as COPD), it can be difficult to conduct a traditional RCT. Under these conditions, an RCT would need enroll a substantial number of patients and have an extensive follow-up period. At the other end of the spectrum, restrictive inclusion or exclusion criteria in a trial can easily remove all external validity from the trial results (220), often at a significant cost (both financial and in terms of resources). The STATCOPE trial provides an excellent example[27] of trial evidence that may not offer the type of real-world evidence required to inform clinical decisions. While the results might be internally valid, the inclusion/exclusion criteria resulted in non-generalizable conclusions about all COPD patients. In the trial, statin therapy was evaluated in COPD patients to validate previous observational evidence that suggested statins reduced acute exacerbations (61,122). Despite this observational evidence, the trial found no benefit from statin therapy in COPD patients, but these results were met with objections of how the study was designed, specifically in terms of the inclusion and exclusion criteria (62,63,139). As stated in Section 7.1 above, by excluding patients with comorbidities, it is likely that the STATCOPE trial excluded those patients with elevated levels of systemic inflammation, and thus, we would not expect that the patients included in the STATCOPE trial would benefit, in terms of COPD-related outcomes, from statin therapy. In reality, the usefulness of the STATCOPE trial may be that it identified those patients that may not benefit from statin therapy, as opposed to

[27] There are many examples of RCTs that have overly restrictive inclusion or exclusion criteria such that patients included in the trial are not indicative of the overall patient population, thus rendering results not generalizable. For example, a study conducted by Travers *et al.* (215) of asthma patients suggested that the vast majority (>90%) of asthma patients would not be have met the criteria to be selected for recently completed trials.

determining the effectiveness of statin therapy in a specific subset of COPD patients who may be at-risk for poor health outcomes due to increased levels of systemic inflammation. The scarcity of available funding for health research means that decisions to conduct such trials should be scrutinized, particularly when the analysis of observational data (population-based data) might be able to produce similar results with a much lower cost and resource burden.

As such, further research to develop approaches to clinical trials that would generate tangible real-world evidence (i.e. pragmatic trials) that can inform treatment decisions would be a valuable endeavour. There is also a need to ensure that observational studies are well-designed to mitigate the potential impact of bias and confounding. Certainly, there has been a move toward using this type of evidence more prominently in the context of regulatory decision-making (221). For example, the United States Food and Drug Administration has a produced a document, in the context of medical devices where conventional randomized controlled trials are difficult to conduct, to describe situations where real-world evidence may be used for regulatory approval (221). Similarly, observational research using administrative data could benefit from improved data collection and the ability to link this data to clinical data that could mitigate potential biases and generate better evidence to inform decisions.

The methodological contributions of this dissertation are the following: (i) the use of an extensive catalogue of exposure metrics; (ii) the use of a recency-weighted approach that has not previously been used in the analysis of cancer diagnosis; (iii) the incorporation of a

latency period in the primary analysis coupled with the recency-weighted exposure metrics, and (iv) the use of a negative control exposure. The use of a variety of exposure metrics allowed for the possibility of evaluating whether or not results differed by the way medication exposure was quantified and subsequently incorporated into regression analyses. The use of several measures also allowed for evaluating whether results were robust across each of these exposure metrics. Limiting the analysis to just one of these metrics of defining exposure may have led to false conclusions. Therefore, I believe it may be important for studies to incorporate several different exposure metrics based on the existing clinical literature and biological plausibility to ensure the robustness of their results[28]. These metrics can then be evaluated according to an *a priori* defined criterion to determine which best suits the study data.

Second, the use of the recency-weighted approach in determining the association between medication exposure and lung cancer risk has not been used previously, to my knowledge. This method is very intuitive, particularly for studies with long follow-up time, and could likely be used for any non-acute event. The theory behind using this method is that medication exposures distal to the outcome should be considered differently than exposures more proximal to the outcome (96). I estimated models using this approach in two ways: recency-weighted duration of use, and recency-weighted cumulative dose. The recency-weighted approach resulted in superior model fit in both Chapters 5 and 6. The

[28] This includes the use of time-dependent covariates where applicable to reduce the possibility of bias (i.e. immortal time bias). In Section 5.4 I exhibited the potential impact that this bias could have on the study results.

choice of exposure metric(s) should reflect the nature of the relationship between the exposure and the outcome, where possible incorporating previous knowledge of this relationship from published literature, clinical expertise, and biological plausibility. In the absence of a solid understanding of the relationship between the exposure and outcome, the best approach is to use a variety of exposure metrics to explore which might best fit the data.

The application of a latency period in the analysis with lung cancer as the study outcome is a significant contribution, as it was not incorporated in the primary analysis of either observational study evaluating ICS use and lung cancer risk. By not incorporating a latency period, ICS exposure which occurred close to the outcome or end of follow-up, would be misclassified as exposed time when it is likely the pathogenesis of lung cancer had already begun. Misclassification of exposure during this time might result in a bias toward a null effect or protopathic bias, whereby those at early stages of lung cancer development are prescribed more medication (an ICS or a statin, or both). As stated, previous studies did not include such a period, which is a significant limitation which was improved upon by the work contained in this thesis. One caveat to inclusion of the latency period is that the exact onset of lung cancer prior to actual diagnosis is not known, thus making the choice of appropriate latency period difficult. In my analysis, the length of the latency period was assumed, based on work by Henschke *et al.* (171) and Chaturvedi *et al.* (40), and was subjected to several sensitivity analyses. The use of the latency period had significant effects on the association between both ICS and statin therapy and lung cancer risk in COPD patients. In Chapters 5 and 6, several sensitivity analyses were conducted to explore the

impact of the assumed latency period on the association between lung cancer risk and ICS or statin exposure. Removal of the latency period resulted in statin and ICS exposure increasing the risk of lung cancer. However, given that it is well-understood that carcinogenesis will have begun prior to lung cancer diagnosis, this result may be an example of protopathic bias. As the latency period was increased, from six months to two years, the protective effect of statins and ICS increased and became statistically significant (see Tables 5.7 and 6.7).

Finally, the use of a negative control exposure provides another example of an epidemiologic analysis to evaluate the effect of unmeasured or unknown confounding or bias. Lipsitch *et al.* (200) argued that this approach should be widely adopted in epidemiology to minimize the chance of spurious results. While not prolifically used in epidemiologic analyses, the method of using negative control exposures is reasonably intuitive, and is akin to using a placebo treatment in a randomized trial (187, 188). The use of a negative control exposure to detect whether or not the results found in Chapters 5 and 6 were due an inherent bias, increases one's confidence that the observed reduction in lung cancer risk is can be correctly attributed to the medication exposure.

7.3 Limitations of this research

The main limitation of this research is the absence of clinical variables in the cohort of COPD patients. Patients with COPD were identified according to their individual

prescription records. Ideally, data would be available that would include patients' level of airflow obstruction and levels of inflammation (systemic and local). Patients with COPD are a heterogeneous group of patients; therefore, in the absence of clinical data that might be included to adjust for confounding, I have used the health services usage, obtained from the linked administrative data (other prescriptions filled, physician encounters, and hospitalizations), to attempt to adjust for the heterogeneity (and the presence of comorbidities) in these patients.

While it would be ideal to have physician-diagnosed COPD via spirometry, the cohort definition employed in this dissertation used has been used previously (144,160). Moreover, the primary concern of this study was not to identify a cohort of COPD patients, but rather to identify a cohort of patients who were at an increased risk of lung cancer, and determine the association with medication exposure and lung cancer risk. Thus, I acknowledge that I cannot be certain that patients who satisfied the cohort definition did indeed have COPD; however, it is likely, due to the receipt of the prescriptions used to identify the patients to be included in the cohort, that each patient does have some degree of obstructive respiratory disease. This inclusion of patients without COPD would also likely result in a conservative bias. That is, if COPD patients are at an increased risk of lung cancer, and might benefit from statins or an ICS, inclusion of patients at lower risk for lung cancer and also less severe COPD, that did not use these medications and did not develop lung cancer, would likely bias results toward the null, showing no benefit from exposure to an ICS or statins.

In addition to the absence of clinical data for COPD diagnosis, smoking status and smoking history were not available within the linked administrative data used in this thesis. I acknowledge this as a limitation given the role that smoking has in both COPD and lung cancer. The literature in this area suggests that approximately 85% of COPD patients have a history of smoking (103). Moreover, the data would likely only be improved if they included very high quality and timely data with regard to smoking behaviour to truly capture the heterogeneity of smokers, which is seldom available. While this is a definite limitation, levels of systemic inflammation have been reported to be higher in COPD patients that continue to smoke, compared both to former smokers, and never smokers (222). Therefore, it might be that the identification of these COPD patients might represent a group that had greatest risk of lung cancer and could the most benefit from statin or ICS therapy. Therefore, the inclusion of never-smokers and former smokers, both who would likely have lower levels of systemic inflammation and lower lung cancer risk, might result in a conservative bias.

7.4 Future direction of research

This dissertation has shown that ICS and statins are both associated with a reduction in lung cancer risk in COPD patients. To do this, a population-based, longitudinal, retrospective design was used. These results were robust across a variety of metrics to define exposure status for both medications, and also stable over several sensitivity analyses performed. There are several avenues that I have identified for future research.

The most obvious would be to conduct a prospective study that evaluates statin and ICS use and lung cancer risk. However, as noted above, lung cancer is a rare outcome, even among COPD patients. As such, a prospective study would need a very large number of participants, and these participants would need to be followed over an extended period of time, which is unlikely to be feasible. Therefore, I would argue that the work contained in this dissertation should provide an impetus for more well-designed observational studies to generate evidence where RCTs are problematic or simply not feasible.

The weighting function that was chosen based on previous literature and on the assumption that prescriptions received by an individual patient nearer the study outcome should be weighted more heavily than those received earlier in follow-up time (96). However, the effect of these medications in the early phases of lung tumor carcinogenesis is not well-understood and future research to better understand medication exposure during the induction period of lung cancer could be extremely valuable. Similarly, more research to provide a better clinical and/or biological understanding of the duration of the induction and latency periods would be a significant contribution of future research in lung cancer.

The rationale behind much of the work presented in this dissertation is that local and systemic inflammation is associated with poor health outcomes – specifically mortality and lung cancer diagnosis. Therefore, a future study that could evaluate the use of ICS and statins while adjusting for measured levels of inflammation would be of interest. Moreover, a better understanding of the link between local and systemic inflammation might improve

the ability to stratify patients according to which patients would benefit the most from statin and ICS therapy.

7.5 Knowledge translation

This dissertation adds to the knowledge base about methods of quantifying exposure in in pharmacoepidemiolgic studies, specifically using administrative data in the context of chronic diseases. The results of this work also support the hypothesis that systemic inflammation is the responsible causal mechanism between COPD and lung cancer incidence, and also the role of ICS and statins to reduce systemic inflammation. These findings of this dissertation should have implications for the management of COPD patients, both in terms of better understanding different phenotypes of the disease and, potentially, treatment for patients. This could further have implications for improving the methods of understanding different manifestations or phenotypes COPD, specifically in terms of a phenotype characterised by the presence of elevated levels of systemic inflammation, and bolster the case for ICS and statins to be prescribed for patients that match the phenotype of those who might derive the most clinical benefit.

The results of individual chapters of this dissertation will be submitted to peer reviewed journals to be published in order to studied by researchers and clinicians. Moreover, results have been and will continue to be presented at research conferences worldwide in hopes of disseminating the knowledge gained through this research as widely as possible.

7.6 Conclusions

The analyses contained within this dissertation represent important contributions to the field of pharmacoepidemiology and respiratory disease. The use of an extensive array of exposure definitions, including a recency-weighted approach, the incorporation of a latency period, and the use of a negative control exposure, are important contributions to the methodological literature. The results of this dissertation also have important implications for the management of patients with COPD, a disease that is associated with considerable morbidity and mortality. Moreover, the findings support the hypothesis that systemic inflammation may be the cause of poor health outcomes in COPD patients, and that a phenotype of COPD, characterized by systemic inflammation, may exist. Future research to better understand this link and to possibly stratify patients according to levels of inflammation may offer specific treatment options for these patients. Certainly, the results will also raise the question of whether or not a trial is warranted to evaluate the effect of inhaled corticosteroids and statins on lung cancer risk. Although, as suggested above, such a trial would be resource-intensive, and would need to be designed very carefully in order for the results to generate answers to the relevant clinical questions. As such, the body of work contained in this dissertation highlights the importance of well-designed observational studies to provide real-world evidence to inform treatment decisions.

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Appendices

Appendix A Primary search strategy

Search Strategy:

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1 Bronchitis, Chronic/
2 bronchitis, chronic.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
3 (chronic adj3 bronchitis).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
4 or/1-3
5 bronchitis.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
6 bronchitis/ or bronchiolitis/
7 bronchitides.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
8 bronchiolitides.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
9 Lung Diseases, Obstructive/
10 (obstructive adj4 lung disease?).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
11 (obstructive adj3 pulmonary disease?).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
12 or/9-11
13 Lung Diseases/
14 ((pulmonary or lung) adj3 disease?).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
15 disease, lung.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
16 diseases, lung.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
17 lung disease.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
18 pulmonary disease.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

19 disease, pulmonary.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
20 diseases, pulmonary.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
21 pulmonary diseases.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
22 or/13-21
23 Airway Obstruction/
24 (airway adj3 obstruction?).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
25 23 or 24
26 Respiratory Tract Diseases/
27 (respiratory tract adj3 disease$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
28 26 or 27
29 Cough/
30 26 or 27
31 cough$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
32 29 or 31
33 Bronchial Diseases/
34 (bronchial adj3 disease$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
35 33 or 34
36 Dyspnea/
37 dyspnea$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
38 (breath adj2 shortness$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
39 or/36-38
40 Pulmonary Disease, Chronic Obstructive/
41 (pulmonary disease? adj3 chronic obstructive).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
42 copd.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
43 coad.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
44 (chronic obstructi$ adj3 airway).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

45 chronic obstructive lung disease$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
46 or/40-45
47 Pulmonary Emphysema/
48 Emphysema/
49 emphysema.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
50 or/47-49
51 or/1-39
52 Lung Neoplasms/
53 exp Lung Neoplasms/
54 Carcinoma, Bronchogenic/
55 Carcinoma, Non-Small-Cell Lung/
56 Small Cell Lung Carcinoma/
57 Adenocarcinoma/
58 Carcinoma, Squamous Cell/
59 Carcinoma, Large Cell/
60 Adenocarcinoma, Bronchiolo-Alveolar/
61 Carcinoma, Small Cell/
62 Multiple Pulmonary Nodules/
63 Pancoast Syndrome/
64 Pulmonary Blastoma/
65 Solitary Pulmonary Nodule/
66 (lung adj3 (cancer?or neoplasm? or carcinoma?)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
67 57 or 58 or 54 or 63 or 61 or 62 or 64 or 52 or 60 or 55 or 56 or 59 or 65
68 or/52-66
69 2 or 1 or 3
70 Bronchitis/
71 70 or 5 or 7
72 Bronchiolitis/
73 bronchiolitis.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
74 72 or 73 or 8
75 10 or 9 or 11
76 14 or 13
77 24 or 23
78 26 or 27
79 31 or 29

80 34 or 33
81 36 or 38 or 37
82 43 or 44 or 42 or 45 or 40 or 41
83 Glucocorticoids/
84 glucocorticoid?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
85 corticosteroid$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
86 glucocorticoid$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
87 Administration, Inhalation/
88 86 or 83 or 85
89 "Nebulizers and Vaporizers"/
90 Inhalation Spacers/
91 Metered Dose Inhalers/
92 Aerosols/
93 or/87,89-92
94 88 and 93
95 88
96 Beclomethasone/
97 BECLOMETHASONE.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
98 Betamethasone/
99 BETAMETHASONE.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
100 Budesonide/
101 BUDESONIDE.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
102 Clobetasol/
103 CLOBETASOL.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
104 Dexamethasone/
105 DEXAMETHASONE.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
106 Dexamethasone Isonicotinate/
107 DEXAMETHASONE ISONICOTINATE.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
108 Fluprednisolone/

109 FLUPREDNISOLONE.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
110 Melengestrol Acetate/
111 MELENGESTROL ACETATE.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
112 Methylprednisolone/
113 METHYLPREDNISOLONE.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
114 Triamcinolone/
115 TRIAMCINOLONE.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
116 or/96-115
117 67 and 82 and 116
118 67 and 82 and 95
119 67 and 82 and 88
120 67 and 82 and 94
121 pulmonary emphysema$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
122 47 or 48 or 121 or 49
123 69 or 122 or 82
124 69 or 75 or 122 or 82
125 123 and 67 and 116
126 67 and 124 and 116
127 123 and 67 and 95
128 67 and 95 and 124
129 Chemoprevention/
130 chemoprevention.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
131 chemoprophylaxis.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
132 or/129-131
133 67 and 132
134 123 and 67 and 132
135 132 and 116
136 132 and 95
137 volon.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
138 aristocort.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

139 metipred.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
140 6-methylprednisolone.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
141 6 methylprednisolone.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
142 urbason.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
143 medrol.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
144 acetate, melengestrol.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
145 melengestrol.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
146 isonicotinate, dexamethasone.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
147 he-111.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
148 he 111.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
149 he111.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
150 auxison.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
151 pulmicort.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
152 budesonide, s-isomer.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
153 budesonide, r-isomer.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
154 horacort.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
155 rhinocort.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
156 flubenisolone.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
157 betadexamethasone.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

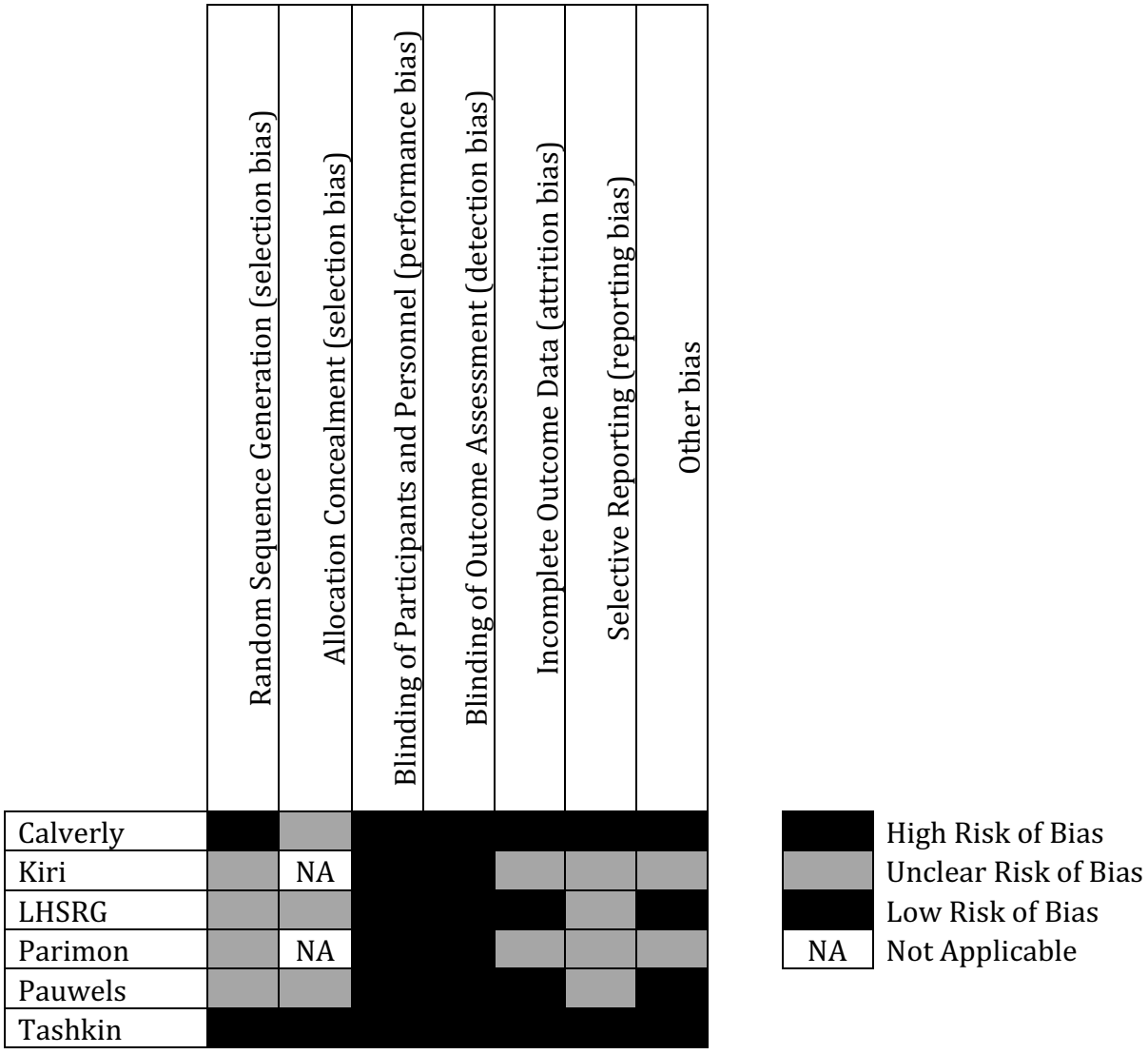
158 cellestoderm.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
159 celestone.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
160 celeston.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
161 celestona.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
162 clofenazon.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
163 clobetasol propionate.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
164 clobetasol 17-propionate.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
165 clobetasol 17 propionate.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
166 clobex.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
167 cormax.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
168 olux.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
169 dermovate.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
170 embeline.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
171 embeline e.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
172 temovate.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
173 or/137-172
174 173 or 116
175 123 and 67 and 174
176 67 and 174 and 124
177 67 and 82 and 174
178 132 and 174
179 fluticasone.mp.
180 Flunisolide.mp.
181 179 or 180

182 181 or 174
183 182 and 123 and 67
184 182 and 67 and 124
185 182 and 67 and 82
186 ((pulmonary or panacinar or panlobular or centriacinar or centrilobular or focal) adj3 emphysema?).tw.
187 186 or 122
188 limit 133 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or controlled clinical trial or randomized controlled trial)
189 Randomized Controlled Trial/
190 Randomized Controlled Trials as Topic/
191 Random Allocation/
192 Double-Blind Method/
193 single-blind method/
194 clinical trial/
195 exp Clinical Trials as Topic/
196 or/189-195
197 (clinic$ adj trial$1).tw.
198 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
199 Placebos/
200 Placebo$.tw.
201 Randomly allocated.tw.
202 (allocated adj2 random).tw.
203 or/197-202
204 196 or 203
205 Case report.tw.
206 case reports/
207 letter/
208 historical article/
209 Review of reported cases.pt.
210 Review, multicase.pt.
211 or/205-210
212 204 not 211
213 epidemiologic studies/
214 exp case control studies/
215 exp cohort studies/
216 Case control.tw.
217 (cohort adj (study or studies)).tw.

218 Cohort analy$.tw.
219 (Follow up adj (study or studies)).tw.
220 (observational adj (study or studies)).tw.
221 Longitudinal.tw.
222 Retrospective.tw.
223 Cross sectional.tw.
224 Cross-Sectional Studies/
225 or/213-224
226 133 and 204
227 133 and 212
228 133 and 225

Appendix B Risk of bias assessment

Sub-appendix: B1 Summary table



Sub-appendix: B2 Detail table of bias assessment (randomized controlled trial studies and observational studies) (114)

	Random Sequence Generation (selection bias)	**Allocation Concealment** (selection bias)	**Blinding of Participants and Personnel** (performance bias)	**Blinding of Outcome Assessment** (detection bias)	**Incomplete Outcome Data** (attrition bias)	**Selective Reporting** (reporting bias)
Calverley (2007)	**Low Risk** As stated in protocol, treatment assignment generated via computer program	**Unclear** As stated in the Methods of this study, patients were randomly assigned, in permuted blocks	**Low Risk** Double-blind study; outcome (vital status) was objective	**Low Risk** Double-blind study; independent committee, whose members were unaware of treatment assignments, determined primary cause-of-death and whether death was attributable to COPD	**Low Risk** Slightly more discontinuations in placebo group during the original study, but vital status at 3 years was known for all but one participant	**Low Risk** Primary outcome matches that listed on clinicaltrials.gov listing and study protocol
Kiri (2009)	**Unclear** Not applicable – non-randomized study	**Not Applicable** Not applicable – non-randomized study	**Low Risk** Observational retrospective study using administrative data: participants were aware of their treatment, but were unaware of the study	**Low Risk** Observational retrospective study using administrative data: lung cancer diagnoses were made during routine care by individuals unaware of the study	**Unclear** Duration of treatment the same for cases and controls, but data were collected retrospectively	**Unclear** No protocol available

Sub-appendix: B2 Detail table of bias assessment (randomized controlled trial studies and observational studies) (114) *(….continued*)

	Random Sequence Generation (selection bias)	**Allocation Concealment** (selection bias)	**Blinding of Participants and Personnel** (performance bias)	**Blinding of Outcome Assessment** (detection bias)	**Incomplete Outcome Data** (attrition bias)	**Selective Reporting** (reporting bias)
Lung Health Study Research Group (2000)	**Unclear** Text only states that participants were "randomly assigned"	**Unclear** Only reports that participants were "randomly assigned"	**Low Risk** Participants and clinical centre staff were unaware of the study-drug assignments	**Low Risk** Participants and clinical centre staff were unaware of the study-drug assignments	**Low Risk** Overall 91% of PFTs and 95% of questionnaires were completed, similar rates of satisfactory adherence in treatment and placebo group, slightly more discontinuations in placebo group (38 vs. 28)	**Unclear** No protocol available
Parimon (2007)	**Unclear** Not applicable – non-randomized study	**Not Applicable** Not applicable – non-randomized study	**Low Risk** Observational retrospective study of administrative data; participants were aware of their treatment, but unaware of the study objective	**Low Risk** Observational retrospective study of administrative data: lung cancer diagnoses were made during routine care	**Unclear** Unlikely to be a problem since exposure and outcome data were obtained from administrative databases, but didn't stratify median follow-up time by exposure or outcome	**Unclear** No protocol available

Sub-appendix: B2 Detail table of bias assessment (randomized controlled trial studies and observational studies) (114) *(….continued*)						
	Random Sequence Generation (selection bias)	**Allocation Concealment** (selection bias)	**Blinding of Participants and Personnel** (performance bias)	**Blinding of Outcome Assessment** (detection bias)	**Incomplete Outcome Data** (attrition bias)	**Selective Reporting** (reporting bias)
Pauwels (1999)	**Unclear** Reports that subjects were "randomly assigned"	**Unclear** Reports that subjects were "randomly assigned"	**Low Risk** Double-blind study; subjects in placebo group used a dry-powder inhaler	**Low Risk** Double-blind study; primary outcome (change in FEV_1) was measured objectively through spirometry	**Low Risk** 71% remained in the study for the whole 3 years, similar withdrawal rates and reasons for withdrawal in treatment and control group (though reasons not broken down by study arm)	**Unclear** No protocol available
Tashkin (2008) (32)	**Low Risk** Computer-generated randomization scheme was used at each site	**Low Risk** Computer-generated randomization scheme was used at each site	**Low Risk** Double-blind study; all participants received both types of inhalers containing either active treatment, placebo, or combinations	**Low Risk** Double-blind study; primary outcome (FEV1) was measured objectively through spirometry	**Low Risk** Discontinuation rates were lower in the combination therapy groups, but rates in placebo and monotherapy groups were similar	**Low Risk** Co-primary efficacy variables match those listed on clinicaltrials.gov listing

Appendix C Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Checklist

TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title, Pgs 1,2,6
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Not applicable in the context of a PhD thesis
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Pgs 47-48
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Pg 48
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not available
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Pgs 50-52
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Pg 50
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix A
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Pgs 50-52
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Pgs 52,53
Data items	11	List and define all variables for which data were sought (PICOS, funding sources) and any assumptions and simplifications made.	Pgs 52,53
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Pgs 56,59,67
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Pg 52 (Tables 3.3,3.4)
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Not applicable

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Checklist (…*continued*)			
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Pgs 56,59,67
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not applicable
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Pg 56; Figure 3.1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Tables 3.1,3.2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Pg 56
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Pgs 57-65; Tables 3.3,3.4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not applicable
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Pgs 67-69
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Pgs 67-70
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Pg 71
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Pg 73
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Not applicable; no funding for this study