# CHRONIC MEDICATION ADHERENCE: ITS ASSOCIATION WITH HEALTH CARE COSTS

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# Abstract

Effective treatment for high-prevalence chronic diseases requires medication adherence. Improved medication adherence increases medication utilization, which leads to higher pharmacy costs. However, higher adherence may reduce medical services use that result in decrease in overall health care costs despite the increase in pharmacy costs.

The objective of this study was to examine the impact of medical adherence on health care costs. The secondary objective of this study was to assess the independent effect of consumer directed health plans (CDHPs) on health care costs. The study samples were three independent cohorts of individuals with the separate conditions of diabetes, hypertension and hypercholesterolemia, identified from a pharmacy benefits management company between January 1, 2007 and December 31, 2009. Medication adherence was measured using Proportion of Days Covered (PDC) endorsed by Pharmacy Quality Assurance (PQA). Health care costs were measured at two levels: all-cause and condition-specific. At each level, pharmacy, medical and total health care costs were calculated. The generalized linear model with a gamma log link was used to fit six statistical models for each disease cohort. Control variables included patients' demographics, socioeconomic information, health status, health services utilization.

There were 22,012 individuals in the diabetes cohort, 64,600 in the hypertension cohort and 59,003 in the hypercholesterolemia cohort. At all-cause level, increased PDC was significant associated with decreased medical costs across the three cohorts ($p<0.05$). At condition-specific level, increased PDC was significant associated with decreased medical costs in the hypertension and hypercholesterolemia cohorts ($p<0.001$), but with increased medical cost in the diabetes cohort ($p<0.001$). Due to the significant increase in pharmacy costs associated with higher PDC ($p<0.001$), total health care costs were increased ($p<0.001$) both at all-cause and condition-specific levels in each cohorts.

Enrollment in CDHPs was generally associated with decreased medical, pharmacy, and total health care costs at all-cause and condition-specific levels across the three cohorts.

As adherence increases, the savings in medical costs are not able to offset the increase in pharmacy costs. Therefore, measures that aim to reduce pharmacy cost while preserving or improving adherence are needed.

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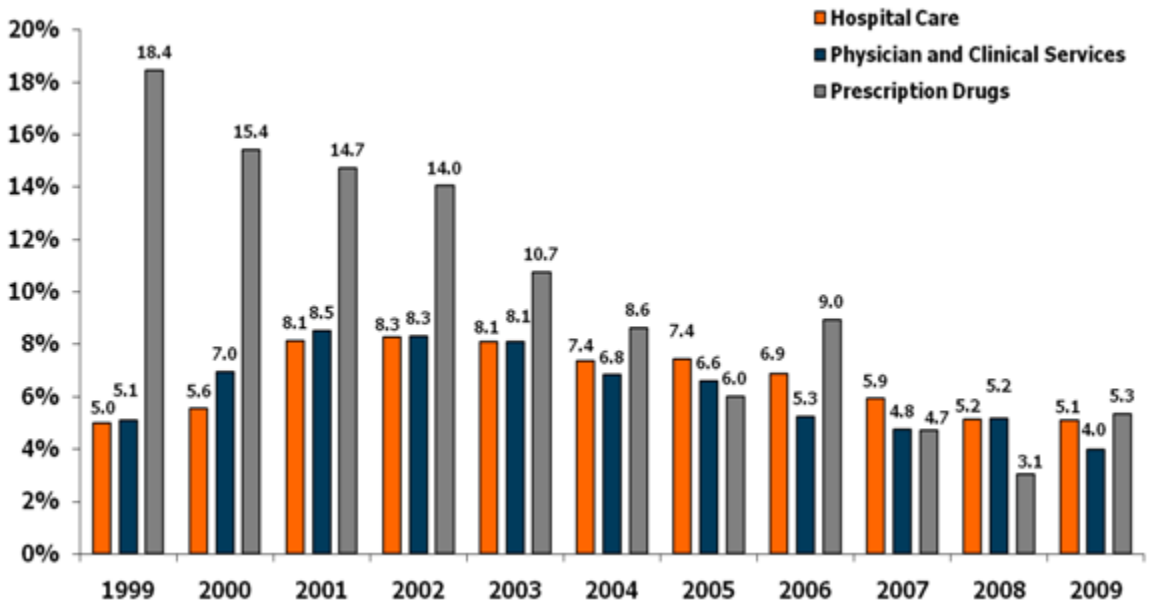
# Chapter 1: INTRODUCTION

## 1.1 Concern with Prescription Spending in the U.S.

In the last decades, spending on prescription drugs has experienced a dramatic growth, receiving considerable public attention. Growth in spending for drugs outpaced spending growth in most of other sectors of the heath care system in the last decade (Martin et al, 2011). Based on the statistics reported by Martin et al and National Health Expenditure Accounts Team (2011), in 2009, US health care spending grew 4.0 percent —a historically low rate of annual increase—to $2.5 trillion, or $8,086 per person. Despite the slower growth, the share of the gross domestic product devoted to health spending increased to 17.6 percent in 2009 from 16.6 percent in 2008. The growth rate of health spending continued to outpace the growth of the overall economy. Particularly, retail prescription drug expenditures grew 5.3 percent in 2009, reaching $249.9 billion, compared with 3.1 percent in 2008. Faster growth in both prescription drug prices and use led to accelerated growth in spending in 2009. In 2009, despite the economic downturn, the number of prescription drugs dispensed rebounded to prerecession rates of growth. From 0.9 percent in 2008, the rate accelerated to 2.1 percent in 2009, which was more in line with the average annual rate of 2.2 percent between 2002 and 2007. Prescription drug prices, as measured by the Consumer Price Index for prescription drugs, rose 3.4 percent in 2009 compared with 2.5 percent in 2008 (Martin et al, 2011).

In an effort to control the large costs of prescription drugs, many organizations have turned to innovative pharmacy benefit plan designs (Malkin, Goldman, & Joyce, 2004). For example, managed care organizations began the multi-tiered plan, requiring employees to pay the least copay for generic drugs, pay a higher copay for preferred name brand drugs (which may have no generic alternative or are less costly than other drugs) and pay the highest copay for nonpreferred brand medications (Burton et al., 2008). Also, many health plans increased prescription cost-sharing across all tiers, due to the frustration with the continued increase in prescription spending (Crown et al., 2003).

Figure 1: Average Annual Percentage Increase in Selected National Health Expenditures, 1999-2009




Source: Kaiser Family Foundation calculations using NHE data from Centers for Medicare and Medicaid Services, Office of the Actuary, National Health Statistics Group, at http://www.cms.hhs.gov/NationalHealthExpendData/ (see Historical; National Health Expenditures by type of service and source of funds, CY 1960-2009; file nhe2009.zip).

Numerous studies in the private sector have shown that pharmacy benefit plans generally result in significant savings in pharmacy costs by reducing the use of prescriptions (Gibson et al., 2005; Goldman et al., 2007). Higher levels of prescription drug cost sharing generally produce intended effects, namely, decreasing the consumption of prescription drugs. The associated decrease in prescription medication utilization has been associated with reductions in the use of essential chronic medications, increasing the risk for negative medical events (Gibson et al., 2005; Goldman et al., 2007).

One of the possible consequences of reductions in medication taking is less optimal medication outcomes, which may cause more health care spending. There is strong evidence that effective treatment for many high-prevalence chronic diseases, such as diabetes, hypertension, and hypercholesterolemia, requires medication adherence (Holman et al., 2008; Shibata et al., 2001; Heart Protection Study Collaboration Group, 2002). When conditions are treated suboptimally, symptoms and complications may worsen, leading to increased use hospital and emergency room (ER) services, physician visits, and other medical resources (Sokol, 2005). The use of more medical resources can lead to more health care spending which may exceed the savings of reduction of medication.

The question is, however, whether the increase in pharmacy therapy costs provides net economic savings to overall health care. There are several studies which show that adherence to pharmacy therapy reduces overall health care costs by decreasing medical events such as hospitalizations and ERs. For example, lipid-lowering drugs can produce a net return on investment by reducing the risk of cardiovascular events (Aubert et al, 2010). This study suggests that though higher levels of medication adherence may increase prescription drug spending, it can reduce medical events and finally generate medical savings that offset the associated increases in prescription drug costs.

Though a growing literature suggests that improved adherence with medications for chronic conditions not only improves clinical outcomes but also reduces medical costs, statements that savings in medical costs can offset increase in drug use are controversial. A well known literature review by the U.S. Congressional Budget Office (2002) concluded that the empirical evidence of cost offsets was insubstantial and rested on questionable methods. A recent systematic review of studies of adherence with anti-diabetic drugs concluded that the research assessing the association between medication adherence and health care costs is limited and of poor quality (Salas et al., 2009). Therefore, a well designed study to examine the effect of medication adherence in chronic conditions on medical costs as well as total health care expenditures would be

helpful for providing good evidence to understand whether increase in pharmacy therapy costs provides net economic savings to overall health care.

## 1.2 Popularity of Consumer Directed Health Plan

In recent years there has also been an increase in the popularity of consumer directed health plans (CDHPs). According to the American Association of Preferred Provider Organizations' (AAPPO) third annual consumer directed health plan study reports (2009), the enrollment in CDHPs grew from 12.5 million people in 2007 to an estimated 18 million people in 2008 – a 44 percent increase. The number of enrollment population continued to grow to 28 million in 2010 (AAPPO, 2011). CDHPs generally combine a high-deductible health insurance policy with a tax-sheltered account that enrollees can use to finance their "out-of-pocket" health care costs. Based on a Congressional Budget Office (CBO) study (2006), CDHP plans represent the latest step in efforts to restructure health insurance coverage to help control spending for health care services in the United States.

The central idea behind CDHP designs is that enrollees will remain insured against catastrophic expenses, but will also be more careful about using health care services because they will pay a much larger share of their initial costs. (Conventional health insurance plans, by contrast, have much lower deductibles and thus cover a larger percentage of enrollees' initial expenses.) Depending on how enrollees in CDHPs respond to those incentives, the end result could be a lower level of spending to achieve the same improvements in health or possibly better health at the same level of spending. Either outcome would represent an increase in the efficiency of the health care sector (CBO, 2006).

In the past 10 years, Health Care Financing and Organization (HCFO) funded several prospective studies exploring the development and impact of CDHPs. The findings of

these studies are mixed. Some suggested CDHPs had a cost-saving effect on prescription drug spending (Feldman, Parente & Christianson), while other research found that families enrolled in CDHPs had more financial burden (Galbraith et al, 2011). Though CDHPs are considered as a solution to overuse of unnecessary medical services and a mechanism to drive down health care costs, the evidence is still inconclusive (HCFO, 2011).

## 1.3 Objective and Specific Aims

The primary objective of this study is to examine the influence of chronic medication adherence on health care expenditures. This study examines this objective in three chronic conditions: diabetes, hypertension and hypercholesterolemia. Specifically, three disease cohorts are constructed: 1) patients who were diagnosed with diabetes; 2) patients who were diagnosed with hypertension; and 3) patients who were diagnosed with hypercholesterolemia.

Throughout this study, health care expenditures are calculated in three components of health care cost are examined: medical cost, pharmacy cost, and total cost. Total cost is the sum of medical and pharmacy costs. Furthermore, each component of cost is explored at two levels: all-cause cost and condition-specific cost. All-cause cost is defined as the sum of all medical cost and drug cost associated with any health condition during the study period. Condition-specific cost is defined as the sum of medical cost and drug cost associated with the health condition of interest during the study period.

In line with this objective, this study has three specific aims:

**Aim 1:** To investigate the effect of adherence on all-cause and condition-specific medical costs.

**Hypothesis 1:** As medication adherence increases, all-cause and condition-specific medical costs will decrease after controlling for potential confounders.

**Aim 2:** To investigate the effect of adherence on all-cause and condition-specific pharmacy costs.

**Hypothesis 2:** As medication adherence increases, all-cause and condition-specific pharmacy costs will increase after controlling for potential confounders.

**Aim 3:** To investigate the effect of adherence on all-cause and condition-specific total costs.

**Hypothesis 3:** As medication adherence increases, all-cause and condition-specific total costs will decrease after controlling for potential confounders.

The secondary objective of this study is to examine the influence of enrollment in CDHPs on health care expenditures. This objective is also examined in diabetes, hypertension and hypercholesterolemia cohorts. The specific aim is:

**Aim 4:** To investigate the effect of CDHPs on all-cause and condition-specific medical, pharmacy and total costs.

**Hypothesis 4:** For members enrolled in CDHPs, all-cause and condition-specific medical, pharmacy and total costs will decrease after controlling for potential confounders.

## 1.4 Underlying Theories

The examination of these specific aims will be based on two theories: Andersen's behavioral model of health services use and theory of demand for health insurance. Both theories are described briefly here, and will be discussed in more detail in the literature review.

Andersen's behavioral model of health services utilization has provided a defining research agenda for the study of health care utilization (Aday, & Awe, 1997). On the basis of this model, people's use of health services is a function of their predisposition to use services, factors which enable or impede their use, and their need for care. Factors associated with health care spending can be identified by searching for factors that influence health care services utilization, because people who use more health care services tend to incur more health care costs. Therefore, covariates associated with health care utilization which in turn reflects expenditure can be constructed by Andersen's Behavioral Model of Health Services Utilization. The use of health care services is predicted by predisposing characteristics, enabling factors, and the need for prescription drugs.

According to the theory of demand for health proposed by Nyman (2003), consumers demand health insurance because they desire an income transfer from those who remain healthy when they become ill. Therefore, when ill, they can buy more of otherwise unaffordable health care. Because of health insurance, patients are insensitive to the total costs of the care they have received. Health care appears inexpensive to consumers, creating an incentive to overuse, which is called moral hazard.

## 1.5 Significance of the Study

The dramatic increase in health care expenditures has been the major concern among health care policy makers. Expectedly, improvements in medication adherence increase pharmacy spending. Health care reformers and payers are interested in knowing whether or not the higher pharmacy costs are more than offset by reductions in the use of medical services (Roebuck et. al., 2011). This study will assess whether the increase in pharmacy expenditures resulting from improvement in medication adherence will reduce medical costs, or even offset total health care costs. By examining the potential cost-saving

benefits of medication adherence, this study will provide justification for the increasing expenditures on prescription drugs, which may, in the long run, offset or reduce overall health care costs.

By quantifying the impact of adherence on health care expenditures, this study will help clinicians better understand the benefits of medication adherence, provide health insurers with projected outcomes and cost avoidance expectations, and provide evidence for consultant recommendations that will help policy making decisions.

In addition, examining the influence of CDHPs on health care spending will provide further information on whether this health benefit design is cost-saving. This study will help provide more evidence as to whether the wide adoption of CDHPs should be encouraged.

This study will use new adherence metrics endorsed by the PQA and NQF in 2009 (National Committee for Quality Assurance, 2008). This newly developed method helps standardize the measure of medication adherence, which will likely result in its adoption by health plans and the Center for Medicaid and Medicare Services (CMS) as quality of care metrics.

# Chapter 2: LITERATURE REVIEW

This chapter will explore the literature relating to the following areas: (1) the theoretical framework of this study; (2) epidemiology and economics of diabetes, hypertension and hypercholesterolemia; (3) medication adherence and health care costs of diabetes, hypertension and hypercholesterolemia; and (4) CHDPs and health care expenditures. Finally, this chapter will finish with specific objectives of this study. The major literature related to the research problem was searched through Ovid Medline and PubMed using the University of Minnesota library system.

## 2.1 Theoretical Framework

As previously described in Chapter 1, the theoretical framework of this study consists of the behavioral model of health services utilization and the theory of demand for health insurance. The behavioral model of health services utilization serves as guidance to identify and classify control variables in examining the association between medication adherence and total health care costs. The theory of demand for health insurance is used to assess whether the extra medication taking due to insurance is a welfare gain or welfare loss to the society.

### 2.1.1 Behavioral Model of Health Services Utilization

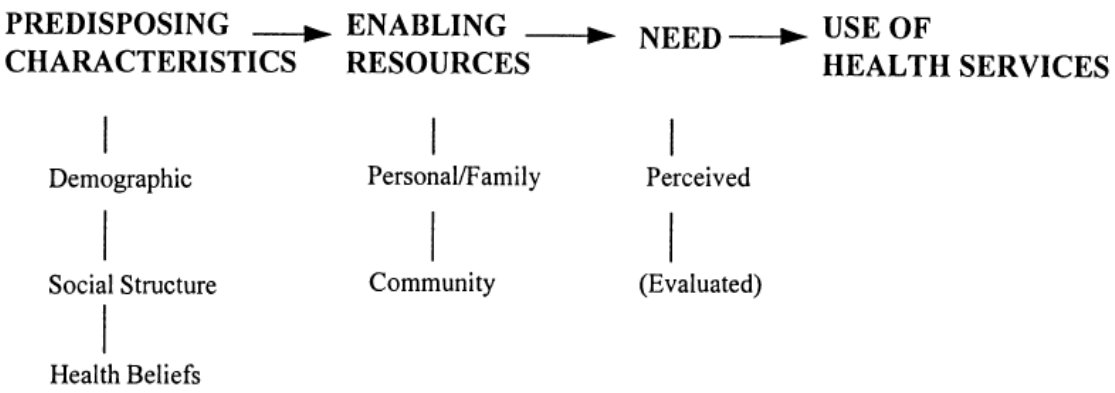
Andersen's behavioral model of health services utilization, also referred to as the "health services utilization model", was developed in the late 1960s and has provided a defining research agenda for the study of health care utilization (Aday, & Awe, 1997). The initial model organized and integrated a number of ideas to understand why families use health services, to define and measure equitable access to health care, and to help in developing policies to promote equitable access (Andersen, 1995). The model of health services' use originally focused on the family as the unit of analysis, because the medical care an individual receives is mostly a function of the demographic, social and economic

characteristics of the family as a unit. However, in subsequent work the unit of analysis was shifted to the individual level because of the difficulty of developing measures at the family level that take into account the potential heterogeneity of family members. (Andersen, 1995)

The model is depicted in Figure 2. It suggests that people's use of health services is a function of their predisposition to use services, factors which enable or impede use, and their need for care. On the one hand, each component might be conceived of as making an independent contribution to predicting use; on the other hand, the model suggests an explanation for where the predisposing factors might be exogenous, some enabling resources are necessary but not sufficient conditions for use, and some need must be defined for use to actually take place (Andersen, 1995).

Among the predisposing characteristics, demographic factors such as age and gender represent biological imperatives suggesting the likelihood that people will need health services. Social structure is measured by a broad array of factors that determine the status of a person in the community, his or her ability to cope with presenting problems and commanding resources to deal with these problems, and how healthy or unhealthy the physical environment is likely to be. Measures used to assess social structure include education, occupation, ethnicity, social networks, social interactions and culture. Health beliefs are attitudes, values, and knowledge that people have about health and health services that might influence their subsequent perceptions of need and use of health services. Both community and personal enabling resources must be present for use to take place. These resources are the means and know-how to get to those services, including income, health insurance, a regular source of care, and travel and waiting times. Among the need factors, how people view their own general health, functional state, and symptoms of illness might account for some of people's help-seeking and consumption of health services. Evaluated need represents professional judgment about people's health status and their need for health care (Andersen, 1995).

Figure 2: The Behavioral Model of Health Services Utilization




Adopted from Andersen, 1995

The use of heath care services is predicted by predisposing characteristics, enabling factors, and the need for health care. In the study of Zhang (2006), this model was used as a guide to classify control variables in examining the association between prescription cost-sharing and medication refill persistence. Yuan (2008) assessed the influence of copayment differential between generic and preferred brand prescription drugs on generic fill rate using Andersen's model as guide.

**Predisposing Characteristics**

In terms of predisposing characteristics, heath care use is affected by age and gender at the demographic level. Several studies have shown that age and gender are major factors for health care spending associated with health services utilization. For example, Basu, Franzini , Krueger, & Lairson (2010) investigated the gender disparities in hypertension-attributable expenditure among noninstitutionalized individuals in the United States using the 2001-2004 Medical Expenditure Panel Survey. They found that mean hypertension-

attributable expenditure per individual was significantly higher for women than for men for prescription drugs, inpatient stays, office visits, outpatient visits and ER visits expenditures. However, as age increased, the gender difference in adjusted mean expenditures became smaller and eventually reversed. Rates rose with age and with the interaction of male gender and age. Rates for non-Hispanic Whites were higher than those for African Americans, whereas those for Hispanics, Asian Americans, and "others" were lower. In a study describing the frequency and costs of hospitalization in a large cohort of low-income patients with diabetes, Robbins & Webb (2006) found that hospitalization rates rose with age and with the interaction of male gender and age.

At the social structural level, medication use can be affected by education and race. Benner et al. (2002) described the patterns and predictors of long-term persistence (PDC $\geq$ 80%) with statins in an elderly U.S. population who were enrolled in the New Jersey Medicaid and Pharmaceutical Assistance to the Aged and Disabled programs. They found that long-term use of statins was especially low for patients of black and other nonwhite races. The influence of education is not as straight forward as that of other social economic factors. Research consistently reports that education is associated with increased health care utilization, most notably with preventive clinic visits. However, education is also negatively associated with acute conditions.

At the level of health beliefs, patients' attitudes, values and knowledge about prescription drugs are associated with their use. For example, patients who have a previous exposure to specific medications will have a higher propensity to take the medications continuously. Caro et al. (1999) found that patients who used antihypertensive medications before were more likely to persist with therapy ($p<0.001$).

**Enabling Resources**

For enabling resources, patient's income level, insurance status, and availability of health services are predictors of their utilization of health care. Based on economic theory of demand, income directly affects the demand for heath care services. Because medical

care is generally assumed to be a normal good, any increase in income should cause the demand for heath care (Santerre & Neun, 2007). Mann et. al (2010) conducted a meta-analysis to identify 22 cohort studies that evaluated predictors of nonadherence to statins. The authors found patients with lower incomes were more likely to be nonadherent than those with higher incomes (odds of nonadherence 1.18; 95% CI 1.10 to 1.28). Also, in a study examining the factors associated with health care utilization among homeless people, Kushel et. al.(2001) found that after adjustment for age, sex, race/ethnicity, medical illness, mental health problems, and other covariates, having health insurance was associated with greater use of ambulatory care, inpatient hospitalization (OR, 2.60; 95% CI, 1.16-5.81), and lower reporting of barriers to needed care (OR, 0.37; 95% CI, 0.15-0.90) and prescription medication compliance (OR, 0.35; 95% CI, 0.14-0.85).

**Need Factors**

For the need for utilization of health care resources, patients' perceived and evaluated burden of comorbidity or more risk factors is the main factor. Diabetes, hypertension or hypercholesterolemia with presence of more risk factors or more comorbid conditions will account for their greater use of health care resources. Numerous studies suggest that persons with more comorbid diseases are associated with increased health care utilization and health care costs. Struijs et. al (2006) studied the impact of comorbidities on medical health care utilization among persons with diabetes. Their results suggested that patients with diabetes, having a heart disease or stroke as a comorbid disease, showed a significantly larger increase in hospital care, and the average length of stay was significantly higher in most of the comorbidities. Using Andersen's model to assess predictors of health services utilization by patients with hypertension, Ham and Lee (2007) found the volume of health services utilization by all hypertensive patients was positively associated with presence of comorbidity. A study by Natarajan and Nietert (2004) found that individuals with no risk factors reported significantly ($P < .0001$) fewer visits than those with risk factors among patients with hypercholesterolemia.

### 2.1.2 Theory of Demand for Health Insurance

According to Nyman (2003), health care policies in the U.S. have been greatly influenced by the model of moral hazard, proposed by Pauly in 1968. Moral hazard is the change in behavior that occurs as a result of becoming insured. When individuals are insured, they may take fewer precautions against illness, and may incur more medical expenditures than those who are uninsured. In his model, Pauly (1968) argued that because health insurance lowers the price of health care to consumers but leaves its costs unchanged, the additional care consumed by insured persons - the moral hazard - is inefficient and represent a loss to society.

Therefore, most health policies were directed at containing health care costs in the U.S. and later around the world in response to the moral hazard model. On the demand side, policies of raising coinsurance rates and deductibles were imposed. On the supply side, imposed policies included utilization review, bundled payments, and managed care.

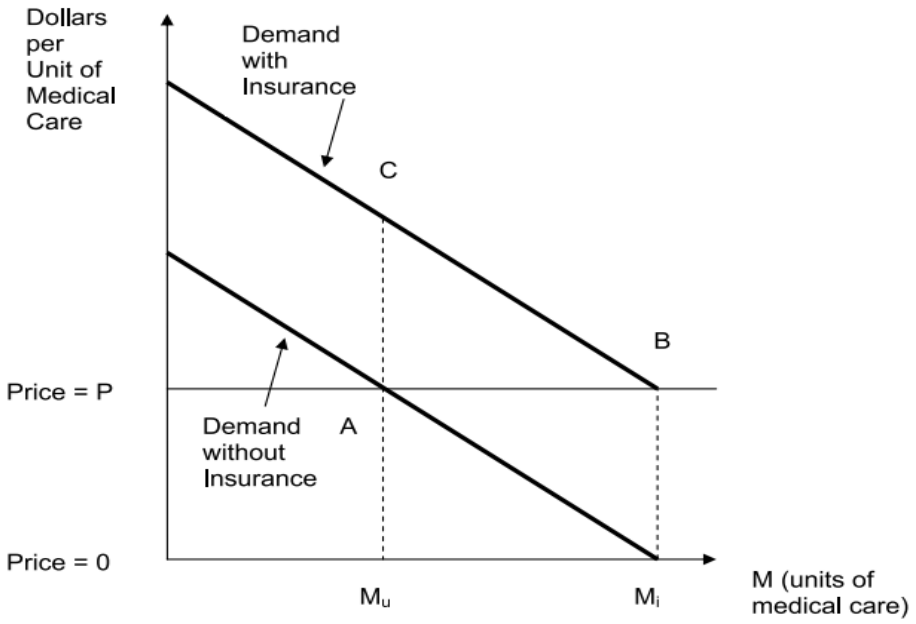
In 2003, Nyman proposed a new theory of the demand for health insurance, in which he suggested that consumers demand health insurance because they desire an income transfer from those who remain healthy in the event that they become ill. This income transfer allows the ill consumer to purchase more medical care and more consumer goods and services than she would purchase without it. In this new model, moral hazard can be decomposed into two portions. One portion is an opportunistic response to the reduced price of medical care when insured, which is called the price reduction effect. The other portion is the original intended response to the income transfers, which is called the income transfer effect. Because of the income transfer effect, the ill consumer can purchase medical care that would otherwise be unaffordable, thus it increases welfare. However, due to the price reduction effect, consumers tend to overuse health care, which decreases welfare. Therefore, the portion of moral hazard caused by the income transfer effect is efficient, and the portion of moral hazard caused by the price reduction effect is inefficient. Based on conservative estimates of the medical care spending share and income elasticity of demand, over 2/3 of moral hazard is due to income transfers, and less

than 1/3 is due to pure price effect. The new health insurance theory suggests that, even though imposing or raising cost-sharing may reduce health care expenditures, there is no assurance that imposing or raising cost-sharing would necessarily result in a welfare gain as there is no mechanism within cost-sharing to selectively focus on the inefficient care.

Nyman's theory of demand for health insurance has been applied in several studies in health care insurance policies. In 2006, Zhang investigated Influence of prescription copayment on hypertensive patients' medication persistence, adopting Nyman's theory of demand for health insurance as the theoretical framework for her paper. Also, Nyman (2007) further explained the new theory and new interpretation of moral hazard, and proposed changes for cost-sharing policies.

Figure 3 illustrates the welfare effect of moral hazard under the new theory, assuming a case in which insurance works only to increase willingness to pay and to shift out of demand. Because of the income transfer by insurance, the consumer's demand curve is shifted out, represented by CB instead of $AM_i$. The value of the additional health care is measured by the area under a new demand curve, based on a patient's willingness to pay for the medical care with the additional income transferred to them by insurance. Because of this increase in income, the patient is assumed to purchase the same $(M_i - M_u)$ additional units of medical care. However, with the new demand curve, the value of this additional care is now area $CBM_i,M_u$. Because the market price of the medical care is P, the cost of the moral hazard $M_i - M_u$ is still $ABM_i,M_u$. This indicates that the moral hazard generates a welfare gain equal to CBA, measured by subtracting the cost of moral hazard from the value of the moral hazard.

Figure 3: New Analysis of Moral Hazard



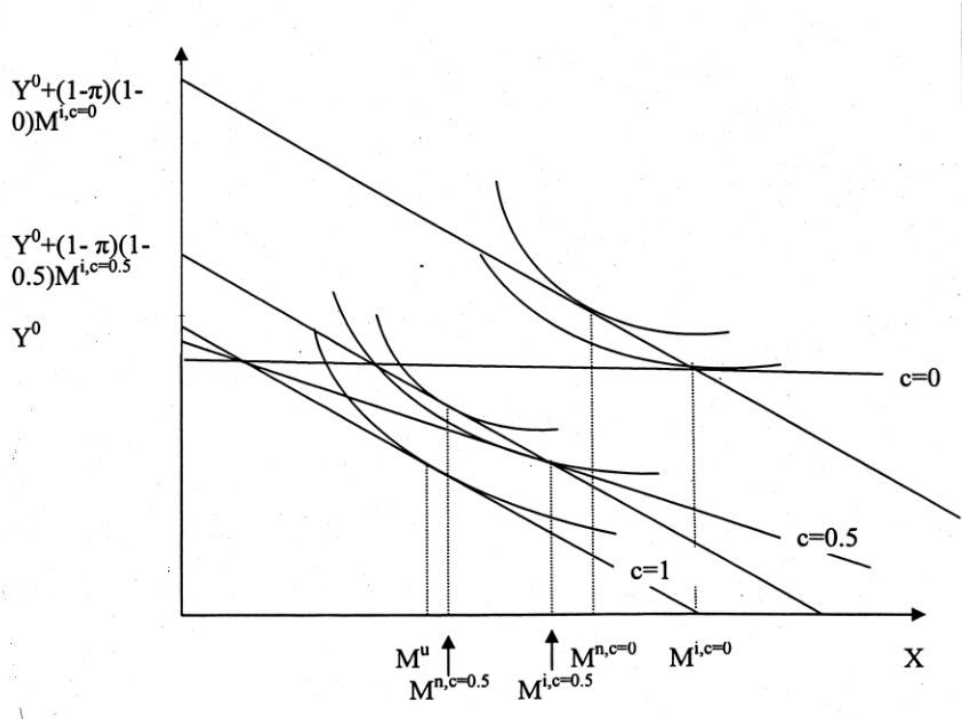

Adopted from Nyman, 2007

In summary, the new theory implies that while some of moral hazard produces a welfare loss, much of moral hazard produces a welfare gain. In contrast to the conventional theory, the voluntary purchase of health insurance makes the consumer better off. It also implies that increasing coinsurance rates to all health care to contain the total health care expenditures is too blunt. Coinsurance rates and other cost-sharing policies should be applied only to inefficient moral hazard.

Figure 4 illustrates the case of prescription cost-sharing based on the new theory. Assume that the probability of illness, $\pi$, lies between 0 and 1. Originally, the uninsured patient faces a price of 1 and if ill consumes $M^u$ units of prescription drugs under the budget constraint income, $Y^0$. The consumer who has purchased insurance with a full coverage (0% coinsurance rate) consumes $M^{i,c=0}$ units of prescription drugs if ill. Of the additional prescription drugs consumed, ($M^{i,c=0}$-$M^u$), income transfers from the healthy ((1-$\pi$)(1-0) $M^{i,c=0}$) account for ($M^{n,c=0}$-$M^u$) additional care, and response to a reduced price generates ($M^{i,c=0}$-$M^{n.c=0}$) additional care. If this patient were required to purchase

insurance with a 50% coinsurance rate, he or she would consume $M^{i,c=0.5}$ units of prescription drugs if ill. Of this ($M^{i,c=0.5}$-$M^{u}$) increase, income transfers from the healthy ((1-π)(1-0.5) $M^{i,c=0}$) generate ($M^{n,c=0.5}$-$M^{u}$) additional care, and response to a reduced price generates ($M^{i,c=0.5}$-$M^{n.c=0.5}$). As drawn in Figure 3, the coinsurance rate would reduce inefficient moral hazard from ($M^{i,c=0}$-$M^{n.c=0}$) to ($M^{i,c=0.5}$-$M^{n.c=0.5}$), but it would also reduce efficient moral hazard from ($M^{n,c=0}$-$M^{u}$) to ($M^{i,c=0.5}$-$M^{u}$). Nyman's theory suggests therefore that imposing prescription cost-sharing reduces both efficient and inefficient care.

Figure 4: Imposing a 0.5 Coinsurance Rate on Insurance




Adopted from Nyman, 2003, Figure 9.1, p146

## 2.2 Epidemiology and Economics of Diabetes, Hypertension and hypercholesterolemia

### 2.2.1 Diabetes

Diabetes mellitus, or simply, diabetes, is a group of diseases characterized by high blood glucose levels that result from defects in the body's ability to produce and/or use insulin. There are major two types of diabetes: type 1 diabetes and type 2 diabetes. Type 1 diabetes is usually diagnosed in children and young adults, and was previously known as juvenile diabetes. In type 1 diabetes, the body does not produce insulin. Insulin is the hormone that is needed to convert sugar, starches and other food into energy needed for daily life. Only 5-10% of people with diabetes have this form of the disease. Type 2 diabetes is the most common form of diabetes. In type 2 diabetes, either the body does not produce enough insulin or the cells ignore the insulin (American Diabetes Association, 2007).

The burden of diabetes is to a large extent the consequence of macrovascular and microvascular complications of the disease, which result in large increases in morbidity and mortality (Permutt, Wasson & Cox, 2005**)**. Complications of diabetes include cardiovascular diseases, hypoglycemia, nephropathy, neuropathy and retinopathy. Based on the data from the 2007 National Diabetes Fact Sheet (Centers for Disease Control and Prevention, 2007), 7.8% of the total population, (23.6 million in the U.S.) has diabetes, leading to the total costs $174 billion in 2007, among which $116 billion was due to direct medical costs, and $58 billion was for indirect costs such as disability, work loss, and premature mortality.

In a study by Sokol et al. (2005) who examined the impact of medication adherence on hospitalization risk and healthcare cost on for chronic conditions, epidemiological factors and yearly expenditures were examined on patients with diabetes. For the 3,260 patients

with diabetes examined, the mean age was 53.9; 45.4 percent of the population were female; the population had a mean cormorbidity score of 4.4. During one year's retrospective observation period, the average diabetes-related cost for each patient was $5,580, among which $5,032 was due to medical costs and $548 due to medication costs. The average all-cause cost (diabetes-related and unrelated) each patient was $10,648, with $8,396 for medical costs and $2,252 for pharmacy costs.

### 2.2.2 Hypertension

Hypertension, defined as systolic blood pressure (SBP) 140mmHg or greater, diastolic blood pressure (DBP) 90mmHg or greater, taking antihypertensive medications, or being told at least twice by a health professional that one has hypertension, is an important health problem (Zhang, 2006). It has been reported that 32 % of non-institutionalized persons 20 years of age and over have hypertension by 2006. According to the Centers for Disease Control/National Center for Health Statistics (CDC/NCHS) (2007), Hypertension increases the risk for heart disease and stroke, the first and third leading causes of death in the United States. About 23,965 adults in the U.S. died of essential hypertension or hypertensive renal disease in 2007. The total direct and indirect cost of high blood pressure in the United States in 2001 was an estimated $47.2 billion (Hodgson & Cai, 2001). Researchers estimate that high blood pressure will cost $76.6 billion in direct and indirect costs in 2010 (Centers for Disease Control and Prevention, 2010).

Hypertension is usually asymptomatic, but can lead to a number of potentially life-threatening conditions if it is not under control. A person with higher blood pressure has a greater risk of developing heart attack, stroke, chronic kidney disease, and retinopathy. Globally, about 62% of cerebrovascular disease and 49% of ischemic heart disease are attributable to suboptimal blood pressure (SBP>115 mmHg) (World Health Organization, 2002).

In 2005, Sokol et al provided demographics and cost information based on 7,981 patients with hypertension. They found that the mean age of this hypertension population was

54.2 years old; 46.7 percent of the population were female; the population had a mean cormorbidity score of 3.4. During one year's observation period, the average hypertension-related cost for each patient was $4,998, among which $4,592 was due to medical costs and $407 due to medication costs. The average all-cause cost (diabetes-related and unrelated) each patient was $8,709, with $7,081 for medical costs and $1,628 for pharmacy costs.

### 2.2.3 Hypercholesterolemia

Hypercholesterolemia is a condition in which levels of cholesterol in the blood are higher than normal. A normal or desirable cholesterol level is less than 200 mg of cholesterol per deciliter of blood. An elevated cholesterol level over 240 is considered to be hypercholesterolemia. Too much cholesterol in the blood will cause plaque to form inside the blood vessel walls, causing them to thicken and narrow. This change can increase the risk of heart disease and heart attacks. (Penn State Milton S. Hershey Medical Center, 2010).

Hypercholesterolemia has no obvious symptoms until problems have already developed. Heart disease or a heart attack can be the result of hypercholesterolemia, and symptoms include chest pain and calf pain when walking (due to narrowed or blocked arteries) (Penn State Milton S. Hershey Medical Center, 2010). In general, the higher the LDL level and the more risk factors present (other than LDL), the greater the risk for developing heart disease or having a heart attack (National Heart Lung and Blood Institute, 2005).

Information about the direct costs of hypercholesterolemia is not available in literature. Most studies discuss the economic burden of coronary heart diseases, for which hypercholesterolemia is a major risk factor. According to the American Heart Association (2010), the cost of cardiovascular diseases in the United States, including health care expenditures and lost productivity from deaths and disability, is estimated to be more than $503 billion in 2010. As the U.S. population ages, the economic impact of

cardiovascular diseases on the nation's health care system will become even greater (CDC, 2010).

In addition, Sokol's study (2005) revealed some cost impact of hypercholesterolemia. Based on 2,981 patients examined, their findings showed that hypercholesterolemia population had a mean age of 54.5 years old; 44.3 percent of them were female; the population had a mean cormorbidity score of 3.2. This population incurred an average all-cause cost of $7,364 per person in one year's analysis period, among which $5,622 was spent on medical services and $1,742 was spent on medications. The average hypercholesterolemia-related cost for each patient was $4,439, which included medical cost of $3,803 and pharmacy cost of $637.

## 2.3 Medication Adherence and Health Outcomes, Utilization and Costs of the Three Conditions

There is strong evidence that effective treatment for many high-prevalence chronic diseases, such as diabetes, hypertension, and hypercholesterolemia, requires medication adherence (Holman et al., 2008; Shibata et al., 2001; Heart Protection Study Collaboration Group, 2002). It has been shown that medication therapy can decrease adverse medical events related to these chronic conditions (American Diabetes Association Position Statement, 2009; Blood Pressure Lowering Treatment Trialists' Collaboration, 2003; Gotto, 2002). Individuals must be adherent to their medication therapy, in order to achieve expected medication therapy benefits.

### 2.3.1 Diabetes

Recently, Asche et. al (2011) performed a systematic review and provided a comprehensive summary of 37 articles that examined the associations between adherence and glycemic control, health care utilization, quality of life, mortality, and economic

outcomes in patients with diabetes. Among these articles, 23 evaluated the association between patient adherence and glycemic control; only one study evaluated the link between improved adherence and disease outcomes or death; 10 studies examined the relationship between adherence and utilization of health care services; 6 studies assessed the link between adherence and health care costs (Asche et. al, 2011).

Based on the 23 articles which studied the link between diabetes medication and glycemic control, the majority (13/23 [56.5%]) reported that improved adherence was associated with better glycemic control, but 8 (34.8%) studies failed to support any statistically significant association between adherence and glycemic control. The remaining 2 (8.7%) studies each used 2 or more model specifications to test the significance of adherence and reported contradictory findings, with the significance of the adherence variable dependent on model specification (Murata et al., 2004; Parchman et al., 2007. Of the studies which used medication possession ratio (MPR) or similar measures of adherence and that found significance, most reported a wide range of estimates regarding the A1C benefit of improved adherence. Depending on the study, for every 10% increase in adherence there were corresponding 0.1% to 0.0014% decreases in A1C.

In the one study that examined the link between improved adherence and disease outcomes or death, Kuo et al (2003) performed a survey to assess disease outcomes and used death certificate data to determine the incidence of death. Their findings suggested that patients with inconsistent use were 59% more likely to report kidney problems, 43% more likely to die from any cause, and 66% more likely to die from a diabetes-related cause compared with patients who used their prescriptions consistently. There were no significant differences in the likelihood of reporting eye and circulatory problems.

According to the review (Asche et. al, 2011), the 10 studies that revealed an effect of adherence and health services utilization all used pharmacy claims data to estimate

adherence. Of the eight studies that evaluated hospitalization as an endpoint, seven (87.5%) showed a statistically significant association between higher levels of adherence and decreased hospitalizations; of the three studies that evaluated emergency department visits as an endpoint, two (66.7%) showed a statistically significant association between higher levels of adherence and decreased visits (Asche et. al, 2011).

Of all the articles reviewed, six studies examined the economic outcomes of diabetes treatment adherence (Asche et. al, 2011). All six studies used retrospective cohort designs, and used pharmacy claims to estimate adherence. In 2003, Balkrishnan et al. conducted a study which evaluated medication adherence and associated health care costs among Medicare enrollees with type 2 diabetes mellitus. Prescription refill pattern was used to measure adherence to antidiabetic medications, calculated with MPR. Demographic, clinical, and utilization-related economic variables were also retrieved from the administrative claims data of the patients' HMO. The results of this study showed that every 10% increase in MPR was associated with 8.6% to 28.9% decreases in annual total health costs ($p < 0.001$), after controlling for covariates.

Sokol et al (2005) used the proportion of days covered (PDC) to measure adherence, and quantified adherence by five levels: 1-19%, 20-39%, 40-59%, 60-79%, and 80-100%. They found that total health care costs tended to decrease at high levels of drug adherence, despite the increased drug costs ($P < 0.0001$); high levels of medication adherence were associated with both lower all-cause and diabetes-related medical costs ($P < 0.05$).

Similarly, Shenolikar et al (2006) reported that a 10% increase in adherence (measured in MPR) was associated with a 2% and 4% reduction ($P < 0.01$) in total health costs and diabetes-related medical costs, respectively. However, this study sample was restricted to Medicaid enrollees with type 2 diabetes who were treated with pioglitazone.

However, other studies have shown different findings. In research which examined the effect of adherence on costs and utilization with diabetes treatment, Hepke et al (2004)

performed the analysis on commercially insured patients with diabetes under 65 years, and their results showed Increased medication adherence (measured in MPR) was associated with decreased medical care costs, but increased medication adherence was not associated with reduced overall health care costs because medication costs offset medical care cost savings. This finding was partially supported by Karve et al (2008), who conducted a retrospective analysis of the Arkansas Medicaid administrative claims data, using 8 different methods for calculating adherence to oral antidiabetic therapy, including MPR, PDC, refill compliance rate (RCR), compliance ratio (CR), medication possession ratio, modified (MPRm), continuous measure of medication gaps (CMG), and continuous multiple interval measure of oversupply (CMOS) and continuous, single interval measure of medication acquisition (CSA). They found that only CSA had a significant coefficient (p=0.013) for all-cause nonpharmacy medical costs, and the coefficient was positive indicating that higher adherence is associated with higher costs; in predicting diabetes-related nonpharmacy medical costs, MPR, PDC, CMG and CMOS measures showed a statistically significant increase in costs associated with increased adherence; while other measures showed no significant association.

In 2008, a study by Kleinman et al. showed mixed results. They examined the impact of insulin adherence (measured in MPR) on annual health costs and absenteeism among employees and spouses with type 2 diabetes. Their findings indicated that among patients in the highest quartile for prior medical costs, a significant decrease in total health care costs was associated with increased adherence (P = 0.0096). Among patients in the lower quartiles for prior medical costs, a significant increase in total health care costs was associated with increased adherence (P =0.0108).

### 2.3.2 Hypertension

The impact of adherence to antihypertensive medications on clinical outcomes and health care utilization has been researched in several studies. Kettani et al (2009) conducted a retrospective cohort study to estimate the use and impact of being adherent to antihypertensive (AH) medication in a real-life setting on incidence of cerebrovascular

disease (CD). The cohort consisted of 83,267 patients who were 45 to 85 year-old, diagnosed with hypertension and were treated with any AH medications between 1999 and 2004. They found high adherence (MPR ≥ 80%) to AH drugs significantly decreased the risk of CD by 22% (rate ratio, 0.78; 95% CI, 0.70 to 0.87) compared with lower adherence (MPR < 80%). In 2010, Perreault et al performed a subsequent analysis on the association between AH medication adherence and the rate of coronary artery disease (CAD) using the same cohort and study period following the study by Kettani et al (2009). They found that the CAD rate decreased by 10% in the group with a high adherence (MPR ≥ 80%) level compared with the reference group (MPR < 80%) for the total follow-up (RR 0.90; 0.86, 0.95) (Perreault et al, 2010).

In the study to determine whether antihypertensive medication refill adherence is associated with decreased stroke and death for community-dwelling patients with hypertension, Bailey et al (2010) found that baseline antihypertensive medication refill adherence was associated with decreased multivariate hazards of stoke [hazard ratio (HR) 0.91; 95% confidence interval (CI), 0.86–0.97 for 15% increase in adherence]. Adherence in the follow-up period 1994-2000 was associated with decreased hazards of stroke (HR 0.92; CI 0.87–0.96) and death (HR 0.93; CI 0.90–0.96). This means that increasing adherence by one pill per week for a once-a-day regimen reduced the hazard of stroke by 8-9% and death by 7% (Bailey et al, 2010).

Based on the search of literature, four articles that examined the relationship between adherence and health care costs for hypertension were found. In a recent study, Pittman et. al. (2010) performed a retrospective analysis to evaluate the relationship between adherence to antihypertensive medications (AHMs), estimated using medication possession ratio, and subsequent hospitalizations, emergency department (ED) visits, and costs of care. This study identified patients with at least two claims for AHMs and divided them into three cohorts in year 1: high adherence (MPR, >80%), moderate adherence (MPR, 60%-79%),and low adherence (MPR, <60%), and then calculated total health care costs during year 2. General linear model (GLM) least squares assessed the

relationship between outcome variables and covariates. Their results showed that patients in the high adherence group had significantly lower total health care costs ($7182) compared with patients in the moderate ($7560) and low ($7995) adherence groups (*P* <.001 for both).

Dragomir et al (2010) evaluated the impact of adherence to antihypertensive agents on hospitalization costs using a cohort of 59,647 patients with essential hypertension aged 45 to 85 years during the period between 1999 and 2002. Adherence was categorized as low adherence (MPR < 80%) and adherence (MPR ≥ 80%). Their results showed that low adherence to antihypertensive therapy was associated with increased costs by approximately $3574 (95% CI, $2897-$4249) per person when compared to the adherence group within a 3-year period. Also, this study found that the low adherence group was had higher medical costs. However, this study did not investigate the association between adherence total health care costs.

In 2009, Lynch et al performed a study to determine whether antihypertensive medication adherence is associated with decreased medical and drug costs, which was examined using a retrospective claims database from large US employers from 2001 to 2008. In this study, medication adherence was measured using PDC. The association between medication adherence and health care costs was calculated separately for high-prior-cost and low-prior-cost employees. High-prior-cost employees were those who accounted for the top 60.0% of total medical costs during the 6 months before the index date. Their findings were that in the group with low prior cost, there was a significant positive association between PDC and the sum of medical and drug costs; however, in the group with high prior cost, as PDC increased, the total of medical and drug costs significantly decreased.

More evidence on the cost impact of antihypertensive medication adherence is provided by the study by Sokol et al (2005), who examined the association between adherence (measured in PDC) to hypertension drugs and condition-specific costs and all-cause costs,

both types of costs included medical costs, drug costs and total health care costs. The results were mixed. For condition-specific costs, both medical and total health care costs for hypertension tended to be lowest at 80% to 100% adherence, but the differences were generally not significant; for all-cause costs, both medical and total costs tended to decrease significantly at high levels of adherence, but the relationship between adherence levels and costs was curvilinear rather than linear, because as PDC increased from 1-19% to 80-100% group, costs firstly increased to the highest for the 20-39% group and then decreased to the lowest for the 80-100% group.

### 2.3.3 Hypercholesterolemia

A number of studies have examined the relationship between hypercholesterolemia medication adherence and clinical outcomes. In 2010, Simpson Jr. and Mendys conducted a systematic literature review of research regarding the association between adherence and persistence to statin therapy and clinical outcomes during 1999 and 2009. After a PubMed search, a total of 19 articles were found and reviewed. 15 studies investigated the association between adherence to statin therapy and clinical events, and four studies reported the relationship between persistence and clinical outcomes. Most studies reported adherence as PDC or MPR, and the most common accepted threshold for full or high adherence was a PDC or MPR of 80% or greater during the observation period (Simpson Jr & Mendys, 2010).

Though direct comparisons of these studies is difficult due to variations in patient populations, and variation in the definitions of adherence and persistence, the findings of these studies suggested a general trend that high levels of adherence (PDC or MPR => 80%) were associated with significant reductions in a range of adverse clinical outcomes, including all-cause mortality, fatal and nonfatal cardiovascular events, and hospitalizations. The most consistent benefits were witnessed at adherence levels of 80% or greater (Simpson Jr & Mendys, 2010).

These general findings were supported by another published study by Corrao et al (2010), which examined the association between statin adherence when used as primary prevention and risk of subsequent ischemic heart diseases (IHD). This study used a retrospective health-services database to analyze people with statin therapies between 2002 and 2003 in Italy. PDC was used to measure adherence, and was categorized into four levels: very low ( ≤ 25%), low (26% - 50%); intermediate (51%-75%), and high (≥75%). They found that patients with PDC > 75% had 14% reductions in IHD risk compared with those with PDC < 25%; IHD risk was significantly lower in those with low adherence (26%-50%).

However, recent research on the association between antihyperlipidemic medication adherence and health care expenditures is limited. Only three articles that examined this association were found through a PubMed search in literature between 2000 and 2011. One study conducted by Pittman et al (2011) examined the relationship among statin adherence, subsequent hospitalizations, and heath care costs. The analysis was performed on a retrospective cohort of 381,422 patients, aged 18 to 61 years, using an integrated pharmacy and medical claims database. Adherence to statin therapy was measured using MPR and divided into three levels: low adherence (MPR 0-59%), moderate adherence (MPR 60-79%) and adherence (80-100%). Adjusted all-cause total heath care costs and medical costs were lowest and the statin costs were greatest in the adherent group. In an additional analysis that evaluated MPR as a continuous variable, they found similar statistically significant associations between a greater MPR and lower medical and total heath care costs.

In another study investigating whether compliance during the first 2 years of statin therapy is associated with reduced direct medical costs during year 3 using claims data between January 1, 2000, and June 30, 2004, Aubert et al (2010) examined 10,227 patients who met the study inclusion criteria. The results showed that compliant patients (MPR ≥ 80%) had significantly lower direct medical costs then non-compliant patients (MPR<80%) when excluding statin therapy costs ($4,040 vs $4,908 per patient, P <.01).

When statin therapy costs were included, the total medical costs were still significantly lower in the compliant group ($4,909 vs $5,290 per patient, *P* <.01).

The third study assessing adherence to cholesterol lowering medications and its associated health care costs was performed by Sokol et al (2005). PDC was used to measure medication adherence, and calculated based on antihyperlipidemic medications including statins, fibrates, niacin preparations, and bile salt sequestrants. The results of this study showed that for both condition-specific and all-cause costs, high levels of adherence with condition-specific drugs were associated with lower medical costs ($p < 0.05$), and total health care costs were generally lowest for patients with 80% to 100% adherence, despite the increased pharmacy costs.

### 2.3.4 Limitations of Previous Studies

There are many limitations found with the previously discussed research. First, limited study has been done to reveal the relationship between medication adherence and health care costs for the three conditions. Though six studies have been done for diabetes, only four and three articles have been found to evaluate the economic impact of adherence for hypertension and hypercholesterolemia respectively. Compared with the literature examining the impact of adherence on clinical outcomes, there is not enough evidence to show the economic benefits of medication adherence.

Second, the results concerning an association between medication adherence and health care costs were inconsistent across the reviewed studies. This problem might be due to the fact that study results were largely dependent on the specific methods used to measure adherence. Currently, there is a wide variety of methods to measure adherence. Selection of different measure methods may lead to different results. As previously discussed, Karve et al (2008) showed that the specific methods used by investigators to measure patient adherence resulted in variable results, even within the same sample. Using non-standardized adherence measures is considered a limitation of these studies.

Another limitation is that the results from most previous studies were restricted to certain samples of population or certain classes of medications. In the studies examining diabetes, Balkrishnan et al (2003) and Hepke et al (2004) only investigated adherence among Medicare enrollees with type 2 diabetes, while the Shenolikar et al (2006) and Karve et al (2008) studies were restricted to Medicaid patients. When examining hypertension adherence, the study by Dragomir et al (2010) only included patients with hypertension aged 45 to 85 years. For the three studies about antihyperlipidemic medication adherence, two studies only examined adherence to statin while neglecting the effect of other classes of antihyperlipidemic drugs. This led to limited generalizability of these studies.

Also, most of the studies used a dichotomous grouping for medication adherence: PDC or MPR equal or above 80% indicated adherence, while PDC or MPR below 80% meant non-adherence. However, the cut point at 80% is quite arbitrary and not based on solid clinical evidence. In addition, in these previous studies, identification of covariates was not theory-based.

The study by Sokol et al. (2005) was most similar to this study in terms of methodology. However, there are several limitations of the Sokol et al. study, including limited generalizability due to the single employer population included in the study, exclusion of Medicare population, cost calculation using only net cost to the plan sponsor which excluded individual out-of-pocket payments, exclusion of the high risk patients with non-adherence. In addition, consumer directed health plans (CDHPs) were not available for analysis at the time of the Sokol et al study.

Very recently, a new study by Stuart et al. (2011) examined whether adherence to renin–angiotensin-aldosterone system (RAAS) inhibitors and statins is associated with lower spending on traditional Medicare services for Medicare beneficiaries with diabetes. Members were followed for 3 years using Medicare Current Beneficiary Survey (MCBS) data from 1997 to 2005. Their results showed that higher adherence was strongly

associated with lower Medicare spending after controlling for extensive covariates. A 10 percentage point increase in statin MPR was associated with $832 lower Medicare spending (SE=219; p<.01). A 10 percentage point increase in MPR for RAAS-Is was associated with $285 lower Medicare costs (SE=114; p<.05).

Stuart et al. study (2011) improved on previous studies by observing study subjects for longer period and reducing much bias through including extensive covariates such as personal characteristics, health service utilization and spending, and diabetes knowledge and self-management practices. However, the study had several limitations as well: (1) study population were restricted to small Medicare sample; (2) lack of service dates and days supply in the MCBS prescription drug event files might lead to less accuracy in MPR measures than measures based on actual claims data; (3): Pill count measure might lead to bias; (4): because the MCBS does not gather data on prescribing, the study was unable to identify beneficiaries who were prescribed RAAS-Is or statins and failed to fill them (nonfulfillment); (5): Since Medicare Part D was not available at the time of study, outcomes measured only included Part A and B services expenditures. Therefore, cost offset effect when counting into prescription drug costs was not able to be measured.

## 2.4 Consumer Directed Health Plan

CDHP consists of two components: a High-Deductible Health Plan (HDHP) and a medical savings account. HDHP is a health insurance policy that requires consumers to pay a higher deductible, but monthly premiums are lower than those in traditional health plans. Health Savings Accounts (HSAs) are private tax-free savings accounts that earn typical savings interest at 1%-4%, depending on the bank that sponsors it. Funds in this account can roll over and accumulate year to year if not spent. However, money deposited in a HSA can only be used for health care expenses (Cleath, 2011).

By combining the option of an HSA with a high-deductible, it was believed that employers are able to provide comprehensive care to employees at a substantially reduced price (HCFO, 2011). It was anticipated that introducing a higher deductible would create an incentive for enrollees to economize their use of medical care, reduce consumption of low-value health services, and stimulate a preference for low-cost and high-quality care (Feldman, Parente & Christianson, 2007). However, evidence on the true cost-saving potential of these plans has been mixed.

In one study, Feldman, Parente & Christianson (2007) examined the three-year spending and utilization trends by employees of a large organization offering both a CDHP and a point of service (POS) plan. They found that CDHP cohort spent considerably more money on hospital care than the POS cohort, but spending was lower for individuals enrolled in CDHPs for prescription drugs compared with those in POS. In 2008, Parente, Feldman and Chen compared pharmaceutical spending and utilization in a CDHP with a traditional three-tier pharmacy benefit plan, and examined whether the CDHP reduced pharmaceutical spending and utilization for chronically ill patients, generic or brand name drugs. They found that CDHP pharmaceutical expenditures were lower than those in the POS cohort in 1 year without differences in the use of brand name drugs, and they found limited evidence of less drug consumption by CDHP enrollees with chronic illnesses. In comparison, Mercer Human Resources Consulting (2005) conducted a survey in 2004 and found that the typical CDHP cost $5,233 per employee compared with $6,095 for the average preferred provider organization (PPO). However, this study did not control for differences in enrollee characteristics that might be related to health care costs, and it controlled for only one plan characteristic – the annual deductible. PPOs with deductibles of $1,000 or more cost less than the average CDHP (Feldman, Parente & Christianson, 2007).

In a study funded by Health Care Financing and Organization (HCFO), Galbraith et al (2011) analyzed the financial impact of High Deductible Health Plans (HDHPs), one form of CDHPs, on families with chronic health conditions. The research team used

survey results, individual interviews, and Harvard Pilgrim Health Care claims data from 494 families; 151 in HDHPs and 345 in traditional health plans. They found that more than twice as many families in HDHPs reported financial burden than families in traditional plans (48 percent compared with 21 percent). Financial burden was defined as difficulty paying family medical bills, participating in payment plans with a doctor's office of hospital, and difficulty paying other necessary bills (e.g. rent, groceries) because of medical bills. Additionally, families in HDHPs paid double the out-of-pocket expenses of families in traditional plans.

In a more recent study, Beeuwkes Buntin et al (2011) investigate the effects of HDHP and CDHP on heath care spending and on the use of recommended preventive care. They examined more than 800,000 U.S. families insured during 2004 and 2005 through one of 53 large employers. Approximately one-half of these employers offered a HDHP option. The findings showed that while overall health care spending grew across all types of health plans, it grew at a 14 percent lower rate for those in HDHPs. Families in HDHPs spent less on both inpatient and outpatient medical services, as well as prescription drugs. However, families in HDHPs received less preventive services, including childhood vaccinations and cancer screenings, than those in traditional health plans. While spending decreased over the limited study period, lack of preventive services could lead to much higher medical costs in the long term.

However, the studies on CDHP/HDHP discussed above focused primarily on arrangements that require full cost sharing for drugs up to the annual deductible level; the relationship between CDHP, medication use and health care costs when prescription copayment amount is fixed, as it is in the traditional copayment model had not been well understood. For this reason, Reiss et al. (2011) examined whether high-deductible health plans (HDHPs) that exempt prescription drugs from full cost sharing preserve medication use for major chronic illness, compared with traditional HMOs with similar drug cost sharing.

Reiss et al. (2011) study assessed the medication use of 3,348 continuously enrolled adults in a Massachusetts health plan that experienced an employer-mandated switch from a traditional HMO plan to a HDHP, compared with 20,534 contemporaneous matched HMO members. Both study groups faced similar three-tiered drug copayments. Medication use was measured by daily medication availability (DMA) for all prescription drugs and four chronic medication classes: hypoglycemics, lipid-lowering agents, antihypertensives, and chronic obstructive pulmonary disease (COPD)/asthma controllers. They found that the HDHP and control groups had comparable changes in the level and trend of all drugs after the index date. They detected similar patterns in the use of lipid-lowering agents, antihypertensives, and COPD/asthma controllers, with a small relative decline in hypoglycemic use among diabetic patients in HDHPs. They also found that overall prescription drug spending showed comparable increasing trends for HDHP and control groups. The findings suggested that switching to an HDHP that included modest drug copayments did not change medication availability or reduce use of essential medications for three common chronic illnesses.

The findings of previous studies suggest that though HDHPs are heralded by supporters as a solution to overuse of unnecessary medical services and a mechanism to drive down health care costs, the evidence is still inconclusive (HCFO, 2011). While studies have examined the relationship between CDHPs and costs or CHDPs and medication use (Reiss et al., 2011; Dixon, Greene & Hibbard, 2008; Greene et al., 2008; Parente, Feldman & Chen, 2008) in isolation, the incremental influence of CDHPs on health care costs after adjusting for the effect of medication adherence has not been examined yet. Therefore, further research should be done to provide more evidence on whether CDHPs can reduce health care spending.

# Chapter 3: RESEARCH DESIGN AND METHODS

## 4.1 Data Source

*Prime Therapeutics, LLC* (Prime), a Pharmacy Benefit Management (PBM) company, is owned by 11 Blue Cross and Blue Shield Plans in Florida, Illinois, Kansas, Minnesota, Montana, Nebraska, New Mexico, North Dakota, Oklahoma, Texas and Wyoming with 14.7 million lives. However, the company provides pharmacy benefit management services for 36.5 million weighted lives across 16 different Blue Cross and Blue Shield Plans. Prime manages over $9 billion of drug spend and processes approximately 149 million pharmacy claims annually, and has over 5 years of integrated medical claims, pharmacy claims, and membership eligibility history available for analysis. Prime provided a HIPPA compliant limited data set for this study.

This study uses the eligibility, medical, and pharmacy claims data from 1.4 million members from employers whose Blue Cross and Blue Shield plans originate in Minnesota. All claims and eligibility files are maintained in a HIPPA compliant secure data warehouse.

## 3.2 Identification of Subjects

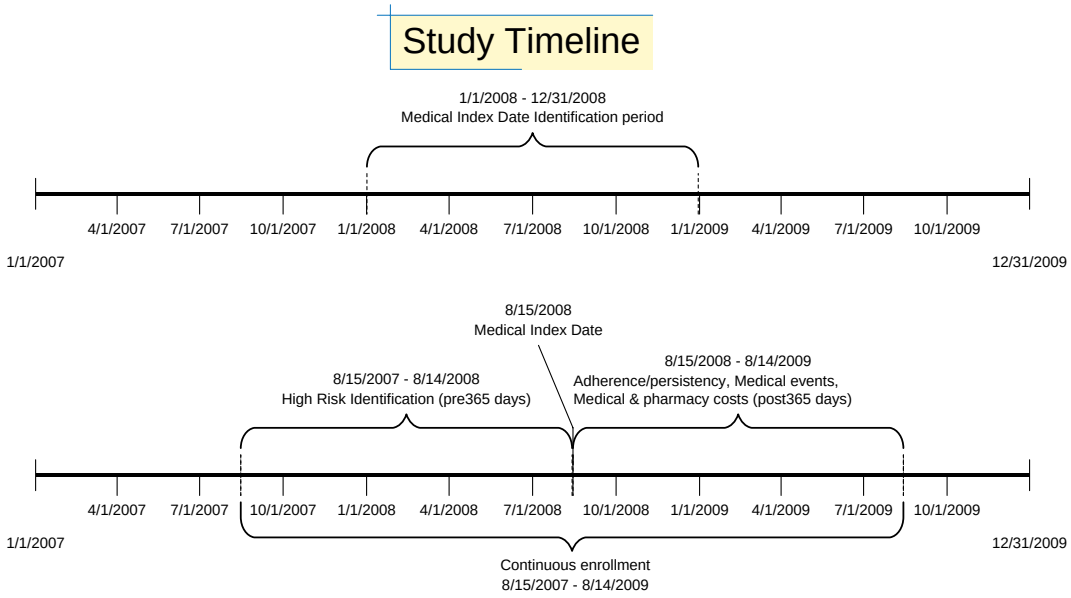
Members who are 18 years of age or older and continuously enrolled from January 1$^{st}$, 2007 to Dec. 31$^{st}$, 2009 (36 months) are used to identify separate study samples: diabetes, hypercholesterolemia, and hypertension. Members are identified if: 1) they have two or more primary or secondary diagnosis field coded outpatient medical claims for the condition of interest (diabetes, hypercholesterolemia, or hypertension) greater than 30 days apart; or 2) they have a hospitalization with the diagnosis in the primary field for condition of interest. The medical index date is the date of the earliest outpatient visit

when two or more outpatient medical claims are present. If there are less than two outpatient medical claims, the medical index date is the hospitalization discharge date.

Presence of diagnosis and medical index dates are established between Jan. 1st, 2008 and Dec. 31, 2008. The study time framework is shown below (Figure 5). Individuals with multiple conditions will be included in each study sample for which they meet the inclusion and exclusion criteria.

Members who meet any of the following criteria are excluded from the study: age 0 to 17, lack of continuous enrollment, pregnancy, diagnosis of dementia, and individuals who are institutionalized or at nursing home, identified via medical claims diagnosis at any time during analysis. The requirement of continuous enrollment is to rule out the enrollment change or benefit change as the reasons for suboptimal adherence. The requirements of age, no long-term care, and no diagnosis of dementia are to make sure that the patients have the ability of making independent decision about their medications, so that patients' voluntary medication taking behavior can be evaluated precisely instead of evaluating their parents' or caregivers' behavior. Pregnant individuals are excluded due to the potential for misclassification of pregnant individuals as having a chronic disease and the contraindication of ACEI/ARB and statins in pregnancy.

Figure 5: Study Time Framework




Example member with medical index date 8/15/2008

### 3.2.1 High Risk Identification

Individuals at high risk for adverse medical events due to their underlying medical diagnoses are identified as high risk group in the study. Identification of individuals with a high risk status is made from January 1$^{st}$, 2007 through their medical index date.

Diabetes Mellitus high risk members are defined as the presence of two or more diagnosis field coded (any field or line) medical claims for a diabetes microvascular complication listed below greater than 30 days apart or a hospitalization with the diagnosis in the primary field:

- nephropathy
- neuropathy
- retinopathy
- peripheral vascular disease

Hypertension high risk members are defined as the presence of two or more diagnosis field coded (any field or line) medical claims for a vascular complication or equivalent vascular risk listed below greater than 30 days apart or a hospitalization with the diagnosis in the primary field:

- myocardial infarction,
- coronary atherosclerosis
- stroke
- congestive heart failure
- chronic kidney disease or
- diabetes mellitus

or a single a surgical procedure in any of the surgical procedure fields for:

- coronary stent placement
- percutaneous transluminal coronary angioplasty (PTCA)
- coronary artery bypass graft (CABG)

Hypercholesterolemia high risk members are defined as the presence of two or more diagnosis field coded (any field or line) medical claims for the presence of cardiovascular disease or equivalent risk listed below greater than 30 days apart or a hospitalization with the diagnosis in the primary field:

- myocardial infarction
- coronary atherosclerosis
- ischemic stroke
- congestive heart failure
- diabetes mellitus

or a single a surgical procedure in any of the surgical procedure fields for:

- coronary stent placement
- percutaneous transluminal coronary angioplasty (PTCA)

- coronary artery bypass graft (CABG)

### 3.2.2 Medical Claims

Each member has 12 months of total medical claims assessed from their index medical claim date. Medical claims associated with their condition of interest are analyzed using the ICD-9-CM specific codes defined in Table 1. Medical costs include all professional services (physician office visit, dialysis), facility services (e.g., hospitalizations, emergency room), laboratory services, nursing home and home care services.

Table 1: Diagnostic Indicators for Patient Identification

| **Conditions** | **ICD-9-CM Codes** | **Description** |
|---|---|---|
| Diabetes | 250.xx | Diabetes mellitus |
| Hypertension | 401.xx<br>402.xx<br>403.xx<br>404.xx | Essential hypertension<br>Hypertensive heart disease<br>Hypertensive renal disease<br>Hypertensive heart and renal disease |
| Hypercholesterolemia | 272.xx | Disorders of lipoid metabolism |

### 3.2.3 Pharmacy Claims

The medication classes associated with the three conditions of interest are identified using Medispan Generic Product Identifier (GPI) codes, which are presented in Table 2. Medispan GPI is a segmented numeric drug code assigned by Medi-Span, using a hierarchical classification scheme encompassing drug group, class, sub-class, name, name extension and dosage. Products assigned the same code should be pharmaceutically equivalent regarding active ingredients, dose form, route of administration, and strength.

The same drug may be classified in multiple therapeutic classes (National Cancer Institute, 2011).

Presence of medication therapy on the medical index date are established through an assessment of the pharmacy claims data using the pharmacy date of service and days of supply starting from the medical index date. Each member has 12 months of total prescription claims assessed from their index medical claim date.

Table 2: GPI Codes for Medications Treating Diabetes, Hypertension, and Hypercholesterolemia

| **Antidiabetics** | |
|---|---|
| **Therapeutic Class** | **GPI** |
| Insulin | 2710 |
| Amylin analogs, incretin mimetic agents | 2715, 2717 |
| Sulfonylureas | 2720, 279970, 279978 |
| Amino Acid Derivatives, Meglitinide Analogues, Alpha glucosidase inhibitor | 2723, 2728, 279950, 2750 |
| Biguanides | 2725, 279925, 279950, 279970, 279980 |
| Dipeptidyl Peptidase-4 (DPP-4)inhibitors | 2755, 279925 |
| Thiazolidinediones | 2760, 279978, 279980 |
| **Antihypertensives** | |
| **Therapeutic Class** | **GPI** |
| ACE inhibitors, Angiotensin II Receptor Blockers (ARBs), renin inhibitors | 3610, 3615, 3617, 369915, 369918, 369930, 369940, 369945, 369960, 369965, 369967 |
| Beta blockers | 33100005, 33100007, 33100010, 33100025, 33100030, 33100040, 33100050, 3320, 3330, 369920 |
| Calcium channel blockers | 34, 409925, 369915, 369930, 369945 |
| Diuretics (includes spironolactone and eplerenone, acetazolamide) | 3710, 3720, 3750, 3760, 379900, 369910, 369918, 369920, 369940, 369945, 369950, 369955, 369960, 369990, 3625 |
| Miscellaneous : vasodilators (hydralazine, | 3620, 3630, 3640, 3660, 369910, |

| | |
|---|---|
| minoxidil, nitroprusside, fenoldopam), clonidine, guanfacine, methyldopa, alpha blockers, Phenoxybenzamine, phentolamine, metyrosine, Diazoxide, mecamylamine, metyrosine, tolazoline | 369950, 369955, 369990 |
| **Antihyperlipidemics** | |
| **Therapeutic Class** | **GPI** |
| HMG CoA Reductase Inhibitors (Statin) | 3940, 399940, 409925 |
| Bile acid sequestrant | 3910 |
| Fibric acid derivatives | 3920, 399920 |
| Nicotinic acid derivatives | 3945 |
| Intestinal cholesterol absorption inhibitors | 3930 |
| Miscellaneous | 3950 |

## 3.3 Measure of Predictors

### 3.3.1 Measure of Medication Adherence

In recent years, the use of administrative claims data as a source for calculating medication adherence has gained prominence. Medication adherence measured using pharmacy claims has been validated using other adherence measures such as patient reports, pill counts, questionnaires, and interviews. Despite these validation studies, there are no standards for the mathematical calculation of adherence using claims data. In a research paper, Karve et. al (2008) compared eight measures of adherence, and recommended that Proportion of Days Covered (PDC) and Medication Possession Ratio (MPR) measures should be considered first when selecting among adherence measures for administrative prescription claims data. Martin et. al (2009) further compared PDC and MPR when analyzing adherence for patients taking multiple drugs within a broad class. They concluded that the PDC provides a more conservative estimate of adherence than the MPR across all types of users, and may confer advantages over MPR-based methods when any disease class is studied for which there are concurrent treatments within a drug class, such as diabetes and hypertension.

This paper uses the PQA-NCQA (2009) endorsed PDC to measure medication adherence. Medication adherence is quantified by using the standardized measures endorsed by the National Quality Foundation (NQF). The adherence measures assess compliance with therapeutic drug regimens for particular therapeutic drug classes.

According to the standards of PQA, adherence is measured by PDC, which is defined as the number of days in the measurement period covered by prescription claims for the same medication or another in its therapeutic category using the days of supply reported on the individual claims. In this study, the calculation of PDC is not based on the same therapeutic class, but also based on the same drug class. This means all available medications used to treat the target condition are included to calculate PDC. Theoretically, PDC can be quantified from 0%-100%; most commonly, PDC is reported as 1%-100%, because people who should take medication but do not are excluded. In this study, people who are classified as high risk but do not have any pharmacy claims during the study period are classified as zero PDC group and are further examined.

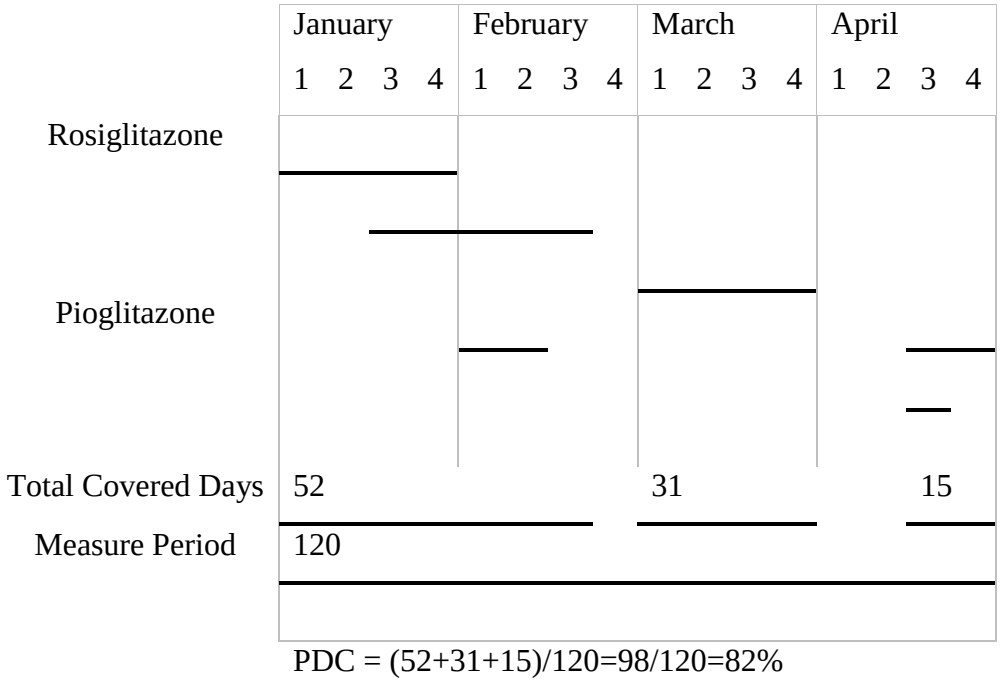
Even though PDC can be considered as a continuous variable, most commonly it is reported categorically. The most frequent categorization is dichotomous – a PDC of 80% or above is considered as adherence, and a PDC of less than 80% is considered not adherent. The PDC threshold of 80% is the level above which the medication has a reasonable likelihood of achieving the most clinical benefit based on clinical evidence (PQA, 2009).

In this study, PDC is used as a continuous variable with values from 0 to 100% in multivariable regression analysis. To better interpret the results of the regression analysis, however, PDC is also categorized into five groups: 0-19%, 20%-39%, 40%-59%, 60%-79%, and 80%-100%.

Table 3: PQA Measures Specifications

| | Calculation Methods |
|---|---|
| Step1 | Determine the patient's measurement period, defined as the index date to the end of the measurement period, disenrollment, or death. |
| Step2 | Within the measurement period, count the days the patient was covered by at least one drug in the class based on the prescription fill date and days of supply. If prescriptions for the same drug overlap, then adjust the prescription start date to be the day after the previous fill has ended. |
| Step3 | Divide the number of covered days found in Step 2 by the number of days found in Step 1. Multiply this number by 100 to obtain the PDC (as a percentage) for each patient. |

Example 1: PDC Calculation Illustration




PDC = (52+31+15)/120=98/120=82%

### 3.3.2 Measure of Enrollment in Consumer Directed Health Plan

Enrollment in CDHPs is examined dichotomously in this study: enrolled in CDHPs or not enrolled in CDHPs. If the member is continuously enrolled in HDHP/CDHP during the study period, the indicator will be scored "1" for that member; otherwise, it will be scored "0". This information was identified form enrollment file.

## 3.4 Measure of Dependent Variables

### 3.4.1 All-Cause Health Care Costs

The first outcome measured is all-cause heath care costs. All-cause heath care costs are defined as the sum of medical cost and drug cost associated with any condition during the 12-month analysis period. Total medical costs include all professional services (physician office visit, dialysis), facility services (e.g., hospitalizations, emergency room), laboratory services, nursing home and home care services. Total drug costs include all costs of ambulatory prescriptions (dispensed by outpatient, community-based, or mail-service pharmacies). Cost is defined as the sum of the cost to the plan sponsor and patient out-of-pocket expense.

### 3.5.2 Condition-Specific Health Care Costs

The second outcome measured is condition-specific health care costs. Condition-specific health care costs are defined as the sum of medical cost and drug cost associated with treatment of the target condition during the 12-month analysis period. Condition-specific costs are a subset of all-cause heath care costs. For medical services, condition-specific costs are identified by primary and secondary ICD-9 codes from medical claims data. For drugs, condition-specific costs are identified by drug classes from prescription medications claims generally accepted for the treatment of the target condition.

## 3.6 Measure of Control Variables

Patients' all-cause health care costs or condition-specific health care costs can be reflected by patients' use of medical services. Obviously, patients who use more medical services incur higher medical expenditures. Therefore, factors that influence medical services utilization will in turn impact total or condition-specific medical costs. According to Anderson's behavioral model of health services utilization, the control variables in this study are classified into three categories: predisposing characteristics, enabling resources, and need factors.

### 3.5.1 Predisposing Characteristics

Age (years) is identified on the index date from the medical claims file, calculated as an integer from the date of birth until the index date. Sex (male/female) is identified form the enrollment file.

As patients' education and race are not available from the claims data, these variables are identified from the Census 2000 Data on the level of a patient's home zip code area.

### 3.5.2 Enabling Resources

**Household Median Income**

As patients' income is not available from the claims data, this information are also controlled on an aggregate level. Census 2000 data are used to obtain the household median income in a patient's home zip code area.

**Generic Medication Use Rate**

The percentage of generic medications filled among total medications during the observation period may have an impact on health care expenditures. This information is

obtained from pharmacy claims for each patient. This variable is calculated as (number of generic pharmacy claims in observation period) / (number of total pharmacy claims in observation period).

**Use of Mail-Order Service (Yes/No)**

The use of mail-order pharmacies tend to be associated with greater likelihood of higher adherence which may have impact on health care costs, because mailed medications eliminate the need for travel to the pharmacy and purchase more medications (90-day supply) than patients using local walk-in pharmacies (Duru et al., 2010). This variable measures whether patients used any mail-order service at some point in time during the follow-up period (12 months from index date). This information is based on the status of the pharmacy where a patient filled his/her prescription in the claims data.

### 3.5.3 Need Factors

**High Risk (Yes/No)**

Individuals at high risk for adverse medical events due to their underlying medical diagnoses are defined as high risk group, which tend to utilize more medical services and incur more heath care costs than non high risk group. The definition and identification of high risk group was discussed previously in the section of Identification of Subjects.

**Comorbidities**

Patients with more comorbid conditions or with more severe comorbidity status tend to use more medical care and incur more medical costs (Struijs et al., 2006). Comorbidities are measured by the enhanced Deyo's Charlson comorbidity index (Quan et al., 2005). The Charlson score is based on ICD-9 codes in patients' medical claims during the study period. Seventeen comorbidity conditions are included in the adapted Charlson comorbidity index. The Charlson score weight for each condition is based on the weighting rule developed by Schneeweiss et al. in 2008 (Appendix 2).

**Depression or Bipolar Disorders (Yes/No)**

Psychological characteristics such as depression or bipolar disorder could influence patients' motivation and desirability to treat their health problems. Therefore, patients who have depression or bipolar disorder may use more health care and incur more health care costs. Patients with depression or bipolar disorder will be identified according to use of antidepressants or bipolar medications, rather than a diagnosis of depression or bipolar disorder, because behavioral health diagnosis are often not accurately represented in administrative claims data (Christian-Herman et al., 2004). Prescription claims during the 12 months before the index date are checked to see whether patients were on any antidepressant or bipolar medications.

Table 4: Variables Definition

| **Variables** | **Definition** | **Possible Range** | **Analytic Measure** |
|---|---|---|---|
| **Dependent Variables** | | | |
| All-cause total cost | The sum of medical costs and drug costs associated with any condition during post-index period | 1—maximum cap | Continuous |
| All-cause medical cost | Costs incurred on medical services associated with any condition during post-index period | 1—maximum cap | Continuous |
| All-cause pharmacy cost | Costs incurred on pharmacy claims associated with any condition during post-index period | 0—maximum cap | Continuous |
| Condition-specific total cost | The sum of medical costs and drug costs associated with the target condition during post-index period | 1—maximum cap | Continuous |
| Condition-specific medical cost | Costs incurred on medical services associated with the target condition during the post-index period | 1—maximum cap | Continuous |
| Condition-specific pharmacy cost | Costs incurred on medical services associated with the target condition during the post-index period | 0—maximum cap | Continuous |
| **Independent** | | | |

| **Variables** | | | |
|---|---|---|---|
| PDC | The number of days in the analysis period covered by prescription claims for the same medication or another in the same drug class during the post-index period | 0—100% | Continuous / Categorical |
| CDHP | Whether the individual was continuously enrolled in CDHP in post-index period | 0: not enrolled in CDHP;<br>1: enrolled in CDHP | Dichotomous |
| **Control variables** | | | |
| Age | The age for the individual up to index date | 0—maximum cap | Continuous |
| Sex | Individual's gender | 0:femle;1: Male | Dichotomous |
| Race | The percentage of residents that were white in the individual's home zip code area | 0—100% | Continuous |
| Education | The percentage of residents that obtained bachelor's degree or above in the individual's home zip code area | 0—100% | Continuous |
| Median income | Median household income that was above $50,000 in the individual's home zip code area | 0: median income<$50,00;<br>1: median income>$50,000 | Dichotomous |
| Generic rate | The percentage of filled generic drug claims in post-index period | 0—100% | Continuous |
| Use of mail-order service | Whether the individual used mail-order service at some point in time during post-index period | 0: no;<br>1: Yes | Dichotomous |
| High risk | Whether the individual was in high risk group, identified in pre-index period | 0: not high risk group;<br>1: high risk group | Dichotomous |
| Comorbidity (Charlson index score) | Charlson score calculated based on individual's comorbid conditions in pre-index period | Diabetes:<br>1—16<br>Hypertension<br>Hypercholesterolemia:<br>0—16 | Continuous |
| Depression/ bipolar | Whether the individual was diagnosed with depression or bipolar disorder in pre-index period | 0: not depression/bipolar;<br>1:depression/bipoar | Dichotomous |

## 3.6 Statistical Analysis

This study is a secondary data analysis. GLM gamma log link model is used to evaluate the two aims of this study. This section will firstly discuss the problems with modeling cost data. Then the rationale of adopting a gamma model is explained. Finally, a description of GLM gamma log link is provided. All the statistical analyses are conducted using SAS 9.2 (SAS Institute Inc., Cary, NC, USA). All results are considered statistically significant at the 0.05 level (2-tailed).

### 3.6.1 Problem with Health Cost Data

Health cost data are typically found to be positively skewed. While most patients have roughly similar costs, a small proportion of patients with complications or severe disease require additional costly treatment and will therefore account for a disproportionately larger amount of the costs (Everitt & Pickles, 1999). The variance of cost data is typically not constant and is usually found to be proportional to the square of the mean (Blough et al. 1999). Therefore, traditional models based on the assumptions of normal distribution and homoscedasticity are considered inappropriate when dealing with cost data, because the non-normal nature of cost data may lead to violations of assumptions required for the calculation of arithmetic mean costs using methods based on the normal distribution (Dodd et al. 2005). Instead, the use of non-parametric methods is advocated for estimating variability when examining highly skewed costs. Unfortunately very few non-parametric methods can be used to assess the effects of multiple covariates on health cost (Lin, 2000). In this case, multivariable regression analysis is useful for controlling for effects of multiple explanatory variables on health costs.

Dodd et al (2005) compared the appropriateness of several multivariable regression analysis methods by examining regression diagnostics, using as an example the costs incurred in the treatment of inflammatory bowel disease. The models compared are normal and bootstrapped multiple linear regression, median regression, gamma model

with the log link and normal linear regression (NLR) of log costs. Based on their findings, the gamma log link model was the best fitting model, because it had the smallest root mean square error (RMSE) and mean absolute error (MAE) (shown in Table 5), and it gave the best estimation of the mean of the outcomes (shown in Table 6).

Table 5: RMSE and MAE based on Model Derivation and Validation

| *Model* | *RMSE* | *MAE* |
|---|---|---|
| NLR | 1333.57 | 749.52 |
| Log NLR | | |
| Duan | 1005.19 | 458.55 |
| Normal | 1011.41 | 461.44 |
| Gamma | 962.01 | 437.18 |
| Median | 1091.13 | 525.62 |

RMSE, root mean square error; MAE, mean absolute error; NLR, normal linear regression.

Table 6: Summary Statistics for Model Predictions

| *Model* | *Mean* | *SD* | *Median* | *Minimum* | *Maximum* |
|---|---|---|---|---|---|
| Actual | 1402.94 | 3024.91 | 506.34 | 73 | 29 166.52 |
| NLR | 1402.94 | 2609.77 | 615.11 | −666.56 | 12 580.47 |
| Log NLR | | | | | |
| Duan | 1449.11 | 2793.87 | 533.13 | 130.86 | 14 871.47 |
| Normal | 1452.33 | 2800.07 | 534.31 | 131.15 | 14 904.46 |
| Gamma | 1401.17 | 2623.44 | 524.04 | 147.71 | 13 917.78 |
| Median | 1189.83 | 2157.89 | 472.76 | −10.07 | 10 246.55 |

SD, standard deviation; NLR, normal linear regression.

### 3.6.2 Generalized Linear Modeling Using the Gamma Distribution with Log Link

The gamma distribution has been found to be appropriate for the analysis of cost data, as it assumes that the data have a constant coefficient of variation, which is often found to be the case with cost data. Although the gamma model may incorporate a reciprocal, log

or identity link, the log link is commonly used when analyzing cost data, as it guarantees non-negative outcomes and has a close connection to the logarithmic transformation of data (Myers et al. 2001). The advantage of using the log link rather than the log transformation is that the former retains the original scale of the data and therefore requires no retransformation.

The gamma model is primarily used with continuous response data, and for data situations in which the response can take only values greater than or equal to 0. The only assumption of gamma model is that positive responses should have a constant coefficient of variation. However, the model is robust to wide deviations from this assumption (Hardin & Hilbe 2001).

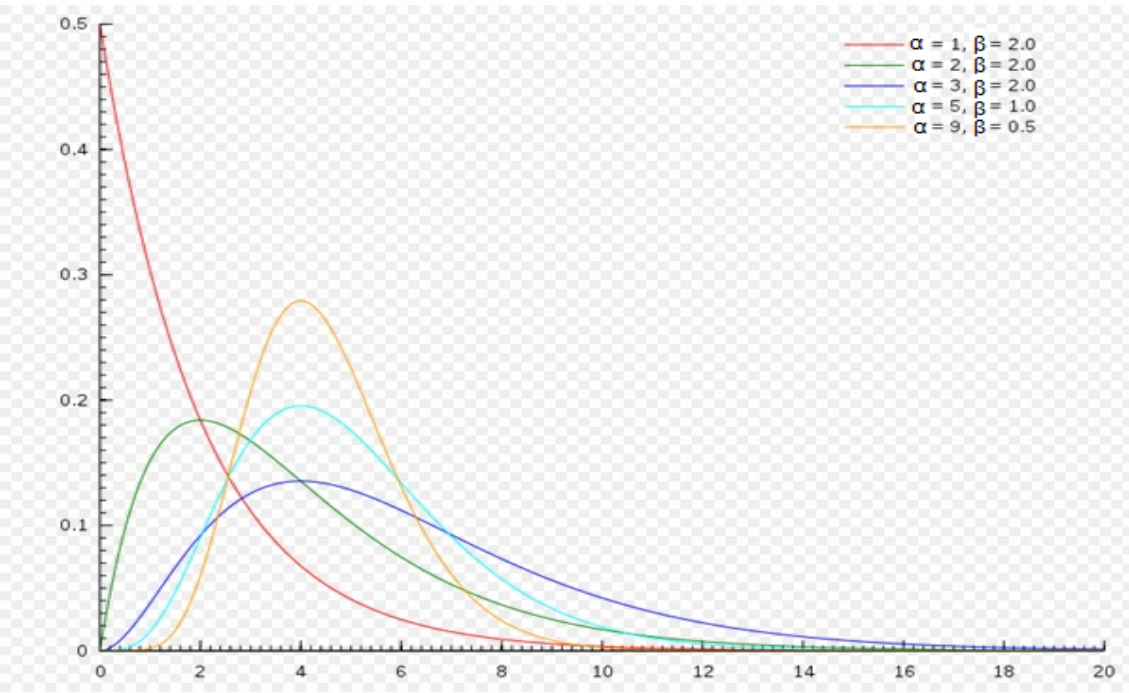
A random variable *y* has a gamma distribution with parameters *α and β* (*α* >0 and *β>0* ) if y has a continuous distribution for which the probability density function (PDF)) f (y/α, β) is specified as follows:

$$f\,(y/\alpha,\,\beta)=\begin{cases}\frac{1}{\beta^{\alpha}\Gamma(\alpha)}\; y^{\alpha-1}\, e^{\frac{-y}{\beta}} & for\ y>0,\\ 0 & for\ y\leq 0.\end{cases}$$

Where α is the shape parameter, β=1/θ for which θ is the scale parameter, and $\Gamma(\alpha)$ = (α-1) !

In this distribution, the mean E(y) = αβ, and the variance Var(y) = $\alpha\beta^2$. The PDF of gamma distribution have different shapes, when the parameters α and β take on different values (see Figure 6). Therefore, a random variable y that is gamma-distributed with shape α and scale β can be denoted as y ~ Gamma(α, β).

Figure 6: PDF of Gamma distribution




The GLM gamma log link model is:

$$\ln[E(Y_i)] = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_k X_k$$

Or $$E(Y_i) = \exp(\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_k X_k)$$

Where $Y_i$ is the dependent variable, $E(Y_i)$ is the expected value of $Y_i$ , $X_k$ are independent variables, and $\beta_k$ are coefficient vectors. Gamma model has a mean as an exponential function of its predictors $X_k$ . The parameters in the model are calculated by maximum likelihood estimation.

### 3.6.3 Generalized linear Model Family Test

Generalized linear models (GLM) contains a large range of probability distributions from the exponential family including normal, exponential, gamma, Gaussion, Poisson and many other distributions. Each distribution has a specific variance function in relationship to its distribution mean, which can be written (Manning & Mullahy, 2001):

$$\text{var}(y|x) = \alpha[E(y|x)]^{\lambda}$$

Where y is the dependent variable and x is the independent variable. The value of λ indicates a specific distribution model to be used in GLM. If λ = 0, the Gaussian distribution nonlinear least-squares model (NLM) should be used. If λ = 1, the Poisson model should be used. If λ = 2, the gamma model should be used. If λ = 3, the inverse Gaussian (or Wald) model should be used.

In order to determine whether the gamma model is appropriate for fitting the observations of the dependent variables in this study, the modified Park test proposed by Manning & Mullahy (2001) will be used to examine the variance functions for the outcomes: all-cause and condition-specific health costs. The test equation of modified Park test is written as below:

$$\ln(y_i - \hat{y}_i)^2 = \lambda_0 + \lambda_1 \ln(\hat{y}_i) + v_i$$

Where $\ln(y_i - \hat{y}_i)^2$ indicates the natural log of the estimated raw-scale residuals squared; $\ln(\hat{y}_i)$ is the natural log of the predicted value of $y_i$ on the raw scale; $\lambda_1$ is the coefficient of the regression of $\ln(y_i - \hat{y}_i)^2$ on $\ln(\hat{y}_i)$, and the value of $\lambda_1$ indicates which model to employ in GLM.

## 3.7 Ethical Consideration

A limited data set was received after all direct individual identifiers were removed from the data according to the requirements of HIPPAA (Health Insurance Portability and Accountability Act). There is no way to identify an individual through the data used in this study. The study was approved by the University of Minnesota's Institutional Review Board (Appendix 1).

# Chapter 4: RESULTS

This chapter presents the results of the statistical analysis of this study. First, a description of the construction of study cohorts is presented. Second, descriptive statistics for the study variables for each study cohort are presented. Third, the results of statistical models are presented for each study cohort.

## 4.1 Data Extraction and Cohort Construction

This study used the administrative data provided by Prime Therapeutics, LLC. After applying all study inclusion and exclusion criteria, three study cohorts with final analyzable data were constructed. The study populations were narrowed to 22,012 people for diabetes, 64,660 people for hypertension and 59,003 people for hypercholesterolemia. Figures 7, 8 and 9 show how the study subjects from the three cohorts were extracted from the large database.

Figure 7: Diabetes Cohort Construction Flow Chart

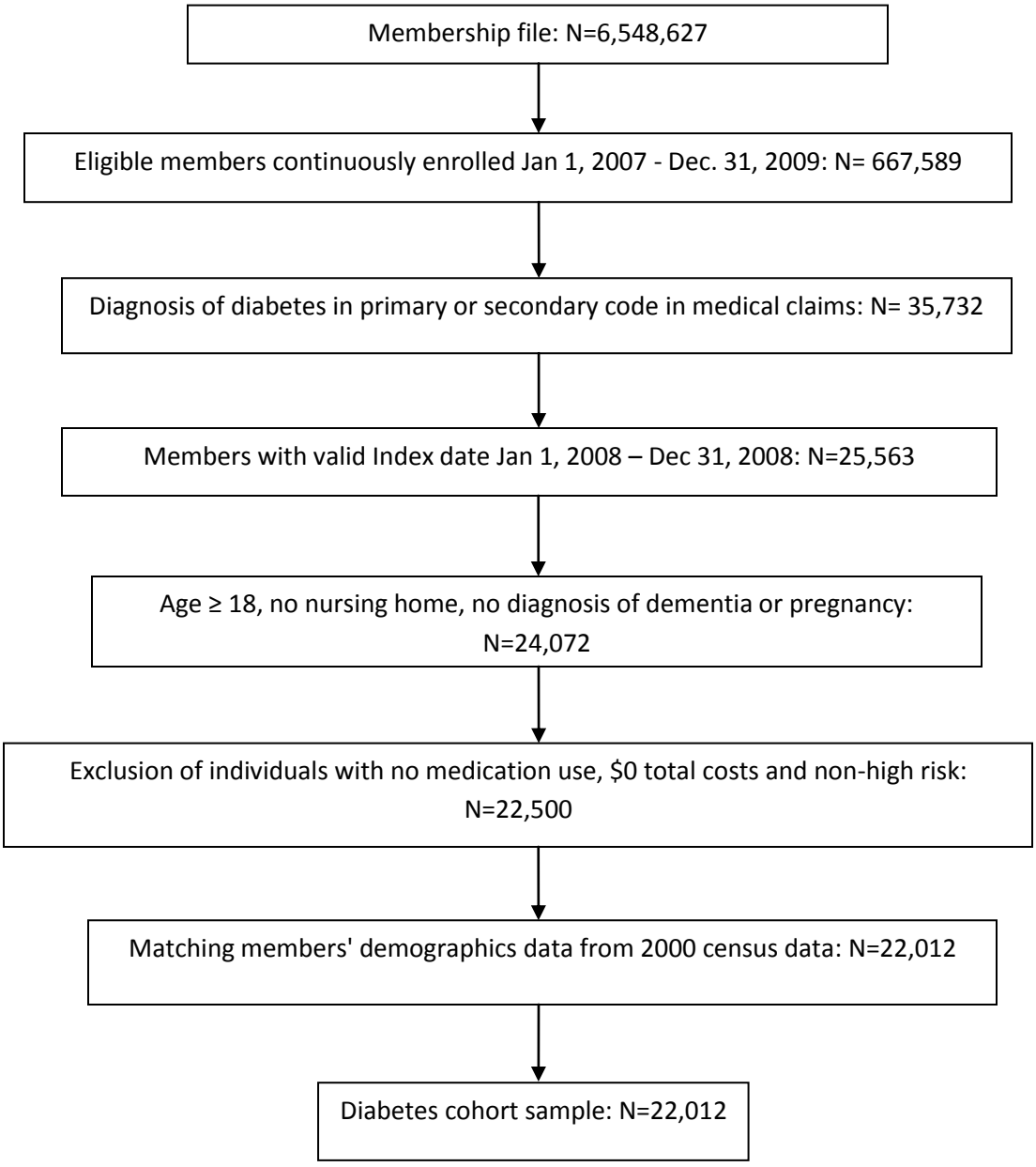


Figure 8: Hypertension Cohort Construction Flow Chart

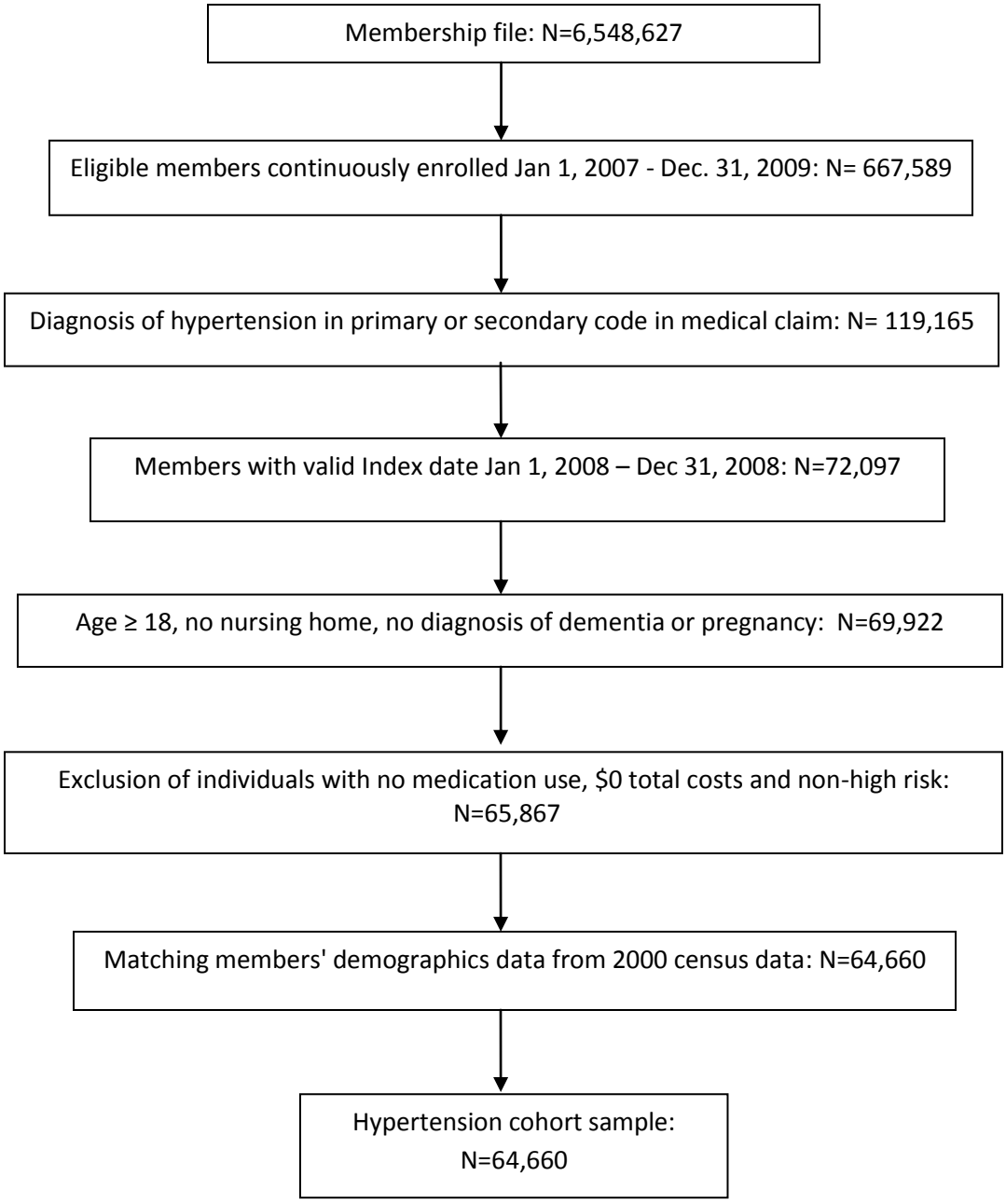
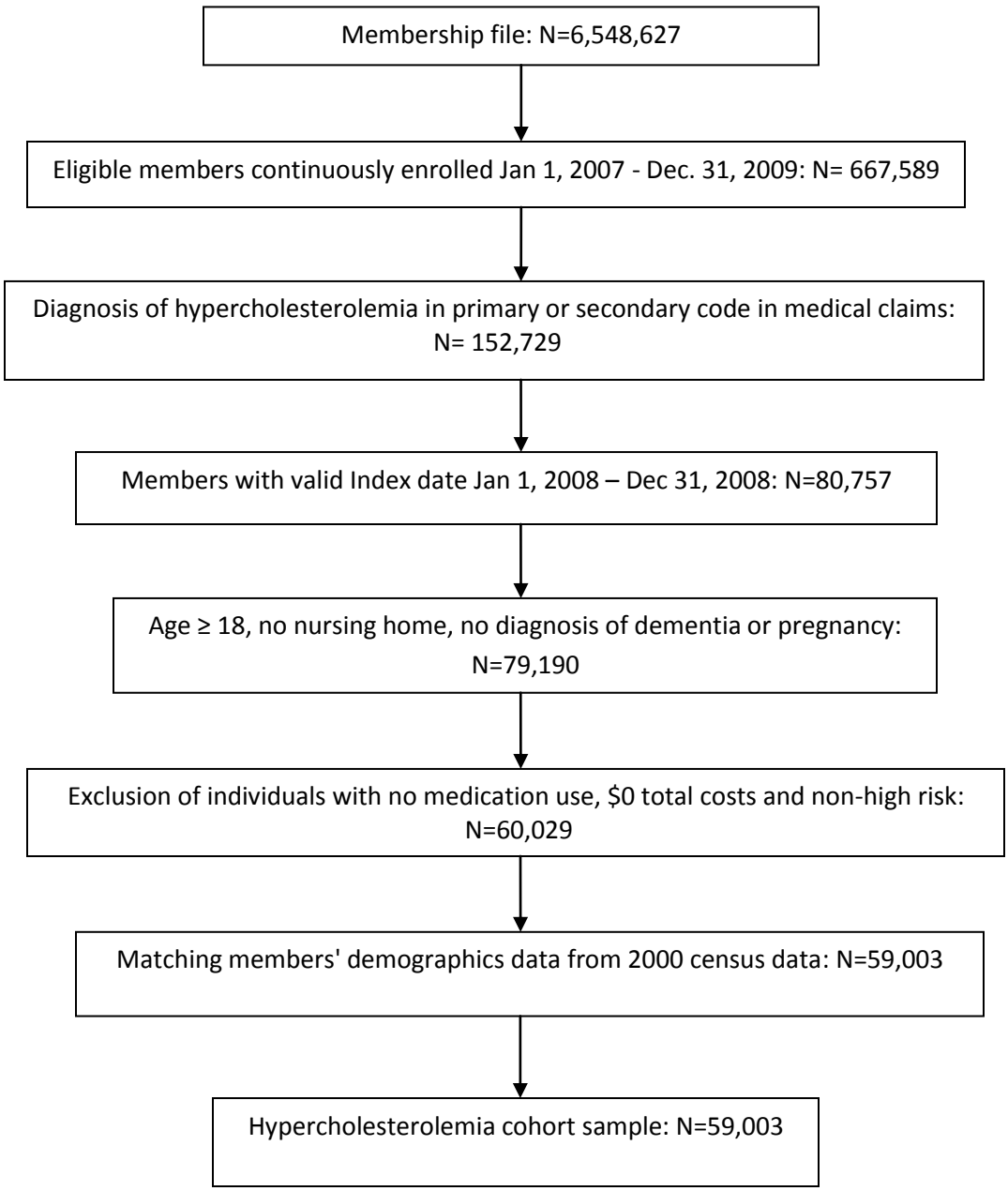


Figure 9: Hypercholesterolemia Cohort Construction Flow Chart



## 4.2 Descriptive Statistics of Study Variables

### 4.2.1 Descriptive Statistics of Dependent Variables

The dependent variables in this study included all-cause health care costs and condition-specific health care costs. This section presents the descriptive statistics for the two general types of costs.

#### 4.2.1.1 All-Cause Health Care Costs

All-cause health care costs (ACHC) included medical cost and pharmacy cost associated with any condition during the 12-month analysis period starting from an individual's index date. ACHC was analyzed in three parts: all-cause total cost, all-cause medical cost, and all-cause pharmacy cost. All-cause total cost was the sum of medical and pharmacy costs. In each study cohort, ACHC was calculated at the individual level. Tables 7, 8, and 9 show the descriptive statistics of all-cause total cost, medical cost, and pharmacy cost for the three disease cohorts respectively.

Table 7: Descriptive Statistics of Individual All-Cause Health Care Costs in Diabetes Cohort

| | All-cause total cost ($) | All-cause medical cost ($) | All-cause pharmacy cost ($) |
|---|---|---|---|
| Mean ± S.D. | 13,730 ± 29,351 | 9,752 ± 28,193 | 3,978 ± 4,503 |
| Minimum | 61 | 9 | 0 |
| 25% Quartile | 3,477 | 1,187 | 1,180 |
| Median | 6,763 | 2,851 | 2,889 |
| 75% Quartile | 13,508 | 7,837 | 5,316 |
| Maximum | 1,007,836 | 1,006,997 | 95,863 |

Table 8: Descriptive Statistics of Individual All-Cause Health Care Costs in Hypertension Cohort

| | All-cause total cost ($) | All-cause medical cost ($) | All-cause pharmacy cost ($) |
|---|---|---|---|
| Mean ± S.D. | 11,236 ± 26,473 | 8,794 ± 25,355 | 2,442±4,047 |
| Minimum | 53 | 0 | 0 |
| 25% Quartile | 2,018 | 927 | 396 |
| Median | 4,533 | 2,416 | 1,273 |
| 75% Quartile | 10,570 | 7,137 | 2,952 |
| Maximum | 1,231,426 | 1,230,185 | 143,108 |

Table 9: Descriptive Statistics of Individual All-Cause Health Care Costs in Hypercholesterolemia Cohort

| | All-cause total cost ($) | All-cause medical cost ($) | All-cause pharmacy cost ($) |
|---|---|---|---|
| Mean ± S.D. | 10,099 ± 20,719 | 7,430 ± 19,598 | 2,669 ± 3,933 |
| Minimum | 20 | 0 | 0 |
| 25% Quartile | 2,314 | 959 | 641 |
| Median | 4,727 | 2,367 | 1,592 |
| 75% Quartile | 9,956 | 6,273 | 3,301 |
| Maximum | 1,498,108* | 1,498,108* | 193,218 |

* The maximum all-cause total cost and all-cause medical cost are the same because the individual had no All-cause pharmacy costs.

With extremely large skewness and kurtosis, the distributions for all-cause total, medical and pharmacy costs were not normal, but positively skewed. Figures 10, 11, and 12 show the distributions of all-cause health care costs in each study cohort.

Figure 10: Distributions of All-Cause Health Care Costs in Diabetes Cohort

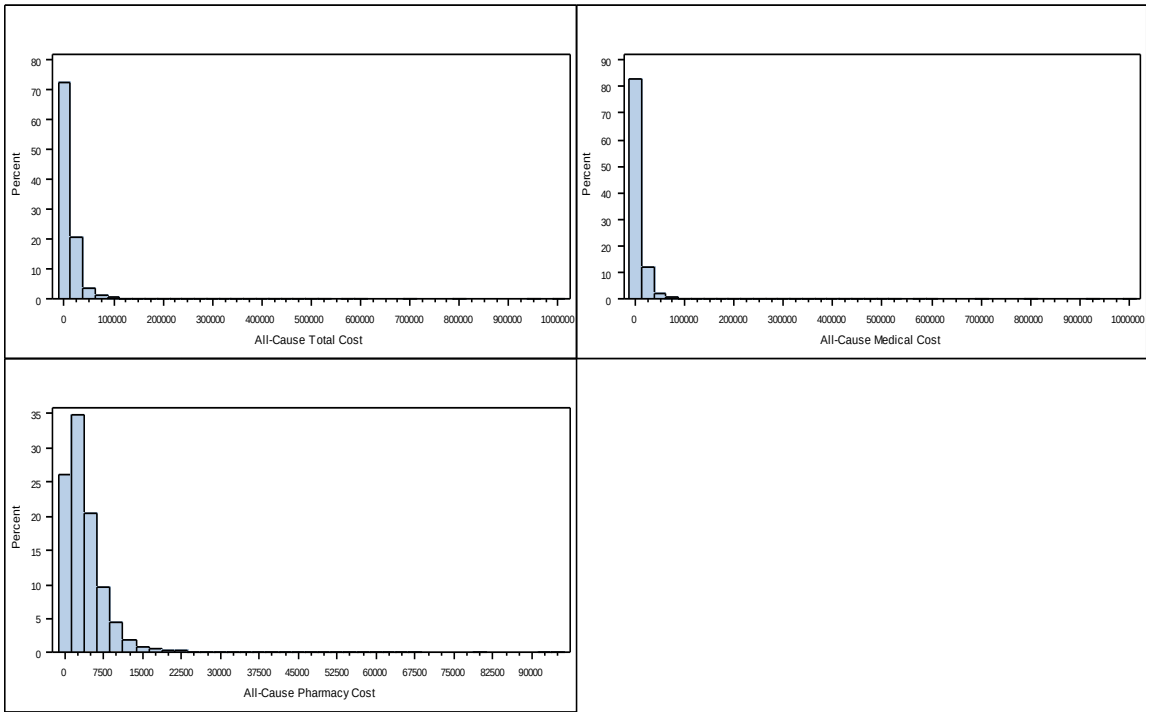


Figure 11: Distributions of All-Cause Health Care Costs in Hypertension Cohort

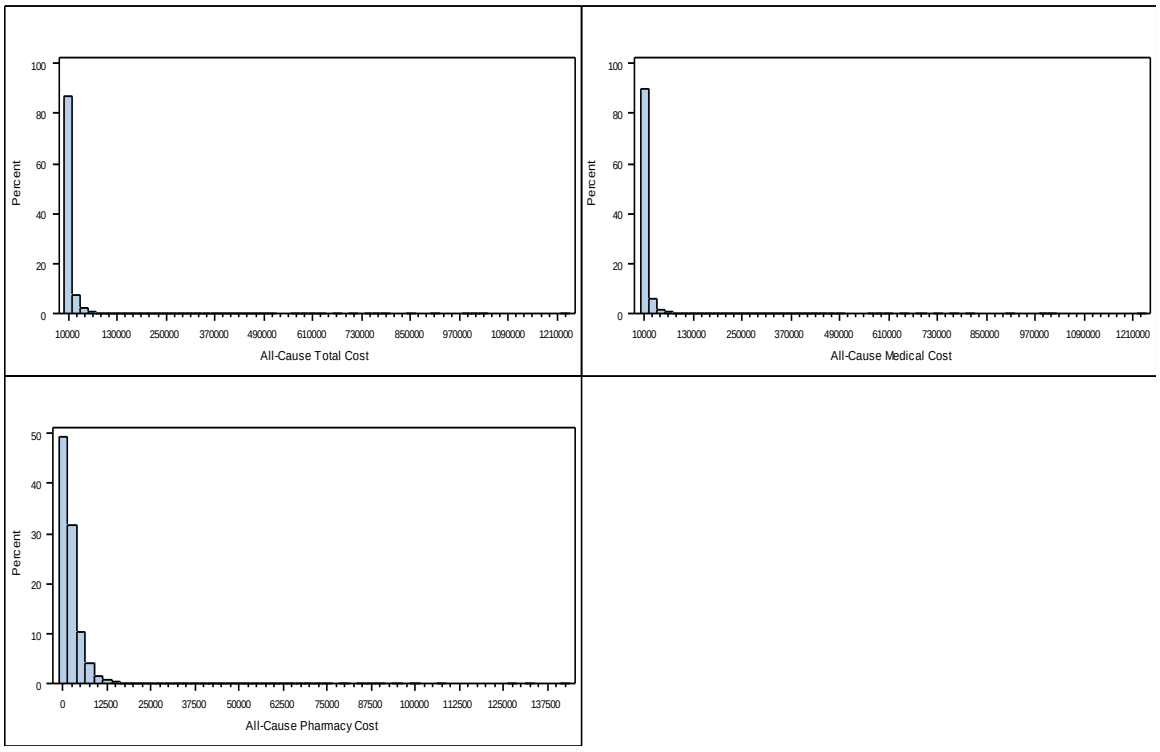
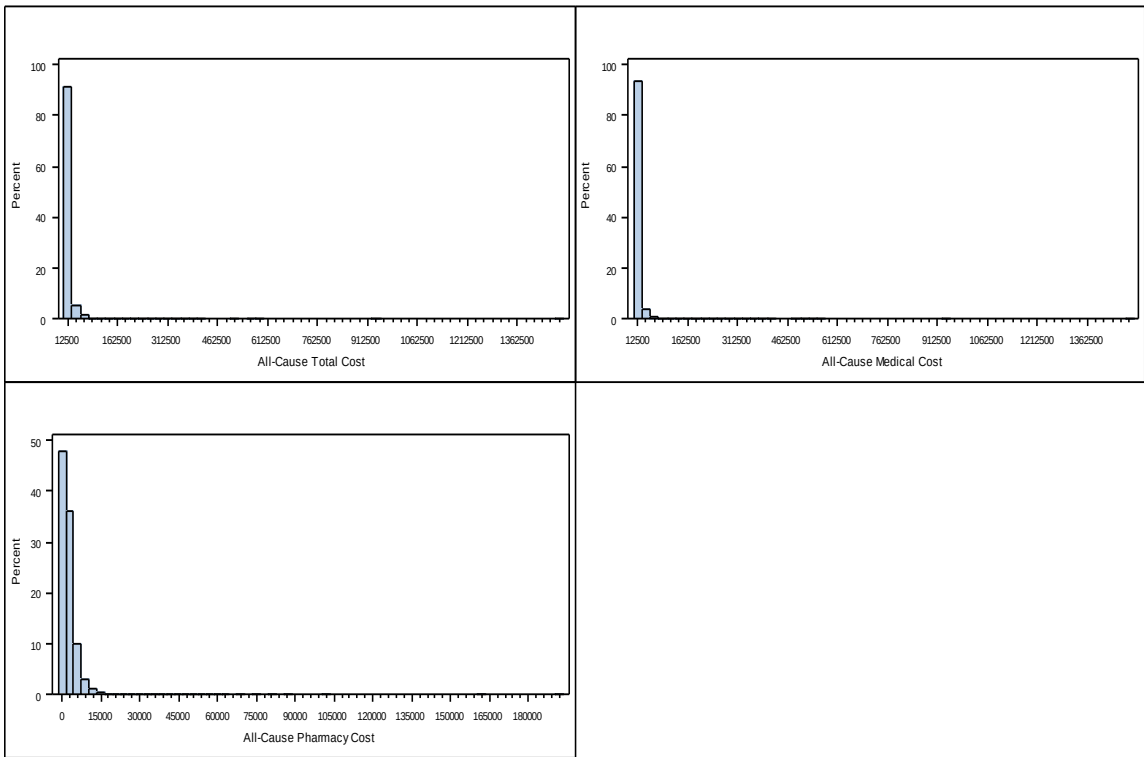


Figure 12: Distributions of All-Cause Health Care Costs in Hypercholesterolemia Cohort




#### 4.2.1.2 Condition-Specific Health care Costs

Condition-specific health care costs (CSHC) included medical cost and drug cost associated with treatment of the target condition during the 12-month analysis period starting from an individual's index date. CSHC was also analyzed in three parts: condition-specific total cost, condition-specific medical cost and condition-specific pharmacy cost. Condition-specific total cost was the sum of medical and pharmacy cost. In each study cohort, CSHC was calculated at the individual level.

The mean condition-specific total cost, medical cost, and pharmacy cost for diabetes, hypertension and hypercholesterolemia cohorts are presented in Tables 10, 11, and 12.

Table 10: Descriptive Statistics of Individual Condition-Specific Health Care Costs in Diabetes Cohort

| | Condition-specific total cost ($) | Condition-specific medical cost ($) | Condition-specific pharmacy cost ($) |
|---|---|---|---|
| Mean ± S.D. | 3,821 ± 15,566 | 2,569 ± 15,437 | 1,252 ± 1,666 |
| Minimum | 2 | 0 | 0 |
| 25% Quartile | 738 | 452 | 69 |
| Median | 1,760 | 809 | 348 |
| 75% Quartile | 3,790 | 1,481 | 2,129 |
| Maximum | 727,645* | 727,645* | 27,271 |

* The maximum condition-specific total cost and condition-specific medical cost are the same because the individual had no condition-specific pharmacy costs.

Table 11: Descriptive Statistics of Individual Condition-Specific Health Care Costs in Hypertension Cohort

| | Condition-specific total cost ($) | Condition-specific medical cost ($) | Condition-specific pharmacy cost ($) |
|---|---|---|---|
| Mean ± S.D. | 2,996 ± 14,417 | 2,621 ± 14,393 | 375 ± 496 |
| Minimum | 11 | 0 | 0 |
| 25% Quartile | 439 | 261 | 59 |
| Median | 815 | 462 | 138 |
| 75% Quartile | 1,607 | 925 | 543 |
| Maximum | 972,635 | 972,123 | 7,844 |

Table 12: Descriptive Statistics of Individual Condition-Specific Health Care Costs in Hypercholesterolemia Cohort

| | Condition-specific total cost ($) | Condition-specific medical cost ($) | Condition-specific pharmacy cost ($) |
|---|---|---|---|
| Mean ± S.D. | 2,348 ± 7,771 | 1,668 ± 7,704 | 679 ± 742 |
| Minimum | 3 | 0 | 0 |
| 25% Quartile | 530 | 248 | 116 |
| Median | 1,066 | 415 | 370 |
| 75% Quartile | 1,815 | 725 | 1,130 |
| Maximum | 512,553 | 512,528 | 7,653 |

The distributions for condition-specific total, medical and pharmacy costs were also positively skewed, which are shown in Figures 13, 14, and 15.

Figure 13: Distributions of Condition-Specific Health Care Costs in Diabetes Cohort

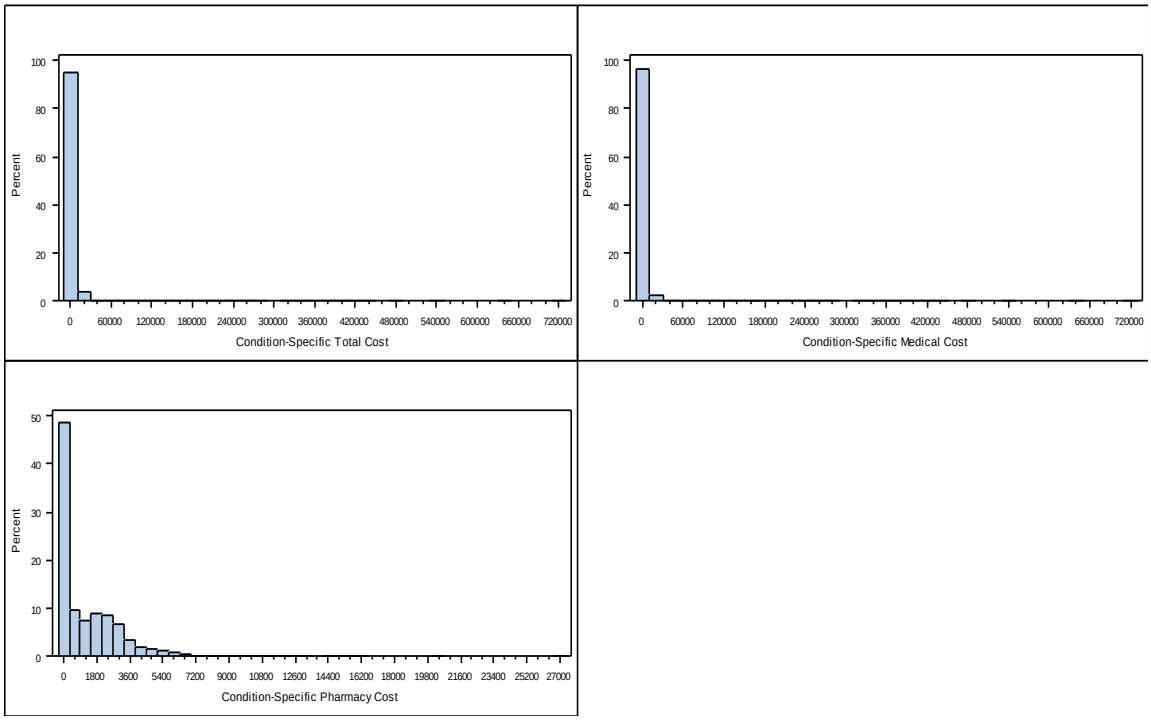


Figure 14: Distributions of Condition-Specific Health Care Costs in Hypertension Cohort

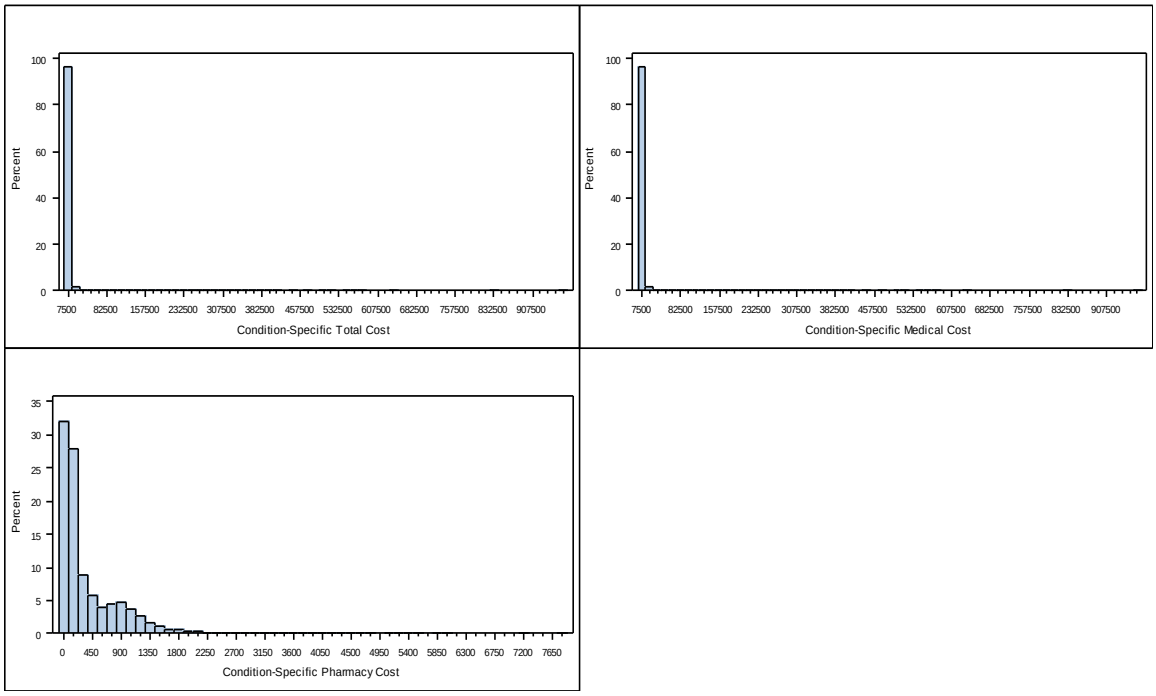
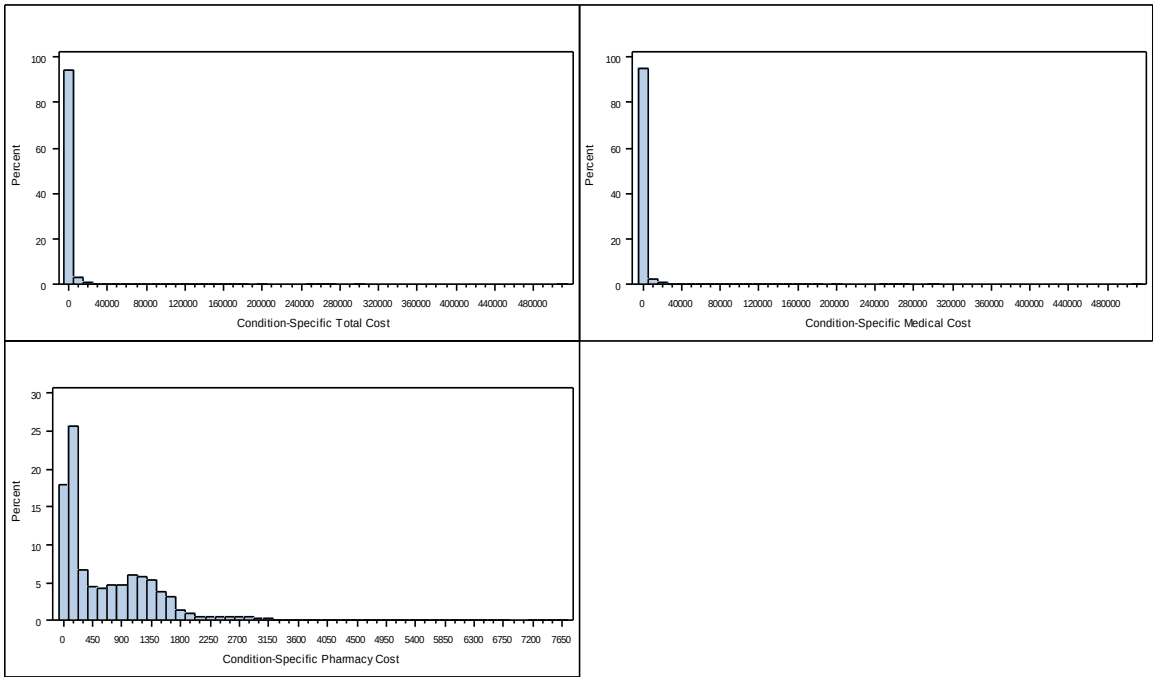


Figure 15: Distributions of Condition-Specific Health Care Costs in Hypercholesterolemia Cohort




### 4.2.2 Descriptive Statistics of Medication Adherence

Medication adherence was measured by Proportion of Days Covered (PDC), which was defined as the percentage of the number of days in the measurement period covered by prescription claims for the same medication or another in its drug class. In this study, the measurement period was 12 months from an individual's index date. PDC was calculated at the individual level. In the diabetes cohort, the mean PDC was 68.28% (S.D. = 36.20%); in the hypertension cohort, the mean PDC was 82.2% (S.D. = 26.72%); in the hypercholesterolemia cohort, the mean PDC was 68.77% (S.D. = 32.92%) (Table 13). The distribution of PDC in each cohort was not normal, which is shown in Figure 16, 17 and 18.

Table 13: Descriptive Statistics of PDC in Three Cohorts

| PDC | Diabetes | Hypertension | Hypercholesterolemia |
|---|---|---|---|
| Mean ± S.D. | 68.28% ± 36.20% | 82.20% ± 26.72% | 68.77% ± 32.92% |
| Minimum | 0 | 0 | 0 |
| 25% Quartile | 45.90% | 79.23% | 49.86% |
| Median | 86.34% | 94.54% | 83.84% |
| 75% Quartile | 97.27% | 98.63% | 95.07% |
| Maximum | 1 | 1 | 1 |

Figure 16: Distribution of PDC in Diabetes Cohort

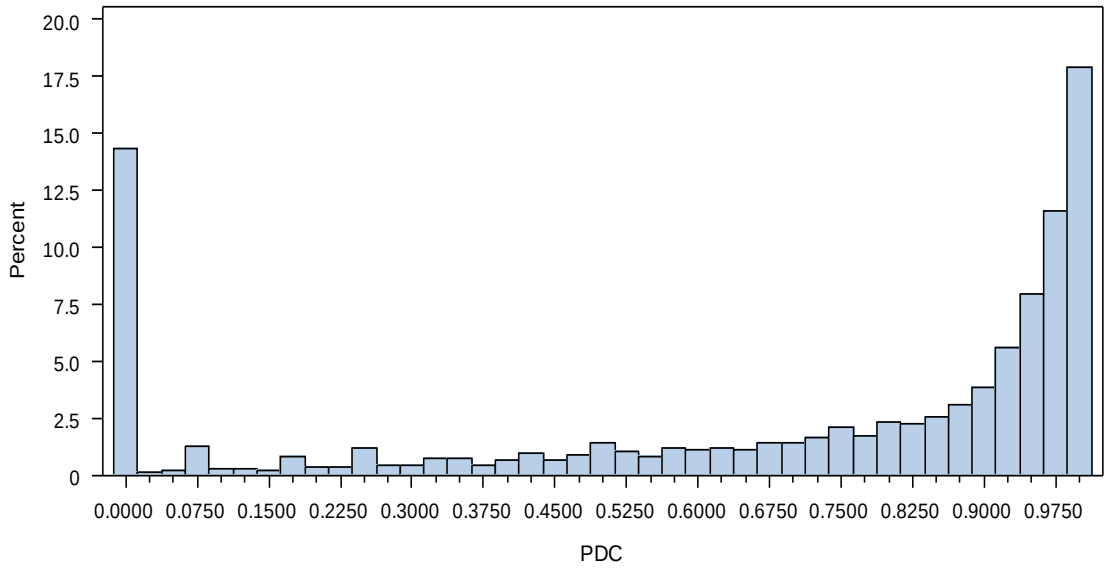


Figure 17: Distribution of PDC in Hypertension Cohort

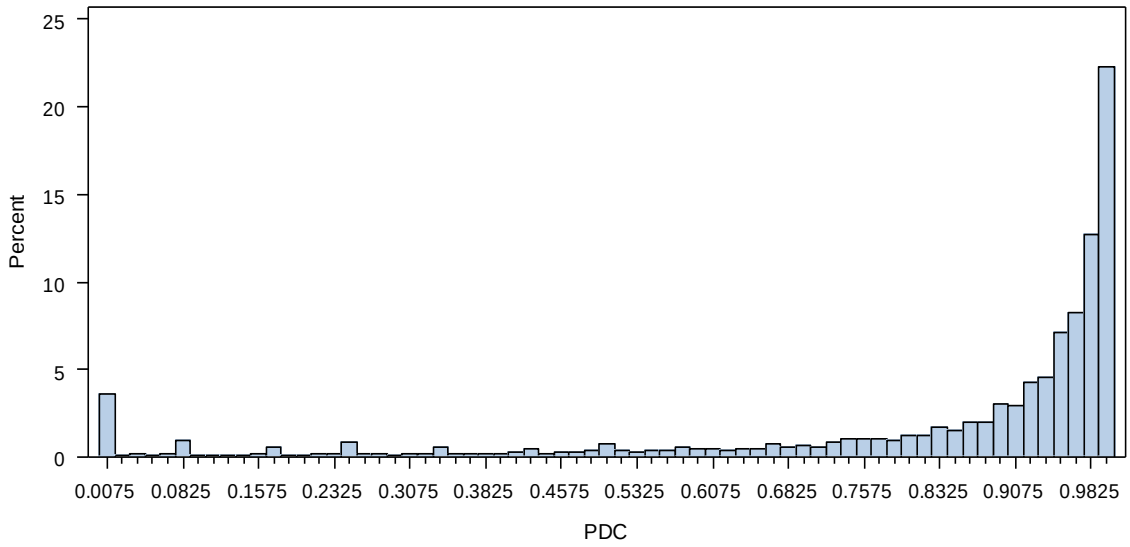
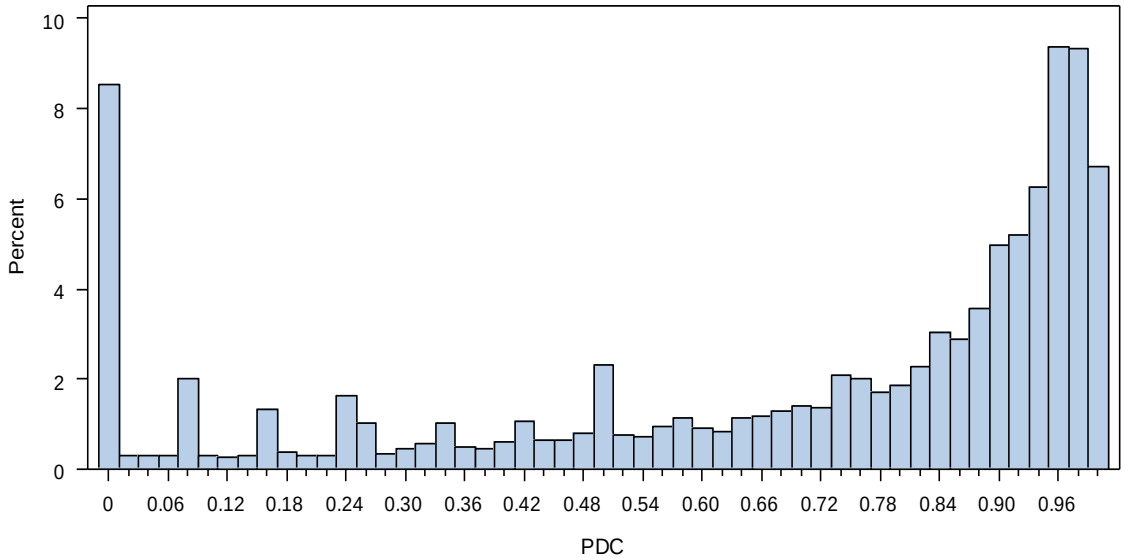



Figure 18: Distribution of PDC in Hypercholesterolemia Cohort



### 4.2.3 Descriptive Statistics of CDHP Enrollment

Enrollment in CDHPs in the study period was measured dichotomously. Table 14 shows the descriptive statistics of enrollment in CDHPs in each cohort. In the diabetes cohort, there were 3, 462 (15.7%) members who were enrolled in CDHPs; in the hypertension cohort, there were 12,925 (20.0%) members enrolled in CDHPs; in the hypercholesterolemia cohort, there were 12,890 (21.9%) members enrolled in CDHPs.

Table 14: Descriptive Statistics of CDHP Enrollment in Three Cohorts

| Continuous Enrolled in CDHP, n (%) | Diabetes | Hypertension | Hypercholesterolemia |
|---|---|---|---|
| Yes | 3,462 (15.7%) | 12,925 (20.0%) | 12,890 (21.9%) |
| No | 18,550 (84.3%) | 51,735 (80.0%) | 46,113 (78.1%) |

### 4.2.4 Descriptive Statistics of Control Variables

Control variables were indentified according to Andersen's behavioral model of health services utilization. They were classified into three categories as described in the methods section. Age, sex, generic use rate, use of mail-order service, enrollment in CDHP, high risk status, comorbidity, and presence of depression were measured at the individual level. Information on race, education and income was not available at the individual level, thus was measured using 2000 census statistics at the 5-digit zip code level based on individual's residence as reported in the enrollment file. Table 15 shows the descriptive statistics of control variables in diabetes, hypertension and hypercholesterolemia cohorts.

Table 15: Descriptive Statistics of Control Variables

| **Control Variables** | **Diabetes** | **Hypertension** | **Hypercholesterolemia** |
|---|---|---|---|
| **Predisposing Characteristics** | | | |
| Age, (mean ± S.D.) | 54.3 years ± 10.5 | 54.8 years ± 10.0 | 55.0 years ± 9.2 |
| Sex, n (%) | | | |
| Female | 9,312 (42.3%) | 30,032 (46.4%) | 24,789 (42.0%) |
| Male | 12,700 (57.7%) | 34,628 (53.6%) | 34,214 (58.0%) |
| Race (% White), (mean ± S.D.) | 89.6% ± 13.9% | 90.5% ± 12.8% | 91.0% ± 11.5% |
| Education (% Bachelor's Degree or above), (mean ± S.D.) | 23.1% ± 12.4% | 23.9% ± 13.0% | 25.3% ± 13.7% |
| **Enabling Resources** | | | |
| Median income, n (%) | | | |
| $0 - $50,000 | 14,922 (67.8%) | 42,362 (65.5%) | 36,281 (61.5%) |
| Greater than $50,000 | 7,090 (32.2%) | 22,298 (34.5%) | 22,722 (38.51%) |
| Generic Drug Use rate, (mean ± S.D.) | 53.2% ± 43.2% | 81.0% ± 34.4% | 43.6% ± 45.9% |
| Use of Mail-Order Service, n (%) | | | |
| Yes | 12,374 (56.2%) | 33,194 (51.3%) | 31,413 (53.2%) |
| No | 9,638 (43.8%) | 31,466 (48.7%) | 27,590 (46.8%) |
| **Need Factors** | | | |
| High risk, n (%) | | | |
| Yes | 3,050 (13.9%) | 18,851 (29.2%) | 20,362 (34.5%) |
| No | 18,962 (86.1%) | 45,809 (70.8%) | 38,641 (65.5%) |
| Depression and bipolar disorder, n (%) | | | |
| Yes | 1,446 (6.6%) | 4,093 (6.3%) | 3,859 (6.5%) |
| No | 20,566 (93.4%) | 60,567 (93.7%) | 55,144 (93.5%) |
| Comorbidity (Charlson Index Score), (mean ± S.D.) | 1.8 ± 1.5 | 0.7 ± 1.3 | 0.7 ± 1.2 |

## 4.3 Analysis Results of Generalized Linear Modeling with Gamma Log Link

The generalized linear model (GLM) with gamma log link was used to examine all hypotheses. First, the results of the GLM with gamma log link in each cohort are presented. Second, the assumptions of this model are examined.

### 4.3.1 Results of GLM with Gamma Log Link in Diabetes Cohort

The dependent variables are all-cause health care costs (medical, pharmacy and total), and condition-specific health care costs (medical, pharmacy and total). An independent model was constructed for each dependent variable. Each model included the same set of independent variables and control variables.

#### 4.3.1.1 Results of All-Cause Costs

Tables 16a and 16b summarize the results of all-cause health care costs from the GLM using gamma with log link in the diabetes cohort. Table 16a presents the main effect model. The coefficient of PDC for all-cause medical cost is -0.059 (p-value=0.022), the coefficient of PDC for all-cause pharmacy cost is 1.317 (p-value<0.001), and the coefficient of PDC for all-cause total cost is 0.335 (p-value<0.001). All three coefficients are statistically significant. This suggests that with all other variables held constant, when PDC increases by 1 unit (from 0% to 100%), all-cause medical cost will decrease by 5.9%, all-cause pharmacy cost will increase by 131.7%, and all-cause total cost will increase by 33.5%.

The coefficients of CDHP for all-cause medical cost is -0.004 (p-value=0.863), which is not statistically significant. However, for all-cause pharmacy and total costs, the coefficients of CDHP are -0.161 (p-value=0.0096) and -0.052 (p-value<0.001) respectively, which are statistically significant. This means that with all other variables

held constant, continuous enrollment in CDHP is associated with the decrease in all-cause pharmacy cost by 16.1%, and the decrease in all-cause total cost by 5.2%.

In addition to PDC and CDHP, most control variables are also significant predictors of all-cause medical, pharmacy and total costs. All-cause costs will increase with the increase in age and percentage of white. Male generally have lower all-cause costs. As the rate of generic drug use increases, all-cause costs will decrease. Use of mail-order service, higher Charlson index score and presence of depression or bipolar disorder are associated with increased all-cause costs. Median income > $50,000 is associated with increased pharmacy cost, but associated with decreased medical and total costs.

Table 16a: The GLM Gamma Log Link Main Effect Results for All-Cause Costs in Diabetes Cohort

| | All-Cause Health Care Costs | | | | | |
|---|---|---|---|---|---|---|
| Variables | Medical Cost | | Pharmacy Cost | | Total Cost | |
| | Coefficient | P-value | Coefficient | P-value | Coefficient | P-value |
| **PDC** | **-0.059*** | **0.022** | **1.317*** | **< 0.001** | **0.335*** | **< 0.001** |
| **Enrollment in CDHP (yes/no)** | **-0.004** | **0.863** | **-0.161*** | **0.0096** | **-0.052*** | **< 0.001** |
| Age | 0.014* | <0.001 | 0.007* | < 0.001 | 0.011* | <0.001 |
| Sex (male/female) | -0.106* | <0.001 | -0.080* | < 0.001 | -0.088* | < 0.001 |
| Race (% white) | 0.329* | <0.001 | 0.274* | < 0.001 | 0.277* | < 0.001 |
| Education (% Bachelor degree or above) | -0.01 | 0.931 | 0.306* | < 0.001 | 0.079 | 0.231 |
| Median Household Income (>$50,000) | -0.089* | <0.001 | 0.044* | < 0.001 | -0.053* | < 0.001 |
| Generic drug use rate | -0.170* | <0.001 | -0.825* | < 0.001 | -0.375* | < 0.001 |
| Use of mail-order service | 0.069* | <0.001 | 0.172* | < 0.001 | 0.092 | < 0.001 |
| High Risk (yes/no) | 0.047 | 0.098 | -0.103* | < 0.001 | -0.001 | 0.982 |
| Comorbidity (Charlson Index score) | 0.280* | <0.001 | 0.162* | < 0.001 | 0.246* | < 0.001 |
| Depression or bipolar disorder (yes/no) | 0.439* | <0.001 | 0.513* | < 0.001 | 0.450* | < 0.001 |

* denotes being statistically significant

Table 16b presents the interaction effect model. The interaction of PDC and CDHP enrollment is associated with increased all-cause medical cost, pharmacy cost and total cost. With enrollment in CDHP, increasing PDC from 0 to 100% is associated with 16.7% increase in medical cost, 18.5% increase in pharmacy cost, and 10.5% increase in total cost. By contrast, the interaction between PDC and generic use rate is associated with decreased all-cause health care costs. When both PDC and the rate of generic drug use increase from 0 to 100%, medical cost, pharmacy cost and total cost will decrease by 78.0%, 81.8% and 89.2% respectively. Interaction between PDC and mail order service use also has a significant and negative effect on all-cause health care costs. CDHP*generic use rate and generic use rate*high risk have negative effects on costs, but these effects are not significant on all costs.

Table 16b: The GLM Gamma Log Link Interaction Effect Results for All-Cause Costs in Diabetes Cohort

| | All-Cause Health Care Costs | | | | | |
|---|---|---|---|---|---|---|
| Variables | Medical Cost | | Pharmacy Cost | | Total Cost | |
| | Coefficient | P-value | Coefficient | P-value | Coefficient | P-value |
| PDC | 0.272* | <0.001 | 1.868* | < 0.001 | 0.757* | < 0.001 |
| Enrollment in CDHP (yes/no) | -0.175* | 0.002 | -0.183* | < 0.001 | -0.166* | < 0.001 |
| Age | 0.016* | <0.001 | 0.008* | < 0.001 | 0.013* | <0.001 |
| Sex (male/female) | -0.104* | <0.001 | -0.076* | < 0.001 | -0.087* | < 0.001 |
| Race (% white) | 0.361* | <0.001 | 0.310* | < 0.001 | 0.314* | < 0.001 |
| Education (% Bachelor degree or above) | -0.021 | 0.807 | 0.311* | < 0.001 | 0.072 | 0.277 |
| Median Household Income (>$50,000) | -0.088* | <0.001 | 0.049* | 0.003 | -0.051* | 0.003 |
| Generic drug use rate | 0.345* | <0.001 | -0.277* | < 0.001 | 0.201* | < 0.001 |
| Use of mail-order service | 0.123* | 0.002 | 0.502* | < 0.001 | 0.191* | < 0.001 |
| High Risk | 0.243* | <0.001 | -0.072 | 0.126 | 0.207* | < 0.001 |

| | | | | | | |
|---|---|---|---|---|---|---|
| (yes/no) | | | | | | |
| Comorbidity (Charlson Index score) | 0.274* | <0.001 | 0.160* | < 0.001 | 0.239* | < 0.001 |
| Depression or bipolar disorder (yes/no) | 0.444* | <0.001 | 0.514* | < 0.001 | 0.454* | < 0.001 |
| **PDC*CDHP** | **0.167*** | **0.017** | **0.185*** | **< 0.001** | **0.105** | **0.057** |
| **PDC*Generic use rate** | **-0.780*** | **<0.001** | **-0.818*** | **< 0.001** | **-0.892*** | **< 0.001** |
| **PDC*High risk** | **-0.108** | **0.177** | **-0.087** | **0.142** | **-0.216*** | **< 0.001** |
| **PDC*Mail order** | **-0.136*** | **0.009** | **-0.491*** | **< 0.001** | **-0.176*** | **< 0.001** |
| **CDHP*High risk** | **-0.052** | **0.465** | **0.036** | **0.496** | **0.013** | **0.815** |
| **CDHP*Generic use rate** | **-0.027** | **0.644** | **-0.228*** | **< 0.001** | **-0.033** | **0.482** |
| **CDHP*Mail order** | **0.140*** | **0.003** | **0.042** | **0.238** | **0.112*** | **0.002** |
| **Generic use rate*High risk** | **-0.248*** | **<0.001** | **-0.021** | **0.673** | **-0.112** | **0.023** |
| **Mail order*High risk** | **-0.035** | **0.493** | **0.042** | **0.266** | **-0.032** | **0.421** |
| **Generic use rate*Mail order** | **0.032** | **0.464** | **-0.031** | **0.354** | **0.002** | **0.948** |

* denotes being statistically significant

#### 4.3.1.2 Results of Diabetes-Specific Costs

Tables 17a and 17b summarize the results of diabetes-specific health care costs from gamma log link model for main effect and interaction effect respectively. Table 17a presents the main effect model. The coefficient of PDC for diabetes-specific medical cost is 0.033 (p-value<0.001), the coefficient of PDC for diabetes-specific pharmacy cost is 4.626 (p-value<0.001), and the coefficient of PDC for diabetes-specific total cost is 1.135 (p-value<0.001). All the three coefficients are statistically significant. This suggests that with all other variables held constant, when PDC increases from 0% to 100%, diabetes-specific medical cost will increase by 3.3%, diabetes-specific pharmacy cost will increase by 462.6%, and diabetes-specific total cost will increase by 113.5%.

The coefficients of CDHP for diabetes-specific medical cost is -0.005(p-value=0.863), which is not statistically significant. However, for diabetes-specific pharmacy and total costs, the coefficients of CDHP are -0.107(p-value<0.001) and -0.040(p-value=0.031) respectively, which are statistically significant. This means that with all other variables held constant, continuous enrollment in CDHP is associated with the decrease in diabetes-specific pharmacy cost by 10.7%, and the decrease in diabetes-specific total cost by 4.0%.

In addition, many of the control variables have significant effects on diabetes-specific costs. Increase in age, percentage of white, percentage of members with a Bachelor's degree or above, and generic drug use rate will all decrease medical, pharmacy and total costs. Male members are associated with decreased medical and total costs. Being in high risk group, higher Charlson index score and presence of depression or bipolar disorder are all associated with increased medical, pharmacy and total costs. Income > $50,000 is associated with increased total cost. Use of mail-order service will increase pharmacy cost.

Table 17a: The GLM Gamma Log Link Main Effect Results for Condition-Specific Costs in Diabetes Cohort

| | Diabetes-Specific Health Care Costs | | | | | |
|---|---|---|---|---|---|---|
| Variables | Medical Cost | | Pharmacy Cost | | Total Cost | |
| | Coefficient | P-value | Coefficient | P-value | Coefficient | P-value |
| **PDC** | **0.033*** | **<0.001** | **4.626*** | **< 0.001** | **1.135*** | **< 0.001** |
| **Enrollment in CDHP (yes/no)** | **-0.005** | **0.836** | **-0.107*** | **< 0.001** | **-0.040*** | **0.031** |
| Age | -0.008* | <0.001 | -0.017* | < 0.001 | -0.008* | <0.001 |
| Sex (male/female) | -0.117* | <0.001 | 0.022 | 0.176 | -0.066* | < 0.001 |
| Race (% white) | -0.236* | <0.001 | -0.433* | < 0.001 | -0.266* | < 0.001 |
| Education (% Bachelor degree or above) | -0.474* | <0.001 | -0.184* | 0.021 | -0.401* | <0.001 |
| Median Household Income (>$50,000) | -0.024 | 0.235 | 0.013 | 0.544 | 0.044* | 0.011 |
| Generic drug use rate | -0.375* | <0.001 | -2.09* | < 0.001 | -0.849* | < 0.001 |
| Use of mail-order service | 0.013 | 0.433 | 0.047* | 0.004 | 0.019 | 0.177 |
| High Risk (yes/no) | 0.467* | <0.001 | 0.312* | < 0.001 | 0.395* | <0.001 |
| Comorbidity (Charlson Index score) | 0.279* | <0.001 | 0.036* | < 0.001 | 0.237* | < 0.001 |
| Depression or bipolar disorder (yes/no) | 0.147* | <0.001 | 0.037 | 0.262 | 0.096* | < 0.001 |

* denotes being statistically significant

Table 17b presents the interaction model. The interaction effect of PDC and CDHP enrollment on diabetes-related health care costs is not significant. The interaction between PDC and generic use rate is significantly associated with decreased all-cause health care costs. When both PDC and generic drug use rate increase from 0 to 100%, medical cost, pharmacy cost and total cost will decrease by 108.8%, 157.3% and 149.6% respectively. In addition, the interaction of PDC and high risk is related to significantly increased medical, pharmacy and total cost. Among other significant interactions, CDHP*mail order and mail order*high risk both have positive effect on diabetes-related costs. Other interaction terms have mixed effects.

Table 17b: The GLM Gamma Log Link Interaction Effect Results for Condition-Specific Costs in Diabetes Cohort

| | Diabetes-Specific Health Care Costs | | | | | |
|---|---|---|---|---|---|---|
| Variables | Medical Cost | | Pharmacy Cost | | Total Cost | |
| | Coefficient | P-value | Coefficient | P-value | Coefficient | P-value |
| PDC | 0.934* | <0.001 | 7.450* | < 0.001 | 2.147* | < 0.001 |
| Enrollment in CDHP (yes/no) | 0.013 | 0.800 | -0.214* | < 0.001 | -0.064 | 0.122 |
| Age | -0.004* | <0.001 | -0.015* | < 0.001 | -0.003* | <0.001 |
| Sex (male/female) | -0.108* | <0.001 | 0.018 | 0.236 | -0.060* | < 0.001 |
| Race (% white) | -0.092 | 0.099 | -0.296* | < 0.001 | -0.070 | 0.127 |
| Education (% Bachelor degree or above) | -0.498* | <0.001 | -0.142 | 0.053 | -0.441* | <0.001 |
| Median Household Income (>$50,000) | -0.017 | 0.405 | 0.007 | 0.728 | 0.028 | 0.090 |
| Generic drug use rate | 0.459* | <0.001 | 0.666* | < 0.001 | 0.393* | < 0.001 |
| Use of mail-order service | -0.106* | 0.004 | 0.242* | < 0.001 | -0.129 | < 0.001 |
| High Risk (yes/no) | 1.163* | <0.001 | 1.025* | < 0.001 | 1.259* | <0.001 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Comorbidity (Charlson Index score) | 0.259* | <0.001 | 0.023* | < 0.001 | 0.206* | < 0.001 |
| Depression or bipolar disorder (yes/no) | 0.155* | <0.001 | 0.009 | 0.766 | 0.116* | < 0.001 |
| **PDC*CDHP** | **0.048** | **0.477** | **0.053** | **0.482** | **-0.045** | **0.420** |
| **PDC*Generic use rate** | **-1.333*** | **<0.001** | **-4.864*** | **< 0.001** | **-2.149*** | **< 0.001** |
| **PDC*High risk** | **-1.088*** | **<0.001** | **-1.573*** | **< 0.001** | **-1.496*** | **< 0.001** |
| **PDC*Mail order** | **0.087** | **0.079** | **-0.431*** | **< 0.001** | **0.131*** | **0.001** |
| **CDHP*High risk** | **-0.149*** | **0.023** | **0.061** | **0.335** | **-0.072** | **0.187** |
| **CDHP*Generic use rate** | **-0.098** | **0.083** | **0.029** | **0.633** | **-0.108*** | **0.025** |
| **CDHP*Mail order** | **0.087*** | **0.044** | **0.094*** | **0.025** | **0.066** | **0.064** |
| **Generic use rate*High risk** | **-0.021** | **0.711** | **0.752*** | **< 0.001** | **0.366*** | **< 0.001** |
| **Mail order*High risk** | **0.155*** | **0.001** | **0.122*** | **0.006** | **0.077*** | **0.048** |
| **Generic use rate*Mail order** | **0.028** | **0.479** | **0.072** | **0.114** | **0.038** | **0.270** |

* denotes being statistically significant

### 4.3.2 Results of GLM with Gamma Log Link in Hypertension Cohort

The dependent variables are all-cause health care costs (medical, pharmacy and total), and condition-specific health care costs (medical, pharmacy and total). An independent model was constructed for each dependent variable. Each model included the same set of independent variables.

#### 4.3.2.1 Results of All-Cause Costs

Tables 18a and 18b summarize the results of all-cause health care costs in hypertension cohort. Table 18a presents the main effect model. The coefficients of PDC for all-cause medical cost, pharmacy cost and total cost are -0.179 (p-value<0.001), 1.097 (p-value<0.001), and 0.061 (p-value<0.001) respectively. All the three coefficients are statistically significant. This suggests that with all other variables held constant, when PDC increases by 1 unit (from 0% to 100%), all-cause medical cost will decrease by 17.9%, all-cause pharmacy cost will increase by 109.7%, and all-cause total cost will increase by 6.1%.

The coefficients of CDHP for all-cause medical cost, pharmacy cost and total cost are -0.041 (p-value=0.002), -0.305 (p-value<0.001), and -0.092 (p-value<0.001) respectively. These coefficients are statistically significant. This means that when all other variables are held constant, continuous enrollment in CDHP is associated with the reduction in medical cost by 4.1%, in pharmacy cost by 30.5%, and in total cost by 9.2%.

For the control variables, costs will increase with an increase in age and percentage of white. Male gender generally decreases costs. While higher percentage of degree earned increases pharmacy cost, it is associated with decreased medical cost. Median income > $50,000 decreases both medical and total costs. As the rate of generic drug use increases, medical cost increases, but pharmacy cost decreases. Use of mail-order service, high risk,

higher Charlson index score and presence of depression or bipolar disorder are associated with increased all-cause costs.

Table 18a: The GLM Gamma Log Link Main Effect Results for All-Cause Costs in Hypertension Cohort

| | All-Cause Health Care Costs | | | | | |
|---|---|---|---|---|---|---|
| Variables | Medical Cost | | Pharmacy Cost | | Total Cost | |
| | Coefficient | P-value | Coefficient | P-value | Coefficient | P-value |
| **PDC** | **-0.179*** | **<0.001** | **1.097*** | **< 0.001** | **0.061*** | **< 0.001** |
| **Enrollment in CDHP (yes/no)** | **-0.041*** | **0.002** | **-0.305*** | **<0.001** | **-0.092*** | **< 0.001** |
| Age | 0.014* | <0.001 | 0.006* | < 0.001 | 0.012* | <0.001 |
| Sex (male/female) | -0.072* | <0.001 | -0.110* | < 0.001 | -0.081* | < 0.001 |
| Race (% white) | 0.484* | <0.001 | 0.177* | < 0.001 | 0.424* | < 0.001 |
| Education (% Bachelor degree or above) | -0.149* | 0.002 | 0.233* | < 0.001 | -0.073 | 0.080 |
| Median Household Income (>$50,000) | -0.063* | <0.001 | 0.008 | 0.472 | -0.046* | < 0.001 |
| Generic drug use rate | 0.157* | <0.001 | -0.530* | < 0.001 | -0.008 | 0.572 |
| Use of mail-order service | 0.105* | <0.001 | 0.214* | < 0.001 | 0.123* | < 0.001 |
| High Risk (yes/no) | 0.174* | 0.098 | 0.457* | < 0.001 | 0.235* | 0.982 |
| Comorbidity (Charlson Index score) | 0.286* | <0.001 | 0.218* | < 0.001 | 0.272* | < 0.001 |
| Depression or bipolar disorder (yes/no) | 0.430* | <0.001 | 0.728* | < 0.001 | 0.486* | < 0.001 |

* denotes being statistically significant

Table 18b presents the model with interaction terms. The interaction of PDC and CDHP enrollment is associated with increased all-cause healthcare costs. With enrollment in CDHP, increasing PDC from 0 to 100% is associated with 28.9% increase in medical cost, 38.1% increase in pharmacy cost, and 24.6% increase in total cost. The interaction between PDC and generic use rate is associated with decreased all-cause costs. Increasing both PDC and the rate of generic drug use increase from 0 to 100% is associated with decreased medical cost, pharmacy cost and total cost, by 22.4%, 38.0% and 24.6% respectively. Besides, several other interactions have significant effects on all-cause costs. PDC*mail order, CDHP*mail order, CDHP*generic use rate and generic use rate*mail order are negatively associated with costs, while CDHP*high risk and generic use rate*high risk are positively associated with costs.

Table 18b: The GLM Gamma Log Link Interaction Effect Results for All-Cause Costs in Hypertension Cohort

| | All-Cause Health Care Costs | | | | | |
|---|---|---|---|---|---|---|
| Variables | Medical Cost | | Pharmacy Cost | | Total Cost | |
| | Coefficient | P-value | Coefficient | P-value | Coefficient | P-value |
| PDC | -0.120* | 0.006 | 1.505* | < 0.001 | 0.223* | < 0.001 |
| Enrollment in CDHP (yes/no) | -0.187* | <0.001 | -0.589* | <0.001 | -0.228* | < 0.001 |
| Age | 0.014* | <0.001 | 0.006* | < 0.001 | 0.012* | <0.001 |
| Sex (male/female) | -0.073* | <0.001 | -0.109* | < 0.001 | -0.081* | < 0.001 |
| Race (% white) | 0.488* | <0.001 | 0.170* | < 0.001 | 0.424* | < 0.001 |
| Education (% Bachelor degree or above) | -0.156* | 0.001 | 0.242* | < 0.001 | -0.081 | 0.054 |
| Median Household Income (>$50,000) | -0.061* | <0.001 | 0.014 | 0.200 | -0.044* | < 0.001 |
| Generic drug use rate | 0.285* | <0.001 | -0.326* | < 0.001 | 0.191 | < 0.001 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Use of mail-order service | 0.200* | <0.001 | 0.824* | < 0.001 | 0.286* | < 0.001 |
| High Risk (yes/no) | 0.002 | 0.960 | 0.112* | 0.001 | 0.037* | 0.279 |
| Comorbidity (Charlson Index score) | 0.286* | <0.001 | 0.216* | < 0.001 | 0.272* | < 0.001 |
| Depression or bipolar disorder (yes/no) | 0.427* | <0.001 | 0.018* | < 0.001 | 0.484* | < 0.001 |
| **PDC*CDHP** | **0.289*** | **<0.001** | **0.381*** | **<0.001** | **0.246*** | **< 0.001** |
| **PDC*Generic use rate** | **-0.224*** | **<0.001** | **-0.380*** | **<0.001** | **-0.332*** | **< 0.001** |
| **PDC*High risk** | **0.041** | **0.335** | **0.063** | **0.084** | **0.053** | **0.151** |
| **PDC*Mail order** | **-0.025** | **0.537** | **-0.687*** | **<0.001** | **-0.108*** | **0.002** |
| **CDHP*High risk** | **0.075*** | **0.014** | **0.178*** | **<0.001** | **0.087*** | **0.001** |
| **CDHP*Generic use rate** | **-0.075** | **0.071** | **-0.104*** | **0.003** | **-0.054** | **0.126** |
| **CDHP*Mail order** | **-0.088*** | **0.001** | **0.025** | **0.254** | **-0.075*** | **0.001** |
| **Generic use rate*High risk** | **0.202*** | **<0.001** | **0.330*** | **<0.001** | **0.214*** | **< 0.001** |
| **Mail order*High risk** | **-0.053*** | **0.021** | **0.016** | **0.422** | **-0.040*** | **0.041** |
| **Generic use rate*Mail order** | **-0.050** | **0.128** | **-0.058*** | **0.034** | **-0.057*** | **0.040** |

* denotes being statistically significant

#### 4.3.2.2 Results of Hypertension-Specific Costs

Tables 19a and 19b summarize the results of hypertension-specific health care costs in main effect model and interaction effect model respectively. Table 19a shows the results of main effect mode. The coefficients of PDC for medical cost, pharmacy cost and total cost are -0.193 (p-value<0.001), 3.342 (p-value<0.001), and 0.149 (p-value<0.001) respectively, which are all statistically significant. This suggests that with all other variables held constant, when PDC increases by 1 unit (from 0% to 100%), medical cost will decrease by 19.3%, pharmacy cost will increase by 334.2%, and total cost will increase by 14.9%.

The coefficients of CDHP for all-cause medical cost, pharmacy cost and total cost are -0.046 (p-value=0.002), -0.171 (p-value<0.001), and -0.070 (p-value=0.031) respectively. These coefficients are statistically significant. This means that when all other variables are held constant, continuous enrollment in CDHP is associated with reduced medical cost by 4.6%, reduced pharmacy cost by 17.1%, and reduced total cost by 7.0%.

Also, many control variables are significant predictors of hypertension-specific costs. Increase of age is associated with increased costs. Male is associated with increased costs. Median income > $50,000 is related with decreased costs. As the rate of generic drug use increases, medical cost increase, but pharmacy cost decrease. Use of mail-order service, high risk, higher Charlson index score and presence of depression or bipolar disorder are associated with increased all-cause costs.

Table 19a: The GLM Gamma Log Link Main Effect Results for Condition-Specific Costs in Hypertension Cohort

| | Hypertension-Specific Health Care Costs | | | | | |
|---|---|---|---|---|---|---|
| Variables | Medical Cost | | Pharmacy Cost | | Total Cost | |
| | Coefficient | P-value | Coefficient | P-value | Coefficient | P-value |
| **PDC** | **-0.193*** | **<0.001** | **3.342*** | **< 0.001** | **0.149*** | **< 0.001** |
| **Enrollment in CDHP (yes/no)** | **-0.046*** | **0.001** | **-0.171*** | **< 0.001** | **-0.070*** | **0.031** |
| Age | 0.017* | <0.001 | 0.004* | < 0.001 | 0.015* | <0.001 |
| Sex (male/female) | 0.230* | <0.001 | 0.113* | <0.001 | 0.213* | < 0.001 |
| Race (% white) | 0.069 | 0.114 | -0.403* | < 0.001 | 0.047 | 0.219 |
| Education (% Bachelor degree or above) | 0.015 | 0.780 | -0.121* | <0.001 | -0.003 | 0.956 |
| Median Household Income (>$50,000) | -0.144* | <0.001 | -0.038* | <0.001 | -0.128* | 0.011 |
| Generic drug use rate | 0.244* | <0.001 | -1.899* | < 0.001 | -0.171* | < 0.001 |
| Use of mail-order service | 0.058* | 0.433 | -0.010 | 0.178 | 0.042* | 0.177 |
| High Risk (yes/no) | 0.501* | <0.001 | 0.136* | < 0.001 | 0.453* | <0.001 |
| Comorbidity (Charlson Index score) | 0.278* | <0.001 | 0.057* | < 0.001 | 0.261* | < 0.001 |
| Depression / bipolar disorder (yes/no) | 0.228* | <0.001 | 0.029 | 0.056 | 0.191* | < 0.001 |

* denotes being statistically significant

Table 19b shows the interaction model. PDC*CDHP enrollment is associated with increased hypertension-related healthcare costs. With enrollment in CDHP, increasing PDC from 0 to 100% is associated with 35.8% increase in medical cost, 12.1% increase in pharmacy cost, and 31.4% increase in total cost. PDC*generic use rate is associated with decreased all-cause costs. Increasing both PDC and the rate of generic drug use increase from 0 to 100% is associated with decreased medical cost, pharmacy cost and total cost, by 16.7%, 298.0% and 67.4% respectively. Among other significant interaction effects, CDHP*high risk and generic use rate*high risk are positively associated with costs; CDHP*generic use rate and generic use rate*mail order are negatively associated with costs; the other interactions have mixed effects.

Table 19b: The GLM Gamma Log Link Interaction Effect Results for Condition-Specific Costs in Hypertension Cohort

| | Hypertension-Specific Health Care Costs | | | | | |
|---|---|---|---|---|---|---|
| Variables | Medical Cost | | Pharmacy Cost | | Total Cost | |
| | Coefficient | P-value | Coefficient | P-value | Coefficient | P-value |
| PDC | -0.352* | <0.001 | 5.362* | < 0.001 | 0.399* | < 0.001 |
| Enrollment in CDHP (yes/no) | -0.260* | 0.001 | -0.180* | 0.036 | -0.256* | <0.001 |
| Age | 0.017* | <0.001 | 0.004* | < 0.001 | 0.015* | <0.001 |
| Sex (male/female) | 0.230* | <0.001 | 0.113* | <0.001 | 0.215* | < 0.001 |
| Race (% white) | 0.091* | 0.037 | -0.470* | < 0.001 | 0.060 | 0.118 |
| Education (% Bachelor degree or above) | -0.001 | 0.982 | -0.144* | <0.001 | -0.034 | 0.467 |
| Median Household Income (>$50,000) | -0.136* | <0.001 | -0.040* | <0.001 | -0.115* | <0.001 |
| Generic drug use rate | 0.243* | <0.001 | -0.259* | 0.031 | 0.154* | < 0.001 |
| Use of mail-order | -0.143* | 0.002 | 0.390* | <0.001 | -0.131* | 0.001 |

| | | | | | | |
|---|---|---|---|---|---|---|
| service | | | | | | |
| High Risk (yes/no) | 0.053 | 0.226 | -1.034* | < 0.001 | 0.043* | 0.269 |
| Comorbidity (Charlson Index score) | 0.280* | <0.001 | 0.050* | < 0.001 | 0.263* | < 0.001 |
| Depression / bipolar disorder (yes/no) | 0.222* | <0.001 | 0.012 | 0.404 | 0.191* | < 0.001 |
| **PDC*CDHP** | **0.358*** | **<0.001** | **0.121*** | **0.001** | **0.314*** | **<0.001** |
| **PDC*Generic use rate** | **-0.167*** | **<0.001** | **-2.980*** | **<0.001** | **-0.674*** | **<0.001** |
| **PDC*High risk** | **0.060** | **0.192** | **0.930*** | **<0.001** | **-0.113*** | **0.005** |
| **PDC*Mail order** | **0.371*** | **<0.001** | **-0.231*** | **<0.001** | **0.335*** | **<0.001** |
| **CDHP*High risk** | **0.067*** | **0.045** | **0.011** | **0.605** | **0.065*** | **0.027** |
| **CDHP*Generic use rate** | **-0.071** | **0.125** | **-0.126*** | **<0.001** | **-0.057** | **0.162** |
| **CDHP*Mail order** | **-0.075*** | **0.008** | **0.014** | **0.420** | **-0.066*** | **0.008** |
| **Generic use rate*High risk** | **0.564*** | **<0.001** | **0.484*** | **<0.001** | **0.688*** | **<0.001** |
| **Mail order*High risk** | **-0.121*** | **<0.001** | **0.044*** | **0.006** | **-0.104*** | **<0.001** |
| **Generic use rate*Mail order** | **-0.070** | **0.051** | **-0.268*** | **<0.001** | **-0.077*** | **0.015** |

* denotes being statistically significant

### 4.3.3 Results of GLM with Gamma Log Link in Hypercholesterolemia Cohort

The dependent variables are all-cause health care costs (medical, pharmacy and total), and condition-specific health care costs (medical, pharmacy and total). An independent model was constructed for each dependent variable. Each model included the same set of independent variables.

#### 4.3.3.1 Results of All-Cause Costs

Table 20a and 20b summarize the results of all-cause health care costs in the hypercholesterolemia cohort. Table 20a presents the main effect model. The coefficients of PDC for medical cost, pharmacy cost and total cost are -0.074 (p-value<0.001), 0.923 (p-value<0.001), and 0.173 (p-value<0.001) respectively. All the three coefficients are statistically significant. This suggests that with all other variables held constant, when PDC increases by 1 unit (from 0% to 100%), medical cost will decrease by 7.4%, pharmacy cost will increase by 92.3%, and total cost will increase by 17.3%.

The coefficients of CDHP enrollment for all-cause medical cost, pharmacy cost and total cost are -0.026 (p-value=0.038), -0.241 (p-value<0.001), and -0.074 (p-value<0.001) respectively, and are all statistically significant. When all other variables are held constant, continuous enrollment in CDHP is associated with the decrease in medical cost by 2.6%, in pharmacy cost by 24.1%, and in total cost by 7.4%.

For the control variables which have significant effects on all-cause costs, increase in age and percentage white will increase both medical and total costs. Male gender generally has lower costs. Median income > $50,000 is associated with lower costs. As the rate of generic drug use increases, medical, pharmacy and total costs all decrease. Use of mail-order service, high risk, higher Charlson index score and presence of depression or bipolar disorder are associated with increased costs.

Table 20a: The GLM Gamma Log Link Main Effect Results for All-Cause Costs in Hypercholesterolemia Cohort

| | All-Cause Health Care Costs | | | | | |
|---|---|---|---|---|---|---|
| Variables | Medical Cost | | Pharmacy Cost | | Total Cost | |
| | Coefficient | P-value | Coefficient | P-value | Coefficient | P-value |
| **PDC** | **-0.074*** | **<0.001** | **0.924*** | **< 0.001** | **0.173*** | **< 0.001** |
| **Enrollment in CDHP (yes/no)** | **-0.026*** | **0.038** | **-0.241*** | **<0.001** | **-0.074*** | **< 0.001** |
| Age | 0.018* | <0.001 | 0.0002 | 0.605 | 0.013* | <0.001 |
| Sex (male/female) | -0.048* | <0.001 | -0.197* | < 0.001 | -0.081* | < 0.001 |
| Race (% white) | 0.440* | <0.001 | 0.048 | 0.192 | 0.342* | < 0.001 |
| Education (% Bachelor degree or above) | 0.048 | 0.315 | 0.163* | < 0.001 | 0.071 | 0.071 |
| Median Household Income (>$50,000) | -0.079* | <0.001 | -0.020 | 0.063 | -0.061* | < 0.001 |
| Generic drug use rate | -0.033* | 0.003 | -0.565* | < 0.001 | -0.172* | < 0.001 |
| Use of mail-order service | 0.077* | <0.001 | 0.180* | < 0.001 | 0.094 | < 0.001 |
| High Risk (yes/no) | 0.164 | 0.098 | 0.349* | < 0.001 | 0.211 | 0.982 |
| Comorbidity (Charlson Index score) | 0.241* | <0.001 | 0.218* | < 0.001 | 0.233* | < 0.001 |
| Depression / bipolar disorder (yes/no) | 0.388* | <0.001 | 0.017* | < 0.001 | 0.446* | < 0.001 |

* denotes being statistically significant

Table 20b presents the interaction model. PDC*CDHP is associated with increased all-cause healthcare costs. When enrolled in CDHP, increasing PDC from 0 to 100% is associated with 13.2% increase in medical cost, 20.6% increase in pharmacy cost, and 10.8% increase in total cost. The interaction PDC*generic use rate is associated with decreased all-cause costs. Increasing both PDC and the rate of generic drug use increase from 0 to 100% is associated with decreased medical cost, pharmacy cost and total cost, by 29.9%, 68.7% and 44.0% respectively. Besides, several other interactions have significant effects on all-cause costs. PDC*high risk, CDHP*high risk and generic use rate*high risk are positively associated with costs, while PDC*mail order, CDHP*generic use rate, CDHP*mail order are negatively associated with costs.

Table 20b: The GLM Gamma Log Link Interaction Effect Results for All-Cause Costs in Hypercholesterolemia Cohort

| | All-Cause Health Care Costs | | | | | |
|---|---|---|---|---|---|---|
| Variables | Medical Cost | | Pharmacy Cost | | Total Cost | |
| | Coefficient | P-value | Coefficient | P-value | Coefficient | P-value |
| PDC | -0.108* | <0.001 | 1.300* | < 0.001 | 0.242* | < 0.001 |
| Enrollment in CDHP (yes/no) | -0.039 | 0.253 | -0.246* | <0.001 | -0.061* | 0.028 |
| Age | 0.018* | <0.001 | 0.0003 | 0.469 | 0.013* | <0.001 |
| Sex (male/female) | -0.054* | <0.001 | -0.202* | < 0.001 | -0.087* | < 0.001 |
| Race (% white) | 0.424* | <0.001 | 0.006 | 0.868 | 0.316* | < 0.001 |
| Education (% Bachelor degree or above) | 0.043 | 0.363 | 0.163* | < 0.001 | 0.067 | 0.085 |
| Median Household Income (>$50,000) | -0.077* | <0.001 | -0.017 | 0.097 | -0.059* | < 0.001 |
| Generic drug use rate | 0.176* | <0.001 | -0.116* | < 0.001 | -0.128* | < 0.001 |
| Use of mail-order service | 0.121* | <0.001 | 0.540* | < 0.001 | 0.193* | < 0.001 |

| | | | | | | |
|---|---|---|---|---|---|---|
| High Risk (yes/no) | -0.014 | 0.610 | 0.202* | < 0.001 | 0.042 | 0.068 |
| Comorbidity (Charlson Index score) | 0.241* | <0.001 | 0.220* | < 0.001 | 0.234* | < 0.001 |
| Depression / bipolar disorder (yes/no) | 0.390* | <0.001 | 0.610* | < 0.001 | 0.447* | < 0.001 |
| **PDC*CDHP** | **0.132*** | **<0.001** | **0.206*** | **<0.001** | **0.108*** | **<0.001** |
| **PDC*Generic use rate** | **-0.299*** | **<0.001** | **-0.687*** | **<0.001** | **-0.440*** | **<0.001** |
| **PDC*High risk** | **0.247*** | **<0.001** | **0.104*** | **<0.001** | **0.218*** | **<0.001** |
| **PDC*Mail order** | **-0.011** | **0.735** | **-0.504*** | **<0.001** | **-0.094*** | **<0.001** |
| **CDHP*High risk** | **0.021** | **0.454** | **0.090*** | **<0.001** | **0.026** | **0.260** |
| **CDHP*Generic use rate** | **-0.073*** | **0.009** | **-0.256*** | **<0.001** | **-0.091*** | **<0.001** |
| **CDHP*Mail order** | **-0.085*** | **<0.001** | **-0.061*** | **0.002** | **-0.085*** | **<0.001** |
| **Generic use rate*High risk** | **0.057*** | **0.022** | **0.198*** | **<0.001** | **0.083*** | **<0.001** |
| **Mail order*High risk** | **-0.024** | **0.280** | **-0.009** | **0.595** | **-0.019** | **0.291** |
| **Generic use rate*Mail order** | **-0.023** | **0.324** | **0.010** | **0.573** | **-0.022** | **0.247** |

* denotes being statistically significant

#### 4.3.3.2 Results of Hypercholesterolemia-Specific Costs

Tables 21a and 21b summarize the results of hypercholesterolemia-specific health care costs in main effect model and interaction effect model respectively. The main effect model is shown by Table 21a. The coefficients of PDC for medical cost, pharmacy cost and total cost are 0.067 (p-value<0.001), 3.144 (p-value<0.001), and 0.637 (p-value<0.001) respectively. All the three coefficients are statistically significant. This suggests that with all other variables held constant, when PDC increases by 1 unit (from 0% to 100%), medical cost will increase by 6.7%, pharmacy cost will increase by 314.4%, and total cost will increase by 63.7%.

The coefficients of CDHP enrollment for all-cause medical cost, pharmacy cost and total cost are -0.035 (p-value=0.009), -0.070 (p-value<0.001), and -0.062 (p-value<0.001) respectively, which are all statistically significant. When all other variables are held constant, continuous enrollment in CDHP is associated with decreased medical cost by 3.5%, decreased pharmacy cost by 7.0%, and decreased total cost by 6.2%.

For the control variables which have significant effects on hypercholesterolemia-specific costs, increase in age is associated with increased medical and total costs, but decreased pharmacy cost. Male generally increase costs. Higher percentage white is associated with increased medical and total costs, but with decreased pharmacy costs. Median income > $50,000 is associated with higher pharmacy cost, but with lower medical and total costs. As the rate of generic drug use increases, pharmacy and total costs decrease. Use of mail-order service, high risk, higher Charlson index score and presence of depression or bipolar disorder are associated with increased costs.

Table 21a: The GLM Gamma Log Link Main Effect Results for Condition-Specific Costs in Hypercholesterolemia Cohort

| | Hypercholesterolemia-Specific Health Care Costs | | | | | |
|---|---|---|---|---|---|---|
| Variables | Medical Cost | | Pharmacy Cost | | Total Cost | |
| | Coefficient | P-value | Coefficient | P-value | Coefficient | P-value |
| **PDC** | **0.067*** | **<0.001** | **3.144*** | **< 0.001** | **0.637*** | **< 0.001** |
| **CDHP (yes/no)** | **-0.035*** | **0.009** | **-0.070*** | **< 0.001** | **-0.062*** | **<0.001** |
| Age | 0.025* | <0.001 | -0.002* | < 0.001 | 0.018* | <0.001 |
| Sex (male/female) | 0.429* | <0.001 | 0.076* | 0.176 | 0.333* | < 0.001 |
| Race (% white) | 0.532* | <0.001 | -0.113* | < 0.001 | 0.432* | < 0.001 |
| Education (% Bachelor degree or above) | -0.035 | 0.484 | 0.018 | 0.590 | -0.085* | 0.035 |
| Median Household Income (>$50,000) | -0.170* | <0.001 | 0.029* | 0.002 | -0.100* | 0.011 |
| Generic drug use rate | 0.006 | 0.648 | -1.787* | < 0.001 | -0.440* | < 0.001 |
| Use of mail-order service | 0.029* | 0.009 | 0.061* | 0.004 | 0.013 | 0.177 |
| High Risk (yes/no) | 0.602* | <0.001 | -0.051* | < 0.001 | 0.447* | <0.001 |
| Comorbidity (Charlson Index score) | 0.126* | <0.001 | 0.013* | < 0.001 | 0.098* | < 0.001 |
| Depression / bipolar disorder (yes/no) | 0.148* | <0.001 | 0.042* | 0.005 | 0.130* | < 0.001 |

* denotes being statistically significant

Table 21b presents the interaction model. PDC*CDHP is associated with increased hypercholesterolemia-specific pharmacy cost by 20.1%, but its effect on medical and total costs is not significant. Again, the interaction PDC*generic use rate is associated with decreased hypercholesterolemia-specific costs. Increasing both PDC and the rate of generic drug use increase from 0 to 100% is associated with decreased medical cost, pharmacy cost and total cost, by 47.4%, 172.2% and 107.6% respectively. Among the significant interaction effects, PDC*high risk and generic use rate*high risk are positively associated with costs, while CDHP*generic use rate and generic use rate*mail order are negatively associated with costs.

Table 21b: The GLM Gamma Log Link Interaction Effect Results for Condition-Specific Costs in Hypercholesterolemia Cohort

| | Hypercholesterolemia-Specific Health Care Costs | | | | | |
|---|---|---|---|---|---|---|
| Variables | Medical Cost | | Pharmacy Cost | | Total Cost | |
| | Coefficient | P-value | Coefficient | P-value | Coefficient | P-value |
| PDC | -0.159* | <0.001 | 3.599* | < 0.001 | 0.784* | < 0.001 |
| CDHP (yes/no) | -0.065 | 0.080 | -0.180* | < 0.001 | -0.074* | 0.012 |
| Age | 0.024* | <0.001 | -0.002* | < 0.001 | 0.018* | <0.001 |
| Sex (male/female) | 0.414* | <0.001 | 0.065* | 0.176 | 0.324* | < 0.001 |
| Race (% white) | 0.508* | <0.001 | -0.220* | < 0.001 | 0.424* | < 0.001 |
| Education (% Bachelor degree or above) | -0.044 | 0.382 | 0.010 | 0.743 | -0.095* | 0.017 |
| Median Household Income (>$50,000) | -0.175* | <0.001 | 0.028* | 0.002 | -0.102* | <0.001 |
| Generic drug use rate | 0.326* | <0.001 | -0.686* | < 0.001 | -0.200* | < 0.001 |
| Use of mail-order service | -0.054 | 0.079 | 0.411* | <0.001 | -0.014 | 0.548 |
| High Risk (yes/no) | 0.009 | 0.760 | -1.079* | < 0.001 | -0.011 | 0.627 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Comorbidity (Charlson Index score) | 0.128* | <0.001 | 0.014* | < 0.001 | 0.102* | < 0.001 |
| Depression / bipolar disorder (yes/no) | 0.148* | <0.001 | 0.029* | 0.039 | 0.139* | < 0.001 |
| **PDC*CDHP** | **0.056** | **0.191** | **0.201*** | **<0.001** | **0.028** | **0.408** |
| **PDC*Generic use rate** | **-0.474*** | **<0.001** | **-1.722*** | **<0.001** | **-1.076** | **<0.001** |
| **PDC*High risk** | **0.760*** | **<0.001** | **1.294*** | **<0.001** | **0.438*** | **<0.001** |
| **PDC*Mail order** | **0.153*** | **<0.001** | **-0.510*** | **<0.001** | **0.089*** | **0.001** |
| **CDHP*High risk** | **0.044** | **0.142** | **0.017** | **0.370** | **0.046** | **0.052** |
| **CDHP*Generic use rate** | **-0.089*** | **0.003** | **-0.050*** | **0.012** | **-0.052*** | **0.029** |
| **CDHP*Mail order** | **0.052** | **0.056** | **-0.010** | **0.5853** | **0.038** | **0.074** |
| **Generic use rate*High risk** | **0.154*** | **<0.001** | **0.247*** | **<0.001** | **0.389*** | **<0.001** |
| **Mail order*High risk** | **0.005** | **0.840** | **0.046*** | **0.002** | **0.002** | **0.930** |
| **Generic use rate*Mail order** | **-0.064*** | **0.011** | **-0.024** | **0.155** | **-0.078*** | **<0.001** |

* denotes being statistically significant

### 4.3.4 Results of Sub-Analysis from Gamma Model with Log Link

In order to better understand how health care costs change as PDC changes, PDC was also measured as a categorical variable. PDC was divided into five levels: 0%-19%, 20%-39%, 40%-59%, 60%-79% and 80%-100%. The adjusted mean of health care costs were calculated under each PDC level after controlling for other variables from the gamma log link model.

Table 22 shows the adjusted mean of all-cause costs at each PDC level. The medical cost in the hypertension cohort tends to decrease monotonically as PDC increases from low level to high level, with the highest cost in the 0%-19% group and the lowest cost in the 80%-100% group. For the diabetes and hypercholesterolemia cohorts, medical cost increases first and then decrease as PDC increases from low level to high level. In the diabetes cohort, the 0%-19% group has the lowest medical cost and the 40%-50% group has the highest medical cost. In the hypercholesterolemia cohort, the 80%-100% group has the lowest medical cost, and 20%-39% group has the highest medical cost. The pharmacy cost in three cohorts increases monotonically as PDC increases. The total cost in the diabetes cohort is highest at the 40%-59% group, while in the hypertension and hypercholesterolemia cohorts, the 20%-39% group has the highest total cost.

Table 22: Adjusted All-Cause Health Care Costs at Different PDC Levels

| **Condition** | **PDC Level (%)** | **N** | **Medical Cost ($)** | **Pharmacy Cost ($)** | **Total Cost ($)** |
|---|---|---|---|---|---|
| Diabetes | 0 – 19 | 3962 | 7727 | 1320 | 8777 |
| | 20 – 39 | 1108 | 10069 | 2249 | 12326 |
| | 40 – 59 | 1753 | 10576 | 2679 | 13426 |
| | 60 – 79 | 2686 | 8847 | 3392 | 12448 |
| | 80 - 100 | 12503 | 7905 | 4462 | 12557 |
| Hypertension | 0 – 19 | 4265 | 8798 | 797 | 9171 |
| | 20 – 39 | 2277 | 8582 | 1215 | 9825 |
| | 40 – 59 | 3471 | 8397 | 1346 | 9775 |
| | 60 – 79 | 6232 | 7907 | 1598 | 9605 |
| | 80 - 100 | 48415 | 7258 | 2142 | 9500 |
| Hypercholesterolemia | 0 – 19 | 8389 | 6712 | 1135 | 7741 |
| | 20 – 39 | 3992 | 7592 | 1651 | 9320 |
| | 40 – 59 | 5796 | 6891 | 1873 | 8835 |
| | 60 – 79 | 8397 | 6602 | 2077 | 8801 |
| | 80 - 100 | 32429 | 6484 | 2618 | 9249 |

Table 23 shows the adjusted mean of condition-specific costs at each PDC level. The medical cost in all three cohorts increases first and then decrease as PDC increases from low level to high level. Specifically, the 40%-59% group has the highest medical cost and the 0-19% has the lowest medical cost in the diabetes cohort; the 20%-39% group has the highest medical cost in both the hypertension and hypercholesterolemia cohorts; in the hypertension cohort, the 80%-100% group has the lowest medical cost, and in the hypercholesterolemia cohort, the 0%-19% group has the lowest medical cost. Pharmacy cost across the three cohorts increases monotonically when PDC increases. The total cost in hypertension cohort is highest in the 20%-39% group, while in the diabetes and hypercholesterolemia cohorts, the 80%-100% group has the highest total cost.

Table 23: Adjusted Condition-Specific Health Care Costs at Different PDC Levels

| Condition | PDC Level (%) | N | Medical Cost ($) | Pharmacy Cost ($) | Total Cost ($) |
|---|---|---|---|---|---|
| Diabetes | 0 – 19 | 3962 | 1291 | 17 | 1210 |
| | 20 – 39 | 1108 | 2290 | 239 | 2620 |
| | 40 – 59 | 1753 | 2713 | 440 | 3341 |
| | 60 – 79 | 2686 | 2195 | 681 | 3055 |
| | 80 - 100 | 12503 | 2004 | 1476 | 3710 |
| Hypertension | 0 – 19 | 4265 | 2403 | 13 | 2133 |
| | 20 – 39 | 2277 | 2479 | 68 | 2593 |
| | 40 – 59 | 3471 | 2232 | 121 | 2397 |
| | 60 – 79 | 6232 | 2016 | 187 | 2303 |
| | 80 - 100 | 48415 | 1956 | 351 | 2409 |
| Hypercholesterolemia | 0 – 19 | 8389 | 1258 | 34 | 1238 |
| | 20 – 39 | 3992 | 1570 | 184 | 1874 |
| | 40 – 59 | 5796 | 1492 | 310 | 1934 |
| | 60 – 79 | 8397 | 1438 | 470 | 2070 |
| | 80 - 100 | 32429 | 1409 | 688 | 2290 |

The adjusted mean of all-cause and condition-specific costs under each PDC level is also calculated after controlling for other variables from the gamma log link model (Table 24 and Table 25). In all three cohorts, members enrolled in CDHPs have lower medical, pharmacy and total costs than those not enrolled in CDHPs.

Table 24: Adjusted All-Cause Health Care Costs on CDHP Status

| Condition | CDHP (Yes/No) | N | Medical Cost ($) | Pharmacy Cost ($) | Total Cost ($) |
|---|---|---|---|---|---|
| Diabetes | Yes | 3462 | 8934 | 2406* | 11515* |
| | No | 18550 | 8974 | 2823 | 12055 |
| Hypertension | Yes | 12925 | 7988* | 1159* | 9143* |
| | No | 51735 | 8320 | 1570 | 10022 |
| Hypercholesterolemia | Yes | 12890 | 6754* | 1598* | 8448* |
| | No | 46113 | 6939 | 2035 | 9105 |

* denotes being statistically significant

Table 25: Adjusted Condition-Specific Costs on CDHP Status

| Condition | CDHP (Yes/No) | N | Medical Cost ($) | Pharmacy Cost ($) | Total Cost ($) |
|---|---|---|---|---|---|
| Diabetes | Yes | 3462 | 2070* | 267 * | 2575 |
| | No | 18550 | 2010 | 301 | 2636 |
| Hypertension | Yes | 12925 | 2159* | 86* | 2282* |
| | No | 51735 | 2257 | 102 | 2446 |
| Hypercholesterolemia | Yes | 12890 | 1401* | 218* | 1780* |
| | No | 46113 | 1459 | 240 | 1909 |

* denotes being statistically significant

### 4.3.5 Assumptions of the Gamma Model and Results of Modified Park Test

The gamma model in GLM requires a constant coefficient of variation. However, the gamma model is robust to wide deviations from this assumption. A modified Park test was performed in each model across three cohorts to test the model assumption and determine which model in GLM is appropriate for analysis. The procedure of the test was discussed in the methods section. Table 26 shows the results of the test. The coefficient $\lambda$ is nearly equal to 2 in all cost types for all three cohorts. This suggests that the distributions of the dependent variables have constant coefficient of variation, and the gamma model is the appropriate model for examining the cost outcomes. Though $\lambda$ is closer to 1 for pharmacy costs, gamma model is still the dominant variance structure to examine the health care cost data in this study.

Table 26: Results of Modified Park Test

| **Disease Cohorts** | **Variables** | **Coefficient λ** | **Standard Error** | **P-value** |
|---|---|---|---|---|
| Diabetes | ***All-cause*** | | | |
| | Total cost | 2.04 | 0.03 | <0.0001 |
| | Medical cost | 1.99 | 0.02 | <0.0001 |
| | Pharmacy cost | 1.02 | 0.02 | <0.0001 |
| | ***Condition-specific*** | | | |
| | Total cost | 1.59 | 0.02 | <0.0001 |
| | medical cost | 2.13 | 0.01 | <0.0001 |
| | pharmacy cost | 1.13 | 0.02 | <0.0001 |
| Hypertension | ***All-cause*** | | | |
| | Total cost | 1.94 | 0.02 | <0.0001 |
| | Medical cost | 2.40 | 0.01 | <0.0001 |
| | Pharmacy cost | 1.43 | 0.01 | <0.0001 |
| | ***Condition-specific*** | | | |
| | Total cost | 2.39 | 0.01 | <0.0001 |
| | medical cost | 2.06 | 0.01 | <0.0001 |
| | pharmacy cost | 1.28 | 0.01 | <0.0001 |
| Hypercholesterolemia | ***All-cause*** | | | |
| | Total cost | 1.90 | 0.02 | <0.0001 |
| | Medical cost | 2.04 | 0.02 | <0.0001 |
| | Pharmacy cost | 1.32 | 0.01 | <0.0001 |
| | ***Condition-specific*** | | | |
| | Total cost | 1.98 | 0.01 | <0.0001 |
| | medical cost | 2.13 | 0.01 | <0.0001 |
| | pharmacy cost | 1.28 | 0.01 | <0.0001 |

# Chapter 5: DISCUSSION

This is a retrospective study using claims data from a large PBM company in Minnesota. There were two objectives in this study. The first was to investigate the influence of chronic medication adherence (measured in PDC) on health care costs. The second was to examine the effect of enrollment in CDHPs on health care costs for population with chronic diseases. The two objectives were examined in three disease cohorts: diabetes, hypertension and hypercholesterolemia.

In this chapter, the first section discusses the study results. The second section discusses the limitations of the study. The third section describes the strengths of the study. The fourth section discusses the implications of the study. Finally, the fifth section presents recommendations for future research.

## 5.1 Summary of Study Results

### 5.1.1 Summary of Descriptive Results

Health care costs vary across different disease cohorts (Table 27). All types of health care costs in the diabetes cohort were generally higher than the costs in the hypertension and hypercholesterolemia cohorts, except that the hypertension cohort had the highest condition-specific medical cost. Different cohorts also had different mean PDC (Table 28). Specifically, the hypertension cohort had the highest PDC. The diabetes and hypercholesterolemia cohorts had similar PDC. Table 29 shows the enrollment in CDHPs during study period. Only a small proportion of members had continuous enrollment in CDHPs across three cohorts. The hypercholesterolemia cohort had the largest proportion of members enrolled in CDHPs, while the diabetes cohort had the smallest proportion of enrollment.

Table 27: Mean Health Care Costs in Each Cohort

| | Diabetes | Hypertension | Hypercholesterolemia |
|---|---|---|---|
| All-cause total cost ($) | 13,730 | 11,236 | 10,099 |
| All-cause medical cost ($) | 9,752 | 8,794 | 7,430 |
| All-cause pharmacy cost ($) | 3,978 | 2,442 | 2,669 |
| Condition-specific total cost ($) | 3,821 | 2,996 | 2,348 |
| Condition-specific medical cost ($) | 2,569 | 2,621 | 1,668 |
| Condition-specific pharmacy cost ($) | 1,252 | 375 | 679 |

Table 28: Mean PDC in Each Cohort

| | Diabetes | Hypertension | Hypercholesterolemia |
|---|---|---|---|
| Mean PDC | 68.28% | 82.2% | 68.77% |

Table 29: CDHP Enrollment in Each Cohort

| Enrollment in CDHP, n (%) | Diabetes | Hypertension | Hypercholesterolemia |
|---|---|---|---|
| Yes | 3,462 (15.7%) | 12,925 (20.0%) | 12,890 (21.9%) |
| No | 18,550 (84.3%) | 51,735 (80.0%) | 46,113 (78.1%) |

### 5.1.2 Summary of Main Effect Model Results

Tables 30, 31 and 32 compare the effect of PDC, enrollment of CDHPs, and other control variables on health care costs in the diabetes, hypertension, and hypercholesterolemia cohorts. There is a negative relationship between PDC and all-cause medical cost across these three cohorts. When medication adherence increases, all-cause medical cost decreases significantly. This finding is consistent with the findings of the study by Sokol et al., who reported that as adherence level increased, the all-cause medical cost decreased in their diabetes, hypertension and hypercholesterolemia groups (Sokol et at., 2005). As expected, as PDC increases, all-cause pharmacy cost increases significantly in each cohort. However, this study shows that as PDC increases, all-cause total cost also increases across all three cohorts. This suggests that the increase in pharmacy cost is not offset by the decrease in medical cost, resulting in the increase in total cost. This finding is supported by the study by Hepke et al (2004) and partly supported by Kleinman et al (2008).

Hepke et al (2004) performed a retrospective data analysis on commercially insured patients with diabetes. Their results showed that increased medication adherence (measured in MPR) was associated with decreased medical care costs, but not associated with reduced overall health care costs because pharmacy costs offset medical care cost savings. However, the population inclusion in Hepke's study is different from this study. Hepke's study only included patients below 65 years of age excluding the Medicare patients. In addition, Hepke's study did not examine hypertension and hypercholesterolemia populations.

Kleinman et al. showed mixed results. They examined the impact of insulin adherence on annual health costs and absenteeism among employees and spouses with type 2 diabetes. Their findings indicated that among patients in the lower quartiles for prior medical costs, increased adherence was associated with a significant increase in total health care costs, which is consistent with the finding of this study. However, among patients in the highest quartile for prior medical costs, increased adherence was associated with a significant

decrease in total health care costs. Different from this study, Kleinman et al only examined adherence to insulin among people with type 2 diabetes. Furthermore, they did not examine hypertension and hypercholesterolemia population.

This current study shows mixed findings for condition-specific health costs across the three cohorts. In diabetes and hypercholesterolemia, condition-specific medical and total costs tend to increase when PDC increases. This finding is consistent with the study by Karve et al (2008), who conducted a retrospective analysis using eight different methods for calculating adherence to oral antidiabetic therapy, including MPR, PDC, refill compliance rate (RCR), compliance ratio (CR), medication possession ratio, modified (MPRm), continuous measure of medication gaps (CMG), continuous multiple interval measure of oversupply (CMOS) and continuous, single interval measure of medication acquisition (CSA). They found in predicting both all-cause and diabetes-related nonpharmacy medical costs, MPR, PDC, CMG and CMOS measures showed a statistically significant increase in costs associated with increased adherence. However, Karve's study examined a Medicaid population that was not included in this study. Karve's study only calculated adherence to oral antidiabetic medications, while this study calculated adherence based on all classes of antidiabetic drugs. Finally, Karve's study did not examine hypercholesterolemia medication adherence.

However, the finding in this study is different from the results of the study by Pittman et al (2011), who examined the relationship among statin adherence and heath care costs. They found statistically significant associations between a greater MPR and lower medical and total heath care costs. Pittman et al. study only looked at adherence to statin therapy and they only included patients from 18 to 61 years.

In this study's hypertension cohort, increased PDC is associated with a statistically significant decrease in hypertension-specific medical cost. However, increased PDC is associated with an increase in hypertension-specific total cost, despite the decrease in medical cost. This finding is partly supported by the general findings from the study

conducted by Dragomir et al (2010). Dragomir et al (2010) evaluated the impact of adherence to antihypertensive agents on medical costs in patients with essential hypertension. This study found that high adherence group was associated with lower medical costs. However, Dragomir's study did not examine total cost. There are several differences between Dragomir's study and this study. In Dragomir's study, adherence was categorized as low adherence (MPR < 80%) and adherence (MPR ≥ 80%), while adherence was measured as a continuous variable in this study. Also, the population in Dragomir's study was patients aged 45 to 85 years old, while this study included patients equal or greater than 18 years of age.

This study's generally finding that medication adherence is associated with lower medical costs are also partly supported by Stuart et al. study (2011), which examined whether adherence to renin–angiotensin-aldosterone system (RAAS) inhibitors and statins is associated with lower spending on traditional Medicare services for Medicare beneficiaries with diabetes. Their results showed that higher adherence was strongly associated with lower Medicare spending after controlling for extensive covariates. However, Stuart et al. study is different from this study in terms of specific study purpose, study population, and adherence measurement. The Stuart et al study aimed to examine the effect of adherence to RAAS inhibitors and statins on the spending of diabetes population; their study population were restricted to small Medicare sample; and they used pill count instead of claims data to measure medication adherence.

Enrollment in CDHPs shows similar effects on both all-cause costs and condition-specific costs across the three cohorts. Specifically, members who were enrolled in CDHPs incur lower medical, pharmacy, and total costs than those who were not enrolled in CDHPs in each cohort. This is the first study to examine the independent effect of CDHPs on health care costs after controlling for medication adherence and other variables that might impact health care costs. This cost-saving effect of CDHP found in this study is consistent with Parente, Feldman & Chen (2008) and Mercer Human Resources Consulting's study (2005).

The study by Parente, Feldman and Chen compared pharmaceutical spending and utilization in a CDHP with a traditional three-tier pharmacy benefit plan, and examined whether the CDHP reduced pharmaceutical spending and utilization for chronically ill patients, generic or brand name drugs. They found that CDHP pharmaceutical expenditures were lower than those in the point of service (POS) cohort in 1 year without differences in the use of brand name drugs, and they found limited evidence of less drug consumption by CDHP enrollees with chronic illnesses. However, this study did not examine the effect of CDHP enrollment on medication use, which was one the main purposes in Parente, Feldman & Chen study. However, Parente, Feldman & Chen study did not assess the association between CDHP enrollment and medical costs and total health care costs. The study by Mercer Human Resources Consulting (2005) reported that CDHP had lower health care costs than traditional PPO. However, Mercer Human Resources Consulting's study did not control for differences in enrollee characteristics that might be related to health care costs.

Patient characteristics including age, sex, race, education and income show quite mix effects on health care costs across different cohorts (shown in Tables 30, 31, and 32). Among other control variables, high risk group, members with higher Charlson comorbidity score and presence of depression or bipolar disorder are all associated with higher health care costs in each cohort. These results are supported by abundant research findings in literature. Increased generic drug use rate is found to be associated with reduced health care costs across three cohorts. Use of mail order service is associated with increased health care costs.

Table 30: Main Effect of Variables in Diabetes Cohort

| | Diabetes | | | | | |
|---|---|---|---|---|---|---|
| | All-cause costs | | | Condition-specific costs | | |
| Variables | Medical | Pharmacy | Total | Medical | Pharmacy | Total |
| **PDC** | **-0.059*** | **1.317*** | **0.335*** | **0.033*** | **4.626*** | **1.135*** |
| **CDHPs (yes/no)** | **-0.004** | **-0.161*** | **-0.052*** | **-0.005** | **-0.107*** | **-0.040*** |
| Age | 0.014* | 0.007* | 0.011* | -0.008* | -0.017* | -0.008* |
| Sex (male/female) | -0.106* | -0.080* | -0.088* | -0.117* | 0.022 | -0.066* |
| Race (% white) | 0.329* | 0.274* | 0.277* | -0.236* | -0.433* | -0.266* |
| Education (% Bachelor degree or above) | -0.01 | 0.306 | 0.079 | -0.474* | -0.184* | -0.401* |
| Median Household Income (>$50,000) | -0.089* | 0.044* | -0.053* | -0.024 | 0.013 | 0.044* |
| Generic drug use rate | -0.170* | -0.825* | -0.375* | -0.375* | -2.09* | -0.849* |
| Use of mail-order service | 0.069* | 0.172* | 0.092 | 0.013 | 0.047* | 0.019 |
| High Risk (yes/no) | 0.047 | -0.103* | -0.001 | 0.467* | 0.312* | 0.395* |
| Comorbidity (Charlson Index score) | 0.280* | 0.162* | 0.246* | 0.279* | 0.036* | 0.237* |
| Depression / bipolar disorder (yes/no) | 0.439* | 0.513* | 0.450* | 0.147* | 0.037 | 0.096* |

* denotes being statistically significant

Table 31: Main Effect of Variables in Hypertension Cohort

| | Hypertension | | | | | |
|---|---|---|---|---|---|---|
| | All-cause costs | | | Condition-specific costs | | |
| Variables | Medical | Pharmacy | Total | Medical | Pharmacy | Total |
| **PDC** | **-0.179*** | **1.097*** | **0.061*** | **-0.193*** | **3.342*** | **0.149*** |
| **CDHP (yes/no)** | **-0.041*** | **-0.305*** | **-0.092*** | **-0.046** | **-0.171*** | **-0.070*** |
| Age | 0.014* | 0.006* | 0.012* | 0.017* | 0.004* | 0.015* |
| Sex (male/female) | -0.072* | -0.110* | -0.081* | 0.230* | 0.113* | 0.213* |
| Race (% white) | 0.484* | 0.177* | 0.424* | 0.069 | -0.403* | 0.047 |
| Education (% Bachelor degree or above) | -0.149* | 0.233* | -0.073 | 0.015 | -0.121* | -0.003 |
| Median Household Income (>$50,000) | -0.063* | 0.008 | -0.046* | -0.144* | -0.038* | -0.128* |
| Generic drug use rate | 0.157* | -0.530* | -0.008 | 0.244* | -1.899* | -0.171* |
| Use of mail-order service | 0.105* | 0.214* | 0.123* | 0.058* | -0.01 | 0.042* |
| High Risk (yes/no) | 0.174* | 0.457* | 0.235* | 0.501* | 0.136* | 0.453* |
| Comorbidity (Charlson Index score) | 0.286* | 0.218* | 0.272* | 0.278* | 0.057* | 0.261* |
| Depression / bipolar disorder (yes/no) | 0.430* | 0.728* | 0.486* | 0.228* | 0.029 | 0.191* |

* denotes being statistically significant

Table 32: Main Effect of Variables in Hypercholesterolemia Cohort

| | Hypercholesterolemia | | | | | |
|---|---|---|---|---|---|---|
| | All-cause costs | | | Condition-specific costs | | |
| Variables | Medical | Pharmacy | Total | Medical | Pharmacy | Total |
| **PDC** | **-0.074*** | **0.924*** | **0.173*** | **0.067*** | **3.144*** | **0.637*** |
| **CDHP (yes/no)** | **-0.026*** | **-0.241*** | **-0.074*** | **-0.035*** | **-0.070*** | **-0.062*** |
| Age | 0.018* | 0.0002 | 0.013* | 0.025* | -0.002* | 0.018* |
| Sex (Male/Female) | -0.048* | -0.197* | -0.081* | 0.429* | 0.076* | 0.333* |
| Race (% white) | 0.440* | 0.048 | 0.342* | 0.532* | -0.113* | 0.432* |
| Education (% Bachelor degree or above) | 0.048 | 0.163* | 0.071 | -0.035 | 0.018 | -0.085* |
| Median Household Income (>$50,000) | -0.079* | -0.02 | -0.061* | -0.170* | 0.029* | -0.100* |
| Generic drug use rate | -0.033* | -0.565* | -0.172* | 0.006 | -1.787* | -0.440* |
| Use of mail-order service | 0.077* | 0.180* | 0.094 | 0.029* | 0.061* | 0.013 |
| High Risk (yes/no) | 0.164 | 0.349* | 0.211 | 0.602* | -0.051* | 0.447* |
| Comorbidity (Charlson Index score) | 0.241* | 0.218* | 0.233* | 0.126* | 0.013* | 0.098* |
| Depression and bipolar disorder (yes/no) | 0.388* | 0.017* | 0.446* | 0.148* | 0.042* | 0.130* |

* denotes being statistically significant

### 5.1.3 Summary of Interaction Model Results

This study also investigated the interaction effects among PDC, CDHP, generic drug use rate, high risk and mail order use, which are variables interesting to plan management organizations. Tables 33, 34, and 35 compare the interaction effects across the three disease cohorts. The interaction PDC*CDHP has a positive effect on health care costs across the three cohorts, but this effect is not significant on all-cause total cost and condition-specific costs in the diabetes cohort, and on condition-specific medical and total costs in the hypercholesterolemia cohort. This means that the interaction between enrollment in CDHP and increasing PDC from 0%-100% is associated with increased health care costs. By contrast, the interaction PDC*generic use rate has a significant and negative effect on health care costs across all three cohorts. This suggests that the interaction between increasing both PDC and generic use rate from 0%-100% is associated with much decrease in health care costs. The interaction CDHP*generic use rate also has a negative effect on health care costs across the three cohorts. This effect is significant on all the type of costs in the hypercholesterolemia cohort, but only significant on all-cause pharmacy cost and condition-specific total cost in the diabetes cohort, and only significant on pharmacy costs in the hypertension cohort.

The interaction PDC*high risk shows mixed effects across the three cohorts. The interaction between PDC and presence of high risk has a negative effect on health care costs in the diabetes cohort, but it has a positive effect on costs in the hypercholesterolemia cohort. However, this interaction generally does not have a significant effect on health care costs in the hypertension cohort. The interaction CDHP*high risk generally does not have a significant effect on health care costs in the diabetes and hypercholesterolemia cohorts, but it has a significant and positive effect on costs in the hypertension cohort. The interaction generic use rate*high risk has a negative effect on all-cause costs in the diabetes cohort, but has a positive effect on condition-specific pharmacy and total costs in the diabetes cohort and a positive effect on health care costs in both the hypertension and hypercholesterolemia cohorts.

Other interactions including PDC*mail order, CDHP*mail order, generic use rate*mail order and high risk*mail order have quite mixed effects on health care costs in the three cohorts.

Table 33: Interaction Effect of Variables in Diabetes Cohort

| | Diabetes | | | | | |
|---|---|---|---|---|---|---|
| | All-cause Costs | | | Condition-specific Costs | | |
| Variables | Medical | Pharmacy | Total | Medical | Pharmacy | Total |
| PDC | 0.272* | 1.868* | 0.757* | 0.934* | 7.450* | 2.147* |
| Enrollment in CDHP (yes/no) | -0.175* | -0.183* | -0.166* | 0.013 | -0.214* | -0.064 |
| Age | 0.016* | 0.008* | 0.013* | -0.004* | -0.015* | -0.003* |
| Sex (male/female) | -0.104* | -0.076* | -0.087* | -0.108* | 0.018 | -0.060* |
| Race (% white) | 0.361* | 0.310* | 0.314* | -0.092 | -0.296* | -0.070 |
| Education (% Bachelor degree or above) | -0.021 | 0.311* | 0.072 | -0.498* | -0.142 | -0.441* |
| Median Household Income (>$50,000) | -0.088* | 0.049* | -0.051* | -0.017 | 0.007 | 0.028 |
| Generic drug use rate | 0.345* | -0.277* | 0.201* | 0.459* | 0.666* | 0.393* |
| Use of mail-order service | 0.123* | 0.502* | 0.191* | -0.106* | 0.242* | -0.129 |
| High Risk (yes/no) | 0.243* | -0.072 | 0.207* | 1.163* | 1.025* | 1.259* |
| Comorbidity (Charlson Index score) | 0.274* | 0.160* | 0.239* | 0.259* | 0.023* | 0.206* |
| Depression or bipolar disorder (yes/no) | 0.444* | 0.514* | 0.454* | 0.155* | 0.009 | 0.116* |
| **PDC*CDHP** | **0.167*** | **0.185*** | **0.105** | **0.048** | **0.053** | **-0.045** |
| **PDC*Generic use rate** | **-0.780*** | **-0.818*** | **-0.892*** | **-1.333*** | **-4.864*** | **-2.149*** |
| **PDC*High risk** | **-0.108** | **-0.087** | **-0.216*** | **-1.088*** | **-1.573*** | **-1.496*** |
| **PDC*Mail order** | **-0.136*** | **-0.491*** | **-0.176*** | **0.087** | **-0.431*** | **0.131*** |
| **CDHP*High risk** | **-0.052** | **0.036** | **0.013** | **-0.149*** | **0.061** | **-0.072** |
| **CDHP*Generic use rate** | **-0.027** | **-0.228*** | **-0.033** | **-0.098** | **0.029** | **-0.108*** |
| **CDHP*Mail order** | **0.140*** | **0.042** | **0.112*** | **0.087*** | **0.094*** | **0.066** |
| **Generic use rate*High risk** | **-0.248*** | **-0.021** | **-0.112** | **-0.021** | **0.752*** | **0.366*** |
| **Mail order*High risk** | **-0.035** | **0.042** | **-0.032** | **0.155*** | **0.122*** | **0.077*** |
| **Generic use rate*Mail order** | **0.032** | **-0.031** | **0.002** | **0.028** | **0.072** | **0.038** |

Table 34: Interaction Effect of Variables in Hypertension Cohort

| | Hypertension | | | | | |
|---|---|---|---|---|---|---|
| | All-cause Costs | | | Condition-specific Costs | | |
| Variables | Medical | Pharmacy | Total | Medical | Pharmacy | Total |
| PDC | -0.120* | 1.505* | 0.223* | -0.352* | 5.362* | 0.399* |
| Enrollment in CDHP (yes/no) | -0.187* | -0.589* | -0.228* | -0.260* | -0.180* | -0.256* |
| Age | 0.014* | 0.006* | 0.012* | 0.017* | 0.004* | 0.015* |
| Sex (male/female) | -0.073* | -0.109* | -0.081* | 0.230* | 0.113* | 0.215* |
| Race (% white) | 0.488* | 0.170* | 0.424* | 0.091* | -0.470* | 0.060 |
| Education (% Bachelor degree or above) | -0.156* | 0.242* | -0.081 | -0.001 | -0.144* | -0.034 |
| Median Household Income (>$50,000) | -0.061* | 0.014 | -0.044* | -0.136* | -0.040* | -0.115* |
| Generic drug use rate | 0.285* | -0.326* | 0.191 | 0.243* | -0.259* | 0.154* |
| Use of mail-order service | 0.200* | 0.824* | 0.286* | -0.143* | 0.390* | -0.131* |
| High Risk (yes/no) | 0.002 | 0.112* | 0.037* | 0.053 | -1.034* | 0.043* |
| Comorbidity (Charlson Index score) | 0.286* | 0.216* | 0.272* | 0.280* | 0.050* | 0.263* |
| Depression or bipolar disorder (yes/no) | 0.427* | 0.018* | 0.484* | 0.222* | 0.012 | 0.191* |
| **PDC*CDHP** | **0.289*** | **0.381*** | **0.246*** | **0.358*** | **0.121*** | **0.314*** |
| **PDC*Generic use rate** | **-0.224*** | **-0.380*** | **-0.332*** | **-0.167*** | **-2.980*** | **-0.674*** |
| **PDC*High risk** | **0.041** | **0.063** | **0.053** | **0.060** | **0.930*** | **-0.113*** |
| **PDC*Mail order** | **-0.025** | **-0.687*** | **-0.108*** | **0.371*** | **-0.231*** | **0.335*** |
| **CDHP*High risk** | **0.075*** | **0.178*** | **0.087*** | **0.067*** | **0.011** | **0.065*** |
| **CDHP*Generic use rate** | **-0.075** | **-0.104*** | **-0.054** | **-0.071** | **-0.126*** | **-0.057** |
| **CDHP*Mail order** | **-0.088*** | **0.025** | **-0.075*** | **-0.075*** | **0.014** | **-0.066*** |
| **Generic use rate*High risk** | **0.202*** | **0.330*** | **0.214*** | **0.564*** | **0.484*** | **0.688*** |
| **Mail order*High risk** | **-0.053*** | **0.016** | **-0.040*** | **-0.121*** | **0.044*** | **-0.104*** |
| **Generic use rate*Mail order** | **-0.050** | **-0.058*** | **-0.057*** | **-0.070** | **-0.268*** | **-0.077*** |

Table 35: Interaction Effect of Variables in Hypercholesterolemia Cohort

| | Hypercholesterolemia | | | | | |
|---|---|---|---|---|---|---|
| | All-cause Costs | | | Condition-specific Costs | | |
| Variables | Medical | Pharmacy | Total | Medical | Pharmacy | Total |
| PDC | -0.108* | 1.300* | 0.242* | -0.159* | 3.599* | 0.784* |
| Enrollment in CDHP (yes/no) | -0.039 | -0.246* | -0.061* | -0.065 | -0.180* | -0.074* |
| Age | 0.018* | 0.0003 | 0.013* | 0.024* | -0.002* | 0.018* |
| Sex (male/female) | -0.054* | -0.202* | -0.087* | 0.414* | 0.065* | 0.324* |
| Race (% white) | 0.424* | 0.006 | 0.316* | 0.508* | -0.220* | 0.424* |
| Education (% Bachelor degree or above) | 0.043 | 0.163* | 0.067 | -0.044 | 0.010 | -0.095* |
| Median Household Income (>$50,000) | -0.077* | -0.017 | -0.059* | -0.175* | 0.028* | -0.102* |
| Generic drug use rate | 0.176* | -0.116* | -0.128* | 0.326* | -0.686* | -0.200* |
| Use of mail-order service | 0.121* | 0.540* | 0.193* | -0.054 | 0.411* | -0.014 |
| High Risk (yes/no) | -0.014 | 0.202* | 0.042 | 0.009 | -1.079* | -0.011 |
| Comorbidity (Charlson Index score) | 0.241* | 0.220* | 0.234* | 0.128* | 0.014* | 0.102* |
| Depression or bipolar disorder (yes/no) | 0.390* | 0.610* | 0.447* | 0.148* | 0.029* | 0.139* |
| **PDC*CDHP** | **0.132*** | **0.206*** | **0.108*** | **0.056** | **0.201*** | **0.028** |
| **PDC*Generic use rate** | **-0.299*** | **-0.687*** | **-0.440*** | **-0.474*** | **-1.722*** | **-1.076** |
| **PDC*High risk** | **0.247*** | **0.104*** | **0.218*** | **0.760*** | **1.294*** | **0.438*** |
| **PDC*Mail order** | **-0.011** | **-0.504*** | **-0.094*** | **0.153*** | **-0.510*** | **0.089*** |
| **CDHP*High risk** | **0.021** | **0.090*** | **0.026** | **0.044** | **0.017** | **0.046** |
| **CDHP*Generic use rate** | **-0.073*** | **-0.256*** | **-0.091*** | **-0.089*** | **-0.050*** | **-0.052*** |
| **CDHP*Mail order** | **-0.085*** | **-0.061*** | **-0.085*** | **0.052** | **-0.010** | **0.038** |
| **Generic use rate*High risk** | **0.057*** | **0.198*** | **0.083*** | **0.154*** | **0.247*** | **0.389*** |
| **Mail order*High risk** | **-0.024** | **-0.009** | **-0.019** | **0.005** | **0.046*** | **0.002** |
| **Generic use rate*Mail order** | **-0.023** | **0.010** | **-0.022** | **-0.064*** | **-0.024** | **-0.078*** |

### 5.1.4 Summary of Sub-analysis Results

This study performed a sub-analysis, dividing PDC into five levels: 0%-19%, 20%-39%, 40%-59%, 60%-79% and 80%-100%. The adjusted mean of health care costs were calculated under each PDC level after controlling for other variables from the gamma log link model.

Figures 19, 20, and 21 are histograms of the adjusted mean of all-cause costs at each PDC level for diabetes, hypertension, and hypercholesterolemia respectively. Medical cost in the hypertension cohort decreases monotonically as adherence increases from low level to high level. For the diabetes and hypercholesterolemia cohorts, medical cost increases first and then decrease as adherence increases from low level to high level. In the diabetes cohort, the 40%-50% group has the highest medical cost. In the hypercholesterolemia cohort, the 20%-39% group has the highest medical cost. However, because of the monotonic growth in pharmacy cost as PDC increases, total cost increases as PDC level increases. These findings are similar to the results of the study by Hepke et al (2004).

Hepke's study showed that although total (medical care and drug) costs increased as the medication adherence level increased, medical care costs showed a slow increase up to the 20% to 39% adherence level for overall costs; after this level was reached, there was a steady decrease. Thus, a threshold effect was observed at the 20% to 39% adherence level; this level of drug adherence was needed before medical care costs were reduced.

Figure 19: Adjusted Mean All-Cause Health Care Costs by PDC Levels in Diabetes Cohort

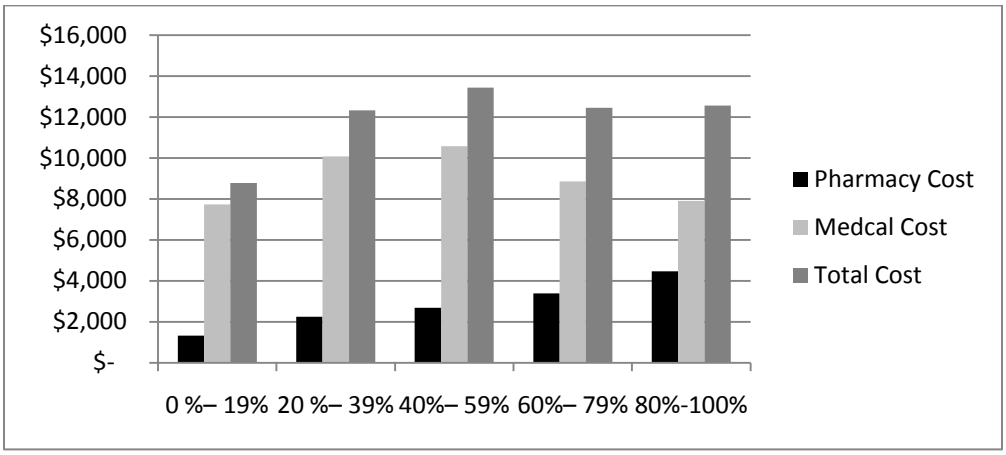



Figure 20: Adjusted Mean All-Cause Health Care Costs by PDC Levels in Hypertension Cohort

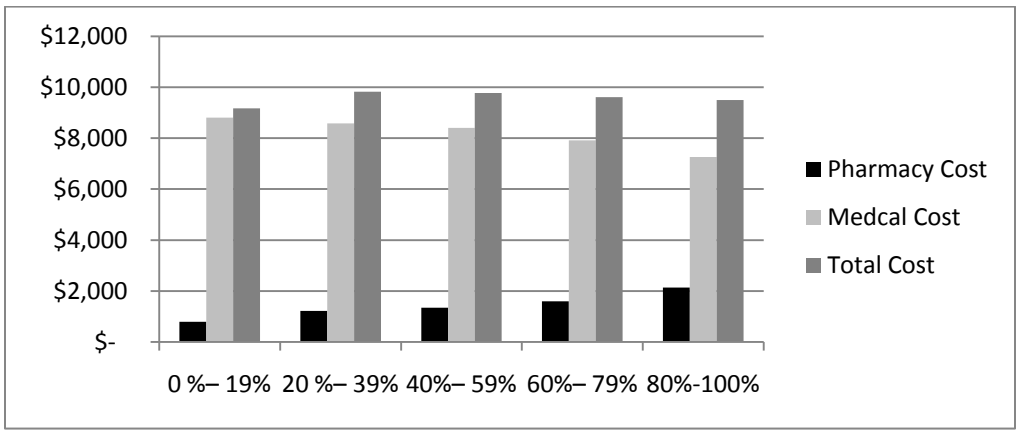
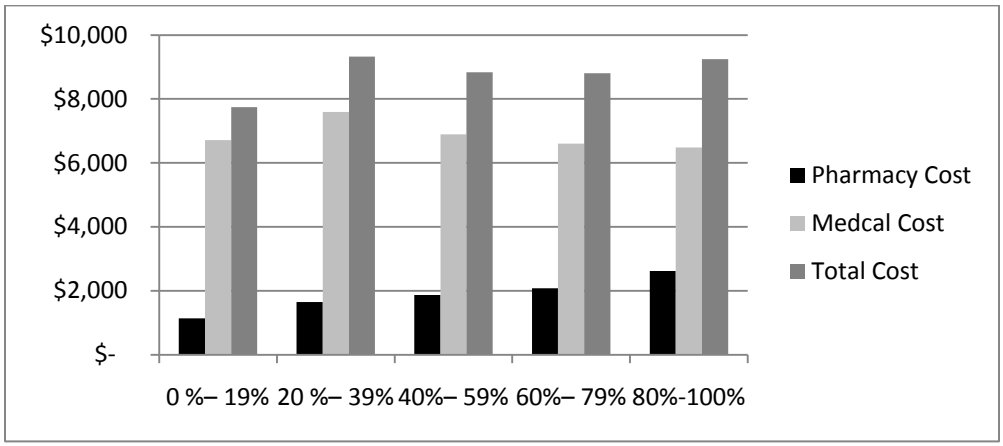


Figure 21: Adjusted Mean All-Cause Health Care Costs by PDC Levels in Hypercholesterolemia Cohort




Figures 22, 23 and 24 are histograms of the adjusted mean of condition-specific costs at each PDC level for diabetes, hypertension, and hypercholesterolemia respectively. PDC and medical cost across three conditions has a curvilinear relationship. Medical cost increases first and then decrease as adherence increases from low level to high level, with the threshold effect at 40%-59% in the diabetes cohort, at 20%-39% in both the hypertension and hypercholesterolemia cohorts. These results are consistent with the study results of Hepke et al (2004), which suggested that for the diabetes-related costs with a primary diabetes diagnosis, the threshold effect was not seen until the 40% to 59% adherence level was reached.

Figure 22: Adjusted Mean Condition-Specific Health Care Costs by PDC Levels in Diabetes Cohort

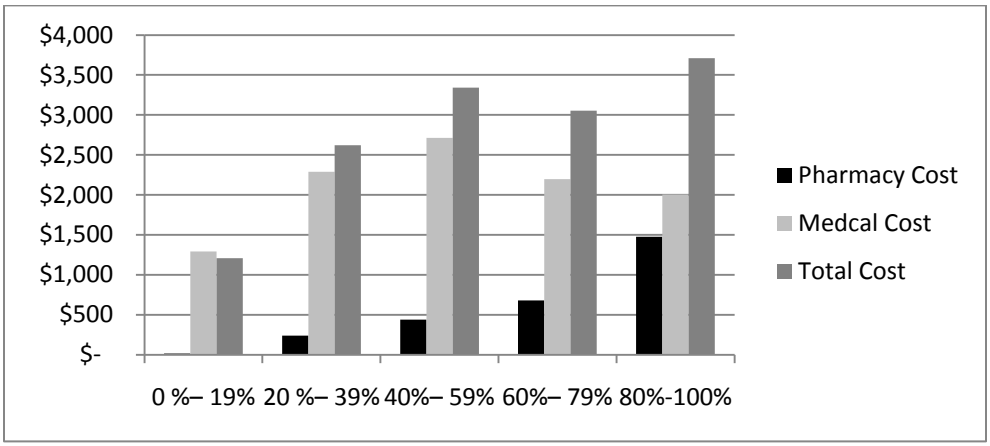



Figure 23: Adjusted Mean Condition-Specific Health Care Costs by PDC Levels in Hypertension Cohort

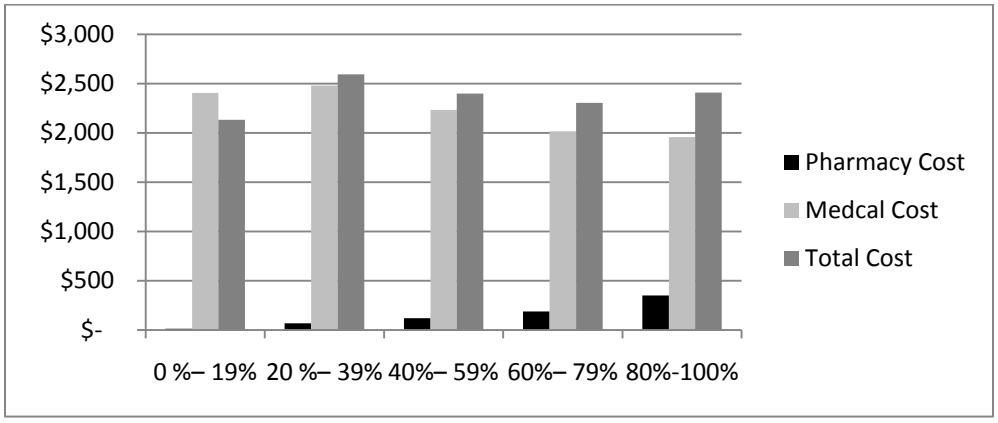
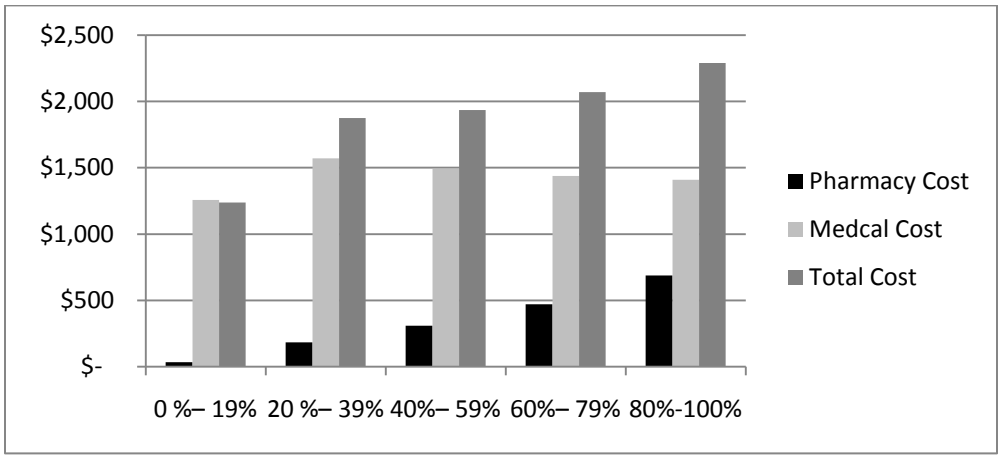


Figure 24: Adjusted Mean Condition-Specific Health Care Costs by PDC Levels in Hypercholesterolemia Cohort



## 5.2 Study Limitations

Several limitations of this study need to be noted. These limitations are related to data source, study design, generalizability, and measurement.

First, the data source of this study is patients' medical and pharmacy claims data supplemented with other administrative data files. The original purpose of claims data is to obtain reimbursement for health services, not for research. Fields related to reimbursement are generally accurate, but coding errors or inaccurate entries in some other fields may occur. Diagnosis in medical claims is not always accurate and both Charlson score and high risk status calculation are dependent assumption of accurate diagnosis information within the claims data in this study. Also, the days supply may not be completely accurate. However, given the large sample size, minor inaccuracy in coding will not make a difference in the results.

Second, claims data records can only be able to detail patients' medication acquisition behaviors instead of their medication consumption behaviors. Patients who fill the prescriptions may not necessarily consume them. Despite these limitations, claims data have been validated for research and have been widely used in pharmacoepidemiologic studies (Perrault et al., 2005). Also, pharmacy claims data are also believed to me more objective in measuring patients compliance compared with other measures (Wang et al., 2004).

Another limitation is related to the generalizability of this study. The subjects of this study are employer-sponsored enrollees and Medicare enrollees in Minnesota Blue Cross and Blue Shield as the health plan. Therefore, the results of this study may not be generalized to persons in Medicaid, who are generally financially disadvantaged; to persons enrolled in government health plans, or to those who self-pay.

Fourth, the length of study is limited. The observational period in this study is one year, which may not be long enough to fully capture the long-term benefits of medications for chronic diseases. In this study, calculation of medication adherence and health care costs were only based on one year's time period. The effect of chronic medications on health care costs in the long term might not be comprehensively researched within one year. However, even within such short time period, this study already found that higher adherence level is associated with reduction in medical costs.

Finally, attention should be paid to the potential selection bias in this study. Using the observational data to examine the research question, this study is not able to examine the marginal causal effect of medication adherence or the marginal causal effect of enrollment in CHDPs on health care expenditures. McClellan et al. (1994) pointed out that there is a general concern in health outcomes research that the potential for selection bias arises because many factors other than the treatment may affect the health outcomes. These factors include severity of illness and other complex details of a patient's health status, as well as patient and physician preference. Such factors are likely to influence treatment decisions but are difficult to capture in recorded data. Standard biostatistical methods can be used to adjust for observable factors, but cannot adjust for unobservable factors.

The problem of unobservable factors that may influence both treatment and outcomes is defined as Endogeneity in econometrics. It has been recommended that instrumental variable (IV) analysis may address endogeneity problem. McClellan et. al. (1994) provided a description of IV analysis: Instrumental variables estimation uses one or more IVs – observable factors that influence treatment but do not directly affect outcomes. When valid, the method is analogous to randomization methods in identifying "balanced" sources of variation in treatment, so that estimates of treatment effects are not contaminated by selection bias. More specifically stated by Cameron and Trivedi (2005), a variable z is called an instrument or instrument variable for the regressor x in the regression model $y=\beta x + \varepsilon$ if (1) z is uncorrelated with the error $\varepsilon$; and (2) z is

correlated with the regressor x. However, the first assumption that the proposed IVs are not correlated with unobserved factors that directly affect outcomes is untestable. Its validity can be explored but not be proven statistically, and therefore determining whether an instrument is exogenous is usually a subjective decision. In addition, in many microeconometric applications it is difficult to find legitimate instruments. The consequences of choosing poor instruments may include the problems of inconsistency of estimators and loss of precision, which leads to greater bias in estimation.

This study investigated each possible variable as a potential IV available from the data source. However, none of these variables met the necessary criteria discussed previously to be considered as valid IVs. In order to avoid more bias likely caused by poor instruments in estimating the effect of medication adherence on health care expenditures, this study did not use the IV analysis. Instead, this study used Andersen's Health Utilization Model to identify observable covariates available in the data sets, and controlled for them in the GLM, which to some extent reduced bias due to endogeneity.

## 5.3 Strengths of This Study

In spite of the noted limitations, this study has several strengths compared to existing studies. First of all, this study examined the effect of medication adherence on health care costs in three chronic conditions: diabetes, hypertension and hypercholesterolemia. By providing a more comprehensive view of the similarities and differences across the three disease cohorts, this study has more generalizability in terms of study populations and drug therapy classes.

Second, this study had large sample sizes and included population from different health providers and with wide classes of characteristics. Though Medicaid population were not included in this study, commercially insured and Medicare population were studied.

Compared with previous studies which were based on restricted sample characteristics, this study has increased robustness of the findings.

Another strength of this study is that the calculation of adherence, measured in PDC, was not only based on single therapeutic class of drugs, but based on all therapeutic classes used to treat a specific condition. This method allows for examination of medication switching between multiple drugs and provides a more comprehensive assessment of patients' medication adherence.

Also, in this study, adherence was measured as both continuous variable and categorical variable. Most commonly, adherence is categorized into two groups: PDC or MPR equal or greater than 80%, and less than 80%. A patient is considered as adherent to a drug therapy, if his or her PDC or MPR is equal or greater than 80%, and not adherent if PDC or MPR is less than 80%. However, the cut point at 80% is arbitrary, not based on solid clinical evidence. Thus, quantifying adherence at both continuous and categorical levels can increase the accuracy of measure adherence and reveal more detailed health care cost information at each adherence level.

## 5.4 Implications

According to the study results, higher level of adherence to chronic medications is associated reduced medical costs. However, due to the enormous increase in pharmacy cost with increased adherence level, the savings in medical cost are not able to offset the increase in pharmacy, leading to total health care costs growing. These findings have several implications for policy-making regarding health care expenditure control for chronic diseases.

First of all, efforts should be done to improve chronic patients' adherence. Based on the results of this study, the mean adherence (measured in PDC) is 68.28%, 82.2% and 68.77%

for diabetes, hypertension and hypercholesterolemia respectively. Though patients in hypertension cohort are quite adherent to antihypertensive medications, there is still much room to improve the adherence in diabetes and hypercholesterolemia cohorts. Moreover, these statistics are based on only one year's observation period in this study. If adherence is calculated for longer period, the mean adherence level is likely to be lower.

Adherence is affected by multiple factors, and no single way is superior to others in effectively improving patients' adherence. Therefore, a multi-strategy approach should be used to improve adherence. First, a patient-centered program that helps overcome patient-specific barriers to medication adherence should be encouraged. According to DiMatteo (2004), patients' social structure, health beliefs and perceived needs (e.g. depression, practical and emotional support and income) have greater effects on adherence than demographic factors such as age and gender. So helping patients to address their personal needs and barriers would be a more effective way to improve their adherence to medications. Second, high prescription cost-sharing is shown as a barrier to adherence (Zhang, 2006). In her study, Zhang found that when per 30 day average cost-sharing increases by $1, the odds of non-persistence (PDC < 80%) will increase by 2.5%. Thus, cost-sharing on necessary medications for a person who has been diagnosed with the specific disease should be reduced or even made free.

Second, generic drug use should be encouraged. According to U.S. Food and Drug Administration (FDA) (2010), generic drugs will perform the same as its respective brand name product. In addition, all generic manufacturing, packaging and testing sites must pass the same quality standards as those of brand name drugs, but generic products are usually sold for significantly lower prices than their branded equivalent, about 80% cheaper than their brand name counterparts (Blue Cross Blue Shield, 2006). Therefore, encouraging patients to choose generic products is a cost-effective strategy to bring down health expenditures. Based on the results of this study, when generic use rate increases from 0 to 100%, condition-specific total cost will decrease by 84.9% in diabetes cohort, by 17.1% in hypertension cohort, and by 44.0% in hypercholesterolemia cohort. The

interaction models in this study also show that when medication adherence and the rate of generic drug use both increase, interaction effect between these two variables have a negative and significant effect on both all-cause and condition-specific health care costs.

Generic drug use could be improved from multiple aspects. From patient side, health care professionals should educate patients about the availability of generic products which have the therapeutically equivalent efficacy as their brand-name counterparts in treating their conditions. In terms of health benefit design, increasing copayment differential between brand name drugs and generic drugs in pharmacy benefit design can help increase generic use rate. Based on the study by Yuan (2008), the mean generic fill rate will increase by 0.1%, when copayment differential increases $1. Also, health care administrators could make policies that promote the use of generic drugs.

However, special attention should be given to individuals with high risk status when improving the generic drug use. Based on the results of the interaction model in this study, the interaction between high risk and generic drug use rate has a negative effect on all-cause health care costs in the diabetes cohort, but it has a positive effect on condition-specific pharmacy and total costs in the diabetes cohort and a positive effect on all-cause and condition-specific health care costs in both the hypertension and hypercholesterolemia cohorts. This means that with the presence of high risk, increasing the rate of generic drug use is associated with increased medical costs and total costs in the hypertension and hypercholesterolemia cohorts. This indicates that increasing the generic drug use among high risk individuals with hypertension and hypercholesterolemia might have a suboptimal medication therapy effect. One explanation may be that newly developed brand name drugs whose generic versions are not available may have better therapy outcomes. However, this relationship requires further research.

## 5.5 Recommendations for Future Research

This study examined the influence of medication adherence on health care costs in the diabetes, hypertension and hypercholesterolemia cohorts. Though increased adherence was associated with decreased all-cause medical cost in general across three conditions, the association varied across three cohorts. In the diabetes cohort, the 40%-50% PDC group had the highest all-cause medical cost; in the hypertension cohort, the highest all-cause medical cost was in 0%-19% group; in the hypercholesterolemia cohort, the 20%-39% group incurred the highest cost. Although the effect of adherence on condition-specific medical cost showed a more similar pattern, it had a little variation in each cohort. In the hypertension and hypercholesterolemia cohorts, the 20%-39% group had the highest condition-specific medical cost, but in diabetes cohort, the 40%-59% had the highest condition-specific medical cost. It indicates that the relationship between adherence and medical cost was more curvilinear than linear, and this relationship varied across conditions. Further research could examine how the pattern of impact of adherence may vary across other chronic conditions. Also, according to the pattern, different strategies may be applied to target disease population to improve adherence and to contain health expenditures.

Second, due to the unavailability of individual level data, this study used patients' five-digit zip code area level information matching from census data to examine the effects of race, education and income on health care costs. However, aggregate proxies may introduce measurement errors. Therefore, if possible, future studies are recommended to examine the effects of race, education using individual level information.

In addition, Medicaid patients were not included in this study, so their health seeking and medication adherence behavior was not able to be examined. Medicaid patients are generally financially disadvantaged and have different socioeconomic characteristics that may lead to a different health services utilization pattern. Future research could include

Medicaid patients in the study population and compare whether the effect of adherence on health care costs is different between Medicaid patients and the other patients.

Another recommendation is that future research should be focused more on standardizing a medication adherence measure. Currently, there are a number of methods to measure medication adherence, including pill count, physical test, medical records, pharmacy claims, self-report, collateral report and electronic monitor (DiMatteo, 2004). Though pharmacy claims data are also believed to be more objective in measuring patients' compliance compared with other measures (Wang et al., 2004), the gold standard for adherence measurement is still unavailable. There is no one adherence measure against which to calibrate others, making concurrent validation impossible. This study adopted the PQA endorsed proportion of days covered (PDC) as a method to measure adherence, which helped to standardize adherence measure. However, there is still no standardization when it comes to counting the number of covered days for a patient who is taking multiple therapeutic classes of drugs treating a specific condition. Therefore, future research could use multiple adherence measure strategies that help develop reliable and valid adherence measurement.

Finally, the effect of enrollment in CDHPs on medication adherence and health care expenditures should be further investigated. According to the results of main effect models of this study, patients who were enrolled in CDHPs during the study period had lower medical, pharmacy, and health expenditure than those who were not across the three disease cohorts. However, based on the results of interaction models, the interaction between medication adherence and enrollment in CDHPs had a positive effect on health care costs in all three disease cohorts. This suggests that the combined effect of these two variables is associated with higher medical, pharmacy and total health care spending. One possible reason is that enrollment in CDHPs may affect medication adherence, because patients enrolled in CDHPs need to pay higher deductibles and therefore are more sensitive to the costs of their medications. Several studies show that CDHP enrollees were not associated with reduced use of essential medications for chronic illnesses,

compared with traditional health plans enrollees (Reiss et al, 2011; Greene et al., 2008; Parente, Feldman & Chen, 2008), while the study by Dixon, Greene & Hibbard (2008) show that enrollees in the high-deductible CDHP were more likely than those in the preferred provider organization (PPO) to start forgoing medical care to save money.

This study did not examine the effect of enrollment in CDHPs on medication adherence. To better understand whether CDHPs should be promoted among employment-based health plans, future studies could further investigate the relationships among CDHP enrollment, medication adherence and health care costs.

# Chapter 6: CONCLUSION

This study contributes to the growing body of literature examining the effect of chronic medication adherence and CDHPs on health care spending. Three cohorts were constructed to examine the research questions in diabetes, hypertension and hypercholesterolemia. Health care expenditures were measured at two levels: all-cause costs and condition-specific costs.

First, this study looked at the effect of adherence on all-cause costs. The study results suggest that medication adherence, measured in PDC, has a significant and negative impact on all-cause medical cost for each condition. As expected, adherence has a significant and positive impact on all-cause pharmacy cost for each condition. Due to the enormous increase in pharmacy cost, adherence has a significant and positive effect on all-cause total cost. This indicates that as adherence increases, the savings in all-cause medical cost is not able to offset the increase in pharmacy cost.

Second, this study examined the effect of adherence on condition-specific costs. The study results suggest that adherence has a significant and positive impact on diabetes-specific medical cost in diabetes cohort, while the impact on condition-specific medical cost in hypertension and hypercholesterolemia cohorts is negative and significant. Again, adherence has a significant and positive impact on condition-specific pharmacy cost for each condition. However, the increase in pharmacy cost exceeds the reduction in medical cost, so the impact of adherence on condition-specific total cost is positive and significant for all three disease cohorts.

In addition, this study divided adherence into five levels: 0-19%, 20%-39%, 40%-59%, 60%-79%, and 80%-100%, and performed a sub-analysis examining the effect of adherence on health care costs at each adherence level. For all-cause costs, medical cost in hypertension cohort decreases monotonically as adherence increases from low level to

high level. For diabetes and hypercholesterolemia, medical cost increases first when adherence increase to 20%-39% or 40%-59% PDC level, and then decrease as adherence increases to 80%-100% level. For condition-specific costs, medical cost first increases and then decreases as adherence increases from low level to high level in each cohort. This indicates that the relationship between adherence and health care costs is more curvilinear rather than linear. Also, the study results demonstrate that in the three cohorts both all-cause and condition-specific pharmacy costs increases monotonically as PDC increases, resulting in final increase in total health costs.

Also, the findings of the study show that enrollment in CDHPs is generally associated with decreased all-cause and condition-specific medical, pharmacy and total costs for the three conditions. Though the association of CDHP enrollment with all-cause and condition-specific medical costs is not significant in diabetes cohort, its association with other costs is significant. However, this study did not examine the association between enrollment in CDHPs and medication adherence.

Therefore, efforts should be done in the following aspects in order to contain or reduce health care spending. First, adherence to chronic medications should be improved by establishing a patient-centered approach to addressing patients' personal needs and barriers to adherence, and lowering prescription drugs cost-sharing. Second, generic drug use should be encouraged from patient education, increasing the copayment differential between brand name drugs and generic drugs, and policy changes, provided optimal medication treatment outcomes are not jeopardized. Finally, CDHPs could be further explored as a potential among employment-based health plans to reduce diabetes, hypertension and hypercholesterolemia health care costs.

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# Appendices

Appendix 1: University of Minnesota Institutional Review Board Approval

The IRB: Human Subjects Committee determined that the referenced study is exempt from review under federal guidelines 45 CFR Part 46.101(b) category #4 EXISTING DATA; RECORDS REVIEW; PATHOLOGICAL SPECIMENS.

Study Number: 1003E79143

Principal Investigator: Siting Zhou

Title(s):
Chronic Medication Adherence: Its Association with Health Care Costs

Appendix 2: Charlson Weights Derived from New Jersey Medicare Data

| *Conditions* | *Prevalence in New Jersey in %* | *Original Charlson Weights* | *New Jersey Odds- ratio Estimates** | *95% Confidence Interval* | *Assigned NJ Medicare Weights*** |
|---|---|---|---|---|---|
| Myocardial infarct | 4.3 | 1 | 1.23 | (1.15–1.31) | 1 |
| Congestive heart failure | 15.1 | 1 | 2.09 | (2.01–2.17) | 2 |
| Peripheral vascular disease | 13.3 | 1 | 1.55 | (1.49–1.61) | 1 |
| Cerebrovascular disease | 11.4 | 1 | 1.42 | (1.36–1.48) | 1 |
| Dementia | 6.2 | 1 | 2.16 | (2.06–2.27) | 3 |
| Chronic pulmonary disease | 12.4 | 1 | 1.66 | (1.59–1.73) | 2 |
| Connective tissue disease | 2.2 | 1 | 1.09 | (0.98–1.21) | 0 |
| Ulcer disease | 3.4 | 1 | 1.03 | (0.96–1.11) | 0 |
| Mild liver disease | 0.3 | 1 | 1.73 | (1.41–2.12) | 2 |
| Diabetes | 12.0 | 1 | 1.37 | (1.31–1.44) | 1 |
| Hemiplegia | 2.1 | 2 | 1.44 | (1.33–1.56) | 1 |
| Moderate or severe renal disease | 1.6 | 2 | 2.54 | (2.34–2.76) | 3 |
| Diabetes with end organ damage | 5.1 | 2 | 1.57 | (1.48–1.67) | 2 |
| Any tumor | 5.8 | 2 | 1.85 | (1.75–1.95) | 2 |
| Leukemia | † | 2 | | | |
| Lymphoma | † | 2 | | | |
| Moderate or severe liver disease | 0.1 | 3 | 3.24 | (2.47–4.26) | 4 |
| Metastatic solid tumor | 1.7 | 6 | 5.94 | (5.50–6.40) | 6 |
| AIDS | 0.1 | 6 | 3.26 | (2.13–4.98) | 4 |