Economic evaluation of treating chronic obstructive pulmonary disease: The effects of early initiation of inhaled corticosteroids on exacerbation risks, utilization and costs

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ABSTRACT

Manabu Akazawa:
Economic evaluation of treating chronic obstructive pulmonary disease: The effects of early initiation of inhaled corticosteroids on exacerbation risks, utilization and costs
(Under the direction of Andrea K. Biddle)

Chronic obstructive pulmonary disease (COPD) is a slowly progressive disease of airway obstruction. Current treatment guidelines recommend a stepwise increase in drug treatment depending on disease severity. Inhaled corticosteroids (ICS) should augment regular bronchodilators for patients with advanced disease and repeated exacerbations.

This dissertation examined the timing and impact of ICS on exacerbation risks, utilization and costs among COPD patients in a large managed care database. A propensity-score-matching approach was used to compare patients who initiated ICS within three months of beginning bronchodilators with those who initiated ICS thereafter. A fixed-effects model approach was used to assess benefits of ICS augmenting regular bronchodilators. Medication persistence and adherence were used to measure ICS exposure level and its association with treatment outcomes.

Early initiation of ICS was associated with a 7%-reduction in exacerbation risks, an 8%-reduction in all-cause medical costs, and a 23%-reduction in COPD-related medical costs. Reduction in medical costs was more than the increase in pharmacy costs indicating early ICS initiation achieved an overall cost reduction. The potential benefit of ICS also depended on the timing of therapy initiation. A six-month delay in ICS initiation was, on average, associated with cost increase of $306 overall or $51 per month for COPD-related services. The magnitude of cost reduction varied by age, and the oldest population had

largest benefits. Access to specialist care and patient understanding of disease and treatment may be key factors to improving medication persistence and adherence. Patients with better persistence and adherence may have lower risks of inpatient admissions or emergency department visits, and treatment costs. However, observed associations were relatively small and inconsistent across various exposure and outcome measures.

In conclusion, the findings consistently support that early ICS initiation, concomitant with bronchodilators rather than in response to exacerbations uncontrolled by bronchodilators, is an important treatment strategy to achieve better symptom control and reduce overall treatment costs. Additional studies are required to address potential time-variant confounders, estimate longer-term outcomes and examine ICS effects among Medicare beneficiaries and patients with severe COPD symptoms.

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Finally, I would like to thank my family, my wife Rie and my mother Kazuko, for their understanding, patience and support. I dedicate this dissertation to my father who, unfortunately, did not have a chance to share this wonderful moment.

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LIST OF ABBREVIATIONS

ATS	American Thoracic Society
BRN	Bronchodilator
CHF	Congestive Heart Failure
CI	Confidence Interval
CMA	Continuous Measure of Medication Acquisition
COPD	Chronic Obstructive Pulmonary Disease
CPT-4	Current Procedural Terminology, Version 4
CVD	Cardiovascular Disease
DX	Diagnosis
ED	Emergency Department
ERS	European Respiratory Society
FEV_1	Forced Expiratory Volume in One Second
FSC	Fluticasone Propionate / Salmeterol Combination
FVC	Forced Vital Capacity
GINA	Global Initiative for Asthma
GLM	Generalized Linear Model
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GPRD	General Practice Research Database
HCPCS	Healthcare Common Procedure Coding System
HIPAA	Health Insurance Portability and Accountability Act of 1996
HR	Hazard Ratio
HRQOL	Health-Related Quality of Life
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification

ICS	Inhaled Corticosteroids
IHCIS	Integrated Healthcare Information Services
IP	Inpatient Admissions
IPR	Ipratropium
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
LABA	Long-Acting β_2 Agonists
MCBS	Medicare Current Beneficiary Survey
MEPS	Medical Expenditure Panel Survey
MPR	Medication Possession Ratio
NSAID	Nonsteroidal Anti-Inflammatory Drug
NDC	National Drug Code
NHLBI	National Heart, Lung, and Blood Institute
NHIS	National Health Interview Survey
OCS	Oral Corticosteroids
OLS	Ordinary Least Square
PDC	Proportion of Days Covered
PSM	Propensity-Score-Matching
RBRVS	Resource-Based Relative Value Scale
RCT	Randomized Clinical Trial
RR	Relative Risk
RX	Prescription
SABA	Short-Acting β_2 Agonists
SAL	Salmeterol

CHAPTER 1

Introduction

1.1 Burden of COPD

Chronic obstructive pulmonary disease (COPD) is a slowly progressive, irreversible disease of the airways that is characterized by a gradual loss of lung function. The major symptoms of COPD are chronic cough, increased sputum production, shortness of breath, and limitation of physical activity (Man et al. 2003). The term COPD is used to describe lung diseases such as chronic bronchitis, emphysema, or combinations of these conditions. It is sometimes difficult to differentiate between COPD and chronic severe asthma. COPD is often associated with exacerbations, which are acute worsening of respiratory symptoms. Many exacerbations are caused by respiratory tract infections or an increase in air pollution. The cause of one-third of severe exacerbations, however, cannot be identified (Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2006).

The diagnosis of COPD is confirmed by a presence of clinical symptoms and by a history of exposure to risk factors, especially cigarette smoking and age. The disease should be confirmed by the presence of airway obstruction on testing with spirometry (GOLD 2006). Pulmonary function tests are used for confirmation of diagnosis, staging, and predicting prognosis in patients with COPD. Standard tests measure total lung capacity and residual volume. Specifically, forced expiratory volume in one second (FEV_1), forced vital capacity (FVC, or the total volume exhaled), and the ratio of FEV_1 to FVC are useful in the assessment of COPD patients.

COPD also is known to be associated with significant systemic effects such as weight loss, cardiovascular disease, depression, and osteoporosis, which contribute to the overall burden of this disease (Agusti 2005). COPD incidence increases with age, with the average age of onset older than 50 years. The major risk factor for the development of COPD is cigarette smoking. By sharing common risk factors, patients with COPD have higher prevalence of chronic conditions, such as cardiovascular disease, associated with aging and smoking (Rennard 2005). Using data from the US Veterans Administration Medical System, Mapel et al. (2005) reported that veterans hospitalized for COPD had a higher prevalence of coronary artery disease, cognitive heart failure, and atrial fibrillation compared with age-matched veterans who were hospitalized for non-COPD causes. In the same study, the rate of COPD hospitalizations showed a large seasonal variation mainly due to respiratory tract infections in winter months. Similarly, Huiart et al. (2005) found that COPD patients had higher cardiovascular morbidity and mortality rates than the general population using data from the Saskatchewan administrative database. In this study, cardiovascular hospitalization and death rates among the COPD patients also varied by gender and age group. In addition, Norwood and Balkissoon (2005) and Eiser et al. (2005) reported that problems with anxiety and depression were very frequent among patients with COPD.

COPD is the fourth leading cause of death (following heart disease, cancer, and stroke), and the only major cause of mortality whose incidence has grown over the previous 40 years in the United States (National Heart, Lung, and Blood Institute [NHLBI] 2004, Chapman et al. 2006). According to the National Health Interview Survey (NHIS) in 2000, the estimated annual prevalence of COPD among adults aged 25 years or older was 6%, or about 10.5 million Americans (Mannino et al. 2002). Nearly 726,000 hospitalizations (from the National Hospital Discharge Survey in 2000) and 119,000 deaths (from the National Vital Statistics in 2000) were attributed to COPD (Mannino et al. 2002). The total estimated cost

of COPD in 2004 was $37.2 billion, which included $20.9 billion in direct costs and $16.3 billion in indirect costs (NHLBI 2004).

Several researchers have estimated the burden of COPD using state and national databases. Using data from Medicaid in California and in Florida, COPD patients used approximately $5,200 to $6,500 more medical costs per patient compared with non-COPD patients in 2001; however, only about half of these costs were attributable to COPD (Marton et al. 2005). According to their estimates, cardiovascular disease, stroke, cancer, and asthma accounted for 43% to 47% of the excess costs. An analysis of the 2000 Medical Expenditure Panel Survey (MEPS) showed COPD subjects used $4,900 more per patient compared with non-COPD patients after adjusting for age, sex, race, smoking, marital status, and education (Miller et al. 2005). They also estimated that only 50% was directly attributable to the treatment of COPD. In addition, healthcare utilization patterns among COPD patients were analyzed in a case-control study using a health maintenance organization database (Mapel et al. 2000). COPD patients used more inpatient, outpatient, and pharmacy services not only for respiratory-related conditions but also for cardiovascular conditions, mental disorders, and other chronic conditions. These findings indicate that the burden of COPD is most appropriately analyzed using not only disease-specific information but also all-cause utilization and costs.

1.2 Treatment Guidelines

At present there is no known cure for COPD. The medications currently available are used to prevent and control symptoms as well as to decrease the frequency and severity of exacerbations. Because COPD is a progressive disease, a stepwise increase in treatment depending on severity of the disease is recommended by the Global Initiative for Chronic Obstructive Lung Disease [GOLD] (Figure 1.1) and by the American Thoracic Society [ATS] and the European Respiratory Society [ERS] (Figure 1.2).

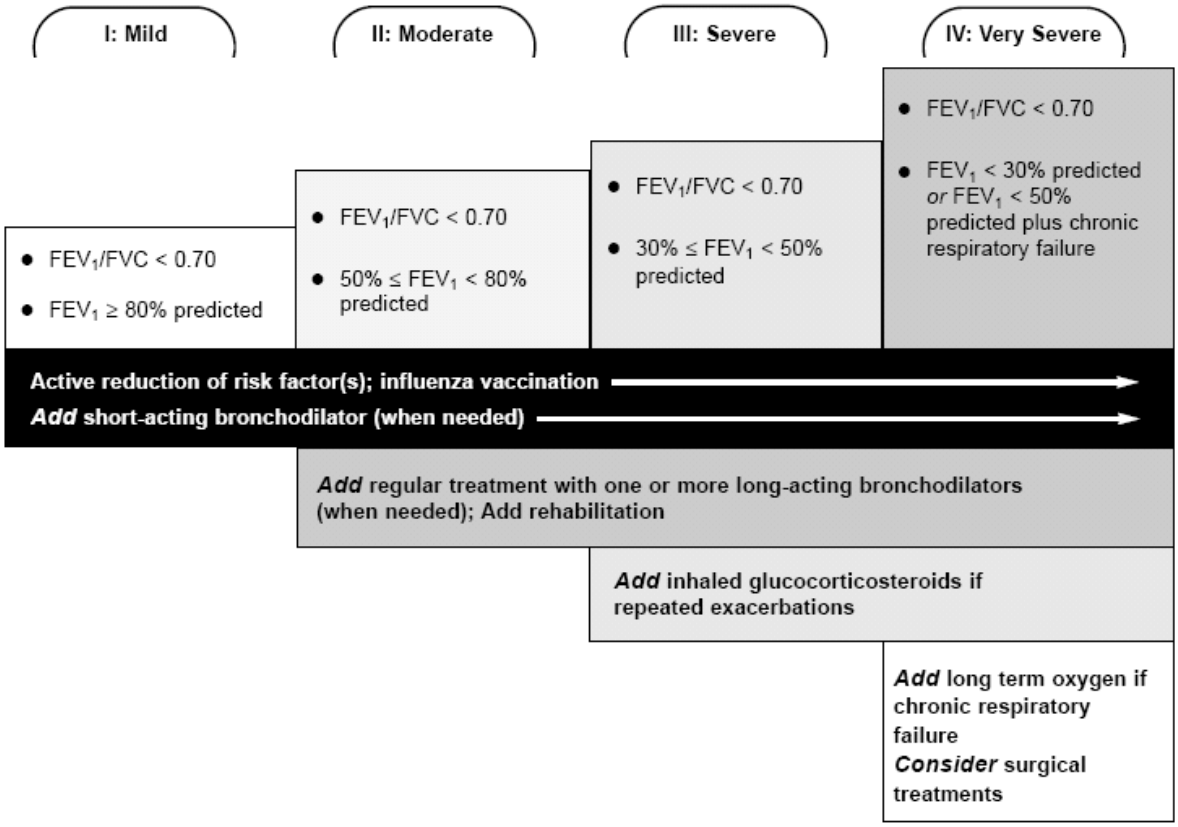


Figure 1.1: Therapy at each stage of COPD.

Post-bronchodilator FEV_1 is recommended for the diagnosis and assessment of severity of COPD. FEV_1: forced expiratory volume in one second, FVC: forced vital capacity,

Source: GOLD (Global Initiative for Chronic Obstructive Lung Disease). Global Strategy for the Diagnosis, Management, and Prevention of COPD: Published November 2006; [Internet]. Available at: http://www.goldcopd.org. Copyright 2006. Reprinted with permission from GOLD.

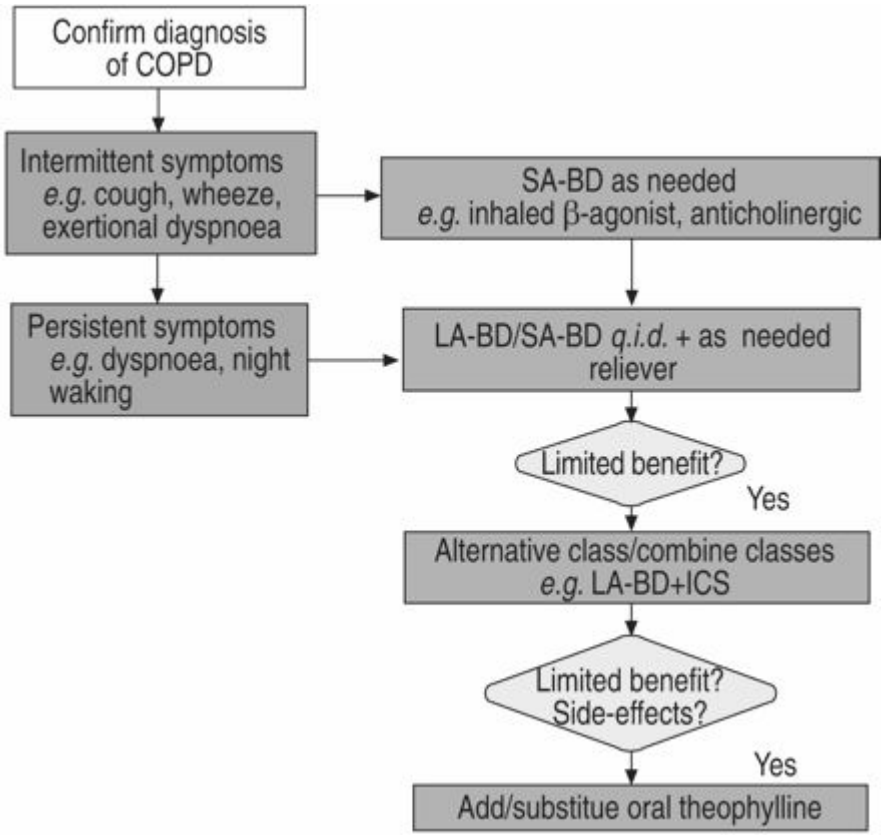


Figure 1.2: Algorithm for pharmacological treatment of COPD.

SA-BD: short-acting bronchodilator; LA-BD: long-acting bronchodilator; ICS: inhaled corticosteroids. Assess effectiveness by treatment response criteria. If forced expiratory volume <50% predicted and exacerbations of COPD requiring a course of oral corticosteroid or antibiotic occurred at least once within the last year, consider adding regular ICS. Always ensure the patient can use an inhaled device effectively and understands its purpose. If an ICS and a long-acting β_2-agonist are used, prescribe a combination inhaler.

Source: Celli BR, MacNee W, American Thoracic Society (ATS) / European Respiratory Society (ERS) Task Force. Standards for the diagnosis and treatment of patients with COPD: A summary of the ATS/ERS position paper. Eur Respir J 2004;23(6):932-946. Copyright 2004. Reprinted with permission from ERS Journals Ltd.

According to the treatment guidelines, for patients with mild conditions, short-acting inhaled therapy as needed is sufficient. For patients who are not adequately controlled with the short-acting inhaled therapy (i.e., short-acting bronchodilators), adding regular use of bronchodilators (such as anticholinergics) is recommended. Combination therapy with medications that have different mechanisms and durations of action also is used to improve

symptom control and to reduce side effects. Finally, regular treatment with inhaled corticosteroids (ICS) should be added to regular bronchodilator treatment for patients with advanced disease (usually classified as FEV_1 < 50% predicted) and repeated exacerbations.

Bronchodilators are commonly used in COPD to provide symptomatic relief. Inhaled formulations are usually preferred (Croxton et al. 2003). Anticholinergics (e.g., ipratropium), short-acting β_2 agonists (e.g., salbutamol), long-acting β_2 agonists (e.g., salmeterol and formoterol), or a combination of these drug classes appear to increase lung function (FEV_1), decrease frequency of exacerbations, and improve quality of life. Theophylline (sustained release oral formulation) is also effective in COPD, but due to its potential toxicity, inhaled bronchodilators are recommended when available.

Antibiotics are often used for exacerbations of COPD because of an association of bacterial infection with exacerbations (Buhl and Farmer 2005). Clinical studies indicate that antibiotic treatments are useful for patients with exacerbations of COPD with symptoms of dyspnea, sputum volume or sputum purulence (GOLD 2006). Amoxicillin, sulfa drugs, cephalosporins, quinolones, tetracylines, and macrolides are the most commonly used antibiotics for COPD (Sin and Tu 2001, Fan et al. 2003).

Oral and inhaled corticosteroids are used as anti-inflammatory agents in COPD (Buhl and Farmer 2005). Due to potential side-effects, oral formulations are used in a short course, especially during an acute exacerbation. Inhaled corticosteroids (ICS), on the other hand, are recommended for regular use in severe patients. Although the benefits of ICS are well established in persistent asthma (Global Initiative for Asthma [GINA 2006]), the role of ICS in patients with COPD is less well established. Recent randomized clinical trials have found that ICS treatment does not modify the decline in lung function and mortality associated with COPD; however, the results of these trials suggest that ICS may be useful to reduce the number of exacerbations, which are related to quality of life and to use of healthcare resources (Alsaeedi et al. 2002, Sin et al. 2003, Sin et al. 2005). The most recent

randomized clinical study showed the combination therapy of ICS and an inhaled bronchodilator reduced the risks of dying and moderate and severe exacerbations during the three-year follow-up (Calverley et al. 2007).

1.3 Purpose of this Dissertation

Since COPD is a progressive disease, the treatment guidelines recommend a stepwise increase in drug treatment depending on severity of the disease. In particular, regular treatment with ICS should be used to augment regular bronchodilator treatment for patients with advanced disease and repeated exacerbations. The long-term effectiveness and safety, as well as dose-response relationships, of inhaled corticosteroids (ICS) treatment in COPD are still unknown. On the other hand, there is evidence that ICS treatment reduces the number of exacerbations per year and the rate of deterioration in health status. Therefore, it is hypothesized that initiation of ICS treatment earlier than the recommended stepwise strategy could be beneficial not only to prevent acute exacerbations but also to reduce healthcare utilization and costs by improving the health conditions associated with COPD.

This dissertation examined the benefits of the earlier initiation of ICS treatment among moderate-to-severe COPD patients in terms of exacerbation risks, utilization, and costs using a large managed care claims database (1997-2005 Integrated Healthcare Information Services, IHCIS). Moderate-to-severe COPD patients were identified by the regular treatment with inhaled bronchodilators (anticholinergics or long-acting β_2 agonists). Multivariable regression techniques were used to estimate the effects of starting ICS treatment as well as the timing of ICS treatment. Also, ICS treatment level was measured by medication persistence and adherence to evaluate the relationship between exposure status and outcomes. Three specific research questions addressed in this dissertation and methods applied are explained briefly as follows:

Question 1: What is the potential benefit of ICS treatment started within three months of initiation of bronchodilators on exacerbation risks, resource utilization and treatment costs compared with ICS treatment started thereafter?

This analysis was conducted using propensity-score-matched samples to adjust for individual background characteristics available in the database such as demographics, comorbid conditions, and pre-term service utilization. Logistic and negative binomial regression models were used to compare the number of exacerbation events as well as other resource use (inpatient admissions, outpatient services and drug prescriptions) per follow-up person-year. A generalized linear model (GLM) with a gamma distribution and log link was used to estimate incremental costs between groups.

Question 2: What is the potential benefit of starting ICS treatment after initiation of bronchodilators on all-cause and COPD-related medical costs?

This analysis was conducted using fixed-effects regression methods for longitudinal or panel data to adjust for stable characteristics that are not measured in the claims database. Individual-level information on ICS exposure status, medical costs, use of rescue medications, and having asthma or congestive heart failure were summarized for monthly intervals from up to one-year before the initiation of bronchodilators ("index date") through a two-year follow-up period. An ordinary least square (OLS) regression model was used to estimate incremental effects of initiating ICS on medical costs adjusting for time-variant conditions. Interaction terms were included to evaluate the timing of ICS treatment as well as impact of patient age.

Question 3: What are the factors associated with better persistence and adherence to ICS treatment? Also, what is the impact of better medication persistence and adherence on medical utilization and costs?

Persistence was defined by the days between initiating and discontinuing ICS therapy. Adherence was measured by medication possession ratio using information describing refill patterns. Multivariable regression analyses were conducted to identify factors associated with better medication persistence and adherence. Inpatient admission or emergency department visit events as well as any and COPD-related costs during the second year were summarized by persistence and adherence during the first year. Multivariable regression models were used to adjust for demographics, comorbidities, and the first year utilization.

1.4 Structure of this Dissertation

A literature review of ICS treatment effects on mortality and morbidity as well as methodological issues assessing the drug treatment effects using administrative claims data is presented in Chapter 2. This review summarizes the current evidence on ICS treatment in COPD patients from both clinical and observational studies. It also summarizes the strengths, limitations and appropriate application of administrative claims databases in health outcome studies. These summaries provide background information to justify the dissertation questions and the approaches used to address these questions.

The conceptual framework and specific research questions and hypotheses are presented in Chapter 3. This chapter also describes the data source, definition of the study population, and measures commonly used in the dissertation. Chapters 4, 5, and 6 comprise individual journal manuscripts that address the three research questions. Because each manuscript will be submitted as an independent publication, each contains an introduction, appropriate literature review, methods, results, discussion, and conclusion. The final chapter briefly summarizes the findings, describes the limitations of the data and analytical approaches employed in this dissertation, and presents recommendations for future research.

CHAPTER 2

Literature Review

2.1 Treatment Effects of ICS on Mortality and Morbidity

Because airway inflammation is one aspect of COPD, anti-inflammatory agents such as inhaled corticosteroids (ICS) may slow the progression of disease and prevent exacerbations. However, unlike the use of ICS in the treatment of asthma conditions (GINA 2006), the evidence on the benefits of ICS is not consistent in COPD (Burney et al. 2003, Schmier et al. 2005).

A summary of clinical trials comparing ICS with placebo among COPD patients followed for at least six months is shown in Table 2.1. Bourbeau et al. (1998) conducted a randomized clinical trial (RCT) of inhaled budesonide (1,600μg/day) versus placebo among 79 COPD patients who were non-responders to oral corticosteroids and 40 years or older in Canada. The primary outcome measure was forced expiratory volume in one second (FEV_1), and secondary outcome measures were exercise capacity, dyspnea with exertion, quality of life, peak expiration flow rate, and respiratory symptoms. No differences were observed in changes in both primary and secondarily outcomes. Thus, they concluded ICS, even at high doses, had no physiological or functional benefits in patients with advanced COPD.

Paggiaro et al. (1998) conducted an RCT of inhaled fluticasone propionate (1,000μg/day) versus placebo among 281 COPD patients ages between 50 and 75 years in 13 European countries, New Zealand and South Africa. The main outcome measures were the number of patients who had at least one exacerbation by the end of treatment, the

number and severity of exacerbations, clinic lung function, diary card symptoms and peak expiratory flow and six minutes walking distance. Significant benefits of ICS treatment were observed in moderate or severe exacerbation risks, symptoms (as measured by diary card) and lung functions (as measured by clinic morning peak expiratory flows, clinic FEV_1, forced vital capacity, and mid-expiratory flow). Thus, they concluded ICS treatment may be of clinical benefit in patients with COPD over at least six months.

Weir et al. (1999) conducted an RCT of inhaled beclomethasone dipropionate (1,500 - 2,000μg/day) versus placebo among 98 patients with nonasthmatic COPD in the United Kingdom (UK). Treatment was given for two years to detect changes in lung function and symptoms. Decline in FEV_1 was observed in ICS group although the differences failed to reach statistical significance, except in patients with more severe airflow obstruction. ICS treated group also had fewer exacerbations per year (mean exacerbation rates per year, placebo 0.57 versus ICS 0.36). They concluded that although the absolute effects of ICS treatment seemed small, reducing the rate of decline in lung function should improve disability from this condition.

Vestbo et al. (1999) conducted an RCT of inhaled budesonide (800 -1,200μg/day) versus placebo among 290 patients with COPD in Denmark. Patients aged 30 to 70 years were followed for three years to investigate the efficacy on decline in lung function and respiratory symptoms. No effects of ICS were observed on either lung function or respiratory symptoms: 316 exacerbations occurred during the study period, 155 in the treatment group and 161 in the placebo group. Nine patients died during the study period, four in the treatment group and five in the placebo group. None of the deaths was caused by COPD and all were unrelated to treatment. Thus, they questioned the role of long-term ICS in the treatment of mild to moderate COPD.

Pauwels et al. (1999) conducted an RCT of inhaled budesonide (800μg/day) versus placebo among 1,277 patients with mild COPD who continued smoking in nine European

countries. Patients aged 30 to 65 years were followed for three years to investigate the efficacy on decline in lung function. During the first six months of the study, the FEV_1 improved at the rate of 17 ml per year in the treatment group, as compared with a decline of 81 ml per year in the placebo group. However, from nine months to the end of treatment, the FEV_1 declined at similar rates in the two groups. As a conclusion, in patients with mild COPD who continue smoking, the use of ICS is associated with a small one-time improvement in lung function but does not appreciably affect the long-term progressive decline.

Burge et al. (2000) conducted an RCT of inhaled fluticasone propionate (1,000µg/day) versus placebo among 751 patients with moderate to severe COPD in the United Kingdom (UK). Patients aged 40 to 75 years were followed for three years. Efficacy measures were rate of decline in FEV_1 after the bronchodilator and in health status, frequency of exacerbations, respiratory withdrawals. Mean FEV_1 remained significantly higher throughout the study with ICS treatment compared with placebo. Median exacerbation rate was reduced by 25% from 1.32 events per year on placebo to 0.99 events per year on ICS. Patients on ICS had fewer exacerbations and a slower decline in health status. These improvements in clinical outcomes support use of ICS in patients with moderate to severe COPD.

The Lung Health Study Research Group (LHSRG, 2000) conducted an RCT of inhaled triamcinolone acetonide (1,200µg/day) versus placebo among 1,116 patients with COPD in the US and Canada. The primary outcome measure was the rate of decline in FEV_1 after the administration of a bronchodilator. The secondary outcome measures included respiratory symptoms, use of health care services, and airway reactivity. The mean duration of follow-up was 40 months. The rate of decline in the FEV_1 after bronchodilator use was similar in the treatment group and the placebo group. Members of the treatment group had fewer respiratory symptoms during the course of the study (21.1 per 100 person-

years versus 28.2 per 100 person-years) and had fewer visits to a physician because of a respiratory illness. ICS does not slow the rate of decline in lung function in people with COPD, but it improves airway reactivity and respiratory symptoms and decreases the use of health care services for respiratory problems.

van der Valk et al. (2002) conducted an RCT to investigate the effect of discontinuation of the inhaled fluticasone propionate (1,000μg/day) on exacerbations and health-related quality of life (HRQOL) in 244 patients with COPD in Netherlands. After four months of treatment with ICS, patients were randomized either to continue ICS or to receive placebo for six months. Primary outcome measures were first and second exacerbations and occurrence of rapid recurrent exacerbations, as well as HRQOL. Exacerbations were defined as worsening of respiratory symptoms that required treatment with a short course of oral corticosteroids or antibiotics as judged by the study physician. This study indicated that discontinuation of ICS in patients with COPD was associated with a more rapid onset (hazard ratio [HR]: 1.5, 95% confidence interval [CI]: 1.1 to 2.1) and higher recurrence-risk of exacerbations (HR: 4.4, 95% CI: 1.9 to 10.3) and a significant deterioration in HRQOL.

Systematic reviews of placebo-controlled RCTs were conducted to evaluate the long-term effects of ICS treatment in COPD patients on clinically important outcomes including death and exacerbation risks. A meta-analyses based on the eight RCTs described previously found that although ICS treatment did not significantly reduce mortality (relative risk [RR] 0.78, 95% CI: 0.58 to 1.05), ICS treatment led to a 24% (RR 0.76, 95% CI: 0.72 to 0.80) reduction in exacerbation risks (Sin et al. 2003). Alsaeedi et al. (2002) also reported their pooled analysis using the seven RCTs excluding a study reported by van der Valk et al. (2002) and reached similar conclusions.

Table 2.1: Summary of clinical trials on effects of ICS in COPD

	Author, year	Drugs	No. of Patients	Mean age (years)	Baseline FEV1 (L)	Duration (months)	Exacerbation RR (95%CI)	Mortality RR (95%CI)
1	Bourbeau et al. 1998	Budesonide	79	66	0.95±0.33	6	0.47 (0.09 to 2.52)	Not Reported
2	Paggiaro et al. 1998	Fluticasone	281	63	1.57±0.60	6	**0.67 (0.49 to 0.90)**	Not Reported
3	Weir et al. 1999	Beclo-methasone	98	66	1.10±0.07	24	**0.62 (0.41 to 0.95)**	Not Reported
4	Vestbo et al. 1999	Budesonide	290	59	2.37±0.82	36	0.96 (0.77 to 1.20)	0.80 (0.22 to 2.92)
5	Pauwels et al. 1999	Budesonide	1,277	52	2.54±0.64	36	Not Reported	0.81 (0.22 to 2.04)
6	Burge et al. 2000	Fluticasone	751	64	1.24±0.45	36	**0.75 (0.71 to 0.80)**	0.77 (0.06 to 1.11)
7	LHSRG 2000	Triam-cinolone	1,116	56	2.13±0.63	40	**0.46 (0.26 to 0.80)**	0.79 (0.40 to 1.53)
8	van de valk et al. 2002	Fluticasone	244	64	1.75±0.53	6	0.83 (0.59 to 1.15)	0.98 (0.06 to 15.6)
	Alsaeedi et al. 2002	Pooled Analysis	3,976	Including studies 1, 2, 3, 4, 5, 6 and 7		6 or longer	**0.70 (0.58 to 0.84)**	0.84 (0.60 to 1.18)
	Sin et al. 2003	Pooled Analysis	4,134	Including studies 1, 2, 3, 4, 5, 6, 7 and 8		6 or longer	**0.76 (0.72 to 0.80)**	0.78 (0.58 to 1.05)

Note: significant results were displayed using bold font.

On the other hand, as shown in Table 2.2, the current evidence for ICS treatment in COPD patients based on observational studies has shown mixed results. Three out of eight observational studies reported that ICS treatment was associated with significant reductions in all-case mortality as well as COPD-related hospitalizations (Sin and Tu 2001, Soriano et al. 2002, Kiri et al. 2005); whereas others did not find such benefits (Bourbeau et al. 2003, Fan et al. 2003, Suissa 2003 and 2004, de Mele et al. 2004).

Sin and Tu (2001) conducted a retrospective cohort study using the Ontario version of Canadian Institute of Health Information hospital discharge database to evaluate the risk of mortality and readmission in elderly patients with COPD (n=22,620). They defined index date as discharge date of first hospitalization with COPD. Patients were classified as the treatment group if they started ICS treatment within 90 days of index date and as the control group if not. Patients who received ICS treatment had 24% (95% CI: 20% to 29%) fewer

repeat hospitalizations for COPD and were 29% (95% CI: 22 to 35%) less likely to experience death for any reason during one year follow-up after adjusting for age, sex, Charlson comorbidity score, use of COPD medications, and history of emergency or office visits for COPD. They concluded ICS therapy was associated with reduced COPD-related morbidity and mortality in elderly patients.

Soriano et al. (2002) conducted a retrospective cohort study using the UK General Practice Research Database (GPRD) to evaluate survival in COPD after regular use of fluticasone propionate and salmeterol (n=4,665). The treatment cohort was defined as physician-diagnosed COPD patients who had received three or more prescriptions of fluticasone propionate, salmeterol or their combination over an initial 6-month period. The control cohort was defined as patients who had not used ICS or long-acting β_2-agonosts (LABA) since diagnosis with COPD. Patients were followed up to three years to look for death for any reason. After adjusting for age, sex, year of entry, smoking status, comorbid conditions, asthma and use of oral corticosteroids, they found that combined users of fluticasone propionate and salmeterol had the lowest risk of death (HR 0.48, 95% CI: 0.31 to 0.73), followed by users of fluticasone propionate alone (HR 0.62, 95% CI: 0.45 to 0.85) and users of salmeterol alone (HR 0.79, 95%CI: 0.58 to 1.07) compared with control cohort. They concluded regular use of ICS alone or in combination with LABA was associated with increased survival of COPD patients managed in the primary care setting.

Bourbeau et al. (2003) conducted a nested case-control study using the Saskatchewan university healthcare insurance system to examine whether use of ICS was associated with a change in risk of a subsequent hospitalization for COPD (n=11,873). Source subjects were identified as those who were 55 years or older, initiated regular COPD treatment and had no asthma diagnosis. First, subjects with a first hospitalization were identified. Then, if subjects had re-hospitalizations with a primary discharge diagnosis of COPD, they were selected as the case subjects (date of the re-hospitalization was taken as

the index date). The control subjects were selected from all possible subjects without re-hospitalization matched on age, time since the prior hospitalization and use of other respiratory therapy. After further adjustment for comorbidities, sex, calendar year and intensity of other drug therapy, ICS was not significantly associated with risk of a subsequent COPD hospitalization (RR 1.02, 95% CI: 0.85 to 1.22). They concluded that no apparent influence of ICS use was found on reduction of COPD exacerbation requiring hospitalization.

Fan et al. (2003) conducted a retrospective cohort study using the Veterans' Health Information System Technology Architecture computerized medical record system. They used time-dependent methods to determine whether ICS use reduced the risk of all-cause mortality and COPD exacerbations (n=8,033). ICS exposure status was calculated using 90-day intervals and described as percentage of days coved by ICS medications. If more than 80% of days during the intervals were covered, it was considered as use of ICS. They further categorized ICS users by dose (in tramcinolone equivalents) into low (less than 400μg/day) and medium/high (more than 400μg/day). Recent ICS use was not associated with a reduction in mortality at low (HR 0.80, 95% CI: 0.60 to 1.07) or medium/high doses (HR 0.88, 95% CI: 0.71 to 1.09). Similarly, there was no association between ICS use and hospitalizations (0.85, 95% CI: 0.64 to 1.13) or COPD exacerbations (HR 1.13, 95% CI: 0.94 to 1.36). According to the time-dependent approach, they concluded that ICS adherence was not associated with a decreased risk of mortality or exacerbations.

Suissa (2003) pointed out that the intent-to-treat approach in observational studies would introduce a bias due to immortal time. If the ICS exposure status was measured as any dispensing within 90 days after hospital discharge, the time before the dispensing was immortal (not risk at all) because patients must survive to get ICS treatment. Using the computerized database of the Saskatchewan Department Health, he examined the association between ICS use and risk of COPD hospitalization or all-cause death during a

one-year follow-up period (n=1,072). When a time-fixed analysis (intent-to-treat approach) was used, ICS use was associated with 31% reduction in hospitalization (HR 0.69, 95% CI: 0.55 to 0.86). However, when a time-dependent analysis (allocate time before starting ICS as non-exposure time) was employed, the effects of ICS use were not observed (HR 1.00, 95% CI: 0.79 to 1.26). He concluded that observed benefits of ICS on mortality and morbidity should be biased due to inappropriate allocation of ICS exposure status and analysis of immortal time.

de Mele et al. (2004) also used a cohort of newly treated COPD patients from the Saskatchewan administrative database to assess whether ICS was effective in preventing a first exacerbation (n=4,455). A moderate exacerbation was identified by prescriptions of a systematic antibiotic and an oral corticosteroid on the same day. A severe exacerbation was defined by hospitalization with a primary discharge diagnosis of COPD. A nested case-control design was used, and cases and controls were matched on year of birth and cohort entry. The risk of a first exacerbation increased with any ICS use (RR 1.27, 95% CI: 1.08 to 1.48) and with current ICS use (RR 1.51, 95% CI: 1.22 to 1.87). Thus, they concluded that ICS was not beneficial in reducing risk of a first COPD exacerbation.

Suissa (2004) also used a cohort of newly treated COPD patients from the Saskatchewan administrative database to compare patients who started regular treatment of ICS or bronchodilators (n=5,645). Patients were followed for three years to assess risk of death. Using a time-fixed (intent-to-treat) approach, he found ICS users had lower risk of death compared with bronchodilator users (HR 0.66, 95% CI: 0.57 to 0.76). However, using a time-dependent (according-to-treat) approach, the effects became not statistically significant (HR 0.94, 95% CI: 0.81 to 1.09). Again, he concluded observed ICS treatment effects were due to bias from unaccounted immortal time.

Kiri et al. (2005) reported two cohort studies accounting for the immortal time bias. Using data from the UK General Practice Research Database (GPRD), one-year risk of

death or re-hospitalization was compared. In a propensity-score-matched analysis, patients who were prescribed ICS on day of discharge were compared with patients without ICS for one year after discharge (n=786). A propensity score was calculated using a logistic regression model with baseline characteristics including asthma diagnosis, smoking, age, sex, comorbidities, and respiratory medications. There was a significant reduction of death or re-hospitalization associated with ICS use (HR 0.69, 95% CI: 0.52 to 0.93). In a nested case-control study, patients prescribed ICS within 90 days of discharge were selected as the cases and patients without ICS treatment during follow-up were selected as the controls matched on age, sex, discharge date and follow-up duration (n=2,222). ICS use in the prior 6-month period was associated with lower risk of death or re-hospitalization (RR 0.71, 95% CI: 0.56 to 0.90). Thus, they concluded that immortal time bias could not account for risk reduction associated with ICS use.

Table 2.2: Summary of observational studies on effects of ICS in COPD

	Author, year	No. of Patients	Study design	Follow-up	Outcomes	Exposure	Findings RR (95% CI)
1	Sin and Tu 2001	22,620	Time-fixed exposure	12 months	Hospital or death	ICS within 90 days	**0.74 (0.71-0.78)**
2	Soriano et al. 2002	4,665	Time-fixed exposure	36 months	Death	ICS within 6 months	**0.62 (0.45-0.85)**
3	Bourbeau et al. 2003	11,873	Nested case-control	N/A	Hospital	Current ICS	1.02 (0.85-1.22)
4	Fan et al. 2003	8,033	Time-dependent exposure	90 days intervals	Hospital or death	ICS within 90 days	0.88 (0.71-1.09)
5	Suissa 2003	1,072	Time-dependent exposure	12 months	Hospital or death	ICS within 90 days	0.94 (0.76-1.17)
6	de Mele et al. 2004	4,455	Nested case-control	12 months	Exacerbation	Current ICS	1.51 (1.22-1.87)
7	Suissa 2004	5,645	Time-dependent exposure	36 months	Death	Regular ICS	0.94 (0.81-1.09)
8	Kiri et al. 2005	2,222	1) Propensity score matched 2) Nested case-control	12 months	Hospital or death	1) 90+ days 2) 6 months before	**1) 0.69 (0.52-0.93) 2) 0.71 (0.56-0.90)**

Note: significant results were displayed using bold font.

Observational studies based on a variety of databases have played an important part in developing information about effectiveness of drug treatments, especially in real world settings (Schneeweiss and Avorn 2005). However, the mixed results shown earlier may be due to possible sources of bias typical in observational studies, including confounding (by indication and severity of disease), patient selection, drug exposure (persistence and adherence), and the choice of outcome measures (mortality or morbidity).

To minimize potential biases due to confounding and patient selection, researchers often use multivariable analyses to control for demographic factors, asthma (mixed phenotype) and other comorbid conditions, and previous resource utilization (drug treatment and hospitalization/emergency department visit) as proxy of disease severity. In addition, sensitivity analyses are conducted by excluding patients with an asthma diagnosis to evaluate the effects of ICS on “pure” COPD conditions. More recently, sophisticated analytical techniques, such as a propensity score matched-cohort design and/or a nested case-control design, have been used to examine association between ICS use and mortality or COPD exacerbations by eliminating systematic differences between ICS users and non-users as well as by considering current drug exposure status (Bourbeau et al. 2003, Kiri et al. 2005).

Measurement of drug exposure status is an important consideration when estimating unbiased effects of drug treatments using observational claims data. Unlike in randomized trials, drug exposure status cannot be controlled in observational studies. An intent-to-treat (time-fixed) approach often is used to approximate a randomized trial. Drug exposure status is usually determined at cohort entry (e.g., date of first drug prescription) or within a fixed time period (e.g., within 90 days of hospital discharge or first COPD diagnosis) and is fixed during the follow-up period (Sin and Tu 2001, Soriano et al. 2002, Sin and Man 2003). However, this allocation method may result in misclassification of exposure because the time before starting ICS treatment is incorrectly allocated as exposure even though

individuals are not exposed for the entire time period. This type of bias is called an immortal time bias because a subject cannot incur the outcome event (such as death), by definition, during the time before starting the drug treatment, especially in survival analysis (Suissa 2003). In other words, the subject must survive until the drug treatment starts, which could create a healthier treatment group by definition.

An alternative approach used in observational studies is a time-dependent approach in which drug exposure status is allowed to change over time and is defined based on the nature of drug use. Suissa (2003 and 2004) and Fan et al. (2003) used the time-dependent methods to allocate person-time according to the drug exposure status and found that there was no association between ICS use and either mortality or COPD exacerbations. However, this approach also has limitations in that not only it is difficult to measure true drug exposure status from claims data but also the approach cannot control for background characteristics or health conditions that may influence drug treatment selections and changes. The time-dependent exposure method creates a non-biased analysis only if the reason for treatment change is independent of the risk of outcomes. In studies of drug treatment on the risk of all-cause death, a change in treatment is often related to the worsening of the condition, so that the assumption of “independence” is violated, suggesting the need for another approach to avoid biased estimates of treatment effects.

2.2 Methods Utilized in this Dissertation

This dissertation used various analytical techniques to minimize potential bias due to observed and unobserved confounders. A propensity-score-method was employed to account for observed confounding factors. A generalized linear model regression was used to account for skewed distributions of cost data. A fixed-effects model regression was employed to account for unobserved stable confounding factors. Medication persistence and adherence was used to assess ICS exposure level and its association with outcomes. The

following summarizes briefly each analytical method and provides an example appearing in scientific literature.

2.2.1 Propensity-Score-Method

A propensity-score-method is a technique to combine a vector of covariates into a single measure to summarize baseline characteristics (Rosenbaum and Robin 1983). It can be estimated using a multivariable logistic regression model. Each individual is assigned an estimated probability of exposure (being treated) ranging from 0 to 1 given the individual's covariates. Individuals with the same propensity score, in theory, have the same chance of receiving the treatment. The propensity score is used to match or stratify based on the score prior to descriptive analyses and in multivariate modeling to adjust for background characteristics (D'Agostino 1998, Joffe and Rosenbaum 1999).

In an observational study, the propensity-score-method is primarily used to reduce selection bias and to increase precision in estimates. However, because the propensity score is conditional on the observed covariates, there is concern that it cannot control for unmeasured or imperfectly measured covariates (Schneeweiss and Avorn 2005). Moreover, individuals in the treatment and control groups must have similar propensity scores to ensure unbiased comparisons, such as those of a randomized allocation process. Plotting and comparing the distribution of the propensity scores is a standard way to check the comparability. As shown in Figure 2.1, individuals with scores in the area of overlap between the two distributions should theoretically have similar background characteristics (Schneeweiss and Avorn 2005). Individuals, however, not in the area of overlap or at the extreme end of the distributions, may have heterogeneous characteristics. If the two groups do not have substantial overlap in the distribution, potential biases may be introduced (Baser 2005 and 2006).

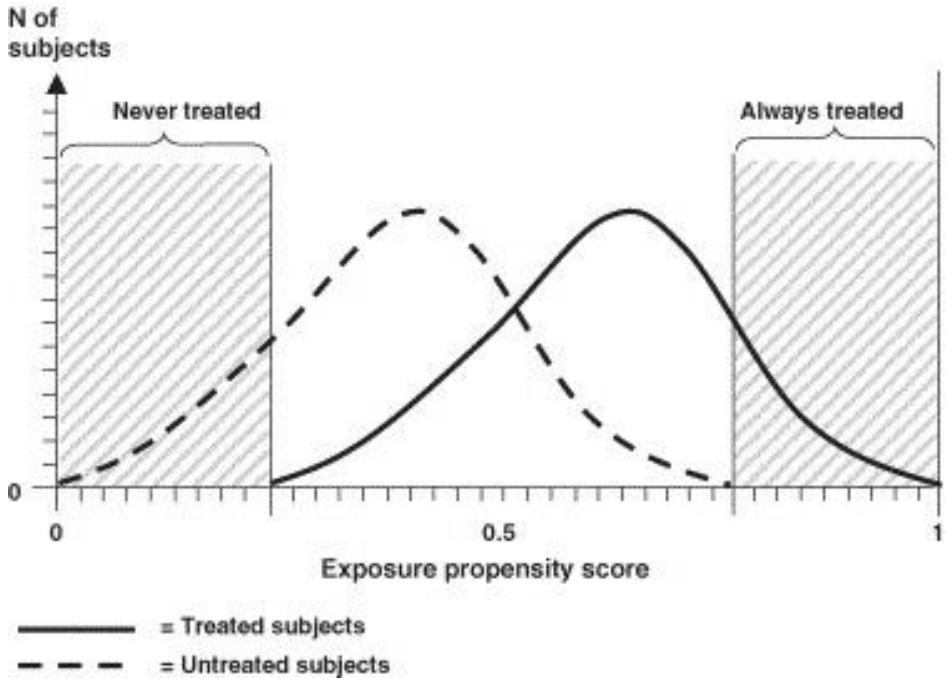


Figure 2.1: Propensity score distribution among treatment and control groups

Source: Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics, J Clin Epidemiol. 2005 Apr;58(4):323-37. Copyright 2005. Reprinted with permission from Elsevier.

One example of using propensity-score-matching (PSM) was reported to compare two different asthma maintenance therapies in children with asthmatic conditions (Luskin et al. 2005). To control for selection bias associated with maintenance therapy selection, children taking inhaled corticosteroids and leukotriene modifiers were matched on propensity scores, which were estimated using known baseline characteristics, including age, sex, asthma severity index, prescriber specialty, index maintenance therapy date, and prior 12 months antihistamine and nasal steroid use. After matching on propensity scores, imbalances in the observed baseline characteristics were reduced, thus allowing the comparison of costs for asthma, allergy, and other respiratory medications between two maintenance therapies.

Hall et al. (2003) provide another example of how selection bias / baseline differences were reduced by PSM. They used PSM to reduce baseline differences in diabetes patients who received two different insulin treatments. This study sought to determine whether insulin lispro would result in no additional costs as compared to regular insulin therapy. However, because the two treatment groups differed significantly in baseline characteristics, to increase comparability, they were matched with each other using propensity scores based on age, gender, health plan, physician specialty, diabetes-related medical procedures and comorbid conditions. All statistically significant differences between treatment groups became non-significant after the matching process.

2.2.2 Generalized Linear Model (GLM) Regression

Healthcare cost data typically have mixed distributions that contain a disproportionate number of zero values (e.g., non users) and a right-skewed distribution among users (Powers et al. 2005). To address the non-normal distribution problem, log-transformed costs are modeled using an ordinary least square (OLS) regression. Once estimated, the transformed outcome variables (i.e., log dollars) are retransformed to the original scale (i.e., dollars) to compare incremental effects among various groups of interest. However, retransformation back from the log scale is not straightforward and the estimate of expected costs on the original scale is not obtained directly by exponentiating the linear predictor. Instead, an adjustment using appropriate “smearing factor” (which is the mean of the exponentiated log scale residuals) is required to avoid the bias due to the retransformation as shown in Equation 2.1 (Duan 1983, Manning et al. 1998).

$$[E(c)] = \exp(\alpha + \beta\ X) + \frac{1}{n}\sum_{i=1}^{n}\exp(\varepsilon_i) \qquad \text{(Equation 2.1)}$$

This additional factor complicates log transformed regression models. An alternative approach for modeling cost data is to use a generalized linear model (GLM), for which a

distribution for the underlying data is assumed together with a scale for the linear procedure as shown in Equation 2.2 (Briggs et al. 2006).

$$g[E(c)] = \alpha + \beta\ X \qquad \text{(Equation 2.2)}$$

where the function g(.) is known as the link function. To model cost data, a gamma distribution and a log link are often assumed. Because the GLM approach uses expected values as the dependent variable, it maintains the original scale and does not require the retransformation. Thus, the back transformation to the original scale is straightforward. The expected cost is calculated by simple exponentiation of the linear predictor (Manning and Mullahy 2001).

Various tests are recommended to select the appropriate approach, either using an OLS-based model or a GLM (Manning and Mullahy 2001). If the log-scale residuals are heteroscedastic with respect to the independent variables, then the OLS estimates are biased unless a correction is used to incorporate the log-scale variance function. On the other hand, if the log-scale residuals are heavy tailed, GLM estimates are less precise than those from the OLS based model.

In addition, to address the issue of zero values, a two-part model is employed with the probabilities of non-zero values analyzed using a logistic model as the first part and with the conditional means given non-zero values analyzed using the GLM (Blough et al. 1999). The logistic regression coefficients are exponentiated to provide odds ratios. The GLM regression coefficients then are exponentiated to represent the ratio of expected costs. Incremental costs are calculated by taking the mean of the predicted values across all subjects alternately coding the drug exposure status. Confidence intervals for the incremental costs are obtained by bootstrapping, taking the 2.5 and 97.5 percentiles of bootstrap samples with replacement (Efron and Tibshirani 1993, Briggs et al. 1997).

Two-part models are often used in the studies to compare treatment costs across various medication regimens. Rascati et al. (2007) compared treatment costs according to the initial maintenance therapies for COPD: fluticasone propionate/salmeterol combination (FSC), inhaled corticosteroids (ICS), salmeterol (SAL) or ipratropium (IPR). As for COPD-related cost analysis, the two-part model with a logistic regression and a GLM were used to adjust for baseline characteristics and pre-index utilization and costs. As a result, COPD-related costs were similar in FSC and ICS, and reduced by $108 ($p<0.05$) in SAL compared to IPR cohort.

A similar regression model approach was used in a matched case-control study (Akazawa et al. 2007). They also used a GLM with a gamma distribution and log link to estimate healthcare costs in undiagnosed COPD patients by accounting for skewed distribution of costs. Patients with COPD diagnosis used $1,362 and $403 more medical and pharmacy costs during the 12 months prior to the diagnosis compared with matched controls even after the risk adjustment.

2.2.3 Fixed-Effects Model Regression

In longitudinal or panel data analyses, an individual has multiple observations of both exposure status and outcomes (Frees 2004). This means he or she can contribute the time before drug exposure to the control group and time after drug exposure to the treatment group. Because each individual is his or her own control, potential bias due to omitted variables that do not change over time (e.g., sex, race, and historical health behaviors) can be eliminated. When there are two observations per person, the treatment effect can be observed by measuring changes before and after the treatment (e.g., pre- and post-paired comparison), and the time-invariant variables disappear by subtraction.

One statistical approach to account for multiple observations per individual is called "fixed-effects" model (Allison 2005). The model can be expressed as below (Equation 2.3):

$$Y_{it} = \beta\ X_{it} + \alpha_i + \varepsilon_{it} \qquad \text{(Equation 2.3)}$$

where the *i* refers to different persons and *t* refers to different points in time; the term *Y* is an outcome of interest, *X* is a main exposure of interest, α_i is a dummy variable to explain individual characteristics; and ε_{it} is a random error. In this model, omitted variables are accounted for without measuring them because individual variations are considered fixed, and thus, explained by the fixed-effect parameter, α_i. On the other hand, the effects of time-variant factors or variables that change over time (e.g., disease symptoms) must be adjusted with common regression approaches to avoid omitted variable bias.

In Equation 2.3, many dummy variables are required to express individual variation, which may influence degrees of freedom or efficiency of estimation. As an alternative approach, a transformation of data is used in the fixed-effects model (Kennedy 2003). The average of all observations for each individual is subtracted from each observation for that individual. An ordinary least squared (OLS) model then is used with the transformed data as described below (Equation 2.4):

$$\begin{aligned}(Y_{it} - \overline{Y}_{it}) &= \beta\ (X_{it} - \overline{X}_{it}) + (\alpha_{it} - \overline{\alpha}_{it}) + (\varepsilon_{it} - \overline{\varepsilon}_{it}) \\ \Delta Y_i &= \beta\ \Delta X_i + \Delta\varepsilon_i\end{aligned} \qquad \text{(Equation 2.4)}$$

where $\overline{Y}_{it}$, $\overline{X}_{it}$, $\overline{\alpha}_i$ and $\overline{\varepsilon}_{it}$ are the person-specific means. The time-invariant variable, α_i, and its mean, $\overline{\alpha}_i$ are the same and automatically dropped from the equation by subtraction. Therefore, the parameter of interest, β, can be estimated directly from the model and is free from the omitted stable variable bias.

Compared with a fixed-effects model, a random-effects model is more efficient because it uses variation both within and between individuals; however, it cannot control for unmeasured, stable characteristics (Allison 2005). To confirm the selection of appropriate panel data model (i.e., fixed-effects versus random-effects), various specification tests such

as heteroskedasticity, endogeneity, autocorrelation, Breusch-Pagan, and Hausman tests are performed (Greene 2000).

Longitudinal or panel data analyses are often used to assess the effects of newly implemented policy or changes on clinical and economic outcomes. One research group used a fixed-effects panel model to determine the effect of prescription drug coverage on inpatient and physician expenditures among Medicare beneficiaries (Briesacher et al. 2005). Data from Medicare claims were summed quarterly and the effect of drug coverage was detected by changes in quarterly spending before and after switching insurance status. Subjects who did not gain any drug coverage during the study period were used as the reference group. Although drug spending was increased after gaining prescription drug coverage, the study found no impact on hospital and physician services using multivariable models.

Another study used a random-effects model to examine the relationship between drug medication adherence and healthcare service utilization among diabetic patients (Balkrishnan et al. 2003). Using data from managed care organizations, the medication possession ratio (MPR) and total healthcare costs were summarized yearly and their relationships were measured across five years. The study reveled that higher level of medication adherence measured by prescription refill pattern was associated with lower healthcare costs independent of type of anti-diabetic medication used as well as severity of conditions during a given year. The aim of these study designs was to eliminate potential biases due to observed and unobserved factors that do not change over time.

2.2.4 Medication Persistence and Adherence

Increasing numbers of claims database studies are reported to describe drug treatment persistence and adherence as well as its treatment consequences. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) recently

issued a check list of items that should be considered when a retrospective database analysis of medication persistence and adherence is undertaken (Peterson at al. 2007). The term “persistence” usually represents the time over which a patient continues to refill a prescription, or the time from the initial filling of the prescription until the patient discontinues refilling the prescription. It is calculated the percentage of patients remaining on therapy at a given time and often is displayed on a persistency curve that similar to a Kaplan-Meier curve.

The term “adherence” often refers to whether a patient takes a prescribed medication according to schedule (note that the terms “compliance” and “adherence” are considered as synonyms). One of the most common methods is to calculate the medication possession ratio (MPR) that is typically calculated using the equation below (Equation 2.5):

$$\frac{\text{Number of days of medication supplied within refill interval}}{\text{Number of days in refill interval}} \qquad \text{(Equation 2.5)}$$

This ratio is usually calculated by summing the number of days for all except the last refill, divided by the number of days between the first and the last refills. Thus, at least two refill dates are required (Andrade et al. 2006, Hess et al. 2006).

Limited studies have been published examining medication persistence and adherence among COPD patients (Rand 2005). Blais et al. (2004) evaluated medication persistence with ICS treatment among elderly COPD patients using a Canadian administrative database. Patients were followed from the date of the first ICS prescription until they stopped treatment. Each ICS prescription was assumed to last for a maximum 50 days and the treatment was considered to be discontinued if the prescription was not renewed within the three months after the end of the last refill. Although guidelines recommend regular ICS treatment should be maintained for long time periods, discontinuation of ICS treatment was common. The proportion of patients who remained on ICS treatment more than one year ranged from 33% to 52% by the end of study year.

Balkrishnan and Christensen (2000a and 2000b) studied medication adherence to ICS treatment in Medicare managed care enrollees with chronic pulmonary disease. Medication adherence was calculated as days of prescription supply dispensed divided by days between prescription refills. The observation period began with the first date of ICS prescription and ended the last prescription date in each year. About 60% of the elderly had poor adherence (i.e., medication adherence ≤ 30%), and only 10% were categorized as having good adherence (i.e., medication adherence ≥ 60%). Patients with good adherence to the treatment also experienced better outcomes, in terms of fewer hospitalizations or emergency department visits.

Similar methods were used in measures of medication persistence and adherence of asthma maintenance therapy. Combination therapy (i.e., ICS and long-acting β_2 agonist [LABA] in the same inhaler) and concurrent therapy (i.e., ICS and LABA in two different inhalers) were compared among adult patients with asthma using a pharmacy claims database in Quebec, Canada (Marceau et al. 2006). Combination users were less likely to stop their treatment compared with concurrent therapy (10% remained on combination therapy versus 5% for concurrent therapy after 12 months). Adherence was also relatively low for both regimens; patients filled, on average, 3.5 prescriptions in combination therapy versus 2.7 prescriptions in concurrent therapy during the first 12 months. Thus, they concluded that combination therapy might be preferred to concurrent therapy for asthma patients with low adherence to maintenance therapies.

Others compared medication persistence and adherence of oral maintenance therapy and inhaled maintenance therapy among asthma patients using a managed care claims database (Jones et al. 2003). The percentage of patients persistent with asthma medications was significantly greater among patients with oral therapy than those with inhaled therapy (43% and 22% after nine months, respectively). Mean adherence was 68% for oral therapy and was 34% for inhaled therapy. These results suggest that because

adherence to treatment is a critical component of treatment responses, both persistence and adherence to different types of therapies should be considered when developing therapeutic plans (oral versus inhaled asthma medications).

CHAPTER 3

Research Questions and Methods

3.1 Overview

This dissertation examined the potential benefits of inhaled corticosteroids (ICS) treatment initiated earlier than the current guideline-recommended stepwise approaches among patients with COPD diagnosis. Specific benefits were measured in terms of exacerbation risks, healthcare resource utilization, and treatment costs. Two statistical techniques were employed to minimize a potential confounding bias due to observed and unobserved factors. Propensity-score-matched samples were used to control for the differences in baseline characteristics between treatment groups. In addition, individual-level fixed-effects regression models for longitudinal or panel data were used to eliminate potential contamination from unmeasured individual characteristics that were constant over time (such as socioeconomic status, smoking, and other time-invariant risk behaviors). The impact of medication persistence and adherence on utilization and cost also was addressed.

3.2 Research Questions and Hypotheses

Three testable hypotheses corresponding to three research questions were summarized in Section 1.3 [Purpose of this Dissertation]. The index date was defined as the earliest pharmacy claim of bronchodilators (anticholinergics or long-acting β_2 agonists).

H1: COPD patients who initiated ICS treatment within three months of index date had lower exacerbation risks, resource use and treatment costs compared with those

who initiated ICS more than three months after index date, after adjusting for background characteristics and pre-index resource utilization.

H2: Within individual COPD patients, initiating ICS treatment was associated with lower medical costs for any condition and for COPD-related condition, after controlling for changes in exacerbations and comorbid conditions.

H3: COPD patients who had better medication persistence and adherence were more likely to have lower medical utilization and costs for any condition and for COPD-related condition.

3.3 Conceptual Framework

Potential confounding factors and measurement factors must be considered to obtain unbiased estimates in observational studies. Potential confounding factors, such as individual demographic characteristics (age, gender), comorbid conditions (and the drugs used to treat them), health service providers (access to specialist care), and baseline healthcare service use, should influence not only treatment choice but also treatment consequences. These are confounders only if they are associated with both the probability of exposure and the risk of outcomes (Figure 3.1).

Also, measurement of drug exposure status is an important issue to avoid misclassification of exposure level. Since drug exposure status is directly related to when and how medications are actually taken, measuring treatment is important to assess the treatment effects. Poor medication persistence and adherence is often associated with increases in healthcare utilization and costs.

The early initiation of ICS treatment is expected to control respiratory conditions and to prevent acute exacerbations, and therefore, it reduces disease-specific healthcare service use and treatment costs. In addition, COPD patients are known to have a higher prevalence of systemic conditions such as cardiovascular-, bone-, and other smoking-related conditions

(Agusti 2005, Soriano et al. 2005). Overall healthcare utilization and costs can be reduced by stabilizing COPD-related conditions and general health status. Therefore, stratified analyses of healthcare utilization and costs by service types and/or disease conditions are useful to understand the potential benefits of ICS treatment.

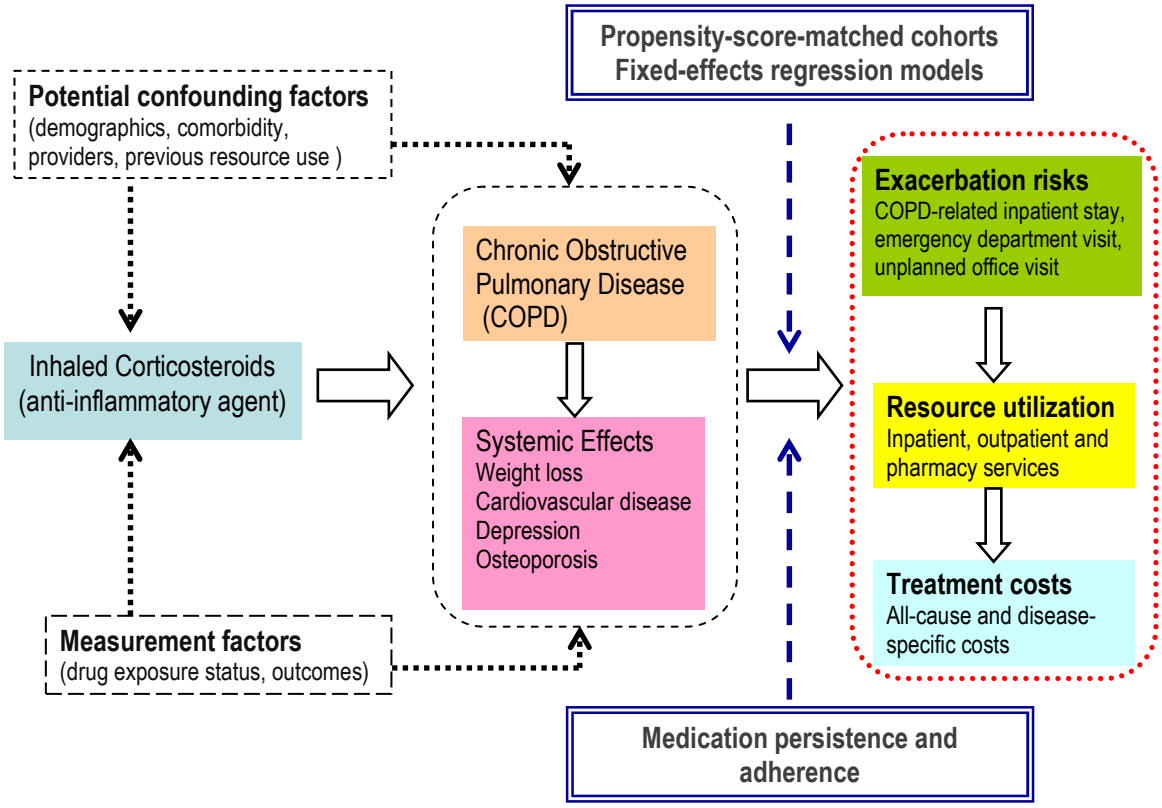


Figure 3.1: Conceptual framework

3.4 Data Source

Data for this dissertation were obtained from the Integrated Healthcare Information Services (IHCIS) database from January 1997 through December 2005. This database includes information on enrollment, facility, professional and pharmacy services from more than 37 million patients covered by approximately 35 different managed care health plans across the United States. Data available for each facility or professional service claim

("medical claim") include dates of service and International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes and ICD-9-CM procedure codes or Current Procedural Terminology, Version 4 (CPT-4) procedure codes. The data also include pharmacy claim with drug name dispensed (in National Drug Code [NDC]), dispensing date and days supply.

In the IHCIS data, cost information is standardized in order to make comparisons easier across all services, data sources, and time periods (IHCIS 2005). For example, (1) facility inpatient costs were calculated based on primary diagnosis categories, length of stay, and presence of ICU/surgery; (2) facility outpatient costs were calculated based on requested (submitted) charges; (3) professional service costs were calculated using a standardized payment schedule based on a resource-based relative value scale (RBRVS); (4) pharmacy service costs were calculated using First Data Bank pricing adjusted by quantity and therapeutic category; and (5) all costs were adjusted for inflation over time (2005 values). All data were HIPAA compliant with all health plan and personal information de-identified to assure confidentiality (IHCIS 2005).

3.5 Study Population

Subjects who met the following criteria were included:

1. One or more medical claims between January 1, 1998 and December 31, 2004 with a diagnosis of COPD (primary or secondary), including ICD-9-diagnosis codes 491.xx (chronic bronchitis), 492.xx (emphysema), or 496.xx (chronic airway obstruction, not elsewhere classified);
2. No medical claims with diagnosis of cystic fibrosis (ICD-9-CM= 277.0x: cystic fibrosis) or respiratory tract cancer (ICD-9-CM= 160.xx: malignant neoplasm of nasal cavities, middle ear, and accessory sinuses, 161.xx malignant neoplasm of larynx, 162.xx: malignant neoplasm of trachea, bronchus, and lung, 163.xx: malignant

neoplasm of pleura, 164.xx: malignant neoplasm of thymus, heart, and mediastinum, and 231.xx: carcinoma in situ of respiratory system);

3. At least three pharmacy claims of inhaled bronchodilators (anticholinergics: ipratropium, tiotropium or albuterol-ipratropium combination; or long-acting β_2 agonists: salmeterol or formoterol); the date of the earliest prescription was designated as “index date”;
4. Continuous enrollment for three months prior to and 12 months following the index date;
5. Ages 40 years or older at the index date;
6. Pharmacy coverage; and
7. Initiated treatment with ICS (i.e., beclomethasone, budesonide, flunisolide, fluticasone, mometasone, triamcinolone, or fluticasone-salmeterol combination) within 24 months of the index date.

3.6 Measures

3.6.1 Baseline Characteristics

The following characteristics at index date were obtained from enrollment file: year of birth (mid-date of year, June 30, was assigned as the birth date to calculate age at the index date and age was categorized into four groups: 40-49, 50-59, 60-69, and 70-79); gender; insurance coverage (Medicare/Medicaid or commercial insurance); and census region of the health plans (categorized into four: Northeast, South, Midwest, or West / others).

The comorbid conditions were identified from medical claims using ICD-9-CM diagnosis codes (primary & secondary diagnosis) as well as CPT-4 procedure codes (Table 3.1). The total number of comorbidities was also counted (maximum 16 conditions).

Table 3.1: Diagnosis and procedure codes to define comorbid conditions

Conditions	Diagnosis or procedure codes
Myocardial Infarction	ICD-9-CM codes: 410.xx, 412.xx
Congestive Heart Failure	ICD-9-CM code: 428.xx
Peripheral Vascular Disease	ICD-9-CM codes: 443.9x, 441.xx, 785.4x, V43.4 CPT codes: 35011, 35013, 35045, 35081, 35082, 35091, 35092, 35102, 35103, 35111, 35112, 35121, 35122, 35131, 35132, 35141, 35142, 35151, 35152, 35153, 35311, 35321, 35331, 35341, 35351, 35506, 35507, 35511, 35516, 35518, 35521, 35526, 35531, 35533, 35536, 35541, 35546, 35548, 35549, 35551, 35556, 35558, 35560, 35563, 35565, 35566, 35571, 35582, 35583, 35585, 35587, 35601, 35606, 35612, 35616, 35621, 35623, 35626, 35631, 35636, 35641, 35646, 35650, 35651, 35654, 35656, 35661, 35663, 35665, 35666, 35671, 35694, 35695, 35355-35381
Cerebrovascular Disease	ICD-9-CM codes: 430.xx – 438.xx CPT codes: 35301, 35001, 35002, 35005, 35501, 35508, 35509, 35515, 35642, 35645, 35691, 35693
Rheumatologic Disease	ICD-9-CM codes: 710.0x, 710.1x, 710.4x, 714.0x-714.2x, 714.81, 725.xx
Peptic Ulcer Disease	ICD-9-CM codes : 531.xx – 534.xx
Diabetes	ICD-9-CM code: 250.xx
Liver Disease	ICD-9-CM codes: 571.2x, 571.4x, 571.5x, 571.6x, 572.2x-572.8x, 456.0x - 456.2x
Dementia	ICD-9-CM code: 290.xx
Paraplegia or Hemiplegia	ICD-9-CM codes: 344.1x, 342.xx
Renal Disease	ICD-9-CM codes: 582.xx, 583.xx, 585.xx, 586.xx, 588.xx
AIDS / Any Malignancy / Lymphoma / Leukemia / Metastatic Solid Tumor	ICD-9-CM codes: 042.xx – 044.xx, 140.xx – 195.xx, 196.xx - 199.xx, 200.xx – 208.xx
Asthma	ICD-9-CM code: 493.xx
Depression	ICD-9-CM codes: 296.xx, 300.xx, 309.xx, 311.xx
Nonvertebral Fracture	ICD-9-CM codes: 807.xx, 808.xx, 810.xx – 829.xx, 733.1x, excluding 733.13
Hypertension	ICD-9-CM codes: 401.xx – 405.xx

Note: Diagnosis and procedure codes were identified from public sources (Deyo et al., 1992 and SEER-Medicare, charlson.comorbidity.macro.txt)

Medical services utilization was identified from medical claims using ICD-9-CM diagnosis codes (primary & secondary diagnosis) as well as procedure codes (CPT codes). The total number of the following events was counted: access to pulmonary medicine specialists, hospitalizations with respiratory conditions or for any reason, emergency department visits with respiratory conditions or for any reason, medical procedures for respiratory conditions,

prescriptions for respiratory-related medications or any medication, and respiratory-related procedures.

Respiratory-related events were identified from medical claims using primary and secondary ICD-9-CM diagnosis codes (Table 3.2).

Table 3.2: Diagnosis codes to define respiratory-related conditions

Conditions	ICD-9-CM diagnosis codes
Acute respiratory infections	460.xx – 466.xx
Other diseases of upper respiratory tract	470.xx – 478.xx
Pneumonia and influenza	480.xx – 487.xx
Chronic obstructive pulmonary disease and allied conditions	490.xx – 496.xx
Pneumoconioses and other lung diseases due to external agents	500.xx – 508.xx
Other diseases of respiratory system	510.xx – 519.xx

Respiratory-related medical procedures were identified from procedure codes (CPT/HCPCS codes) with following services (Table 3.3).

Table 3.3: Procedure codes to define respiratory-related medical procedures

Procedures	CPT/HCPCS codes
Oxygen therapy	A4611-A4629, E0424-E0484, E0550-E0590, E1353-E1406, S8120, S8121
Spirometry test	94010, 94060, 94620, 94014-94016
Pulmonary rehabilitation	G0110-G0116, S9473, G0237-G0239, 97001-97004, 97110, 97116, 97150, 97530, 97535, 97750
Nebulized treatment	E0565, E0570, E0571, E0572, E0574, E0575, E0580, E0585, A4627, A7003- A7008, A7010-A7015, A7017, S8096, S8100, S8101
Bronchoscopy / Intubation / Tracheostomy	31615, 31622, 31625, 31628, 31629, 31645, 31646, 31500, 31600, 31610

Respiratory-related medications were defined using National Drug Codes (NDC), and included the following medications: methylxanthines (sustained-release Theophylline); short-acting β_2 agonists (SABA), inhalation only; oral corticosteroids (OCS); oral antibiotics; leukotriene modifiers; and mast cell stabilizers.

3.6.2 Outcome Measures

The main outcomes of this study were exacerbations, other resource utilization and treatment costs. The exacerbations were identified by the following events and their combinations: COPD-related hospitalizations, COPD-related emergency department visits, or COPD-related unplanned office visits. Because it was difficult to distinguish between regular (planned) and unplanned office visits, only office visits with immediate prescriptions of rescue medications (i.e., antibiotics or oral corticosteroids within three days of the office visit claim as identified using NDC codes) were considered as unplanned. The mean values were calculated as total number of events or costs divided by follow-up person-time (year or month).

Other resource utilization of interest included: inpatient admissions (any reason, respiratory-related or cardiovascular-related conditions); outpatient services (emergency department, primary care physicians, pulmonary medicine specialists, cardiology specialists or psychiatry specialists); and prescriptions (any medication, COPD-related medications, cardiovascular disease (CVD)-related medications, antidepressants, or anti-diabetics). Moreover, treatment costs were categorized as: all-cause medical costs, all-cause pharmacy costs, all-cause total costs, COPD-related medical costs, COPD-related pharmacy costs, or COPD-related total costs. Disease-specific events (i.e., COPD-related and CVD-related cares) were identified using definitions summarized in Table 3.4.

Table 3.4: Definition of disease specific cares

Outcomes	Definitions to identify disease specific cares
COPD-related care	▪ All facility claims with a primary diagnosis of COPD (ICD-9-CM codes 491.xx, 492.xx, and 496.xx), all claims occurring during an inpatient stay were assigned the primary diagnosis associated with that stay); ▪ All professional-service claims with a primary or secondary diagnosis of COPD; ▪ All professional service claims for oxygen therapy, spirometry test, pulmonary rehabilitation, nebulized treatment, bronchoscopy, intubation, and tracheostomy; or ▪ All prescriptions for ICS, anticholinergics, SABA, LABA, sustained release theophylline, OCS, and selected oral antibiotics (cephalosporin, amoxicillin, ampicillin, quinolone [excluding norfloxacin and enoxacin], tetracycline, and macrolide antibiotics)
CVD-related care	▪ All medical claims with a primary or secondary diagnosis of cardiovascular disease (ICD-9-CM codes of 390.xx-448.xx); or ▪ All prescriptions for Angiotensin-converting Enzyme (ACE), angiotensin II inhibitors, beta-blockers, diuretics, and digoxins

3.6.3 Exposure Measures

ICS treatment status was defined as the main exposure of interest. Three different measures of drug exposure status were used according to the research questions. An intent-to-treatment measure was used in the first study in Chapter 4 (propensity-score-matching approach). A time-dependent measure was used in the second study in Chapter 5. Persistence and adherence were used to assess the relationship between drug exposure level and outcomes in the third study in Chapter 6.

In Chapter 4, ICS users were classified by the initial date of ICS treatment into: (1) the treatment group if patients started ICS within three months of the index; or (2) the control group if they started ICS between three and 24 months post index. Similar to the intent-to-treatment approach used by Sin and Tu (2001), assigned treatment status was considered to continue from the index date through the end of study period. On the other hand, in Chapter 5, the ICS exposure status was determined by the first ICS prescription as used in the time-dependent approach (Suissa 2003). The period before the first ICS claim was

defined as unexposed time, whereas the period after the first ICS claim was defined as ICS exposed time. Therefore, this approach eliminates immortal time bias.

A basic assumption of these studies was that ICS exposure continued during the follow-up period. However, patients may stop or switch their medications according to their preferences and/or for clinical reasons. Therefore, in Chapter 6, patient treatment behavior was assessed using persistence and adherence to ICS treatment. Medication persistence was defined as having ICS prescriptions continuously, and was measured by the number of days from the first ICS prescription to the discontinuation of treatment. If patients did not have another ICS prescription within 180 days or reached to the end of follow-up, the last observed prescription date was defined as the discontinuation date. Medication adherence was defined by the medication possession ratio (MPR), which was calculated as sum of drug supply days divided by duration of days between prescriptions. Three types of MPR were defined according to the observation period. One is measured as mean MPR during the first 12 months of follow-up; the second is measured as mean MPR during the entire follow-up period; and the third is measured a recent MPR just before measuring outcomes.

3.7 Study Design and Analytical Strategy

Study design and statistical analysis varied based on the research questions. Propensity-score-matching analysis was used to examine the timing of ICS initiation on healthcare utilization and costs as described in Chapter 4. Longitudinal data analysis was used to examine impact of ICS initiation on medical costs as described in Chapter 5. And, two-period analysis was used to evaluate temporal relationship between persistence and adherence to ICS treatment and outcomes in Chapter 6.

Figure 3.2 illustrates study design used in Chapter 4. Patients who initiated ICS within three months of index date were categorized into the treatment group and those who initiated ICS between three and 24 months were categorized into the control group. All

eligible patients were required to have 15 months continuous health plan coverage from three months before to 12 months after the index date. To adjust for background differences, these patients were matched one-to-one using a propensity score. The propensity score was estimated using a multivariable logistic regression model with age, gender, census region, insurance, comorbid conditions, and pre-index resource utilization. At the index date, patients with the same or similar propensity score would have equal probability of being treatment.

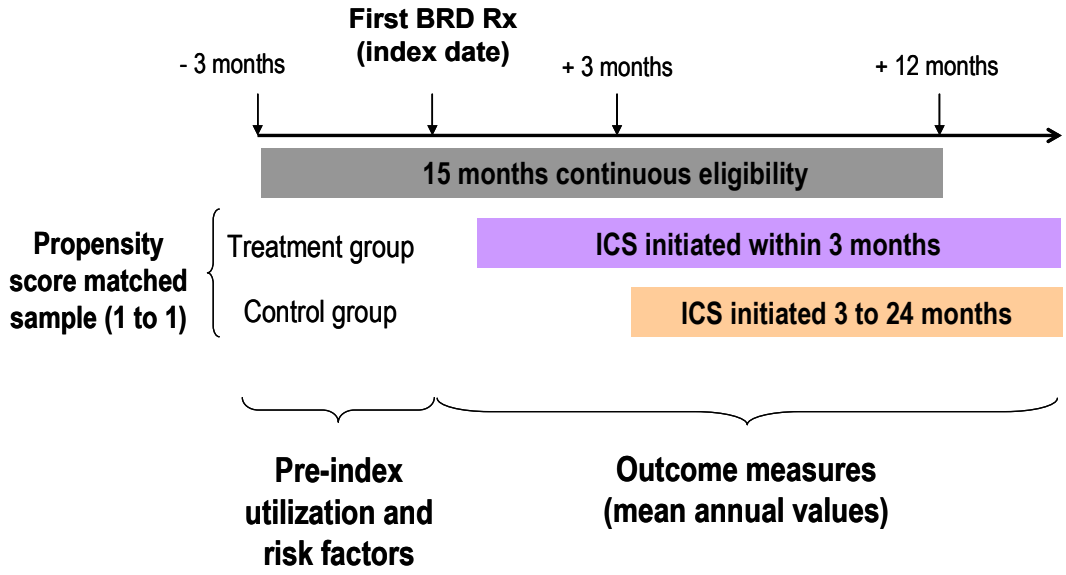


Figure 3.2 Study design used in Chapter 4

BRD: inhaled bronchodilators (anticholinergics or long-acting β_2 agonists), ICS: inhaled corticosteroids. Rx: prescription.

Patients were followed until end of follow-up period. The number of COPD exacerbation events, other resource utilization and treatment costs were summarized as annual values. The proportion of patients who had positive values and means among patients with the positive values were compared between the two groups using a logistic regression for categorical outcomes and a negative binomial model for continuous values (Kleinbaum et al. 1998, Allison 1999). A two-part model was used to estimate treatment

costs. A logistic regression model was first used to predict the probability of having any costs. Costs for patients with positive values then were modeled using a generalized linear model (GLM) with a gamma distribution and log link (Manning and Mullahy 2001).

Figure 3.3 illustrates study design used in Chapter 5. Monthly data were created for the following variables from up to 12 months prior to the index through 24 months after the index date. Dependent variables were COPD-related and all-cause medical costs obtained from institutional and professional claims. The primary exposure variable was the use of ICS. The period before the first ICS claim was defined as unexposed time, whereas the period after the first ICS claim was defined as ICS-exposed time. To adjust for exacerbation episodes, the months with medications for acute exacerbations (oral antibiotics or corticosteroids) were identified. To adjust for having condition changes, the first month with asthma or congestive heart failure was identified, and then, the subsequent months were defined as months with these conditions.

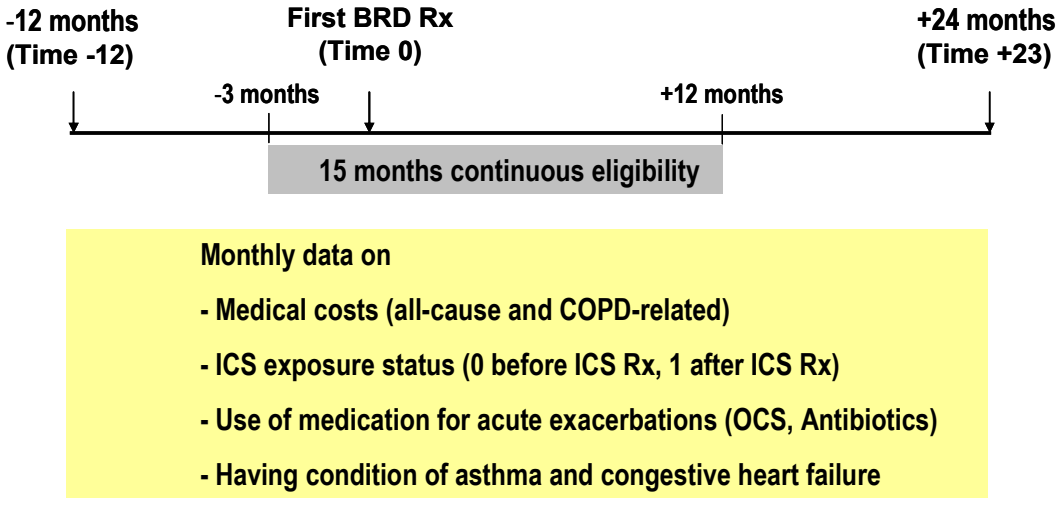


Figure 3.3 Study design used in Chapter 5

BRD: inhaled bronchodilators (anticholinergics or long-acting β_2 agonists), ICS: inhaled corticosteroids, OCS: oral corticosteroids. Rx: prescription.

An individual-level, fixed-effects model was used to estimate the impact of starting ICS treatment on medical costs among patients with COPD. The expected COPD-related and all-cause costs were modeled using the following equation (Equation 3.1):

$$E[COST_{it}] = \beta_1 TIME_t + \beta_2 ONSET_{it} + \beta_3 PST_{it} + \beta_4 ICS_{it} + \beta_5 TIME_t * ICS_{it}$$
$$+ \beta_6 (TIME_t * PST_{it} - TIME_t * ICS_{it}) + \gamma_1 ICS_{it} * AGE40_i + \gamma_2 ICS_{it} * AGE50_i \quad \text{(Equation 3.1)}$$
$$+ \gamma_3 ICS_{it} * AGE60_i + \delta_1 ANT_{it} + \delta_2 OCS_{it} + \delta_3 ASM_{it} + \delta_4 CHF_{it} + \delta_5 MONTH_t$$

where *TIME* is a continuous variable indicating month from -12 to +23, month 0 at the index; *ONSET* is a dummy variable indicating one month prior to the index; *PST* is a dummy variable indicating months after patients received the first bronchodilator treatment; *ICS* is a dummy variable indicating ICS use; *AGE40* to *AGE60* indicate age group variables with reference category of age in 70s; *ANT* and *OCS* indicate use of rescue medications (i.e., antibiotics and oral corticosteroids); and *ASM* and *CHF* indicate having comorbid conditions (i.e., asthma and congestive heart failure).

Changes in treatment costs after the index were expressed either by $\beta_1 + \beta_3 + (\beta_6 * TIME)$ during the time without ICS treatment or by $\beta_1 + \beta_3 + \beta_4 + (\beta_5 * TIME)$ during the time with ICS treatment. Therefore, the ICS treatment effect was calculated by the change in the slope, $\beta_4 + (\beta_5 - \beta_6) * TIME$. The ICS treatment effects for different age categories were explained by coefficients γ_1, γ_2 and γ_3 for the interaction terms between *ICS* and age dummy variables.

Figure 3.4 illustrates study design used in Chapter 6. Two-period analyses were conducted; ICS exposure levels (medication persistence and adherence) were measured in the first year and outcomes (inpatient admissions or emergency department visits and medical costs) were measured in the second year. Medication persistence or treatment duration was measured as the time between initiating and discontinuing ICS therapy; and medication adherence was measured by medication possession ratio (MPR) using

information about days supply and days between refills. Three types of adherence measures were used as described previously; average MPR, recent MPR and overall MPR.

Multivariable regression models were used to estimate the factors associated with medication persistence and adherence. Time to discontinuation within one year of ICS treatment was assessed using a Cox proportional hazard regression model (Allison 1995). The patient's follow-up time was censored at the end of the first year. MPR was estimated using an ordinary least square (OLS) model (Wooldridge 2003). Two MPR measures, average MPR and overall MPR, were used as dependent variables.

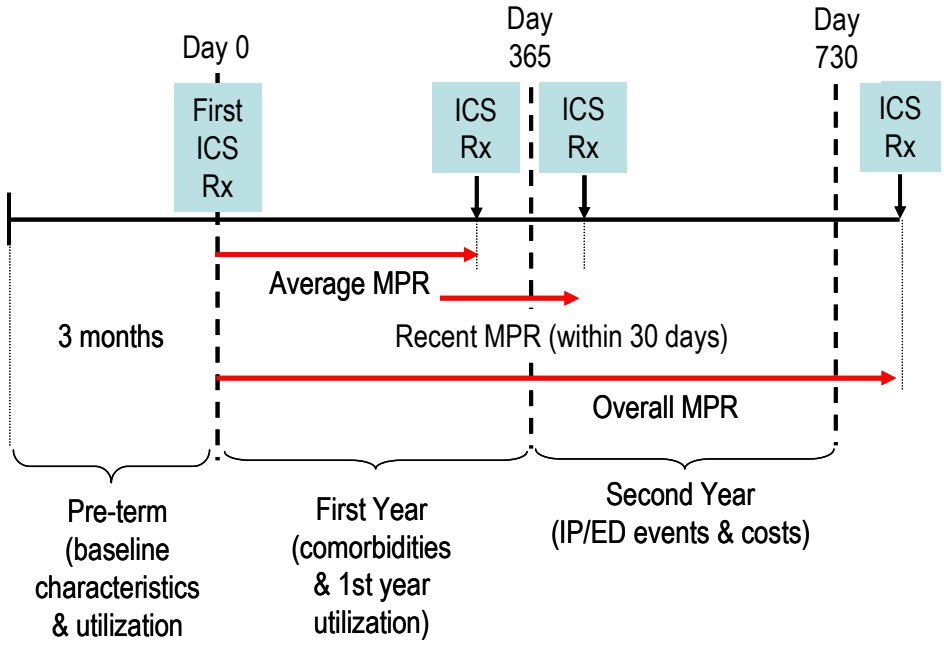


Figure 3.4 Study design used in Chapter 6

ICS: inhaled corticosteroids, MPR: medication possession ratio, IP: hospitalization, ED: emergency department visit, Rx: prescription.

The number of inpatient admissions or emergency department visits and medical costs during the second year were summarized according to three categories of medication persistence (ICS treatment was terminated within six months, terminated between six and

12 months, or continued more than 12 months) and quintiles of the MPR (average MPR and recent MPR). Proportions having exacerbation events were compared using a logistic regression model, and means among patients with any event were compared using a negative binominal model across the categories (Kleinbaum et al. 1998, Allison 1999). Treatment costs were compared using a generalized linear model (GLM) with a log link and gamma distribution (Manning and Mullahy 2001). Multivariable models were used to control for baseline patient characteristics (age, gender, insurance coverage, and census region), comorbidities (having asthma, congestive heart failure, depression, hypertension and the total number of chronic conditions during the first year) and pre-term healthcare utilization (i.e., specifically, specialist care, oxygen therapy, a spirometry test, number of any medication, and use of oral corticosteroids, oral antibiotics, short- and long-acting β_2-agonists, anticholinergics and theophylline during the first year). Because about 20% of patients had no COPD-related medical costs in the second year, a two-part model was used: a logistic regression to predict the probability of positive costs and a GLM to predict costs among patients with the positive costs (Blough et al. 1999).

CHAPTER 4

Impact of Early Initiation of Inhaled Corticosteroids on Resource Utilization and Costs in Patients with COPD: A Propensity-Score-Matching Approach.

4.1 Abstract

Objective: Economic benefits of early initiation of inhaled corticosteroids (ICS) treatment in patients diagnosed with chronic obstructive pulmonary disease (COPD) were assessed using a large managed care claims database.

Methods: Early initiation was defined as beginning ICS within three months of initiation of regular bronchodilators and was compared with patients who initiated ICS therapy thereafter. To avoid biases due to treatment selection, a propensity-score-matching technique was used. COPD exacerbation risks and other resource utilization per person-year were compared between the two groups. A two-part model with a logistic and a generalized linear model (GLM) regression was used to estimate differences in medical, pharmacy and total service costs.

Results: A total of 7,712 matched COPD patients with comparable background characteristics were identified. Early initiation of ICS was associated with lower exacerbation risks and resource utilization. Patients who started ICS within three months had more ICS prescriptions (3.7 vs. 2.4 prescriptions per year) and higher pharmacy costs ($4,105 vs. $3,985; $p<0.05$). However, because of lower medical services use, early initiation of ICS could save medical costs ($14,239 vs. $15,461; $p<0.05$) and total costs ($18,334 vs.

$19,446; p<0.05). The same trends were observed for services directly attributable to COPD conditions.

Conclusion: Initiating ICS earlier than the current clinical guideline recommendation may be beneficial to avoid exacerbations and to reduce treatment costs.

Key words: Chronic obstructive pulmonary disease (COPD), inhaled corticosteroids (ICS), propensity-score-matching, exacerbation, treatment cost

4.2 Introduction

Chronic obstructive pulmonary disease (COPD), a disease characterized by airway obstruction and inflammation leading to chronic bronchitis and emphysema, is an important cause of morbidity, mortality, and increased healthcare utilization and costs (Man et al. 2003, Mannino et al. 2006). In the US, COPD affects more than 6% of adults and is responsible for about 726,000 hospitalizations and 119,000 deaths annually (Mannino et al. 2002). The economic cost of COPD in 2004 was estimated to be $37 billion, including $21 billion in direct healthcare spending and $16 billion in productivity losses (National Heart, Lung, and Blood Institute [NHLBI] 2004).

The burden of disease attributable to COPD has been examined using various state and national databases. Using the 2001 Medicaid data from California and Florida, Marton et al. (2005) found that COPD patients used approximately $5,200 to $6,500 more medical costs, on average, compared with non-COPD patients; however, only about half of these costs were directly attributable to COPD. Another analysis of the 2000 Medical Expenditure Panel Survey (MEPS) also showed that COPD patients used $4,900 more compared with non-COPD patients after adjusting for age, sex, race, smoking, marital status, and education (Miller et al. 2005). Research consistently reports that COPD patients use more inpatient,

outpatient, and pharmacy services not only for respiratory conditions but also for cardiovascular conditions, mental disorders, and other chronic conditions.

There is no known cure for COPD. The medications currently available are used to prevent and control symptoms as well as to decrease the frequency and severity of exacerbations. Because COPD is a progressive disease, clinical guidelines recommend a stepwise increase in treatment depending on severity of the disease (Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2006). Bronchodilator medications, such as anticholinergics, β_2-agonists (short- and long-acting), theophylline or their combinations, are central to the symptomatic management of COPD. They are given on an as-needed basis for relief of airflow limitations, or on a regular basis to prevent worsening symptoms. Treatment with inhaled corticosteroids (ICS), which attenuate airway hyper-responsiveness and inflammation, is added to the regular treatment for patients with advanced disease and repeated exacerbations.

Although there are conflicting data on the effect of ICS treatment on improvement in lung function or reduction in mortality, evidence suggests that ICS is useful to decrease risks of acute exacerbations that affect quality of life and increase use of healthcare resources. A meta-analysis of eight randomized control trials comparing ICS with placebo among COPD patients followed for at least six months found that although ICS treatment did not significantly reduce mortality, ICS treatment led to a 24% (relative risk [RR] 0.76, 95% confidence interval [CI]: 0.72 to 0.80) reduction in exacerbation risks (Sin et al. 2003). Another pooled analysis using ten controlled trials found that use of ICS reduced the rate of exacerbations by 33% (RR 0.67, 95% CI: 0.59 to 0.77) compared with placebo treatment over a mean follow-up period of 20.8 months (Gartlebner et al. 2006).

In the current clinical guidelines, use of ICS treatment is suggested to augment regular bronchodilator treatment. However, because patients with moderate to severe COPD are at high risk of exacerbations, such sudden worsening of respiratory conditions

(Donaldson and Wedzicha 2006, Mannino et al. 2006), earlier initiation of ICS treatment than the recommended strategy may be effective to reduce such exacerbation risks. Moreover, exacerbations often result in additional hospitalizations or emergency department visits (Ramsey and Sullivan 2003, Holgum et al. 2005, Shaya 2006), and thus, economic benefits may accrue from reducing the exacerbation risks. To assess the effects of earlier treatment on healthcare utilization and costs, data from long-term follow-up in real world clinical settings are required (Schneeweiss and Avorn 2005). Therefore, this study uses a large managed care claims database in which patients can be followed for relatively long time periods to evaluate the economic consequence of early initiation of ICS treatment.

4.3 Methods

Study design and population

A retrospective cohort study was conducted to examine the benefits of ICS treatment initiated earlier than what is recommended in national and international guidelines on health service use and costs in moderate-to-severe COPD patients. Data for this study were obtained from the Integrated Healthcare Information Services (IHCIS) database from January 1997 through December 2005. This database includes information on enrollment, facility, professional and pharmacy services for more than 37 million patients covered by approximately 35 managed care health plans in nine census regions in the United States. Data available for each facility or professional service claim ("medical claim") include dates of service, International Classification of Diseases 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes, and ICD-9-CM procedure codes or Current Procedural Terminology, Version 4 (CPT-4) procedure codes. The data also include pharmacy claims with drug name dispensed (in National Drug Code [NDC]), the dispensing date and days supply.

In the IHCIS data, cost information is standardized in order to make comparisons easier across all services, data sources, and time periods (IHCIS 2005). For example, (1)

facility inpatient costs were calculated based on primary diagnosis categories, length of stay, and presence of ICU/surgery; (2) facility outpatient costs were calculated based on requested (submitted) charges; (3) professional service costs were calculated using a standardized payment schedule based on a resource-based relative value scale (RBRVS); and (4) pharmacy service costs were calculated using First Data Bank pricing adjusted by quantity and therapeutic category; and (5) all costs were adjusted for inflation over time (2005 US dollars). All data were HIPAA compliant with all health plan and personal information de-identified to assure confidentiality (IHCIS 2005).

COPD patients were identified using medical and pharmacy claims. The inclusion criteria were patients who (1) had one or more medical claims of COPD (ICD-9-CM: 491.xx, 492.xx or 496.xx in primary or secondary positions) between January 1998 and December 2004, (2) had regular treatment with inhaled bronchodilators (defined by at least three pharmacy claims of anticholinergics or long-acting β_2-agonists [LABA]), and (3) were 40 years of age or older. All eligible patients were required to have continuous health plan coverage from three months before the first pharmacy claim of bronchodilators ("index date") through 12 months after the date. Patients were excluded from the analysis if they had diagnosis of cystic fibrosis (ICD-9-CM: 277.0x) or respiratory tract cancer (ICD-9-CM: 160.xx-164.xx, or 231.xx), had no ICS treatment during the 24-month follow-up period, or had initiated ICS before the index date. ICS users were classified by the initial date of ICS treatment into: (1) the treatment group if patients started ICS within three months of the index; or (2) the control group if they started ICS between three and 24 months post index. Patients in the groups were matched to each other using the following propensity-score-method.

The propensity score was defined as the conditional probability of initiating ICS within three months (being in the treatment group) given a set of observed individual characteristics. Matching on the propensity score is a method for controlling for baseline

characteristics that could influence treatment choices and outcomes (D'Agostino 1998, Joffe and Rosenbaum 1999). The propensity score was estimated using a multivariable logistic regression model with observed baseline characteristics (e.g., age, sex, and census region), access to specialist care, comorbidities, and pre-index resource utilization (e.g., inpatient, outpatient and pharmacy services). Then, patients in the treatment group were matched one-to-one with patients in the control group who had the closest propensity score. The nearest neighbor with caliper method was used to match within 20% of the standard deviation of associated propensity scores (Baser 2006). Patients without a propensity-score-match were excluded. At the index date, patients with the same propensity score would have the same probability of being assigned in treatment group.

Measures

The main outcomes of interest were exacerbation events, other resource utilization, and treatment costs. Exacerbation events were defined as COPD-related hospitalizations, emergency department visits, unplanned office visits, or their combinations. Because it was difficult to distinguish between regular (planned) and unplanned office visits, only office visits with immediate prescriptions of rescue medications (oral antibiotics or corticosteroids within three days of the office visit claim) were defined as unplanned. The total numbers of services used were summarized as inpatient admissions (for any reason, respiratory-related or cardiovascular-related conditions), outpatient services (emergency department, primary care physicians, pulmonary medicine specialists, cardiology specialists or psychiatry specialists) or prescriptions (all medications, COPD-related medications, cardiovascular-related medications, antidepressants, or anti-diabetics). Services associated with non-COPD-related conditions that are often observed in COPD patients also were examined (Mapel et al. 2005, Soriano et al. 2005). Treatment costs were categorized as medical costs, pharmacy costs, and total costs for both all-cause and COPD-related services. The mean

annual values were calculated as total number of events or costs divided by the number of years of follow-up after the index date.

Explanatory variables were age at index, gender, year and month of the index date, main provider (i.e., whether patients received care from a pulmonary medicine specialist or not during three months prior to the index date), census regions (categorized into four: Northeast, South, Midwest or West), types of health plans (government or commercial), comorbid conditions and pre-index resource use. Chronic conditions used to calculate the Charlson index (Charlson et al. 1987, Deyo et al. 1992), as well as major comorbid conditions usually observed in COPD patients (e.g., asthma, depression, non-vertebral fracture, and hypertension) were identified during the 6-month observation time (from three months before to three months after the index date). In addition, respiratory-related medical services (such as use of a spirometry test, oxygen therapy, or pulmonary rehabilitation), respiratory and non-respiratory medications, hospitalizations and emergency department visits were identified during the 3-month observation time before the index date.

Analysis

Baseline characteristics and resource utilization were compared for propensity-score-matched samples to check the fidelity of the matching process. Exacerbation risks and other resource utilization patterns after the index were summarized descriptively, using means and standard deviations. Since many observations had a zero value, the number of patients and percentage with the positive values were reported. For matched samples, categorical values, including the proportion of patients with non-zero values, were compared using a logistic regression model, and a negative binomial model was employed to test differences in continuous variables among patients with non-zero values (Kleinbaum et al. 1998, Allison 1999).

Differences in treatment costs were analyzed using two-part regression models to address the large number of zero values and skewed distribution (Blough et al. 1999). A logistic regression was first used to predict the probability of having any treatment costs. Costs for patients with positive (i.e., > $0) values were then modeled using a generalized linear model (GLM) with a gamma distribution and log link (Manning and Mullahy 2001). GLM regression coefficient estimates were exponentiated to represent the ratio of expected costs in the treatment group compared with those in the control group. All tests of statistical significance employed an alpha level of 0.05. All analyses were conducted using SAS statistical software, version 8.2 (SAS Institute, Cary NC).

Sensitivity analysis

In the main analysis, the early initiation of ICS treatment was defined as starting ICS within three months of the index date (initiation of inhaled bronchodilator therapy). Some patients may start ICS treatment soon after beginning the maintenance therapy with inhaled bronchodilators, whereas others may delay ICS treatment until they experience worsening symptoms. The rationale for selecting three months was that it might take several months for repeated exacerbations to occur on inhaled bronchodilator treatment. However, if patients started ICS treatment within three months as a result of worsening symptoms or the joint influence of comorbid conditions, the findings could be negatively biased due to confounding by indication; that is, more severe patients are more likely to use more effective treatment and thus be in the treatment group. Therefore, we conducted a sensitivity analysis changing the threshold of early initiation of ICS treatment from three months to one month after the index date to evaluate the influence of selecting the decision point.

4.4 Results

Study subjects

There were 785,759 COPD patients without diagnoses of cystic fibrosis or respiratory tract cancer in the IHCIS database between 1998 and 2004. Of those, 10,271 eligible patients (treatment group: 6,280, and control group: 3,991) who met inclusion / exclusion criteria were identified (Figure 4.1). After applying propensity-score-matching (PSM), the analytic sample included 7,712 individuals (or 3,856 pairs). Mean, median and rage of the follow-up duration are 1,040 days (2.8 years), 862 days (2.4 years) and 365 (1.0 year) to 2,554 days (7.0 years), respectively. Demographic characteristics before and after PSM are summarized in Table 4.1. Also, pre-index utilization after PSM is summarized in Table 4.2. Prior to PSM, there were significant differences in baseline characteristics between two study groups. Patients in the treatment group were more likely to be younger, have commercial insurance and asthmatic conditions, and use services from a specialist, a spirometry test and respiratory-related medical / pharmacy services during the pre-index period than those in the control group. However, no statistical differences were observed in any of these factors after PSM.

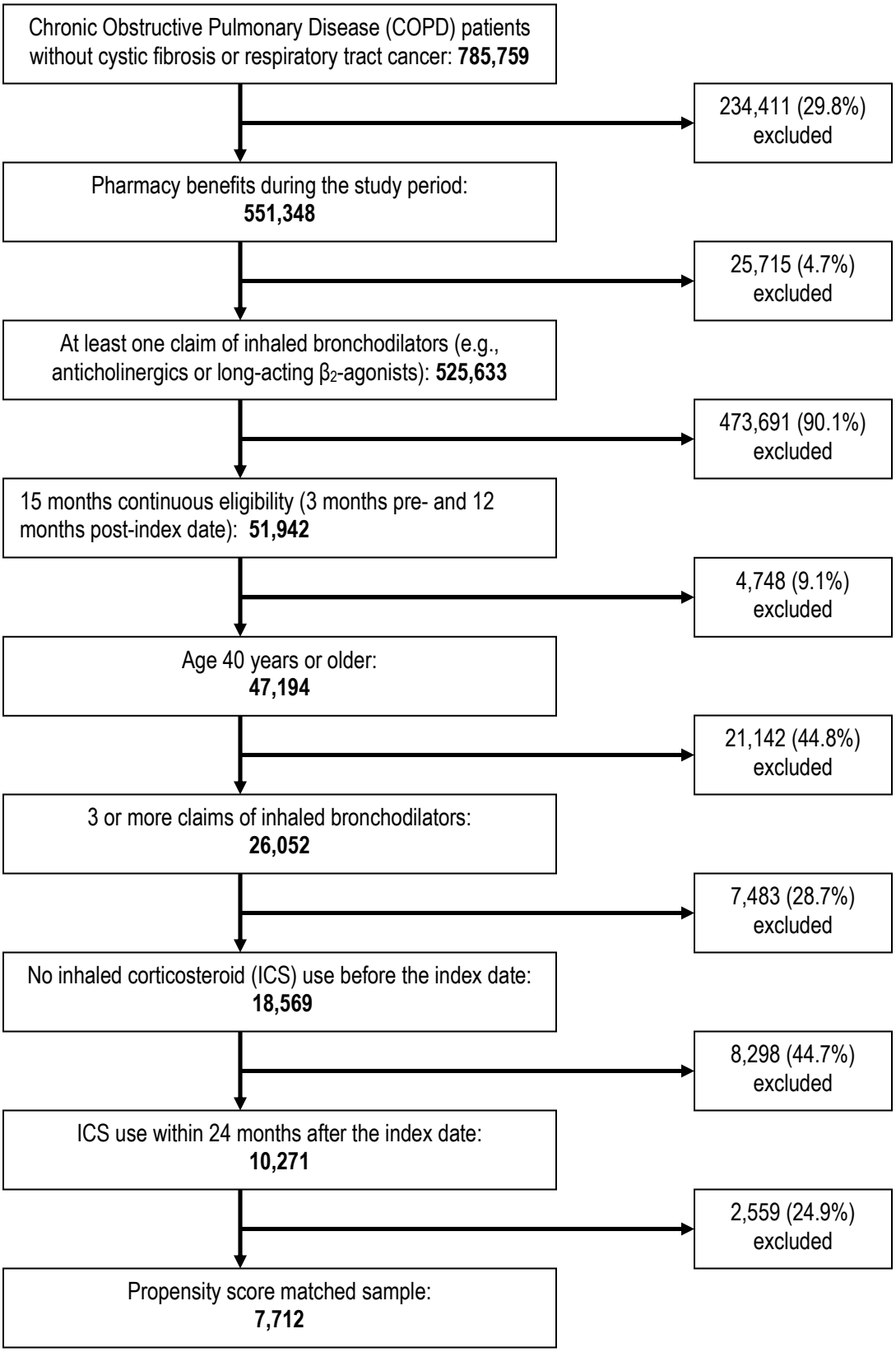


Figure 4.1: Study sample selection

Table 4.1: Baseline characteristics before and after propensity-score-matching

	Before PSM			After PSM		
Patient groups	Treatment	Control		Treatment	Control	
Number of patients	6,280	3,991		3,856	3,856	
Variables	%	%	p-values	%	%	p-values
Age Categories (in years)						
40-49	15.59	13.88	<0.0001	13.49	14.06	0.9056
50-59	33.71	30.49		31.72	31.33	
60-69	29.11	28.09		28.73	28.63	
70-79	21.59	27.54		26.06	25.99	
Male	46.13	45.70	0.6716	46.45	46.03	0.7148
Pulmologist care	21.83	15.89	<0.0001	16.23	16.29	0.9508
Insurance coverage						
Medicaid/Medicare	13.65	17.97	<0.0001	16.83	16.47	0.6687
Commercial	86.35	82.03		83.17	83.53	
Census region						
Northeast	52.88	49.94	0.0277	50.78	50.36	0.9824
South	11.86	12.63		12.79	12.76	
Midwest	10.75	11.88		11.75	11.88	
West / others	24.51	25.56		24.69	25.00	
Comorbidities						
Myocardial infarction	3.93	3.16	0.0404	3.27	3.22	0.8977
Congestive heart failure	12.95	11.63	0.0482	12.27	11.57	0.3426
Peripheral vascular disease	4.16	4.54	0.3560	4.72	4.41	0.5126
Cerebrovascular disease	5.49	6.01	0.2678	6.09	5.89	0.7011
Rheumatologic disease	2.15	2.53	0.2091	2.33	2.39	0.8807
Diabetes	14.04	14.83	0.2664	14.45	14.47	0.9742
Renal disease	2.10	1.83	0.3353	1.79	1.87	0.7987
Malignancy / AIDS	7.45	6.82	0.2237	6.72	6.87	0.7860
Asthma	42.68	28.11	<0.0001	29.46	29.02	0.6704
Depression	12.12	11.68	0.5012	11.75	11.62	0.8593
Nonvertebral fracture	3.20	3.36	0.6626	3.06	3.19	0.7435
Hypertension	36.54	38.91	0.0157	38.64	37.97	0.5425
COPD-related procedures						
Oxygen therapy	8.41	7.74	0.2297	7.55	7.73	0.7641
Spirometry test	21.40	16.24	<0.0001	16.03	16.70	0.4235
Pulmonary rehabilitation	2.15	2.18	0.9182	2.13	2.07	0.8738
Nebulized therapy	2.88	2.41	0.1460	2.49	2.49	1.0000
Bronchoscopy, Intubation, or Tracheostomy	1.34	1.08	0.2449	0.96	1.09	0.5718

Note: Chi-square tests were used to compare percentage of positive values. Comorbid conditions that had fewer than 50 observations (peptic ulcer disease, liver disease, dementia, paraplegia or hemiplegia) as well as month and year dummy variables were excluded from the table. PSM: propensity-score-matching.

Table 4.2: Pre-index utilization after propensity-score-matching

Service category	Pre-index utilization after PSM		p-values	
	Treatment group (n=3,856)	Control group (n=3,856)	Logistic	Negative binomial
Inpatient admissions				
for any reason				
Patients with any use, no. [%]	661 [17.1]	623 [16.2]	0.2455	
Mean (SD) among any use	1.21 (0.58)	1.28 (0.68)		0.2416
for respiratory-related conditions				
Patients with any use, no. [%]	358 [9.3]	354 [9.2]	0.8750	
Mean (SD) among any use	1.08 (0.32)	1.09 (0.38)		0.9183
for non-respiratory-related conditions				
Patients with any use, no. [%]	303 [7.9]	269 [7.0]	0.1398	
Mean (SD) among any use	1.20 (0.51)	1.36 (0.75)		0.0884
Emergency department visits				
for any reason				
Patients with any use, no. [%]	754 [19.6]	733 [19.0]	0.5444	
Mean (SD) among any use	1.34 (0.76)	1.32 (0.67)		0.7954
for respiratory-related conditions				
Patients with any use, no. [%]	433 [11.2]	428 [11.1]	0.8565	
Mean (SD) among any use	1.17 (0.43)	1.14 (0.39)		0.6330
for non-respiratory-related conditions				
Patients with any use, no. [%]	321 [8.3]	305 [7.9]	0.5047	
Mean (SD) among any use	1.22 (0.49)	1.25 (0.59)		0.6834
Medications				
Oral corticosteroids				
Patients with any use, no. [%]	612 [15.9]	584 [15.1]	0.3785	
Mean (SD) among any use	1.39 (0.73)	1.47 (0.82)		0.2697
Oral antibiotics				
Patients with any use, no. [%]	1,272 [33.0]	1,257 [32.6]	0.7160	
Mean (SD) among any use	1.50 (0.84)	1.51 (0.86)		0.7933
Short-acting β_2-agonists				
Patients with any use, no. [%]	807 [20.9]	791 [20.5]	0.6531	
Mean (SD) among any use	1.81 (1.28)	1.85 (1.27)		0.5380
Theophylline				
Patients with any use, no. [%]	182 [4.7]	174 [4.5]	0.6642	
Mean (SD) among any use	1.69 (0.80)	1.67 (0.93)		0.8446
Other medications				
Patients with any use, no. [%]	3,195 [82.9]	3,240 [84.0]	0.1681	
Mean (SD) among any use	8.66 (8.01)	8.49 (7.76)		0.3356

Note: The first row describes the number of patients with positive values (>0) and their percentage [%] and the second row describes means and standard deviations (SD) among patients who had positive values (>0). A logistic regression model was used to compare percentage of positive values and a negative binominal model was used to compare means among patients with positive values.

Exacerbation events

Exacerbation events per person-year are summarized in Table 4.3. Selected patients who initiated ICS treatment within three months of the index ("PSM selected treatment group") had a significantly lower probability of having at least one exacerbation event compared with those who started ICS after three months ("PSM selected control group"). When the exacerbation events were defined by either COPD-related hospitalizations or emergency department visits ("severe exacerbation"), the selected treatment group had 7% lower risk of exacerbations. Similar risk reduction was observed when the exacerbation events were defined by unplanned office visits with rescue medications ("mild exacerbation"). There were no major differences in the mean number of events among patients who experienced events.

Table 4.3: Summary of exacerbation events

	Resource utilization per person-year		p-values	
Exacerbations events (defined by)	Treatment group (n=3,856)	Control group (n=3,856)	Logistic	Negative binomial
Inpatient admissions				
Patients with any event, no. [%]	441 [11.4]	631 [16.4]	<0.0001	
Mean (SD) among any event	0.74 (0.86)	0.72 (0.78)		0.6702
Emergency department visits				
Patients with any event, no. [%]	542 [14.1]	672 [17.4]	<0.0001	
Mean (SD) among any event	0.68 (0.62)	0.64 (0.59)		0.3928
Inpatient admissions or emergency department visits (severe exacerbations)				
Patients with any event, no. [%]	804 [20.9]	1,074 [27.9]	<0.0001	
Mean (SD) among any event	0.86 (0.98)	0.82 (0.89)		0.3408
Unplanned office visits (mild exacerbations)				
Patients with any event, no. [%]	1,914 [49.6]	2,172 [56.3]	<0.0001	
Mean (SD) among any event	1.18 (1.40)	1.27 (1.58)		0.0188

Note: The first row describes the number of patients with positive values (>0) and their percentage [%] and the second row describes means and standard deviations (SD) among patients who had positive values (>0). A logistic regression model was used to compare percentage of positive values and a negative binominal model was used to compare means among patients with positive values.

Resource utilization

The annual healthcare utilization of COPD patients is summarized in Table 4.4 (inpatient and outpatient services) and Table 4.5 (pharmacy services). Patients in the selected treatment group had a significantly lower probability of having inpatient admissions for any reason, for respiratory-related reasons, and for cardiovascular-related conditions than those in the selected control group. Lower utilization also was observed in outpatient services provided by emergency departments, primary care physicians, pulmonary medicine specialists and cardiology specialists. There were no differences in the total use of any medication. The mean number of COPD-related medications per person-year was higher in the selected treatment group compared with the control group. In particular, the selected treatment group tended to use more ICS (3.7 vs. 2.4 prescriptions) and LABA (47% and 2.5 prescriptions vs. 42% and 2.3 prescriptions), but fewer anticholinergics, short-acting β_2-agonists, oral corticosteroids, and oral antibiotics. Both groups used similar amounts of cardiovascular-related medications, antidepressants, and anti-diabetics.

Table 4.4: Summary of resource utilization – inpatient and outpatient services

Reason for service use	Resource utilization per person-year		p-values	
	Treatment group (n=3,856)	Control group (n=3,856)	Logistic	Negative binomial
Inpatient admissions				
Any reason				
Patients with any use, no. [%]	1,798 [46.6]	2,051 [53.2]	<0.0001	
Mean (SD) among any use	1.18 (1.70)	1.18 (1.44)		0.9184
Respiratory-related conditions				
Patients with any use, no. [%]	903 [23.4]	1,145 [29.7]	<0.0001	
Mean (SD) among any use	0.82 (0.97)	0.83 (0.99)		0.7992
Cardiovascular-related conditions				
Patients with any use, no. [%]	562 [14.6]	631 [16.4]	0.0299	
Mean (SD) among any use	0.71 (0.75)	0.76 (0.80)		0.3314
Outpatient services				
Visit to emergency department				
Patients with any use, no. [%]	1,899 [49.2]	2,086 [54.1]	<0.0001	
Mean (SD) among any use	1.07 (1.29)	1.05 (1.16)		0.4869
Visit to primary care physicians				
Patients with any use, no. [%]	3,461 [89.8]	3,524 [91.4]	0.0142	
Mean (SD) among any use	6.70 (6.97)	7.02 (5.76)		0.0100
Visit to pulmonary medicine specialists				
Patients with any use, no. [%]	1,698 [44.0]	1,795 [46.6]	0.0265	
Mean (SD) among any use	2.41 (2.74)	2.46 (3.01)		0.4067
Visit to cardiology specialists				
Patients with any use, no. [%]	1,705 [44.2]	1,794 [46.5]	0.0418	
Mean (SD) among any use	2.41 (3.54)	2.22 (3.17)		0.0346
Visit to psychiatry specialists				
Patients with any use, no. [%]	292 [7.6]	316 [8.2]	0.3106	
Mean (SD) among any use	4.58 (6.95)	3.31 (4.50)		0.0003

Note: The first row describes the number of patients with positive values (>0) and their percentage [%] and the second row describes means and standard deviations (SD) among patients who had positive values (>0). A logistic regression model was used to compare percentage of positive values and a negative binominal model was used to compare means among patients with positive values.

Table 4.5: Summary of resource utilization – pharmacy services

	Resource utilization per person-year		p-values	
Prescription claims	Treatment group (n=3,856)	Control group (n=3,856)	logistic	Negative binomial
Any medication				
Patients with any use, no. [%]	3,856 [100.0]	3,856 [100.0]	n/a	
Mean (SD) among any use	28.81 (18.58)	29.55 (17.77)		0.0597
COPD-related medications				
Patients with any use, no. [%]	3,856 [100.0]	3,856 [100.0]	n/a	
Mean (SD) among any use	13.94 (9.53)	13.46 (8.88)		0.0136
ICS				
Patients with any use, no. [%]	3,856 [100.0]	3,856 [100.0]	n/a	
Mean (SD) among any use	3.74 (3.09)	2.43 (2.16)		<0.0001
Anticholinergics				
Patients with any use, no. [%]	3,215 [83.4]	3,474 [90.1]	<0.0001	
Mean (SD) among any use	4.10 (3.70)	4.35 (3.91)		0.0029
LABA				
Patients with any use, no. [%]	1,813 [47.0]	1,607 [41.7]	<0.0001	
Mean (SD) among any use	2.54 (2.45)	2.29 (2.28)		0.0009
SABA				
Patients with any use, no. [%]	2,365 [61.3]	2,602 [67.5]	<0.0001	
Mean (SD) among any use	3.09 (3.70)	3.32 (4.01)		0.0151
OCS				
Patients with any use, no. [%]	2,483 [64.4]	2,678 [69.5]	<0.0001	
Mean (SD) among any use	1.89 (2.29)	1.92 (2.25)		0.5541
Oral antibiotics				
Patients with any use, no. [%]	3,332 [86.4]	3,498 [90.7]	<0.0001	
Mean (SD) among any use	2.27 (2.10)	2.35 (2.09)		0.1069
Theophylline				
Patients with any use, no. [%]	496 [12.9]	472 [12.2]	0.4095	
Mean (SD) among any use	4.06 (3.55)	3.67 (3.37)		0.0863
Cardiovascular-related medications				
Patients with any use, no. [%]	2,563 [66.5]	2,562 [66.4]	0.9808	
Mean (SD) among any use	9.52 (8.04)	9.29 (8.02)		0.3031
Antidepressants				
Patients with any use, no. [%]	1,676 [43.5]	1,723 [44.7]	0.2811	
Mean (SD) among any use	5.72 (4.94)	5.36 (4.98)		0.0430
Anti-diabetics				
Patients with any use, no. [%]	583 [15.1]	605 [15.7]	0.4877	
Mean (SD) among any use	7.08 (5.70)	6.73 (5.30)		0.2812

Note: The first row describes the number of patients with positive values (>0) and their percentage [%] and the second row describes means and standard deviations (SD) among patients who had positive values (>0). Logistic regression model was used to compare percentage of positive values and negative binominal model was used to compare means among patients with positive values. ICS: inhaled corticosteroids, LABA: long-acting β_2-agonists, SABA: short-acting β_2-agonists, OCS: oral corticosteroids. n/a: not applicable.

Treatment costs

All-cause and COPD-related treatment costs by service category are summarized in Table 4.6. Because approximately 3% of patients had no COPD-related medical costs, a two-part model was used to estimate the probability of having any medical costs as well as mean medical costs among patients with positive values. The earlier initiation of ICS treatment was associated with reduced medical costs for both all-cause and COPD-related services.

Table 4.6: Estimated all-cause and COPD-related treatment costs

Treatment costs	Logistic regression	GLM for costs > 0	Treatment group	Control group	Incremental costs (vs. controls)
	Odds ratio (95% IC)	Exp(coef.) (95% CI)	Annual costs ($)	Annual costs ($)	Mean ($)
All-cause costs					
Medical	n/a	0.92 (0.87, 0.97)	14,239	15,461	-1,222
Pharmacy	n/a	1.03 (1.00, 1.07)	4,105	3,985	+120
Total	n/a	0.94 (0.90, 0.97)	18,334	19,446	-1,112
COPD-related costs					
Medical	0.53 (0.40, 0.69)	0.79 (0.74, 0.84)	1,871	2,419	-548
Pharmacy	n/a	1.13 (1.09, 1.16)	1,283	1,137	+146
Total	n/a	0.88 (0.85, 0.92)	3,214	3,634	-420

Note: Estimated costs were calculated using a two-part model [first part: a logistic regression to predict any costs if more than 3% were zero values (COPD-related medical cost only), second part: a generalized liner model (GLM) among those with positive costs] among propensity-score-matched subjects (n=7,712). n/a: not applicable.

Patients in the selected treatment group had, on average, significantly lower all-cause (8% lower) and COPD-related (23% lower) medical costs. Mean medical costs compared with those of the selected control group were $1,222 and $548 lower, respectively.

All-cause and COPD-related pharmacy costs were significantly higher in the selected treatment group with the mean incremental costs of $120 and $146, respectively. However, the reduction in medical costs was more than the increase in pharmacy costs, resulting in an overall total cost savings compared to the selected control group. The cost savings for all-cause and COPD-related services were $1,112 and $420, respectively.

Sensitivity analysis

When using the threshold of one month as the early initiation of ICS treatment, 8,764 (4,382 in each group) patients had matched pairs. No statistical differences in baseline characteristics and pre-index utilization were observed after PSM. The trends for exacerbation risks and other resource utilization were nearly identical with the results from the main analysis. Patients in the selected treatment group, who started ICS treatment within one month, experienced exacerbations less frequently, used fewer inpatient and outpatient services, and used fewer medications, except ICS and LABA, than those in the control group. They had lower medical costs, higher pharmacy costs, and lower total costs for both all-cause and COPD-related services as observed in the main analysis.

4.5 Discussion

Our analysis suggests that selected COPD patients who are treated with ICS along with regular inhaled bronchodilators consume fewer services and have lower treatment costs for both any reason and COPD-related conditions compared with those who treated ICS after three months of the initial inhaled bronchodilator treatment. Although pharmacy costs for ICS medications are higher, the potential reduction in use of medical services compensates for the additional ICS costs. Moreover, early initiation of ICS treatment appears to alter required COPD management and may lead to savings in overall treatment costs.

This study used managed care claims to analyze utilization and costs for patients with COPD. Observational studies based on a variety of databases have played an important part in developing information about effectiveness of drug treatments (Schneeweiss and Avorn 2005). However, the current evidence for ICS treatment in COPD patients is mixed (Burney et al. 2003). Several researchers reported that ICS treatment was associated with significant reduction of all-cause mortality as well as COPD-related hospitalizations (Sin and Tu 2001, Soriano et al. 2002, Kiri et al. 2005), whereas others reported no such benefits (Fan et al. 2003, Suissa 2003 and 2004). These mixed results may be due to possible sources of bias in observational studies including patient selection and confounders.

To minimize the potential bias, researchers often use multivariable analyses to control for demographic factors, comorbid conditions, and previous resource utilization as proxy of disease severity (Iezzoni 2003). In addition, sensitivity analyses are sometimes used to evaluate influence of uncertainty and misclassification of measurements (Rothman and Greenland 1998). More recently, different analytical techniques, such as the propensity-score-method has been used to minimize selection bias. For example, Kiri et al. (2005) used the propensity-score-matching method to examine association between ICS use and mortality or COPD exacerbations by eliminating systematic differences between ICS users and non-users.

In this study, after selecting COPD patients with diagnosis codes as well as use of COPD-related medications (inhaled bronchodilators and ICS), patients were classified by the timing of ICS treatment. Then, the propensity score of having ICS treatment within three months was estimated using observed background characteristics. At the time of the index date, matched patients had balanced characteristics and equal likelihood of receiving the treatment (Baser 2006). Therefore, we could assume that observed differences in healthcare utilization and costs after the index could be explained by the treatment choice:

to start ICS treatment along with inhaled bronchodilators or to use inhaled bronchodilators first and add ICS after having uncontrolled symptoms.

Even though the possible sources of bias were carefully addressed in this study, there are fundamental limitations in observational studies based on administrative claims. First, no clinical information is available in the claims. Clinical practice guidelines define COPD clinical stages by lung function (e.g., FEV_1) and the addition of regular treatment with ICS to bronchodilator treatment is recommended for patients with an $FEV_1 < 50\%$ predicted (GOLD 2006). However, because no lung function data were available, we had to infer the clinical stage from information about resource use. Specifically, we used at least three claims of inhaled bronchodilators as the proxy measure of moderate-to-severe condition. Moreover, utilization and cost associated with death could not be considered due to lack of mortality information. However, the misclassification of the disease severity may be non-differential that is, having no association with the treatment; and therefore, the direction of the bias, if any, should be toward the null.

Second, patients have different patterns of disease prognosis and treatment. Once patients experience an acute exacerbation, their lung function tends to decline more quickly, increasing the likelihood of subsequent exacerbations (Donaldson and Wedzicha 2006). Even though baseline characteristics were comparable across patients, it would be difficult to control for disease progression. Although some patients require ICS soon after bronchodilator treatment, others continue to be stable and do not require any additional treatments. To reduce this type of bias, we limited the study population to persons who started the ICS within 24 months of the index date. Descriptive assessments (not shown) indicated that disease progression as measured by resource utilization was fundamentally different for patients who did not use ICS during the entire follow-up or started the ICS after 24 months when compared with the study population.

Third, the propensity score approach is useful to eliminate selection bias only if all relevant variables are correctly measured (Stürmer et al. 2005). However, several important factors such as clinical information (e.g., lung function) and risk behaviors (e.g., smoking) are not typically available in claims data and must be estimated. We used pre-index utilization to proxy these unobserved factors in order to minimize the selection bias; however, a study using these factors should be conducted to provide definitive evidence.

Finally, prior to propensity-score-matching (PSM), the number of patients in the treatment group was larger than the number of patients in the control group. All analyses in this study were conducted using the PSM-selected patients in the treatment group who had matched controls (about 60% of all patients who initiated ICS treatment within three months of the index date). Therefore, observed benefits due to the early initiation of ICS treatment would be generalizable only to patients who were like the control patients. The findings, however, would suggest that prophylactic use of ICS treatment is beneficial among patients who do not experience worsened symptoms or repeated exacerbations.

4.6 Conclusion

Economic benefits of the early initiation of ICS treatment among COPD patients were observed in the administrative data from a real world clinical setting. Our findings from this observational study, which carefully addressed potential sources of bias, provide supportive evidence for initiation of ICS combination therapy earlier than currently is recommended in clinical guidelines.

CHAPTER 5

Assessing Treatment Effects of Inhaled Corticosteroids on Medical Costs among COPD Patients: Longitudinal Analysis of Managed Care Claims

5.1 Abstract

Objective: A longitudinal analysis of managed care claims data was conducted to estimate the treatment effects of inhaled corticosteroids (ICS) on medical costs.

Methods: Patients with chronic obstructive pulmonary disease (COPD) (ICD-9-CM: 491.xx, 492.xx or 496.xx), ages 40 years or older, who had 15 months continuous eligibility, and received both ICS and regular inhaled bronchodilators (i.e., anticholinergics or long-acting β_2-agonists) were selected from the claims database. Individual-level data on drug exposure status and costs were summarized for monthly intervals from up to one year before the initiation of bronchodilators ("index date") through a two-year follow-up period. A fixed-effects approach accounting for potential omitted variable biases was used to estimate the incremental effects of initiating ICS on medical costs. Interaction terms were included to evaluate the timing of ICS treatment as well as impact of patient age.

Results: A total of 10,271 COPD patients were used in the analysis. After adjusting for time-variant factors including use of medications for acute exacerbations and having conditions of asthma or congestive heart failure, ICS treatment was associated with a monthly cost reduction of $43 in COPD-related medical services and $55 in all-cause medical services. Moreover, a one-month delay of ICS initiation was associated with an additional $2 to $3 per

month in medical costs. The largest cost reduction was observed among older COPD patients.

Conclusion: The findings support evidence that initiation of ICS treatment earlier than the current guideline recommended strategy would be beneficial to prevent exacerbation risks and to reduce overall medical costs from the managed care perspective.

Key words: Chronic obstructive pulmonary disease (COPD), inhaled corticosteroids (ICS), longitudinal studies, claims analysis, healthcare costs.

5.2 Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by progressive airflow limitation and airway inflammation leading to a gradual loss in lung function (Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2006). Acute exacerbations of COPD (i.e., sudden worsening respiratory symptoms) are common for many COPD patients and are most often caused by respiratory tract infections (White et al. 2003). These exacerbations are an important part of the morbidity, mortality and progression of the disease. Patients with lower levels of lung function are more likely to experience more exacerbations, and frequent exacerbations may lead to reduced lung function (Seemungal et al. 2000, Calverley et al. 2005). Exacerbations are strongly related to increases in healthcare utilization including inpatient admissions, emergency department visits and use of rescue medications (Donaldson and Wedzicha 2005).

Because airway inflammation is one aspect of COPD, anti-inflammatory agents such as inhaled corticosteroids (ICS) may slow disease progression and prevent exacerbations. Current treatment guidelines recommend a stepwise increase in drug treatment depending on severity of the disease (GOLD 2006). In particular, ICS treatment should be used to

augment regular bronchodilator treatment for patients with advanced disease and repeated exacerbations. However, unlike the use of ICS in asthma treatment, the evidence for ICS efficacy is not consistent in COPD (Calverley 2004). In six randomized clinical studies in which COPD patients were followed for more than 12 months, ICS treatment was associated with a 4% to 26% reduction in exacerbation events defined by either respiratory-related hospitalizations, emergency department visits, worsening of respiratory symptoms, or their combinations (Vestbo et al. 1999, Lung Health Study Research Group [LHSRG] 1999, Burge et al. 2000, Calverley et al. 2003a and 2003b, Szafranski et al. 2003). The most recent randomized clinical study showed that the combination therapy of ICS and an inhaled bronchodilator reduced the risks of dying and moderate and severe exacerbations during the three-year follow-up (Calverley et al. 2007).

Because severe exacerbations are not common in COPD patients, large studies with adequate follow-up periods are required to detect significant effects of drug treatments. Pooled analyses using more than 4,000 COPD patients from randomized clinical trials of ICS showed significant effects of ICS in reducing the exacerbation rates by 24% to 33% compared with a placebo (Sin et al. 2003, Gartlebner et al. 2006). On the other hand, observational studies using more than 4,000 COPD patients did not find preventive effects associated with ICS (Bourbeau et al. 2003, Fan et al. 2003, de Melo et al. 2004, Suissa 2004) even though potential misclassification of ICS exposure status was carefully addressed by using either a time-dependent approach or a nested case-control study design.

One possible explanation for these mixed results may be lack of a consistent definition of exacerbation. Because significant individual variation occurs in exacerbation patterns, exacerbation episodes are operationally defined in various ways across studies, ranging from “mild exacerbation” defined by increased use of rescue therapy to “severe exacerbation” defined by respiratory conditions that require hospitalization (Calverley 2004, Pauwels et al. 2004). Other reasons for these mixed results may be related to individual

factors that are not observed in claims data but that will influence disease prognosis. These important unobserved characteristics include socioeconomic characteristics, smoking behaviors and chronic comorbid conditions (Burney et al. 2003, Spencer et al. 2004, Mannino et al. 2006).

In cross-sectional data analysis, omission of important factors from the regression model will lead biased estimation. However, in longitudinal or panel data analysis, an individual has multiple observations in both exposure status and outcomes (Frees 2004). Each individual can contribute the time before drug exposure to the control group and the time after drug exposure to the treatment group. Because each individual is his or her own control, potential bias due to omitted variables that do not change over time (e.g., sex, race, and historical health behaviors) can be eliminated. When there are two observations per person, the treatment effect can be observed by measuring changes before and after the treatment (e.g., pre- and post-paired comparison), and thus time-invariant variables disappear by subtracting one from the other.

One statistical approach to account for multiple observations per individual is called the“fixed-effects” model (Allison 2005). The model can be expressed as below (Equation 5.1):

$$Y_{it} = \beta\ X_{it} + \alpha_i + \varepsilon_{it} \qquad \text{[Equation 5.1]}$$

The notation *i* refers to different persons and *t* refers to different points in time; the term *Y* is an outcome of interest, *X* is a main exposure of interest, α_i is a dummy variable representing individual characteristics; and ε_{it} is a random error. In this model, because individual variations are considered fixed, and they are explained by the fixed-effect parameter, α_i, omitted variables are accounted for without measuring them. On the other hand, time-variant factors or variables that change over time (e.g., disease symptoms) must be adjusted with common regression approaches to avoid omitted variable bias.

In previous observational studies using claims data, limited information was available to measure and adjust for the effects of important predictors of prognosis of COPD, such as smoking behaviors or chronic conditions. Therefore, concerns about the omitted variable bias could not be eliminated. In this study, however, we address the potential bias that is likely to exist in the cross-sectional studies by using monthly data from a managed care claims database to obtain repeated measures over time for each individual. We use an individual fixed-effects model to estimate the unbiased effects of initiating ICS treatment on COPD-related and all-cause medical costs in COPD patients who were under treatment with regular bronchodilators.

5.3 Methods

Data source

Data for this study were obtained from the Integrated Healthcare Information Services (IHCIS) database from January 1997 through December 2005. This database includes information on enrollment, institutional (inpatient/outpatient), professional, and pharmacy services for more than 37 million patients covered by approximately 35 managed care health plans in nine census regions in the United States. Data available for each institutional or professional service claim ("medical claim") include dates of service, International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes, and ICD-9-CM procedure codes or Current Procedural Terminology, Version 4 (CPT-4) procedure codes. The data also include pharmacy claims with drug name dispensed (in National Drug Code [NDC]), the dispensing date and days supply.

In the IHCIS data, cost information is standardized in order to make comparisons easier across all services, data sources, and time periods (IHCIS 2005). For example, (1) inpatient costs were calculated based on primary diagnosis categories, length of stay, and presence of ICU/surgery; (2) outpatient costs were calculated based on requested

(submitted) charges; (3) professional service costs were calculated using a standardized payment schedule based on a resource-based relative value scale (RBRVS); (4) pharmacy service costs were calculated using First Data Bank pricing adjusted by quantity and therapeutic category; and (5) all costs were adjusted for inflation over time (2005 values). All data were HIPAA compliant with all health plan and personal information de-identified to assure confidentiality (IHCIS 2005).

COPD patients were identified using both medical and pharmacy claims. Included were patients who (1) had one or more medical claims of COPD (ICD-9-CM: 491.xx, 492.xx or 496.xx in primary or secondary positions) between January 1998 and December 2004, (2) had regular treatment with inhaled bronchodilators (defined by at least three pharmacy claims of anticholinergics or long-acting β_2-agonists [LABA]), and (3) were 40 years of age or older. All eligible patients were required to have continuous health plan coverage from three months before the first pharmacy claim of inhaled bronchodilators ("index date") through 12 months after the date. Patients were excluded from the analysis if they had diagnosis of cystic fibrosis (ICD-9-CM: 277.0x) or respiratory tract cancer (ICD-9-CM: 160.xx-164.xx, or 231.xx), had no ICS treatment during the 24-months follow-up period, or had initiated ICS before the index date.

Measures

Monthly data were created for the following variables from up to 12 months prior to the index through 24 months after the index date ("study period"). Dependent variables were COPD-related and all-cause medical costs obtained from institutional and professional claims. COPD-related costs were identified from services related to the primary COPD-diagnosis or COPD-related procedures (e.g., oxygen therapy, a spirometry test, pulmonary rehabilitation, nebulized treatment, bronchoscopy, intubation or tracheostomy). Total costs of the services consumed each month were calculated during the study period.

The primary exposure variable was the use of inhaled corticosteroids (ICS). The period before the first ICS claim was defined as unexposed time, whereas the period after the first ICS claim was defined as ICS exposed time. To adjust for symptom changes over time, a continuous variable indicating "*TIME*" in months (months from -12 to +23, month 0 at the index), dummy variables indicating "*ONSET*" (one month prior to the index when many patients receive medical services that lead to the first bronchodilator claim, and therefore having extremely high medical costs as described in Figure 5.1) and "*POST-ONSET (PST)*" (months after patients receive the first bronchodilator claim) were included.

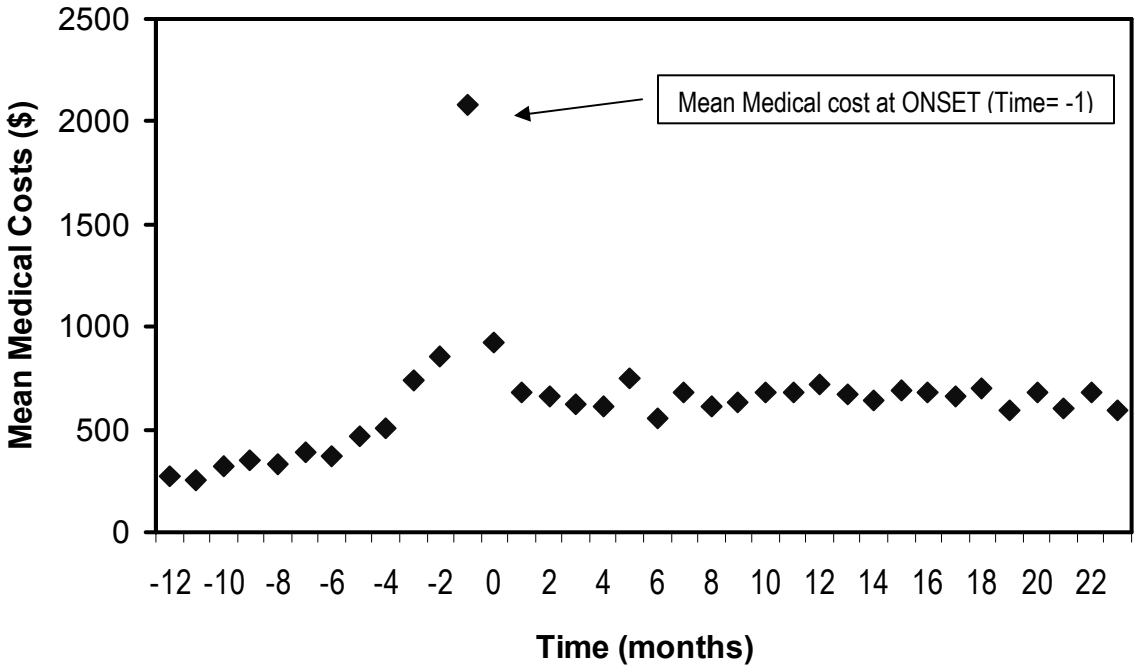


Figure 5.1: Changes in mean monthly medical costs

Covariates were age at index and selected comorbid conditions such as asthma and congestive heart failure (CHF). Because patients with asthma or CHF might not experience claims on a monthly basis, we defined time with the conditions in the following way. We identified the first month with asthma (ICD-9-CM: 493.xx) or CHF (ICD-9-CM: 428.xx), and then, defined the subsequent months as months with the conditions. For example, if a

patient had a claim with an asthma diagnosis on October 19, 2003, the months after October 2003 were assigned as having asthma. In addition, to adjust for exacerbation episodes, the months with medications for acute exacerbations (oral antibiotics or corticosteroids) were identified. Even though increased costs associated with death were anticipated, they could not be controlled due to lack of mortality information in the database. All variables used in this study are listed in Table 5.1.

Table 5.1: Variables and their definitions

Variables	Definitions	Characteristics
Dependent variables		
COPDCOST	COPD-related monthly medical costs defined by COPD Dx (ICD-9-CM: 491.xx, 492.xx, 496.xx) and COPD-related procedures	Time-variant, continuous
ALLCOST	All-cause monthly medical costs	Time-variant, continuous
Main exposure variables		
ICS	A dummy variable indicating inhaled corticosteroids (ICS) exposure	Time-variant, dichotomous (1: ICS treatment and 0: no ICS treatment)
TIME	Follow-up time from 12 months before the index through 24 months after index	Time-variant, continuous (-12 to +23)
ONSET	A dummy variable indicating one month prior to index	Time-variant, dichotomous (1: month -1 and 0: others)
POST ONSET (PST)	A dummy variable indicating months after index	Time-variant, dichotomous (1: in months after index and 0: in months before index)
Covariates		
AGE40, AGE50, AGE60	Age (in years) at index (dummy variables indicating age groups: 40-49, 50-59, 60-69, and 70 or over)	Time-fixed, dichotomous (1: designated age group and 0: others)
ASM	Months with asthma (ICD-9-CM: 493.xx) condition	Time-variant, dichotomous (1: months after having first asthma Dx and 0: months before asthma Dx)
CHF	Months with congestive heart failure (ICD-9-CM: 428.xx) condition	Time-variant, dichotomous (1: months after having first CHF Dx and 0: months before CHF Dx)
ANT	Prescription of oral antibiotics as a rescue medication	Time-variant, dichotomous (1: months with Rx of antibiotics and 0: without Rx of antibiotics)
OCS	Prescription of oral corticosteroids (OCS) as a rescue medication	Time-variant, dichotomous (1: months with Rx of OCS and 0: without Rx of OCS)
MONTH	Dummy variables indicating month of observation (January through December to adjust for seasonality)	Time-variant, dichotomous (1: designated month and 0: others)

Note: ICD-9-CM: International Classification of Diseases, 9th Revision, Clinical Modification, Rx: prescription, Dx: diagnosis

Analysis

An individual-level, fixed-effects model was used to estimate the impact of starting ICS treatment on medical costs among patients with COPD. The expected COPD-related and all-cause costs were modeled using the following equation (Equation 5.2):

$$E[COST_{it}] = \beta_1 TIME_t + \beta_2 ONSET_{it} + \beta_3 PST_{it} + \beta_4 ICS_{it} + \beta_5 TIME_t * ICS_{it} + \beta_6 (TIME_t * PST_{it} - TIME_t * ICS_{it}) + \gamma_1 ICS_{it} * AGE40_i + \gamma_2 ICS_{it} * AGE50_i + \gamma_3 ICS_{it} * AGE60_i + \delta_1 ANT_{it} + \delta_2 OCS_{it} + \delta_3 ASM_{it} + \delta_4 CHF_{it} + \delta_5 MONTH_t$$

[Equation 5.2 (refer to the variable names in Table 5.1)]

The interpretation of estimated coefficients is summarized in Figure 5.2. Before the index, the association between disease progression over time and expected treatment costs is expressed by β_1. The coefficient β_2 explains the spike in costs just before the index (i.e., index associated costs). Then, changes in treatment costs after the index (or during post-onset period) are expressed either by $\beta_1 + \beta_3 + (\beta_6 * TIME)$ during the time without ICS treatment or by $\beta_1 + \beta_3 + \beta_4 + (\beta_5 * TIME)$ during the time with ICS treatment. Therefore, the ICS treatment effect is calculated by the change in the slope, $\beta_4 + (\beta_5 - \beta_6)$*TIME. The ICS treatment effects for different age categories are explained by coefficients γ_1, γ_2 and γ_3 for the interaction terms between "*ICS*" and dummy variables indicating age groups ("*AGE40*", "*AGE50*" and "*AGE60*"). We hypothesized that the sign of β_4 would be negative if initiating ICS was associated with cost reduction at *TIME = 0*, and that the sign of $(\beta_5 - \beta_6)$ would be negative if earlier initiation of ICS was more effective in reducing medical costs than initiating ICS later at *TIME > 0*.

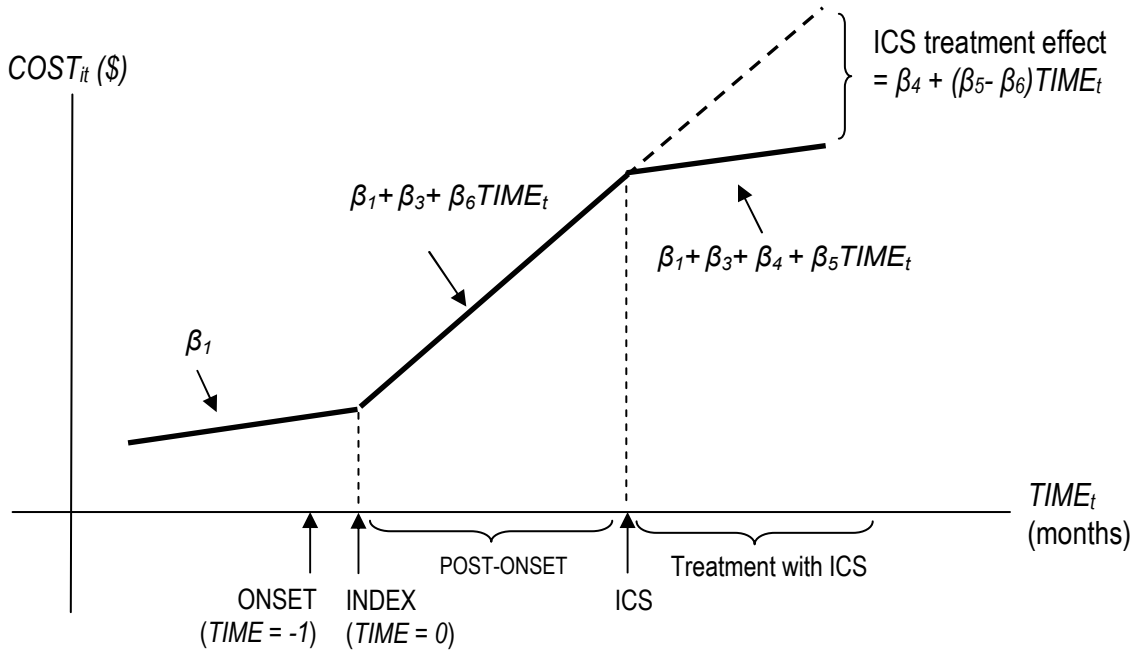


Figure 5.2: Graphical representation of estimated coefficients

The solid line represents the association between treatment costs and follow-up time estimated from the following model. It was simplified to help understanding of β coefficients.

$$E[costs_{it}] = \beta_1 TIME_t + \beta_2 ONSET_{it} + \beta_3 PST_{it} + \beta_4 ICS_{it} + \beta_5 TIME_t * ICS_{it} + \beta_6 (TIME_t * PST_{it} - TIME_t * ICS_{it})$$

where ONSET: a month with an event to lead the first bronchodilator treatment; INDEX: a month to start the bronchodilator treatment; and ICS: a month to start ICS treatment.

The use of the fixed-effects model to obtain unbiased estimation was tested using specification tests (Kennedy 2003): a Breusch-Pagan test (to test whether the error terms were independent within individual) and a Hausman test (to test whether the estimates from random-effects model would be consistent and efficient). All analyses were conducted using statistical software, SAS version 8.2 (SAS Institute Inc., Cary NC) or STATA version 9.2 (StataCorp LP, College Station TX).

5.4 Results

There were 785,759 COPD patients without diagnoses of cystic fibrosis or respiratory tract cancer in the IHCIS database between 1998 and 2004. Of those, 10,271 eligible patients met the inclusion and exclusion criteria (Figure 5.3). Sixty-one percent of patients had complete follow-up data for 24 months after the index. Approximately half of study population was male and aged 60 years or older (Table 5.2). About 20% of them received services from a pulmonary medicine specialist and a spirometry test during the three months prior to initiating inhaled bronchodilator therapy. They had a variety of comorbid conditions including hypertension (38%), asthma (37%), diabetes (14%), congestive heart failure (12%) and depression (12%). In terms of pre-index utilization, about 25% of patients used either respiratory-related inpatient services or emergency department visits.

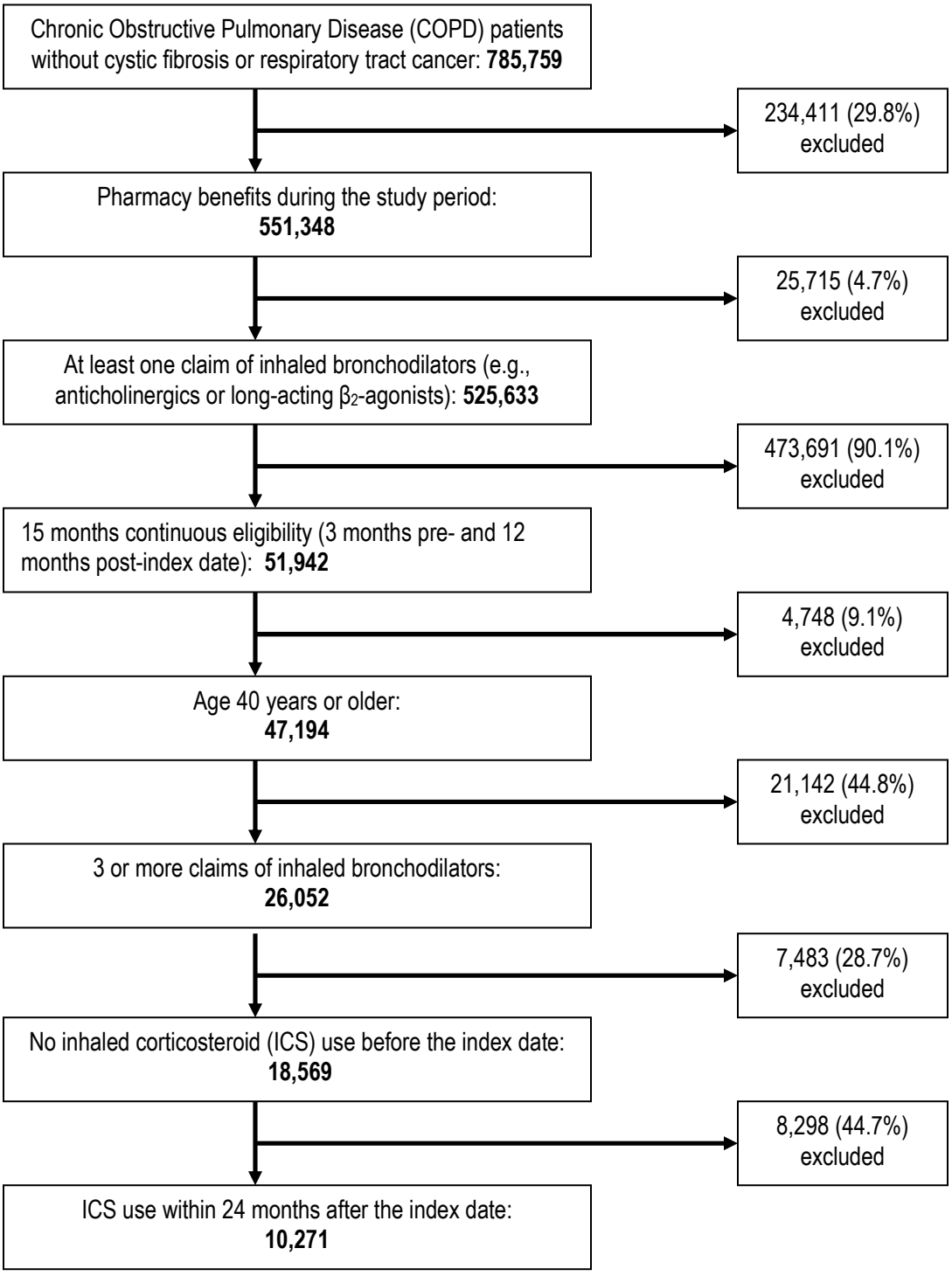


Figure 5.3: Study sample selection

Table 5.2: Baseline patient characteristics

Total observations (n=10,271)	n	(%)
Gender		
Male	4,721	(46.0)
Age Categories		
40-49	1,533	(14.9)
50-59	3,334	(32.5)
60-69	2,949	(28.7)
70-79	2,455	(23.9)
Main provider		
Pulmologist (reference group: any other)	2,005	(19.5)
Insurance coverage		
Medicaid/Medicare (reference group: commercial)	1,574	(15.3)
Census region		
Northeast	5,314	(51.7)
South	1,249	(12.2)
Midwest	1,149	(11.2)
West / others	2,559	(24.9)
Comorbidities		
Myocardial Infarction	373	(3.6)
Congestive Heart Failure	1,277	(12.4)
Peripheral Vascular Disease	442	(4.3)
Cerebrovascular Disease	585	(5.7)
Rheumatologic Disease	236	(2.3)
Diabetes	1,474	(14.4)
Renal Disease	205	(2.0)
Malignancy / AIDS	740	(7.2)
Asthma	3,802	(37.0)
Depression	1,227	(11.9)
Nonvertebral Fracture	335	(3.3)
Hypertension	3,848	(37.5)
COPD-related procedures		
Oxygen therapy	837	(8.1)
Spirometry test	1,992	(19.4)
Pulmonary rehabilitation	222	(2.2)
Nebulized therapy	277	(2.7)
Bronchoscopy, Intubation, or Tracheostomy	127	(1.2)
Inpatient admissions		
Any reason	1,972	(19.2)
Respiratory-related conditions	1,205	(11.7)
Emergency department visits		
Any reason	2,194	(21.4)
Respiratory-related	1,368	(13.3)
Medications		
Oral corticosteroids	1,754	(17.1)
Oral antibiotics	3,447	(33.6)
Short-acting β_2-agonists	2,242	(21.8)
Theophylline	484	(4.7)
Other medications	8,537	(83.1)

Table 5.3 presents results of longitudinal analyses to estimate the effect of ICS treatment on monthly medical costs ("treatment effects"). In the model of COPD-related medical costs, the coefficient on "*ICS*" was negative, indicating ICS treatment was associated with a cost reduction. However, when two sets of time-variant variables, use of exacerbation treatments ("*ANT*" and "*OCS*") and selected comorbid conditions ("*ASM*" and "*CHF*"), were excluded from the model, the sign of the coefficient on "*ICS*" become positive (results not shown). Thus, the time-variant variables related to exacerbations and comorbidities were important predictors of costs, and omitting these variables caused positive or upward bias. Moreover, the two specification tests confirmed that the fixed-effects model was appropriate. Similar results were observed for all-cause medical costs.

To evaluate the effects of early initiation of ICS ("timing effects") on COPD-related medical costs, patients who initiated ICS treatment at *TIME = 6* (the seventh month after the index) were compared with those who initiated ICS treatment at *TIME = 0* (the first month after the index) while keeping other factors as constant (Figure 5.4). As a result, ICS treatment was associated with a monthly cost reduction of $43 in the first month. In addition, earlier ICS initiation would lead an additional cost reduction. A one-month early initiation was associated with a cost reduction of $3 per month. According to the simulation for COPD-related costs, patients who initiated ICS treatment six months earlier could save $306 overall or $51 per month, on average. The monthly cost reduction was expressed by the factor of "*TIME*" and calculated by the equation: [*43 +3*TIME*]. Similar "timing effects' were observed in all-cause medical costs and were expressed by the cost reduction of [*55 + 2*TIME*] dollars per month.

In addition, as shown in Table 5.3 and Figure 5.4, age interactions were estimated to examine the "treatment effects" on various age categories by including interaction terms between "*ICS*" and three age categories (patients aged 70 and older were used as the reference category). The interaction model indicated that ICS treatment effects on COPD-

related and all-cause medical costs depend on age. The magnitude of cost reduction reflected different "treatment effects" by age in the first month. For COPD-related services, the largest cost reduction was observed in the patients aged over 70 years ($128 in the first month). However, the treatment effects were relatively small for patients in their 50s ($34 reduction in the first month) and 60s ($23 reduction in the first month) or were not observed in their 40s ($48 increase in the first month).

Table 5.3: Longitudinal analyses to estimate ICS effects on medical costs

	COPD-related costs						All-cause costs					
	Base model			Age interaction model			Base model			Age interaction model		
VARIABLES	β	(SE)		β	(SE)		β	(SE)		β	(SE)	
TIME	37.54	(5.63)	**	37.37	(5.63)	**	42.40	(5.89)	**	42.09	(5.89)	**
ONSET	1160.73	(58.66)	**	1161.16	(58.66)	**	1256.49	(61.36)	**	1257.14	(61.36)	**
PST	-347.88	(54.38)	**	-349.12	(54.39)	**	-297.83	(56.89)	**	-299.94	(56.89)	**
ICS	-42.78	(48.12)		-128.23	(59.43)	*	-54.85	(50.34)		-198.59	(62.17)	**
TIME*ICS	-43.32	(5.92)	**	-43.14	(5.92)	**	-50.04	(6.19)	**	-49.73	(6.20)	**
TIME*PST-TIME*ICS	-40.03	(7.56)	**	-39.85	(7.56)	**	-48.43	(7.91)	**	-48.12	(7.91)	**
ICS*AGE40				176.38	(64.91)	**				263.90	(67.90)	**
ICS*AGE50				94.63	(53.07)					171.05	(55.52)	**
ICS*AGE60				105.13	(54.29)					179.81	(56.79)	**
ANT	557.46	(28.30)	**	557.39	(28.30)	**	766.06	(29.60)	**	765.88	(29.60)	**
OCS	601.45	(37.43)	**	602.44	(37.43)	**	723.23	(39.16)	**	724.89	(39.16)	**
ASM	386.82	(34.76)	**	375.80	(35.05)	**	442.26	(36.37)	**	425.27	(36.66)	**
CHF	1703.07	(49.46)	**	1723.20	(50.08)	**	1899.96	(51.74)	**	1932.25	(52.39)	**
January	10.14	(42.01)		9.79	(42.01)		14.13	(43.95)		13.57	(43.95)	
February	66.26	(42.13)		65.88	(42.13)		91.89	(44.08)	*	91.26	(44.07)	*
March	-0.37	(42.25)		-0.68	(42.25)		46.67	(44.19)		46.17	(44.19)	
April	-38.06	(42.37)		-38.30	(42.37)		-4.34	(44.33)		-4.73	(44.33)	
May	-13.03	(42.50)		-13.08	(42.50)		15.98	(44.46)		15.91	(44.46)	
June	-3.80	(42.59)		-3.66	(42.59)		28.00	(44.56)		28.25	(44.55)	
July	-81.88	(42.63)		-81.63	(42.63)		-39.17	(44.59)		-38.76	(44.59)	
August	-47.06	(42.67)		-46.61	(42.67)		-20.86	(44.64)		-20.14	(44.64)	
September	-56.22	(42.70)		-55.67	(42.70)		-20.63	(44.67)		-19.74	(44.67)	
October	-65.29	(42.71)		-64.77	(42.71)		-24.95	(44.68)		-24.07	(44.68)	
November	-111.45	(42.39)	**	-111.04	(42.39)	**	-115.65	(44.34)	**	-114.97	(44.34)	**

Note: β: estimated coefficients, SE: robust standard errors, * indicates statistical significance at the 5% level; ** at the 1% level. Please refer to the variable names in Table 5.1

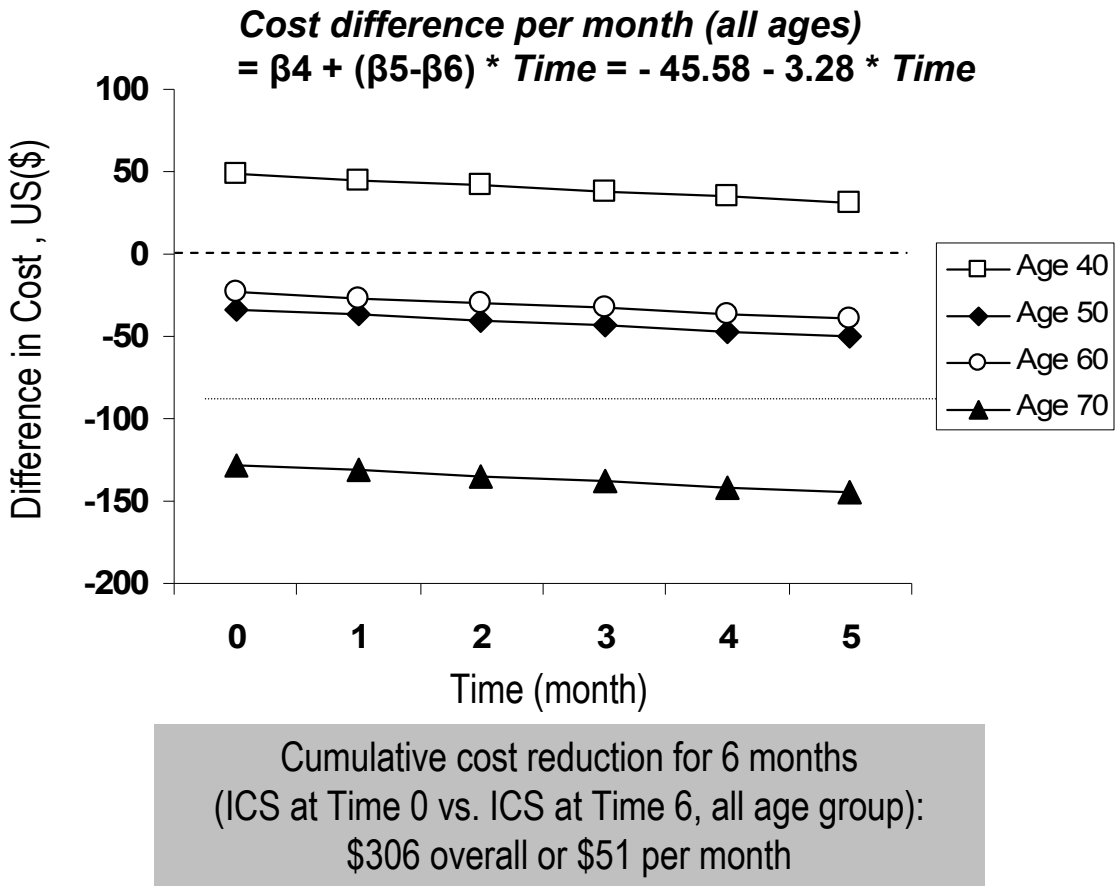


Figure 5.4: Simulation results to compare initiating ICS at time 0 versus time 6

This simulation compared two possible scenarios based on when ICS treatments were initiated. One is when patients initiated ICS treatment within a month of initiating bronchodilators (time=0). The other is when patients initiated ICS treatment in the seventh month of initiating bronchodilators (time=6). Since expected costs were the same at time < 0 and time > 5, only differences in estimated costs were displayed during time=0 through time=5.

5.5 Discussion

Our findings using longitudinal data demonstrated that initiating ICS treatment in COPD patients with regular inhaled bronchodilators could reduce COPD-related medical costs by $43 per month and all-cause medical costs by $55 per month. Moreover, the earlier patients initiated ICS treatment, the greater the cost reduction expected. Each one-month delay in initiating ICS treatment was estimated to increase COPD-related costs and all-cause costs by $3 and $2 per month, respectively. The largest cost reduction was observed in the oldest patients. The findings also revealed that treatment costs were driven by rescue medication use and comorbidities. Having a prescription for oral antibiotics or corticosteroids was associated with a $500 increase in medical costs, on average, per month. Also, having asthma or congestive heart failure was associated with increases for both COPD-related and all-cause costs.

Our results were consistent with the published studies evaluating benefits of ICS treatment among patients with COPD (Sin and Tu 2001, Soriano et al. 2002, Kiri et al. 2005, Schmier et al. 2005). Using the data from the UK General Practice Research Database (GPRD), Soriano et al. (2002) reported that ICS treatment reduced risks of either hospitalization or death (hazard ratio [HR]: 0.62, 95% confidence interval [CI]: 0.45 to 0.85) during the three-year follow-up period compared with regular use of bronchodilators. In addition, Kiri et al. (2005) found a significant risk reduction associated with ICS treatment in a propensity-score-matched cohort analysis (HR: 0.69, 95%CI: 0.52 to 0.93) as well as in a matched, nested case-control analysis (HR: 0.71, 95%CI: 0.56 to 0.90).

Moreover, in a different analysis using the propensity-score-matching technique (Chapter 4), we found that patients who initiated ICS treatment within three months of the initiation of regular inhaled bronchodilators had significantly lower risks of exacerbation (defined by hospitalization, emergency department visit or office visit with prescription of rescue medications), other resource utilization and COPD-related and all-cause treatment

costs than those who initiated ICS after three months. The “timing effects” observed in the fixed-effects models also supported the evidence that earlier initiation of ICS treatment than the currently recommended stepwise strategy would be beneficial for achieving better control of the COPD conditions and reducing overall treatment costs.

Several important limitations associated with claims data deserve discussion. Because there was no clinical information available about COPD and other comorbid conditions, we estimated symptoms from resource utilization patterns in the claims. Acute exacerbation events were evaluated with pharmacy claims of oral antibiotics or oral corticosteroids, which are often used to relieve acute exacerbations. In addition, comorbid conditions were detected with the first medical claims associated with the diagnosis and assumed that the conditions would continue until the end of study period. These proxy measures could be the source of bias due to the misclassification of explanatory variables; however, this type of measurement error should be random (i.e., not associated with drug selection and outcomes) and result in bias toward the null.

Also, we did not have access to data that might explain the reason for initiating ICS treatment. We assume some physicians may prescribe it to prevent exacerbations, whereas others may prescribe it only to patients having frequent exacerbations. Without having the clinical information, it was difficult to distinguish whether estimated costs were results of the treatment effects or the treatment was initiated due to the expected outcomes. To minimize the bias from this temporal causal relationship, we used a narrow time frame to measure both drug exposure status and outcomes and used monthly values in the analysis. Also, we include month indicator variables to adjust for seasonality. If patients used ICS because they experienced frequent exacerbations, ICS should be associated with increased medical costs. We anticipated, therefore, the direction of the bias would be one way only: ICS treatment effects on cost reduction would be underestimated and our estimated benefits would be conservative.

Finally, to identify an appropriate study population, we used various inclusion and exclusion criteria such as diagnosis codes, COPD-related medications and patient age. To assess impact of changes in ICS treatment status over time, all patients were required to have at least 15 months continuous eligibility. Because of this restriction, patients at risk of immediate death or those who could not survive for 15 months were automatically excluded. Therefore, the findings have limited generalizability to selected COPD patients from managed care population.

Despite these limitations, two fundamental potential biases often observed with observational data were carefully addressed in this analysis using advanced statistical techniques. One problem was the issue of individual factors not observed in the claims-based data. COPD patients with smoking history will experience more rapid decline in lung function than non-smokers (Chapman et al. 2006). COPD patients are also known to have significant systematic effects such as weight loss, cardiovascular disease, depression, and osteoporosis that contribute to the burden of the disease (Agusti 2005). Omitting these time-invariant variables, which would be associated with both treatment choices and outcomes, would cause biased estimates. Because the longitudinal data allowed having multiple observations per each individual, we could eliminate the conditions and behaviors which were stable or fixed during the observational period for each individual (Allison 2005). In the individual fixed-effects model, the treatment effects could be detected by comparing individual variations before and after the treatment as well as comparing patients with and without treatment.

In addition, the reason for prescribing a specific medication is often associated with clinical outcomes, especially for symptomatic conditions. This type of bias is called confounding by indication (Collet and Boivin 2000). In the case of COPD treatment, as recommended by clinical guidelines (GOLD 2006), patients with repeated exacerbations or declining lung function are more likely to get ICS treatment than those with milder conditions.

If so, without controlling for potential confounders, the treatment effects would be biased. In fact, by controlling for time-variant factors related to onset of comorbidities, signs of the coefficient on "*ICS*" were reversed. Having comorbid conditions may be positively related to treatment costs (signs of the coefficients on the conditions are expected to be positive). At the same time, patients with advanced conditions are more likely to get ICS treatment (association between ICS treatment and comorbidities are expected to be positive). Therefore, omitting these conditions would cause the upward bias. Adding time-variant variables explaining changes in conditions over time are essential to minimize the confounding effects.

5.6 Conclusion

Current clinical guidelines recommend that ICS treatment should be initiated in patients who do not have adequate symptom control using a regular bronchodilator regimen. Our findings provide the additional information that supports early initiation of ICS in order to reduce COPD disease burden. Especially for patients with moderate-to-severe conditions, early investment in ICS treatment may avoid additional costs due to repeated exacerbations and preventable disease progression.

CHAPTER 6

Medication Persistence and Adherence to Inhaled Corticosteroids Treatment and Association with Medical Costs among COPD Patients

6.1 Abstract

Objective: A retrospective database study was conducted to assess medication persistence, adherence and economic consequences of inhaled corticosteroids (ICS) treatment among chronic obstructive pulmonary disease (COPD) patients.

Methods: Patients ages 40 years and older with COPD (ICD-9-CM: 491.xx, 492.xx or 496.xx), and regular inhaled bronchodilator (≥3 prescriptions) and ICS (≥2 prescriptions) treatment were identified from pharmacy and medical claims data between January 1998 and December 2004. Persistence was defined by the days between initiating and discontinuing ICS therapy. Adherence was measured using information describing refill patterns that were used to calculate a medication possession ratio (MPR). Multivariable regression analyses were conducted to identify factors associated with better medication persistence and adherence. The number of inpatient admissions (IP) or emergency department visits (ED) as well as any and COPD-related costs during the second year were summarized by persistence and adherence categories during the first year. Multivariable regression models were used to adjust for demographics, comorbidities, and the first year utilization.

Results: A total of 6,873 patients were identified for analysis of persistence/adherence, whereas 3,499 patients were identified for the outcome analysis, respectively. Having

commercial insurance, using specialist care, and having a spirometry test were associated with better persistence and adherence, whereas the number of chronic conditions had a negative impact. Age, census region and pre-term use of anticholinergics were also important determinants of persistence and adherence. Patients with longer ICS treatment were more likely to have lower treatment costs for any condition. Patients with better medication adherence had lower risk of IP/ED events and treatment costs; however, their trends varied according to MPR measures.

Conclusion: Improvement of ICS treatment persistence and adherence among COPD patients may be an important strategy to achieve better symptom control and to reduce treatment costs. Further analysis is required to understand patient treatment behavior of inhaled medication on symptomatic conditions and its impact of treatment outcomes.

Key words: Chronic obstructive pulmonary disease (COPD), inhaled corticosteroids (ICS), persistence, adherence, retrospective database.

6.2 Introduction

Medication usage in patients is often evaluated by medication persistence (i.e., whether a patient stays on the drug therapy) and by medication adherence (i.e., whether a patient takes a prescribed drug according to schedule) (Andrade et al. 2006). Understanding persistence and adherence is important because accurate assessment of drug treatment requires evidence about how and when drugs are consumed. A variety of measures have been used to quantify patient medication usage such as pill counts, patient self-report, serum drug levels, assessment of physiologic drug effects, and electronic compliance monitors (Steiner and Prochazka 1997). Pharmacy claims databases also provide a rich source of information to monitor drug use (Peterson et al. 2007).

Andrade et al. (2006) and Hess et al. (2006) summarize various measures of patient persistence and adherence to treatment utilized in pharmacoepidemiology and pharmacoeconomic studies. The medication possession ratio (MPR) and related measures of medication availability (e.g., proportion of days covered [PDC] and continuous measure of medication acquisition [CMA]) are most often used. MPR is calculated as (1) the number of days of drug supply during a specified follow-up period (e.g., 12 months) divided by the number of days from the first dispensing to the end of a predefined follow-up period, or (2) the number of days of drug supply (excluding the last refill) divided by the number of days between the first and last dispensing dates. They also describe other adherence measures appearing in the literature including discontinuation and continuation rates (e.g., whether a patient stays on therapy or time to the discontinuation), switching (e.g., time to dispensing a different drug), medication gaps (e.g., proportion of days without drug during a specific time period) and refill compliance (e.g., refill rates during a specific time period).

Chronic obstructive pulmonary disease (COPD) is characterized by progressive airflow limitation and airway inflammation. Anti-inflammatory agents such as inhaled corticosteroids (ICS) are often used to prevent and control symptoms in patients with COPD (Man et al. 2003). However, few studies examining adherence to ICS in COPD patients are available (Schmier et al. 2005). Unlike studies of oral medications, it is challenging to quantify medication availability of inhaled medications from pharmacy claims because such information is often inadequate and inaccurate (Andrade et al. 2006). The current evidence suggests that adherence to ICS treatment is generally poor and that poor adherence has a negative influence on outcomes (Rand 2005).

Balkrishnan and Christensen (2000a, 2000b) studied adherence to ICS treatment in Medicare managed care enrollees with chronic pulmonary disease. About 60% of the elderly had poor adherence (MPR ≤ 30%), and only 10% were categorized as having good adherence (MPR ≥ 60%). Patients with good adherence to the treatment also experienced

better outcomes, in terms of fewer hospitalizations or emergency department visits. Blais et al. (2004) evaluated patterns of ICS treatment among elderly COPD patients using a Canadian administrative database. Patients who initiated ICS were more likely to have severe disease conditions, experience an exacerbation, see a specialist in the previous month, and have multiple physician visits in the prior three months compared to patients without ICS treatment. Although regular ICS treatment should be maintained for long time periods, discontinuation of ICS treatment was common. The proportion of patients who remained on ICS treatment more than one year ranged from 33% to 52% by the end of the year of study. Furthermore, a randomized clinical study found that discontinuation of ICS was associated with increased risk of COPD exacerbations and reduced health status (van der Valk et al. 2002).

In our study, we found that COPD patients who initiated ICS with regular inhaled bronchodilator treatment (i.e., earlier than the guideline recommendation) could save substantial treatment costs compared with those who initiated ICS later (Chapter 4 and Chapter 5). The current treatment guideline recommends ICS treatment to augment regular bronchodilators for patients with repeated exacerbations or reduced lung function (Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2006). However, in real world clinical settings, physicians may initiate ICS treatment earlier than the recommended stepwise strategy as prophylactic therapy to prevent exacerbations and reduce medical service utilization. A previous study suggested that poor adherence to ICS treatment may be due to misunderstanding the treatment purpose (George et al. 2005). Specifically, some patients may use ICS regularly to reduce the likelihood of acute exacerbations whereas others may use it as needed to relieve symptomatic conditions.

In this study, based on ICS prescription refill patterns as the measure of medication persistence and adherence among COPD patients, we assessed: (1) factors that may determine better medication persistence and adherence; and (2) any association of

medication persistence and adherence with use of healthcare services and costs, using various multivariable regression techniques.

6.3 Methods

A retrospective, longitudinal cohort study using managed care claims data was conducted to measure ICS treatment pattern and its impact on resource utilization and costs. Medication persistence and adherence were used to express drug exposure status. Multivariable regression models were used to identify factors associated with better medication persistence and adherence as well as to examine their impact on healthcare utilization and costs.

Data and study population

Data for this study were obtained from the Integrated Healthcare Information Services (IHCIS) database. Data include information on enrollment status, institutional (inpatient/outpatient), professional, and pharmacy services for more than 37 million patients covered by approximately 35 managed care health plans in nine census regions in the United States (IHCIS 2005). Data available for each institutional or professional service claim ("medical claim") include dates of service, International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes, and ICD-9-CM procedure codes or Current Procedural Terminology, Version 4 (CPT-4) procedure codes. The data also include pharmacy claims with drug name dispensed (in National Drug Code [NDC]), the dispensing date, and days supply. All data were Health Insurance Portability and Accountability Act (HIPAA) compliant with all health plan and personal information de-identified to assure confidentiality (IHCIS 2005).

COPD patients were identified using medical and pharmacy claims. The inclusion criteria were patients who had one or more medical claims for COPD (ICD-9-CM: 491.xx, 492.xx or 496.xx in primary and secondary diagnosis) between January 1998 and December 2004, were 40 years or older, had regular treatment with inhaled bronchodilators (defined by at least three pharmacy claims of anticholinergics or long-acting β_2-agonists), and had at least two different dates of ICS prescriptions (each separated by 30 days). All eligible patients were required to have 15 months continuous health plan coverage from three months before to 12 months after the initial bronchodilator treatment. Patients were excluded from the analysis if they had diagnosis of cystic fibrosis (ICD-9-CM: 277.0x) or respiratory tract cancer (ICD-9-CM: 160.xx-164.xx, or 231.xx).

Three different sub-cohorts were defined based on required follow-up and ICS treatment period. The first sub-cohort was patients who met inclusion and exclusion criteria listed above [sub-cohort (1) for persistence and adherence analysis]. The second sub-cohort was patients who had two years of follow-up data after initiating ICS in addition to the first sub-cohort criteria [sub-cohort (2) for outcome analysis]. The third sub-cohort was patients who had recent ICS exposure 30 days before outcome measures in addition to the second sub-cohort criteria [sub-cohort (3) for outcome analysis]. The period of the first 365 days after ICS initiation were defined as the “first year”, and days 366 through 730 were defined as the “second year”. Selection of sub-cohorts is described in Figure 6.1 and study design and period are summarized in Figure 6.2.

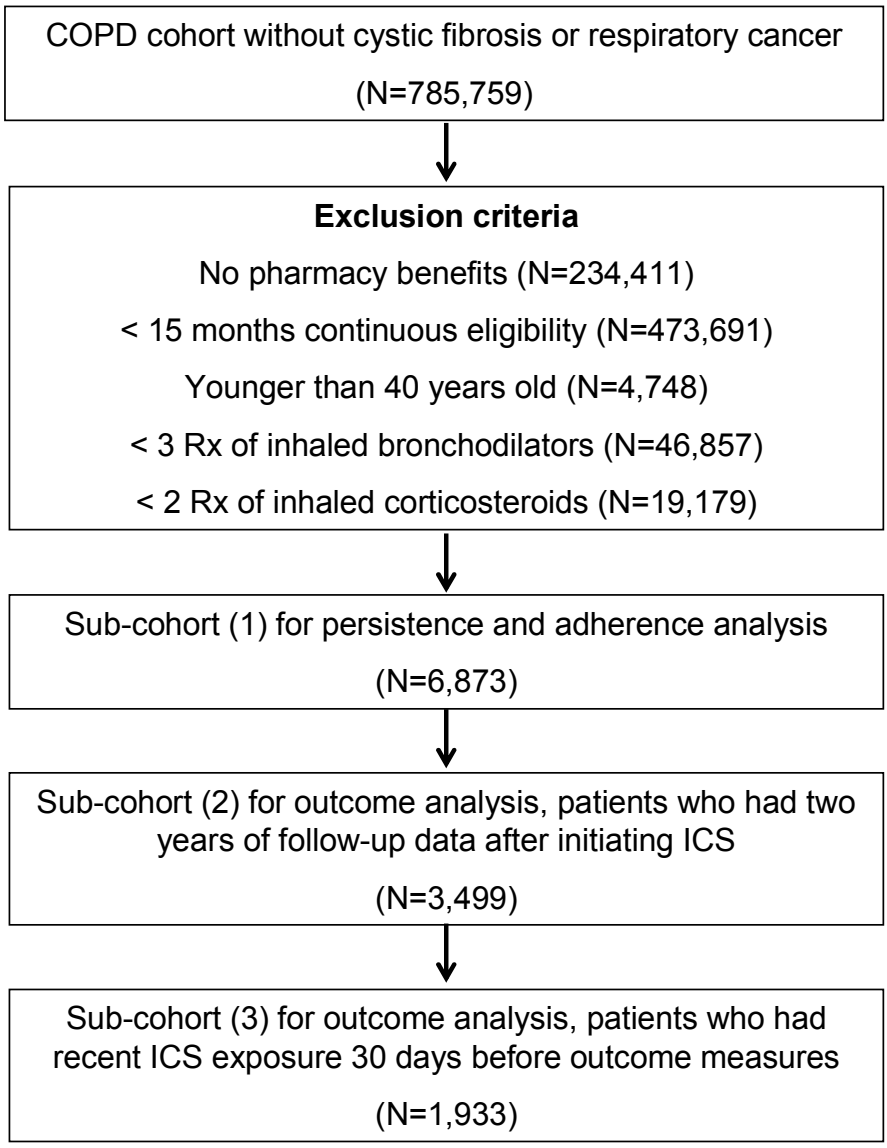


Figure 6.1: Number of patients who met inclusion and exclusion criteria.

Three sub-cohorts were defined based on the length of follow-up and ICS treatment. COPD: chronic obstructive pulmonary disease, ICS: inhaled corticosteroids.

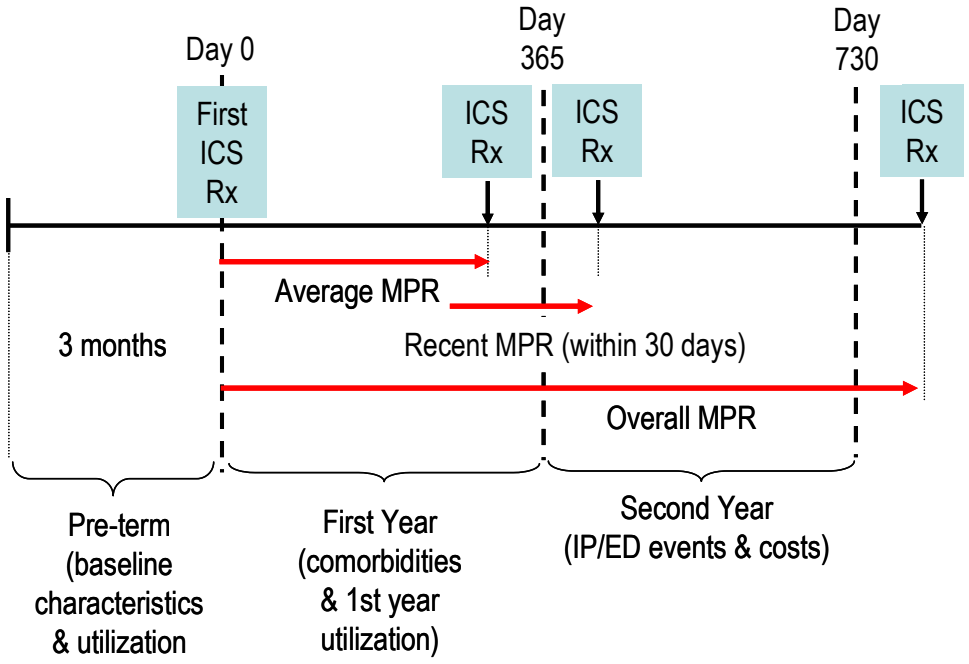


Figure 6.2: Study design and time period.

Two study periods were used: the first year was used to evaluate persistence and adherence, and the second year was used to evaluate outcomes. Also, adherence was evaluated using three measures of medication possession ratio (MPR): Average MPR, Recent MPR and Overall MPR. ICS: inhaled corticosteroids, IP: inpatient admissions, ED: emergency department visits, Rx: prescription.

Measures

ICS prescription refill patterns were employed as a measure of patient medication usage (or drug exposure level), assuming that patients used all medications prescribed. Medication persistence was defined as having ICS prescriptions continuously, and was measured by the number of days from the first ICS prescription to discontinuation. If patients did not have another ICS prescription within 180 days or reached the end of follow-up period, the last observed prescription day was defined as the discontinuation date. Medication adherence was defined by the medication possession ratio (MPR), which was calculated as sum of drug supply days divided by duration between prescriptions. Because “days supply” information was missing for 2.3% of prescriptions, missing values were imputed from standardized pharmacy costs.

Three types of MPR were defined according to the observation period (Figure 6.2). The “Average MPR” was calculated as the MPR between the first ICS prescription and the last one in the “first year”. The “Overall MPR” was calculated as the MPR between the first ICS prescription and the discontinuation date. In addition, to measure the recent impact of MPR on outcomes, ICS prescription 30 days before the end of first year was identified and the “Recent MPR” was calculated as the number of drug supply on the prescription divided by the number of days to the next prescription.

Outcomes of interest were inpatient admissions (IP), emergency department visits (ED), and medical costs observed during the second year. The percentages of having IP/ED events as well as the number of events for any condition and for COPD-related condition were calculated for each individual. Also, medical costs associated with these events were totaled and described as annual costs per patient.

Other explanatory variables included the season of ICS initiation, demographic characteristics, comorbidities and pre-term resource utilization patterns. The season of ICS initiation was categorized as: Winter (December, January, February), Spring (March, April,

May), Summer (June, July, August), and Fall (September, October, November). Demographic characteristics were age, gender, census regions (categorized as: Northeast, South, Midwest or West), and type of health plans (government or commercial). Comorbid conditions (congestive heart failure [CHF], asthma, depression, and hypertension) as well as the number of chronic conditions listed in Charlson Index (Charlson et al. 1987) were identified from medical claims during the first year. In addition, respiratory-related medical services (i.e., use of a spirometry test, oxygen therapy, medications) and IP/ED events (both any and respiratory-related conditions) were identified prior to each study period. The pre-term utilization 3-month prior to the first year was measured for the analysis of medication persistence and adherence. The pre-term utilization during the first year was used for outcomes analysis in the second year.

Statistical Analyses

Differences in background characteristics and pre-term utilization were summarized for three sub-cohorts. Chi-square tests were used to compare proportions for categorical measures and t-tests were used to compare continuous measures, using the sub-cohort (1) as the reference group (Swinscow and Campbell 2002). Multivariable regression models were used to estimate the factors associated with medication persistence and adherence. Time to discontinuation within one year of ICS treatment was assessed using a Cox proportional hazard regression model (Allison 1995). The patient's follow-up period was censored at the end of the first year. Because all patients were required to have one year of follow-up data, no patients were censored by death. MPR was estimated using an ordinary least square (OLS) models (Wooldridge 2003). Two MPR measures, "Average MPR" and "Overall MPR" were used as dependent variables.

The number of IP/ED events and medical costs during the second year were summarized according to three categories of medication persistence (ICS treatment was

terminated within six months, terminated between six and 12 months, or continued more than 12 months) and quintiles of the MPR ("Average MPR" and "Recent MPR"). Proportions having exacerbation events were compared using a logistic regression model and means among patients with any events were compared using a negative binominal model across the categories (Kleinbaum et al. 1998, Allison 1999). Treatment costs were compared using a generalized linear model (GLM) with a log link and gamma distribution (Manning and Mullahy 2001). Multivariable models were used to control for baseline patient characteristics (age, gender, insurance coverage, and census region), comorbidities (having CHF, asthma, depression, hypertension and the total number of chronic conditions during the first year) and pre-term healthcare utilization (i.e., specifically, specialist care, oxygen therapy, a spirometry test, number of any medication, and use of oral corticosteroids, oral antibiotics, short- and long-acting β_2-agonists, anticholinergics and theophylline during the first year). Because about 20% of patients had no COPD-related medical costs in the second year, a two-part model was used: a logistic regression model was used to predict probability of positive costs and a GLM to predict costs among patients with the positive costs (Blough et al. 1999). Statistical significance in cost differences was examined using a bootstrap method with 1,000 replications (Efron and Tibshirani 1993, Briggs et al. 1997). All analyses were conducted using statistical software, SAS version 8.2 (SAS Institute Inc., Cary NC) or STATA version 9.2 (StataCorp LP, College Station TX).

6.4 Results

Study population

The study sample selection is described in Figure 6.1. A total of 6,873 patients met the inclusion and exclusion criteria and these patients were used for persistence and adherence analysis [sub-cohort (1)]. Of those, 3,499 patients (50% of eligible patients) who had two years of follow-up data after initiating ICS were selected for average MPR and outcome analysis [sub-cohort (2)]. We also select 1,933 patients (28% of eligible patients) who had ICS exposure 30 days before the end of first year for recent MPR and outcome analysis [sub-cohort (3)].

Table 6.1 summarizes the baseline characteristics of COPD patients used in the analyses. For the sub-cohort (1), mean age was 61 years old. About half of study population was male and approximately 13% had government insurance. They had a variety of comorbid conditions including asthma (46%), hypertension (47%), CHF (14%) and depression (16%). Patients, on average, experienced 0.7 chronic conditions other than COPD. Compared with sub-cohort (1), sub-cohorts (2) and (3) were younger, more likely to have commercial insurance, and less likely to have CHF, asthma and other chronic conditions.

Table 6.1 also presents healthcare utilization during the three months prior to the first year study period. Sub-cohorts (2) and (3) were more likely to use specialist care, have a spirometry test and use regular bronchodilators, but less likely to experience IP/ED visits compared with the sub-cohort (1) of whom 26% had specialist care, 13% had oxygen therapy, 27% had a spirometry test, 77% had any use of medications, 50% used inhaled bronchodilators and 16% to 28% experienced IP/ED events for any condition and for respiratory-related condition, respectively.

Table 6.1: Baseline characteristics of COPD patients

	Sub-cohort (1) (n=6,873)	Sub-cohort (2) (n=3,499)	Sub-cohort (3) (n=1,933)
Male, %	46.9	46.0	46.5
Age, mean (SD)	61.0 (9.8)	59.5 (9.4)**	59.3 (9.0)**
Commercial insurance, %	86.6	84.9*	88.5*
Census region, %			
Northeast	52.4	61.6	62.2
South	12.2	7.1	6.6
Midwest	11.5	4.8	5.2
West / others	23.9	26.5	26.0
Season to ICS treatment began, %			
Winter (Dec, Jan, Feb)	23.5	24.5	24.3
Spring (Mar, Apr, May)	27.9	28.5	29.0
Summer (Jun, Jul, Aug)	25.0	23.6	23.9
Fall (Sep, Oct, Nov)	23.7	23.4	22.8
Comorbidities (during study period)			
Congestive heart failure, %	14.1	11.0**	9.8**
Asthma, %	45.7	52.1**	52.2**
Depression, %	15.9	15.4	15.1
Hypertension, %	46.9	46.0	45.1
Chronic conditions, mean (SD)	0.7 (1.0)	0.6 (0.9)**	0.5 (0.8)**
Pre-term utilization (3-month prior to the first year study period)			
Specialist care, %	25.6	26.5	29.0**
Oxygen therapy, %	12.5	10.8*	11.0
Spirometry test, %	26.6	28.3	30.4**
IP for any condition, %	23.9	20.5**	19.9**
IP for respiratory condition, %	15.5	13.9*	14.4
ED for any condition, %	27.7	25.4*	24.3**
ED for respiratory condition, %	18.2	17.2	16.9
Any medication, %	76.6	75.3	76.7
Oral corticosteroids, %	29.9	29.0	29.4
Oral antibiotics, %	46.2	44.8	45.1
Short-acting β_2-agonists, %	33.8	34.1	35.5
Long-acting β_2-agonists, %	13.0	14.4*	15.9**
Anticholinergics, %	37.4	31.0*	32.3**
Theophylline, %	6.2	5.9	6.1

Note: Chi-square tests were used for categorical measures and t-tests were used for continuous measures to compare baseline characteristics between sub-cohorts using the sub-cohort (1) as the reference. Comparisons between sub-cohorts (2) and (3) were not conducted. * indicates statistical significance at the 5% level; ** at the 1% level. ICS: inhaled corticosteroids, IP: inpatient admissions, ED: emergency department visits, Rx: prescription, SD: standard deviation.

Factors associated with medication persistence and adherence

Figure 6.3 presents medication persistence for ICS treatment among the 6,873 patients in sub-cohort (1). Approximately 44% of patients remained on ICS treatment after 12 months. Figure 6.4 presents the distributions of adherence for the first 12 months of treatment (measured by "Average MPR") and entire treatment period (measured by "Overall MPR"). There were no statistically significant differences between the two MPR measures. The mean values (standard deviations) of the average MPR and overall MPR were 0.58 (0.30) and 0.59 (0.30), respectively.

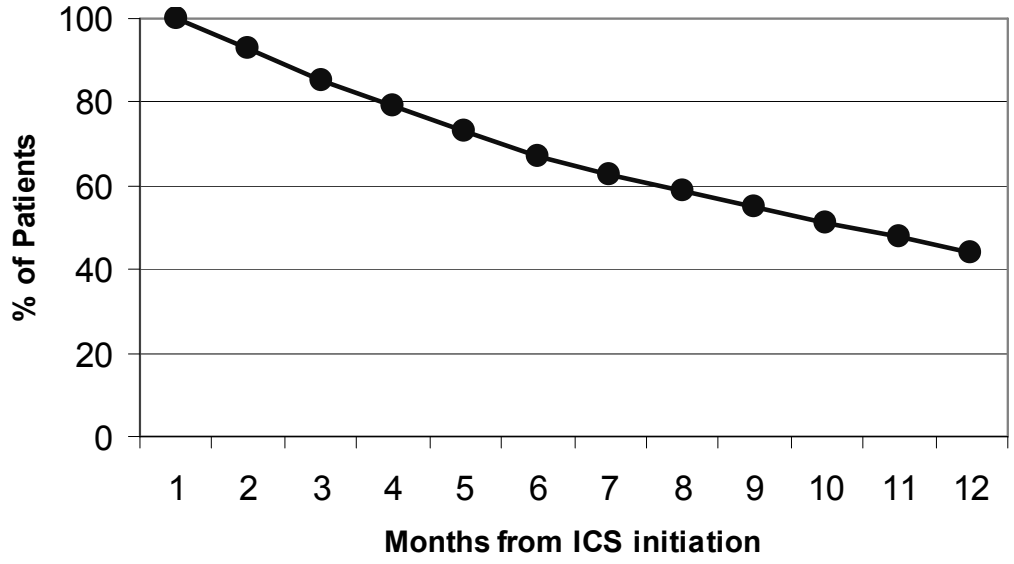


Figure 6.3: Cumulative percentage of patients who were still on ICS treatment.

Months were calculated from the first ICS prescription to discontinuation.

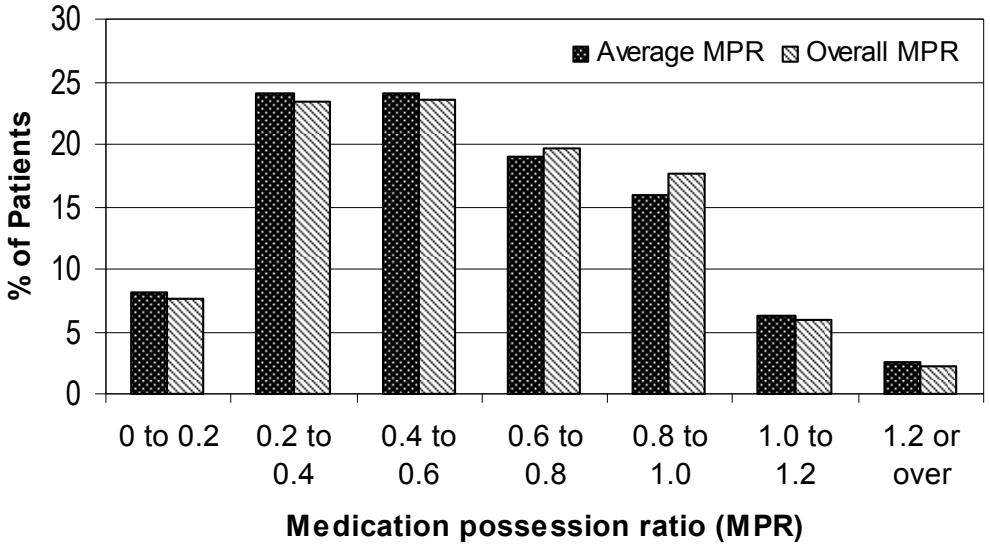


Figure 6.4: Distributions of adherence as measured by average medication possession ratio (MPR) and overall MPR.

There were no statistical differences between the MPR measures (t-test). The mean values (standard deviation) of MPR were 0.58 (0.30) for the average MPR and 0.59 (0.30) for the overall MPR, respectively.

Table 6.2 presents the results of the Cox proportional hazard model to estimate time to ICS discontinuation and OLS models to estimate medication availability measured by both "Average MPR" and "Overall MPR". Having commercial insurance, specialist care and a spirometry test were associated with better persistence (negative sign of coefficient on the Cox regression model indicates late discontinuation) and better adherence (positive sign of coefficient on the OLS indicates higher MPR). The number of chronic conditions was associated with poor persistence and adherence, perhaps because these patients were more likely to have multiple and complex medication regimens. Age, census regions and pre-term use of anticholinergics were also important factors determining medication persistence and adherence. In particular, patients with advanced age (ages 70-79 as a reference category) and those under anticholinergics treatment were more likely to have

higher MPR but to discontinue ICS treatment earlier. These apparently counterintuitive results maybe due to survival effects (these patients may have more severe disease and shorter survival time, and therefore, they use ICS more but for shorter time period). Season of ICS treatment initiation, comorbid conditions and pre-term healthcare utilization had relatively little effect.

Table 6.2: Regression models to estimate factors associated with persistence and adherence

Explanatory variables	Dependent variables (regression models)								
	Persistence (Cox proportional)			Average MPR (OLS)			Overall MPR (OLS)		
Ages 40-49 (vs ages 70-79)	0.0819	(0.0602)		-0.1130	(0.0137)	**	-0.1135	(0.0135)	**
Ages 50-59 (vs ages 70-79)	-0.1237	(0.0496)	*	-0.0677	(0.0112)	**	-0.0650	(0.0110)	**
Ages 60-69 (vs ages 70-79)	-0.1041	(0.0464)	*	-0.0390	(0.0106)	**	-0.0343	(0.0105)	**
Commercial insurance	-0.3399	(0.0511)	**	0.0884	(0.0121)	**	0.0943	(0.0119)	**
Census region: Northeast	-0.0173	(0.0416)		-0.0293	(0.0092)	**	-0.0303	(0.0090)	**
Census region: South	0.2924	(0.0573)	**	-0.0095	(0.0131)		-0.0179	(0.0129)	
Census region: Midwest	0.1458	(0.0601)	*	0.0763	(0.0135)	**	0.0648	(0.0133)	**
Congestive heart failure	0.0245	(0.0569)		-0.0018	(0.0132)		0.0065	(0.0130)	
Asthma	-0.0907	(0.0342)	**	-0.0124	(0.0076)		-0.0103	(0.0075)	
Depression	0.0207	(0.0452)		0.0081	(0.0101)		0.0075	(0.0099)	
Hypertension	0.0190	(0.0339)		0.0239	(0.0075)	**	0.0176	(0.0074)	*
No. of chronic conditions	0.1020	(0.0198)	**	-0.0168	(0.0047)	**	-0.0205	(0.0046)	**
Pre-term specialist care	-0.1203	(0.0412)	**	0.0186	(0.0090)	*	0.0166	(0.0088)	
Pre-term oxygen therapy	-0.0372	(0.0514)		0.0274	(0.0115)	*	0.0276	(0.0114)	*
Pre-term spirometry test	-0.1346	(0.0403)	**	0.0274	(0.0087)	**	0.0265	(0.0086)	**
Pre-term IP events with respiratory condition	0.0173	(0.0521)		-0.0131	(0.0116)		-0.0144	(0.0114)	
Pre-term ED events with respiratory condition	0.0546	(0.0489)		-0.0043	(0.0109)		-0.0095	(0.0108)	
Pre-term use of long-acting β_2-agonists	-0.0842	(0.0501)		0.0167	(0.0108)		0.0178	(0.0107)	
Pre-term use of anticholinergics	0.0906	(0.0347)	**	0.0678	(0.0078)	**	0.0628	(0.0077)	**

Note: Regression models also included variables for season to start ICS treatment, gender, and use of oral corticosteroids, oral antibiotics, short-acting β_2-agonists and theophylline. These variables were excluded from Table 6.2 because no statistical significant effect was observed. MPR: medication possession ratio, ICS: inhaled corticosteroids, OLS: ordinary least square, IP: inpatient admissions, ED: emergency department visits. Standard errors shown in parentheses.* indicates statistical significance at the 5% level; ** at the 1% level.

Association between medication persistence/adherence and IP/ED events

Table 6.3 summarizes the mean and range of persistence as well as the proportion and number of IP/ED events among 3,499 patients in sub-cohort (2) who had complete follow-up data in the second year. A total of 1,864 (53%) patients were still on ICS treatment beyond 12 months. For any condition, patients who continued ICS treatment over 12 months were less likely to experience an IP/ED event (37%) and to experience fewer events per year, if any (2.1 per patient), than patients who terminated ICS between six and 12 months (42% and 2.3 per patient, respectively). However, statistically significant trends were not observed after adjusting for background characteristics. For COPD-related events, no significant differences were observed associated with medication persistence.

Table 6.3: Inpatient admissions or emergency department visits by medication persistence

	Months on ICS treatment			Statistical tests
	< 6 (n=1,038)	6 -12 (n=597)	≥12 (n=1,864)	
Any condition				
% having event	39.0	42.2	36.7	Logistic
# of events, if any mean (SD)	2.28 (2.10)	2.28 (2.44)	2.08 (1.91)	Negative binomial
COPD condition				
% having event	9.0	8.4	9.6	Logistic
# of events, if any mean (SD)	1.52 (1.38)	1.68 (1.19)	1.54 (1.03)	Negative binomial
Mean months (SD)	3.4 (1.5)	8.7 (1.7)	32.5 (15.5)	

Note: Patients were categorized into three groups according to months on ICS treatment. A logistic regression model was used to compare % having event and a negative binomial model was used to compare mean number of events among patients who had any event (regression results are shown in Appendix 1 and 2). Demographic characteristics (age, gender, insurance, and census region), comorbid condition (congestive heart failure, asthma, depression, hypertension and number of chronic conditions) and healthcare utilization during the first year (specialist care, oxygen therapy, a spirometry test, number of any medication, use of oral antibiotics, short- and long-acting β_2-agonists, anticholinergics and theophylline) were used to adjust for baseline differences. No statistical significance was observed at the 5% level (patients with ≥12 months on ICS treatment were used as reference category). SD: standard deviation.

Table 6.4 summarizes the relationship between medication adherence and IP/ED events. The “Average MPR” was used as an explanatory variable to measure the temporal relationship between the average ICS exposure level in the first year and outcomes in the second year. We then used the “Recent MPR” as an explanatory variable to explain the effect of recent ICS exposure status (i.e., just before the second year) on the second year outcomes.

For the analysis of IP/ED events with any condition, the patients in the 2nd quintile of average MPR (range 0.29 to 0.42) were most likely to have any IP/ED event (42%) and had more IP/ED events (2.5 per patient). The proportion and mean number of events decreased with increasing MPR. COPD-related condition showed similar trends; however, no significant differences were observed. Furthermore, similar downward trends were observed between recent MPR and IP/ED events. The highest proportion of having IP/ED event were observed in the 1st quintile of recent MPR (range 0.01 to 0.25) for any condition (39%, not significant) and for COPD-related condition (11%, $p<0.01$) even though some random variation was also observed. In a sensitivity analysis, we eliminated patients who had MPR larger than 2.0 (i.e., two patients in the average MPR analysis) to examine the influence of outliers. No significant differences were observed.

Table 6.4: Inpatient admissions or emergency department visits by medication adherence

Average MPR [sub-cohort (2)]						
Quintile	1	2	3	4	5	
Number of patients	700	699	700	700	700	
Mean MPR (range)	0.20 (0.01-0.29)	0.36 (0.29-0.42)	0.50 (0.42-0.58)	0.68 (0.58-0.80)	0.97 (0.80-2.45)	Statistical tests
Any condition						
% having event	38.4	42.1*	39.6	35.9	35.7	Logistic
# of events, if any mean (SD)	2.20 (2.27)	2.48 (2.57)**	2.01 (1.85)	2.17 (1.92)	2.00 (1.50)	Negative binomial
COPD condition						
% having event	7.4	10.3	10.0	9.6	8.6	Logistic
# of events, if any mean (SD)	1.35 (0.84)	1.65 (1.10)	1.70 (1.65)	1.55 (1.10)	1.47 (0.79)	Negative binomial
Recent MPR [sub-cohort (3)]						
Quintile	1	2	3	4	5	
Number of patients	387	381	392	382	391	
Mean MPR (range)	0.18 (0.01-0.25)	0.33 (0.25-0.43)	0.52 (0.43-0.64)	0.76 (0.64-0.90)	1.07 (0.91-1.86)	Statistical tests
Any condition						
% having event	38.8	37.3	34.4	36.9	36.1	Logistic
# of events, if any mean (SD)	2.27 (2.16)*	2.07 (2.12)	2.55 (2.53)**	1.87 (1.40)	1.85 (1.42)	Negative binomial
COPD condition						
% having event	11.1**	7.9	10.5*	10.2*	7.4	Logistic
# of events, if any mean (SD)	1.60 (1.07)	1.50 (0.73)	1.73 (1.36)	1.36 (0.74)	1.38 (0.98)	Negative binomial

Note: Patients were categorized into quintiles according to medication possession ratio (MPR). A logistic regression model was used to compare % having event and a negative binomial model was used to compare mean number of events among patients who had any event (regression results are shown in Appendix 3 through 6). Demographic characteristics (age, gender, insurance, and census region), comorbid condition (congestive heart failure, asthma, depression, hypertension and number of chronic conditions) and healthcare utilization during the first year (specialist care, oxygen therapy, a spirometry test, number of any medication, use of oral antibiotics, short- and long-acting β_2-agonists, anticholinergics and theophylline) were used to adjust for baseline differences. Two patients in the average MPR analysis had MPR larger than 2.0. No differences were observed excluding such patients with outlier values. * indicates statistical significance at the 5% level; ** at the 1% level (patients with 5th quintile were used as reference category). SD: standard deviation.

Association between medication persistence/adherence and medical costs

Figure 6.5 presents the effects of medication persistence on any and COPD-related medical costs. Annual costs were calculated by controlling for baseline patient characteristics, comorbidities, and pre-term healthcare utilization. There were statistically significant differences between the number of months on ICS treatment and annual costs associated with any condition. Patients who terminated ICS treatment between six and 12 months of follow-up had the highest costs ($13,850, p<0.01), whereas patients who were on ICS treatment longer than 12 months had lower costs ($11,962, reference). Thus, improving persistence with ICS treatment would be expected to result in a 14% reduction in costs. No statistically significant differences were observed in COPD-related costs.

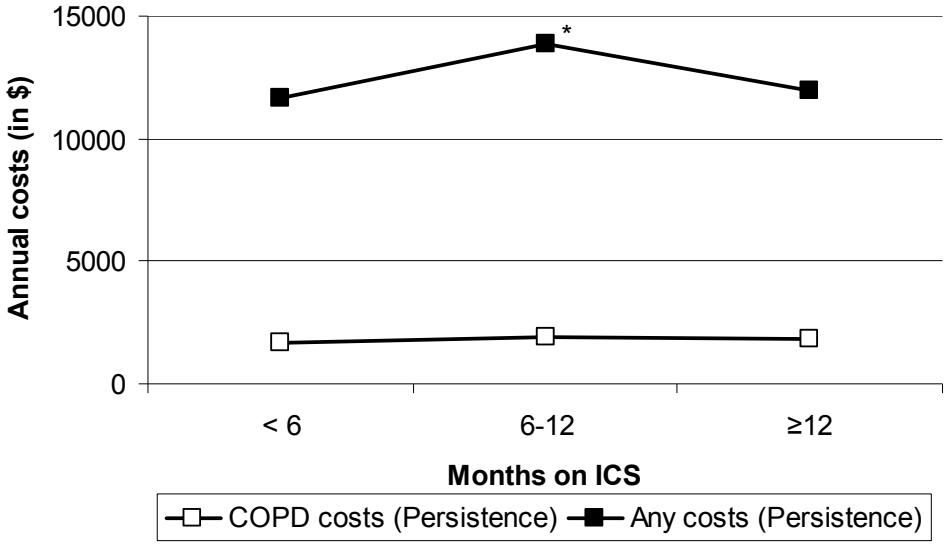
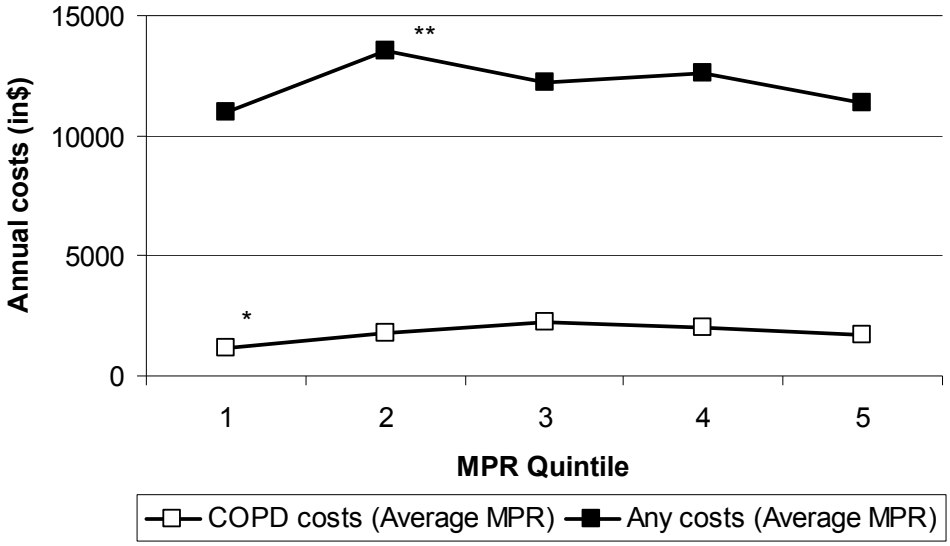


Figure 6.5: Mean values of estimated costs by medication persistence.

Annual costs were calculated controlling for demographic characteristics (age, gender, insurance, and census region), comorbid condition (congestive heart failure, asthma, depression, hypertension and number of chronic conditions) and healthcare utilization during the first year (specialist care, oxygen therapy, a spirometry test, number of any medication, use of oral antibiotics, short- and long-acting β_2-agonists, anticholinergics and theophylline). Regression results are shown in Appendix 7 and 8. * indicates statistical significance at the 5% level (for two-part model, statistical significance in cost differences was examined using a bootstrap method with 1,000 replications, patients with ≥12 months on ICS treatment were used as reference category)

Figure 6.6 presents the effects of medication adherence on any and COPD-related medical costs. Observed associations were consistent with those for IP/ED events. When the relationship was evaluated using the average MPR, the highest cost for any condition was observed in the 2nd quintile of MPR ($13,536, $p<0.01$). The annual costs tended to decrease with increasing MPR ($11,356 at the 5th quintile of MPR as reference). Similarly, the highest cost for COPD-condition was observed in the 3rd quintile of MPR ($2,212, not significant) and lower cost was observed in the 5th quintile ($1,721 as reference).

No statistically significant association was observed between the recent MPR and treatment costs. For any condition, the highest cost was observed in the 3rd quintile ($11,827) and the lowest cost was observed in the lowest exposure level (1st quintile, $10,173). On the other hand, for COPD-related conditions, the highest cost was observed in the 4th quintile ($1,962) and the lowest cost was observed in the 2nd quintile ($1,594). Even though an inverse association was observed in COPD-related IP/ED events, such trend was not clearly observed in the cost analysis.



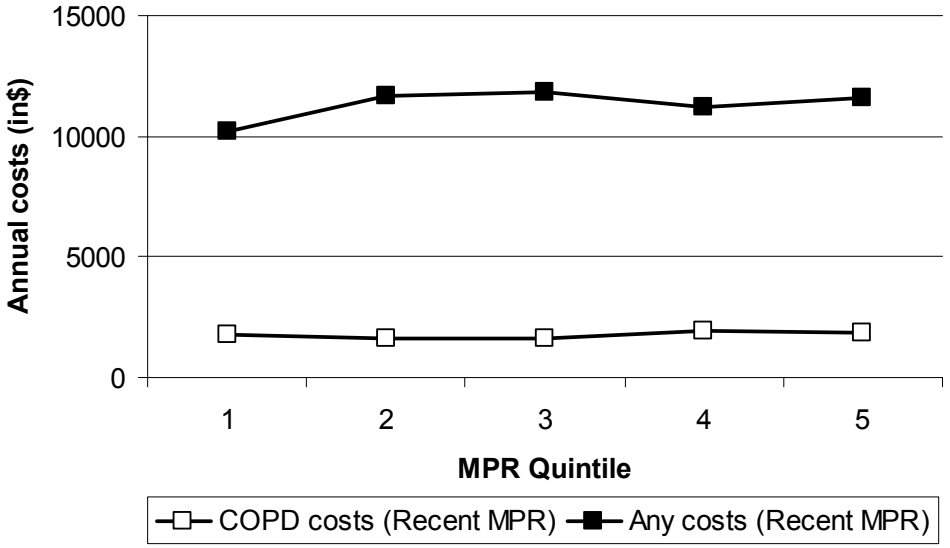


Figure 6.6: Mean values of estimated costs by medication adherence.

The upper figure shows the relationship between the average MPR and costs and the bottom figure shows the relationship between the recent MPR and costs. Annual costs were calculated using regression models similar to those described in Figure 6.5. Regression results are shown in Appendix 9 through 12. * indicates statistical significance at the 5% level; ** at the 1% level (for two-part model, statistical significance in cost differences was examined using a bootstrap method with 1,000 replications, patients with 5th quintile were used as reference category).

6.5 Discussion

Increasing numbers of studies evaluate medication persistence and adherence using retrospective databases (Peterson et al. 2007). We employed various measures commonly used in these studies to quantify the drug exposure level. This study suggested that age, census region, insurance coverage, number of chronic conditions, and having specialist care, a spirometry test, and anticholinergics use during pre-term period were strong predictors of ICS treatment persistence and adherence among COPD patients. Patients with better medication persistence were more likely to have lower treatment costs for any condition. Observed association between medication adherence and outcomes varied according to time frame of measuring MPR. Patients with higher average MPR had lower treatment costs for any condition, whereas no significant association was observed between recent MPR and treatment costs for both any and COPD-related conditions.

Medication persistence was used to understand how long patients were on ICS treatment using the permissible gap of 180 days between refills (Sikka st al., 2005). Since COPD is a progressive disease, regular drug treatment is recommended to maintain symptoms, to stabilize disease progress and to reduce exacerbation risk for longer periods (GOLD 2006). In fact, we found that longer ICS treatment might have benefits in preventing inpatient admissions or emergency department visits, and reducing overall costs. However, this result must be interpreted carefully. Not only the results were not statistically significant for COPD-related outcomes, but patients who discontinued ICS treatment within six months also had lower events and costs. Those patients may have milder COPD symptoms and may not yet have required regular ICS therapy (i.e., they only use ICS when needed). Additional research should be conducted to investigate the relationship between medication persistence and outcomes using patients with similar severity stages of COPD.

Medication possession ratios (MPR) have long been used to assess the benefits of drug treatments on healthcare utilization and costs (Stoupe et al. 2004, Siris et al. 2005,

Sokol et al. 2005). In this study, two types of MPR measured in different time frame were used to evaluate association between ICS exposure level and outcomes. We used a time lag approach to understand causal relationship between the average MPR in the first year and outcomes in the second year (Twisk 2003). This approach is useful to avoid the possibility that, if ICS exposure levels and outcomes are measured during the same period, patients with severe symptoms are more likely to use ICS and have higher treatment costs than those with less severe symptoms.

This MPR measure describes the average ICS treatment use by assuming patients use ICS regularly as indicated. However, because COPD is a symptomatic disease, patients may use the medication according to their symptoms. Unlike oral medications to control asymptomatic conditions (e.g., hypertension or hypercholesterolemia), it may be difficult to assume that patients use ICS regularly. The current evidence suggests that COPD patients tend to underuse medications when their symptoms are stable and overuse medications when they are experiencing respiratory distress (Rand 2005). This treatment behavior may be one reason that relatively poor adherence is often observed with ICS therapy compared with adherence for oral medications (Balkrishnan and Christensen 2000a and 2000b, Kelloway et al. 2000, Jones et al. 2003, Marceau et al. 2006). For this reason, even though our research shows patients with lowest MPR tend to have lower IP/ED risks and treatment costs, we consider this finding to be biased because these patients may have very stable conditions that do not require ICS treatment or other healthcare service use.

Moreover, this average MPR measure also reflects overall patient behavior of any medication use. Even though average MPR is associated with utilization and costs for any reason, it is difficult to consider ICS treatment itself is effective to reduce overall burden of disease. Patients who have better average MPR also may have good compliance with any other medications for their comorbid conditions (i.e., cardiovascular disease), and therefore, they have better overall outcomes. Even though the effects of major comorbid conditions

were adjusted in the regression models, the impact of patients' behavioral factors must be considered when interpreting the observed association between average MPR and outcomes.

By considering the time between MPR measures and outcomes (i.e., some patients discontinued ICS during the middle of the first year), we alternatively used the recent medication availability on the ICS prescription filled just before measuring outcomes. When this recent MPR is used to describe ICS exposure level, we find patients with higher MPR tend to have lower risk of IP/ED events for COPD-related conditions. This finding is consistent with the previous study results that support ICS treatment as effective to control symptoms. However, such benefit was not observed in COPD-related costs. Thus, ICS treatment effects must be confirmed with a study that links ICS exposure with clinical data.

In addition to the potential limitations related to measurements of medication persistence and adherence, we also must consider the limited generalizability of our findings. Economic consequences were investigated only for selected patients who had at least two years of follow-up data after initiating ICS treatment (about 50% of eligible patients were dropped due to this restriction). Appropriate maintenance medications also would be important for patients with a high risk of mortality or morbidity to prevent future outcomes. However, we eliminated patients who left the database for any reason, including death during the study period according to the follow-up requirement. These patients may have had extremely high medical costs due to their terminal care or might have had only few costs due to short period of follow-up. Either way, the outcome measures would be biased (Collet and Boivin 2000), and therefore, we should carefully address these limitations when we include this high-risk population in the analysis. Thus, our findings are only relevant for patients who have relatively stable COPD.

The result suggests that patients with specialist care and a spirometry test result are more likely to have better ICS persistence and adherence. These variables are associated

with more severe disease. Patients with more severe conditions are more likely to use ICS, in greater doses for longer. However, these factors are still powerful predictors after adjusting for risk factors including comorbidities and pre-term resource utilization for respiratory conditions. Thus, this tendency can be explained not only by ICS treatment needs but also by patient recognition about disease and treatment (George et al. 2005). Increased specialist care and improved patient education may enhance patient understanding of the importance of ICS maintenance therapy for COPD conditions.

On the other hand, age and the number of comorbidities were negatively associated with treatment adherence. COPD patients tend to be older and have multiple comorbidities, and those factors are often associated with complex medication regimens and poor adherence (Dolce et al. 1991). Thus, studies focusing on elderly patients (i.e., using Medicare population) are essential to understand their treatment behavior and to find appropriate strategies to control the burden of COPD.

6.6 Conclusion

Step-down adjustment of pharmacotherapy is not recommended for COPD. However, patients tend to reduce and stop their medications according to their maintained symptomatic condition. The study findings suggest that access to specialist care and patient understanding of disease and treatment may be key factors to improving medication persistence and adherence. Observed association of ICS persistence and adherence with treatment outcomes is relatively small and not consistent. Therefore, further studies are required to understand use of inhaled medications for symptomatic conditions and their impact on healthcare utilization and costs.

CHAPTER 7

Study Limitations and Future Research Agenda

7.1 Summary of Findings

This dissertation was conducted to examine the benefits of early initiation of ICS treatment among patients with COPD using a managed care claims database. Large administrative databases, including electronic medical records and insurance claims, have been used frequently for studies analyzing drug exposure and clinical outcomes. Because these databases are generated through routine clinical practice, researchers can study real-world utilization patterns and their consequences in large populations. However, because the databases often do not have detailed patient clinical information and risk factors, the ability to adjust for confounding biases is limited (Schneeweiss and Avorn 2005).

The first analysis (Chapter 4) used the propensity-score-matching (PSM) approach to answer the question "what is the potential benefit of early initiation of ICS therapy among COPD patients?" The PSM approach was used to adjust for potential bias resulting from observed confounders. Two study groups, patients who initiated ICS treatment within three months of or after three months of the index date, were compared in terms of exacerbation risks, resource utilization and treatment costs. Because differences in clinical needs and risk factors between two groups likely would affect treatment choices and resultant outcomes, patients were matched one-to-one using a propensity score calculated based on observed patient characteristics, comorbidities and prior utilization. After applying PSM, the analytic sample included 7,712 individuals who had comparable background characteristics. Early

ICS treatment was associated with a 7% reduction in exacerbations (i.e., inpatient admissions, emergency department visits and/or office visits with rescue medications). Furthermore, early treatment initiation was associated with an 8% reduction in all-cause medical costs, and a 23% reduction in COPD-related medical costs. The reduction in medical costs was more than the increase in pharmacy costs, indicating that early ICS initiation achieved an overall total cost reduction.

The analysis described in Chapter 5 used an individual-level, fixed-effects model approach to answer the question "what is potential benefit of beginning ICS therapy among COPD patients?" Because the study design allowed me to detect changes within individuals in treatment costs before and after initiating ICS, it was possible to adjust for potential bias resulting from unobserved factors that do not change over time (i.e., smoking or other risk behaviors). The model also included variables to explain the time trend (i.e., time from initiating bronchodilators and ICS as well as month dummies to adjust for seasonality) and symptom changes (i.e., having exacerbations as well as asthma and congestive heart failure). The results of this analysis suggested that the potential benefit of ICS treatment depends on the timing of therapy initiation. For example, a six-month early initiation of ICS therapy was, on average, associated with cost reduction of $306 overall or $51 per month in COPD-related services. The magnitude of the cost reduction varied by age, and the oldest population had largest benefits. Similar results were observed in all-cause medical costs.

In the final analysis (Chapter 6), I evaluated medication persistence and adherence for ICS therapy and their association with economic consequences. I hypothesized that patients with better medication persistence and adherence were more likely to experience better outcomes. Medication persistence or treatment duration was measured as the time between initiating and discontinuing ICS therapy; medication adherence was measured by medication possession ratio using information about days supply and days between refills. Two-period analyses were conducted to establish the causal relationship. Having

commercial insurance, using specialist care, and having a spirometry test were associated with better persistence and adherence, whereas the number of chronic conditions had a negative impact. Age, census region and pre-term use of anticholinergics were also important determinants of persistence and adherence. Access to specialist care and patient understanding of disease and treatment also may be the key factors to improving medication persistence and adherence. Improvement of persistence and adherence may be effective to prevent exacerbation events and to reduce treatment costs. However, observed association was relatively small and not consistent across various measures.

The current clinical guidelines recommend step-wise increase in pharmacotherapy for COPD patients according to disease progression and exacerbation risks, and include ICS to augment regular bronchodilator therapy (Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2006). However, the current study findings consistently support that early initiation (i.e., concomitant with bronchodilator therapy rather than in response to exacerbations that are uncontrolled by bronchodilator therapy) and continuous maintenance therapy with ICS is an important treatment strategy to achieve better symptom controls and to reduce overall treatment costs.

7.2 Study Limitations

Although various analytical techniques were used to minimize confounding biases due to observed and unobserved factors, there are fundamental limitations in observational studies based on administrative data. In order to find the most appropriate approaches to minimize the impact of such limitations and to obtain definitive conclusions, one must identify the sources of bias as well as predict the strength and direction of them. The following first summarizes the biases that could be addressed in the dissertation, and then describes those that must be addressed with additional research.

First, there are confounding biases associated with observed patient characteristics. Physicians prescribe drugs based on diagnostic and prognostic information available at the time of writing prescriptions. The factors influencing the decision vary by physician and over time, and frequently involve clinical, functional, or behavioral characteristics of patients (Schneeweiss et al. 2005b). If these factors are also independent predictors of the study outcome, failing to control for such factors can lead to the confounding bias (Signorello 2002).

To reduce this bias, a propensity score, defined as the conditional probability of drug exposure given measured variables, was used in Chapter 4. To have comparable groups with similar background characteristics, patients were matched using the nearest score without replacement. As a result, about 40% of patients who initiated ICS within three months (treatment group) were eliminated from the analysis because there was no match for them. That is, they were fundamentally different: treatment patients excluded from the analysis were more likely to be younger, to have commercial insurance, to have comorbid conditions of asthma, congestive heart failure and hypertension, and to use specialist care and spirometry tests three months prior to the index than treatment patients who had matched pairs. Thus, one must be cautious in interpreting the results, as that the findings are only relevant to the selected patients. In addition, the majority of COPD patients tend to be older than the managed care population; and therefore, the findings are not generalizable to all COPD patients.

The propensity score technique cannot control for unmeasured or imperfectly measured variables. Because there was no clinical information available in the claims database, patient disease severity had to be predicted from past resource utilization patterns (e.g., numbers of hospital admissions, emergency department visits or medications). Additionally, only limited adjustments could be made for risk behaviors and conditions (e.g., comorbidities identified by medical claims used during the time period observed). If these

proxy measures of disease severity are non-differential (i.e., not associated with treatment choice), the direction of the bias is toward the null. However, if the misclassification of the disease severity measures is differential (i.e., associated with treatment choice), it is difficult to predict strength and direction of the bias.

Second, there are confounding biases associated with unobserved patient characteristics. To reduce the potential bias, a fixed-effects model approach, in which each individual could contribute as both treatment and control groups at different times, was used in Chapter 5. This approach can exclude the bias due to unmeasured time-invariant patient characteristics (e.g., smoking behavior). However, time-variant variables, such as improvement or worsening of COPD symptoms or overall health during the follow-up period, must be addressed explicitly. Again, because only limited proxy measures could be included to adjust for time-variant factors, unobserved factors and potential misclassification of the proxy measures would be a potential source of bias, with the resultant impact on the estimates difficult to predict.

Moreover, we had to assume drug exposure status and treatment effects were constant over time regardless of clinical stage and length of treatment. However, patients may often adjust their medications according to their symptomatic conditions (i.e., reduce or stop medication with better symptom control or increase medication to alleviate symptoms and distress) even though the treatment guideline suggests that regular ICS use is required for maintenance treatment (GOLD 2006). Also, since current evidence suggests that ICS does not alter lung function and progression of COPD (Alsaeedi et al. 2002, Sin et al. 2003, Sin et al. 2005), the potential effectiveness of ICS treatment may vary across individuals and depend on patient clinical characteristics. Thus, the assumptions of constant exposure and treatment effects are violated, and likely are the source of bias for which magnitude and direction cannot be accurately predicted.

Third, the impact of drug exposure status on exacerbation events and treatment costs was examined in Chapter 6. Initially, a longitudinal analysis using multiple observations for each individual was planned. However, because patients with a high degree of ICS exposure were more likely to use other services because of their worsening symptoms, the expected ICS effects on preventing utilization and cost tended to be biased toward the null or underestimated. Therefore, a two-period analysis (drug exposure status was measured in the first year and outcomes were measured in the second year) was conducted to assess the relationship. Although a potential benefit of continuous ICS treatment was observed in the analysis, the association between medication adherence and outcomes was not clearly observed. According to the study design, which required a full two years of follow-up data after initiating ICS, patients who had high risk of death were automatically excluded from the analysis. Thus, in addition to considering that COPD is generally a slowly progressing disease, a longer observation period would be required to observe the preventive effects of regular maintenance therapy with ICS. Recently, the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) published a checklist for medication compliance and persistence studies using retrospective databases (Peterson 2007). To improve the quality of study, a future analysis must address these requirements.

Lastly, the findings are only applicable to a managed care population, and cannot represent all COPD patients in the United States. Only 15% of study population had government insurance (Medicare or Medicaid coverage). These patients may be older and sicker compared with the managed care population. They also may have limited access to appropriate medications, as well as multiple comorbidities and complex medication regimens that have been shown to affect treatment behavior. Because COPD is the disease found primarily in the elderly, studies using the Medicare population or patients in long-term

care facilities would be required to understand overall COPD burden and benefits of regular ICS treatment.

7.3 Future Research Agenda

The limitations listed earlier logically lead to the following future research agenda, which includes the development and refinement of analytical methods to reduce confounding biases due to observed and unobserved factors, the use of decision analysis to predict long-term consequences of ICS treatment, and the extension of analyses to the Medicare population. Specific approaches to each of these avenues are outlined in Table 7.1.

Table 7.1: Future research agenda

Compare methods to minimize confounding bias	1. Propensity-score-method (matching, stratification, weight, etc) 2. Sensitivity analysis and external adjustment 3. Instrumental variables
Estimate long-term outcomes	1. Decision modeling 2. Analysis of survival and censored cost data
Focus on Medicare population	1. Comorbidities and multiple medications 2. Adherence to treatment and outcomes 3. Medicare Part D prescription drug coverage

The development, refinement, and use of various bias minimization techniques offer a logical starting point for future research. In observational studies, because treatment is not randomly assigned, treatment and control groups are not comparable before the treatment, and therefore, observed outcomes may reflect these pre-treatment differences rather than treatment effects (Stukel et al. 2007). A variety of approaches have been proposed to address this selection bias – propensity-score-methods, external calibration, and instrumental variables.

In the first of these approaches, the propensity score can be used to reduce such a selection bias through matching, stratification, regression adjustment and weighing (D'agostino 1998, Kurth et al. 2005, Seeger et al. 2005, Rosenbaum and Rubin 2006, Stürmer et al. 2006). Moreover, various matching techniques using the propensity score (such as stratified, nearest neighbor, radius, kernel, and Mahalanobis matching) have been introduced to obtain the most appropriate matched samples (Baser 2006). In this dissertation, the nearest neighbor matching with caliper (20% of standard deviation) approach was used to create two balanced comparative groups conditional on observed characteristics. The approach was selected only because a validated SAS program was available when the data were analyzed (Martin and Ganguly 2003). In addition, because of the limited sample size, only part of patients in the treatment group could be matched to patients in the control group. A recent study by Baser (2006) suggests that the matching algorithm used may affect the results obtained in later analyses. Therefore, a logical extension of this dissertation is to compare the various propensity-score-methods and matching techniques to find the best way to fit the data and to minimize the potential bias as it applies to COPD patients.

Analyses also may be biased by unobserved characteristics (e.g., disease severity defined by lung function, smoking and other risk factors). In this study, I used longitudinal analysis to control for unobserved time-invariant characteristics (e.g., smoking and other risk behaviors those do not change over time), and proxy measures (e.g., prior healthcare service utilization) were employed to minimize the impact of unobserved time-variant characteristics. However, no quantitative assessment of the potential bias (magnitude and direction) was undertaken in this dissertation. Therefore, a systematic approach is required to evaluate impact of unobserved confounders to lead conclusions. Schneeweiss (2006) summarized strategies to control for unmeasured confounders in pharmacoepidemiology studies (Figure 7.1).

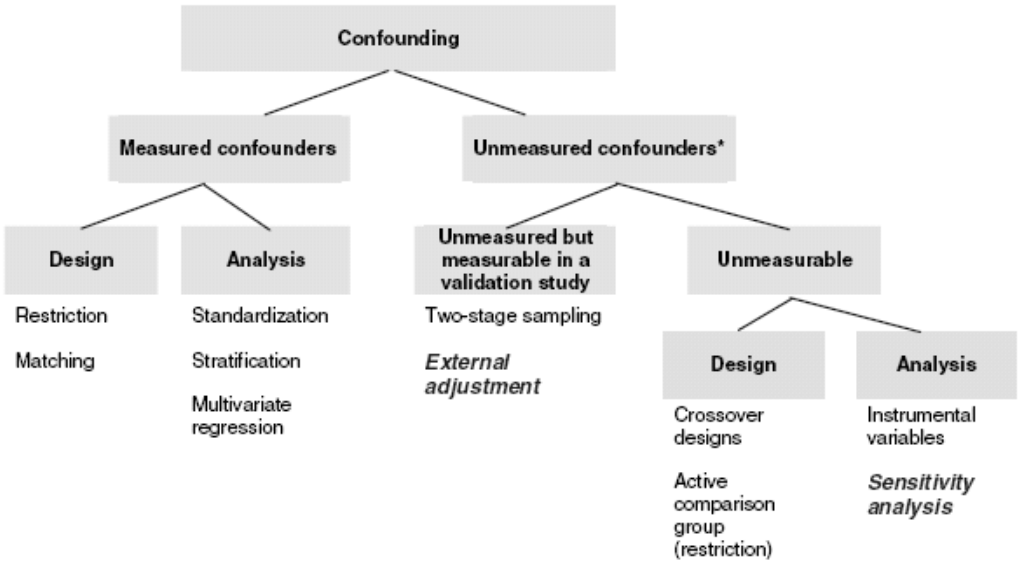


Figure 7.1 Strategies to control for unmeasured cofounders in pharmacoepidemiology

Source: Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. Pharmacoepidemiol Drug Saf. 2006 May;15(5):291-303. Copyright 2006. Reprinted with permission from John Wiley & Sons Limited.

One approach to analyze the impact of unobserved cofounders is a sensitivity analysis. Using a graphical exploration, one can understand how the strength of an unmeasured confounder and imbalance between groups affects the observed association. Moreover, even if the important confounders are not available in the main database, data from external sources can be used for the external adjustment. For example, Schneeweiss and colleagues (2004, 2005a), in order to evaluate association between drug treatments and risks of adverse events, used external data from the Medicare Current Beneficiary Survey (MCBS) to determine the impact of potential confounding factors that were unavailable in the Medicare claims.

Recently, a new technique of propensity-score-calibration was introduced to externally adjust for multiple unmeasured confounders (Stürmer et al. 2005). In order to evaluate the association between nonsteroidal anti-inflammatory drugs (NSAID) and mortality using New Jersey Medicaid data, Stürmer and colleagues estimated the propensity

of NSAID use from the MCBS (the external source), to adjust for unobserved confounders in the main data (i.e., smoking, body mass index, activities of daily living, education, income, and lifetime rheumatoid arthritis and osteoarthritis). Then, the authors quantified the bias by comparing the estimates obtained using traditional multivariable adjustments with the estimates using this propensity-score-calibration. Currently, this calibration technique is only applicable to evaluate the potential bias on dichotomous outcomes (e.g., hazard ratio). More studies are required to evaluate the benefit of this new adjustment technique, including studies involving patients with COPD. Thus, the external adjustment combined with the propensity-score-method would be an important avenue for future research.

Instrumental variable (IV) methods present a possible solution for the confounding bias due to unobserved factors if suitable instruments can be identified. The valid instrument should be 1) strongly associated with the exposure of interest, 2) not associated with the outcomes other than through the exposure of interest, and 3) not associated with any potential confounders (Hernan and Robins 2006, Martens et al. 2006). The IV estimation approach has been applied in several observational studies. These studies have used various instruments, including distance to a cardiac catheterization facility (McClellan et al. 1994), a start date of the new drug reimbursement policy (Schneeweiss et al. 2002) and a physician's NSAID preference (Brookhart et al. 2006). Thus, additional research might identify potential instruments and evaluate their utility in predicting economic consequences of ICS treatment in COPD patients.

This dissertation evaluated ICS treatment over two-year period: analysis over a longer period is desirable. Although the number of years covered by managed care databases is increasing rapidly, researchers currently must compromise sample size or follow-up time. Specifically, the longer the follow-up period required, the smaller the sample size available, and vice versa. An alternative approach, while waiting for additional data to become available, is to use decision analysis techniques to estimate long-term outcomes

and costs. Because COPD is a progressive disease, drug treatment effects on prolonged survival requires long-term follow-up data. Gagnon et al. (2005) conducted a cost-effectiveness analysis of comparing various COPD treatment strategies over lifetime. Using survival and censored cost data analysis techniques, they calculated the incremental cost-effectiveness ratio between drug treatments, and then, applied probabilistic sensitivity analyses to address the uncertainty of the input data. This analytical framework could be useful not only for analyzing the value of additional treatment costs to improve outcomes but also for predicting long-term consequences with uncertainty of the data (Briggs et al. 2006). Once longer-term data become available, then one can conduct the longitudinal analyses that will confirm (or not) the results obtained through decision analysis techniques.

Another fruitful research avenue would be to use the various methods employed in this dissertation and the proposed research agenda using data from the Medicare population. Not only because COPD is a chronic disease for elderly, but also Medicare beneficiaries may have different treatment behaviors and risk factors of outcomes compared with managed care population. We found that patients with multiple comorbidities, very much like the Medicare population, were more likely to have poor medication persistence and adherence. These patients often have multiple and complex medications that influence treatment behavior and outcomes. To reduce the potential burden of COPD, another strategy may be required to improve drug treatment for this at-risk population. Currently, data for outpatient pharmacy services among Medicare population are limited. Thus, many researchers have utilized the Medicare Current Beneficiary Survey (MCBS) data as an alternative source to analyze drug utilization and treatment costs (Stuart et al. 2004, Briesacher et al. 2005). However, with the introduction of Medicare part D prescription drug coverage in January 2006, Medicare claims data including pharmacy information will become available for outcomes research purposes in the near future (ISPOR 2005). This would provide a tremendous opportunity for pharmacoeconomics and outcomes researchers

to analyze the use of chronic medications and their economic consequences among Medicare beneficiaries.

Appendix: Regression results for persistence and adherence analyses (Chapter 6)

Appendix 1: Parameter estimated for persistence vs. COPD-related IP/ED events

Model	Logistic			Negative binomial		
(Dependent variables)	(Having any event)			(# of events, if any)		
Parameter	β	SE		β	SE	
Intercept	-2.5862	0.2864	**	0.2407	0.2006	
ICS treatment for <6 mo (vs ≥12 mo)	0.0272	0.1503		0.0996	0.1126	
ICS treatment for 6-12 mo (vs ≥12 mo)	-0.1367	0.1795		0.1814	0.1266	
Ages 40-49 (vs ages 70-79)	-0.8226	0.2493	**	-0.4485	0.1933	*
Ages 50-59 (vs ages 70-79)	-0.3693	0.1887		-0.4154	0.1457	**
Ages 60-69 (vs ages 70-79)	-0.3894	0.1855	*	-0.1493	0.1333	
Male	-0.0131	0.1266		0.0941	0.0942	
Commercial insurance	-0.0702	0.1815		0.2215	0.1346	
Census region: Northeast	-0.5480	0.1363	**	0.0551	0.0986	
Census region: South	-0.7714	0.2936	**	0.1925	0.2050	
Census region: Midwest	-0.3793	0.2921		-0.0363	0.2107	
Congestive heart failure	0.4862	0.1978	*	0.1756	0.1402	
Asthma	-0.2079	0.1333		0.0174	0.0947	
Depression	0.5321	0.1520	**	0.1251	0.1055	
Hypertension	-0.1631	0.1280		-0.2366	0.0947	*
No. of chronic conditions	0.0219	0.0744		-0.0221	0.0535	
Pre-term specialist care	0.0716	0.1355		-0.0339	0.0986	
Pre-term oxygen therapy	0.2636	0.1435		0.0586	0.1002	
Pre-term spirometry test	-0.2538	0.1336		-0.0629	0.1002	
Pre-tern no. of any medication	0.0166	0.0069	*	0.0153	0.0044	**
Pre-term use of oral corticosteroids	0.5412	0.1403	**	0.1169	0.1052	
Pre-term use of oral antibiotics	-0.2329	0.1451		-0.0416	0.1107	
Pre-term use of short-acting β_2-agonists	0.2732	0.1371	*	-0.0455	0.1034	
Pre-term use of long-acting β_2-agonists	0.141	0.1378		-0.0529	0.0970	
Pre-term use of anticholinergics	0.684	0.1672	**	-0.0975	0.1268	
Pre-term use of theophylline	0.0917	0.1957		-0.2222	0.1405	

Note: β: estimated coefficients, SE: standard errors. * indicates statistical significance at the 5% level; ** at the 1% level. IP/ED events: inpatient admissions or emergency department visits

Appendix 2: Parameter estimated for persistence vs. any IP/ED events

Model	Logistic			Negative binomial		
(Dependent variables)	(Having any event)			(# of events, if any)		
Parameter	β	SE		β	SE	
Intercept	-0.2546	0.1759		0.6060	0.1005	**
ICS treatment for <6 mo (vs ≥12 mo)	0.0001	0.0903		0.0860	0.0526	
ICS treatment for 6-12 mo (vs ≥12 mo)	0.1526	0.1032		0.0799	0.0589	
Ages 40-49 (vs ages 70-79)	-0.4025	0.1423	**	-0.0422	0.0780	
Ages 50-59 (vs ages 70-79)	-0.4694	0.1213	**	-0.1759	0.0664	**
Ages 60-69 (vs ages 70-79)	-0.5813	0.1191	**	-0.1600	0.0652	*
Male	-0.1083	0.0758		-0.0009	0.0450	
Commercial insurance	0.0370	0.1201		0.0226	0.0625	
Census region: Northeast	-0.6792	0.0866	**	-0.1937	0.0473	**
Census region: South	-0.7069	0.1591	**	-0.2477	0.1017	*
Census region: Midwest	-0.6807	0.1845	**	-0.2651	0.1155	*
Congestive heart failure	0.2383	0.1412		0.2363	0.0677	**
Asthma	0.1442	0.0806		-0.0155	0.0470	
Depression	0.3359	0.1024	**	0.1549	0.0532	**
Hypertension	0.1044	0.0767		-0.0932	0.0452	*
No. of chronic conditions	0.3010	0.0495	**	0.0972	0.0233	**
Pre-term specialist care	-0.0154	0.0821		0.0574	0.0481	
Pre-term oxygen therapy	-0.0259	0.0996		0.0654	0.0532	
Pre-term spirometry test	-0.1402	0.0798		-0.1052	0.0471	*
Pre-tern no. of any medication	0.00342	0.0048		0.0060	0.0026	*
Pre-term use of oral corticosteroids	0.2531	0.0826	**	0.0779	0.0489	
Pre-term use of oral antibiotics	0.253	0.0862	**	0.0145	0.0533	
Pre-term use of short-acting β_2-agonists	0.0661	0.0810		0.0825	0.0475	
Pre-term use of long-acting β_2-agonists	-0.1278	0.0870		0.0176	0.0488	
Pre-term use of anticholinergics	0.00614	0.0936		0.0326	0.0542	
Pre-term use of theophylline	0.1393	0.1329		-0.0969	0.0746	

Note: β: estimated coefficients, SE: standard errors. * indicates statistical significance at the 5% level; ** at the 1% level. IP/ED events: inpatient admissions or emergency department visits

Appendix 3: Parameter estimated for average MPR vs. COPD-related IP/ED events

Model	Logistic			Negative binomial		
(Dependent variables)	(Having any event)			(# of events, if any)		
Parameter	β	SE		β	SE	
Intercept	-2.8220	0.3086	**	0.1468	0.2229	
MPR Quintile 1 vs 5	0.0892	0.2104		0.1366	0.1642	
MPR Quintile 2 vs 5	0.3814	0.1947		0.2308	0.1451	
MPR Quintile 3 vs 5	0.3058	0.1929		0.2133	0.1403	
MPR Quintile 4 vs 5	0.1830	0.1935		0.1106	0.1420	
Ages 40-49 (vs ages 70-79)	-0.8392	0.2496	**	-0.4608	0.1940	*
Ages 50-59 (vs ages 70-79)	-0.3769	0.1885	*	-0.4199	0.1449	**
Ages 60-69 (vs ages 70-79)	-0.3906	0.1854	*	-0.1464	0.1329	
Male	-0.0154	0.1270		0.0989	0.0943	
Commercial insurance	-0.0517	0.1811		0.1773	0.1341	
Census region: Northeast	-0.5414	0.1366	**	0.0533	0.0987	
Census region: South	-0.7377	0.2936	*	0.2271	0.2085	
Census region: Midwest	-0.4053	0.2930		-0.0220	0.2127	
Congestive heart failure	0.4932	0.1983	*	0.1554	0.1392	
Asthma	-0.2100	0.1338		-0.0074	0.0952	
Depression	0.5358	0.1527	**	0.1569	0.1060	
Hypertension	-0.1547	0.1282		-0.2149	0.0942	*
No. of chronic conditions	0.0181	0.0743		-0.0274	0.0537	
Pre-term specialist care	0.0694	0.1358		-0.0216	0.0988	
Pre-term oxygen therapy	0.2655	0.1439		0.0588	0.1002	
Pre-term spirometry test	-0.2495	0.1338		-0.0240	0.1020	
Pre-tern no. of any medication	0.0175	0.0068	**	0.0148	0.0044	**
Pre-term use of oral corticosteroids	0.5248	0.1403	**	0.1117	0.1070	
Pre-term use of oral antibiotics	-0.2445	0.1450		-0.0326	0.1115	
Pre-term use of short-acting β_2-agonists	0.2714	0.1376	*	-0.0391	0.1035	
Pre-term use of long-acting β_2-agonists	0.1358	0.1383		-0.0576	0.0972	
Pre-term use of anticholinergics	0.7027	0.1674	**	-0.0687	0.1263	
Pre-term use of theophylline	0.0960	0.1962		-0.2095	0.1410	

Note: β: estimated coefficients, SE: standard errors. * indicates statistical significance at the 5% level; ** at the 1% level. IP/ED events: inpatient admissions or emergency department visits

Appendix 4: Parameter estimated for average MPR vs. any IP/ED events

Model	Logistic			Negative binomial		
(Dependent variables)	(Having any event)			(# of events, if any)		
Parameter	β	SE		β	SE	
Intercept	-0.3749	0.1871	*	0.5699	0.1071	**
MPR Quintile 1 vs 5	0.1589	0.1206		0.1232	0.0722	
MPR Quintile 2 vs 5	0.2908	0.1182	*	0.2059	0.0688	**
MPR Quintile 3 vs 5	0.1999	0.1167		-0.0007	0.0705	
MPR Quintile 4 vs 5	0.0206	0.1171		0.0820	0.0707	
Ages 40-49 (vs ages 70-79)	-0.4201	0.1427	**	-0.0695	0.0785	
Ages 50-59 (vs ages 70-79)	-0.4785	0.1216	**	-0.1900	0.0664	**
Ages 60-69 (vs ages 70-79)	-0.5808	0.1192	**	-0.1713	0.0649	**
Male	-0.1060	0.0759		0.0039	0.0449	
Commercial insurance	0.0431	0.1200		0.0258	0.0624	
Census region: Northeast	-0.6852	0.0867	**	-0.2008	0.0472	**
Census region: South	-0.7040	0.1589	**	-0.2311	0.1009	*
Census region: Midwest	-0.6861	0.1850	**	-0.2734	0.1153	*
Congestive heart failure	0.2285	0.1413		0.2315	0.0675	**
Asthma	0.1407	0.0808		-0.0148	0.0470	
Depression	0.3331	0.1026	**	0.1529	0.0532	**
Hypertension	0.1130	0.0768		-0.0818	0.0451	
No. of chronic conditions	0.2990	0.0494	**	0.0944	0.0232	**
Pre-term specialist care	-0.0071	0.0823		0.0586	0.0480	
Pre-term oxygen therapy	-0.0219	0.0996		0.0773	0.0529	
Pre-term spirometry test	-0.1362	0.0799		-0.0986	0.0470	*
Pre-tern no. of any medication	0.0051	0.0047		0.0060	0.0025	*
Pre-term use of oral corticosteroids	0.2435	0.0825	**	0.0753	0.0487	
Pre-term use of oral antibiotics	0.2473	0.0861	**	0.0114	0.0532	
Pre-term use of short-acting β_2-agonists	0.0648	0.0812		0.0790	0.0474	
Pre-term use of long-acting β_2-agonists	-0.1434	0.0875		0.0038	0.0490	
Pre-term use of anticholinergics	0.0091	0.0937		0.0396	0.0542	
Pre-term use of theophylline	0.1367	0.1330		-0.0963	0.0743	

Note: β: estimated coefficients, SE: standard errors. * indicates statistical significance at the 5% level; ** at the 1% level. IP/ED events: inpatient admissions or emergency department visits

Appendix 5: Parameter estimated for recent MPR vs. COPD-related IP/ED events

Model	Logistic			Negative binomial		
(Dependent variables)	(Having any event)			(# of events, if any)		
Parameter	β	SE		β	SE	
Intercept	-3.1938	0.4455	**	0.1290	0.2953	
MPR Quintile 1 vs 5	0.7473	0.2735	**	0.2361	0.1952	
MPR Quintile 2 vs 5	0.3005	0.2880		0.1325	0.2100	
MPR Quintile 3 vs 5	0.5375	0.2672	*	0.2612	0.1977	
MPR Quintile 4 vs 5	0.5843	0.2691	*	-0.0047	0.2063	
Ages 40-49 (vs ages 70-79)	-0.7835	0.3463	*	-0.3222	0.2668	
Ages 50-59 (vs ages 70-79)	-0.1081	0.2637		-0.2276	0.2133	
Ages 60-69 (vs ages 70-79)	-0.3207	0.2700		0.0789	0.1993	
Male	-0.1854	0.1697		-0.1090	0.1286	
Commercial insurance	0.3083	0.2843		0.1399	0.2081	
Census region: Northeast	-0.8671	0.1852	**	0.0475	0.1348	
Census region: South	-0.6341	0.3589		0.0244	0.2596	
Census region: Midwest	-0.6298	0.3752		0.0701	0.2464	
Congestive heart failure	0.6019	0.2764	*	0.2115	0.1861	
Asthma	-0.1799	0.1800		-0.0240	0.1303	
Depression	0.5420	0.2044	**	0.1024	0.1403	
Hypertension	-0.3483	0.1751	*	-0.2967	0.1235	*
No. of chronic conditions	0.0042	0.1124		-0.0368	0.0754	
Pre-term specialist care	-0.1808	0.1872		-0.0203	0.1386	
Pre-term oxygen therapy	0.0793	0.1976		0.0520	0.1390	
Pre-term spirometry test	-0.5324	0.1853	**	-0.0421	0.1474	
Pre-tern no. of any medication	0.0180	0.0086	*	0.0153	0.0051	**
Pre-term use of oral corticosteroids	0.4803	0.1900	*	0.0980	0.1481	
Pre-term use of oral antibiotics	-0.1257	0.2001		-0.3465	0.1556	*
Pre-term use of short-acting β_2-agonists	0.4102	0.1889	*	0.0612	0.1426	
Pre-term use of long-acting β_2-agonists	0.1179	0.1849		0.0878	0.1292	
Pre-term use of anticholinergics	0.8366	0.2282	**	0.0181	0.1712	
Pre-term use of theophylline	0.0234	0.2616		-0.1542	0.1790	

Note: β: estimated coefficients, SE: standard errors. * indicates statistical significance at the 5% level; ** at the 1% level. IP/ED events: inpatient admissions or emergency department visits

Appendix 6: Parameter estimated for recent MPR vs. any IP/ED events

Model	Logistic			Negative binomial		
(Dependent variables)	(Having any event)			(# of events, if any)		
Parameter	β	SE		β	SE	
Intercept	-0.1736	0.2670		0.5694	0.1490	**
MPR Quintile 1 vs 5	0.1333	0.1616		0.1859	0.0934	*
MPR Quintile 2 vs 5	0.0874	0.1612		0.1291	0.0951	
MPR Quintile 3 vs 5	-0.0417	0.1582		0.3866	0.0924	**
MPR Quintile 4 vs 5	0.0920	0.1580		0.0945	0.0965	
Ages 40-49 (vs ages 70-79)	-0.6564	0.2017	**	-0.1400	0.1125	
Ages 50-59 (vs ages 70-79)	-0.5151	0.1665	**	-0.1777	0.0913	
Ages 60-69 (vs ages 70-79)	-0.5689	0.1649	**	-0.1384	0.0898	
Male	-0.0316	0.1024		-0.1230	0.0598	*
Commercial insurance	-0.0042	0.1759		0.1359	0.0920	
Census region: Northeast	-0.7914	0.1185	**	-0.2943	0.0635	**
Census region: South	-0.8489	0.2250	**	-0.3348	0.1461	*
Census region: Midwest	-0.6681	0.2399	**	-0.3495	0.1417	*
Congestive heart failure	0.4024	0.1991	*	0.2663	0.0889	**
Asthma	0.2707	0.1097	*	-0.0495	0.0638	
Depression	0.3035	0.1408	*	0.1458	0.0728	*
Hypertension	-0.0695	0.1046		-0.1490	0.0597	*
No. of chronic conditions	0.2633	0.0740	**	0.1233	0.0342	**
Pre-term specialist care	-0.1827	0.1121		0.0803	0.0657	
Pre-term oxygen therapy	-0.2889	0.1365	*	0.0383	0.0733	
Pre-term spirometry test	-0.1572	0.1090		-0.1774	0.0642	**
Pre-tern no. of any medication	0.0066	0.0060		0.0064	0.0030	*
Pre-term use of oral corticosteroids	0.2638	0.1131	*	0.0402	0.0661	
Pre-term use of oral antibiotics	0.3532	0.1178	**	-0.0593	0.0721	
Pre-term use of short-acting β_2-agonists	0.0616	0.1111		0.0978	0.0645	
Pre-term use of long-acting β_2-agonists	-0.1136	0.1176		0.0667	0.0659	
Pre-term use of anticholinergics	0.0036	0.1285		0.0157	0.0749	
Pre-term use of theophylline	0.1737	0.1744		-0.0825	0.0940	

Note: β: estimated coefficients, SE: standard errors. * indicates statistical significance at the 5% level; ** at the 1% level. IP/ED events: inpatient admissions or emergency department visits

Appendix 7: Parameter estimated for persistence vs. COPD-related costs

Model	Logistic			GLM		
(Dependent variables)	(Having any cost)			(Costs, if any)		
Parameter	β	SE		β	SE	
Intercept	1.0189	0.2112	**	7.6041	0.1253	**
ICS treatment for <6 mo (vs ≥12 mo)	-0.2917	0.1016	**	0.0179	0.0665	
ICS treatment for 6-12 mo (vs ≥12 mo)	-0.3583	0.1169	**	0.1114	0.0761	
Ages 40-49 (vs ages 70-79)	-0.6592	0.1665	**	-0.8841	0.1085	**
Ages 50-59 (vs ages 70-79)	-0.2971	0.1495	*	-0.3594	0.0917	**
Ages 60-69 (vs ages 70-79)	-0.1568	0.1474		-0.3747	0.0881	**
Male	0.1032	0.0865		-0.1562	0.0545	**
Commercial insurance	-0.0714	0.1485		-0.0630	0.0882	
Census region: Northeast	-0.2251	0.1080	*	-0.4871	0.0623	**
Census region: South	-0.5916	0.1752	**	-0.2432	0.1164	*
Census region: Midwest	-0.3485	0.2131		-0.4955	0.1309	**
Congestive heart failure	0.0691	0.1873		0.6693	0.1008	**
Asthma	-0.3722	0.0933	**	-0.4373	0.0555	**
Depression	0.2574	0.1253	*	0.0367	0.0734	
Hypertension	0.0298	0.0881		-0.1992	0.0556	**
No. of chronic conditions	-0.0439	0.0586		0.0403	0.0355	
Pre-term specialist care	0.1678	0.0967		0.1894	0.0582	**
Pre-term oxygen therapy	1.1614	0.1599	**	0.8956	0.0692	**
Pre-term spirometry test	0.4544	0.0933	**	-0.2538	0.0582	**
Pre-tern no. of any medication	0.017	0.0063	**	0.0120	0.0035	**
Pre-term use of oral corticosteroids	0.1692	0.0958		0.2278	0.0595	**
Pre-term use of oral antibiotics	0.0988	0.0945		0.0826	0.0623	
Pre-term use of short-acting β_2-agonists	0.0319	0.0922		0.0103	0.0595	
Pre-term use of long-acting β_2-agonists	0.0291	0.1022		0.0285	0.0619	
Pre-term use of anticholinergics	0.3196	0.1055	**	0.2709	0.0683	**
Pre-term use of theophylline	0.0898	0.1684		0.2407	0.0947	*

Note: β: estimated coefficients, SE: standard errors. * indicates statistical significance at the 5% level; ** at the 1% level.

Appendix 8: Parameter estimated for persistence vs. any events

Model	GLM		
(Dependent variables)	(Costs)		
Parameter	β	SE	
Intercept	9.4633	0.0992	**
ICS treatment for <6 mo (vs ≥12 mo)	-0.0275	0.05	
ICS treatment for 6-12 mo (vs ≥12 mo)	0.1465	0.0578	*
Ages 40-49 (vs ages 70-79)	-0.3651	0.0799	**
Ages 50-59 (vs ages 70-79)	-0.3181	0.0676	**
Ages 60-69 (vs ages 70-79)	-0.33	0.0663	**
Male	-0.0507	0.0426	
Commercial insurance	-0.1416	0.0667	*
Census region: Northeast	-0.6971	0.0483	**
Census region: South	-0.6067	0.0866	**
Census region: Midwest	-0.6824	0.1017	**
Congestive heart failure	0.4703	0.0803	**
Asthma	-0.1148	0.0439	**
Depression	0.1275	0.0579	*
Hypertension	-0.0209	0.0419	
No. of chronic conditions	0.2855	0.0277	**
Pre-term specialist care	0.1271	0.0453	**
Pre-term oxygen therapy	0.1813	0.0572	**
Pre-term spirometry test	0.0782	0.0439	
Pre-tern no. of any medication	0.0046	0.0028	
Pre-term use of oral corticosteroids	0.1236	0.046	**
Pre-term use of oral antibiotics	0.2394	0.0472	**
Pre-term use of short-acting β_2-agonists	-0.0013	0.0446	
Pre-term use of long-acting β_2-agonists	-0.0374	0.0478	
Pre-term use of anticholinergics	-0.0057	0.0513	
Pre-term use of theophylline	0.0586	0.0774	

Note: β: estimated coefficients, SE: standard errors. * indicates statistical significance at the 5% level; ** at the 1% level.

Appendix 9: Parameter estimated for average MPR vs. COPD-related costs

Model	Logistic			GLM		
(Dependent variables)	(Having any cost)			(Costs, if any)		
Parameter	β	SE		β	SE	
Intercept	0.9120	0.2237	**	7.3909	0.1364	**
MPR Quintile 1 vs 5	-0.1743	0.1369		-0.0830	0.0873	
MPR Quintile 2 vs 5	-0.2260	0.1357		0.2229	0.0867	**
MPR Quintile 3 vs 5	0.0015	0.1378		0.3986	0.0844	**
MPR Quintile 4 vs 5	-0.0120	0.1387		0.2182	0.0812	**
Ages 40-49 (vs ages 70-79)	-0.6666	0.1666	**	-0.7934	0.1080	**
Ages 50-59 (vs ages 70-79)	-0.2931	0.1495	*	-0.3110	0.0909	**
Ages 60-69 (vs ages 70-79)	-0.1443	0.1474		-0.3365	0.0869	**
Male	0.1010	0.0864		-0.1492	0.0545	**
Commercial insurance	-0.0486	0.1483		-0.1113	0.0876	
Census region: Northeast	-0.2189	0.1080	*	-0.4580	0.0618	**
Census region: South	-0.6076	0.1748	**	-0.1891	0.1166	
Census region: Midwest	-0.3541	0.2129		-0.4803	0.1308	**
Congestive heart failure	0.0768	0.1871		0.6530	0.1006	**
Asthma	-0.3791	0.0933	**	-0.4399	0.0553	**
Depression	0.2714	0.1255	*	0.0566	0.0734	
Hypertension	0.0300	0.0881		-0.1536	0.0558	**
No. of chronic conditions	-0.0555	0.0585		0.0345	0.0353	
Pre-term specialist care	0.1633	0.0968		0.1896	0.0575	**
Pre-term oxygen therapy	1.1501	0.1597	**	0.9159	0.0687	**
Pre-term spirometry test	0.4550	0.0932	**	-0.2427	0.0576	**
Pre-tern no. of any medication	0.0209	0.0061	**	0.0114	0.0033	**
Pre-term use of oral corticosteroids	0.1520	0.0954		0.2160	0.0596	**
Pre-term use of oral antibiotics	0.0828	0.0941		0.0851	0.0618	
Pre-term use of short-acting β_2-agonists	0.0246	0.0922		0.0270	0.0591	
Pre-term use of long-acting β_2-agonists	0.0447	0.1028		0.0305	0.0616	
Pre-term use of anticholinergics	0.2965	0.1053	**	0.2897	0.0681	**
Pre-term use of theophylline	0.0582	0.1680		0.3036	0.0937	**

Note: β: estimated coefficients, SE: standard errors. * indicates statistical significance at the 5% level; ** at the 1% level.

Appendix 10: Parameter estimated for average MPR vs. any events

Model	GLM		
(Dependent variables)	(Costs)		
Parameter	β	SE	
Intercept	9.4251	0.1052	**
MPR Quintile 1 vs 5	-0.0327	0.0665	
MPR Quintile 2 vs 5	0.1756	0.0657	**
MPR Quintile 3 vs 5	0.0756	0.0643	
MPR Quintile 4 vs 5	0.1063	0.0641	
Ages 40-49 (vs ages 70-79)	-0.3757	0.0797	**
Ages 50-59 (vs ages 70-79)	-0.3298	0.0675	**
Ages 60-69 (vs ages 70-79)	-0.3404	0.0660	**
Male	-0.0622	0.0425	
Commercial insurance	-0.1419	0.0666	*
Census region: Northeast	-0.7001	0.0483	**
Census region: South	-0.6212	0.0862	**
Census region: Midwest	-0.7023	0.1018	**
Congestive heart failure	0.4342	0.0801	**
Asthma	-0.1127	0.0439	*
Depression	0.1202	0.0581	*
Hypertension	-0.0163	0.0420	
No. of chronic conditions	0.2874	0.0276	**
Pre-term specialist care	0.1248	0.0454	**
Pre-term oxygen therapy	0.1925	0.0570	**
Pre-term spirometry test	0.0830	0.0439	
Pre-tern no. of any medication	0.0042	0.0027	
Pre-term use of oral corticosteroids	0.1283	0.0459	**
Pre-term use of oral antibiotics	0.2308	0.0471	**
Pre-term use of short-acting β_2-agonists	0.0005	0.0447	
Pre-term use of long-acting β_2-agonists	-0.0259	0.0482	
Pre-term use of anticholinergics	0.0064	0.0514	
Pre-term use of theophylline	0.0640	0.0770	

Note: β: estimated coefficients, SE: standard errors. * indicates statistical significance at the 5% level; ** at the 1% level.

Appendix 11: Parameter estimated for recent MPR vs. COPD-related costs

Model	Logistic			GLM		
(Dependent variables)	(Having any cost)			(Costs, if any)		
Parameter	β	SE		β	SE	
Intercept	1.1635	0.3367	**	7.4267	0.1931	**
MPR Quintile 1 vs 5	-0.3217	0.2005		0.3003	0.1159	**
MPR Quintile 2 vs 5	-0.4291	0.1981	*	0.1813	0.1127	
MPR Quintile 3 vs 5	-0.0808	0.2029		0.0515	0.1045	
MPR Quintile 4 vs 5	-0.3364	0.1980		0.2624	0.1080	*
Ages 40-49 (vs ages 70-79)	-0.6768	0.2424	**	-0.9028	0.1511	**
Ages 50-59 (vs ages 70-79)	-0.2690	0.2140		-0.3672	0.1250	**
Ages 60-69 (vs ages 70-79)	-0.0347	0.2138		-0.4060	0.1226	**
Male	0.1718	0.1226		-0.0926	0.0701	
Commercial insurance	0.0751	0.2213		0.0055	0.1285	
Census region: Northeast	-0.1986	0.1550		-0.6046	0.0829	**
Census region: South	-0.4983	0.2598		-0.3084	0.1532	*
Census region: Midwest	-0.4316	0.2893		-0.5701	0.1671	**
Congestive heart failure	-0.1516	0.2672		0.7263	0.1365	**
Asthma	-0.4797	0.1328	**	-0.3274	0.0742	**
Depression	0.4280	0.1860	*	-0.0785	0.0961	
Hypertension	-0.1298	0.1244		-0.3332	0.0705	**
No. of chronic conditions	-0.0295	0.0927		0.0640	0.0505	
Pre-term specialist care	0.2003	0.1379		0.0986	0.0793	
Pre-term oxygen therapy	1.0952	0.2222	**	0.7887	0.0888	**
Pre-term spirometry test	0.5705	0.1338	**	-0.3841	0.0801	**
Pre-tern no. of any medication	0.0105	0.0081		0.0190	0.0042	**
Pre-term use of oral corticosteroids	0.2770	0.1387	*	0.1547	0.0778	*
Pre-term use of oral antibiotics	0.2287	0.1333		0.0141	0.0794	
Pre-term use of short-acting β_2-agonists	-0.2122	0.1316		0.0532	0.0772	
Pre-term use of long-acting β_2-agonists	-0.0153	0.1449		0.0184	0.0790	
Pre-term use of anticholinergics	0.4186	0.1510	*	0.4134	0.0888	**
Pre-term use of theophylline	0.1451	0.2337		-0.0892	0.1194	

Note: β: estimated coefficients, SE: standard errors. * indicates statistical significance at the 5% level; ** at the 1% level.

Appendix 12: Parameter estimated for recent MPR vs. any events

Model	GLM		
(Dependent variables)	(Costs)		
Parameter	β	SE	
Intercept	9.5447	0.1499	**
MPR Quintile 1 vs 5	-0.1307	0.0883	
MPR Quintile 2 vs 5	0.0077	0.0902	
MPR Quintile 3 vs 5	0.0199	0.0876	
MPR Quintile 4 vs 5	-0.0308	0.0877	
Ages 40-49 (vs ages 70-79)	-0.4340	0.1136	**
Ages 50-59 (vs ages 70-79)	-0.4346	0.0954	**
Ages 60-69 (vs ages 70-79)	-0.2971	0.0931	**
Male	-0.0506	0.0570	
Commercial insurance	-0.0749	0.1009	
Census region: Northeast	-0.8025	0.0655	**
Census region: South	-0.6990	0.1208	**
Census region: Midwest	-0.8661	0.1343	**
Congestive heart failure	0.6522	0.1125	**
Asthma	-0.0110	0.0597	
Depression	0.0550	0.0784	
Hypertension	-0.0338	0.0562	
No. of chronic conditions	0.2436	0.0410	**
Pre-term specialist care	0.0518	0.0612	
Pre-term oxygen therapy	0.0953	0.0770	
Pre-term spirometry test	0.0985	0.0599	
Pre-tern no. of any medication	0.0041	0.0034	
Pre-term use of oral corticosteroids	0.1145	0.0626	
Pre-term use of oral antibiotics	0.2714	0.0633	**
Pre-term use of short-acting β_2-agonists	0.0168	0.0617	
Pre-term use of long-acting β_2-agonists	-0.0239	0.0643	
Pre-term use of anticholinergics	-0.0101	0.0706	
Pre-term use of theophylline	-0.0273	0.1005	

Note: β: estimated coefficients, SE: standard errors. * indicates statistical significance at the 5% level; ** at the 1% level.

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