HOSPITAL INPATIENT COST AND DISCHARGE STATUS OF DIABETES AND ITS COMPLICATIONS IN THE U.S.

A DISSERTATION

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To my parents

Abstract

Diabetes is a huge economic and clinical burden to the health care system in the U.S. However, the incremental effect of diabetes complications has not been well documented in the literature. In addition, diabetes-related hospitalization discharge status has not been thoroughly examined.

This study was carried out with two objectives: the primary objective of this study was to examine the association between the presence and severity of diabetes-related complications and diabetes-related hospitalization costs and discharge status. The secondary objective of this study was to explore how the presence and type of diabetes influenced complications-related hospitalization costs and discharge status. This study was a cross-sectional study with secondary data analysis of the 2010 to 2012 National Inpatient Sample (NIS). The study sample consisted of four disease cohorts: diabetes-related hospitalization cohort, peripheral lower-extremity (PLE) diseases-related hospitalization cohort, kidney diseases-related hospitalization cohort, and coronary atherosclerosis-related hospitalization cohort. In each cohort, hospitalization cost was calculated by multiplication of the total hospitalization charge by the cost-to-charge ratio. Hospitalization discharge status was dichotomized as routine discharge and non-routine discharge. Two statistical models were fit: a generalized linear model with gamma distribution and log link was used for modeling hospital inpatient cost; multivariate logistic regression was adopted for modeling hospitalization discharge status. The covariates in the regression model included complications and other variables identified by the Andersen's behavioral model of health service utilization.

The diabetes-related hospitalization contained 804,192 discharge records. The incremental cost of severe PLE was approximately $6,849. Severe PLE and less severe PLE increased diabetes-related hospitalization cost by 66.6% and 1.35% respectively. Comorbid kidney diseases were not found to be associated with an apparent increase in diabetes-related hospitalization cost. The incremental cost of severe coronary atherosclerosis was approximately $1,200. Severe PLE was also associated with increased odds of having non-routine discharges after hospitalization.

The final peripheral lower extremity (PLE) diseases-related hospitalization cohort contained 219,752 discharge records. The presence of type 1 diabetes was associated with a 12% decrease in PLE-related hospitalization cost, while the presence of type 2 diabetes was associated with a 3.85% decrease in PLE-related hospitalization cost. The association between diabetes and PLE-related hospitalization cost was modified by age. PLE-related hospitalization cost was highest among patients younger than 65 years and without diabetes ($17,075). Diabetes was also significantly associated with hospitalization discharge status. PLE patients with diabetes were 1.37 times more likely to have a non-routine discharge compared to PLE patients without diabetes. The presence of type 2 diabetes was associated with even greater odds (a 26.2% increase) of having non-routine discharges.

The final cohort of kidney diseases-related hospitalization contained 504,320 discharge records. The association between diabetes and kidney diseases-related hospitalization cost was also modified by age. The incremental cost of type 1 diabetes to kidney diseases-related hospitalization was $922 for patient below 65 years and $1,320 for patient age 65 years or older. Among patients below 65 years, the kidney diseases

hospitalization cost for patients with type 2 diabetes was $785 lower than that for patients without diabetes. However, among patients age 65 years or older, the cost for patients with type 2 diabetes was only $84 lower than the patients without diabetes. The presence of type 1 diabetes was associated with a 33.2% increase in the odds of having non-routine discharges; while the presence of type 2 diabetes was associated with a 20.2% increase in the odds of having non-routine discharges.

The coronary atherosclerosis-related hospitalization cohort contained 546,488 discharge records. The association between diabetes and coronary-atherosclerosis related hospitalization cost was also modified by age. The incremental cost of type 1 diabetes was $1,796 among hospitalized coronary atherosclerosis patients age 65 years or older, while the cost for patients with type 1 diabetes comorbidity was $550 lower than patients without diabetes among those age below 65 years. Type 1 diabetes was associated with a 35.4% increase in the odds of having non-routine discharges, while type 2 diabetes did not have any significant effect on coronary atherosclerosis-related hospitalization discharge status.

In sum, this study found that severe peripheral lower-extremity diseases and severe coronary atherosclerosis are associated with significant increases in diabetes-related hospitalization cost. In addition, severe PLE was also associated with increased likelihood of having non-routine discharges after diabetes-related hospitalization. The impact between diabetes and complications-related hospitalization cost varies by age group and diabetes type. Among patients with PLE-related hospitalization, cost was highest among patients age <65 years and without comorbid diabetes. In the kidney diseases-related hospitalization cohort, cost was highest for patients younger than 65

years and also had comorbid type 1 diabetes. Among patients with coronary atherosclerosis-related hospitalization, cost was highest for patients 65 years and older and who had type 1 diabetes comorbidity. Both type 1 and type 2 diabetes are associated with higher odds of having non-routine discharges after complications-related hospitalization.

The findings of this study highlighted the importance of peripheral lower extremity diseases as a driver of diabetes-related hospitalization cost. Optimal diabetes disease management programs should be adopted nationwide to reduce the incidence and prevalence of diabetes complications and improve the overall population health.

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Chapter 1: Introduction

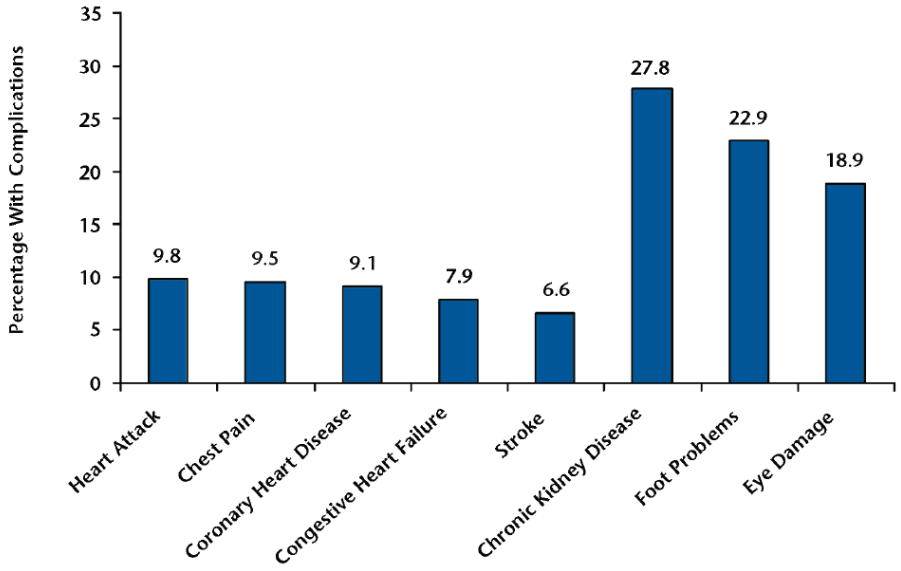
1.1 Introduction

Diabetes is an increasing burden for the health care system in the United States (U.S.). The 2014 National Diabetes Statistics Report indicated that 29.1 million people or 9.3% of the U.S. population have diabetes. Among people whose age is 65 years or older, the prevalence of diabetes is 25.9% (CDC, 2014). The total direct medical cost of diabetes in the U.S. has reached a stunning $176 billion in 2012, of which the largest proportion was attributed to hospital inpatient care (43%) (American Diabetes Association, 2013). The economic burden that diabetes have imposed onto the health care system in the U.S. is likely to worsen with the projection that diabetes prevalence will increase to 21% of the U.S. population by 2050 (Boyle et al., 2010).

Diabetes contributes to the development of various microvascular and macrovascular complications that result in increased morbidity and mortality. Among diabetes-related complications, diabetic retinopathy, diabetic nephropathy and diabetic neuropathy are three major microvascular complications, while peripheral arterial disease and cardiovascular diseases are two leading macrovascular complications. For example, diabetes increases the risk of peripheral vascular disorders 2- to 4- fold (Hirsch et al., 2005). In 2010, about 73,000 non-traumatic lower-limb amputations due to peripheral vascular disorders or neuropathy were performed in adults with diabetes (ADA, 2013). Diabetes was listed as the primary cause of kidney failure in 4% of all new cases in 2011. (CDC, 2014). Figure 1 shows the prevalence of several diabetes complications among

patients with type 2 diabetes based on the 1999-2004 National Health and Nutrition Examination Survey (NHANES).

Figure 1: Prevalence of diabetes complications among patients with type 2 diabetes



Diabetes and its complications are associated with increased rate of health care resource use. Table 1 summarizes the rate ratio of U.S. national health care use among patients with diabetes compared to the general population (Dall et al., 2010). For instance, the rate of physician office visits among patients with type 2 diabetes is 2.9 times the rate of office visits among patients without diagnosis of diabetes. The health care resource use rate is even higher among diabetes patients with various complications. The average hospital inpatient stays for type 1 diabetes with peripheral vascular disorders is 6.0 times the inpatient stays for the population without diabetes. Type 2 diabetes patients with peripheral vascular disorders have inpatient days 5.7 times longer than those without diabetes.

Table 1: Use of ambulatory visits, emergency visits, and hospital inpatient days by diabetes status for the U.S. population ages 45-67, 2007

Service setting	Utilization rate ratios			
Ambulatory visits	**Type 1 diabetes**	**Type 2 diabetes**	**Undiagnosed**	**Pre-diabetes**
Peripheral vascular diseases	3.5	2.9	1.5	1.1
Neurological symptoms	7.9	4.9	1.3	1.4
Cardiovascular disease	1.7	2.0	1.7	1.1
Renal complications	4.1	2.9	1.5	1.6
Endocrine complications	1.3	1.4	1.3	1.7
Ophthalmic complications	5.7	3.6	1.0	1.0
Other diabetes complications	4.1	3.1	1.0	1.0
Emergency visits				
Peripheral vascular diseases	5.4	3.7	1.0	1.0
Neurological symptoms	4.0	2.5	1.0	1.0
Cardiovascular disease	3.1	3.0	1.4	1.0
Renal complications	3.1	2.8	1.0	1.0
Endocrine complications	14.7	8.3	1.0	1.0
Ophthalmic complications	2.3	2.3	1.0	1.0
Other diabetes complications	2.8	2.7	1.0	1.0
Hospital inpatient days				
Peripheral vascular diseases	6.0	5.3	2.2	1.0
Neurological symptoms	10.9	5.8	1.8	1.0
Cardiovascular disease	7.1	6.1	2.2	1.0
Renal complications	15.3	6.7	2.1	1.0
Endocrine complications	23.0	9.8	1.0	1.0
Ophthalmic complications	7.4	7.2	1.0	1.0
Other diabetes complications	12.9	10.3	1.0	1.0

(Source: Dall et al., 2010)

Diabetes has imposed huge economic burden to the health care system worldwide. Studies have estimated that an average of 11.6% of the total health care expenditure in the world is spent on diabetes in 2010. An average of $703 per person is spent on diabetes globally in 2010 (Zhang et al., 2010). In the U.S., the total estimated cost of diagnosed diabetes in 2012 is $245 billion, including $176 billion direct medical costs and $69 billion indirect cost (ADA, 2012).

Treatment of diabetes-related complications accounts for a significant proportion of the medical care/treatment costs for diabetes. According to a 2007 ADA report estimate, one third of the total medical cost for diabetes is spent on treating complications. When compared to regular diabetes patients with no complications, a

European-based study found that the presence of microvascular and macrovascular complications increased the direct medical costs by 70% and a 100% respectively. The presence of both microvascular and macrovascular complications resulted in a 3.5-fold increase in costs as compared to those without the two vascular complications (Williams et al., 2002). Many studies in the past have consistently shown that diabetes complications are associated with increased total medical costs by aggregating all health care-related costs (e.g., hospital inpatient, hospital outpatient, physician office, emergency department visit costs, prescription drugs, and durable medical equipment) (Galarraga et al., 2015; Gilmer et al., 2005; Yeaw et al., 2014).

Although it is well understood that hospitalization cost account for a large portion of total medical costs, hospitalization cost for care/treatment specific to diabetes-related complications have not been completely examined. Therefore, this dissertation research is carried out with a focus on estimating the incremental impact of several highly prevalent diabetes complications on hospital inpatient cost. Understanding of the incremental cost of diabetes complications addresses an important gap in our current knowledge about the underlying factors that contribute to high cost diabetes-related hospitalizations. Furthermore, studies that have looked at diabetes-related complications and health care cost usually have taken into account only the presence or absence of complication(s) without regard for the severity of the complication(s). However, from an economic and a clinical perspective, disease severity is an important consideration and should be incorporated in the analysis in order to obtain a reliable estimate (Young et al., 2008). Thus, this study aims to explore the association between the presence and severity of diabetes-related complications and diabetes-related hospitalization costs.

In addition, in estimating hospitalization cost and health care utilization, it is important to consider the patients' hospitalization discharge status. A patient who has a non-routine discharge (e.g. to a skilled nursing facility or a short-term hospital) will incur more subsequent cost and impose heavier care burdens on the healthcare system when compared with a patient who has a routine discharge (e.g. discharge to home without home healthcare) (Mor et al., 2010). The possible associations between diabetes-related complications and discharge status also have not been well documented in literature, and will also be examined as a focus of this study.

This study expands current knowledge in four important ways: by taking into account only inpatient hospital cost for diabetes-related hospitalizations instead of aggregating total medical cost; by defining not only the presence, but also the severity of complications highly associated with diabetes; by estimating the incremental impact of individual complication and combinations of complications on hospital encounter costs; and finally by illustrating the association between diabetes complications and hospitalization discharge status.

1.2 Objectives and Specific Aims

The overall objective of the study is to investigate the hospital inpatient cost and healthcare utilization of diabetes and its complications from two perspectives: the influence that complications play on diabetes-related hospitalizations and the influence diabetes has on hospitalizations for major complications. The primary objective of this study is to examine the association between the presence and severity of diabetes-related complications and diabetes-related hospitalization cost and discharge status. The secondary objective of this study is to explore how the presence and type of diabetes

influence complications-related hospitalization cost and discharge status. The three diabetes complications included in this study are:

i) Peripheral lower-extremity (PLE) diseases (peripheral arterial diseases and neuropathy);
ii) Kidney diseases;
iii) Coronary atherosclerosis.

There are three reasons for choosing these three complications as examples out of all the microvascular and macrovascular complications of diabetes. First of all, peripheral arterial diseases and neuropathy are both classified under peripheral lower extremity diseases because they can both result in lower extremity amputation, which is considered as one of the most severe forms of diabetes-related complications. This grouping is consistent with CDC reporting on diabetes complications (http://www.cdc.gov/diabetes/statistics/hosplea/allthree.htm). Secondly, kidney diseases are a severe form of diabetes microvascular complications, leading to end stage renal diseases and the ultimate need for dialysis (Go et al., 2004; Chertow et al., 2005). Thirdly, coronary atherosclerosis is the main cause of coronary heart disease including myocardial infarction and angina (Burchfiel, 1993). Cardiovascular diseases generally have varying definitions across literature (Labarthe, 2010). Usually the differences in definition center around which of the multiple cardiovascular diseases are included in any one study. This increases the difficulty in interpreting and applying research findings. Thus focusing on coronary atherosclerosis will simplify the research question and avoid potential confounding influence from inconsistent or overlapping definitions. While all forms of diabetes complications could potentially carry some incremental cost, the three

complications included in this study are highly prevalent and interrelated and therefore could represent a huge burden to the health care system.

In keeping with the primary and the secondary objective, this study has four specific aims:

Aim 1: To examine the association between the presence and severity of diabetes complications and diabetes-related hospitalization cost.

> **Hypothesis 1a:** Diabetes-related hospitalization cost is significantly higher for hospitalized diabetes patients with peripheral lower extremity disease than diabetes patients without peripheral lower extremity diseases.
>
> **Hypothesis 1b:** Diabetes-related hospitalization cost is significantly higher for hospitalized diabetes patients with kidney diseases than diabetes patients without kidney diseases.
>
> **Hypothesis 1c:** Diabetes-related hospitalization cost is significantly higher for hospitalized diabetes patients with coronary atherosclerosis than diabetes patients without coronary atherosclerosis.

Aim 2: To examine the association between the presence and severity of diabetes-related complications and hospitalization discharge status.

> **Hypothesis 2a:** Hospitalized diabetes patients with peripheral lower extremity diseases are more likely to have non-routine discharges when compared to hospitalized diabetes patients without peripheral lower extremity diseases.

Hypothesis 2b: Hospitalized diabetes patients with kidney diseases are more likely to have non-routine discharges when compared to hospitalized diabetes patients without kidney diseases.

Hypothesis 2c: Hospitalized diabetes patients with coronary atherosclerosis are more likely to have non-routine discharges when compared to hospitalized diabetes patients without coronary atherosclerosis.

Aim 3: To explore the association between the presence and type of diabetes and complications-related hospitalization cost.

Hypothesis 3a: PLE-related hospitalization cost is significantly higher for hospitalized PLE patients with diabetes than PLE patients without diabetes.

Hypothesis 3b: Kidney diseases-related hospitalization cost is significantly higher for hospitalized kidney diseases patients with diabetes than kidney diseases patients without diabetes.

Hypothesis 3c: Coronary atherosclerosis-related hospitalization cost is significantly higher for hospitalized coronary atherosclerosis patients with diabetes than hospitalized coronary atherosclerosis patients without diabetes.

Aim 4: To explore the association between the presence and type of diabetes and complications-related hospitalization discharge status.)

Hypothesis 4a: Hospitalized PLE patients with diabetes are associated with increased likelihood of having non-routine discharges when compared to hospitalized PLE patients without diabetes.

Hypothesis 4b: Hospitalized kidney diseases patients with diabetes are associated with increased likelihood of having non-routine discharges when compared to hospitalized kidney diseases patients without diabetes.

Hypothesis 4c: Hospitalized coronary atherosclerosis patients with diabetes are associated with increased likelihood of having non-routine discharges when compared to hospitalized coronary atherosclerosis patients without diabetes.

1.3 Key terms

The key terms of this study and their definitions are listed in Table 2.

Table 2: Study key terms and definitions

Study Term	Definition
Healthcare Cost and Utilization Project (HCUP)	The HCUP is a family of health care databases and related software tools and products developed through a Federal-State-Industry partnership and sponsored by the Agency for Healthcare Research and Quality. HCUP databases bring together the data collection efforts of State data organizations, hospital associations, private data organizations, and the Federal government to create a national information resource of encounter-level health care data. (http://www.hcup-us.ahrq.gov/overview.jsp)
National Inpatient Sample (NIS)	The NIS is one of the HCUP databases. The NIS is the largest publicly available all-payer inpatient health care database in the United States, yielding national estimates of hospital inpatient stays. (http://www.hcup-us.ahrq.gov/nisoverview.jsp)
Hospital inpatient stay (Hospitalization)	https://www.medicare.gov/Pubs/pdf/11435.pdf https://www.cms.gov/Newsroom/MediaReleaseDatabase/Fact-sheets/2015-Fact-sheets-items/2015-07-01-2.html
Hospital discharge	Hospitalizations are expressed as number of discharges, not as unduplicated patients; as a result a single patient with multiple hospitalizations can be counted more than once.
Cost-to-charge ratio (CCR)	The CCR is the ratio that allows the conversion of hospital inpatient charge to cost estimate. The CCR is constructed using all-payer, inpatient cost and charge information from the detailed reports by hospitals to the Centers for Medicare &

	Medicaid Services (CMS) each year. (http://www.hcup-us.ahrq.gov/db/state/CCR2012NISUserGuide.pdf)

1.4 Study design and limitations

This study adopts a cross-sectional study design with secondary data analysis. It utilizes the 2010 – 2012 National Inpatient Sample (NIS) database from the Healthcare Cost and Utilization Project (HCUP). Exploratory statistical analyses including generalized linear model and logistic regression are used to examine the twelve hypotheses. Model fit and assumptions are examined accordingly.

Several limitations related to the study need to be acknowledged beforehand.

1. This study depends on medical coding in the data record. There might be incorrect or inconsistent diagnosis or procedure coding or other misspecifications in the dataset that may affect the reliability and validity of the study. For this study, the diagnosis codes that appear within a hospitalization record are assumed to be correct ones but error can exist.

2. The dataset contains only diagnosis and procedure codes while other important information such as laboratory test of HbA1c level or diabetes prescriptions used are unknown. The HbA1c level is an important predictor of diabetes-related hospitalization and health care resource use.

3. The NIS dataset contains inpatient data from participating U.S. community hospitals but has some noticeable patient population exception. Participating hospitals for

instances do not include Veterans administration (VA) or Indian Health Service (IHS) hospitals. This may affect the generalizability of the study results.

4. Only Zip code level household income is available in the dataset. Though Zip code level income has been extensively used in health care literature, the effect estimate for income level may not be precise enough for making inferences related to the association between household income and hospitalization costs.

5. This study is an observational cross-sectional study. It may show that diabetes complications are associated with hospitalization costs and hospitalization discharge status. No causal relationship between diabetes complications and health care utilization, however, can be drawn from this study.

6. This study proposes the use of the cost-to-charge ratio to determine the cost of a hospitalization. The cost-to-charge ratio is the cost divided by the hospital charge: the closer the cost-to-charge ratio is to 1, the less difference there is between the actual costs and the hospital's gross charges. The cost-to-charge ratio is determined by CMS using data from each state. It therefore varies from state to state. Applying cost-to-charge ratio to calculate the costs of hospitalization will not be the true costs of hospitalization had hospitalization records been available. Nonetheless, the cost-to-charge ratio is the accepted industry standard and because of its specificity by hospital, it is the closet measure available to assess costs.

1.5 Significance

There is a plethora of studies that examine the association between diabetes complications and total medical costs; however, the incremental impact of diabetes

complications on hospital inpatient cost has rarely been explored at per episode level. What's more, studies that have looked at diabetes complications and health care costs usually have taken into account only the presence or absence of complication(s) without regard for the severity of the complication. Incorporating the severity of complications is essential for obtaining a reliable estimate on the association between diabetes complications and health care costs. Last but not least, previous studies seldom explore the association between diabetes complications and hospitalization discharge status. Therefore this study is significant for a number of reasons:

First, this study will provide reliable estimates of hospital inpatient cost and health care utilization needs for patients with diabetes and related complications versus those without. The incremental cost of each diabetes complication from this study will improve current understanding of the economic cost of diabetes. Innovative care delivery models such as Accountable Care Organizations (ACOs) and Patient Centered Medical Homes (PCMHs) are currently emerging for diabetes disease management in the U.S. to reduce the per capita cost of health care. The incremental cost estimates obtained from my study can be applied in various health economic models to evaluate these diabetes management programs in ACOs or PCMHs.

Second, this study can be used for identifying patients at a higher probability of needing additional health care services, which will enhance resource allocation efforts and reduce overall health care expenditures. Identifying high-cost complications could also help pinpoint targets for secondary prevention among diabetes patients using strategies such as screening and early intervention, which will have the potential of

producing cost-savings in the long term by reducing morbidity and mortality of diabetes patients.

Third, elucidating factors associated with hospitalization discharge status will help reasonable planning for discharge during hospital inpatient stay and effective resource allocation to patients for whom additional care is needed.

The significance of this study increases with the growing recognition of diabetes as an epidemic in the U.S. It has been predicted that the annual diagnosed diabetes incidence will increase from about 8 cases per 1,000 in 2008 to about 15 per 1,000 in 2050. The prevalence of diabetes will increase from 14% in 2010 to 21%-33% by 2050 (Boyle et al., 2010). These increases are due to the aging of the U.S population and increasing numbers of high-risk minority groups in the population. Effective disease management strategies need to be designed and implemented to alleviate the national diabetes burden.

Chapter 2: Literature review

This chapter reviews the existing literature related to the following areas: (1) the epidemiology of diabetes and its complications; (2) the health care costs and utilization associated with diabetes and its complications: (3) the incremental costs of comorbidities.

This literature was searched using PubMed, Ovid Medline and Google Scholar with the University of Minnesota library system. Key search terms include: diabetes, peripheral artery diseases, diabetic neuropathy, peripheral lower-extremity diseases, diabetic nephropathy, kidney diseases, coronary atherosclerosis, hospitalization, hospital inpatient cost, discharge status, routine discharge, and non-routine discharge.

2.1 Background

2.1.1 Diabetes mellitus

Diabetes mellitus is a family of metabolic diseases in which blood glucose levels are above normal (hyperglycemia). Diabetes is generally caused by deficiency of pancreas in insulin secretion, insulin action, or both. Multiple pathological processes are present in the development of diabetes such as β−cells destruction with subsequent insulin deficiency or resistance to insulin action. Insulin secretion damage and insulin deficient action may be both present in the same patient; therefore it is often not clear which abnormality is the primary cause of hyperglycemia.

Most diabetes cases fall into two broad etiopathogenetic categories: Type1 diabetes and Type 2 diabetes. Type 1 diabetes, also known as insulin-dependent diabetes or juvenile-onset diabetes, results from a cellular-mediated autoimmune destruction of the β-cells of the pancreas, which usually leads to absolute insulin deficiency. Type 1

diabetes accounts for 5-10% of the diabetes cases. Type 2 diabetes accounts for 90-95% cases of diabetes and was previously known as non-insulin dependent diabetes or adult-onset diabetes. Type 2 diabetes is insulin resistance, relative (rather than absolute) insulin deficiency, and insulin secretory defect with insulin resistance. Other specific types of diabetes also include genetic defects of the β-cell, genetic defects in insulin action, diseases of exocrine pancreas, endocrinopathies, drug- or chemical-induced diabetes, and gestational diabetes.

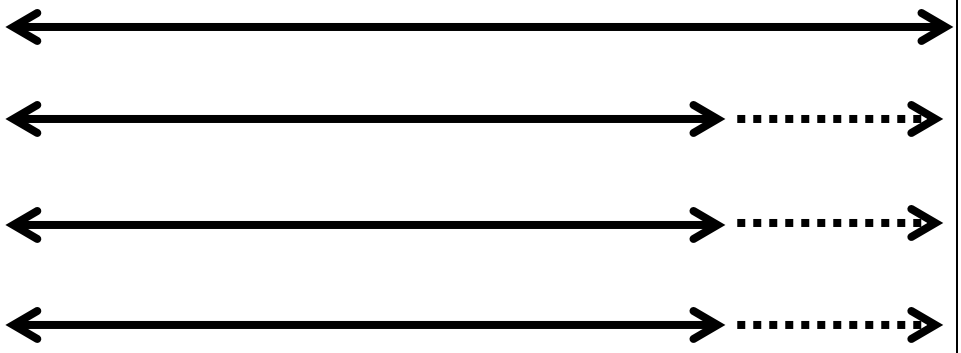
The diagnosis of diabetes is based on the following three criteria in the position statement of the American Diabetes Association (ADA, 2005):

(1) Symptoms of diabetes plus casual plasma glucose concentration ≥200 mg/dl (11.1 mmol/l). or

(2) FPG (fasting plasma glucose) ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8h. or

(3) 2-hour post load glucose ≥200 mg/dl during an oral glucose tolerance test (OGTT). The test should be performed as described by WHO, using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water.

Figure 2: Disorders of glycaemia: etiologic types and stages

	Normoglycemia	**Hyperglycemia**			
	Normal Glucose regulation	Impaired Glucose Tolerance or Impaired Fasting Glucose (Pre-Diabetes	**Diabetes Mellitus**		
			Not insulin requiring	Insulin requiring for control	Insulin requiring for survival
Type 1					
Type 2					
Other Specific Types					
Gestational Diabetes					

(Source: adapted from ADA position statement, 2005)

Common risk factors for Type 2 diabetes include: age (especially after 45 years of age); being overweight or obese; a family history of diabetes; having an African American, Hispanic/Latino, American Indian, Asian American, or Pacific Islander racial or ethnic background; a history of gestational diabetes or having given birth to a baby weighing nine pounds or more; and being physically active less than three times a week. Risk factors for Type 1 diabetes are less well defined; however, autoimmune, genetic, and environmental factors are involved in the development of Type 1 diabetes.

Diabetes can be treated and managed by healthy eating, regular physical activity, and medications to lower blood glucose levels. Persons diagnosed with type 1 diabetes are required to have insulin while patients with type 2 diabetes are treated with a number of oral anti-hyperglycemic medications, non-insulin injectable agents, and/or insulin. Some patients with diabetes may also undergo organ transplant in an attempt to “cure”

diabetes. In addition to managing diabetes itself, diagnosed diabetes complications are also managed using medications, surgeries, or in some cases, such as kidney diseases, highly invasive procedures like the chronic need for dialysis. The result is a patient with a complex array of medications, therapies, and health care needs requiring a number of health care professionals to manage the condition.

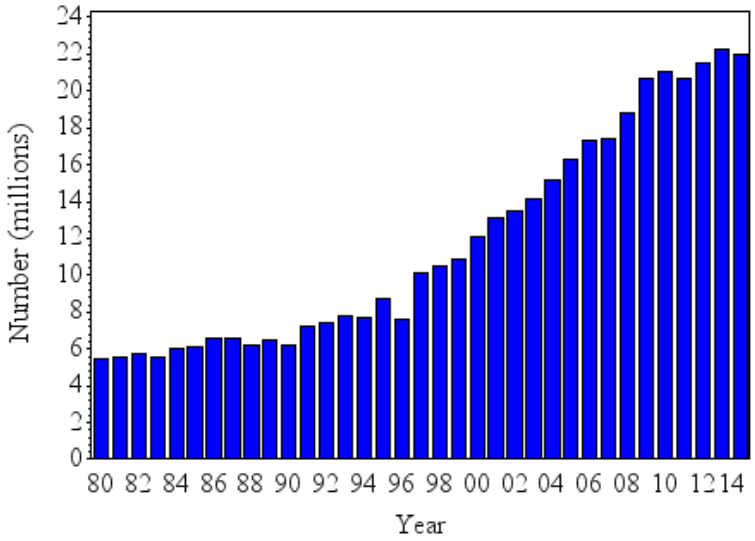
Reducing cardiovascular disease risk factors is another important aspect of good diabetes management. Patient education and self-care practices are also crucial in diabetes management.

2.1.2 Epidemiology of Diabetes

Diabetes is an important public health problem both in the U.S. and worldwide. According to the Center for Disease Control (CDC), 29.1 million people or 9.3% of the U.S. population have diabetes: 21.0 million people with diagnosed diabetes and 8.1 million people with undiagnosed diabetes. The number of Americans with Diagnosed diabetes has increased fourfold (from 5.5 million to 22.0 million) from 1980 to 2014 (Figure 3). The distribution of diabetes prevalence by age and sex is presented in Table 1. In 2009 – 2012, based on fasting glucose or HbA1C levels, 37% of U.S. adults aged 20 years or older had prediabetes (51% of those aged 65 years or older). It had been projected that annual diagnosed diabetes incidence would increase from 8 per 1,000 in 2008 to about 15 in 2050. The prevalence of diabetes was projected to be from 21% to 35% in the U.S. by 2050 (Doyle et al., 2010). The prevalence of diabetes worldwide was estimated to rise from 4.0% in 1995 to 5.4% by the year 2025. The prevalence was predicted to be higher in developed countries than developing countries. The majority of people with diabetes are in the age range of 45 – 64 years in developing countries; while

the majority of patients with diabetes are aged ≥65 years in developed countries (King et al., 1998).

Figure 3: Number of civilian, non-institutionalized persons with diagnosed diabetes, United States, 1980 – 2014



(Source: http://www.cdc.gov/diabetes/statistics/prev/national/figpersons.htm)

Table 3: Diagnosed and undiagnosed diabetes among people aged 20 years or older in the U.S. (2012)

	Number with diabetes (millions)	**Percentage with diabetes** (unadjusted)
Total		
20 years or older	28.9	12.3%
By age		
20 – 44	4.3	4.1%
45 – 64	13.4	16.2%
65 years or older	11.2	25.9%
By sex		
Men	15.5	13.6%
Women	13.4	11.2%

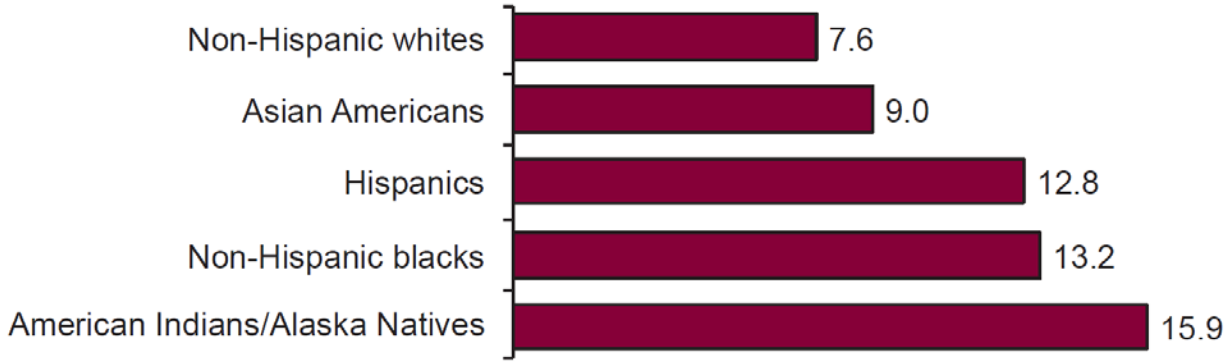
(Source: 2009 – 2012 National Health and Nutrition Examination Survey estimates applied to 2012 U.S. Census data.)

There are remarkable racial and ethnic differences in diagnosed diabetes among people aged 20 years or older in the U.S. As indicated in Figure 4, the percentage of

diagnosed diabetes is generally higher among racial/ethnic minority groups than Whites. Taken into account the specific classification of racial/ethnic groups, the prevalence of diabetes is as the following:

- Among Hispanic adults, the age-adjusted rate of diagnosed diabetes was 8.5% for Central and South Americans, 9.3% for Cubans, 13.9% for Mexican Americans, and 14.8% for Puerto Ricans.
- Among Asian American adults, the age-adjusted rate of diagnosed diabetes was 4.4 % for Chinese, 11.3% for Filipinos, 13.0% for Asian Indians, and 8.8% for other Asians.
- Among American Indian and Alaska Native adults, the age-adjusted rate of diagnosed diabetes differed by region from 6.0% among Alaska Natives to 25.1% among American Indians in southern Arizona.

Figure 4: Age-adjusted percentage of people aged 20 years or older with diagnosed diabetes, by race/ethnicity, United States, 2010 – 2012

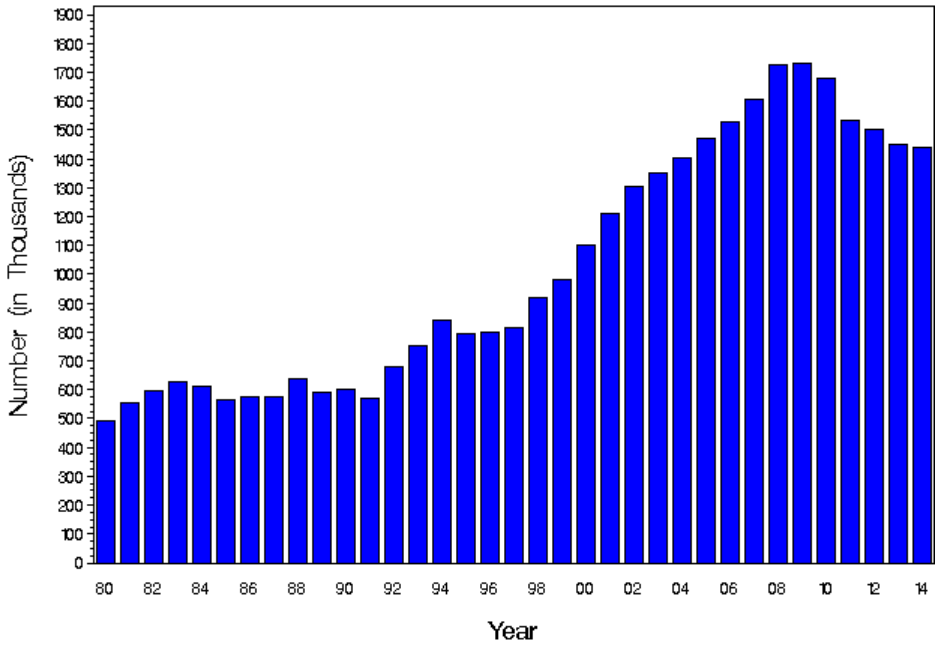


(Source: 2010 – 2012 National Health Interview Survey and 2012 Indian Health Service's National Patient Information Reporting System.)

The incidence rate trend of diabetes during the past thirty years was different from the trend of diabetes prevalence. The number of adults in the U.S. with newly diagnosed

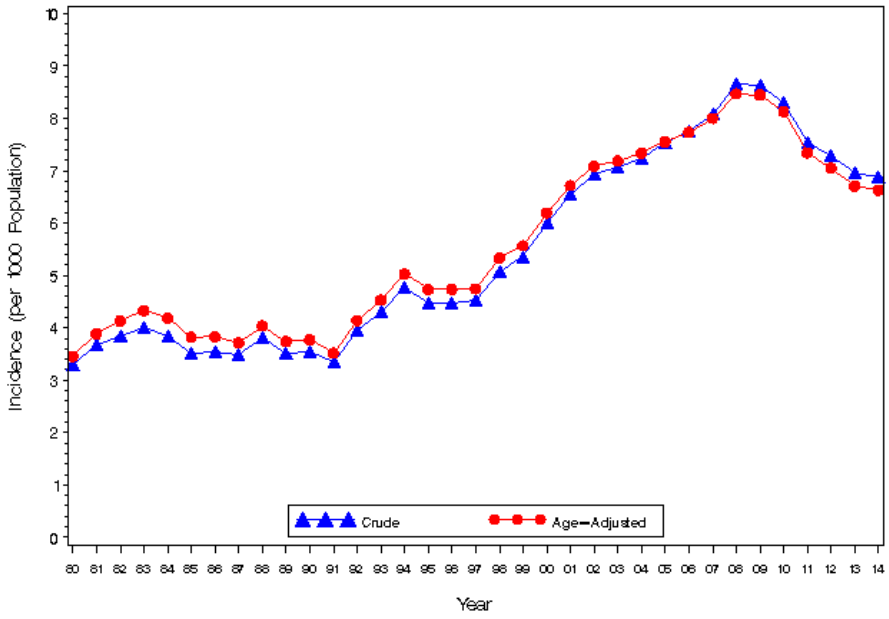
diabetes has increased by threefold from 493,000 in 1980 to more than 1.4 million in 2014. The number of new cases increased sharply from 1991 to 2009; however, the number of new cases dropped by a small amount from 2009 to 2014 (Figure 5). In terms of incidence rate, the age-adjusted incidence rate more than doubled from 3.8 to 8.5 per 1,000 between 1990 and 2008. However, from 2008 to 2014, there is a significant decline in age-adjusted incidence rate of diabetes from 8.5 to 6.5 per 1,000 (Figure 6).

Figure 5: Annual number (in thousands) of new cases of diagnosed diabetes among adults aged 18 – 79 years, United States, 1980 – 2014



(Source: http://www.cdc.gov/diabetes/statistics/incidence/fig1.htm)

Figure 6: Crude and age-adjusted incidence of diagnosed diabetes per 1,000 population aged 18 – 79 years, United States, 1980 – 2014



(Source: http://www.cdc.gov/diabetes/statistics/incidence/fig2.htm)

2.1.3 Epidemiology of diabetes complications

Diabetes is a rising problem worldwide and in the U.S. not only due to the diseases itself but also because of the growing burden of diabetes complications. Overall, diabetes complications are classified as short-term (acute) complications and long-term (chronic) complications. Short-term complications include diabetic ketoacidosis, hyperglycemia hyperosmolar state, hypoglycemia, and diabetic coma. Short-term complications are associated with higher health care utilization. For example, around 282,000 emergency room visits for adults had hypoglycemia as the primary cause in 2011. In 2011, about 175,000 emergency room visits had diabetic ketoacidosis and hyperglycemic hyperosmolar state as the primary cause. However, this study will focus

primarily on long-term complications because long-term complications represent a recurring and constant need to health care system.

All forms of diabetes contribute to the development of long-term complications, which are major factors in both the mortality and morbidity among patients with diabetes. Long-term diabetes complications can be classified as microvascular or macrovascular. Among diabetes-related complications, diabetic retinopathy, diabetic nephropathy and diabetic neuropathy are three major microvascular complications. Peripheral arterial disease and cardiovascular diseases are two leading macrovascular complications. Figure 1 showed the prevalence of the most common diabetes complications among patients with type 2 diabetes. As indicated by Figure 1, the prevalence of microvascular complications (chronic kidney diseases, foot problems, and eye damage) was much higher than the prevalence of macrovascular complications (heart attack, chest pain, coronary heart disease, congestive heart failure, and stroke).

However, another epidemiology study among patients with type 2 diabetes in a large integrated health system found different prevalence trends for each of the chronic complications. In that study, the most prevalent type 2 diabetes complication was cardiovascular diseases (26.9% in 2008 and 22.3% in 2013). On the other hand, retinopathy had lowest prevalence (3.2% in 2008 and 3.4% in 2013). The prevalence of peripheral artery diseases was 5.4% in 2008 and 4.9% in 2013. The prevalence of neuropathy was 19.5% and 18.0% for 2008 and 2013 respectively. The prevalence of nephropathy was 26.8% and 25.9% for 2008 and 2013 (Pantalone et al., 2015). The epidemiology trend of diabetes complications is changing over time. A recent study found that the incidence rates of complications such as lower-extremity amputation, acute

myocardial infarction, stroke, and end-stage renal diseases were decreasing from 1990 to 2010. Nonetheless, a huge burden of diabetes complications persisted due to continual increase in the prevalence of diabetes (Gregg et al., 2014).

Cardiovascular diseases

Epidemiologic data from the 1950s to 2003 indicated that the incidence of cardiovascular complications among patients with diabetes have declined significantly over time (Fox et al., 2004; Booth et al., 2006). The greatest declines occurred during the 1980s and 1990s, which coincided with medicine advances in controlling glycemic levels, blood pressure, and cholesterol levels. However, subclinical coronary artery diseases among patients with diabetes may be a more severe problem. For example, coronary artery calcium scanning of asymptomatic patients showed that patients with diabetes had a significant increase in the prevalence of coronary artery calcium scores ≥ 400 (25.9%) compared to the matched nondiabetic control groups (14.4%) (Schurgin et al., 2001).

More importantly, cardiovascular diseases play a crucial role in diabetes-related mortality though its prevalence is lower compared to microvascular complications. Studies estimated that up to 65% of all deaths in people with diabetes were caused by cardiovascular diseases (Geiss et al., 2005). Cardiovascular disease death rates were about 2 – 4 times higher among adult patients with diabetes than patients without diabetes with adjustment for population age differences (Deshpande et al., 2008).

Risk factors for cardiovascular diseases among patients with diabetes are consistent with those among patients without diabetes, including hypertension,

hypercholesterolemia, and smoking. However, a prospective cohort study found that the presence of even one of these risk factors results in poorer outcomes among patients with diabetes than among those without diabetes (Stamler et al., 1993).

Peripheral Arterial Diseases (PAD)

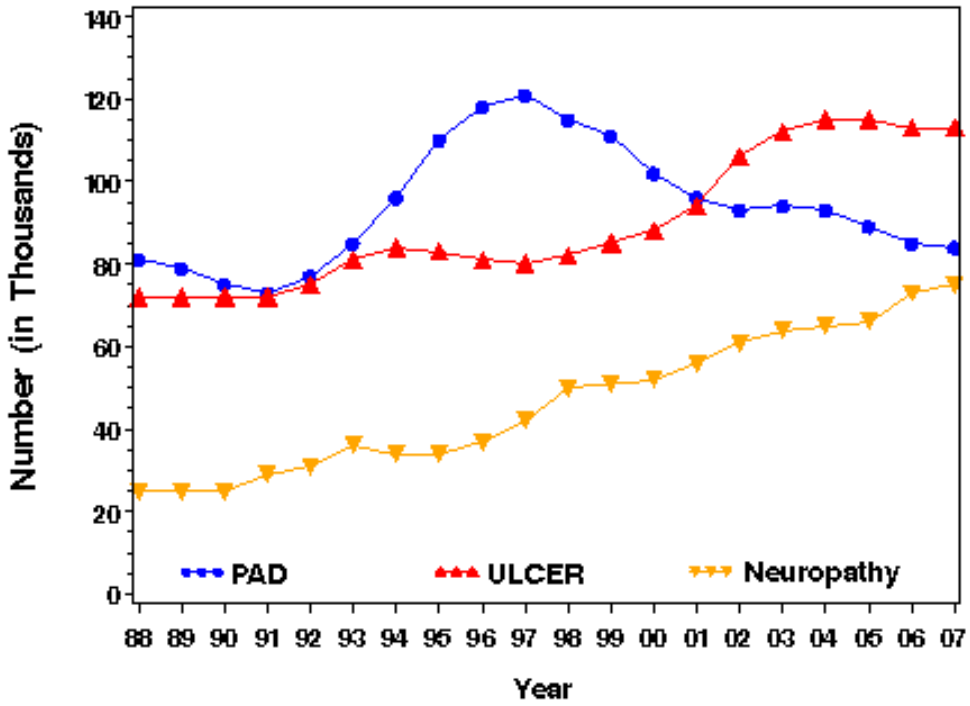
Peripheral arterial diseases (PAD) or peripheral vascular diseases (PVD) is caused by the narrowing of peripheral arteries which carry blood to the arms, legs, stomach, and kidneys. Among patients with diabetes, the risk factors for PAD include age, duration of diabetes, and presence of neuropathy. Other cardiovascular diseases risk factors are also associated with an increased risk for PAD (King et al., 2005). Peripheral arterial diseases have two types of symptoms: intermittent claudication and critical limb ischemia (Hirsh et al., 2005). The disease progression and severity of PAD are commonly by two scales: Fontaine classification system and Rutherford classification system (Rutherford et al., 1991). PAD and neuropathy are two major risk factors for lower extremity amputation. In 2010, around 73,000 non-traumatic lower-limb amputations were performed in adults with diagnosed diabetes.

The Framingham Heart Study demonstrated that the annual incidence of lower extremity PAD increased with age and in response to the prevalence of atherosclerosis risk factors. The incidence of intermittent claudication was 61 per 10,000 men and 54 per 10,000 women within the ages of 65 to 74 years (Kannel et al., 1970). Criqui et al. showed that the prevalence of lower extremity in a Southern California population was 2.5% among patients 60 years and younger, 8.3% among those aged 60 to 69 years, and 18.8% among those 70 years and older (Criqui et al., 1985). The San Luis Valley

Diabetes study examined the prevalence of lower extremity PAD among diabetes patients. The prevalence of lower extremity PAD was 13.7% based on the study diagnosis criteria (Hiatt et al., 1990).

Using data from the National Center for Health Statistics, Figure 7 plots the trend of hospital discharges with PAD, ulcer/inflammation/infection (ULCER), or neuropathy in the U.S. from 1988 to 2007. The number of hospital discharges for PAD increased from 1991 to 1996 and decreased from 1996 to 2007. However, the number of discharges for neuropathy and ulcer increased throughout the period. In 2007, about 113,000 hospital discharges were for ulcer, 84,000 were for PAD, and 75,000 were for neuropathy.

Figure 7: Number (in thousands) of hospital discharges with peripheral arterial disease (PAD), ulcer/inflammation/infection (ULCER), or neuropathy as first-listed diagnosis and diabetes as any-listed diagnosis United States, 1988–2007



Retinopathy

Diabetic retinopathy is caused by damage to the small blood vessels in the retina which may result in vision loss. Diabetic retinopathy has the highest prevalence compared to other microvascular complications among patients with diabetes. However, retinopathy usually does not result in acute hospitalizations like nephropathy. Each year more than 10,000 new cases of blindness occur among patients with diabetes. In 2005 – 2008, among adults with diabetes aged 40 years or older, 4.2 million (28.5%) patients had diabetic retinopathy. 655,000 (4.4%) of those patients had advanced diabetic retinopathy such as macular edema or proliferative diabetic retinopathy that could lead to severe vision loss (ADA report, 2014).

Nephropathy (Kidney diseases)

Diabetic nephropathy is defined as persistent proteinuria (more than 500 mg of protein or 300 mg of albumin per 24 hours) in patients without urinary tract infection or other diseases causing the proteinuria. Development of clinical nephropathy differs by diabetes types. Progression to nephropathy is relatively late stage in patients with type 1 diabetes (Andersen et al., 1983; Kofoed-Enevoldsen et al., 1987; Bojestig et al., 1994). An epidemiology study of Type 1 diabetes patients 31 years or younger in Denmark observed two incidence peaks of the onset of proteinuria: one after 16 years and another after 31 years duration of diabetes. The cumulative incidence was 45% after 40 years of diabetes (Andersen et al., 1983). However, proteinuria could be present as early at diagnosis of type 2 diabetes though the actual onset of type 2 diabetes may precede its clinical diagnosis by many years (Harris et al., 1992; Gall et al., 1991). This may explain

part of the reason why the prevalence of nephropathy is high at the diagnosis of type 2 diabetes.

Diabetes was listed as the primary cause of kidney failure in 4% of all new cases in 2011. In the same year, 49,677 people of all ages began treatment for kidney failure due to diabetes (the exact nature of treatment – dialysis or transplant – was not specified, however). A total of 228,924 people with kidney failure due to diabetes were living on chronic dialysis or with a kidney transplant (CDC, 2014).

Peripheral Neuropathy

The clinical manifestation of diabetic neuropathy are varying with peripheral, symmetric sensorimotor neuropathy as the most common form along with other forms such as cranial and peripheral motor neuropathies and autonomic neuropathy (Nathan 1993). The onset of peripheral neuropathy is gradual so the disease may go undetected for years. However, peripheral neuropathy can result in a number of impairments, ranging from sensory loss, muscle pain, to foot ulceration and subsequent lower extremity amputations (Boulton et al., 2005; Apelqvist et al., 1993; Pecoraro et al., 1990; Gonzales et al., 2000).

Peripheral neuropathy is a common complication which has estimated prevalence 30% to 50% among patients with diabetes (Candrilli et al., 2007; Gregg et al., 2004; Pirart 1978; Adler et al., 1997). Hyperglycemia is the primary risk factor for peripheral neuropathy (Pirart 1978; Shaw et al., 1999). Other independent risk factors for neuropathy are: age, duration of diabetes, smoking, hypertension, elevated triglycerides,

higher BMI, alcohol consumption, and taller height (Adler et al., 1997; Shaw et al., 1999; Perkins et al., 2001; Tesfaye et al., 2005).

2.2 Health care cost and utilization of diabetes and its complications

This section focuses on health care costs and utilization related to diabetes and its complications. Most of studies reviewed were based in the U.S.; however, certain European or Asian studies were cited as well for the completion of the review.

2.2.1 Overall health economic burden of diabetes and its complications

The American Diabetes Association (ADA) published a series of reports on the economic costs of diabetes in 2002, 2007, and 2012. The ADA adopts a prevalence-based approach that encompasses the U.S. demographics, epidemiologic data, health care cost, and economic data into a Cost of Diabetes Model (ADA report, 2002, 2007, and 2012). A summary table of the cost estimates for these three years is presented in Table 4. The total costs include both direct medical costs and indirect medical costs. Indirect costs associated with diabetes include missing workdays due to health conditions (absenteeism), reduced work productivity while working due to health conditions (presenteeism), reduced workforce participation due to disability, and productivity loss due to premature mortality (Cawley et al., 2008; Fu et al., 2009; Lee et al., 2008).

Table 4: Total medical expenditure attributed to diabetes in 2002, 2007, and 2012.

Year	Direct medical costs	Indirect medical costs	Total medical costs
2002	$91.8 billion	$39.8 billion	$132 billion
2007	$153 billion	$65 billion	$218 billion
2012	$176 billion	$69 billion	$245 billion

As shown in table 4, the total estimated cost of diagnosed diabetes in 2012 was $245 billion, including $176 billion direct medical costs and $69 billion indirect costs. The cost components for the direct medical cost of diabetes are listed in Table 5. The largest component of medical expenditure attributed to diabetes in 2012 was hospital inpatient care (43% of the total medical costs), followed by prescription medication (18%), antidiabetic agents and diabetes supplies (12%), physician office visits (9%), and nursing/residential facility stays (8%).

Table 5: Health care expenditures attributed to diabetes in the U.S. by age-group and type of service, 2012

	Age (years)			
Cost component	<45 (n = 3.3 M)	45–64 (n = 10.2 M)	≥65 (n = 8.8 M)	Total* (N = 22.3 M)
Institutional care				
Hospital inpatient	4,924 (6%)	2,934 (30%)	48,015 (63%)	75,872
Nursing/residential facility	211 (1%)	2,781 (19%)	11,757 (80%)	14,748
Hospice	0 (0%)	3 (9%)	29 (91%)	32
Outpatient care				
Physician office	1,334 (9%)	4,882 (32%)	9,005 (59%)	15,221
Emergency department	1,435 (22%)	2,363 (36%)	2,856 (43%)	6,654
Ambulance services	20 (9%)	169 (77%)	29 (13%)	218
Hospital outpatient	679 (13%)	1,943 (39%)	2,405 (48%)	5,027
Home health	564 (13%)	1,806 (40%)	2,096 (47%)	4,466
Podiatry	43 (20%)	61 (29%)	108 (51%)	212
Outpatient medications and supplies				
Insulin	1,102 (18%)	2,817 (46%)	2,239 (36%)	6,157
Diabetic supplies	238 (10%)	1,003 (44%)	1,056 (46%)	2,296
Other antidiabetic agents†	1,297 (11%)	5,767 (48%)	5,073 (42%)	12,137
Prescription medications	2,443 (8%)	10,398 (33%)	18,875 (60%)	31,716
Other equipment and supplies‡	117 (11%)	309 (29%)	637 (60%)	1,063
Total	14,406 (8%)	57,235 (33%)	104,178 (59%)	175,819

Data sources: NIS (2010), NNHS (2004), NAMCS (2008–2010), NHAMCS (2007–2009), MEPS (2006–2010), NHHCS (2007), and NHIS (2009–2011). †Includes oral medications and noninsulin injectable antidiabetic agents. ‡Includes but not limited to eyewear, orthopedic items, hearing devices, prosthesis, bathroom aids, medical equipment, and disposable supplies. *Numbers do not necessarily sum to totals because of rounding.

(Source: American Diabetes Association, 2013)

The total medical cost attributed diabetes could be interpreted at both country level and individual level. On the one hand, in 2012, the total national health spending in the U.S. was $2.8 trillion (Martin et al., 2014) with $176 billion spent on diabetes. That is to say, diabetes alone accounted for a significant proportion the national health spending. On the other hand, a study in 2010 reported the cost per individual based on the ADA's Cost of Diabetes model and the 2007 cost estimates. According to this study, the total $153 billion direct medical cost of diabetes in 2007 represented an average annual cost per case $2,864 for undiagnosed diabetes, $9,975 for diagnosed diabetes ($9,677 for type 2 and $14,856 for type 1), and $443 for prediabetes. For each American, regardless of diabetes status, this burden denotes a cost of approximately $700 annually (Dall et al., 2010).

Diabetes has imposed a huge economic burden worldwide. Studies had estimated that 11.6% of the total health care expenditure in the world would be spent on diabetes in 2010. Around $376 billion would be spent to prevent and treat diabetes and its complications in 2010. By 2030, this number will increase to $490 billion. An average of $703 per person will be spent on diabetes in 2010 globally (Zhang et al., 2010). A systematic review on the economics of type 2 diabetes found that the direct medical cost of diabetes ranged from $242 in Mexico to $11,917 in the U.S. and the indirect cost ranged from $35 to Pakistan to $16,914 for the Bahamas (Seuring et al., 2015).

With regard to health care resource among patients with diabetes, 85.3% of adults with diagnosed diabetes reported taking insulin or pills for their diabetes (CDC, 2011). About 14 emergency department (ED) visits occurred per 1,000 patients with diabetes in

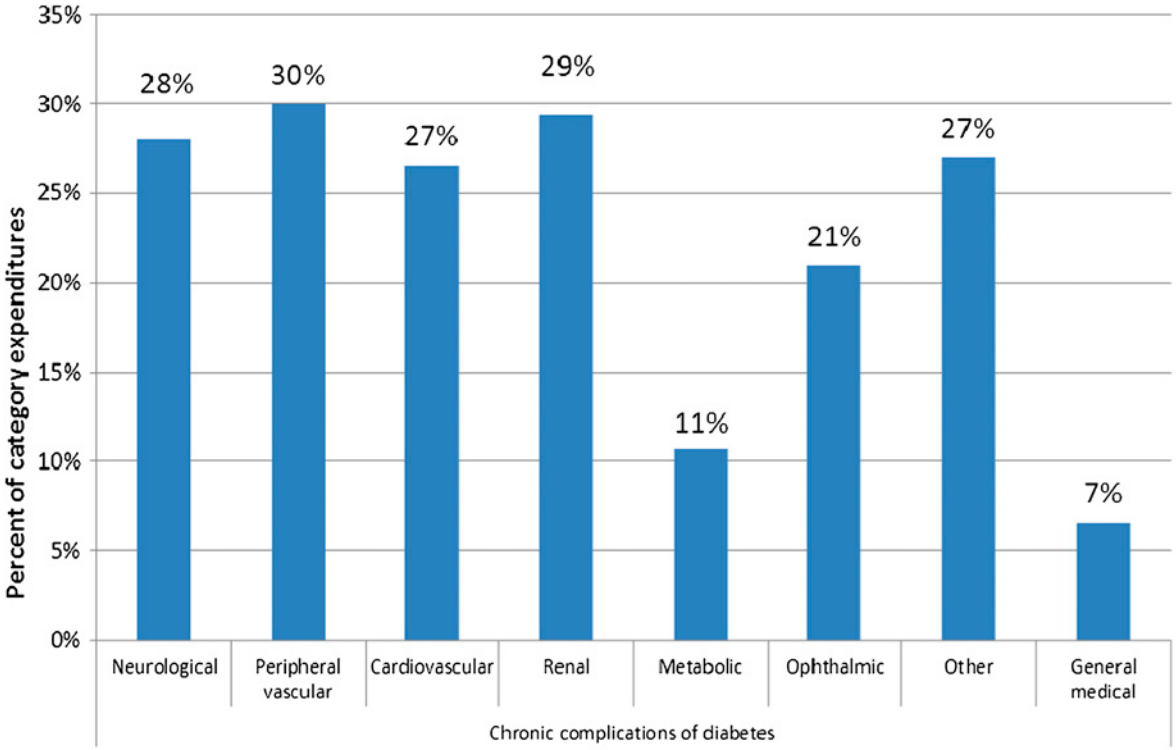
2009 due to hypoglycemia, while 16.2 ED visits per 1,000 patients with diabetes were for hyperglycemic crisis in 2009.

Treatment of diabetes-related complications accounts for one third of the medical care/treatment cost for diabetes according to a 2007 ADA report estimate. Figure 8 summarizes the proportion of medical expenditures attributed to diabetes for each chronic complication over the total U.S. health expenditure (including hospital inpatient, hospital outpatient, emergency department visits, physician office visits, and prescription medications). Five out of the eight conditions in Figure 8 has more than a quarter of expenditures attributed to diabetes.

In a study of diabetes patients from a German health insurance database, 53% of the medical costs per diabetes patient in 2001 (€4,457) were spent for management of complications (€2,380) (Von Ferber et al., 2007). A large mail survey study was carried out in the U.S. to evaluate the relative contributes of diabetes complications, depression and other medical disorders to health service costs in adults with diabetes. This study showed that diabetes complications were the strongest predictor of total health service cost (US $6,845 for those with three or more complications vs. US $1,719 for those with none) (Simon et al., 2005). Brown et al. estimated the progressive cost of complications in diabetes patients by analyzing 9 years clinical data from a health maintenance organization. The baseline diabetes treatment cost was found to be $2,033. After initiation of cardiovascular drug therapy, the per-person cost for diabetes patients increased by more than 50% ($1,087); after a major cardiovascular event, the per-person cost increased by 360%. The cost increase associated with abnormal renal function,

advanced renal diseases, and end-stage renal diseases was 65%, 195%, and 771% respectively (Brown et al., 1999).

Figure 8: Percent of medical condition–specific expenditures associated with diabetes.



Data sources: NIS (2010), NAMCS (2008–2010), NHAMCS (2007–2009), and MEPS (2006–2010 or 2008–2010).

2.2.2 Diabetes health care costs and utilization: peripheral lower extremity diseases

Peripheral lower extremity (PLE) diseases in this study refer to peripheral artery diseases, ulcer/inflammation, and neuropathy. Literature related to the association between PLE and diabetes-related health care cost and diabetes and PLE-related health care cost were reviewed.

Six U.S. studies were identified that estimated the direct cost of foot ulcers in diabetes patients: four studies calculated the average ulcer episode cost; one study

evaluated the aggregate cost; one study examined the cost in a one year frame. A prospective study found that the average ulcer episode cost was $6,664 (Apelqvist et al., 1994). Using retrospective analysis of private insurance claims, Holzer estimated that the average ulcer episode cost was $4,595 (the cost for primary healing was $1,929 while that for healing by amputation was $44,790). The cost differed by ulcer severity grade, ranging from $1,929 for grade 1 or 2 to $15,792 for grade 4 or 5 (Holzer et al., 1998). A similar trend of cost according to ulcer severity was established in another retrospective claims data analysis (Stockl et al., 2004). This study also identified that the average ulcer episode cost was $13,179 (Grade 1 ulcers cost $1,892 while Grade 4 or 5 ulcers cost $27,721). These three studies all suffer from lack of a comparison group without diabetic foot ulcer. Ramsey et al. conducted a retrospective case-control study and found that the average cost of ulcer episode over 1 year was $29,490 and the total attributable cost of foot ulcer was $27,987 (Ramsey et al., 1999). This estimate is relative more reliable because of a more rigorous study design. A study on Medicare population reported that the aggregate ulcer cost was $1.45 billion (Harrington et al., 2000). Rice et al. estimated the annual per-patient incremental burden of diabetic foot ulcers (DFUs) with a case-control study design. He found that increased utilization in diabetic foot ulcer patients had a $11,710 incremental annual health care costs for Medicare and $16,883 for private insurance (Rice et al., 2014). These studies show the same pattern that these complications added incrementally to the cost for caring of patients with diabetes.

In the U.S., a cost-of-illness model was developed for peripheral neuropathy complications among patients with diabetes. The annual cost of diabetic peripheral

neuropathy in the U.S. was estimated to be $0.8 billion for Type 1 diabetes and $10.1 billion for Type 2 diabetes (Gordois et al., 2003).

Compared to diabetic foot ulcer, studies that look at health care costs associated with peripheral artery diseases and diabetes are sparse. A cost analysis relying on SEER-Medicare data and Medicare claims estimated that $4.37 billion were spent on PAD-related treatment in Medicare every year and 88% of the expenditure was on inpatient care (Hirsch et al., 2008). A retrospective analysis of an East Coast health plan found that the annual cost of Type 2 diabetes patients with macrovascular complications (including cardiovascular and peripheral complications) was three times that cost of Type 2 diabetes patients without diagnosis of macrovascular complications ($10,450 vs. $3,385 respectively) (Gandra et al., 2006). One recent study found that symptomatic PAD patients with diabetes and/or prior acute coronary syndrome have significantly higher medical resource use and costs compared to symptomatic PAD patients without these risk factors. The annualized PAD-related cost differences ranged from $695 to $1,997 based on the retrospective longitudinal analysis using the 2005-2013 MarketScan databases (Chase et al., 2016). However, the incremental cost of PAD on diabetes or the incremental cost of diabetes to PAD hasn't been well documented to the best of our knowledge.

2.2.3 Diabetes health care costs and utilization: kidney diseases

Bruns et al. explored the cost of care for patients with end-stage renal diseases (ESRD) based on the University of Pittsburg Medical Center (UPMC)'s hospital financial transaction records and compared that to the cost estimate from the U.S. Renal Data Service (USRDS). During 1994 to 1995, the average annual cost per dialysis patient was

$63,340 at UPMC compared to the $57,660 from the USRDS. The average annual cost for ESRD patients with diabetes was significantly higher than that for ESRD patients without diabetes ($68,228 vs. $55,581 respectively from UPMC records; $64,322 vs. $54,369 respectively from USRDS records) (Bruns et al., 1998). A retrospective cohort study among the Medicare patients with chronic kidney diseases found that patients with diabetes or cardiovascular comorbidities incurred higher costs compared to those without diabetes or cardiovascular diseases (St. Peter et al., 2004). A cohort study based on a large HMO population indicated that patients with chronic kidney diseases had significantly higher health care utilization (prescription drugs, outpatient visits, inpatient stays) than matched controls without chronic kidney diseases. Total per patient follow-up costs increased as kidney diseases severity increases. What's more, comorbidities related to chronic kidney diseases were more costly to manage than CKD alone (Smith et al., 2004). However, a limitation of this study is that comorbidities related to CKD are examined as group instead of examining the individual effect.

The overall economic burden of diabetic nephropathy has been examined in the U.S. and other countries. Gordois et al. developed a cost-of-illness model to estimate the burden of diabetic nephropathy in the U.S. and the U.K. The analysis showed that the total medical cost incurred by all payers in managing diabetic nephropathy was $16.8 billion (range: $8.5 – 25.2 billion) in the U.S. In the UK, the total annual cost to the National Health Services (NHS) for managing diabetic nephropathy was $1.2 billion. At per-patient level, the annual total cost for a patient with diabetic nephropathy in the U.S. and in the U.K was $3,755 and $2,672 respectively (Gordois et al., 2004).

Four studies were reviewed that examined health care cost for patients with diabetes and their association with nephropathy. Pelletier et al. compared the resource utilization and medical cost over a year period among Type 2 diabetes patients with versus without microvascular complications (neuropathy, nephropathy, and retinopathy). They found that patients with microvascular complications are associated with higher health care utilization and higher cost compared to patients without the microvascular complications ($14,414 and $8,669 respectively). However, this study did not explore the individual effect of each microvascular complication. What's more, the severity of microvascular complication hasn't been taken into account in the analysis (Pelletier et al., 2009). Using health care claims data, Burke et al. found that Type 2 diabetes patients with renal impairment incurred 41.8% higher diabetes-related health care costs compared to diabetes patients without renal impairment. In addition, diabetes-related health care cost was independently associated with the severity of renal impairment (Burke et al., 2012). A retrospective cohort study was conducted among Kaiser Permanente members to track the rate of progression of CKD among type 2 diabetes patients and calculate the medical costs associated with progression. It was established that progression of CKD in type 2 diabetes drives a substantial medical care cost (Incremental cost was $4,569, $12,617, and $33,162 per patient per year higher among patients who progressed from baseline stage 0-2, stage 3, and stage 4 CKD patients compared to those who did not progress (Vupputuri et al., 2014). An analysis the 2011 Medical Expenditure Panel Survey (MEPS) showed that the unadjusted mean expenditure of diabetes patients with CKD were $20,726 compared to $9,689 for diabetes patients without CKD. The adjusted

mean expenditure for diabetes patients with CKD were $8,473 higher compared to individual without CKD (Ozieh et al., 2015).

2.2.4 Diabetes health care costs and utilization: cardiovascular diseases

Four studies examined health care cost associated with macrovascular complications (including CVD and PAD) among diabetes patients. Gandra et al. showed that macrovascular complications are associated with a three times increase in annual health care costs in patients with type 2 diabetes based on data from a non-Medicare HMO plan (Gandra et al., 2006). At the national level, a study with the 2004-2006 MEPS data found that diabetes patients with macrovascular complications had significantly higher annual health care costs ($5,120 extra cost) compared with diabetes patients without macrovascular complications (Fu et al., 2009). A model-based analysis revealed that macrovascular complications account for 52% of the life-time cost of diabetes, representing the largest cost component of diabetes. In addition, macrovascular complications started to contribute to the cost of diabetes earlier in life than microvascular complications (Caro et al., 2002). A European-based study found that the presence of macrovascular complications was associated with a two-fold increase in total medical costs for diabetes compared to patients without macrovascular complications. The presence of both macrovascular complication and microvascular complication increased cost by 3.5-fold compared to the absence of both complications (Williams et al., 2002).

Six studies examined the specific impact of cardiovascular diseases (CVD) on health care cost of diabetes. A case-control study of a HMO found that CVD directly accounted for at least 24% of the total medical care cost among diabetes patients,

compared to 12% of cost for patients without diabetes. The definition of cardiovascular diseases was broad in this study as it included peripheral artery diseases in examining cardiovascular diseases. Overall, the cost attributed to CVD was $858,000 for 1000 diabetes patients. When aggregated to all diabetes patients in that HMO the total cost was $3.59 million in 1988 with ischemic heart disease, stroke, and hypertension the most costly CV conditions treated (Glaumer et al., 1994). At an episode level, O'Brien et al. showed that the event cost of diabetes patients with acute myocardial infarction was $27,630 and that for diabetes patients with angina was $2,477 (all based on 1996 U.S. dollar) (O'brien et al., 1998). However, the estimates from this study were not adjusted for other covariates. A retrospective study in a HMO in the state of Washington found that the annual excess expenditure for diabetes with myocardial infarction was more than two times higher than diabetes without complications (Ramsey et al., 1999). In addition, the incremental cost was higher for the younger patients compared to the older patients. Another study using data from Kaiser Permanente Northwest found that the annual medical cost for patients with both CVD and diabetes is remarkably higher than patients with diabetes only ($10,172 vs. $4,402) (Nichols et al., 2002). The CVD in this study included acute myocardial infarction, other ischemic heart diseases, angina, congestive heart failure, and dysrhythmia. A prospective study analyzed medical claims in a 3-year frame. It was found that the adjusted mean 3-year costs for diabetes patients with coronary heart disease (CHD) and hypertension were three times higher than patients with diabetes only ($46,879 vs. $14,233 respectively) (Gilmer et al., 2005). Finally, a recent study explored cost of episode of care associated with diabetes and complications with the analysis of MarketScan claims data. It was shown that the adjusted total episode

cost for diabetes patients with coronary artery diseases (CAD) was $16,435 (Candrilli et al., 2015). However, this study lacked a comparison group.

There were relatively few studies on the impact of diabetes on the economic outcome of care for patients with cardiovascular diseases. Abizaid et al. conducted a randomized prospective study to examine the impact of diabetes on percutaneous coronary stenting and coronary artery bypass grafting (CABG). The total 1-year cost for stenting was $12,855 for patients with diabetes and $10,164 for patients without diabetes. The total 1-year costs for CABG was $16,585 for patients with diabetes and $13,082 for patients without diabetes (Abizaid et al., 2001). Clark et al. analyzed Medicare Standard Analytic File to explore predicotrs of 1-year medical cost of percutaneous coronary interventions (PCI) in the elderly. The adjusted mean cost for patients with diabetes was $1,057 higher than patients without diabetes (95% CI: $541 to $1,572) (Clark et al., 2004).

2.2.5 Hospital inpatient care of diabetes and its complications

In existing literature, diabetes-related hospitalization is usually explored either with first-listed diagnosis of diabetes or with diabetes as any-listed diagnosis (National Diabetes Data Group (US), 1995). On the one hand, the age-adjusted hospital discharge rates for diabetes as first-listed diagnosis was around 20.0 per 10,000 general population from 1988 to 2009 in the U.S. according to CDC. In diabetes population, the age-adjusted hospital discharge rate has decreased from 113.3 per 1,000 diabetic population in 1988 to 46.7 per 1,000 diabetic population in 2009. On the other hand, the age-adjusted hospital discharge rate for diabetes as any-listed diagnosis increased from 122.4 per 10,000 population in 1988 to 170.2 per 10,000 population in 2009. However, the age-adjusted

hospital discharge rate for diabetes as any-listed diagnosis declined from 379.4 per 1,000 diabetic population in 1988 to 223.7 per 1,000 diabetic population in 2009. These estimates were based on the National Hospital Discharge Survey (NHDS), National Center for Health Statistics, and CDC. Long-term and federal hospitals were not included in NHDS; therefore the hospitalization rates for patients with diabetes may be underestimated. In addition, while reported per diabetic population, NHDS hospital discharge rates may not necessarily reflect rates per person because NHDS samples hospital discharges and not individual persons (Dennison and Pokras, 2000; Hall et al., 2010; Botman et al., 2000).

Previous studies have found that patients with diabetes use more hospital inpatient care than those without diabetes. According to a Finish study with registry data, 14.2% of the diabetes patients had at least one hospital stay because of diabetes in year, while 50.7% had at least one hospital stay for any cause. Only 12.4% of the nondiabetic population was hospitalized annually (Aro et al., 1994). A retrospective cohort study based in Scotland found that 25% of the population with diabetes had at least one hospital admission, compared to 12% of the nondiabetic population (Donnan et al., 2000). Using U.S. commercially insured data, Laditka et al. found that the rates of hospital inpatient care use were more than 4 times higher for the total population with diabetes than the population without diabetes: the rate of hospital inpatient care use is 7 times more for the patient with type 1 diabetes than the general population; the rate of hospital inpatient care use is 3 times higher for the patients with type 2 diabetes than the general population (Laditka et al., 2001). An Italy study also confirmed that patients with type 2 diabetes had elevated hospitalization rates compared to the general population (Bo et al., 2004).

Several principal risk factors have been identified that predict the risk of hospitalization among diabetes patients. These factors include increasing age (Bo et al., 2004; Fu et al., 2014), chronic complications (Panser et al., 1990), dysphoria in older patients (Rosenthal et al., 1998), high glycated hemoglobin (HbA1c) levels and hypertension (Moss et al., 1999). An UK study also found that low socioeconomic status (SES) is associated with increased likelihood of having a hospital records for diabetic kidney diseases, diabetic ketoacidosis, hypoglycemia, ischemic heart diseases, stroke, and peripheral artery diseases (Wild et al., 2010).

A recent study analyzed hospitalization charge for diabetes and its association with complications using Pennsylvania hospitalization discharge data (Ma et al., 2014). This is one of the few studies that examined diabetes hospitalization at a hospital episode of care level. The author's findings indicated that approximately 86% of the diabetes-related hospitalizations in Pennsylvania had discharged diagnosis codes indicating diabetes complications, which included both short- and long-term diabetes complications. The average unadjusted charge for hospital stays with any type of complication was 158% more than the charge for hospitalizations without any complications. Among the comorbidities studied, renal manifestations among diabetes patients was associated with a 75.1% increase in hospitalization charge; peripheral vascular disorders and neurological disorders increases hospitalization charge by 38% and 30% respectively. With regard to demographic variables, age demonstrated a curvilinear relationship with hospitalization charge increasing until age 65 and after age 65 there was decreasing trend between and age and hospitalization charge. Racial/ethnic minority groups such as Hispanic and Black had higher hospitalization charge than White. This study, however, included the

experiences of a single state and used hospitalization charge, which is different from both the reimbursed and the real cost of a hospitalization. From a policy perspective, analyzing hospitalization cost may be more meaningful.

Diabetes-related hospitalization and complications-related hospitalization are interrelated. As stated before, chronic complication is one of the principal risk factors for diabetes-related hospitalization. Furthermore, when defining diabetes-related hospitalization with all-listed diabetes as criteria, diabetes complications are usually the main cause for that hospitalization (Fu et al., 2014). Diabetes with complications ranks 16 among the top 20 most expensive conditions treated in the U.S. hospitals in 2011 (Torio & Andrews, 2011). An aggregated $5,380 million (1.4% of the national costs) was spent on inpatient care of diabetes with complications. In addition, hospitalizations for coronary atherosclerosis, one of the major macrovascular complications of diabetes, ranked 9th among the top 20 most expensive conditions treated in the U.S. hospitals.

Several studies were identified that examined peripheral lower extremity diseases-related hospitalizations and diabetes. Currie et al. analyzed U.K. hospital admission data for patients with a primary diagnosis of peripheral vascular diseases, infection, neuropathy, or ulceration. The findings suggest that the age-standardized relative risk for admission for patients with diabetes to the patients without diabetes was 7.61 for men and 6.85 for women. The length of stay for patients with diabetes was 15.5 days compared to 8.7 days among patients without diabetes. The relative risk of in-hospital mortality was 2.83 (diabetes vs. non-diabetes). Overall an excess of 87% of the inpatient care cost for peripheral vascular diseases was attributed to diabetes care (Currie et al., 1998). A U.S study of registry data found that the relative risk of vascular-related hospitalization was

1.52 for PAD patients with diabetes compared to PAD patients without diabetes (95% CI: 1.33 – 1.73). An excess cost of 52% of the hospitalization cost for PAD was attributed to diabetes care (Mahoney et al., 2010). A retrospective Australian study also found that comorbid diabetes is associated with increased length of stay and increased hospitalization cost among patients with hospital admission for PAD (Malone et al., 2014). Hicks et al. studied the trends and determinants of inpatient care costs of diabetic foot ulcers in the U.S. between 2005 and 2010. It is shown that the presence of patient comorbidities is associated with significant increase in hospitalization cost (Hicks et al., 2014).

In general, studies that examined coronary atherosclerosis-related hospitalization and diabetes or kidney diseases-related hospitalization and diabetes have been sparse. A UK study showed that patients with diabetes accounted for 16.9% of coronary heart diseases related admissions. What's more, diabetes increased the probability of undergoing a cardiac procedure by 4-fold. With regard to expenditure, patients with diabetes accounted for 16% of the coronary heart diseases related health expenditure (Currie et al., 1997).

2.3 Summary of literature review

In review, to date, a number of studies have investigated the health care cost and utilization associated with diabetes and its complications. Overall, diabetes complications played important roles in driving diabetes-related healthcare cost and utilization. Diabetes complications were shown to be associated with elevated health care utilization, such as outpatient visits, emergency department visits and hospital inpatient admissions. Diabetes complications were also found to be associated with increased medical cost for diabetes.

Most of the previous studies focused on total medical cost of diabetes in a particular time frame (e.g., 1 year frame); while the cost for diabetes for a single hospital inpatient episode and its association with diabetes complications was rarely explored.

Diabetes and its complications are interrelated with regard to hospital inpatient care. When all-listed diagnoses are used to define diabetes-related hospitalization, diabetes complications are usually the main cause for that hospital admission. Very few studies have explored the incremental effect of diabetes on complications-related hospitalization cost.

Hospitalization discharge status is another important indicator of subsequent health care utilization. Additional health care is expected if a patient is discharged to a short-term hospital or a skilled nursing facility. Furthermore, discharge to a skilled nursing facility has been found to be associated with worse outcomes such as re-hospitalization (Mor et al., 2015; Hakkarainen et al., 2016). The impact of diabetes complications on diabetes-related hospitalization discharge status was rarely examined. Only one study was identified that explored diabetes's influence on ischemic stroke hospitalization discharge status (Reeves et al., 2010). Therefore hospitalization discharge status is included as a second aim in this study.

No studies have proposed to examine the complications on diabetes-related hospitalization cost and discharge status and diabetes on complications-related hospitalization cost and discharge status using the same data source. Therefore this study is carried out to address the gap in current knowledge.

Chapter 3: Conceptual Framework

The theoretical framework for this study combines elements from the Chronic Care Model and Andersen's Behavioral Model of Health Service Utilization. This study mainly focuses on how we can improve clinical information systems element in the Chronic Care model to improve chronic care for diabetic patients. The behavioral model of health service utilization is used to identify control variables in testing the association between diabetes complications and hospitalization costs.

3.1 The Chronic Care Model

The Chronic Care Model was proposed by Edward Wagner in 1998 for reconfiguration and quality improvement of the health care system to meet the needs of patients with chronic diseases (Wagner, 1998). In the past, the health care systems were better prepared to respond efficiently to any acute illness or emergencies than to the needs of patients with chronic diseases. However, the work of medical practice has been drastically changed by the modern advancement in medicine and the demographic shifts of the population. According to CDC, as of 2012, about half of all U.S. adults (117 million people) had one or more chronic health conditions. In addition, chronic diseases accounted for seven of the tope 10 causes of death in 2010. Though effective clinical and behavioral interventions have been developed for major chronic diseases such as diabetes and hypertension, many patients were still not reaping the benefits of these advances. For example, a study suggested that less than half of U.S. patients with diabetes obtained proper treatment (Clark et al. 2000). A 2001 IOM report attributed the gap in quality of care for chronic diseases to two aspects: the increased demands on medical care due to increases in chronic disease prevalence; and the inability of the system to meet the

demands because of poor structure and constraints in using modern information technology (Institute of Medicine (US), 2001; Wagner et al.; 2001).

The Chronic Care Model was derived on the basis of Wagner's previous work at Group Health Cooperative to apply population-based care to improve outcomes for diabetes patients (Wagner, 1995; Wagner, 1997). The Chronic Care Model highlights that high-quality chronic illness care is characterized by productive interaction between practice team and patients. These interactions constantly offer the support for self-management, optimization of therapy, timely assessments, and follow-up associated with good outcomes. Productive interactions dependent on two indispensable aspects: patients need to be active and confident and must have the necessary information and skills to better involve with their practice team; practice teams must have the expertise and sources to act proactively to ensure effective clinical and behavioral management (Wagner et al., 2001). The model suggests that the patient-provider interactions resulting in care quality improvement are found in health systems that:

- have well-developed processes and incentives for making changes in the care delivery system
- assure behaviorally sophisticated self-management support that gives priority to increasing patients' confidence and skills so that they can be the ultimate manager of their illness
- reorganize team function and practice systems (e.g., appointments and follow-up) to meet the needs of chronically ill patients

- develop and implement evidence-based guidelines and support those guidelines through provider education, reminders, and increased interaction between generalists and specialists
- enhance information systems to facilitate the development of disease registries, tracking systems, and reminders and to give feedback on performance.

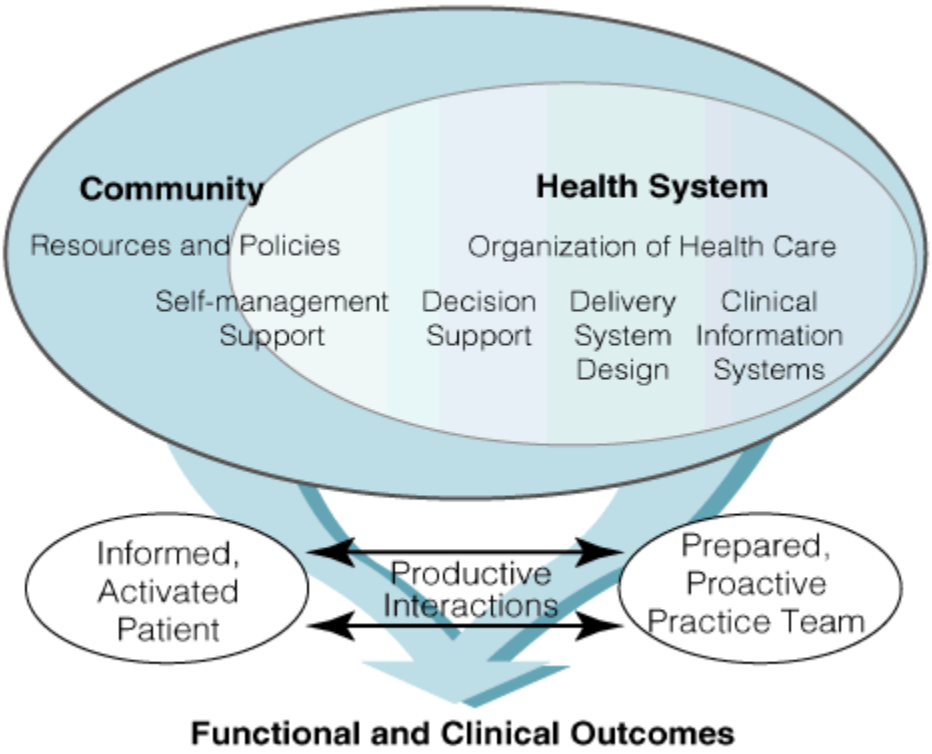
The Chronic Care Model identifies six essential elements of a health care system that enable high-quality chronic disease care. The six elements are posited based on reviews of effective chronic disease interventions in the literature (Renders et al., 2001). They are: the community, the health system, self-management support, delivery system design, decision support and clinical information systems. The six elements are interdependent and building on one another.

- *The health system*: the health system is depicted as part of the larger community. A well-organized health care system linked with complementary community resources outside the organization is essential for effective chronic disease management.
- *Community resources and policies*: linkages between provider organizations and community-based resources are crucial in improving chronic care. For example, community linkages with hospitals offering patient education classes are of particular help for small physician offices with limited resources.
- *Self-management support*: effective self-management support and links to patient-oriented community resources help to inform patients and families to better cope with the challenges of living with chronic diseases.

- *Delivery system design*: the medical practice structure needs to be altered to create practice teams with a clear division of labor. Physicians treat patients with acute problems, intervene in stubbornly difficult chronic cases, and train team members. Non-physician personnel are trained to support patient self-management, arrange for routine periodic tasks, and ensure appropriate follow-up.
- *Decision support*: optimal chronic care is provided by evidence-based clinical practice guidelines, which should be incorporated into daily practice. Physicians serve as champions could lead educational sessions.
- *Clinical information systems*: computerized information plays three essential roles: (1) as reminder systems which facilitate primary care team to comply with practice guidelines; (2) as feedback to physicians to show performance on chronic illness measure; (3) as registries for planning individual patient care and conducting population-based care.

Change strategies have been implemented in each of the six areas and in all six areas of the chronic care Model (Wagner et al.; 1996, Von Korff et al, 1997; Pearson et al., 2005). For example, the RAND/Berkeley Improving Chronic Illness Care Evaluation (ICICE) team assessed the implementation and the impact of the chronic care collaborative. The study showed that collaborative participants were able to implement a large number of diverse quality improvement strategies. Quality improvement collaborative was a useful way to foster change in real world settings.

Figure 9: The Chronic Care Model



(Source:http://www.improvingchroniccare.org/index.php?p=The_Chronic_CareModel&s=2)

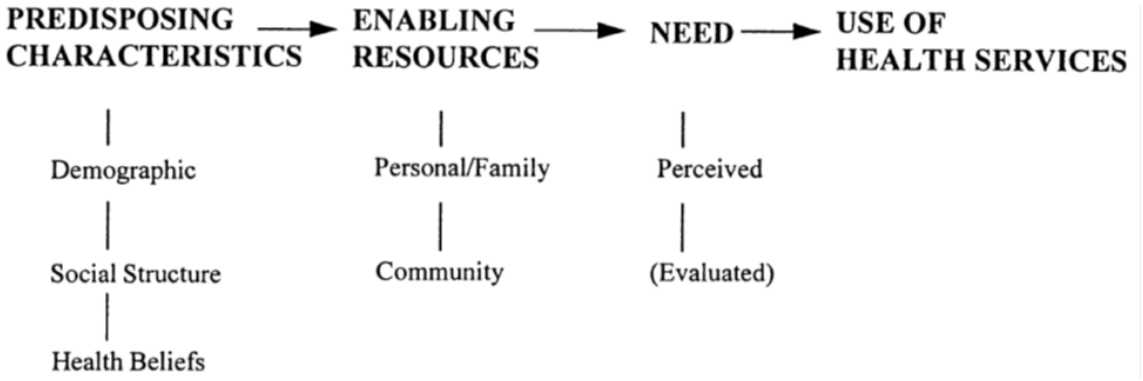
Of the six elements, this study will mainly focus on how we can improve clinical information systems to improve chronic care for diabetic patients. The clinical information systems element in CCM means organizing patient and population data to deliver efficient and effective care. A clinical information system is able to identify patients groups which are in need of proactive care or additional care at the systemic level. It also makes performance monitoring and quality improvement efforts possible. This study uses clinical information systems data (hospital discharge data) to examine the patient groups that are associated with elevated care utilization needs. The patient groups to be identified from the study could serve as potential targets for early proactive care or

preventative care, which facilitates the interaction between the two critical players under the CCM: an informed active patient, and a prepared proactive practice team.

3.2 The Behavioral Model of Health Service Utilization

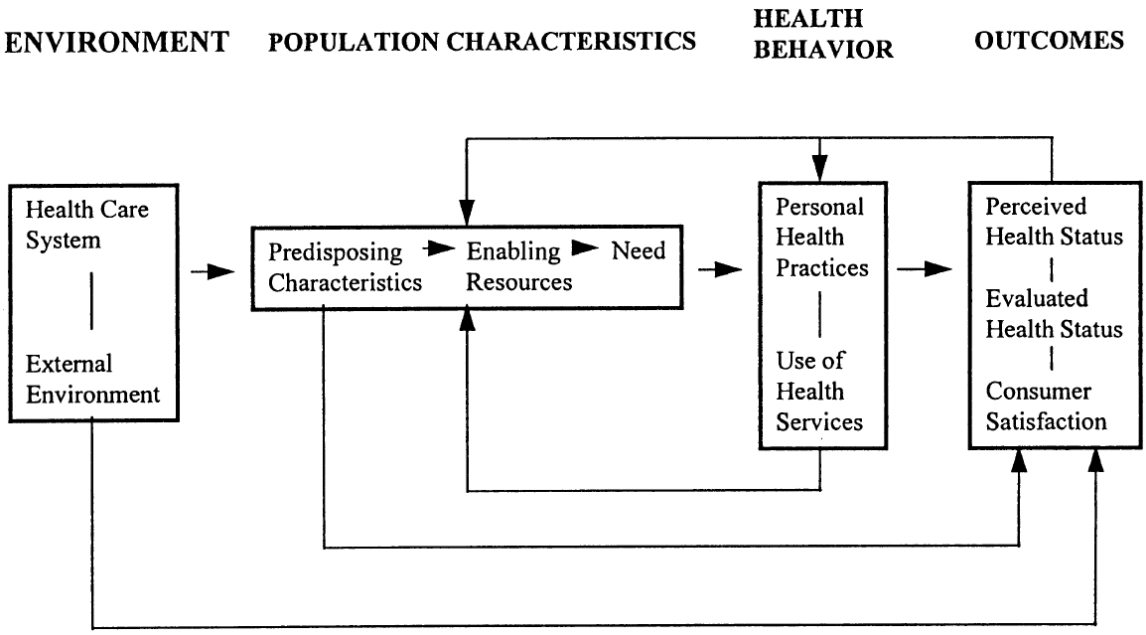
The Behavioral Model of Health Service Utilization is one of the most widely acknowledged models in explaining and predicting health care utilization. It was initially developed in the 1960s to assist the understanding of family use of health services – to define and measure equitable access to health care, and to help the development of policies to promote equitable care. According to the model, people's use of health services is a function of predisposing characteristics, enabling resources, and need factors. Predisposing characteristics are variables that describe the predisposition of individuals to see care, which could exist before illness, including demographics (age and gender), social structure (education, occupation, race/ethnicity and social network), and health beliefs. Enabling resources, containing both community (source of care, travel, and waiting time) and personal enabling resources (income and health insurance benefits), are factors that must be present for use to take place. Need factors are categorized into two components – perceived need (individual or provider judgments of the presence of illness) and evaluated needs (judgments of the severity of conditions (Andersen et al., 1973; Aday and Andersen, 1974; Aday et al., 1993; Bradley et al., 2002). Figure 10 depicts the elements in the original Andersen's model.

Figure 10: The Initial Behavioral Model



During the past several decades, Andersen's model has been continually developed in order to better explain and predict health care utilization. The Phase 2 of the model explicitly incorporated health care system, in recognition of the importance of national health care policy and the health system organization as key determinants of the population's use of services. The Phase 3 development included health status outcomes to integrate dimensions which are particularly important for health policy and health reform. The Phase 4 model (Figure 11) lay emphasis on the dynamic and recursive nature of a health service utilization model, portraying the multiple influences on health service's use, and subsequently, on health status. It also allows for feedback loops that show outcome affects subsequent predisposing factors and perceived need for services as well as health behavior (Andersen 1995; Andersen 2008).

Figure 11: The Phase 4 of the Behavioral Model



Andersen's model has been applied extensively in the field of study of health services utilization, including diabetes-related hospitalizations. In this study, the main explanatory variable of interest – diabetes-related complications – represents one of the need factors in the model. Other control variables of the study will follow the predisposing and enabling factors in Andersen's model.

Predisposing Characteristics

Age: Age is generally regarded as a risk factor of developing diabetes, peripheral lower extremity diseases, kidney diseases and coronary atherosclerosis. For example, patients older than 60 years of age are at increased risk of developing chronic kidney diseases (Levey et al., 2003). The prevalence of peripheral arterial diseases among patients age >75 years was more than 20%; while the prevalence of PAD among patients age <60 was below 5% (Criqui et al., 1985). Although aging is related to chronic illness

and increased overall healthcare utilization, the effect of age on cost per episode is not consistent. For example, a study on lower extremity ulcer among patients with diabetes found that total ulcer-related cost were significantly higher for patients below 65 years compared to those above 65 years (Stockl et al., 2004). Nonetheless, age is an important indicator of health service utilization and should be included as a covariate in the model.

Sex: Studies have shown that the age specific prevalence of coronary heart diseases and peripheral arterial diseases was higher for men than that for women (Currie et al., 1997; Criqui et al., 1985).Although the trend of age-adjusted incidences of diabetes among male and females has changed over the years; the prevalence of diabetes was still slightly higher for males than for females (CDC website). However, the prevalence of chronic kidney diseases was greater in women than in men across age categories and also in various ethnic groups (Zhang & Rothenbacher, 2008).

Race: Racial and ethnic disparities in the epidemiology of diabetes and its complications have been observed in existing studies. As mentioned early, the prevalence of diabetes was much higher in minority groups. Racial or ethnic minority groups (African-American, Hispanic, and Native American) are associated with increased risk in developing chronic kidney diseases (Levey et al., 2003). Black patients were also found to have increased likelihood of undergoing amputation for lower extremity ischemia compared to White. Coronary atherosclerosis, however, is a condition that is more common in White. Both White men and Women were found to have the highest coronary artery calcium (CAC) score than other racial/ethnic groups in the Multi-Ethnic Study of Atherosclerosis (MESA) (McClelland et al., 2006). Racial/ethnic disparities were also observed in hospitalization rates: Blacks had significantly higher rates of ambulatory care

sensitive conditions hospitalization that Whites for five of eight conditions (O'Neil et al, 2008).

Enabling Resources

Income: Socioeconomic status has been shown to be associated with hospital use. Hospitalization rates were higher in lower-income areas than in higher-come areas for ambulatory care sensitive conditions in New York City (Billings et al., 1993). The area where the patient resides is also related to hospital inpatient cost: the cost is higher in an affluent area than a relatively poor area.

Primary Payer: The payer type of hospital inpatient care has been found to be associated with hospitalization charge. Compared to patients without insurance, the charge for Medicare and Medicaid is 13% and 10% higher respectively; while the cost for patients paid by commercial insurance 11% after adjusting for other factors (Ma et al., 2014).

Need Factors

Comorbidities: The presence of other comorbidities is common among patients with diabetes and the three main complications in this study. Comorbidities are associated with increased health care utilization. Therefore they will be included as covariates in the model. .

Diabetes short-term complications: Diabetes short-term complications, such as ketoacidosis, are also significantly associated with hospital inpatient care use (Wagner et al., 2015). Diabetic ketoacidosis was the most common reason for hospitalization and

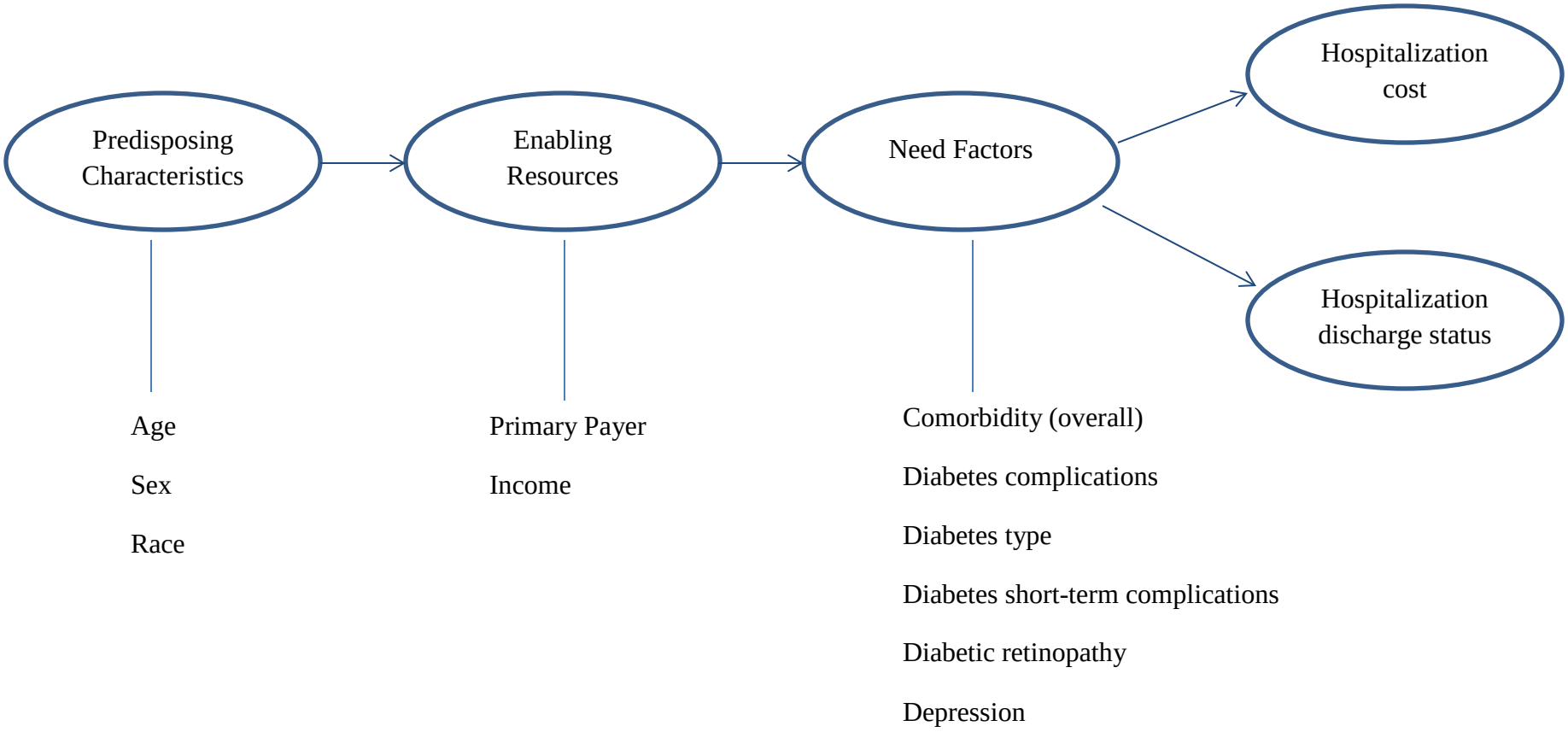
mortality in children and adolescents with type 1 diabetes (Edge et al., 1999). Readmission for diabetic ketoacidosis is also common among diabetes patients (Tieder et al., 2013).

Diabetes type: As mentioned previously, type 1 and type 2 diabetes have different pathology and are associated with different onset age and treatment medications. Therefore the resource utilization for diabetes may be different.

Diabetic retinopathy: Diabetic retinopathy is one of the common microvascular complications of diabetes. A large-scale longitudinal study in Taiwan found increased healthcare costs associated with progressive diabetic retinopathy among diabetes patients (Woung et al., 2010).

Depression: Depression and diabetes may influence each other, which could in turn, influence health care cost and utilization of each other (Molosankwe et al, 2012). The annual health care cost in a low income population with diabetes and depression were $12,353 compared to the cost of $8,131 for diabetes patients without complications (Kalsekar et al., 2006). An insurance claims data based analysis indicated that the cost for diabetes patients with and without depression was $19,700 and $11,200 respectively (Le et al., 2011). However, there was also a study that found no association between minor depression and diabetes related health care expenditure (Nichols et al., 2003).

Figure 12: Study Model Illustration



Chapter 4: Methods

This is an observational cross-sectional study using inpatient hospital administrative data from the Healthcare Cost and Utilization Project (HCUP). This chapter describes the data and research methodology of this study, including the main data source, the study cohort construction, the measurement of study variables, and the statistical models used in the study.

4.1 Data source

This study utilizes the 2010-2012 National Inpatient Sample (NIS) datasets. The NIS is a stratified sample of discharges from participating U.S. community hospitals, excluding rehabilitation facilities, long-term acute care hospitals, Veteran Administration facilities, and Indian Health Service facilities. It is the largest publicly available all-payers inpatient health care database in the United States. The NIS covers all patients, including individuals covered by Medicare, Medicaid, or private insurance, as well as the uninsured within the participating hospitals. The NIS dataset contains 7 million unweighted hospital stays and 36 million weighted hospitalizations nationally each year.

A typical annual NIS dataset consists of four parts: 1. Core data elements, which include primary and secondary diagnoses and procedures; patient demographic characteristics, total charges; discharge status; length of stay; 2. Hospital file data elements which shows information of the hospital characteristics such as ownership, location, and size; 3. Severity file data elements which indicate the severity and comorbidity measures in the discharge record; 4. Diagnosis and procedure groups file, which contains information of the classification of diagnosis and procedures using

HCUP's clinical classification software. This study appends the 2010-2012 discharge records and select sample based on the appended datasets.

There are several reasons why NIS datasets are selected for use in this study: First, the NIS data contains all the necessary clinical and resource use information that is needed for this study. It includes information such as principal and secondary diagnoses and procedures, patient demographics (e.g., sex, age, race, and median zip code level income), hospital characteristics, payment sources, total charges, cost-to-charge ratios, discharge statuses, severity, and comorbidity measures. Second, the NIS dataset is a representative sample of hospital discharges in the United States. NIS is drawn from all states participating in HCUP, and it covers more than 95% of the U.S. population. Therefore, the use of this dataset will ensure that the results of the study are applicable at the national level. Third, NIS data is sponsored by AHRQ and has been used for informed decision making at the national, state, and community levels.

4.2 Cohort construction

The study design includes four cohorts: diabetes-related hospitalization cohort, peripheral lower extremity (PLE) disease-related hospitalization cohort, kidney diseases-related hospitalization cohort, and coronary atherosclerosis-related hospitalization cohort. Each cohort is identified by discharge records which has a principal or secondary diagnosis of the diseases examined (diabetes, PLE, kidney diseases, or coronary atherosclerosis). In the preliminary cohort, any discharge records that have principal or secondary diagnosis of cancer, liver diseases, pregnancy complications, or age < 18 years is excluded from the final cohort.

Rationale for these inclusion and exclusion criteria are: (1) diabetes-related hospitalization was defined either by first diagnosis or all-listed diagnosis in existing literature. However, the limitations for this approach are that first diagnosis of diabetes may underestimate the study population of interest while all-listed diagnosis could over identify the study population. Therefore, this study proposes to use principal and secondary diagnosis as inclusion criteria; (2) hospitalization with cancer, liver diseases, pregnancy complications as principal or secondary diagnosis are usually associated with higher costs and higher health care utilization rates. Therefore those discharge records are excluded from final sample in order to make a precise estimate of the costs and health care utilization associated with diabetes; (3) diabetes in the pediatric population have different profiles than that in the adult population. This study focuses on the adult population.

4.3 Dependent variables (Outcome variables)

4.3.1 Hospitalization cost

The primary outcome variable of interest is hospitalization cost. The NIS datasets provide both the original and the cleaned total charges. A separate cost-to-charge ratio file is provided by HCUP which could be merged with the NIS datasets. The hospitalization cost is obtained by multiplication of the cleaned total hospitalization charge by the cost-to-charge ratio file. This study includes the data from 2010 to 2012. The cost in 2010 and 2011 was converted to the cost in 2012 by the medical consumer price index.

4.3.2 Discharge status

The secondary outcome variable of interest for this study is discharge status. Discharge status is treated as a dichotomous variable: routine discharge (discharge to home without additional care) and non-routine discharge (including transfer to a short-term hospital, transfer to a skilled nursing facility or intermediate care facility, home health care, and death). This classification of routine and non-routine discharge was based a previous paper that used NIS data to examine the impact of diabetes on perioperative patient outcomes (including disposition of patients) after total hip and total knee arthroplasty in the U.S. (Bolognesi et al., 2008)

4.4 Main explanatory variables – diabetes complications definition

Diabetes complications are defined based on ICD-9-CM diagnosis codes, procedure codes or DRG codes. The diagnosis, procedure codes or DRG for a particular complication are selected based on established algorithms in literature or consultation with a medical coding specialist. Each diabetes complication (nephropathy, peripheral lower extremity diseases, and coronary atherosclerosis) examined in this study are coded into three categories: “0” indicates absence of that complication; “1” indicates complication present but less severe; “2” indicates severe complication present. If a patient’s record contains diagnosis codes for both severe and less severe complication, a “2” will be coded. The severity classification for diabetic nephropathy, and peripheral lower extremity diseases is adopted mainly based on the algorithm used in diabetes complications severity index (DCSI) with a few corrections based on ICD-9-CM coding handbook (Young et al., 2008). A limitation of DCSI algorithm is that procedure codes and DRG are not taken into account in the severity coding. Therefore this study also

includes procedure codes and DRG which could reflect the severity of the complication. There hasn't been an established classification of severity of coronary atherosclerosis based on diagnosis codes. Therefore a severity classification of coronary atherosclerosis based on diagnosis codes, procedure codes and DRG is proposed in this study which is also based on consultation with a medical coding specialist. In this study, coronary atherosclerosis patients that have chronic total occlusions or that have any endovascular procedures or percutaneous coronary intervention on record will be considered to have a "severe" coronary atherosclerosis. The complication classification with corresponding ICD-9-CM coding is presented in Table 6.

Table 6: Diabetes complications and corresponding ICD-9-CM diagnosis codes, procedure codes, or DRG

Complication	**ICD-9-CM Diagnosis**	**ICD-9-CM Codes**	**Procedure Codes**	**MS-DRG**	**Operationalization in this study**
Nephropathy	Diabetic nephropathy	250.4			Categorical: 1: Less severe nephropathy
	Acute glomerulonephritis	580.0, 580.4, 580.81, 580.89, 580.9			
	Nephrotic syndrome	581.0, 581.1, 581.2, 581.3, 581.81, 581.89, 581.9			
	Hypertension, nephrosis	581.81			
	Chronic glomerulonephritis	582.0, 582.1, 582.2, 582.4, 582.81, 582.89, 582.9			
	Nephritis/nephropathy	583.0, 583.1, 583.2, 583.4, 583.6, 583.7, 583.81, 583.89, 583.9			
	Chronic renal failure	585.1, 585.2, 585.3, 585.4, 585.5, 585.6, 585.9			2: Severe nephropathy
	Renal failure NOS	586			
	Renal dialysis	V45.11, V56.0			
	Renal	593.9	Operations of	55.0, 55.01, 55.02,	

	insufficiency		Kidney (55.XX)	55.03, 55.04, 55.1, 55.11, 55.12, 55.2, 55.21 55.22, 55.23, 55.24, 55.29, 55.3, 55.31, 55.32, 55.33, 55.34, 55.35, 55.39, 55.4, 55.5, 55.51, 55.52, 55.53, 55.54, 55.6, 55.61, 55.69, 55.7, 55.8, 55.81, 55.82, 55.83, 55.84, 55.85, 55.86, 55.87, 55.89, 55.9, 55.91, 55.92, 55.93, 55.94, 55.95, 55.96, 55.97, 55.98, 55.99	
			Kidney transplant (55.6)		
Peripheral lower extremity diseases	Diabetic PVD	250.7			Categorical 1.Less severe lower extremity diseases
	Other aneurysm, LE	442.3			
	PVD	443.81, 443.9			
	Foot wound + complication	892.1			
	Intermittent claudication	443.9			
	Atherosclerosis of native arteries of the extremities	440.2, 440.20, 440.21, 440.22			
	Diabetic neuropathy	356.9, 250.6			

	Amyotrophy	358.1			
	Mononeuropathy	355.0, 355.1, 355.2, 355.3, 355.4, 355.5, 355.6, 355.71, /355.79, 355.8, 355.9			
	Charcot's arthropathy	713.5			
	Polyneuropathy	357.2			
	Autonomic neuropathy	337.0, 337.1			
	Orthostatic hypotension	458.0			
	Embolism/Thrombosis (LE)	444.22			2. Severe lower extremity diseases
	Gangrene	785.4			
	Gas gangrene	0.40			
	Ulcer of lower limb	707.1			
	Atherosclerosis of native arteries of the extremities with ulceration	440.23			
	Atherosclerosis of native arteries of the extremities with gangrene	440.24			
	Lower limb amputation status	V49.7X			

			Lower extremity amputation (84.10, 84.12, 84.13, 84.14, 84.15, 84.16, 84.17, 84.18, 84.19)	DRG-252 (Other Vascular Procedures with Major Complications or Comorbidities) DRG-253 (Other Vascular Procedures with Complications or Comorbidities) DRG-254 (Other Vascular Procedures without Complications or Comorbidities or Major Complications or Comorbidities)	
			Lower extremity stents (39.90, 00.55, 00.60, 00.45, 00.46, 00.47, 00.48)		
			Lower extremity endovascular procedure (39.50, 00.40, 00.41, 00.42, 00.43, 00.44)		
			Percutaneous atherectomy of other noncoronary vessels (17.56)		
Coronary atherosclerosis	Atherosclerosis of Aorta	440.0			Categorical: 1. Less severe coronary atherosclerosis
	Coronary atherosclerosis	414.0, 414.00, 414.01, 414.06			
	Coronary atherosclerosis due to lipid rich plaque	414.3			
	Coronary atherosclerosis due to calcified coronary lesion	414.4			
	Chronic total	414.2			2. Severe coronary

	occlusion of coronary artery				atherosclerosis
	Bypass procedures	V45.81			
	Angioplasty procedures	V45.82			
			Endovascular procedures (39.7X): e.g., endovascular balloon catheter (39.77) endovascular implantation of branching or fenestrated grafts (39.78)	39.71	
			Operations on the vessels of heart (36.XX)	36.0, 36.03, 36.04, 36.06, 36.07, 36.09, 36.1, 36.10, 36.11, 36.12, 36.13, 36.14, 36.15, 36.16, 36.17, 36.19, 36.2, 36.3, 36.31, 36.32, 36.33, 36.34, 36.39, 36.9, 36.91, 36.99	
			Transluminal coronary atherectomy (17.55 or 00.66)		

4.5 Independent variables

The independent variables (or control variables/explanatory variables) are determined based on the Behavioral Model of Health Services Utilization and are classified into three categories: predisposing characteristics, enabling resources, and need factors.

4.5.1 Predisposing characteristics

Demographic variables such as age, sex, and race considered as predisposing characteristics in the Andersen's model.

Age (years): age in years is calculated from the birth date and the admission date in the HCUP databases.

Sex: the sex of the patient (Male or Female) is provided by the data source.

Race/Ethnicity: race and ethnicity are coded as one data element (RACE) in HCUP. If the source supplied raced and ethnicity in separate data elements, ethnicity takes precedence over race in setting the HCUP value for race.

4.5.2 Enabling resources

Zip code level income and payer type (Medicare, Medicaid, Private Insurance, self-pay or other) are regarded as an enabling factor.

Median household income for patient's ZIP Code: HCUP provides this categorical variable as a quartile classification of the estimated median household income of the residents in the patient's zip code. The quartiles are identified by values of 1 to 4, indicating the poorest to the wealthiest populations.

Payer type: payer type is the expected primary payer for the hospital inpatient care. The expected primary payer for the hospitalization is grouped into general groups such as Medicare, Medicaid, private insurance, self-pay, no charge, and other. Medicare includes both fee-for-service and managed care Medicare patient. Medicaid includes both fee-for-service and managed care Medicaid patients. Private insurance includes Blue Cross, commercial carriers, and private HMOs and PPOs. Other includes Worker's Compensation, CHAMPUS, CHAMPVA, Title V, and other government programs.

4.5.3 Need factors

Diabetes complications and other comorbidities represent the need factors in the Andersen model.

Severity of illness: this study uses the All Patient Refined DRG (APR-DRG) as the severity of illness measure. The All Patient Refined DRGs (APR-DRGs) are assigned using software developed by 3M Health Information Systems. This severity measure classifies the severity of illness into five groups: no class specified (0); minor loss of function (1); minor loss of function (2); moderate loss of function (3); major loss of function (4); extreme loss of function (5).

Diabetes short-term complication: diabetes short-term complications include ketoacidosis, hyperosmolarity, and coma. In this study, diabetes short-term complication is classified as a dichotomous variable – "1" indicates the presence of short-term complication while "0" indicates the absence of short-term complications. The short-term complications are identified by ICD-9 diagnosis codes: 250.1X, 250.2X, and 250.3X.

Retinopathy: diabetic retinopathy is a dichotomous variable in this study – "1" indicate the presence of diabetic retinopathy on the discharge records; "0" means the absence of diabetic retinopathy on the discharge records. The ICD-9 codes used for identification of diabetic retinopathy are listed in Table 7.

Table 7: ICD-9 diagnosis codes for diabetic retinopathy

ICD-9-CM Diagnosis	**ICD-9-CM Codes**
Diabetic ophthalmologic disease	250.50, 250.51, 250.52, 250.53
Background retinopathy	362.01
Other retinopathy	362.1
Retinal edema	362.83
CSME	362.53
Other retinal disorders	362.81, 362.82
Proliferative retinopathy	362.02
Retinal detachment	361.00, 361.01, 361.02, 361.03, 361.04, 361.05, 361.06, 361.07, 361.10, 361.11, 361.12, 361.13, 361.14, 361.19, 361.2, 361.30, 361.31, 361.32, 361.33, 361.81, 361.89, 361.9
Blindness	369.00, 369.01, 369.02, 369.03, 369.04, 369.05, 369.06, 369.07, 369.08, 369.10, 369.11, 369.12, 369.13, 369.14, 369.15, 369.16, 360.17, 369.18, 369.20, 369.21, 369.22, 369.23, 369.24, 369.25, 369.3, 369.4, 369.60, 369.61, 369.62, 369.63, 369.64, 369.65, 369.66, 369.67, 369.68, 369.69, 369.70, 369.71, 369.72, 369.73, 369.74, 369.75
Vitreous hemorrhage	379.23

Diabetes type: diabetes type is included as an indicator variable. The classification of type 1 and type 2 diabetes follows the diagnosis codes and the coding convention. If any diagnosis of the discharge records contains diagnosis codes for type 1 diabetes, the

diabetes type 1s specified as type 1. If the discharge records only contain diagnosis codes for type 2 diabetes or unspecified diabetes, that record is classified as type 2 diabetes.

Depression: depression is included as a dichotomous variable – "0" indicates comorbid depression is not present while "1" indicates the presence of comorbid depression. This study uses the pre-defined variable "CM_DEPRESS" in the dataset that are assigned using the AHRQ comorbidity software (http://www.hcup-us.ahrq.gov/db/vars/nisnote_multi.jsp).

Table 8: Study variable definition and operationalization

Variable	**Definition**	**Operationalization**
Dependent variables		
Hospital inpatient cost (Hospitalization cost)	Total costs of inpatient care	Continuous: Total charge*cost-to-charge ratio
Discharge status	Disposition of patient at discharge	Dichotomous: 1: Non-routine, including transfer to a short-term hospital, transfer to a skilled nursing facility or intermediate care facility, home health care; 0: Routine
Independent variables		
Nephropathy	ICD-9-CM code for renal problems in all-listed diagnoses	Categorical: 0: absent 1: Less severe renal problem 2: Severe renal problem
Peripheral lower extremity diseases	ICD-9-CM diagnosis and procedure codes for peripheral arterial diseases and peripheral neuropathy in all-listed diagnoses	Categorical: 0: absent 1: Less severe lower extremity diseases 2: Severe lower extremity diseases
Coronary atherosclerosis	ICD-9-CM diagnosis and procedure codes for Coronary atherosclerosis in in all-listed diagnoses	Categorical: 0: absent 1: less severe coronary atherosclerosis 2: severe coronary

		atherosclerosis
Age	Age in years at admission, calculated from the birth date and the admission date	Continuous: ≥18
Sex	Sex of the patient, provided by the data source	Categorical: 1: Male 2: Female
Race	Race, HCUP coding includes race and ethnicity in one data element.	Categorical: 1: White 2: Black 3: Hispanic 4: Asian or Pacific Islander 5: Native American 6: Other
Median household income	Median household income of the patient's Zip code of residence	Categorical: 1: 0 to 25th percentile 2: 26th to 50th percentile 3: 51st to 75th percentile 4: 76th to 100th percentile
Diabetes type	ICD-9-CM diagnosis codes for Type 1 and Type 2 diabetes	Categorical: 1: Type 1 2: Type 2
Depression	ICD-9-CM code for depression in all-listed diagnoses	Categorical: 0: absent 1: depression present
Diabetes short-term complications	ICD-9-CM codes for ketoacidosis, hypoglycemia, hyperosmolarity	Categorical: 0: absent 1: present
Retinopathy	ICD-9-CM code for eye problems in all-listed diagnoses	Categorical: 0: absent 1: present
APR DRG severity	All Patient Refined Diagnosis Related Group severity	Categorical: 0: No class specified 1: Minor loss of function (includes cases with no comorbidity or complications) 2: Moderate loss of function 3: Major loss of function 4: Extreme loss of function
Payer	Expected primary payer for hospitalization	Categorical: 1: Medicare 2: Medicaid 3: Private insurance

		4: Self-pay 5: No charge

4.6 Statistical analysis

This is a cross-sectional study using secondary data analysis. All statistical analyses are conducted using SAS 9.3 (SAS Institute, Cary, NC, USA). The statistical significance level is set at 0.0001 (2-tailed). This relatively more rigorous significance level is taken in order to take into account the large sample size (Lin et al., 2013). Missing data is not regarded as a serious concern because this is a sample of hospitalization discharge records and the proportion of missing data is minimal in this dataset. The proportion of patients with missing outcome data is below 2%. The variable for race/ethnicity has the highest proportion of missing data but it is still around 6%. Therefore no specific statistical technique for missing data is adopted in this study.

4.6.1 Descriptive analysis

Descriptive statistics are used to summarize the descriptive information of the outcome and explanatory variables, including the patient population characteristics, hospital inpatient cost, and hospitalization discharge status. Numbers and percentages are provided for dichotomous or categorical variables. Means, standard deviations (S.D.), minimum values, 25% percentiles, medians, 75% percentiles, and maximum values are calculated for continuous variables.

4.6.2 Exploratory analysis

Exploratory statistical analyses with multivariate regression are used to analyze the association between diabetes complications and hospital inpatient cost and utilization.

Generalized linear model is employed to explore the impact of diabetes complications on hospitalization cost. Multivariate logistic regression is adopted to examine the influence of diabetes complications on hospitalization discharge status.

For every regression model, only observations with complete non-missing data are used for analysis by SAS default. This default is a feature of both generalized linear modeling and logistic regression. For studies that include multiple dependent variables, this default allows for inclusion of appropriate cases for each variable from the larger identified cohort.

4.6.2.1 Generalized linear model using Gamma distribution with Log link

Problems with modeling health care costs data

Health care cost data is typically right-skewed or positively skewed (median< mean). A small percentage of patients with severe diseases necessitate costly treatment while common less expensive treatment is enough for most of the patients. That small group of severe patients account for a disproportionately large amount of the cost (Everitt & Pickles, 1999). The variance of cost data is usually not constant and has been found to be proportionate to the square of the mean (Blough et al. 1999). Since traditional multivariate regression models are based on the assumptions of normal distribution and equal variance (homoscedasticity), using these traditional models is inappropriate for modeling cost data because the model assumptions will be violated (Dodd et al., 2006). In fact, the use of non-parametric methods is advocated for examining highly skewed cost data. However, very few non-parametric methods can be used to assess the effects of multiple covariates on health care costs (Lin, 2000). In the past, one common approach

for modeling health care cost data is to do a log transformation of the outcome variable (cost) and then ordinal least square (OLS) linear regression (Duan et al., 1983). One drawback of log transformation of cost is that all inference must be made on the log-dollar scale instead of the on the original dollar scale. Bias can be added in retransforming predictions to the dollar scale.

Generalized linear model

Generalized linear model (GLM) has been proposed as an alternative approach for modeling medical costs. Generalized linear model is an extension that builds on the traditional linear model. There are three components in a generalized linear model (McCullagh and Nelder, 1989):

1) The linear component (similar to the traditional linear models):

$$\eta_i = x'_i \beta$$

Where x_i is a column vector of covariates for observation i, β is a column vector of regression coefficients.

2) A link function g which describes how the expected value of a response y_i ($\mu_i = E(y_i)$) is related to the linear predictor:

$$g(\mu_i) = x'_i \beta$$

3) The response variables y_1, y_2 … are independent, each having a probability distribution from an exponential family. This suggests that the variance depends on the mean by way of the variance function:

$$Var(y_i) = \sigma_i^2 = \phi V(\mu_i)$$

The exponential family includes the normal (Gaussian), the binomial, the Poisson, the gamma and the inverse Gaussian distributions. Each distribution has a corresponding natural link function and a variance function. For example, the natural link function for the gamma distribution is the reciprocal

$$g(\mu_i)=1/\mu_i$$

And the variance function is

$$\sigma_i^2= \phi\mu_i^2$$

For a given distribution, other link functions instead of the natural link function can be used. For instance, the log-link function

$$g(\mu_i)=\log(\mu_i)$$

is often used with the gamma distribution.

Generalized linear model become popular in modeling health care cost for two reasons: First, the use of generalized linear model eliminates the need to retransform the parameter estimates. In addition, it also accommodates the skewness in the cost distribution by specifying gamma or inverse Gaussian distribution as the underlying distributions (Blough and Ramsey, 2000).

Modified Park test

The performance of generalized linear modeling of medical cost relies on appropriate specification of the exponential family distribution and link function. If the variance of medical cost is proportional to the square of the mean, the gamma distribution is preferred. The Poisson or inverse Gaussian distribution can also offer alternative applicable variance functions. However, it could be possible that the relationship between

the mean and the variance falls somewhere between the inverse Gaussian the gamma models.

In order to test whether a proper distribution family is adopted in a generalized linear model, modified Park test is commonly used to examine the relationship between the mean and the variance function (Manning & Mullahy, 2001). 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 $(y_i - \hat{y}_i)^2$ 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; λ_1 is the coefficient of the regression of on, and the value of λ_1 indicates which distribution family to apply in GLM.

If $\lambda_1=0$, the normal distribution non-linear least square distribution should be used;

If $\lambda_1=1$, the Poisson distribution should be used;

If $\lambda_1=2$, the gamma distribution should be used;

If $\lambda_1=3$, the inverse Gaussian distribution should be used.

A recent paper compared GLMs with several distribution families for modeling health care cost. It concluded that a GLM with inverse Gaussian family distribution and log link function had the optimal performance by residual analysis (Moran et al., 2007). In the pilot work of this study, hospitalization cost was modeled and compared between

GLM with gamma distribution and GLM with inverse Gaussian distribution. The modified Park test from both gamma model and inverse Gaussian model had λ around 1.8. Therefore, GLM with gamma distribution and log link function was used as the final study model.

4.6.2.2 Multivariate Logistic Regression

The secondary outcome of the study – hospitalization discharge status – is a dichotomous variable; therefore multivariate logistic regression is used to examine the effect of complications and other factors on hospitalization discharge status. In logistic regression, the probability of a binary outcome is modeled as a combination of the predictor variables. Logistic regression can also been regarded as a special case of the generalized linear model (Moore et al., 2012; Harrell, 2015):

$$\text{Given } Y_i|X_i \sim \text{Binomial } (1, \pi_i),\ E(Y_i|X_i) = \pi_i = g(X\beta)$$

The link function for the logistic model is:

$$\log\left(\frac{\pi}{1-\pi}\right) = X\beta$$

Predictors with p-values below 0.001 were considered to be statistically significant. The adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) are reported in the results.

4.6.2.3 Stratified random matching

The estimation of causal inference in either randomized trials or observational studies are subject to the counterfactual model (Rubin 1973). That is to say, the estimation is essentially a comparison of potential outcomes. For each individual, we can

only observe one of these potential outcomes, since each individual at a particular point in time will receive either the treatment or control, but not both (Morgan & Harding, 2016). In order to make efficient and valid inferences of the treatment effect, it is desirable to compare the treatment and control groups that are as similar as possible. Matching methods have been proposed and developed as early as in the 1940s to minimize the variance between the treatment and control groups (Stuart, 2010).

The theory for matching originated from the early work by Cochran and Rubin (Cochran & Rubin, 1973). Several studies indicate that linear regression adjustment can possibly result in increasing bias in the estimated treatment effect when the true relationship between the covariate and outcome is even moderately non-linear. This issue is more serious in cases when there are large differences in the means and variances of the covariates in the treatment and control groups (Rubin, 1973; Heckman, 1998; Rubin & Thomas, 2000; Rubin, 2001). Though there were critics for matching in economics, that case had been reevaluated and matching was still shown as a good solution (LaLonde, 1986; Dehejia & Wahaba, 1999).

Matching methods include nearest neighbor matching, subclassification, full matching, weighting and so on. Four key steps have been consistently identified for these matching methods (Stuart, 2010). The four key steps are:

1) Defining the distance measure used to determine whether an individual is a good match for another;
2) Implementing a match method
3) Assessing the quality of the resulting matched samples

4) Analysis of the outcome and estimation of the treatment effect.

Currently matching is regarded as complementary with regression adjustment and are best when used in combination with regression adjustment (Stuart, 2010). Therefore this study includes a matched subgroup from the original cohort. The group with a complication is considered as “treatment” group while the group without complications is regarded as “control” group in this study. A stratified matched subgroup is drawn from the group without complications and made comparable to the group with a complication. The strata are determined by three key demographic variables: age, sex, and race. Age is classified into two categories: < 65 and ≥ 65. Sex includes male and female. Race is divided into: White and Non-White. Thus each group has eight strata. There are two reasons that stratified random matching is selected out of all the available matching methods: First, the strata variables are important characteristics associated with the comorbidities examined in this study and the hospitalization cost; Second, complicated matching methods like propensity score matching has the potential of giving the same score to two completely different individuals because of the complex logistic regression algorithm. Stratified random matching, however, is more straightforward and avoid the drawback of propensity score matching.

4.7 Ethical Considerations

This dataset meets all HIPAA compliance standards. The study dataset is de-identified without the ability to identify an individual through the dataset. The data use agreement is in Appendix 1.

The study was approved by the University of Minnesota's Institutional Review Board. A copy of the IRB approval is in Appendix 2.

Chapter 5: Results

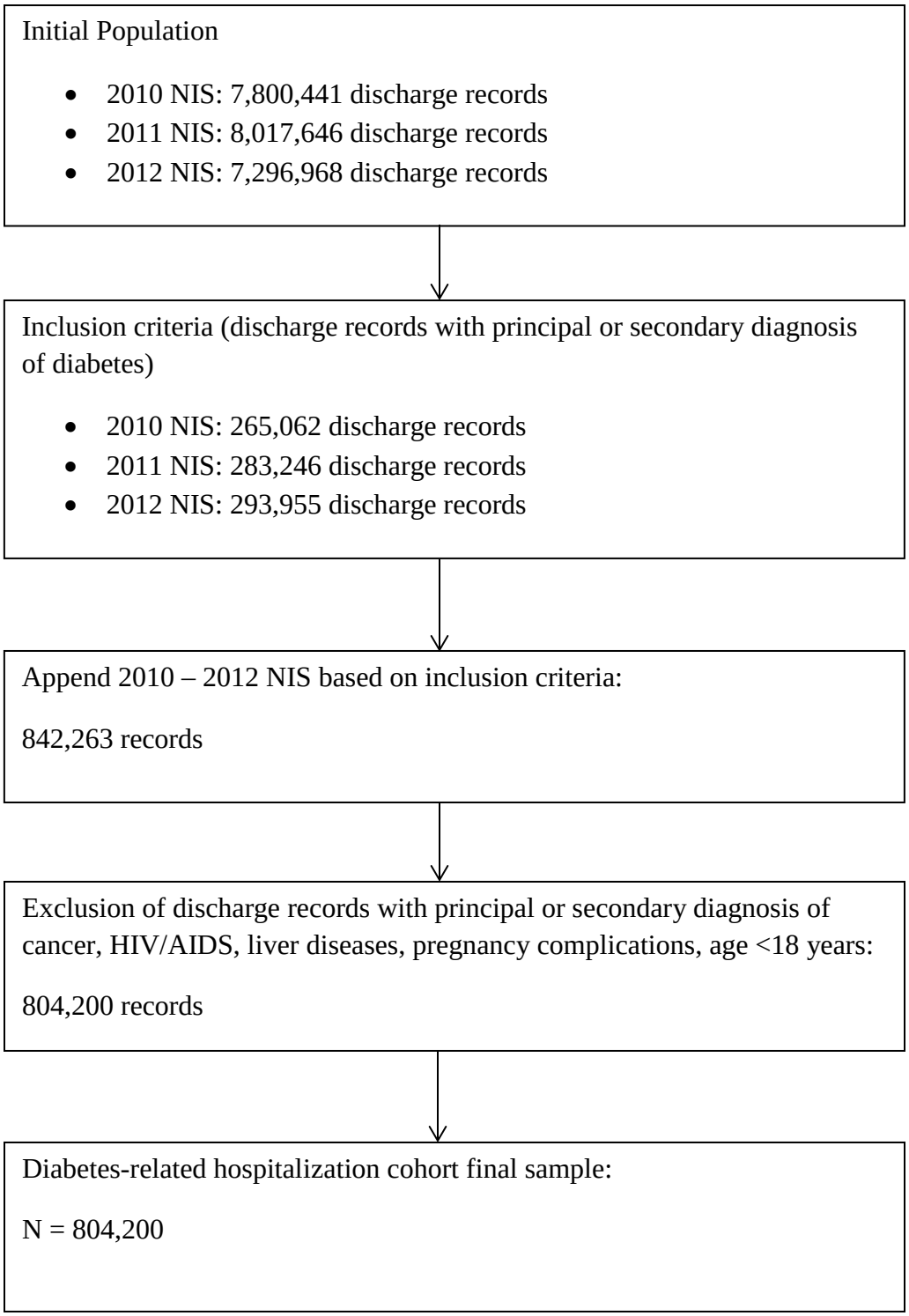
This chapter presents the statistical analysis findings of the study. The study results are presented by each of the study cohort: diabetes-related hospitalization, peripheral lower extremity diseases-related hospitalization, kidney diseases-related hospitalization, and coronary atherosclerosis-related hospitalization. In each study cohort, the results presented include a description of the construction of study cohort; descriptive statistics for the study variables; and the results of exploratory statistical analyses.

5.1 Diabetes-related hospitalization analysis results

5.1.1 Data extraction and cohort construction

This study used hospital discharge data from the 2010 – 2012 National Inpatient Sample. After applying all study inclusion and exclusion criteria, four study cohorts with final analyzable data were constructed. Figure 13 shows how the subjects for the diabetes-related hospitalization cohort were extracted. The final diabetes-related hospitalization cohort contained 804,200 discharge records.

Figure 13: Diabetes-related hospitalization cohort construction flow chart



5.1.2 Descriptive statistics of study variables

5.1.2.1 Descriptive statistics of dependent variables

The dependent variables of this study include hospitalization costs and discharge status. This section presents the descriptive statistics for the two outcome variables.

Hospitalization cost

Diabetes-related hospitalization cost was obtained by multiplication of the total hospitalization charge by the cost-to-charge ratio. Since the dataset contains 2010-2012 data, all the cost were converted to the 2012 dollars using the medical consumer price index (CPI) with the data published by the bureau of labor statistics. Table 9 shows the descriptive statistics and the distribution of the diabetes-related hospitalization cost respectively. Out of the total 804,200 discharge records, 8 observations had cost>$1,000,000 and were considered to be outliers. After removing outliers, the descriptive statistics of diabetes-related hospitalization were summarized in Table 10. The histogram with the distribution of cost was presented in Figure 14. The mean diabetes-related hospitalization cost was $10,342 and the median cost was $6,847.

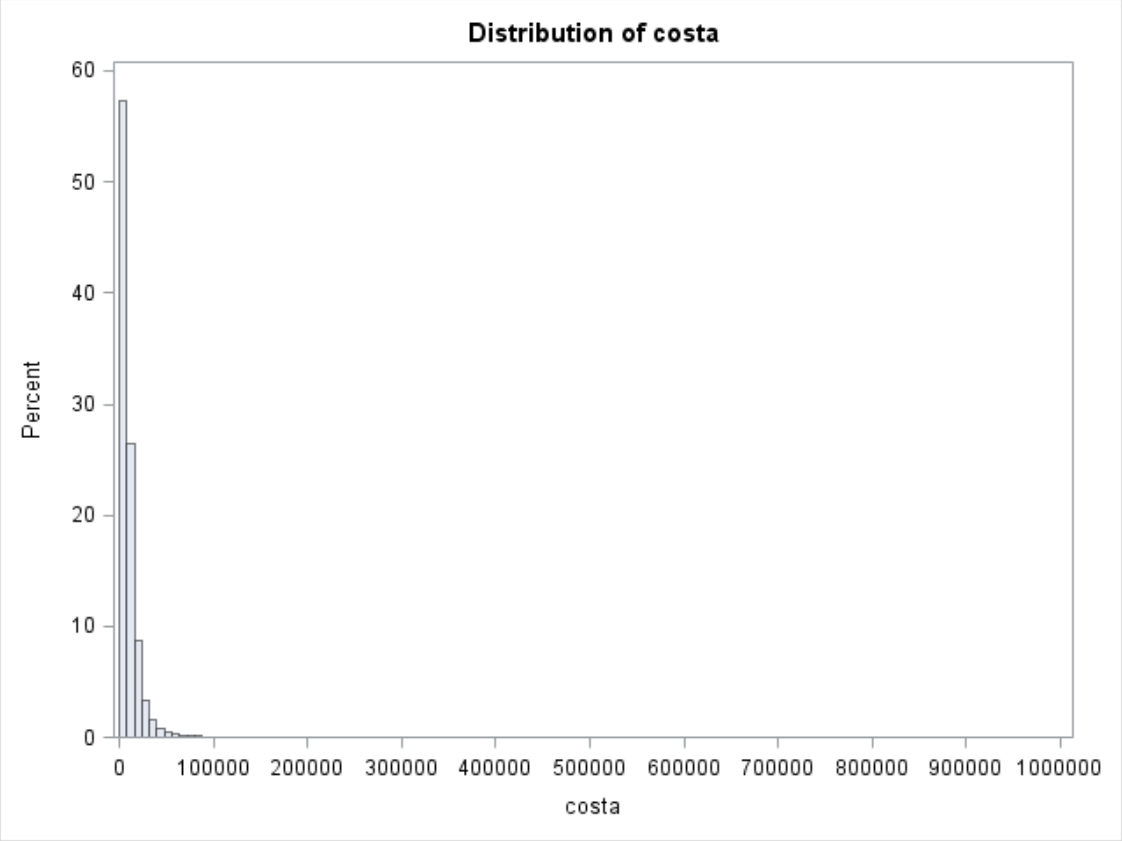
Table 9: Descriptive statistics of diabetes-related hospitalization cost

Statistics	**Diabetes-relate hospitalization cost**
Mean ± S.D.	$10,357 ± $13,696
Minimum	$16.9
25% Quartile	$4,166
Median	$6,875
75% Quartile	$12,239
99% Quartile	$57332
Maximum	$2,020,379

Table 10: Descriptive statistics of diabetes-related hospitalization cost without outlier

Statistics	Diabetes-related hospitalization cost
Mean ± S.D.	$10,342 ± $12,813
Minimum	$16.9
25% Quartile	$4,166
Median	$6,847
75% Quartile	$12,239
99% Quartile	$57,311
Maximum	$988,625

Figure 14: Distribution of diabetes-related hospitalization cost without outlier



Discharge status

The disposition of patient at discharge had several categories in the original dataset and was grouped into two major categories: routine discharge and non-routine

discharge. Table 11 listed frequency distribution of discharge status. 67.9% of the hospitalized diabetes patients had a routine discharge; while 32.1% of the patients with diabetes-related hospitalization had a non-routine discharge.

Table 11: Diabetes-related hospitalization discharge status

Discharge status	**Description**	**Percentage**	**Total percentage**
Routine discharge	Discharge to home	67.91%	67.91%
Non-Routine discharge	Transfer to short-term hospital	1.83%	32.09%
	Transfer other: includes skilled nursing facility (SNF), Intermediate Care Facility (ICF), Another type of facility	13.81%	
	Home Health Care	13.94%	
	Against Medical Advice	1.90%	
	Died in hospital	0.58%	
	Discharge alive, destination unknown	0.02%	

5.1.2.2 Descriptive statistics of diabetes complications

The three diabetes complications are the main explanatory variable of interest. The presence and the severity of three diabetes complications examined in this study – peripheral lower extremity (PLE) diseases, kidney diseases, and coronary atherosclerosis – were identified by ICD-9-CM diagnosis codes, procedure codes, and DRG. Table 12 presents the presence of the three complications in the diabetes-related hospitalization cohort; while Table 13 summarizes the severity of the complications. Overall, 50.58% of the patients with diabetes-related hospitalization did not have any of the three complications; 10.97% only had PLE; 10.40% only had coronary atherosclerosis; 8.77% only had kidney diseases; 6.46% had both PLE and kidney diseases; 5.27% had both PLE and kidney diseases; 3.69% had both coronary atherosclerosis and kidney diseases; 3.8% had all the three complications. Among patients with PLE comorbidity, 30.9% had severe

PLE (66,135/214,003) while 69.1% had less severe PLE (147,868/214,003). 53% of the patients with coronary atherosclerosis comorbidity had the severe form and 47% of them had the less severe form. Most the patients with kidney diseases comorbidity had the severe form rather than the less severe form (92% vs. 8% respectively).

Table 12: The presence of complications in the diabetes-related hospitalization cohort

Comorbidities	Kidney diseases (0)		Kidney diseases (1)	
	Coronary atherosclerosis (0)	Coronary atherosclerosis (1)	Coronary atherosclerosis (0)	Coronary atherosclerosis (1)
Peripheral lower extremity (PLE) diseases (0)	N=406,762 (50.58%)	N=83,664 (10.40%)	N=70,504 (8.77%)	N=29,702 (3.69%)
Peripheral lower extremity (PLE) diseases (1)	N=88,251 (10.97%)	N=51,951 (6.46%)	N=42,379 (5.27%)	N=30,979 (3.85%)

Table 13: The severity of complications in the diabetes-related hospitalization cohort

	Coronary atherosclerosis	Kidney diseases	Peripheral Lower extremity diseases
Less severe	11.4% (n = 92,834)	1.69% (n = 13,556)	18.4% (n = 147,868)
Severe	12.9% (n = 103, 842)	19.9% (n = 160,010)	8.22% (n = 66,135)
Not present	73.4% (n = 607,524)	78.4% (n=630,634)	73.39% (n = 590,197)

5.1.2.3 Descriptive statistics of other independent variables

Independent variables for multivariate statistical models were identified according to the Andersen's behavioral model of health services utilization. They were classified

into three categories as described in the methods section. Age, sex, race, primary payer, and comorbidities were measured at the individual level; household income level information was only available at the 5-digit zip code level. Table 14 shows the descriptive statistics of control variables by the presence or the absence of the three complications.

With regard to the predisposing characteristics, hospitalized diabetes patients with complications (PLE, kidney diseases, or coronary atherosclerosis) were generally older and more likely to be male than hospitalized diabetes patients without any of these complications. For example, 43% of the hospitalized diabetes patients with PLE were 65 years or older; 47.8% of the hospitalized diabetes patients with kidney diseases were 65 years or older; 59% of the hospitalized diabetes patients with coronary atherosclerosis were 65 years or older; while only 31.2% of the hospitalized diabetes patients without any of these complications were 65 years or older. More than 50% of the patients with diabetes-related hospitalization and either PLE, kidney diseases, or coronary atherosclerosis as comorbidity were male; however, less than half of the hospitalized diabetes patients without these complications were male. The distribution of race/ethnicity is not always consistent between hospitalized diabetes patients with complications and patients without complications. For instance, hospitalized diabetes patients with coronary atherosclerosis were predominantly White. However, a higher Black percentage was present among hospitalized diabetes-patients with kidney diseases and hospitalized diabetes patients without any of these complications.

Concerning the enabling resources, more than 50% of the hospitalized diabetes patients lived in area where the median household income is below the 50^{th} percentile.

More than half of the hospitalized diabetes patients with PLE, kidney diseases, or coronary atherosclerosis had Medicare as the primary payer. Among hospitalized diabetes patients without complications, only 37.9% were paid by Medicare, followed by private insurance, which paid for 28.5% of the care.

The frequency distribution of other comorbidity as need factors are also summarized in Table 14. More than 80% of the hospitalized diabetes patients with PLE or kidney diseases had moderate or major loss of function. 72.8% of hospitalized diabetes patients with coronary atherosclerosis had moderate or major loss of function. 61.5% of hospitalized diabetes patients without any complications had moderate or major loss of function. Among hospitalized diabetes patients without complications, 20% of them had short-term complications. 7% to 14% of the hospitalized diabetes patients with complications had short-term complications. 11% to 14% of the hospitalized diabetes patients have depression. Diabetic retinopathy was observed in 1.53% of the hospitalized diabetes patients without complications. Among patients with diabetes-related hospitalization and PLE comorbidity, 12.4% of them had diabetic retinopathy. Among patients with diabetes-related hospitalization and kidney diseases comorbidity, 15.1% of them had diabetic retinopathy. Among patients with diabetes-related hospitalization and coronary atherosclerosis, 7.0% of them had diabetic retinopathy.

Table 14: Descriptive statistics of independent variables (n=804,192)

Independent variables	Diabetes-related hospitalization with PLE (n = 213,560)	Diabetes-related hospitalization with kidney diseases (n = 173,564)	Diabetes-related hospitalization with coronary atherosclerosis (n = 196,296)	Diabetes-related hospitalization without any of these three complications (n=406,762)

Predisposing characteristics				
Age				
<65	57.02%	52.20%	41.0%	68.8%
>=65	42.98%	47.80%	59.0%	31.2%
Sex				
Female	43.7%	45.2%	42%	54.7%
Male	53.3%	54.8%	58%	45.3%
Race				
White	63.3%	53.5%	68.1%	55.9%
Black	19.6%	27.3%	15.7%	23.5%
Hispanic	11.9%	13.2%	10.1%	14.2%
Asian	1.73%	2.65%	2.38%	2.18%
Native American	0.91%	0.92%	0.81%	0.93%
Other	2.70%	2.52%	2.85%	3.29%
Enabling resources				
Median zip code income				
0 to 25th percentile (Quartile 1)	33.3%	34.6%	31.9%	35.3%
26th to 50th percentile (Quartile2)	25.7%	25.3%	26.1%	25.5%
51st to 75th percentile (Quartile 3)	23.8%	23.4%	24.2%	23.0%
76th to 100th percentile (Quartile 4)	17.2%	16.8%	17.8%	16.2%
Primary payer				
Medicare	56.7%	63.4%	66.3%	37.9%
Medicaid	14.0%	12.4%	9.20%	17.2%
Private insurance	20.6%	17.4%	18.8%	28.5%
Self-pay	5.36%	4.15%	3.27%	10.9%
No charge	0.58%	0.41%	0.31%	1.06%
Other	2.75%	2.25%	2.17%	4.50%
Need Factors				
Complications				
PLE	100%	52.3%	42.3%	0%
Kidney diseases	34.4%	100%	30.1%	0%

Coronary atherosclerosis	38.8%	34.5%	100%	0%
Diabetes type				
Type 1	11.4%	14.0%	5.7%	16.2%
Type 2	88.6%	86.0%	95.3%	83.8%
APRDRG: severity of illness (loss of function)				
0 (no class)	0.02%	0.06%	0.03%	0.05%
1 (minor loss)	12.01%	5.57%	22.1%	35.4%
2 (moderate loss)	43.2%	35.5%	44.1%	49.7%
3 (major loss)	38.3%	49.7%	28.7%	12.8%
4 (extreme loss)	6.54%	9.19%	5.05%	2.04%
Short-term complications				
Yes	9.77%	14.4%	7.07%	20.05%
No	90.2%	85.6%	92.93%	79.95%
Depression				
Yes	13.9%	11.5%	11.8%	11.2%
No	86.1%	88.5%	88.2%	88.8%
Retinopathy				
Yes	12.4%	15.1%	7.02%	1.53%
No	87.6%	84.9%	92.98%	98.47%

Most of the independent variables were not equally distributed between hospitalized diabetes patients with complication and hospitalized diabetes patients without complication. To reduce the degree of confounding caused by imbalance of demographic variables, stratified random matching was carried out. For each subgroup with PLE, coronary atherosclerosis, or kidney diseases, a matched subgroup was drawn from the group of hospitalized diabetes patients without complications. The strata for matching were determined by three demographic variables: age group (<65 or ≥ 65); sex (female or male); and race (White or Non-White). The frequency distribution of age group, sex, and race in each of the three subgroups (PLE, coronary atherosclerosis, and

kidney diseases) was used as the reference for selecting the matched subgroup. Table 15a), 15b), 15c) summarizes the distribution of demographic variables after match.

Table 15: Demographic characteristics in the stratified matched cohorts

15a) Diabetes cohort with and without PLE

Variables	Diabetes-related hospitalization with PLE (n=213,560)	Diabetes-related hospitalization without any of these three complications (n=109,978)	Chi square test p-value
Age (>=65 years)	42.98%	43.01%	0.8641
Sex (Female)	43.67%	43.99%	0.0809
Race (Non-White)	36.75%	36.99%	0.1951
Income			0.0369
0 to 25th percentile	33.32%	33.58%	
26th to 50th percentile	25.70%	25.33%	
51st to 75th percentile	23.77%	23.36%	
76th to 100th percentile	17.21%	17.73%	
Primary Payer			<0.0001
Medicare	56.67%	45.96%	
Medicaid	14.01%	13.69%	
Private insurance	20.63%	26.20%	
Self-pay	5.36%	9.23%	
No charge	0.58%	0.90%	
Other	2.75%	4.02%	

15b) Diabetes cohort with and without KD

Variables	Diabetes-related hospitalization with KD (n=173,5644)	Diabetes-related hospitalization without any of these three complications (n=9,000)	Chi square test p-value
Age (>=65 years)	47.81%	48.00%	0.3546
Sex (Female)	45.22%	45.00%	0.2885
Race (Non-White)	46.54%	47.00%	0.0235
Income			
0 to 25th percentile	34.58%	35.04%	0.0087
26th to 50th percentile	25.26%	24.81%	
51st to 75th percentile	23.39%	23.14%	
76th to 100th percentile	16.77%	17.01%	

Primary Payer			<0.0001
Medicare	63.38%	48.74%	
Medicaid	12.44%	13.75%	
Private insurance	17.37%	24.04%	
Self-pay	4.15%	8.86%	
No charge	0.41%	0.82%	
Other	2.25%	3.78%	

15c) Diabetes cohort with and without coronary atherosclerosis

Variables	Diabetes-related hospitalization with coronary atherosclerosis	Diabetes-related hospitalization without coronary atherosclerosis	Chi square test p-value
Age (>=65 years)	58.97%	59.02%	0.7717
Sex (Female)	42.00%	42.00%	0.9879
Race (Non-White)	31.87%	31.97%	0.5993
Income			<0.0001
0 to 25th percentile	31.87%	31.92%	
26th to 50th percentile	26.12%	25.61%	
51st to 75th percentile	24.19%	23.88%	
76th to 100th percentile	17.82%	18.59%	
Primary Payer			<0.0001
Medicare	66.28%	57.06%	
Medicaid	9.20%	10.23%	
Private insurance	18.76%	22.08%	
Self-pay	3.27%	6.82%	
No charge	0.31%	0.64%	
Other	2.17%	3.18%	

5.1.3 Results of generalized linear model

5.1.3.1 Cost comparison between diabetes patients with PLE and diabetes patients without PLE

To estimate the incremental cost of PLE on diabetes-related hospitalization cost, the cost between hospitalized diabetes patients with PLE were compared to hospitalized diabetes patients without PLE by generalized linear model (GLM) with gamma

distribution and log link. Control variables were adjusted in GLM. The regression coefficient estimates from GLM were presented in Table 16. The adjusted mean cost by the categorical variables was presented in Table 17. The results from the original cohort and the matched cohort are presented. The group that combined diabetes patients with PLE and diabetes patients without complications contained 620,322 discharge records. In the regression analysis, there were 523,389 discharge records included which contained non-missing values for every variables included in the model. The stratified matched cohort contained 323,538 discharge records; 278,538 observations with non-missing values were used for the analysis.

PLE and other comorbidities: The presence of severe PLE was associated with a 66.6% increase in diabetes-related hospitalization cost. The presence of less severe PLE increased diabetes-related hospitalization cost by 1.4%. The presence of diabetes short-term complications lowered hospitalization cost by 21%. The presence of diabetic retinopathy increased diabetes-related hospitalization cost by 10.5%. Severe kidney diseases were associated with a 1.5% increase in diabetes-related hospitalization cost. The similar effect was observed in the stratified matched cohort; however, less severe PLE was no longer associated with significant increase in diabetes-related hospitalization cost as the P-value is above the significance threshold. Based on the results from the matched cohort, diabetes-related hospitalization cost was highest among patients with severe PLE (mean: $17,212; 95% CI: $16,610 - $17,835) compared to patients with less severe PLE (mean: $10,432; 95% CI: $10,072 - $10,806) or without PLE (mean: $10,363; 95% CI: $10,000 -- $10,740). The adjusted mean diabetes-related hospitalization cost among patients with retinopathy was $12,955; while the cost among

patients without retinopathy was $11,678. Figure 15 displays the adjusted mean diabetes-related hospitalization by PLE severity.

Other statistical significant effect: In the full cohort, 1 year increase in age was associated with 0.23% increase in diabetes-related hospitalization cost. However, age was not a significant effect in the matched cohort. Diabetes-related hospitalization cost was 5.5% lower for Black patients than White patients. The racial/ethnic gap between Black and White in terms of hospitalization cost was narrowed in the matched cohort. In the matched cohort, the diabetes-related hospitalization cost for Black patients was 2% lower compared to the cost for White patients. The adjusted mean hospitalization cost was slightly higher for White diabetes patients than Black diabetes patients but confidence intervals overlap. Figure 16 displays the adjusted mean diabetes-related hospitalization cost by race/ethnicity in the full cohort and in the stratified matched cohort. Patient with other government entitlement programs as primary payer had the highest hospitalization cost than patient paid by Medicare, Medicaid, private insurance or patients without insurance. The adjusted mean hospitalization cost for patients paid by Medicare, Medicaid, and private insurance was $12,288, $12,406 and $13,008 respectively; while the adjusted mean hospitalization cost for patients paid by other government entitlement programs was $13,546. Figure 17 displays the adjusted mean diabetes-related hospitalization cost by primary payer in the full cohort and in the stratified matched cohort.

Nonsignificant effect: The model results for peripheral lower extremity diseases indicate that several variables did not add a significant incremental cost to diabetes-related hospitalization cost using the significance rule set for this study. These variables

included: depression (p=0.1415) and severity of illness (APRDRG_Severity). The adjusted mean hospitalization cost for patients with or without depression was $12,263 and $12,337 respectively). Though hospitalization cost was highest for patients with major or extreme loss of function, the hospitalization cost did not differ between patients with minor loss of function or moderate loss of function.

Table 16: The GLM results for the effect of PLE on diabetes-related hospitalization cost

Variables	Full cohort (n=620,322)		Stratified match cohort (n=323,538)	
	Coefficient	P-value	Coefficient	P-value
PLE (ref: no PLE)				
Severe	0.5103	<0.0001	0.5073	<0.0001
Less severe	0.0134	<0.0001	0.0066	0.0667
Age	0.0023	<0.0001	0.0004	0.0003
Sex (ref: Female)				
Male	0.0083	<0.0001	0.0126	<0.0001
Race (ref: White)				
Black	-0.0565	<0.0001	-0.0200	<0.0001
Hispanic	0.0373	<0.0001	0.0642	<0.0001
Asian	0.0830	<0.0001	0.1087	<0.0001
Native American	-0.0670	<0.0001	-0.0828	<0.0001
Other	0.0669	<0.0001	0.0954	<0.0001
Payer (ref: Other)				
Medicare	-0.1225	<0.0001	-0.0975	<0.0001
Medicaid	-0.1116	<0.0001	-0.0879	<0.0001
Private	-0.0561	<0.0001	-0.0406	<0.0001
Self-Pay	-0.2381	<0.0001	-0.1945	<0.0001
No charge	-0.1948	<0.0001	-0.1586	<0.0001
Income (ref: Quartile 4)				
Quartile 1	-0.1626	<0.0001	-0.1585	<0.0001
Quartile 2	-0.1184	<0.0001	-0.1209	<0.0001
Quartile 3	-0.0589	<0.0001	-0.0548	<0.0001
Short term complication (ref: No)				
Yes	-0.2352	<0.0001	-0.2542	<0.0001
Diabetes type				
Type 1 vs. Type 2	-0.0597	<0.001	-0.0422	<0.0001
Kidney disease (ref: No)				
Severe	0.0152	<0.0001	0.0148	<0.0001
Less Severe	0.0030	07637	0.0003	0.9802
Coronary atherosclerosis (ref: No)				
Severe	0.0996	<0.0001	0.1139	<0.0001
Less Severe	-0.0312	<0.0001	-0.0112	0.0114

Depression (ref: No)				
Yes	0.0046	0.0088	-0.0060	0.1415
Retinopathy (ref: No)				
Yes	0.0994	<0.0001	0.1019	<0.0001
APRDRG_Severity (ref: 0)				
1	0.0509	0.3656	01083	0.0128
2	0.1158	0.0386	0.2704	0.0012
3	0.4497	<0.0001	0.5998	<0.0001
4	1.2409	<0.0001	1.3618	<0.0001

Table 17: The adjusted mean diabetes-related hospitalization cost by PLE and control variables

	Full cohort		Stratified matched cohort	
	Adjusted mean cost	95% Confidence interval	Adjusted mean cost	95% Confidence interval
PLE				
Severe	$17,548	$17,117 -- $17,989	$17,212	$16,610 -- $17,835
Less Severe	$10,676	$10,419 -- $10,939	$10,432	$10,072 -- $10,806
Not present	$10,534	$10,276 -- $10,798	$10,363	$10,000 -- $10,740
Race				
White	$12,411	$12,117 -- $12,712	$11,965	$11,557 -- $12,388
Black	$11,729	$11,448 -- $12,017	$11,729	$11,323 -- $12,149
Hispanic	$12,882	$12,572 -- $13,201	$12,758	$12,314 -- $13,218
Asian	$13,485	$13,118 -- $13,863	$13,340	$12,817 -- $13,884
Native American	$11,606	$11,249 -- $11,974	$11,014	$10,533 -- $11,517
Other	$13,269	$12,925 -- $13,622	$13,163	$12,673 -- $13,672
Sex				
Male	$12,595	$12,292 -- $12,906	$12,385	$11,956 -- $12,830
Female	$12,491	$12,190 -- $12,799	$12,215	$11,792 -- $12,654
Primary payer				
Medicare	$12,518	$12,220 -- $12,823	$12,288	$11,868 -- $12,723
Medicaid	$12,656	$12,350 -- $12,969	$12,406	$11,975 -- $12,853
Private	$13,378	$13,057 -- $13,708	$13,008	$12,558 -- $13,473
Self-Pay	$11,152	$10,877 -- $11,433	$11,152	$10,756 -- $11,563
No charge	$11,645	$11,290 -- $12,011	$11,559	$11,039 -- $12,104
Other	$14,150	$13,789 -- $14,519	$13,546	$13,049 -- $14,063
Income				
Quartile 1	$11,606	$11,326 -- $11,893	$11,412	$11,015 -- $11,823
Quartile 2	$12,131	$11,838 -- $12,432	$11,849	$11,437 -- $12,277
Quartile 3	$12,874	$12,562 -- $13,194	$12,659	$12,217 -- $13,116
Quartile 4	$13,656	$13,323 -- $13,997	$13,372	$12,903 -- $13,858
Short term complication				
Yes	$11,152	$10,879 -- $11,431	$10,832	$10,450 -- $11,227
No	$14,108	$13,769 -- $14,456	$13,967	$13,484 -- $14,468
Kidney disease				
Severe	$12,658	$12,355 -- $12,968	$12,421	$11,992 -- $12,865

Less Severe	$12,505	$12,134 -- $12,887	$12,241	$11,769 -- $12,733
Not present	$12,467	$12,175 -- $12,767	$12,238	$11,820 -- $12,672
Coronary atherosclerosis				
Severe	$13,544	$13,208 -- $13,888	$13,324	$12,856 -- $13,809
Less Severe	$11,884	$11,586 -- $12,191	$11,746	$11,331 -- $12,177
Not present	$12,260	$11,967 -- $12,561	$11,890	$11,480 -- $12,315
Depression				
Yes	$12,572	$12,264 -- $12,887	$12,263	$11,832 -- $12,710
No	$12,514	$12,215 -- $12,821	$12,337	$11,912 -- $12,777
Diabetes type				
Type 1	$12,175	$11,877 -- $12,480	$12,043	$11,619 -- $12,482
Type 2	$12,923	$12,612 -- $13,242	$12,562	$12,127 -- $13,013
Retinopathy				
Yes	$13,182	$12,852 -- $13,521	$12,955	$12,496 -- $13,430
No	$11,935	$11,650 -- $12,227	$11,678	$11,275 -- $12,095
APRDRG_Severity				
0	$8,634	$7,733 -- $9,637	$7,550	$6,405 -- $8,899
1	$9,085	$8,981 -- $9,190	$9,298	$9,164 -- $9,434
2	$9,694	$9,590 -- $9,799	$9,894	$9,763 -- $10,027
3	$13,537	$13,395 -- $13,682	$12,755	$13,576 -- $13,935
4	$30,163	$29,741 -- $30,590	$29,649	$28,977 -- $29,968

Figure 15: Adjusted mean diabetes-related hospitalization cost by PLE severity (stratified matched cohort)

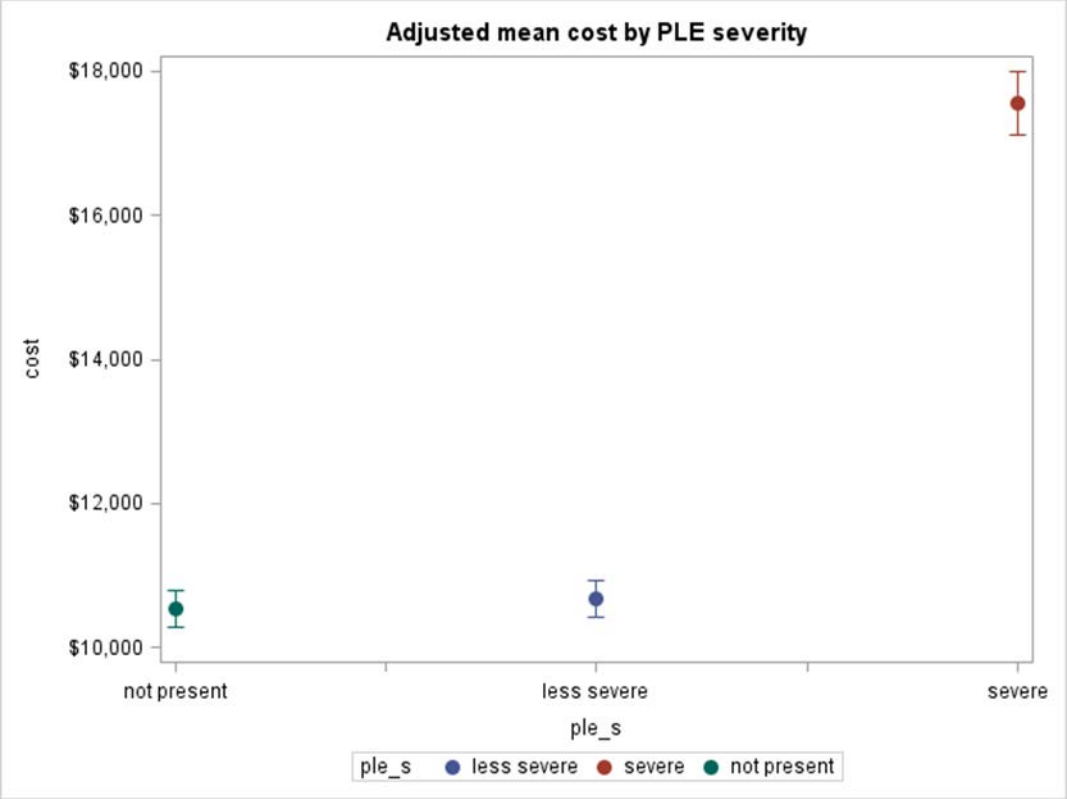
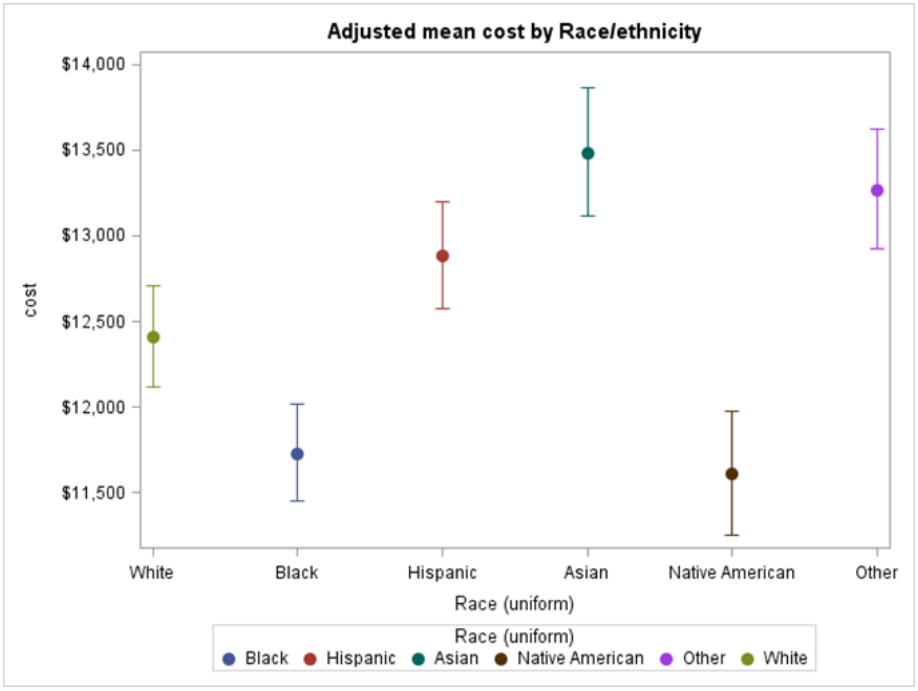


Figure 16: Adjusted mean diabetes-related hospitalization cost by race/ethnicity (full cohort and stratified matched cohort)



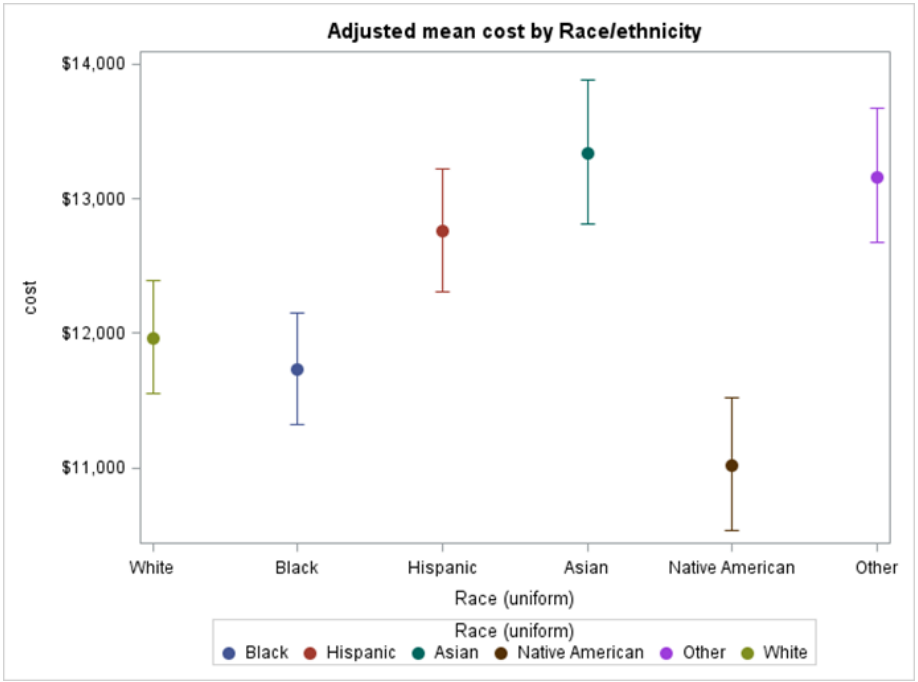
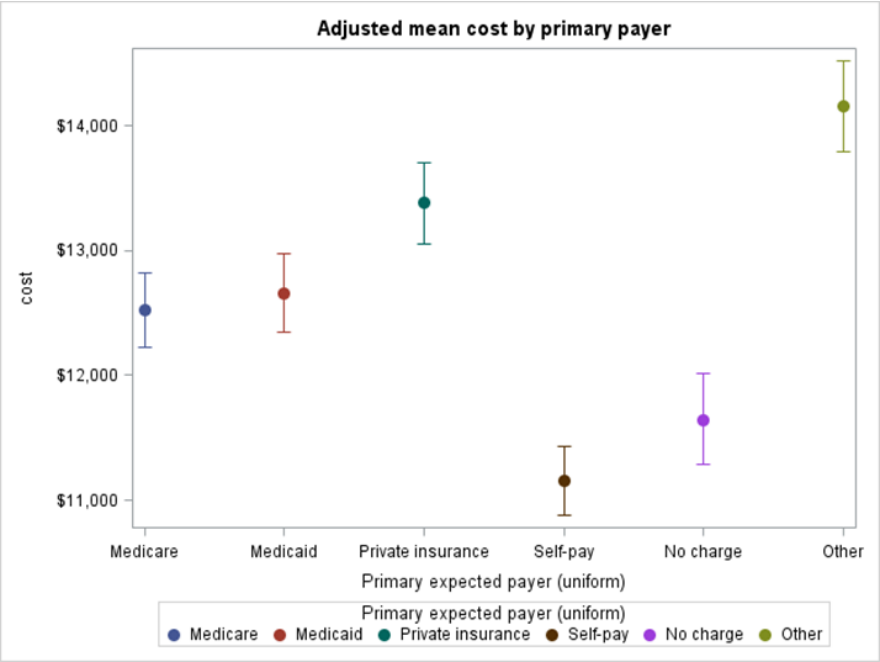
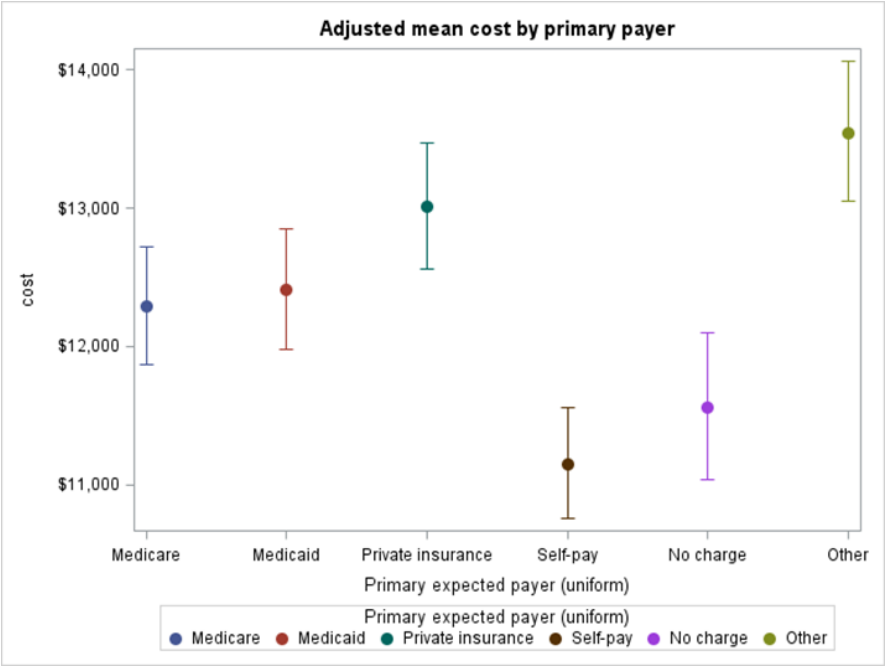


Figure 17: Adjusted mean diabetes-related hospitalization cost by primary payer (full cohort and stratified matched cohort)





5.1.3.2 Cost comparison between diabetes patients with kidney diseases and diabetes patients without kidney diseases

Generalized linear model was used to estimate the incremental impact of kidney diseases on diabetes-related hospitalization cost. The regression coefficient estimates from GLM were presented in Table 18 for the full cohort and the stratified matched cohort. The adjusted mean costs for the categorical variables in the model were presented in Table 19. The group that combined diabetes patients with kidney diseases and diabetes patients without complications contained 580,326 discharge records. In the regression analysis, there were 489,781 discharge records included which contained non-missing values for every variables included in the model. The stratified matched cohort contained 263,564 discharge records; 226,266 observations with non-missing values were used for the analysis.

Kidney diseases and other comorbidities: In the full cohort, severe kidney diseases was associated with 1.2% increase in diabetes-related hospitalization cost; while less severe kidney diseases was associated with a small yet insignificant decrease in diabetes-related hospitalization cost. The effect of severe kidney diseases on diabetes-related hospitalization cost was altered in the stratified matched cohort. Both severe kidney diseases and less severe kidney diseases were associated with a small and insignificant decrease in diabetes-related hospitalization cost. In the original cohort, the adjusted mean hospitalization cost for diabetes patients with severe kidney diseases was $12,701; the adjusted mean hospitalization cost for diabetes patients was $12,497; while that for diabetes patients without kidney diseases was $12,551 (Figure 18). In the matched cohort, the adjusted mean hospitalization cost for diabetes patients with severe

kidney diseases, less severe kidney diseases, or without kidney diseases was $12,523, $12,252, and $12,549 respectively.

Other statistical significant effects: The hospitalization cost for Black diabetes patients was 0.94 times the hospitalization cost for White diabetes patients in the original cohort. The cost difference between Black and White patients were narrowed in the stratified matched cohort: the hospitalization cost for Black patients was 4.1% lower than the hospitalization cost for White patients. The effect of age on hospitalization cost was inconsistent in the original cohort compared to the stratified matched cohort. In the original cohort, older patients had higher hospitalization costs; however, older patients had lower hospitalization cost in the stratified matched cohort. Asian patients had significantly higher hospitalization cost than White and Black patients.

Nonsignificant effects: In the full cohort, GLM parameter estimates indicated that these variables did not have a significant effect on diabetes-related hospitalization cost: severe coronary atherosclerosis (p=0.6627), depression (p=0.3793), and severity of illness (APRDRG_Severity: 1 vs 0, p=0.9921; 2 vs. 0, p=0.2134).

Table 18: The GLM results for the effect of kidney diseases on diabetes-related hospitalization cost (n=580,326)

Variables	Full cohort (n=580,326)		Stratified matched cohort (n=263,564)	
	Coefficient	P-value	Coefficient	P-value
Kidney disease (ref: No)				
Severe	0.0119	<0.0001	-0.0021	0.6266
Less Severe	-0.0043	0.6414	-0.0240	0.0043
Age	0.0012	<0.0001	-0.0022	<0.0001
Sex (ref: Female)				
Male	0.0112	<0.0001	0.0196	<0.0001
Race (ref: White)				
Black	-0.0622	<0.0001	-0.0422	<0.0001
Hispanic	0.0397	<0.0001	0.0625	<0.0001
Asian	0.0919	<0.0001	0.1318	<0.0001

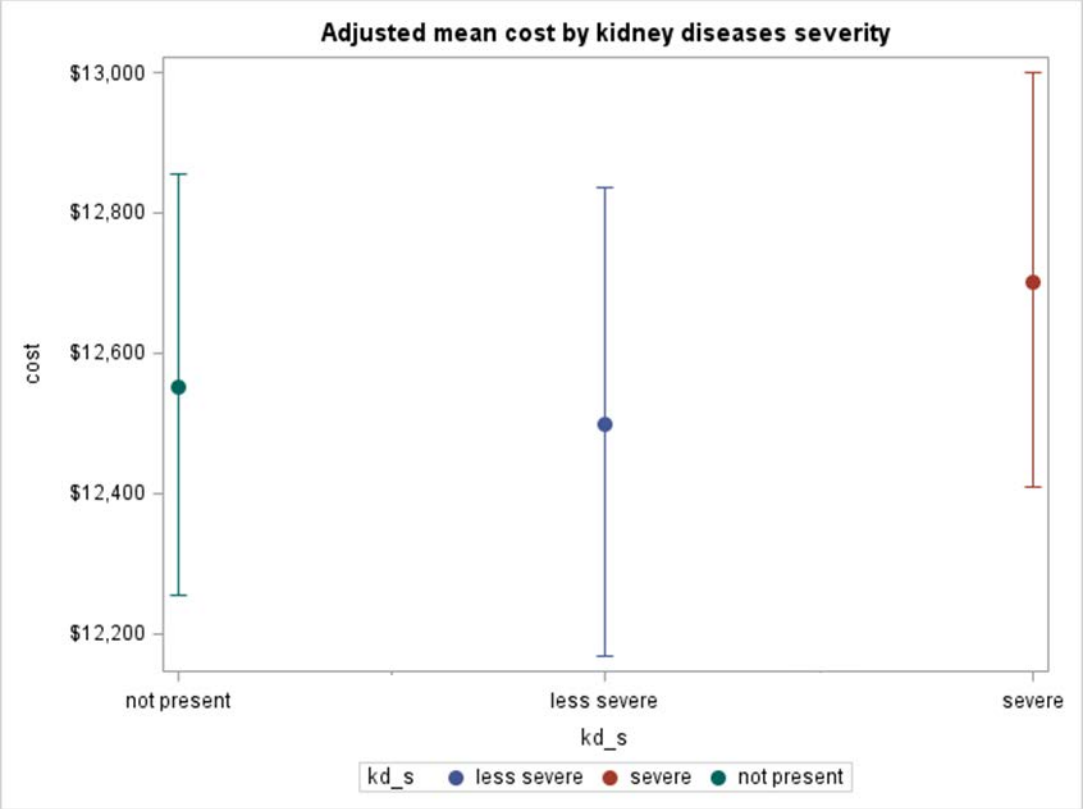
Native American	-0.0538	<0.0001	-0.0729	<0.0001
Other	0.0716	<0.0001	0.1057	<0.0001
Payer (ref: Other)				
Medicare	-0.1000	<0.0001	-0.0535	<0.0001
Medicaid	-0.1261	<0.0001	-0.1097	<0.0001
Private	-0.0541	<0.0001	-0.0294	0.0029
Self-Pay	-0.2686	<0.0001	-0.2636	<0.0001
No charge	-0.2280	<0.0001	-0.2153	<0.0001
Income (ref: Quartile 4)				
Quartile 1	-0.1676	<0.0001	-0.1695	<0.0001
Quartile 2	-0.1227	<0.0001	-0.1327	<0.0001
Quartile 3	-0.0670	<0.0001	-0.0815	<0.0001
Short term complication (ref: No)				
Yes	-0.2556	<0.0001	-0.2811	<0.0001
Coronary atherosclerosis (ref: No)				
Severe	0.0024	0.6627	0.0311	<0.0001
Less Severe	-0.0773	<0.0001	-0.0454	<0.0001
PLE (ref: no PLE)				
Severe	0.5197	<0.0001	0.5305	<0.0001
Less severe	0.0385	<0.0001	0.0348	<0.0001
Depression (ref: No)				
Yes	-0.0030	03793	-0.0273	<0.0001
Retinopathy (ref: No)				
Yes	0.1687	<0.0001	0.1638	<0.0001
Diabetes type				
Type 1 vs. Type 2	-0.0193	<0.0001	0.0399	<0.0001
APRDRG_Severity (ref: 0)				
1	0.0005	0.9921	0.0706	0.3613
2	0.0671	0.2134	0.1497	0.0528
3	0.3788	<0.0001	0.4400	<0.0001
4	1.2297	<0.0001	1.2627	<0.0001

Table 19: Adjusted mean diabetes-related hospitalization cost by kidney diseases and control variables

Variables	Full cohort		Matched cohort	
	Adjusted mean cost	95% Confidence interval	Adjusted mean cost	95% Confidence interval
Kidney disease				
Severe	$12,701	$12,408 -- $13,000	$12,523	$12,112 -- $12,948
Less Severe	$12,497	$12,167 -- $12,837	$12,252	$11,820 -- $12,700
Not present	$12,551	$12,254 -- $12,855	$12,549	$12,128 -- $12,985
Sex				
Female	$12,512	$12,219 -- $12,812	$12,320	$11,911 -- $12,742
Male	$12,654	$12,358 -- $12,957	$12,563	$12,147 -- $12,993
Race				
White	$12,401	$12,117 -- $12,692	$12,061	$11,671 -- $12,465
Black	$11,653	$11,382 -- $11,931	$11,563	$11,183 -- $11,957

Hispanic	$12,903	$12,601 -- $13,213	$12,851	$12,424 -- $13,293
Asian	$13,595	$13,232 -- $13,968	$13,760	$13,242 -- $14,297
Native American	$11,752	$11,387 -- $12,128	$11,213	$10,707 -- $11,744
Other	$13,322	$12,981 -- $13,671	$13,406	$12,916 -- $13,915
Primary payer				
Medicare	$12,958	$12,659 -- $13,265	$13,189	$12,763 -- $13,629
Medicaid	$12,625	$12,329 -- $12,930	$12,469	$12,055 -- $12,897
Private	$13,568	$13,251 -- $13,892	$13,510	$13,066 -- $13,970
Self-Pay	$10,949	$10,686 -- $11,218	$10,689	$10,321 -- $11,071
No charge	$11,402	$11,049 -- $11,766	$11,219	$10,656 -- $11,812
Other	$14,322	$13,964 -- $14,689	$13,914	$13,406 -- $14,441
Income				
Quartile 1	$11,636	$11,363 -- $11,915	$11,558	$11,174 -- $11,956
Quartile 2	$12,170	$11,883 -- $12,464	$11,992	$11,592 -- $12,405
Quartile 3	$12,866	$12,562 -- $13,177	$12,621	$12,199 -- $13,058
Quartile 4	$13,758	$13,431 -- $14,093	$13,693	$13,232 -- $14,171
Short term complication				
Yes	$11,073	$10,810 -- $11,343	$10,809	$104,45 -- $11,187
No	$14,298	$13,964 -- $14,640	$14,318	$13,846 -- $14,806
Diabetes Type				
Type 1	$12,462	$12,165 -- $12,766	$12,691	$12,261 -- $13,137
Type 2	$12,705	$12,408 -- $13,009	$12,195	$11,793 -- $12,610
Coronary atherosclerosis				
Severe	$12,931	$12,612 -- $13,259	$12,895	$12,456 -- $13,350
Less Severe	$11,942	$11,648 -- $12,243	$11,945	$11,539 -- $12,365
Not present	$12,901	$12,602 -- $13,207	$12,500	$12,090 -- $12,925
PLE				
Severe	$17,566	$17,121 -- $18,022	$17,514	$16,908 -- $18,142
Less Severe	$10,856	$10,597 -- $11,122	$10,669	$10,313 -- $11,037
Not present	$10,447	$10,203 -- $10,697	$10,304	$9,965 -- $10,655
Depression				
Yes	$12,564	$12,264 -- $12,872	$12,272	$11,856 -- $12,703
No	$12,601	$12,309 -- $12,900	$12,612	$12,198 -- $13,039
Retinopathy				
Yes	$13,690	$13,354 -- $14,034	$13,502	$13,042 -- $13,979
No	$11,565	$11,298 -- $11,839	$11,462	$11,086 -- $11,851
APRDRG_Severity				
0	$8,999	$8,092 -- $10,007	$8,469	$7,274 -- $9,860
1	$9,004	$8,897 -- $9,112	$9,088	$8,934 -- $9,245
2	$9,623	$9,519 -- $9,729	$9,836	$9,688 -- $9,985
3	$13,144	$13,005 -- $13,284	$13,149	$12,958 -- $13,342
4	$30,777	$30,352 -- $31,209	$29,938	$29,405 -- $30,481

Figure 18: Adjusted mean diabetes-related hospitalization cost by kidney diseases severity



5.1.3.3 Cost comparison between patients with or without coronary atherosclerosis

Generalized linear model was used to estimate the incremental impact of coronary atherosclerosis on diabetes-related hospitalization cost. The coefficient estimates for the full cohort and the matched cohort were presented in Table 20. The adjusted mean hospitalization cost for the categorical covariates were presented in Table 21. The group that combined diabetes patients with coronary atherosclerosis and diabetes patients without complications contained 603,058 discharge records. In the regression analysis, there were 511,818 discharge records included which contained non-missing values for every variables included in the model. The stratified matched cohort contained 296,396

discharge records; 258,111 observations with non-missing values were used for the analysis.

Coronary atherosclerosis: The presence of severe coronary atherosclerosis was associated with a 13% increase in diabetes-related hospitalization cost. In the matched cohort, the cost for hospitalized diabetes patients with severe coronary atherosclerosis was 1.12 times the cost for hospitalized diabetes patients without severe coronary atherosclerosis. The presence of less severe coronary atherosclerosis was associated with a small but insignificant decrease in hospitalization cost in the matched cohort. The incremental cost of severe coronary atherosclerosis was $1,567 from the full cohort and $1,388 from the matched cohort. This incremental effect was statistically significant. The diabetes-related hospitalization cost was similar between patients with less severe coronary atherosclerosis and patients without coronary atherosclerosis. Figure 19 displays the adjusted mean hospitalization cost by coronary atherosclerosis severity in the original cohort.

Other significant effect: The effect of age on diabetes-related hospitalization cost was not consistent in the full cohort and in the matched cohort: cost was higher for older patients in the full cohort; while cost was lower for older patients in the matched cohort. The hospitalization cost for male was 4.5% higher than the cost for females in the matched cohort. Native Americans had the lowest diabetes-related hospitalization cost compared to White, Black, Hispanics and Asian. The hospitalization cost for Asian was 1.1 times the hospitalization cost for White; while the hospitalization cost for Native American was 0.9 times the hospitalization cost for White. Diabetes-related hospitalization cost was higher for patients paid by Medicare, Medicaid, private

insurance, or other government programs than patients who paid out-of-pocket or who did not have any charges for that hospitalization.

Non-significance effect: In the full cohort, these variables didn't add significantly to diabetes-related hospitalization cost: less severe kidney diseases, less severe PLE, depression, and APRDRG_severity.

Table 20: The GLM results for the effect of coronary atherosclerosis on diabetes-related hospitalization cost

Variables	Full cohort (n=603,058)		Matched cohort (n=296,396)	
	Coefficient	P-value	Coefficient	P-value
Coronary atherosclerosis (ref: No)				
Severe	0.1231	<0.0001	0.1145	<0.0001
Less Severe	-0.0145	<0.0001	-0.0150	0.0002
Age	0.0020	<0.0001	-0.0016	<0.0001
Sex (ref: Female)				
Male	0.0205	<0.0001	0.0440	<0.0001
Race (ref: White)				
Black	-0.0661	<0.0001	-0.0396	<0.0001
Hispanic	0.0291	<0.0001	0.0396	<0.0001
Asian	0.0894	<0.0001	0.1106	<0.0001
Native American	-0.0791	<0.0001	-0.1149	<0.0001
Other	0.0647	<0.0001	0.0944	<0.0001
Payer (ref: Other)				
Medicare	-0.1306	<0.0001	-0.0807	<0.0001
Medicaid	-0.1263	<0.0001	-0.1128	<0.0001
Private	-0.0490	<0.0001	-0.0078	0.4096
Self-Pay	-0.2575	<0.0001	-0.2125	<0.0001
No charge	-0.2147	<0.0001	-0.1874	<0.0001
Income (ref: Quartile 4)				
Quartile 1	-0.1618	<0.0001	-0.1598	<0.0001
Quartile 2	-0.1115	<0.0001	-0.1103	<0.0001
Quartile 3	-0.0572	<0.0001	-0.0558	<0.0001
Short term complication (ref: No)				
Yes	-0.2297	<0.0001	-0.2467	<0.0001

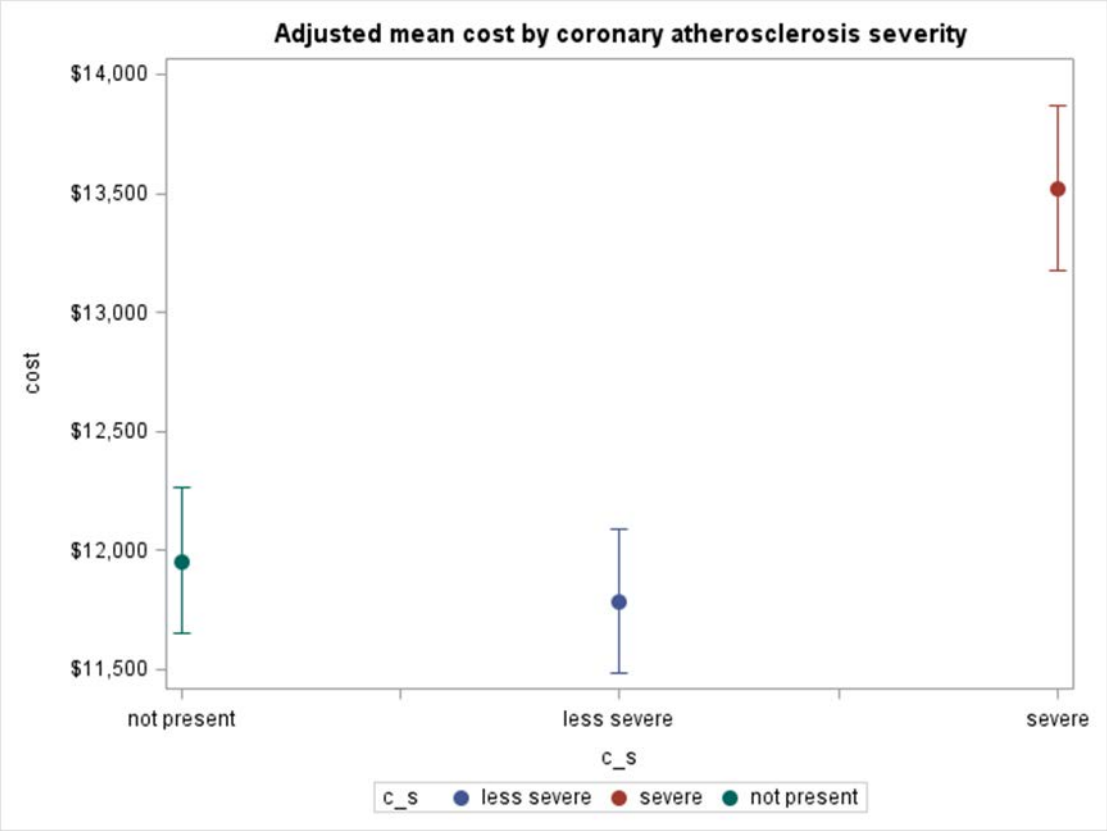
Kidney disease (ref: No)				
Severe	-0.0694	<0.0001	-0.0646	<0.0001
Less Severe	0.0229	0.0939	0.0224	0.1058
Retinopathy (Ref: No)				
Yes	0.1047	<0.0001	0.1169	<0.0001
PLE (ref: no PLE)				
Severe	0.5490	<0.0001	0.5463	<0.0001
Less severe	-0.0045	0.3065	-0.0093	0.0379
Depression (ref: No)				
Yes	-0.0020	0.5317	-0.0306	<0.0001
Diabetes type				
Type 1 vs. Type 2	-0.0792	<0.0001	-0.0597	<0.0001
APRDRG_Severity (ref: 0)				
1	0.0474	0.3993	0.2195	0.0057
2	0.1306	0.0201	0.3098	<0.0001
3	0.4439	<0.0001	0.6013	<0.0001
4	1.2457	<0.0001	1.3418	<0.0001

Table 21: Adjusted mean hospitalization cost by coronary atherosclerosis severity and control variables

Variables	Full cohort		Stratified matched cohort	
	Adjusted mean cost	95% Confidence interval	Adjusted mean cost	95% Confidence interval
Coronary atherosclerosis				
Severe	$13,521	$13,179 -- $13,871	$12,822	$12,377 -- $13,283
Less Severe	$11,782	$11,484 -- $12,088	$11,264	$10,873 -- $11,668
Not present	$11,954	$11,651 -- $12,266	$11,434	$11,035 -- $11,848
Sex				
Female	$12,269	$11,961 -- $12,585	$11,562	$11,162 -- $11,977
Male	$12,523	$12,209 -- $12,845	$12,083	$11,665 -- $12,516
Race				
White	$12,317	$12,013 -- $12,628	$11,644	$11,248 -- $12,053
Black	$11,529	$11,241 -- $11,825	$11,192	$10,805 -- $11,592
Hispanic	$12,681	$12,362 -- $13,008	$12,114	$11,692 -- $12,552
Asian	$13,469	$13,092 -- $13,857	$13,005	$12,501 -- $13,529
Native American	$11,380	$12,786 -- $13,503	$10,380	$9,901 -- $10,882
Other	$13,140	$11,015 -- $11,757	$12,797	$12,316 -- $13,295
Primary payer				
Medicare	$12,384	$12,077 -- $12,699	$12,052	$11,646 -- $12,472
Medicaid	$12,437	$12,124 -- $12,758	$11,672	$11,266 -- $12,091
Private	$13,436	$13,100 -- $13,781	$12,964	$12,520 -- $13,424
Self-Pay	$10,908	$10,629 -- $11,195	$10,564	$10,184 -- $10,960
No charge	$11,385	$11,018 -- $11,764	$10,833	$10,261 -- $11,438
Other	$14,111	$13,737 -- $14,496	$13,066	$12,575 -- $13,576
Income				

Quartile 1	$11,451	$11,163 -- $11,747	$10,930	$10,050 -- $11,323
Quartile 2	$12,042	$11,738 -- $12,353	$11,484	$11,084 -- $11,898
Quartile 3	$12,715	$12,394 -- $13,044	$12,127	$11,704 -- $12,565
Quartile 4	$13,463	$13,121 -- $13,814	$12,823	$12,374 -- $13,288
Short term complication				
Yes	$11,050	$10,769 -- $11,339	$10,448	$10,078 -- $10,832
No	$13,904	$13,555 -- $14,261	$13,372	$12,910 -- $13,850
Diabetes Type				
Type 1	$11,914	$11,610 -- $12,226	$11,472	$11,064 -- $11,896
Type 2	$12,896	$12,572 -- $13,227	$12,178	$11,758 -- $12,614
Kidney disease				
Severe	$11,745	$11,459 -- $12,038	$11,238	$10,855 -- $11,634
Less Severe	$12,880	$12,435 -- $13,342	$12,259	$11,745 -- $12,795
Not present	$12,588	$12,288 -- $12,896	$11,987	$11,583 -- $12,406
Depression				
Yes	$12,383	$12,067 -- $12,707	$11,641	$11,230 -- $12,066
No	$12,408	$12,099 -- $12,724	$12,002	$11,590 -- $12,428
PLE				
Severe	$17,900	$17,431 -- $18,381	$17,066	$16,461 -- $17,692
Less Severe	$10,291	$10,028 -- $10,561	$9,791	$9,449 -- $10,146
Not present	$10,338	$10,078 -- $10,604	$9,883	$9,542 -- $10,236
Retinopathy				
Yes	$13,062	$12,714 -- $13,418	$12,531	$12,079 -- $13,000
No	$11,763	$11,471 -- $12,061	$11,149	$10,767 -- $11,545
APRDRG_Severity				
0	$8,532	$7,636 -- $9,532	$7,209	$6,165 -- $8,428
1	$8,946	$8,826 -- $9,067	$8,978	$8,819 -- $9,140
2	$9,722	$9,598 -- $9,847	$9,826	$9,661 -- $9,994
3	$13,299	$13,133 -- $13,468	$13,153	$12,937 -- $13,372
4	$26,950	$29,172 -- $30,137	$27,580	$27,019 -- $28,154

Figure 19: Adjusted mean diabetes-related hospitalization cost by coronary atherosclerosis severity



5.1.4 Discharge status analysis

5.1.4.1 Crosstab of discharge status by complications

The unadjusted association between diabetes complications and diabetes-related hospitalization discharge status was explored by cross-tabulation and Chi-square test. Table 22 summarizes the crosstab results. 47.7% of the hospitalized diabetes patients with severe PLE had non-routine discharges; while only 28.5% of the hospitalized diabetes patients without PLE had non-routine discharges. 43.3% of the diabetes-related hospitalizations with kidney diseases complications ended up with non-routine discharges; compared to 29.1% non-routine discharges for diabetes-related hospitalizations without kidney diseases. 30% of the hospitalized diabetes patients without coronary atherosclerosis had non-routine discharges; 45% of the hospitalized diabetes patients with less severe coronary atherosclerosis had non-routine discharges; 33% of the hospitalized diabetes patients with severe coronary atherosclerosis had non-routine discharges.

Table 22: Crosstab of discharge status by complications

	Peripheral Lower extremity diseases			Kidney diseases			Coronary atherosclerosis		
	Not present	Less severe	Severe	Not present	Less severe	Severe	Not present	Less severe	Severe
Routine discharge	71.48%	60.39%	52.93%	70.90%	61.69%	56.66%	70.02%	55.03%	67.13%
Non-Routine discharge	28.52%	33.61%	47.07%	29.10%	38.31%	43.34%	29.98%	44.97%	32.87%
Chi-square P value	<0.0001			<0.0001			<0.0001		

5.1.4.2 Logistic regression analysis results

Multivariate logistic regression was used to examine the impact of diabetes complications on diabetes-related hospitalization discharge status with adjustment of confounding variables. The results from logistic regression were summarized in Table 23. The full diabetes-related hospitalization cohort contained 804,192 discharge records; 723,992 observations with non-missing values for the study variables were incorporated in the logistic regression model.

Effect of comorbidities: The presence of severe PLE was associated with a 49.4% increase in the odds of having a non-routine discharge compared to diabetes patients without PLE; the presence of less severe PLE was associated with a 22.1% increase in the odds of having a non-routine discharge compared to diabetes patients without PLE, but this effect was not significant with a p-value 0.9313. The presence of severe or less severe kidney diseases was not associated with increased likelihood of having a non-routine discharge. The presence of severe coronary atherosclerosis was associated with a 32.4% decrease in the odds of having a non-routine discharge.

Other significant effects: The other statistically significant predictors for discharge status included: age, race/ethnicity, primary payer, depression, and comorbidity severity as measured by APRDRG severity of illness. 1 year increase in age was associated a 3.2% increase in the odds of having non-routine discharges. Compared to White patients, Blacks, Hispanics, and Asians were less likely to have non-routine discharges. Hospitalized diabetes patients with Medicare, Medicaid, or private insurance as primary payer were associated with increased odds of having non-routine discharges compared to patients paid out-of-pocket or paid by other government entitlement

programs. The presence of depression was associated with a 20% increase in the odds of having non-routine discharges. Compared to patients whose severity class is 0, patients with major loss (severity class 3) or extreme loss (severity class 4) had increased likelihood of non-routine discharges.

Non-significant effects: Several variables did not have a significant effect to diabetes-related hospitalization discharge status, including sex (p=0.6642), zip code income level, retinopathy (p=0.6284), diabetes type (p=0.1581). The c-statistic (equivalent to the area under the receiver operating characteristics curve) is 0.737 from the logistic regression model, indicating the model has good discrimination and prediction.

Table 23: Logistic regression results of diabetes-related hospitalization discharge status

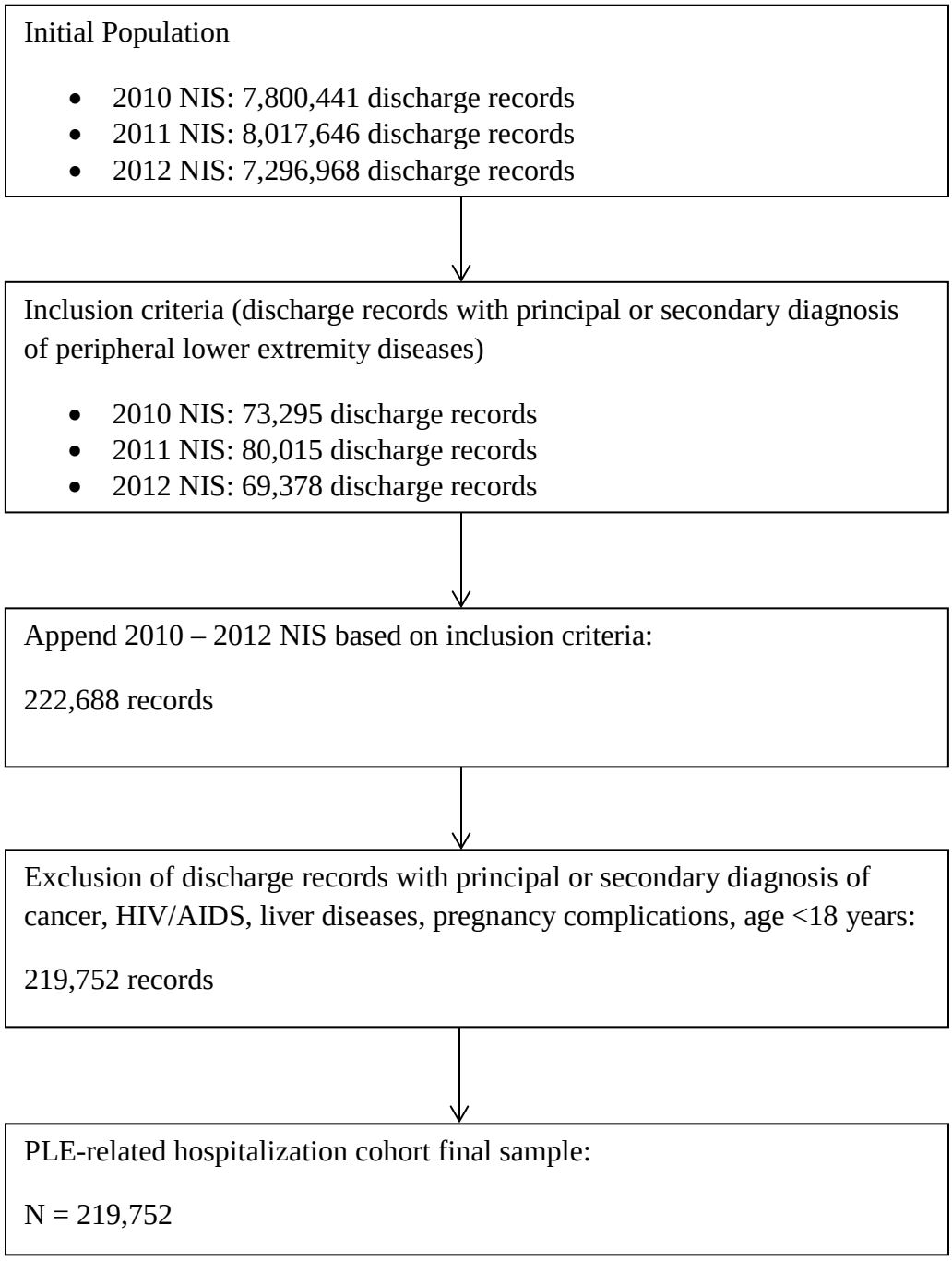
	Odds Ratio	95% Confidence interval		P value
Age	1.032	1.032	1.033	<0.0001
Male vs. Female	0.998	0.987	1.009	0.6642
Race				
Black vs. White	0.990	0.976	1.004	<0.0001
Hispanic vs. White	0.773	0.760	0.787	<0.0001
Asian vs. White	0.719	0.692	0.747	<0.0001
Native American vs. White	0.795	0.747	0.845	0.0029
Other vs. White	0.926	0.896	0.957	<0.0001
Median Zip code household income				
Quartile 1 vs. Quartile 4	0.999	0.983	1.016	0.0320
Quartile 2 vs. Quartile 4	0.977	0.961	0.994	0.0068
Quartile 3 vs. Quartile 4	0.983	0.966	1.000	0.1531
Payer type				
Medicare vs. Other	1.753	1.694	1.815	<0.0001
Medicaid vs. Other	1.551	1.496	1.608	<0.0001
Private vs. Other	1.140	1.100	1.180	<0.0001
Self-pay vs. Other	0.720	0.690	0.751	<0.0001
No charge vs. Other	0.645	0.588	0.707	<0.0001
Short term complication (1 vs. 0)	0.631	0.619	0.644	<0.0001

Peripheral lower extremity diseases				
Less severe vs. None	1.221	1.204	1.239	0.9313
Severe vs. None	1.494	1.465	1.522	<0.0001
Kidney diseases				
Less severe vs. None	0.956	0.918	0.996	0.2400
Severe vs. None	0.959	0.946	0.973	0.1062
Coronary atherosclerosis				
Less severe vs. None	1.036	1.019	1.053	<0.0001
Severe vs. None	0.676	0.665	0.688	<0.0001
Retinopathy (1 vs. 0)	0.994	0.971	1.108	0.6284
Type 1 diabetes vs. Type 2 diabetes	1.016	0.994	1.039	0.1581
Depression (1 vs. 0)	1.208	1.188	1.228	<0.0001
APRDRG_Severity				
1 vs. 0	0.357	0.284	0.450	<0.0001
2 vs. 0	0.568	0.451	0.715	<0.0001
3 vs. 0	1.125	0.894	1.416	<0.0001
4 vs. 0	3.175	2.518	4.002	<0.0001

5.2 Peripheral lower extremity diseases-related hospitalization analysis results

5.2.1 Data extraction and cohort construction

Figure 20: Peripheral lower-extremity diseases-related hospitalization cohort sample selection and cohort construction



The data extraction and sample selection for the peripheral lower extremity diseases-related hospitalization cohort is summarized in Figure 20. The final peripheral lower extremity diseases-related hospitalization cohort consists of 219,752 discharge records based on the 2010 – 2012 National Inpatient Sample.

5.2.2 Descriptive statistics of study variables

5.2.2.1 Descriptive statistics of dependent variables

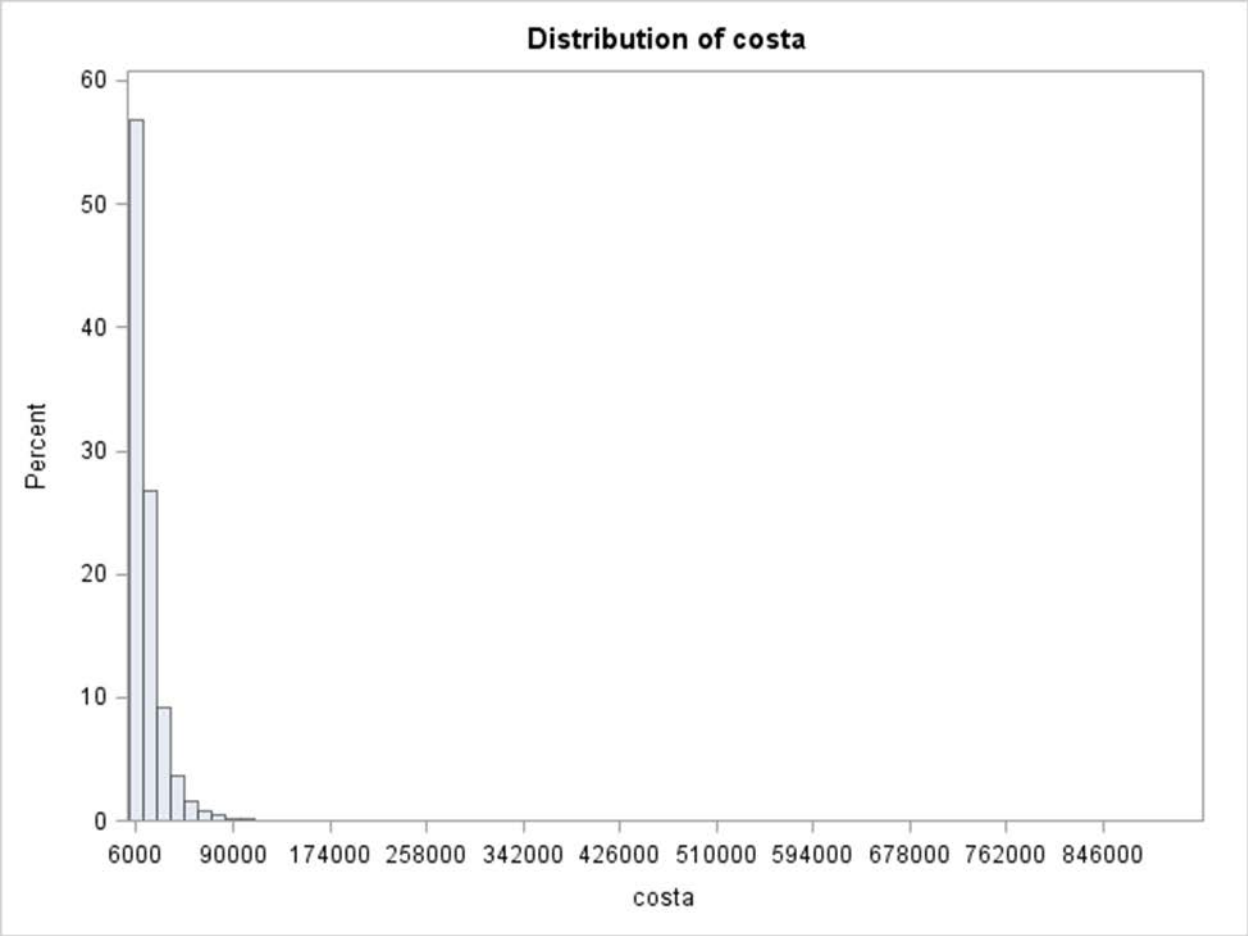
Hospitalization cost

The primary outcome of interest is peripheral lower extremity (PLE) diseases-related hospitalization cost. Table 24 shows the descriptive characteristics of PLE-related hospitalization cohort. The mean PLE-related hospitalization was $15,004 (± $16,415) while the median PLE-related hospitalization cost was $10,314. The maximum PLE-related hospitalization was $920,623 and was not exceeding the $1,000,000 threshold. Therefore all the PLE-related hospitalization discharge records were included in the exploratory analysis.

Table 24: Descriptive statistics of PLE-related hospitalization cost

Statistics	PLE-relate hospitalization cost
Mean ± S.D.	$15,004 ± $16,415
Minimum	$40.99
25% Quartile	$5,715
Median	$10,314
75% Quartile	$18,573
99% Quartile	$76,284
Maximum	$920,623

Figure 21: The histogram for distribution of the PLE-related hospitalization cost



Discharge status

The secondary outcome is PLE-related hospitalization discharge status. 57% of the hospitalized PLE patients had a routine discharge (discharge to home); 43% of the hospitalized PLE patients had a non-routine discharge. The two major subcategories for non-routine discharge were discharged to SNF, ICF or another type of facility (21.9%) and home health care (17.4%) (Table 25).

Table 25: Descriptive statistics of PLE-related hospitalization discharge status

Discharge status	Description	Percentage	Total percentage
Routine discharge	Discharge to home	56.97%	56.97%
Non-Routine discharge	Transfer to short-term hospital	1.94%	43.03%
	Transfer other: includes skilled nursing facility (SNF), Intermediate Care Facility (ICF), Another type of facility	21.90%	
	Home Health Care	17.38%	
	Against Medical Advice	0.74%	
	Died in hospital	1.04%	
	Discharge alive, destination unknown	0.03%	

5.2.2.2 Comorbidities among patients with PLE-related hospitalization

The presence of comorbidities (diabetes, kidney diseases, and coronary atherosclerosis) among hospitalized PLE patients is summarized in Table 26. 32.2% of the hospitalized PLE patients did not have any of the three comorbidities. 44.8% of the hospitalized PLE patients had diabetes as comorbidity (18.5 % with diabetes only; 12.6% with both diabetes and coronary atherosclerosis; 6.5% with both diabetes and kidney diseases; 7.2% with diabetes, coronary atherosclerosis and kidney diseases). 22.3% of the hospitalized PLE patients had kidney diseases as comorbidity (4.7% with kidney diseases only; 3.9% with both kidney diseases and coronary atherosclerosis; 6.5% with both diabetes and kidney diseases; 7.2% with diabetes, coronary atherosclerosis and kidney diseases). 38.1% of the hospitalized PLE patients had coronary atherosclerosis (14.4% with coronary atherosclerosis only; 12.6% with both diabetes and coronary atherosclerosis; 3.9% with both coronary atherosclerosis and kidney diseases; 7.2% with diabetes, coronary atherosclerosis and kidney diseases).

Table 26: Descriptive statistics of the presence of comorbidities in the PLE-related hospitalization cohort

Comorbidities	Kidney diseases (0)		Kidney diseases (1)	
	Coronary atherosclerosis (0)	Coronary atherosclerosis (1)	Coronary atherosclerosis (0)	Coronary atherosclerosis (1)
Diabetes (0)	N=70,795 (32.2%)	N=31,750 (14.45%)	N=10,241 (4.66%)	N=8,526 (3.88%)
Diabetes (1)	N=40,653 (18.5%)	N=27,775 (12.64%)	N=14,198 (6.46%)	N=15,814 (7.20%)

Table 27: Descriptive statistics of comorbidities severity in the PLE-related hospitalization cohort

Comorbidities	**Frequency (N)**	**Percentage**
Diabetes type		
Type 1	2963	1.35%
Type 2	95478	43.45%
Coronary atherosclerosis severity		
Less Severe	39765	18.10%
Severe	44498	20.25%
Kidney diseases severity		
Less Severe	1576	0.72%
Severe	47203	21.48%

5.2.2.3 Descriptive statistics of independent variables

Table 28 presents the frequency distribution of other independent variables by the presence or absence of diabetes. The independent variables are grouped by the Andersen's Behavioral Model of Health Services Utilization.

With regard to predisposing characteristics, overall more than half of the patients with PLE-related hospitalization were 65 years or older. The percentage of patients with age 65 years or older was higher among hospitalized PLE patients without diabetes than hospitalized PLE patients with diabetes (64.8% vs. 53.4%). The percentage of male patients was slightly higher than the percentage of female patients (53.4% male among

hospitalized PLE patients without diabetes and 56.9% male among hospitalized PLE patients with diabetes). Among hospitalized PLE patients, 78.3% of the patients without diabetes were White while 64.5% of hospitalized PLE patients with diabetes were White. 13.6% of hospitalized PLE patients without diabetes were Black while 19.0% of hospitalized PLE patients with diabetes were Black.

In terms of enabling resources, 55.3% of the hospitalized PLE patients without diabetes lived in an area where the median zip code level income was below the 50^{th} percentile, while that percentage for PLE patients with diabetes was 59.4%. The percentage with Medicare as the primary payer was roughly equal between hospitalized PLE patients without diabetes (67.2%) and hospitalized PLE patients with diabetes (66.0%). Among patients with PLE-related hospitalization, 10.1% of the patients with diabetes had Medicaid as the primary payer for care; while 7.1% of the patients without diabetes had Medicaid as the primary payer.

Looking at the frequency distribution of need factors, 30.5% of the hospitalized PLE patients with diabetes had kidney diseases as comorbidity; while 15.7% of the hospitalized PLE patients without diabetes had kidney diseases as comorbidity. Among the hospitalized PLE patients, 44.8% of the patients with diabetes had coronary atherosclerosis as comorbidity; while 33.2% of the hospitalized PLE patients without diabetes had coronary atherosclerosis. Among PLE patients with diabetes, 56.3% had severe PLE; while 49.5% of the PLE patients without diabetes had severe PLE. Using APRDRG as severity of illness measure, 42.7% of the hospitalized PLE patients with diabetes had major or extreme loss of function. 28.7% of the hospitalized PLE patients without diabetes had major or extreme loss of function.

A stratified matched subgroup from PLE-related hospitalization without diabetes was drawn to match the PLE-related hospitalization with diabetes group based on the frequency distribution of age, sex, and race. The distribution of demographic characteristics after match was presented in Table 29.

Table 28: Descriptive statistics of control variables (n=219,752)

Control variables	PLE-related hospitalizations without Diabetes (n=121,312)	PLE-related hospitalization with Diabetes (n=98,440)
Predisposing characteristics		
Age		
<65	35.24%	42.66%
>=65	64.76%	57.34%
Sex		
Female	46.63%	43.14%
Male	53.37%	56.86%
Race		
White	78.27%	64.53%
Black	13.63%	19.04%
Hispanic	4.62%	11.11%
Asian	0.93%	1.71%
Native American	0.45%	0.87%
Other	2.10%	2.74%
Enabling resources		
Median zip code income		
0 to 25th percentile	29.57%	34.21%
26th to 50th percentile	25.73%	25.15%
51st to 75th percentile	24.39%	23.25%
76th to 100th percentile	20.31%	17.39%
Primary payer		
Medicare	67.24%	66.03%
Medicaid	7.14%	10.13%
Private insurance	19.65%	17.71%
Self-pay	3.16%	3.38%
No charge	0.33%	0.35%
Other	2.49%	2.41%
Need Factors		
Comorbidity		
Kidney diseases	15.7%	30.49%
Less Severe	0.21%	1.35%
Severe	15.26%	29.14%

Coronary atherosclerosis	33.20%	44.28%
Less Severe	16.51%	20.05%
Severe	16.97%	24.29%
PLE severity		
Less Severe	50.48%	43.72%
Severe	49.52%	56.28%
APRDRG: severity of illness (loss of function)		
0 (no class)	0.03%	0.04%
1 (minor loss)	26.03%	11.11%
2 (moderate loss)	45.25%	46.14%
3 (major loss)	24.24%	37.21%
4 (extreme loss)	4.44%	5.50%
Depression	10.65%	11.81%

Table 29: Demographic characteristics in the stratified matched cohort

	PLE-related hospitalization with diabetes (n=98,440)	PLE-related hospitalization without diabetes (n=49,730)	Chi square test p-value
Age (>=65 years)	57.34%	56.77%	0.0337
Sex (Female)	43.14%	42.69%	0.1026
Race (Non-White)	64.53%	64.81%	0.2911
Income			<0.0001
Quartile 1	34.21%	32.74%	
Quartile 2	25.15%	24.86%	
Quartile 3	23.25%	23.22%	
Quartile 4	17.39%	19.18%	
Primary Payer			<0.0001
Medicare	66.03%	61.19%	
Medicaid	10.13%	9.16%	
Private insurance	17.71%	22.39%	
Self-pay	3.38%	3.98%	
No charge	0.35%	0.37%	
Other	2.41%	2.90%	

5.2.3 Results of generalized linear model

The impact of diabetes and other covariates on PLE-related hospitalization costs was examined in generalized linear model with gamma distribution and log link function.

The regression coefficient estimates and their p-values are presented in Table 30. The adjusted mean hospitalization costs by categorical variables are summarized in Table 31. The results were presented in the original PLE-related hospitalization cohort and in the stratified matched cohort. The original cohort contained 219,752 discharge records; in the regression, 183,180 observations were used that contained non-missing values for all the variables included in the model. There were 148,170 discharge records in the matched cohort; 127,375 observations with non-missing values were included in the final analysis.

Diabetes: The regression coefficient estimate for type 1 and type 2 diabetes were both negative, indicating that the presence of diabetes was associated with a decrease in PLE-related hospitalization cost. The hospitalization cost was highest for PLE patients without diabetes ($15,494) than PLE patients with type 1 ($13,530) or type 2 diabetes ($14,975) in the full cohort (Figure 22). Similar trend was retained in the stratified matched cohort.

Other statistical significant effects: Increase in age was associated with a slight decline in PLE-related hospitalization in both the original cohort and the stratified matched cohort. The hospitalization cost for Hispanic was 4.5% higher than that for White; the hospitalization cost for Asian was 9.8% higher than that for White. PLE-related hospitalization cost was highest for Asian ($15,903) and lowest for Native American ($13,280) (Figure 24). Compared to patients paid by other government entitlement programs, patients with Medicare, self-pay or no charge had the lowest hospitalization cost (Figure 23). Hospitalization cost was lower for patients residing in relatively low income neighborhood compared to patients residing in relatively high income neighborhood. Comorbid coronary atherosclerosis among patients with PLE-

related hospitalization was also associated with slightly elevated hospitalization cost (3.9% increase for less severe coronary atherosclerosis and 7.3% increase for severe coronary atherosclerosis).

Non-significant effects: The PLE-related hospitalization cost was comparable between Black, White, and Native American as the p-values are above the significance threshold (0.0001). Depression was not associated with change in hospitalization cost (p=0.6346). PLE-related hospitalization cost was similar between male and female (p=0.1272). With regard to the severity of illness, patients with extreme loss of function (APRDRG_4) had the highest hospitalization cost; cost did not differ between the other severity groups.

Table 30: Coefficient estimates from the generalized linear model

Variables	Original PLE cohort		PLE matched cohort	
	Coefficient	P-value	Coefficient	P-value
Diabetes (ref: No)				
Type 1	-0.1356	<0.0001	-0.1280	<0.0001
Type 2	-0.0340	<0.0001	-0.0393	<0.0001
Age	-0.0048	<0.0001	-0.0037	<0.0001
Sex (ref: Female)				
Male	0.0019	0.5649	-0.0061	0.1272
Race (ref: White)				
Black	-0.0118	0.0124	-0.0122	0.0195
Hispanic	0.0444	<0.0001	0.0439	<0.0001
Asian	0.1114	<0.0001	0.0938	<0.0001
Native American	-0.689	0.0008	-0.0757	0.0005
Other	0.0977	<0.0001	0.0944	<0.0001
Payer (ref: Other)				
Medicare	-0.0863	<0.0001	-0.0860	<0.0001
Medicaid	-0.0618	<0.0001	-0.0443	0.0009
Private	-0.0400	0.0002	-0.0350	0.0055
Self-Pay	-0.1329	<0.0001	-0.1262	<0.0001
No charge	-0.0995	0.0005	-0.1391	<0.0001
Income (ref: Quartile 4)				
Quartile 1	-0.1607	<0.0001	-0.1606	<0.0001
Quartile 2	-0.1225	<0.0001	-0.1223	<0.0001
Quartile 3	-0.0629	<0.0001	-0.0581	<0.0001
Kidney disease (ref: No)				
Less Severe	-0.0031	0.8780	0.0074	0.7243

Severe	-0.0476	<0.0001	-0.0398	<0.0001
Coronary atherosclerosis (ref: No)				
Less Severe	0.0404	<0.0001	0.0390	<0.0001
Severe	0.0736	<0.0001	0.0703	<0.0001
PLE severity				
Less severe vs. Severe	-0.7005	<0.0001	-0.6883	<0.0001
Depression (ref: No)				
Yes	-0.0164	0.0016	-0.0030	0.6346
APRDRG_Severity (ref: 0)				
1	0.0007	0.9937	-0.0469	0.6671
2	0.1224	0.1993	0.0858	0.4309
3	0.3605	0.0002	0.3305	0.0024
4	1.1540	<0.0001	1.1090	<0.0001

Table 31: Adjusted mean hospitalization cost in the PLE-related hospitalization cohort

Variables	Full cohort		Stratified matched cohort	
	Adjusted mean cost	95% Confidence interval	Adjusted mean cost	95% Confidence interval
Diabetes				
Type 1	$13,530	$12,869 - $14,225	$13,856	$13,116 - $14,638
Type 2	$14,975	$14,358 - $15,620	$15,142	$14,438 - $15,881
Not present	$15,494	$14,853 - $16,163	$15,749	$15,012 - $16,522
Sex				
Female	$14,629	$14,012 - $15,272	$14,940	$14,232 - $15,683
Male	$14,656	$14,039 - $15,301	$14,850	$14,146 - $15,588
Race				
White	$14,227	$13,640 - $14,839	$14,541	$13,865 - $15,250
Black	$14,060	$13,471 - $14,675	$14,365	$13,688 - $15,075
Hispanic	$14,872	$14,240 - $15,532	$15,193	$14,469 - $15,953
Asian	$15,903	$15,118 - $16,729	$15,971	$15,099 - $16,893
Native American	$13,280	$12,532 - $14,073	$13,481	$12,651 - $14,366
Other	$15,687	$14,974 - $16,434	$15,981	$15,170 - $16,835
Primary payer				
Medicare	$14,407	$13,817 - $15,022	$14,684	$14,009 - $15,391
Medicaid	$14,765	$14,142 - $15,415	$15,309	$14,584 - $16,069
Private	$15,090	$14,463 - $15,743	$15,453	$14,733 - $16,208
Self-Pay	$13,751	$13,141 - $14,389	$14,106	$13,402 - $14,846
No charge	$14,218	$13,298 - $15,201	$13,925	$12,894 - $15,039
Other	$15,706	$14,996 - $16,449	$16,003	$15,186 - $16,864
Income				
Quartile 1	$13,596	$13,022 - $14,195	$13,814	$13,159 - $14,502
Quartile 2	$14,125	$13,527 - $14,750	$14,353	$13,669 - $15,071
Quartile 3	$14,992	$14,356 - $15,656	$15,304	$14,574 - $16,071
Quartile 4	$15,996	$15,287 - $16,675	$16,220	$15,443 - $17,036
Kidney disease				
Severe	$14,200	$13,623 - $14,802	$14,469	$13,804 - $15,166
Less Severe	$14,846	$14,033 - $15,706	$15,168	$14,260 - $16,135
Not present	$14,892	$14,292 - $15,517	$15,056	$14,371 - $15,774

Coronary atherosclerosis				
Severe	$15,173	$14,528 - $15,846	$15,406	$14,670 - $16,180
Less Severe	$14,677	$14,054 - $15,329	$14,934	$14,220 - $15,683
Not present	$14,097	$13,504 - $14,715	$14,362	$13,684 - $15,074
PLE				
Severe	$20,784	$19,908 - $21,699	$21,014	$20,018 - $22,059
Less Severe	$10,316	$9,881 - $10,769	$10,557	$10,057 - $11,082
Depression				
Yes	$14,523	$13,901 - $15,172	$14,873	$14,156 - $15,625
No	$14,763	$14,146 - $15,408	$14,917	$14,216 -$15,652
APRDRG_Severity				
0	$10,553	$8,744 - $12,736	$11,082	$8,942 - $13,734
1	$10,561	$10,326 - $10,801	$10,575	$10,316 - $10,839
2	$11,927	$11,674 - $12,184	$12,074	$11,798 - $12,357
3	$15,133	$14,814 - $15,459	$15,423	$15,071 - $15,783
4	$33,461	$32,634 - $34,309	$33,594	$32,675 - $34,538

Figure 22: Adjusted mean PLE-related hospitalization cost by diabetes type

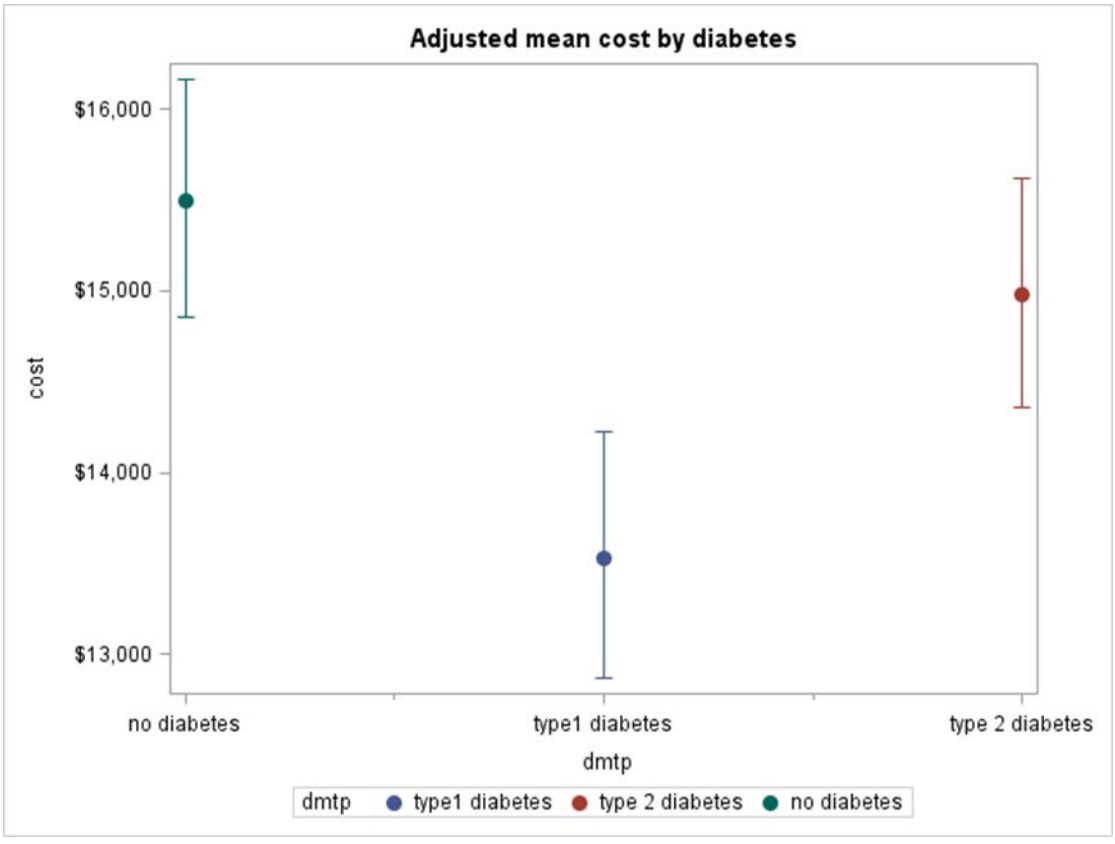


Figure 23: Adjusted mean PLE-related hospitalization cost by primary payer

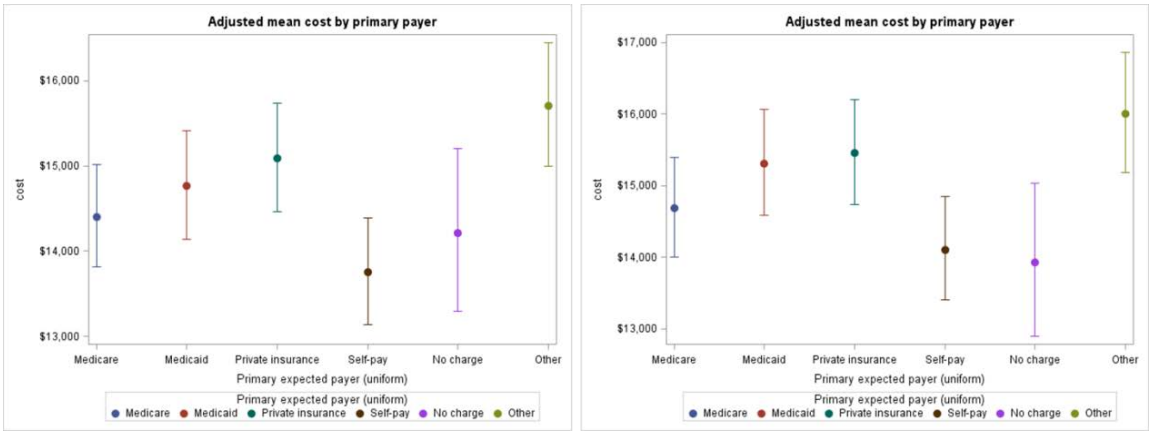


Figure 24: Adjusted mean PLE-related hospitalization cost by race/ethnicity

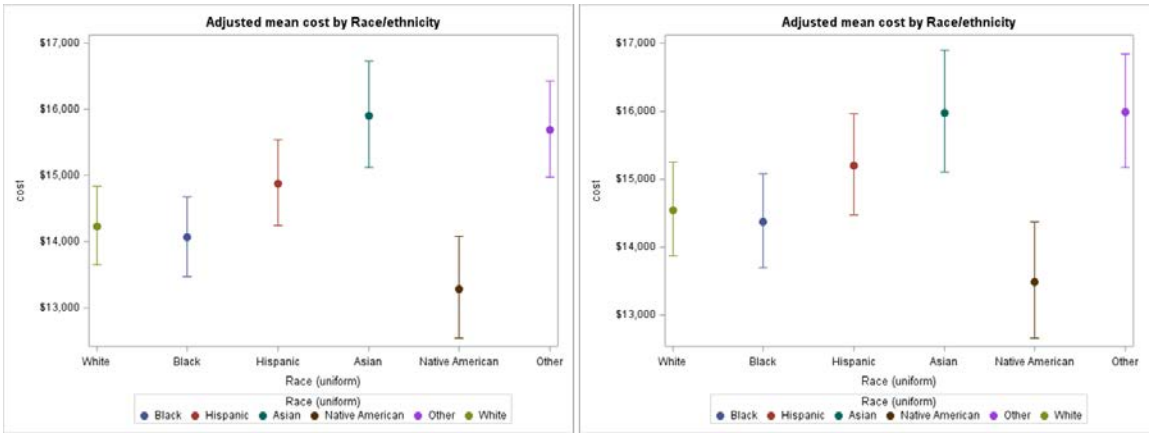
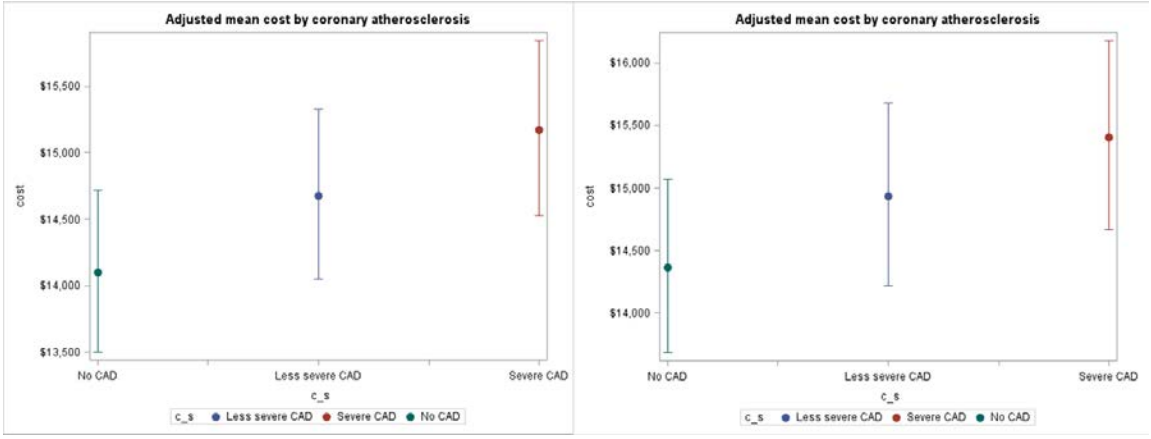


Figure 25: Adjusted mean PLE-related hospitalization cost by coronary atherosclerosis



Interaction between age and diabetes type

Age is associated with diabetes type, PLE, and hospitalization cost. An interaction model was explored to examine whether the impact of diabetes and its type on PLE-related hospitalization cost was modified by age. For the purpose of the interaction analysis, age was classified into two groups: younger (<65) and older (≥65). The regression coefficient estimates from the interaction model are presented in Table 32. The adjusted mean PLE-related hospitalization costs by categorical variables from the interaction are summarized in Table 33. There was a statistically significant interaction between diabetes type and age based on the p-value. PLE-related hospitalization cost was highest among younger patients without diabetes (mean: $17,043; 95% CI: $16,334 -- $17,783) than other diabetes type and age group combinations in the full cohort. Similar trend remains in the stratified matched cohort. As displayed in Figure 26, PLE-related hospitalization cost did not differ significantly between younger patients with type 1 diabetes, younger patients with type 2 diabetes, older patients without diabetes, older patients with type 1 diabetes, or older patients with type 2 diabetes. The effect of other control variables on PLE-related hospitalization cost was similar between the interaction model and the non-interaction model.

Table 32: Coefficient estimates from the generalized linear model (interaction model)

Variables	Original cohort		Stratified matched cohort	
	Coefficient	P-value	Coefficient	P-value
Diabetes (ref: No)				
Type 1	0.0258	0.3914	0.0203	0.5042
Type 2	0.0023	0.5901	-0.0035	0.5252
Age group (ref: >=65)				
<65	0.1344	<0.0001	0.1316	<0.0001
(Age <65)*(Type 1)	-0.1755	<0.0001	-0.1761	<0.0001
(Age<65)*(Type 2)	-0.0845	<0.0001	-0.0806	<0.0001
Sex (ref: Female)				
Male	0.0060	0.0709	-0.0025	0.5283

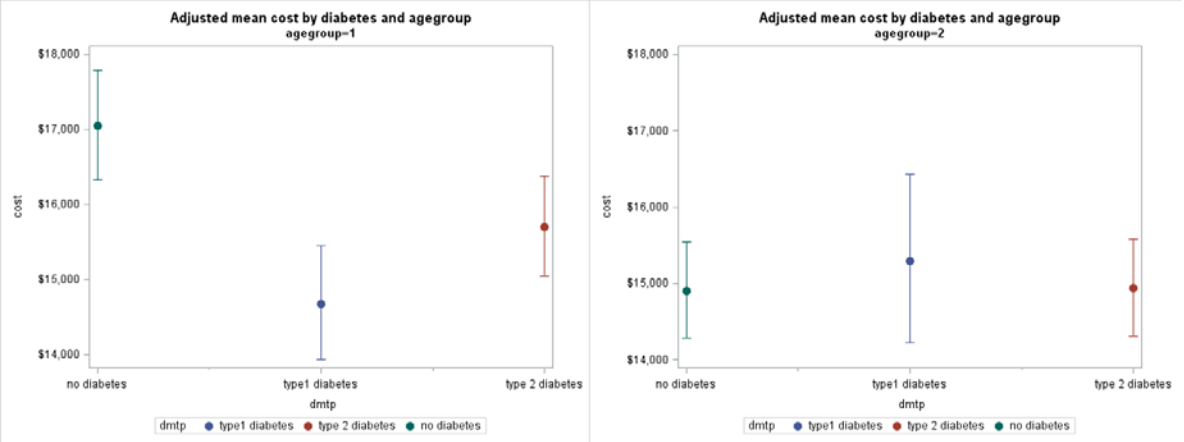
Race (ref: White)				
Black	-0.0062	0.1846	-0.0071	0.1750
Hispanic	0.0490	<0.0001	0.0487	<0.0001
Asian	0.1068	<0.0001	0.0934	<0.0001
Native American	-0.0607	0.0031	-0.0675	0.0019
Other	0.1012	<0.0001	0.0990	<0.0001
Payer (ref: Other)				
Medicare	-0.1015	<0.0001	-0.0904	<0.0001
Medicaid	-0.0568	<0.0001	-0.0404	0.0025
Private	-0.0460	<0.0001	-0.0389	0.0020
Self-Pay	-0.1266	<0.0001	-0.1212	<0.0001
No charge	-0.0950	0.0008	-0.1325	<0.0001
Income (ref: Quartile 4)				
Quartile 1	-0.1545	<0.0001	-0.1568	<0.0001
Quartile 2	-0.1170	<0.0001	-0.1190	<0.0001
Quartile 3	-0.0595	<0.0001	-0.0561	<0.0001
Kidney disease (ref: No)				
Less Severe	0.0018	0.9276	0.0107	0.6126
Severe	-0.0531	<0.0001	-0.0428	<0.0001
Coronary atherosclerosis (ref: No)				
Less Severe	0.0332	<0.0001	0.0341	<0.0001
Severe	0.0691	<0.0001	0.0674	<0.0001
PLE severity				
Less Severe vs. Severe	-0.6979	<0.0001	-0.6857	<0.0001
Depression (ref: No)				
Yes	-0.0111	0.0325	0.0006	0.9216
APRDRG_Severity (ref: 0)				
1	0.0009	0.9927	-0.0473	0.6639
2	0.1203	0.2075	0.0852	0.4339
3	0.3565	0.0002	0.3287	0.0025
4	1.1514	<0.0001	1.1076	<0.0001

Table 33: Adjusted mean PLE-related hospitalization cost from the interaction model

Variables	Original cohort		Matched cohort	
	Adjusted mean cost	95% Confidence interval	Adjusted mean cost	95% Confidence interval
Diabetes				
Type 1	$14,978	$14,201 -- $15, 799	$14,940	$14,101 -- $15,828
Type 2	$15,311	$14,680 -- $15,970	$15,303	$14,591 -- $16,049
Not present	$15,935	$15,276 -- $16,624	$15,988	$15,239 -- $16,772
Age group				
<65	$15,776	$15,111 -- $16,470	$15,763	$15,017 -- $16,545
>=65	$15,040	$14,355 -- $15,757	$15,053	$14,295 -- $15,853
(Age < 65)* (Type 1)	$14,674	$13,934 -- $15,453	$14,611	$13,811 -- $15,457
(Age < 65)* (Type 2)	$15,698	$15,048 -- $16,377	$15,698	$14,966 -- $16,466
(Age < 65)* (No diabetes)	$17,043	$16,334 -- $17,783	$17,075	$16,269 -- $17,921

(Age >= 65)* (Type 1)	$15,289	$14,223 -- $16,435	$15,276	$14,162 -- $16,477
(Age >= 65)* (Type 2)	$14,934	$14,310 -- $15,584	$14,918	$14,216 -- $15,654
(Age >= 65)* (No diabetes)	$14,899	$14,276 -- $15,550	$14,969	$14,259 -- $15,715
Sex				
Female	$15,357	$14,704 -- $16,040	$15,423	$14,687 -- $16,196
Male	$15,449	$14,793 -- $16,135	$15,385	$14,651 -- $16,155
Race				
White	$14,923	$14,301 -- $15,572	$14,983	$14,281 -- $15,719
Black	$14,830	$14,203 -- $15,485	$14,877	$14,171 -- $15,618
Hispanic	$15,673	$15,001 -- $16,375	$15,730	$14,975 -- $16,523
Asian	$16,605	$15,779 -- $17,474	$16,449	$15,546 -- $17,404
Native American	$14,044	$13,248 -- $14,887	$14,004	$13,139 -- $14,927
Other	$16,512	$15,755 -- $17,305	$16,541	$15,697 -- $17,431
Primary payer				
Medicare	$14,940	$14,320 -- $15,587	$15,101	$14,400 -- $15,836
Medicaid	$15,623	$14,957 -- $16,318	$15,876	$15,119 -- $16,670
Private	$15,794	$15,131 -- $16,485	$15,900	$15,154 -- $16,684
Self-Pay	$14,570	$13,919 -- $15,252	$14,643	$13,909 -- $15,416
No charge	$15,037	$14,061 -- $16,082	$14,479	$13,404 -- $15,640
Other	$16,536	$15,783 -- $17,326	$16,530	$15,682 -- $17,425
Income				
Quartile 1	$14,336	$13,726 -- $14,974	$14,308	$13,624 -- $15,025
Quartile 2	$14,884	$14,248 -- $15,549	$14,859	$14,147 -- $15,608
Quartile 3	$15,766	$15,091 -- $16,471	$15,824	$15,063 -- $16,622
Quartile 4	$16,732	$16,014 -- $17,483	$16,736	$15,929 -- $17,585
Kidney disease				
Severe	$14,859	$14,249 -- $15,495	$14,917	$14,227 -- $15,642
Less Severe	$15,697	$14,833 -- $16,612	$15,737	$14,790 -- $16,744
Not present	$15,669	$15,031 -- $16,333	$15,570	$14,856 -- $16,318
Coronary atherosclerosis				
Severe	$15,952	$15,268 -- $16,666	$15,930	$15,163 -- $16,735
Less Severe	$15,389	$14,729 -- $16,079	$15,408	$14,666 -- $16,187
Not present	$14,887	$14,256 -- $15,546	$14,892	$14,184 -- $15,635
PLE				
Severe	$21,835	$20,906 -- $22,806	$21,703	$20,668 -- $22,791
Less severe	$10,866	$10,404 -- $11,349	$10,933	$10,412 -- $11,481
Depression				
Yes	$15,318	$14,657 -- $16,009	$15,409	$14,662 -- $16,194
No	$15,489	$14,835 -- $16,172	$15,399	$14,670 -- $16,164
APRDRG_Severity				
0	$11,120	$9,212 - $13,425	$11,471	$9,255 - $14,218
1	$11,130	$10,875 -- $11,391	$10,940	$10,667 -- $11,221
2	$12,542	$12,267 -- $12,823	$12,491	$12,196 -- $12,793
3	$15,883	$15,536 -- $16,237	$15,935	$15,561 -- $16,318
4	$35,169	$34,278 -- $36,083	$34,721	$33,753 -- $35,718

Figure 26: Adjusted mean PLE-related hospitalization cost by diabetes type and age group



5.2.4 Discharge status after PLE-related hospitalization

5.2.4.1 Crosstab of discharge status by comorbidities in the PLE cohort

The crude association between comorbidities and PLE-related hospitalization discharge status was examined by cross-tabulation and Chi-square test. 47.6% of the hospitalized PLE patients with type 2 diabetes had non-routine discharges; 35.2% of the hospitalized PLE patients with type 1 diabetes had non-routine discharges; 39.6% of the hospitalized PLE patients without diabetes as comorbidity had non-routine discharges. 56% of the PLE patients with severe kidney diseases had non-routine discharges while only 39% of the PLE patients without kidney diseases had non-routine discharges. 49% of the hospitalized PLE patients with less severe coronary atherosclerosis had non-routine discharges; 42% of the hospitalized PLE patients without coronary atherosclerosis had non-routine discharges. Among all the PLE-related hospitalizations, 63.5% of the patients with severe PLE had non-routine discharges; 51.1% of the patients with less severe PLE had non-routine discharges (Table 34).

Table 34: Crosstab of PLE-related hospitalization discharge status

	Diabetes			Kidney diseases			Coronary atherosclerosis		
	Not present	Type 1	Type 2	Not present	Less severe	Severe	Not present	Less severe	Severe
Routine discharge	60.36%	64.83%	52.42%	60.63%	47.68%	44.02%	57.99%	50.68%	59.47%
Non-Routine discharge	39.64%	35.17%	47.58%	39.37%	52.32%	55.98%	42.01%	49.32%	40.53%
Chi-square P value	<0.0001			<0.0001			<0.0001		

5.2.4.2 Logistic regression analysis results

Multivariate logistic regression was used to examine the association between comorbidities and PLE-related hospitalization discharge status controlling the effects of confounding variables. The results of logistic regression were presented in Table 35. Of the total 219,752 discharge records, 196,655 observations were used in the logistic regression model because they contain non-missing values for all the study variables.

Effect of diabetes and other comorbidities: The presence of type 1 diabetes was associated with a 37% increase in the odds of having a non-routine discharge. The presence of type 2 diabetes was associated with a 26.2% increase in the odds of having a non-routine discharge though the p value was above the significance threshold (p=0.0024). Hospitalized PLE patients with severe coronary atherosclerosis had a 28.5% decrease in the odds of having a non-routine discharge compared to hospitalized PLE patients without coronary atherosclerosis. Depression increased the odds of having non-routine discharges by 41%. Patients with major or extreme loss of function were

associated with much higher odds of having non-routine discharges compared to patients with moderate or minor loss of function.

Other significant effects: The odds ratio was 1.296 for Blacks to have a non-routine discharge compared to White. The odds of having a non-routine discharge was 21% lower for Asian than that for White. On the one hand, patients with Medicare or Medicaid as primary payer had higher likelihood of having non-routine discharges compared to patients paid by other government entitlement programs; on the other hand, patients who paid out-of-pocket or with no charges had decreased likelihood of having non-routine discharges compared to patients paid by other government entitlement programs.

Non-significant effect: Median household income did not have a significant effect on PLE-related hospitalization discharge status. Severe or less severe kidney diseases didn't show a significant effect on PLE-related hospitalization discharge status. The logistic regression model has a c statistics of 0.748, indicating good discrimination and prediction.

Table 35: Logistic regression results of PLE-related hospitalization discharge status

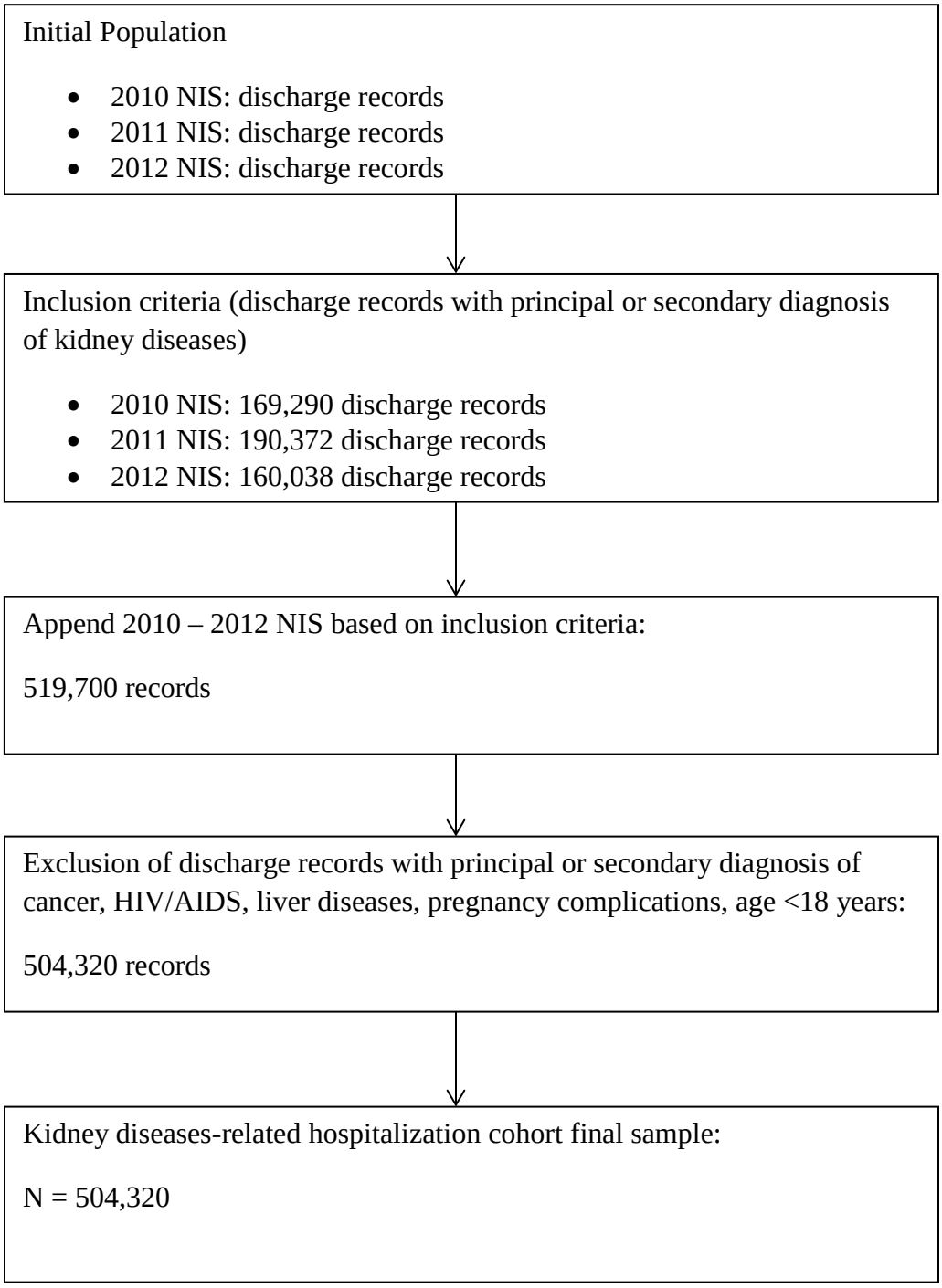
Variable	**Odds Ratio**	**95% Confidence interval**		**P value**
Age	1.037	1.036	1.038	<0.0001
Male vs. Female	0.908	0.889	0.926	<0.0001
Race				
Black vs. White	1.296	1.259	1.334	<0.0001
Hispanic vs. White	0.931	0.895	0.969	0.1281
Asian vs. White	0.790	0.722	0.864	<0.0001
Native American vs. White	0.783	0.685	0.896	0.0004
Other vs. White	1.064	0.996	1.137	0.0013
Median zip code household income				
Quartile 1 vs. Quartile 4	1.015	0.986	1.045	0.0883
Quartile 2 vs. Quartile 4	1.000	0.971	1.031	0.9766
Quartile 3 vs. Quartile 4	0.987	0.958	1.017	0.1293
Payer type				

Medicare vs. Other	1.442	1.341	1.551	<0.0001
Medicaid vs. Other	1.405	1.297	1.521	<0.0001
Private vs. Other	1.029	0.955	1.109	0.0161
Self-pay vs. Other	0.636	0.576	0.702	<0.0001
No charge vs. Other	0.645	0.516	0.807	<0.0001
PLE Severe vs. Less Severe	1.494	1.464	1.526	<0.0001
Diabetes				
Type 1 vs. None	1.370	1.248	1.505	<0.0001
Type 2 vs. None	1.262	1.236	1.289	0.0024
Kidney diseases				
Less severe vs. None	0.981	0.873	1.102	0.8616
Severe vs. None	0.982	0.957	1.007	0.7844
Coronary atherosclerosis				
Less severe vs. None	0.919	0.895	0.943	<0.0001
Severe vs. None	0.715	0.697	0.734	<0.0001
Depression (1 vs. 0)	1.410	1.366	1.456	<0.0001
APRDRG Severity				
1 vs. 0	0.462	0.277	0.771	<0.0001
2 vs. 0	0.946	0.568	1.577	<0.0001
3 vs. 0	2.220	1.332	3.700	<0.0001
4 vs. 0	7.834	4.686	13.096	<0.0001

5.3 Kidney diseases-related hospitalization analysis results

5.3.1 Data extraction

Figure 27: Kidney diseases-related hospitalization sample selection and cohort construction



Kidney diseases-related hospitalization sample selection and cohort construction process are summarized in Figure 27. Appling the inclusion and exclusion criteria, the final kidney diseases-related hospitalization cohort contained 504,320 discharge records.

5.3.2 Descriptive statistics of study variables

5.3.2.1 Descriptive statistics of dependent variables

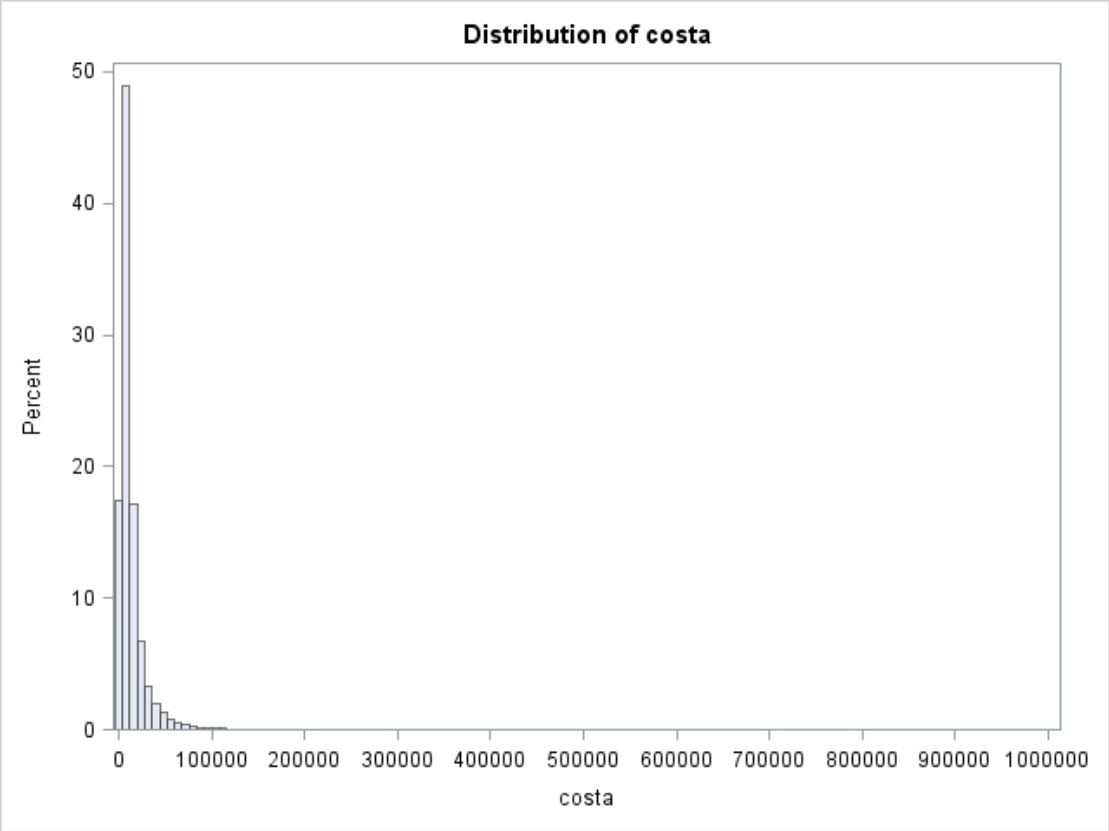
Hospitalization cost

The descriptive characteristics of kidney diseases-related hospitalization are presented in Table 36. Kidney diseases-related hospitalizations had a mean cost of $13,360 and a median cost of $8,313. The maximum kidney diseases-related hospitalization cost was $931,520, not exceeding $1,000,000. Therefore all the available observations were included in the final analysis. Kidney diseases-related hospitalization was right-skewed, as shown in Figure 28.

Table 36: Descriptive statistics of kidney diseases-related hospitalization cost

Statistics	Kidney diseases-related hospitalization cost
Mean ± S.D.	$13,360 ± $17,859
Minimum	$32.94
25% Quartile	$4,887
Median	$8,313
75% Quartile	$15,048
99% Quartile	$81,985
Maximum	$931,520

Figure 28: Histogram of kidney diseases-related hospitalization cost



Discharge status

The descriptive characteristics of kidney diseases-related hospitalization are presented in Table 37. 59.1% of the kidney diseases-related hospitalizations had a routine discharge (discharge to home without additional health care). 40.9% of the kidney diseases-related hospitalizations had a non-routine discharge (2.4% were transferred to a short-term hospital; 19.4% were transferred to skilled nursing facility, intermediate care facility, or another type of facility; 15.5% had home health care; 1.6% were against medical advice; 2.4% died in hospital; and 0.05% had an unknown discharge destination).

Table 37: Descriptive statistics of kidney diseases-related hospitalization discharge status

Discharge status	**Description**	**Percentage**	**Total percentage**
Routine discharge	Discharge to home	59.10%	59.10%
Non-Routine discharge	Transfer to short-term hospital	2.36%	40.90%
	Transfer other: includes Skilled Nursing Facility (SNF), Intermediate Care Facility (ICF), and another type of facility	19.43%	
	Home Health care (HHC)	15.05%	
	Against medical advice	1.60%	
	Died in hospital	2.41%	
	Discharged alive, destination unknown	0.05%	

5.3.2.2 Descriptive statistics of comorbidities

The descriptive characteristics of comorbidities among hospitalized patients with kidney diseases are summarized in Table 38. 55.9% of the kidney diseases-related hospitalizations had diabetes as comorbidity: 21.6% only had diabetes; 13.5% had both diabetes and coronary atherosclerosis; 9.9% had diabetes and PLE; 10.9% had diabetes, coronary atherosclerosis, and PLE. 27.4% of the hospitalized kidney diseases patients had PLE: 3.3% only had PLE; 3.3% had PLE and coronary atherosclerosis; 9.9% had PLE and diabetes; 10.9% had diabetes, PLE, and coronary atherosclerosis. 37.2% of the kidney diseases-related hospitalizations had coronary atherosclerosis as comorbidity: 9.5% only had coronary atherosclerosis; 13.5% had both coronary atherosclerosis and diabetes; 3.3% had both coronary atherosclerosis and PLE; 10.9% had diabetes, PLE, and coronary atherosclerosis.

Table 38: Descriptive statistics of comorbidities among kidney diseases-related hospitalization patients

	Peripheral Lower extremity (PLE) diseases (0)		Peripheral Lower extremity (PLE) diseases (1)	
	Coronary atherosclerosis (0)	Coronary atherosclerosis (1)	Coronary atherosclerosis (0)	Coronary atherosclerosis (1)
Diabetes (0)	N=141,745 (28.1%)	N=47,905 (9.50%)	N=16,743 (3.32%)	N=16,450 (3.26%)
Diabetes (1)	N=109,025 (21.6%)	N=67,919 (13.5%)	N=49.774 (9.87%)	N=54,759 (10.9%)

(Note: 0 indicates “absence of the condition”; 1 indicates “presence of the condition”)

5.3.2.3 Descriptive statistics of independent variables

Table 39 lists the descriptive statistics of independent variables among patients with kidney diseases-related hospitalization by the presence or absence of diabetes.

With regard to predisposing characteristics, the distribution of age and sex were similar across hospitalized kidney diseases patients with diabetes and hospitalized kidney diseases patients without diabetes. 51.1% of the hospitalized kidney diseases patients with diabetes had age 65 years or older; while 50.9% of the hospitalized kidney diseases patients without diabetes were 65 years or older. 50.4% of the kidney diseases-related hospitalizations with diabetes were male; while 53.2% of the kidney diseases-related hospitalizations without diabetes were male. Hospitalized kidney diseases patients with diabetes were more likely to be non-White. For example, 15.1% of the hospitalized kidney diseases patients with diabetes were Hispanic, compared to the 9.4% Hispanics among hospitalized kidney diseases patients without diabetes.

In terms of enabling resources, more than 60% of the patients with kidney diseases-related hospitalizations lived in an area where the median household income was

below the 50th percentile – this trend was true both among patients with diabetes comorbidity and patients without diabetes. Medicare was the primary payer for most of the kidney diseases-related hospitalizations: 75.6% of the hospitalizations with diabetes comorbidity were paid by Medicare and 73.7% of the hospitalizations without diabetes were paid by Medicare.

Looking at the need factors, among kidney diseases-related hospitalizations with diabetes, 37.1% had PLE as comorbidity; while only 14.9% had PLE among hospitalized kidney diseases patients without diabetes. 43.6% of the hospitalized kidney diseases patients with diabetes also had coronary atherosclerosis; compared to the 28.9% coronary atherosclerosis among hospitalized kidney diseases patients without diabetes.

Although the distribution of demographic variables like age, sex and race by the presence or absence of diabetes was much more similar among patients with kidney diseases-related hospitalization than patients with PLE-related hospitalization, a stratified matched cohort was still drawn to be consistent with the study methodology. A matched subgroup was drawn from the kidney diseases-related hospitalization patients without diabetes based on the frequency distribution of age, sex, and race in the subgroup with diabetes. Table 40 presents the demographic characteristics in the stratified matched cohort.

Table 39: Descriptive statistics of control variables among patients with kidney diseases-related hospitalization

Control variables	Kidney diseases-related hospitalizations without Diabetes (n=222,843)	Kidney diseases-related hospitalization with Diabetes (n=281,477)
Predisposing characteristics		
Age		
<65	49.12%	48.93%
>=65	50.88%	51.07%
Sex		
Female	46.76%	49.54%
Male	53.24%	50.46%
Race		
White	52.11%	45.61%
Black	33.20%	32.20%
Hispanic	9.35%	15.07%
Asian	1.98%	2.85%
Native American	0.55%	1.25%
Other	2.81%	3.02%
Enabling resources		
Median zip code income		
0 to 25th percentile	36.58%	38.44%
26th to 50th percentile	24.19%	24.71%
51st to 75th percentile	21.93%	21.67%
76th to 100th percentile	17.29%	15.19%
Primary payer		
Medicare	73.74%	75.58%
Medicaid	8.76%	8.50%
Private insurance	12.80%	12.32%
Self-pay	2.60%	1.87%
No charge	0.31%	0.21%
Other	1.79%	1.52%
Need Factors		
Comorbidity		
PLE	14.90%	37.14%
Less severe	9.24%	27.22%
Severe	6.38%	10.39%
Coronary atherosclerosis	28.88%	43.58%
Less severe	15.18%	21.80%
Severe	13.78%	21.80%
Kidney diseases severity		
Less Severe	2.41%	3.57%
Severe	97.59%	96.43%

APRDRG: severity of illness (loss of function)		
0 (no class)	0.12%	0.07%
1 (minor loss)	7.67%	2.47%
2 (moderate loss)	33.09%	30.11%
3 (major loss)	50.21%	59.13%
4 (extreme loss)	8.92%	8.22%
Depression	9.15%	10.85%

Table 40: Demographic characteristics in the stratified matched cohort

Variables	Kidney diseases-related hospitalization with diabetes (n=200,000)	Kidney diseases-related hospitalization without diabetes (n=100,000)	P-value
Age (>=65 years)	51.06%	51.00%	0.7586
Sex (Female)	49.61%	50.00%	0.0437
Race (Non-White)	54.39%	54.00%	0.0442
Income			<0.0001
Quartile 1	38.50%	38.32%	
Quartile 2	24.56%	23.64%	
Quartile 3	21.67%	21.43%	
Quartile 4	15.27%	16.62%	
Primary Payer			<0.0001
Medicare	75.56%	73.25%	
Medicaid	8.55%	8.69%	
Private insurance	12.32%	13.38%	
Self-pay	1.87%	2.62%	
No charge	0.20%	0.32%	
Other	1.50%	1.75%	

5.3.3 GLM results for kidney diseases-related hospitalization cost

Generalized linear model was used to estimate the effect of diabetes on kidney diseases-related hospitalization cost. Table 41 summarizes the coefficient estimate while Table 42 presents the adjusted mean hospitalization cost by categorical variables. The kidney diseases-related hospitalization cohort contained 504,320 discharge records; 419,111 observations without missing-values for the variables were used for the

regression model. The matched cohort contained 300,000 discharge records; 256,680 observations with non-missing values for the study variables were included in the analysis.

Diabetes: In the full cohort, the presence of type 1 diabetes was associated with a 6.4% increase in kidney diseases-related hospitalization cost. Type 2 diabetes decreased the cost of kidney diseases-related hospitalization though this effect was not significant ($p>0.0001$). However, in the matched cohort, the presence of type 2 diabetes was associated with a significant 2.4% decrease in kidney diseases-related hospitalization cost. In the matched cohort, the adjusted mean hospitalization cost for kidney diseases patients with type 1 diabetes was $14,735 (95% CI: $14,234 - $15,253); the adjusted mean cost for hospitalized kidney diseases patients with type 2 diabetes was $13,602 (95% CI: $13,205 - $14,011); the hospitalization cost for kidney diseases patient without diabetes was $13,945 (95% CI: $13,533 - $14,369)

Other significant effect: Kidney diseases-related hospitalization cost was slightly yet significantly higher for younger patients compared to older patients. The cost for male patients was 1.0158 times the cost for female patients. Based on the matched analysis, the adjusted mean hospitalization cost for female patients was $13,942 (95% CI: $13,526 - $14,371) while that for male was $14,231 (95% CI: $13,807 - $14,669). The cost for Hispanics was 5.5% higher than the cost for White; while the cost for Asian was 15.2% higher than that for White. On the one hand, hospitalization cost for patients with Medicare as the primary payer was 7.0% higher than the cost for patients with other government programs as primary payer. On the other hand, the cost for patients paid by private insurance was 16.1% higher than that for the patients paid by other programs.

Hospitalization cost was lowest for patients who paid out-of-pocket or who didn't have any charges for that hospitalization. Kidney diseases-related hospitalization also differed by median household income: cost was higher in high income neighborhood than low income neighborhood. Comorbid severe PLE among patients with kidney diseases-related hospitalization increased hospitalization cost by 68.8%. Comorbid severe coronary atherosclerosis was associated with a 6.2% increase kidney diseases-related hospitalization cost.

Non-significant effect: The cost was comparable between Black and White (p=0.3806) and Native American and White (p=0.642). In the matched cohort, the adjusted mean hospitalization cost for White was $13,352 (95% CI: $12,963 - $13,753); the cost for Black was $13,418 (95% CI: $13,021 - $13,827); the cost for Native American was $13,119 (95% CI: $12,579 - $13,682). What's more, less severe PLE and less severe coronary atherosclerosis did not have a significant incremental effect to kidney diseases-related hospitalization. Last but not least, kidney diseases patients with no class of severity, minor loss of function, and moderate loss of function had comparable hospitalization cost.

Table 41: Coefficient estimates from the generalized linear model

Variables	Full cohort		Stratify matched cohort	
	Coefficient	P-value	Coefficient	P-value
Diabetes (ref: No)				
Type 1	0.0619	<0.0001	0.0551	<0.0001
Type 2	-0.0081	0.0004	-0.0249	<0.0001
Age	-0.0038	<0.0001	-0.0036	<0.0001
Sex (ref: Female)				
Male	0.0157	<0.0001	0.0205	<0.0001
Race (ref: White)				
Black	0.0026	0.3806	0.0049	0.1889
Hispanic	0.0537	<0.0001	0.0498	<0.0001
Asian	0.1418	<0.0001	0.1378	<0.0001
Native American	-0.0180	0.642	-0.0176	0.2562

Other	0.1346	<0.0001	0.1460	<0.0001
Payer (ref: Other)				
Medicare	0.0673	<0.0001	0.0244	0.0462
Medicaid	0.0060	0.5595	-0.0296	0.0249
Private	0.149	<0.0001	0.1166	<0.0001
Self-Pay	-0.1235	<0.0001	-0.1350	<0.0001
No charge	-0.1363	<0.0001	-0.1535	<0.0001
Income (ref: Quartile 4)				
Quartile 1	-0.1976	<0.0001	-0.1976	<0.0001
Quartile 2	-0.1510	<0.0001	-0.1546	<0.0001
Quartile 3	-0.0831	<0.0001	-0.0814	<0.0001
PLE (ref: No)				
Less Severe	0.0074	0.0232	0.5236	<0.0001
Severe	0.5250	<0.0001	0.0117	0.0036
Coronary atherosclerosis (ref: No)				
Less Severe	-0.0106	0.014	-0.0068	0.1010
Severe	0.0577	<0.0001	0.0598	<0.0001
Kidney disease severity (ref: Severe)				
Less Severe vs. Severe	-0.0806	<0.0001	-0.0749	<0.0001
Depression (ref: No)				
Yes	-0.0248	<0.0001	-0.0242	<0.0001
APRDRG_Severity (ref: 0)				
1	-0.0298	0.5589	0.0114	0.8586
2	0.0265	0.7016	0.0761	0.2298
3	0.3257	<0.0001	0.3813	<0.0001
4	1.2276	<0.0001	1.2665	<0.0001

Table 42: Adjusted mean hospitalization cost in the kidney diseases-related hospitalization cohort

	Full cohort		Matched cohort	
	Adjusted mean cost	95% Confidence interval	Adjusted mean cost	95% Confidence interval
Diabetes				
Type 1	$14,553	$14,150 -- $14,967	$14,735	$14,234 -- $15,253
Type 2	$13,569	$13,251 -- $13,894	$13,602	$13,205 -- $14,011
Not present	$13,679	$13,356 -- $14,010	$13,945	$13,533 -- $14,369
Sex				
Female	$13,817	$13,486 -- $14,157	$13,942	$13,526 -- $14,371
Male	$14,037	$13,700 -- $14,381	$14,231	$13,807 -- $14,669
Race				
White	$13,215	$12,906 -- $13,531	$13,352	$12,963 -- $13,753
Black	$13,249	$12,935 -- $13,572	$13,418	$13,021 -- $13,827
Hispanic	$13,944	$13,608 -- $14,288	$14,034	$13,614 -- $14,468
Asian	$15,228	$14,805 -- $15,663	$15,325	$14,800 -- $15,868
Native American	$12,980	$12,542 -- $13,433	$13,119	$12,579 -- $13,682
Other	$15,118	$14,713 -- $15,534	$15,451	$14,938 -- $15,983
Primary payer				
Medicare	$14,950	$14,612 -- $15,296	$14,867	$14,451 -- $15,295

Medicaid	$14,060	$13,727 -- $14,402	$14,085	$13,670 -- $14,512
Private	$16,483	$16,098 -- $16,877	$16,302	$15,829 -- $16,789
Self-Pay	$12,353	$12,020 -- $12,695	$12,675	$12,247 -- $13,119
No charge	$12,196	$11,609 -- $12,812	$12,443	$11,674 -- $13,262
Other	$13,977	$13,578 -- $14,387	$14,508	$13,988 -- $15,047
Income				
Quartile 1	$12,732	$12,426 -- $13,045	$12,884	$12,499 -- $13,281
Quartile 2	$13,339	$13,016 -- $13,669	$13,450	$13,045 -- $13,868
Quartile 3	$14,277	$13,931 -- $14,632	$14,471	$14,034 -- $14,922
Quartile 4	$15,514	$15,134 -- $15,903	$15,699	$15,220 -- $16,193
PLE				
Severe	$19,713	$19,221 -- $20,218	$19,893	$19,275 -- $20,530
Less Severe	$11,749	$11,464 -- $12,040	$11,923	$11,563 -- $12,293
Not present	$11,662	$11,385 -- $11,946	$11,784	$11,436 -- $12,143
Coronary atherosclerosis				
Severe	$14,524	$14,170 -- $14,886	$14,692	$14,247 -- $15,151
Less Severe	$13,565	$13,235 -- $13,904	$13,745	$13,329 -- $14,175
Not present	$13,710	$13,383 -- $14,044	$13,840	$13,429 -- $14,263
Kidney diseases				
Severe	$14,499	$14,165 -- $14,842	$14,263	$14,203 -- $15,056
Less Severe	$13,376	$13,022 -- $13,740	$13,568	$13,122 -- $14,030
Depression				
Yes	$13,755	$13,415 -- $14,103	$13,917	$13,489 -- $14,358
No	$14,101	$13,767 -- $14,442	$14,257	$13,838 -- $14,689
APRDRG_Severity				
0	$10,214	$9,239 -- $11,293	$9,955.51	$8,784.18 -- $11,283
1	$9,914	$9,745-- $10,086	$10,069	$9,848.49 -- $10,295
2	$10,489	$10,344 -- $10,636	$10,743	$10,557 -- $10,932
3	$14,147	$13,955 -- $14,342	$14,576	$14,328 -- $14,829
4	$34,861	$34,320 -- $35,411	$35,327	$34,639 -- $36,028

Figure 29: Adjusted mean kidney diseases-related hospitalization cost by diabetes type

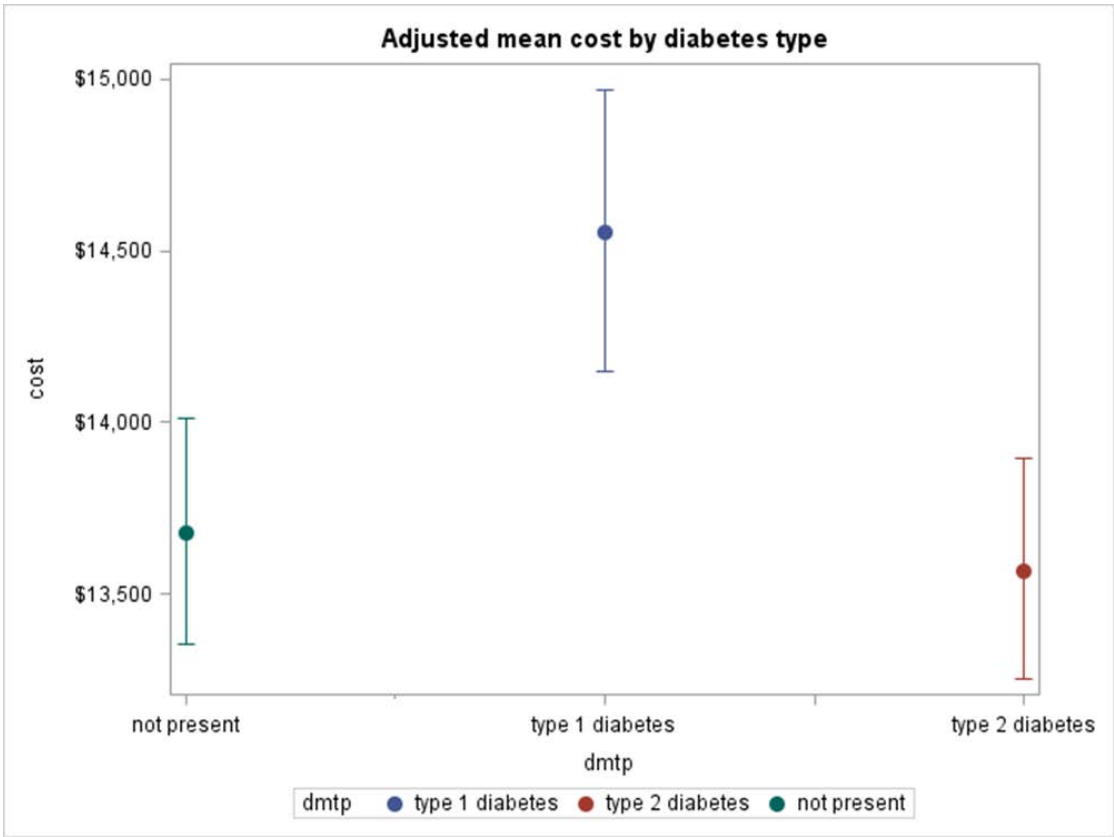


Figure 30: Adjusted mean kidney diseases-related hospitalization cost by race/ethnicity

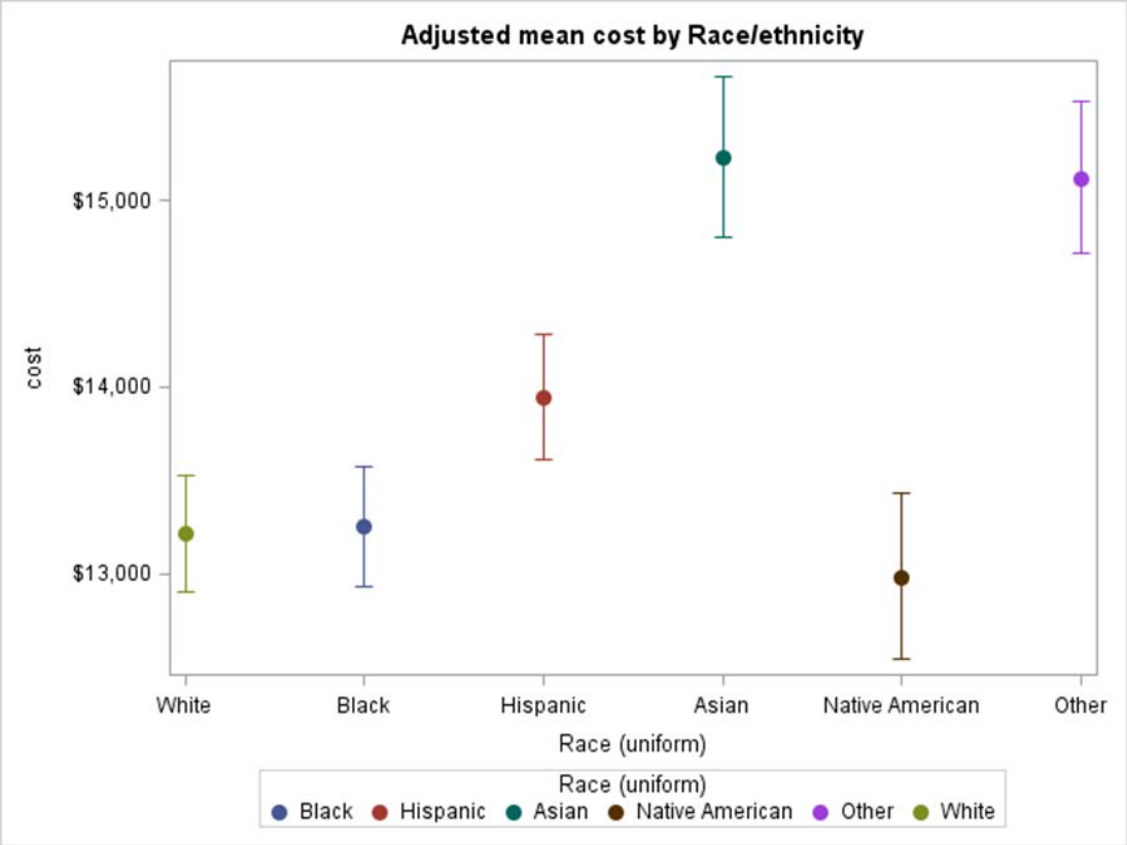
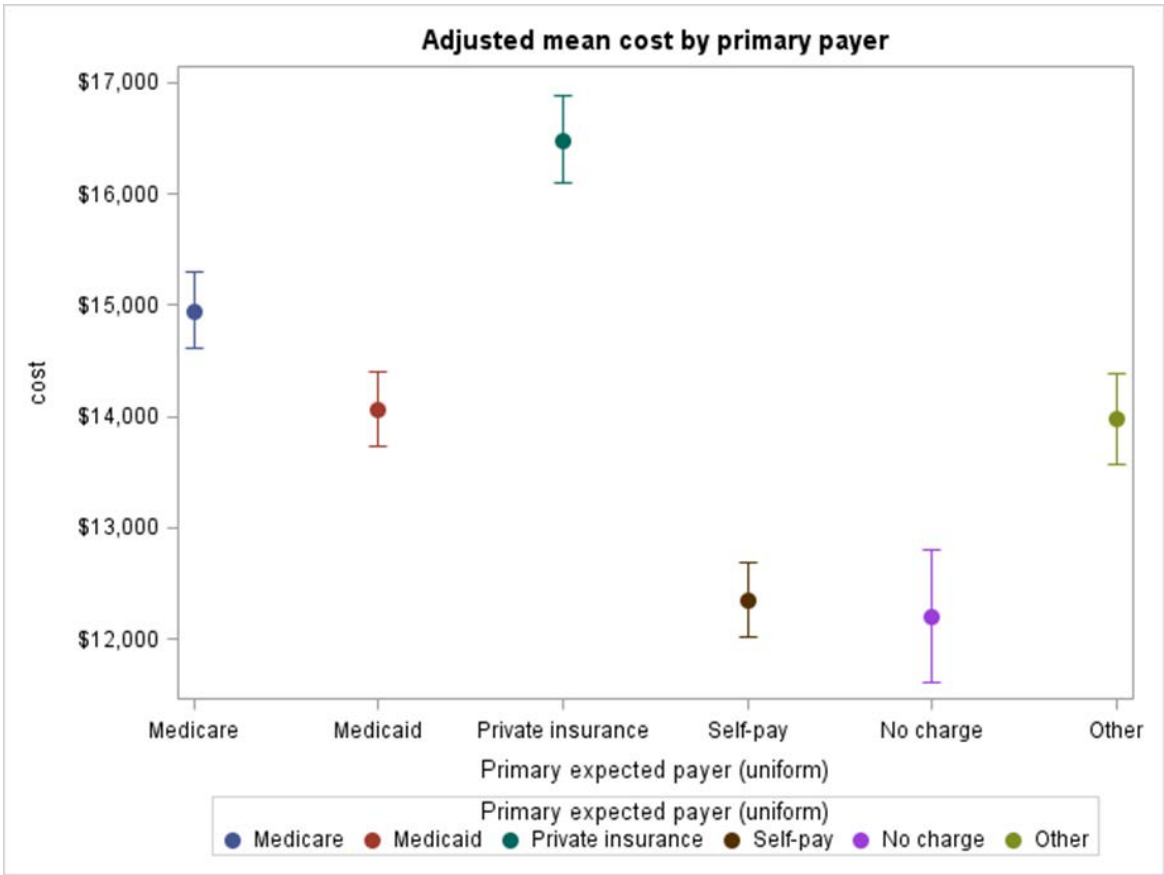


Figure 31: Adjusted mean kidney diseases-related hospitalization cost by primary payer



Interaction model between diabetes type and age group

The results from generalized linear model with an interaction term between diabetes type and age group indicate that the effect of diabetes on kidney diseases-related hospitalization cost was modified by age group. Table 43 lists the coefficient estimates based on interaction analysis; Table 44 presents the adjusted mean hospitalization cost from the interaction model.

Kidney diseases-related hospitalization was highest among younger patients with type 1 diabetes (Figure 30). In the stratified matched cohort, among patients age < 65 years, the adjusted mean kidney diseases hospitalization cost for patients with type 1

diabetes, type 2 diabetes and without diabetes was $15,871, $14,094 and $14,879 respectively. Among patients age ≥ 65 years, the adjusted mean hospitalization cost for patients with type 1 diabetes, type 2 diabetes and without diabetes was $14,574, $13,160 and $13,244 respectively.

Table 43: Coefficient estimates from the interaction model

Variables	Full cohort		Matched cohort	
	Coefficient	P-value	Coefficient	P-value
Diabetes (ref: No)				
Type 1	0.0855	0.0001	0.0957	0.0002
Type 2	0.0112	0.0039	-0.0064	0.1663
Age group (ref: >=65)				
<65	0.1216	<0.0001	0.1164	<0.0001
(Age <65)*(Type 1)	-0.0095	0.6884	-0.0311	0.2660
(Age<65)*(Type 2)	-0.0490	<0.0001	-0.0478	<0.0001
Sex (ref: Female)				
Male	0.0169	<0.0001	0.0221	<0.0001
Race (ref: White)				
Black	0.0085	0.0039	0.0121	0.0010
Hispanic	0.0614	<0.0001	0.0577	<0.0001
Asian	0.1432	<0.0001	0.1402	<0.0001
Native American	-0.0116	0.3703	-0.0105	0.5011
Other	0.1391	<0.0001	0.1514	<0.0001
Payer (ref: Other)				
Medicare	0.0666	<0.0001	0.0244	0.0467
Medicaid	0.0140	0.1815	-0.0216	0.01024
Private	0.1650	<0.0001	0.1172	<0.0001
Self-Pay	-0.1159	<0.0001	-0.1281	<0.0001
No charge	-0.1330	<0.0001	-0.1483	<0.0001
Income (ref: Quartile 4)				
Quartile 1	-0.1950	<0.0001	-0.1950	<0.0001
Quartile 2	-0.1487	<0.0001	-0.1526	<0.0001
Quartile 3	-0.0811	<0.0001	-0.0799	<0.0001
PLE (ref: No)				
Less Severe	0.0087	0.0078	0.5243	<0.0001
Severe	0.5254	<0.0001	0.0132	0.0010
Coronary atherosclerosis (ref: No)				
Less Severe	-0.0193	<0.0001	-0.0145	0.0005
Severe	0.0505	<0.0001	0.0532	<0.0001
Kidney severity				
Less Severe vs. Severe	-0.0768	<0.0001	-0.0718	<0.0001
Depression (ref: No)				
Yes	-0.0224	<0.0001	-0.0216	<0.0001
APRDRG_Severity (ref: 0)				
1	-0.0229	0.6534	0.0156	0.8067
2	0.0327	0.5200	0.0802	0.2059

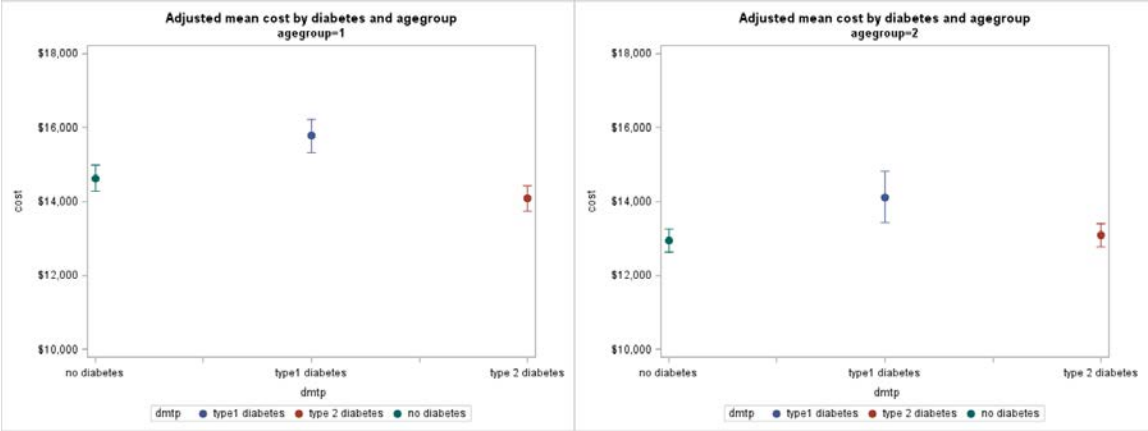
3	0.3323	<0.0001	0.3858	<0.0001
4	1.2335	<0.0001	1.2706	<0.0001

Table 44: Adjusted mean kidney diseases-related hospitalization cost from the interaction model

Variables	Full cohort		Stratified matched cohort	
	Adjusted mean cost	95% Confidence interval	Adjusted mean cost	95% Confidence interval
Diabetes				
Type 1	$14,914	$14,433 -- $15,411	$15,208	$14,613 -- $15,828
Type 2	$13,575	$13,257 -- $13,901	$13,619	$13,221 -- $14,028
Not present	$13,757	$13,432 -- $14,090	$14,038	$13,623 -- $14,465
Age group				
<65	$14,807	$14,453 -- $15,169	$14,930	$14,486 -- $15,388
≥65	$13,369	$13,004 -- $13,745	$13,644	$13,186 -- $14,118
(Age < 65)* (Type 1)	$15,755	$15,332 -- $16,230	$15,871	$15,326 -- $16,435
(Age < 65)* (Type 2)	$14,077	$13,745 -- $14,416	$14,094	$13,680 -- $14,520
(Age < 65)* (No diabetes)	$14,619	$14,271 -- $14,976	$14,879	$14,433 -- $15,338
(Age ≥ 65)* (Type 1)	$14,101	$13,429 -- $14,806	$14,574	$13,746 -- $15,451
(Age ≥ 65)* (Type 2)	$13,091	$12,781 -- $13,410	$13,160	$12,770 -- $13,561
(Age ≥ 65)* (No diabetes)	$12,945	$12,634 -- $13,264	$13,244	$12,846 -- $13,654
Sex				
Female	$13,951	$13,608 -- $14,303	$14,116	$13,685 -- $14,560
Male	$14,190	$13,841 -- $14,547	$14,431	$13,991 -- $14,886
Race				
White	$13,293	$12,974 -- $13,621	$13,642	$13,059 -- $13,876
Black	$13,407	$13,080 -- $13,742	$13,626	$13,213 -- $14,052
Hispanic	$14,135	$13,786 -- $14,493	$14,261	$13,824 -- $14,713
Asian	$15,340	$14,905 -- $15,788	$15,488	$14,948 -- $16,048
Native American	$13,140	$12,691 -- $13,606	$13,322	$12,767 -- $13,901
Other	$15,277	$14,859 -- $15,706	$15,662	$15,131 -- $16,210
Primary payer				
Medicare	$15,048	$14,697 -- $15,407	$15,012	$14,580 -- $15,457
Medicaid	$13,924	$13,924 -- $14,629	$14,337	$13,905 -- $14,783
Private	$16,604	$16,205 -- $17,013	$16,471	$15,982 -- $16,976
Self-Pay	$12,537	$12,192 -- $12,892	$12,888	$12,444 -- $13,347
No charge	$12,325	$11,728 -- $12,952	$12,630	$11,846 -- $13,467
Other	$14,078	$13,669 -- $14,500	$14,649	$14,116 -- $15,203
Income				
Quartile 1	$12,875	$12,557 -- $13,200	$13,069	$12,669 -- $13,481
Quartile 2	$13,484	$13,150 -- $13,827	$13,635	$13,214 -- $14.068
Quartile 3	$14,427	$14,068 -- $14,795	$14,663	$14,210 -- $15,130
Quartile 4	$15,646	$15,254 -- $16,049	$15,883	$15,387 -- $16,394
PLE				

Severe	$19,914	$19,404 -- $20,436	$20,155	$19,515 -- $20,815
Less Severe	$11,878	$11,583 -- $12,181	$12,090	$11,718 -- $12,475
Not present	$11,775	$11,488 -- $12,070	$11,932	$11,570 -- $12,304
Coronary atherosclerosis				
Severe	$14,645	$14,279 -- $15,020	$14,859	$14,399 -- $15,334
Less Severe	$13,658	$13,317 -- $14,008	$13,887	$13,457 -- $14,331
Not present	$13,924	$13,584 -- $14,274	$14,090	$13,662 -- $14,531
Kidney diseases				
Less Severe	$13,540	$13,174 -- $13,916	$13,769	$13,308 -- $14,247
Severe	$14,620	$14,273 -- $14,976	$14,794	$14,358 -- $15,243
Depression				
Yes	$13,913	$13,561 -- $14,274	$14,120	$13,676 -- $14,578
No	$14,228	$13,883 -- $14,582	$14,427	$13,993 -- $14,875
APRDRG_Severity				
0	$10,267	$9,284 -- $11,354	$10,053	$8,868 – $11,397
1	$10,034	$9,854 -- $10,217	$10,211	$9,978 -- $10,450
2	$10,608	$10,450 -- $10,768	$10,893	$10,691 -- $11,098
3	$14,314	$14,104 -- $14,527	$14,787	$14,517 -- $15,061
4	$35,247	$34,667 -- $35,838	$35,821	$35,086 -- $36,571

Figure 32: Adjusted mean kidney diseases-related hospitalization cost by age group and diabetes type



5.3.4 Discharge after hospitalization analysis

5.3.4.1 Crosstab of discharge status by comorbidities in the Kidney diseases cohort

The association between comorbidities and kidney diseases-related hospitalization was examined first by crosstab and Chi square test. 43.9% of the hospitalized kidney diseases patients with type 2 diabetes had non-routine discharges; 31.8% of these patients

with type 1 diabetes comorbidity had non-routine discharges; 37.8% of the patients without diabetes had non-routine discharges. 48.2% of the kidney diseases-related hospitalizations with severe PLE had non-routine discharges; 46.9% of the hospitalized PLE patients with less severe PLE had non-routine discharges; 38.4% of the patients without PLE had non-routine discharges. 38.2% of the patients without coronary atherosclerosis had non-routine discharges; 49.3% of the patients had less severe coronary atherosclerosis have non-routine discharges; 41.6% of the patients with severe coronary atherosclerosis had non-routine discharges. In terms of kidney diseases severity, 41.2% of the patients with severe kidney diseases had non-routine discharges; while 32.6% of the patients with less severe kidney diseases had non-routine discharges.

Table 45: Crosstab of coronary atherosclerosis-related hospitalization discharge status by comorbidities

	Diabetes			Peripheral Lower extremity diseases			Coronary atherosclerosis		
	Not present	Type 1	Type 2	Not present	Less severe	Severe	Not present	Less severe	Severe
Routine discharge	62.16%	68.16%	56.12%	61.38%	53.10%	51.76%	61.81%	50.75%	58.37%
Non-Routine discharge	37.84%	31.84%	43.88%	38.42%	46.90%	48.24%	38.19%	49.25%	41.63%
Chi-square P value	<0.0001			<0.0001			<0.0001		

5.3.4.2 Logistic regression analysis results

Multivariate logistic regression was used to examine the effect of comorbidities and other covariates on the kidney diseases-related hospitalization discharge status. Table 46 summarizes the odds ratio and 95% confidence intervals from the logistic regression.

453,714 observations out of the total 504,320 observations were included in the logistic regression model because they contain non-missing values for all the study variables.

Diabetes: The presence of type 1 diabetes was associated with a 33.2% increase in the odds of having non-routine discharges ($p<0.0001$). The presence of type 2 diabetes is associated with a 20.2% increase in the odds of having non-routine discharges; however, this effect is marginally significant with a p-value 0.0012.

Other significant effects: 1 year increase in age was associated with a 3.9% increase in the odds of having a non-routine discharge ($p<0.0001$). Compared to females, males were less likely to have non-routine discharges ($p<0.0001$). Black, Hispanic, Asian, and Native American had decreased odds of having non-routine discharges compared to White. Patients with Medicare or Medicaid as primary payer were more likely to have non-routine discharges than patients paid by other government entitlement programs. On the contrary, patients with self-pay or no charge are less likely to had non-routine discharges compared to patients paid by other government programs. The odds of having non-routine discharges for the patients with severe loss of function was 3.2 times the odds of having non-routine discharges for the patients without loss of function. The odds ratio off having non-routine discharges for kidney diseases patients with severe PLE was 1.3 compared to patients without PLE; while the odds ratio of having non-routine discharges for patients with less severe PLE was 1.2 compared to patients without PLE. The presence of less severe coronary atherosclerosis was associated with a 5.2% increase in the odds of having non-routine discharges; while the presence of severe coronary atherosclerosis was associated with a 21.6% decrease in the odds of having non-routine

discharges. The presence of depression increased the odds of having non-routine discharges by 35.3%

Non-significant effects: The median household income of patients with kidney diseases did not have a significant effect on kidney diseases-related hospitalization discharge status. The C statistic of logistic regression was 0.723, indicating good model fit.

Table 46: Logistic regression results of kidney diseases-related hospitalization discharge status

Variable	Odds Ratio	95% Confidence Interval		P value
Age	1.039	1.038	1.039	<0.0001
Male vs. Female	0.894	0.883	0.906	<0.0001
Race				
Black vs. White	0.988	0.973	1.004	<0.0001
Hispanic vs. White	0.739	0.723	0.755	<0.0001
Asian vs. White	0.700	0.671	0.731	<0.0001
Native American vs. White	0.764	0.711	0.822	0.0008
Other vs. White	0.951	0.914	0.989	<0.0001
Median zip code household income				
Quartile 1 vs. Quartile 4	0.980	0.961	1.000	0.6208
Quartile 2 vs. Quartile 4	0.977	0.957	0.997	0.2710
Quartile 3 vs. Quartile 4	0.975	0.955	0.995	0.1734
Payer type				
Medicare vs. Other	1.292	1.224	1.363	<0.0001
Medicaid vs. Other	1.104	1.042	1.171	<0.0001
Private vs. Other	0.882	0.833	0.933	<0.0001
Self-pay vs. Other	0.500	0.461	0.543	<0.0001
No charge vs. Other	0.428	0.345	0.507	<0.0001
PLE				
Less Severe vs. None	1.215	1.195	1.236	<0.0001
Severe vs. None	1.304	1.274	1.334	<0.0001
Kidney diseases severity				
Severe vs. Less severe	1.127	1.083	1.172	<0.0001
Coronary atherosclerosis				
Less Severe vs. None	1.052	1.035	1.070	<0.0001
Severe vs. None	0.784	0.770	0.798	<0.0001

Depression (1 vs. 0)	1.353	1.325	1.382	<0.0001
Diabetes				
Type 1 vs. None	1.332	1.273	1.395	<0.0001
Type 2 vs. None	1.202	1.185	1.219	0.0012
APRDRG Severity				
1 vs. 0	0.383	0.313	0.469	<0.0001
2 vs. 0	0.534	0.437	0.652	<0.0001
3 vs. 0	0.929	0.761	1.134	0.2477
4 vs. 0	3.222	2.636	3.937	<0.0001

5.4 Coronary atherosclerosis-related hospitalization analysis results

5.4.1 Data extraction

Figure 33: Coronary atherosclerosis-related hospitalization sample selection and cohort construction

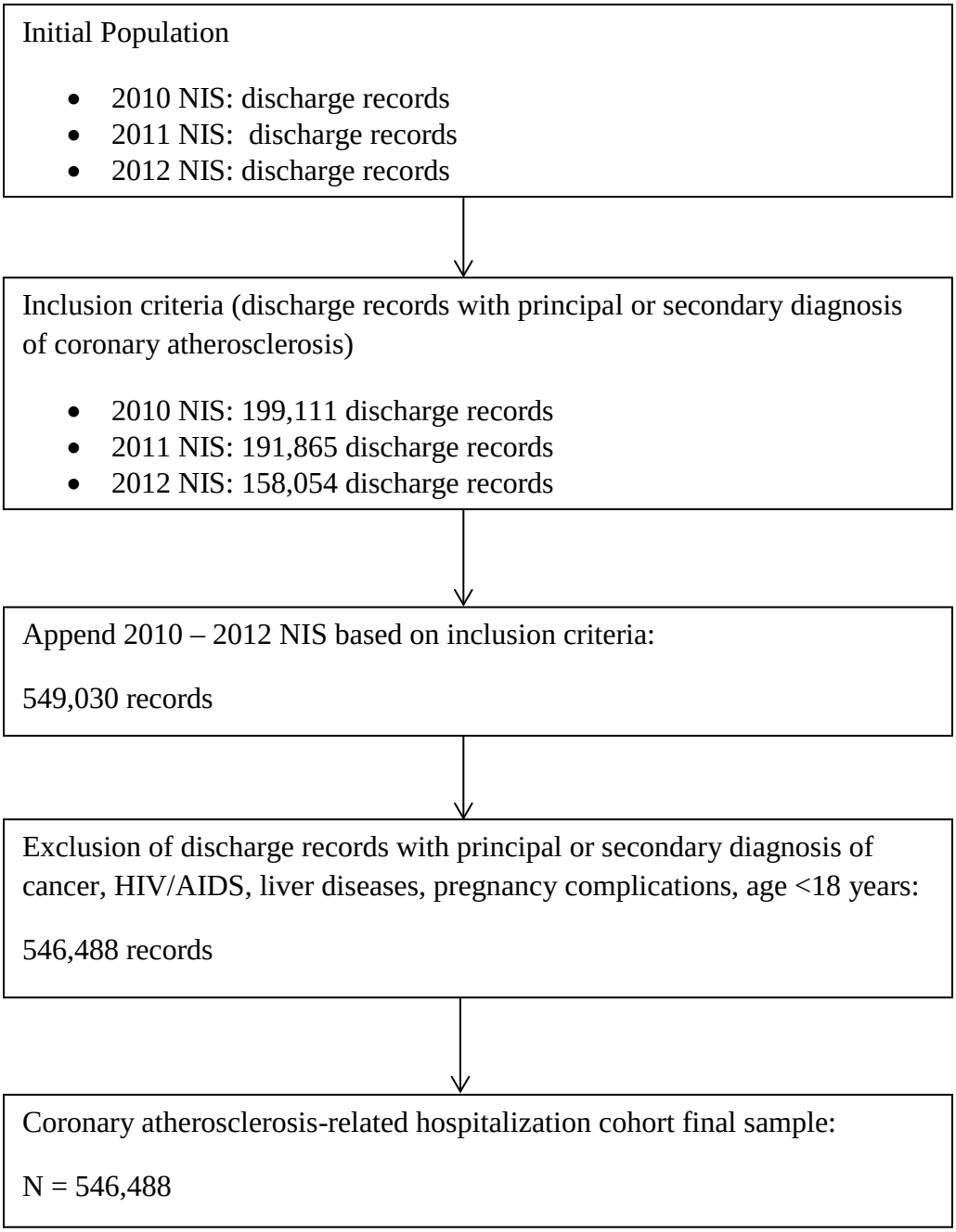


Figure 31 summarizes the sample selection and cohort construction process for patients with coronary atherosclerosis-related hospitalization. Applying the inclusion and exclusion criteria, the final coronary atherosclerosis-related hospitalization cohort contained 546,488 discharge records based on the 2010 to 2012 NIS.

5.4.2 Descriptive statistics of study variables

5.4.2.1 Descriptive statistics of dependent variable

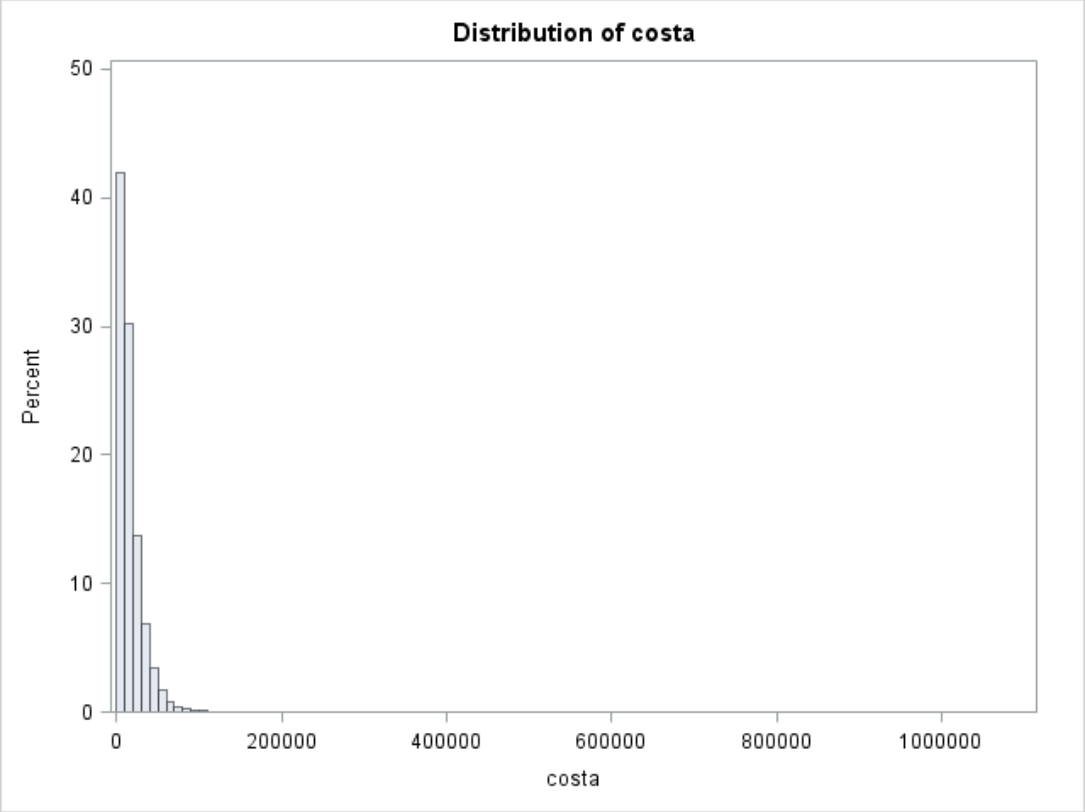
Hospitalization cost

The primary outcome was coronary atherosclerosis-related hospitalization cost. Table 47 presents the descriptive characteristics of coronary atherosclerosis-related hospitalization cost. The mean coronary atherosclerosis-related hospitalization cost was $16,718 and the median is $12,232. The maximum coronary atherosclerosis-related hospitalization cost was around the $1 million threshold. Therefore all the observations were retained in the exploratory analysis.

Table 47: Descriptive statistics of coronary atherosclerosis-related hospitalization cost

Statistics	Coronary atherosclerosis-related hospitalization costs
Mean ± S.D.	$16,718 ± $16,962
Minimum	$30.396
25% Quartile	$6,192
Median	$12,232
75% Quartile	$21,439
99% Quartile	$75,794
Maximum	$1,058,948

Figure 34: Histogram of the distribution of coronary atherosclerosis-related hospitalization cost



Discharge status

The secondary outcome was coronary atherosclerosis-related hospitalization discharge status. Table 48 lists the coronary atherosclerosis-related hospitalization discharge status. 76.25% of the hospitalized coronary atherosclerosis patients were discharged to home; while 23.75% of the hospitalized coronary atherosclerosis patients had non-routine discharges. The largest component of non-routine discharge was home health care (10.68% of the total patients), followed by transfer to another type of facility (6.96%) and transfer to a short-term hospital (4.58%).

Table 48: Coronary atherosclerosis-related hospitalization discharge status

Discharge status	Description	Percentage	Total percentage
Routine discharge	Discharge to home	76.25%	76.25%
Non-Routine discharge	Transfer to short-term hospital	4.58%	23.75%
	Transfer other: includes Skilled Nursing Facility (SNF), Intermediate Care Facility (ICF), and another type of facility	6.96%	
	Home Health care (HHC)	10.68%	
	Against medical advice	0.96%	
	Died in hospital	0.56%	
	Discharged alive, destination unknown	0.01%	

5.4.2.2 Descriptive statistics of comorbidities

The descriptive characteristics of comorbidities in the coronary atherosclerosis-related hospitalization cohort are presented in Table 49. 37.2% of the hospitalized coronary atherosclerosis patients had diabetes (16.3% only had diabetes; 4.2% had kidney diseases and diabetes; 12.6% had PLE and diabetes; 4.1% had PLE, diabetes, and kidney diseases). 41.8% of the patients with coronary atherosclerosis-related hospitalization had comorbid PLE (22.5% only had PLE; 12.6% had PLE and diabetes; 2.6% had PLE and kidney diseases; 4.1% had PLE, kidney diseases, and diabetes). 15.1% of the hospitalized coronary atherosclerosis patients had kidney diseases (4.2% only had kidney diseases; 4.2% had kidney diseases and diabetes; 2.6% had kidney diseases and PLE; 4.1% had PLE, kidney diseases, and diabetes).

Table 49: Descriptive characteristics of comorbidities in the coronary atherosclerosis-related hospitalization cohort

Comorbidities	Peripheral Lower extremity (PLE) diseases (0)		Peripheral Lower extremity (PLE) diseases (1)	
	Kidney diseases (0)	Kidney diseases (1)	Kidney diseases (0)	Kidney diseases (1)
Diabetes (0)	N=183,978 (33.66%)	N=22,775 (4.17%)	N=122,906 (22.49%)	N=14,090 (2.58%)
Diabetes (1)	N=88,912 (16.27%)	N=22,924 (4.19%)	N=68,596 (12.55%)	N=22,307 (4.08%)

5.4.2.3 Descriptive statistics of other independent variables

Table 50 summarizes the descriptive statistics of independent variables among patients with coronary atherosclerosis-related hospitalization. The control variables were grouped by the behavioral model of health services utilization.

In terms of predisposing characteristics, more than half of the patients with coronary atherosclerosis-related hospitalization were 65 years or older. Furthermore, the hospitalized coronary atherosclerosis patients were predominantly male (more than 60%) and White (81.0% among the patients without comorbid diabetes; 69.6% among the patients with diabetes comorbidity).

With regard to the enabling resources, more than 50% of the hospitalized coronary atherosclerosis patients lived in a neighborhood where the median household income was below the 50^{th} percentile. What's more, most of these patients had Medicare as the primary payer (above 50%), followed by private insurance and Medicaid.

With respect of need factors, around 84% of the hospitalized coronary atherosclerosis patients without diabetes had minor or moderate loss of function; while

25% of the patients with diabetes comorbidity had major or extreme loss of function. More than 75% the hospitalized coronary atherosclerosis patients had the severe form of atherosclerosis.

Table 50: Descriptive statistics of control variables in the coronary atherosclerosis-related hospitalization cohort

Control variables	Coronary atherosclerosis-related hospitalizations without Diabetes (n=343,749)	Coronary atherosclerosis-related hospitalization with Diabetes (n=202,739)
Predisposing characteristics		
Age		
<65	42.46%	44.94%
>=65	57.54%	55.06%
Sex		
Female	34.10%	39.33%
Male	65.90%	60.07%
Race		
White	80.68%	69.60%
Black	8.24%	12.49%
Hispanic	5.73%	10.36%
Asian	1.86%	2.96%
Native American	0.56%	0.86%
Other	2.93%	3.73%
Enabling resources		
Median zip code income		
0 to 25th percentile	28.62%	32.84%
26th to 50th percentile	26.38%	26.82%
51st to 75th percentile	24.26%	23.53%
76th to 100th percentile	20.74%	16.81%
Primary payer		
Medicare	57.39%	59.94%
Medicaid	6.21%	8.69%
Private insurance	28.60%	24.31%
Self-pay	4.65%	3.96%
No charge	0.45%	0.40%
Other	2.70%	2.71%
Need Factors		
Comorbidity		
PLE	39.85%	44.84%
(Less severe)	33.56%	31.42%

(Severe)	6.36%	13.47%
Kidney diseases	10.72%	22.31%
(Less severe)	0.09%	0.81%
(Severe)	10.63%	21.50%
Coronary atherosclerosis		
Less Severe	25.26%	23.77%
Severe	74.74%	76.23%
APRDRG: severity of illness (loss of function)		
0 (no class)	0.03%	0.03%
1 (minor loss)	42.13%	25.01%
2 (moderate loss)	42.68%	49.77%
3 (major loss)	12.68%	21.76%
4 (extreme loss)	2.48%	3.43%
Depression	7.71%	9.31%

To reduce the degree of confounding, a stratified matched cohort was drawn from the subgroup without diabetes comorbidity to make it comparable to the subgroup with diabetes. Table 51 summarizes the demographic characteristics in the stratified matched cohort.

Table 51: Demographic characteristics in the stratified matched cohort

Variables	Coronary atherosclerosis-related hospitalization with diabetes (n=202,739)	Coronary atherosclerosis-related hospitalization without diabetes (n=150,004)	P-value
Age (>=65 years)	55.06%	55.0%	0.7207
Sex (Female)	39.33%	39.00%	0.0445
Race (Non-White)	30.40%	30.00%	0.0121
Income			<0.0001
Quartile 1	32.84%	30.38%	
Quartile 2	26.82%	25.46%	
Quartile 3	23.53%	23.51%	
Quartile 4	16.81%	20.65%	
Primary Payer			<0.0001
Medicare	59.94%	55.21%	
Medicaid	8.69%	7.59%	
Private insurance	24.31%	28.76%	
Self-pay	3.96%	5.16%	

No charge	0.40%	0.50%	
Other	2.71%	2.79%	

5.4.3 Generalized linear model results

Generalized linear model was used to examine the impact of diabetes and other factors on the cost of coronary atherosclerosis-related hospitalization cost. The regression coefficient estimates from GLM are summarized in Table 52. Table 53 presents the adjusted mean coronary atherosclerosis-related hospitalization cost by categorical variables. The coronary atherosclerosis cohort contained 546,488 discharge records; 451,280 observations with non-missing values for the study variables were used in the regression model. The stratified matched cohort contained 352,743 discharge records; there were 305,677 observations with non-missing values that were used for the regression analysis.

Diabetes: In the full cohort, the presence of type 2 diabetes was associated with a 2.1% decrease in coronary atherosclerosis-related hospitalization cost. The presence of type 1 diabetes did not decrease coronary atherosclerosis-related hospitalization cost significantly. In the matched cohort, the mean coronary atherosclerosis-related hospitalization cost was $16,190 for patients without diabetes; $15,859 for patients with type 2 diabetes; $15,955 for patients with type 1 diabetes.

Other statistical significant effect: 1 year increase in age was associated with a 0.03% decrease in hospitalization cost. The hospitalization cost for male was 1.1 times the cost for female patients with coronary atherosclerosis. The cost for hospitalized coronary atherosclerosis patients with severe PLE comorbidity was 1.2 times the cost for

hospitalized coronary atherosclerosis without PLE. The hospitalization cost for male coronary atherosclerosis patients (mean: $16,670; 95% CI: $16,180 - $17,176) was significantly higher than that for females (mean: $15,391; 95% CI: $14,939 - $15,857). In terms of race/ethnicity, hospitalization cost for Asian was significantly higher than that for White, Black, Hispanic, and Native American. The mean hospitalization cost for patients with comorbid severe PLE (mean: $18,478; 95% CI: $17,932 - $19,041) was significantly higher than patients with less severe (mean: $14,810; 95% CI: $14,367 - $15,265) or without PLE (mean: $15,019; 95% CI: $14,578 - $15,472). Similar trends retained in the stratified matched cohort.

Non-significant effect: Several variables did not add to coronary atherosclerosis-related hospitalization cost significantly: type 1 diabetes, less severe PLE, less severe kidney diseases, minor or moderate loss of function.

Table 52: Coefficient estimates from the generalized linear model

Variables	Full cohort		Stratified matched cohort	
	Coefficient	P-value	Coefficient	P-value
Diabetes (ref: No)				
Type 1	-0.0171	0.2361	-0.0146	0.3149
Type 2	-0.0211	<0.0001	-0.0206	<0.0001
Age	-0.0028	<0.0001	-0.0024	<0.0001
Sex (ref: Female)				
Male	0.0798	<0.0001	0.0765	<0.0001
Race (ref: White)				
Black	-0.0425	<0.0001	-0.0378	<0.0001
Hispanic	0.0521	<0.0001	0.0553	<0.0001
Asian	0.1238	<0.0001	0.1224	<0.0001
Native American	0.0059	0.6395	0.0114	0.4040
Other	0.0636	<0.0001	0.0699	<0.0001
Payer (ref: Other)				
Medicare	-0.0632	<0.0001	-0.0775	<0.0001
Medicaid	-0.0846	<0.0001	-0.0866	<0.0001
Private	0.0383	<0.0001	0.0303	0.0001
Self-Pay	-0.0811	<0.0001	-0.0776	<0.0001
No charge	-0.0291	0.0762	-0.0245	0.2177
Income (ref: Quartile 4)				
Quartile 1	-0.1223	<0.0001	-0.1248	<0.0001

Quartile 2	-0.0794	<0.0001	-0.0843	<0.0001
Quartile 3	-0.0436	<0.0001	-0.0432	<0.0001
PLE (ref: No)				
Less Severe	-0.0140	0.0002	-0.0094	0.0320
Severe	0.2073	<0.0001	0.2058	<0.0001
Kidney diseases (ref: No)				
Less Severe	-0.0393	0.0301	-0.0406	0.0319
Severe	-0.1119	<0.0001	-0.1138	<0.0001
Coronary atherosclerosis severity (ref: Severe)				
Less Severe vs. Severe	-0.5664	<0.0001	-0.5741	<0.0001
Depression (ref: No)				
Yes	-0.0784	<0.0001	-0.0802	<0.0001
APRDRG_Severity (ref: 0)				
1	-0.1771	0.0044	-0.1414	0.0635
2	0.0994	0.1100	0.1414	0.0635
3	0.5707	<0.0001	0.6110	<0.0001
4	1.3702	<0.0001	1.3957	<0.0001

Table 53: Adjusted mean coronary atherosclerosis-related hospitalization cost

Variables	Full cohort		Stratified matched cohort	
	Adjusted mean cost	95% Confidence interval	Adjusted mean cost	95% Confidence interval
Diabetes				
Type 1	$15,948	$15,327 -- $16,595	$15,955	$15,273 -- $16,668
Type 2	$15,885	$15,440 -- $16,343	$15,859	$15,333 -- $16,403
Not present	$16,224	$15,768 -- $16,692	$16,190	$15,651 -- $16,747
Sex				
Female	$15,391	$14,939 -- $15,857	$15,400	$14,871 -- $15,948
Male	$16,670	$16,180 -- $17,176	$16,625	$16,053 -- $17,216
Race				
White	$15,485	$15,037 -- $15,948	$15,422	$14,898 -- $15,964
Black	$14,842	$14,403 -- $15,294	$14,850	$14,338 -- $15,381
Hispanic	$16,313	$15,828 -- $16,813	$16,298	$15,733 -- $16,883
Asian	$17,526	$16,968 -- $18,103	$17,429	$16,789 -- $18,094
Native American	$15,578	$14,992 -- $16,187	$15,599	$14,934 -- $16,292
Other	$16,502	$15,992 -- $17,028	$16,538	$15,946 -- $17,153
Primary payer				
Medicare	$15,597	$15,148 -- $16,060	$15,402	$14,883 -- $15,938
Medicaid	$15,268	$14,815 -- $15,735	$15,262	$14,734 -- $15,809
Private	$17,264	$16,762 -- $17,781	$17,154	$16,572 -- $17,758
Self-Pay	$15,321	$14,856 -- $15,801	$15,400	$14,852 -- $15,967
No charge	$16,139	$15,479 -- $16,827	$16,240	$15,451 -- $17,068
Other	$16,616	$16,098 -- $17,150	$16,642	$16,034 -- $17,274
Income				
Quartile 1	$15,071	$14,627 -- $15,528	$15,043	$14,525 -- $15,579
Quartile 2	$15,731	$15,267 -- $16,210	$15,664	$15,123 -- $16,224
Quartile 3	$16,305	$15,823 -- $16,801	$16,323	$15,759 -- $16,906
Quartile 4	$17,031	$16,526 -- $17,551	$17,043	$16,452 -- $17,655

PLE				
Severe	$18,478	$17,932 -- $19,041	$18,411	$17,775 -- $19,070
Less Severe	$14,810	$14,367 -- $15,265	$14,847	$14,329 -- $15,383
Not present	$15,019	$14,578 -- $15,472	$14,987	$14,473 -- $15,519
Kidney diseases				
Severe	$15,063	$14,648 -- $15,489	$15,034	$14,542 -- $15,543
Less Severe	$16,197	$15,494 -- $16,933	$16,175	$15,403 -- $16,987
Not present	$16,846	$16,387 -- $17,318	$16,846	$16,299 -- $17,411
Coronary atherosclerosis				
Severe	$21,262	$20,638 -- $21,905	$21,321	$20,589 -- $22,079
Less Severe	$12,068	$11,712 -- $12,435	$12,008	$11,594 -- $12,437
Depression				
Yes	$15,402	$14,941 -- $15,878	$15,372	$14,834 -- $15,930
No	$16,658	$16,173 -- $17,159	$16,655	$16,088 -- $17,243
APRDRG_Severity				
0	$11,035	$9,758 -- $12,480	$10,711	$9,217 -- $12,448
1	$9,244	$9,083 -- $9,407	$9,299	$9,126 -- $9,475
2	$12,189	$11,980 -- $12,401	$12,338	$12,114 -- $12,567
3	$19,527	$19,187 -- $19,873	$19,734	$19,368 -- $20,107
4	$43,434	$42,545 -- $44,342	$43,249	$42,278 -- $44,243

Figure 35: Adjusted mean coronary atherosclerosis-related hospitalization cost by diabetes type

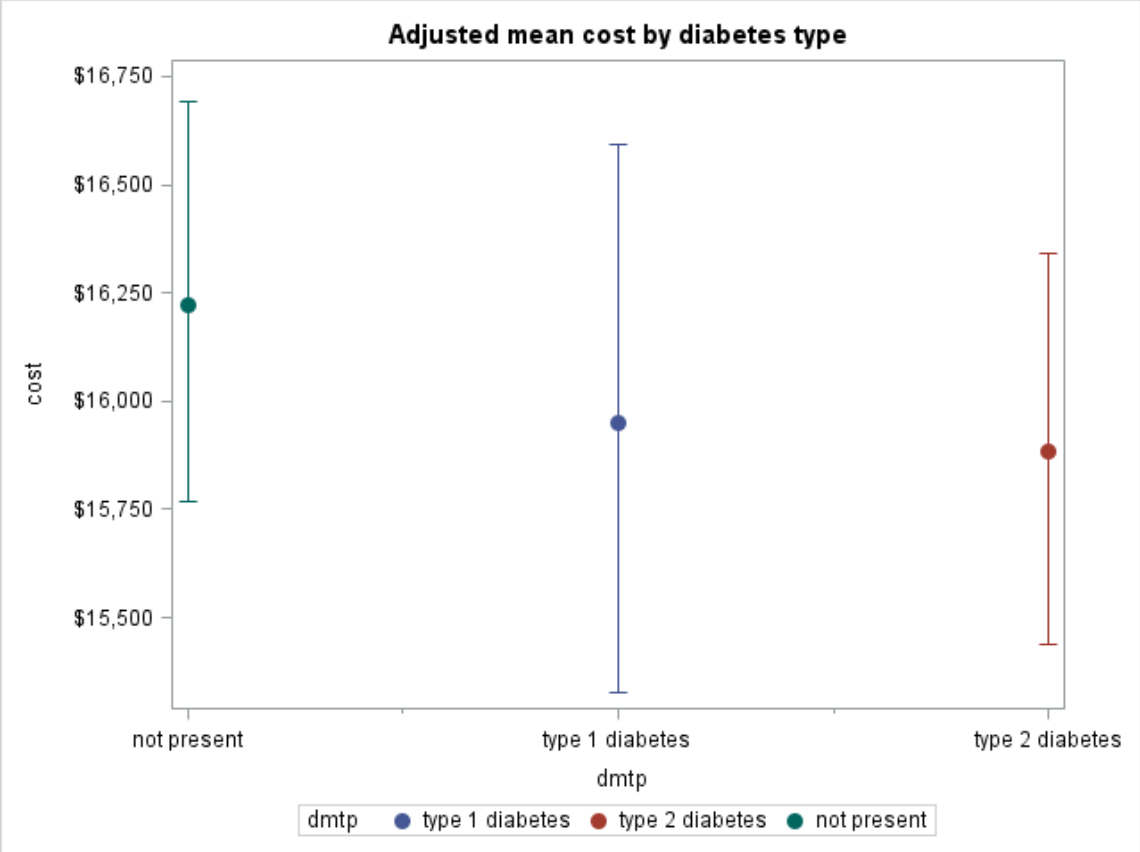


Figure 36: Adjusted mean coronary atherosclerosis-related hospitalization cost by race/ethnicity

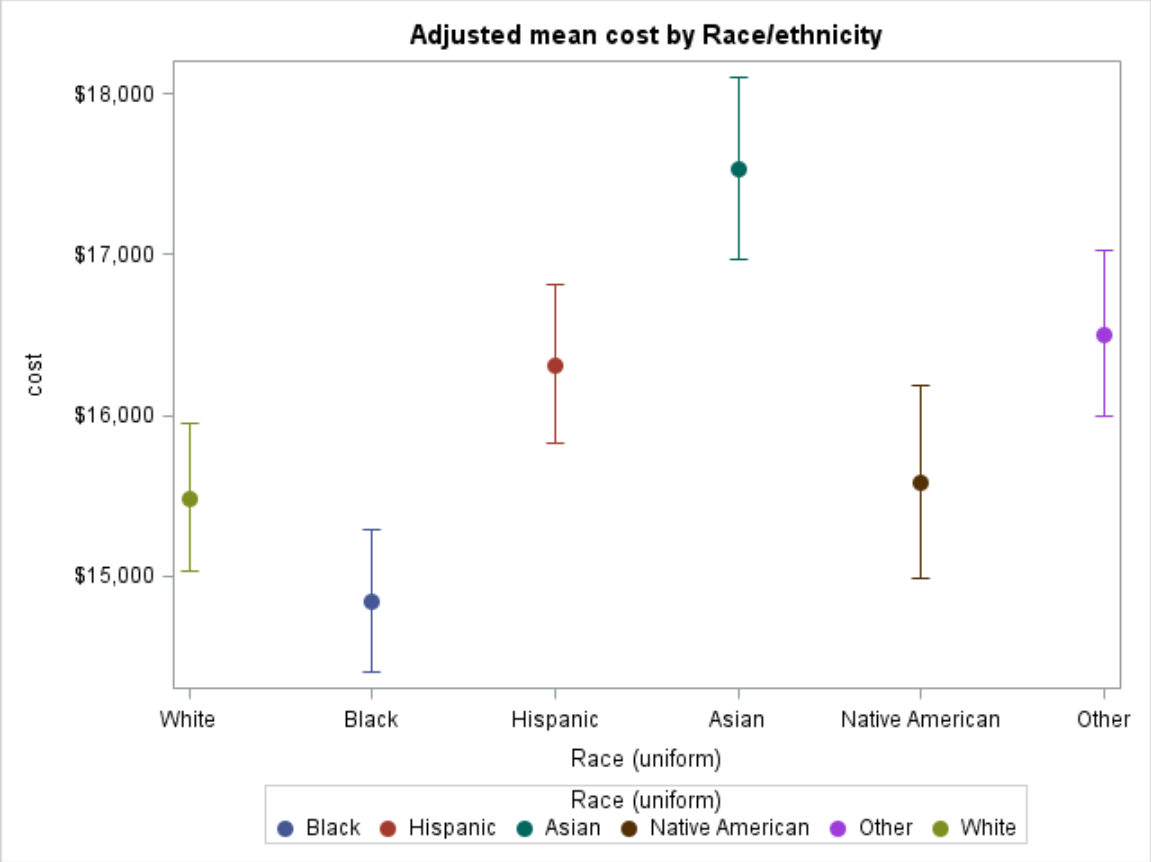
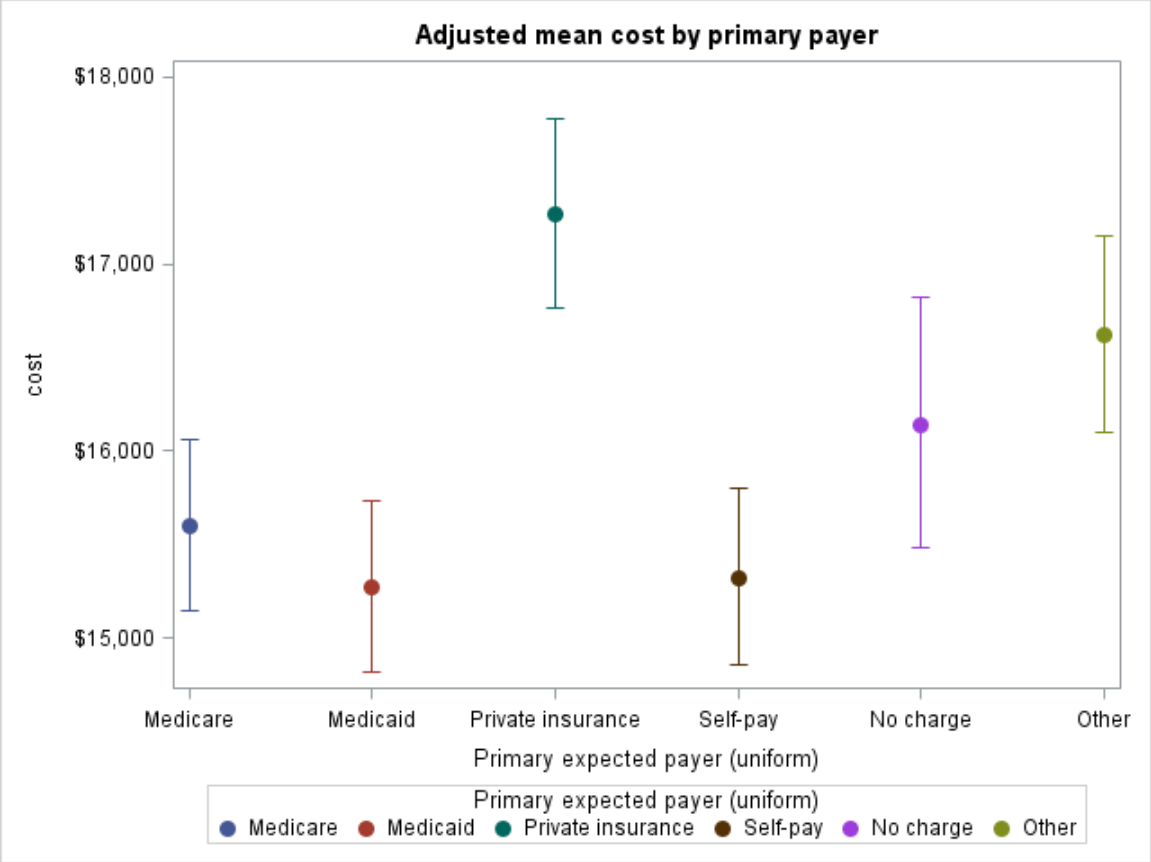


Figure 37: Adjusted mean coronary atherosclerosis-related hospitalization cost by primary payer



Interaction between age group and diabetes type

An interaction model was also explored to examine whether the impact of diabetes of diabetes on coronary atherosclerosis-related hospitalization cost is modified by age. Table 54 lists the coefficient estimates from the interaction model and Table 55 presents the adjusted mean hospitalization cost in the interaction model. There was a statistical significant interaction between diabetes type and age group: coronary atherosclerosis-related hospitalization cost is highest for patients with type 1 diabetes and age ≥ 65 years than patients with other diabetes type and age group combinations (Figure 34). Among patients with age ≥ 65 years, the adjusted mean coronary atherosclerosis-

related hospitalization cost for patients with type 1 diabetes, type 2 diabetes and without diabetes was $18,580, $16,510 and $16,784 respectively. For patients age <65 years, the adjusted mean cost for patients with type 1 diabetes, type 2 diabetes and without diabetes was $15,818, $16,074 and $16,368 respectively. Therefore the incremental cost of type 1 diabetes was $1,796 among patients ≥65 years; while the cost for patients with type 1 diabetes was lower than those without diabetes among patients <65 years.

Table 54: Coefficient estimates from the interaction model

Variables	Full cohort		Stratified matched cohort	
	Coefficient	P-value	Coefficient	P-value
Diabetes (ref: No)				
Type 1	0.1013	0.0001	0.1016	0.0001
Type 2	-0.0171	<0.0001	-0.0165	<0.0001
Age group (ref: >=65)				
<65	-0.0302	<0.0001	-0.0251	<0.0001
(Age <65)*(Type 1)	-0.1303	<0.0001	-0.1359	<0.0001
(Age<65)*(Type 2)	0.0027	0.5440	-0.0017	0.7473
Sex (ref: Female)				
Male	-0.0302	<0.0001	0.0792	<0.0001
Race (ref: White)				
Black	-0.0305	<0.0001	-0.0300	<0.0001
Hispanic	0.0542	<0.0001	0.0551	<0.0001
Asian	0.1208	<0.0001	0.1179	<0.0001
Native American	0.0111	0.3815	0.0134	0.3250
Other	0.0639	<0.0001	0.0679	<0.0001
Payer (ref: Other)				
Medicare	-0.1195	<0.0001	-0.1249	<0.0001
Medicaid	-0.0763	<0.0001	-0.0801	<0.0001
Private	0.0400	<0.0001	0.0315	<0.0001
Self-Pay	-0.0633	<0.0001	-0.0629	<0.0001
No charge	-0.0129	0.4333	-0.0115	0.5614
Income (ref: Quartile 4)				
Quartile 1	-0.1148	<0.0001	-0.1182	<0.0001
Quartile 2	-0.0745	<0.0001	-0.0798	<0.0001
Quartile 3	-0.0404	<0.0001	-0.0400	<0.0001
PLE (ref: No)				
Less Severe	-0.0135	0.0004	-0.0082	0.0626
Severe	0.2109	<0.0001	0.2088	<0.0001
Kidney diseases (ref: No)				
Less Severe	-0.0345	0.0569	-0.0364	0.0542
Severe	-0.1190	<0.0001	-0.1192	<0.0001
Coronary atherosclerosis				
Less Severe vs. Severe	-0.5685	<0.0001	-0.5758	<0.0001
Depression (ref: No)				
Yes	-0.0681	<0.0001	-0.0710	<0.0001

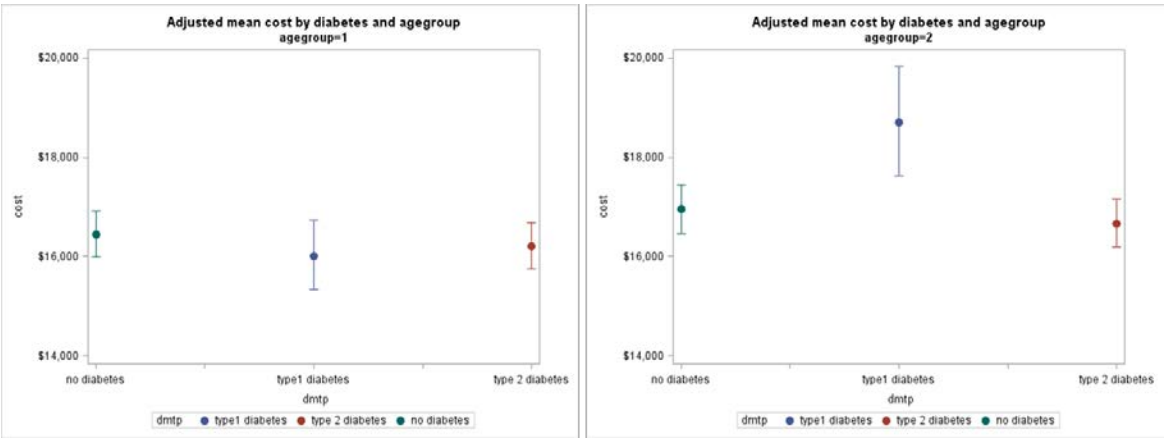
APRDRG_Severity (ref: 0)				
1	-0.1728	0.0055	-0.1394	0.0675
2	0.1006	0.1060	0.1412	0.0640
3	0.5724	<0.0001	0.6115	<0.0001
4	1.3704	<0.0001	1.3949	<0.0001

Table 55: Adjusted mean hospitalization cost from the interaction model

Variables	Full cohort		Matched cohort	
	Adjusted mean cost	95% Confidence interval	Adjusted mean cost	95% Confidence interval
Diabetes				
Type 1	$17,306	$16,601 -- $18,041	$17,143	$16,383 -- $17,938
Type 2	$16,341	$15,971 -- $16,905	$16,290	$15,750 -- $16,849
Not present	$16,693	$16,224 -- $17,175	$16,575	$16,023 -- $17,146
Age group				
<65	$16,205	$15,722 -- $16,703	$16,085	$15,527 -- $16,663
≥65	$17,429	$16,858 -- $18,019	$17,267	$16,623 -- $17,936
(Age < 65)*(Type 1)	$15,971	$15,290 -- $16,683	$15,818	$15,089 -- $16,581
(Age < 65)*(Type 2)	$16,206	$15,750 -- $16,676	$16,074	$15,540 -- $16,626
(Age < 65)*(No diabetes)	$16,442	$15,979 -- $16,919	$16,368	$15,821 -- $16,935
(Age ≥ 65)*(Type 1)	$18,752	$17,684 -- $19,886	$18,580	$17,474 -- $19,755
(Age ≥ 65)*(Type 2)	$16,659	$16,185 -- $17,146	$16,510	$15,955 -- $17,084
(Age ≥ 65)*(No diabetes)	$16,947	$16,465 -- $17,442	$16,784	$16,218 -- $17,370
Sex				
Female	$16,095	$15,618 -- $16,587	$16,019	$15,464 -- $16,593
Male	$17,548	$17,027 -- $18,085	$17,339	$16,739 -- $17,960
Race				
White	$16,202	$15,728 -- $16,691	$16,054	$15,505 -- $16,623
Black	$15,715	$15,247 -- $16,198	$15,579	$15,038 -- $16,140
Hispanic	$17,104	$16,591 -- $17,633	$16,964	$16,372 -- $17,577
Asian	$18,283	$17,696 -- $18,890	$18,062	$17,394 -- $18,756
Native American	$16,383	$15,763 -- $17,028	$16,271	$15,576 -- $16,998
Other	$17,272	$16,734 -- $17,827	$17,182	$16,563 -- $17,824
Primary payer				
Medicare	$15,501	$15,049 -- $15,966	$15,330	$14,809 -- $15,869
Medicaid	$16,186	$15,701 -- $16,686	$16,032	$15,474 -- $16,611
Private	$18,181	$17,647 -- $18,731	$17,925	$17,312 -- $18,560
Self-Pay	$16,396	$15,894 -- $16,914	$16,309	$15,726 -- $16,914
No charge	$17,245	$16,536 -- $17,984	$17,169	$16,333 -- $18,048
Other	$17,468	$16,919 -- $18,035	$17,368	$16,730 -- $18,032
Income				
Quartile 1	$15,868	$15,397 -- $16,355	$15,715	$15,171 -- $16,280
Quartile 2	$16,522	$16,030 -- $17,029	$16,331	$15,764 -- $16,919
Quartile 3	$17,094	$16,585 -- $17,620	$16,994	$16,403 -- $17,606
Quartile 4	$17,799	$17,267 -- $18,348	$17,687	$17,070 -- $18,327
PLE				
Severe	$19,430	$18,851 -- $20,027	$19,207	$18,538 -- $19,899
Less Severe	$15,525	$15,057 -- $16,007	$15,461	$14,918 -- $16,023
Not present	$15,735	$15,270 -- $16,216	$15,588	$15,049 -- $16,145

Kidney diseases				
Severe	$15,703	$15,266 -- $16,153	$15,581	$15,067 -- $16,112
Less Severe	$17,089	$16,343 -- $17,868	$16,925	$16,113 -- $17,777
Not present	$17,668	$17,201 -- $18,189	$17,553	$16,979 -- $18,146
Coronary atherosclerosis				
Less Severe	$12,648	$12,271 -- $13,036	$12,496	$12,062 -- $12,946
Severe	$22,331	$21,670 -- $23,013	$22,226	$21,458 -- $23,022
Depression				
Yes	$16,243	$15,752 -- $16,749	$16,084	$15,517 -- $16,672
No	$17,388	$16,876 -- $17,915	$17,268	$16,676 -- $17,882
APRDRG_Severity				
0	$11,561	$10,221 -- $13,076	$11,153	$9,596 -- $12,963
1	$9,726	$9,553 -- $9,903	$9,701.75	$9,518 -- $9,889.20
2	$12,784	$12,559 -- $13,013	$12,844	$12,605 -- $13,088
3	$20,492	$20,125 -- $20,865	$20,558	$20,167 -- $20,956
4	$45,513	$44,564 -- $46,483	$44,997	$43,970 -- $46,047

Figure 38: Adjusted mean coronary atherosclerosis-related hospitalization cost from the interaction model



5.4.4 Discharge after hospitalization analysis

5.4.4.1 Crosstab of discharge status by comorbidities in the coronary atherosclerosis-related hospitalization cohort

The association between comorbidities and coronary atherosclerosis-related hospitalization discharge status was first explored by cross-tabulation and Chi-square test. 22.4% of the hospitalized coronary atherosclerosis patients without diabetes had non-routine discharges; 27.7% of the hospitalized coronary atherosclerosis patients with

type 1 diabetes had non-routine discharges; 26.1% of the hospitalized coronary atherosclerosis patients with type 2 diabetes had non-routine discharges. Coronary atherosclerosis patients with less severe PLE had more non-routine discharges (36.3%) than patients with severe PLE (7.4%) or without PLE (31.1%). 33.4% of the patients with less severe kidney diseases comorbidity had non-routine discharges; 32.7% of the patients with severe kidney diseases had non-routine discharges; 22.2% of the patients without kidney diseases had non-routine discharges.

Table 56: Crosstab of coronary atherosclerosis-related hospitalization discharge status

Discharge status	Diabetes			Peripheral Lower extremity diseases			Kidney diseases		
	Not present	Type 1	Type 2	Not present	Less severe	Severe	Not present	Less severe	Severe
Routine discharge	77.65%	72.34%	73.88%	68.95%	63.72%	92.65%	77.82%	66.62%	67.34%
Non-Routine discharge	22.35%	27.66%	26.12%	31.05%	36.28%	7.35%	22.18%	33.38%	32.66%
Chi-square P value	<0.0001			<0.0001			<0.0001		

5.4.4.2 Logistic regression analysis results

Multivariate logistic regression was used to examine the effect of comorbidities and other factors on coronary atherosclerosis-related hospitalization discharge status. Table 57 summarizes the odds ratios and their 95% confidence intervals from the logistic regression results. Out of the 546,488 discharge records in the full cohort, 480,260 discharge records with non-missing values for the study variables were used for the logistic regression analysis.

Diabetes: The presence of type 1 diabetes was associated with a 35.4% increase in the odds of having a non-routine discharge after coronary atherosclerosis-related hospitalization. Type 2 diabetes, however, was not significantly associated with coronary atherosclerosis-related hospitalization discharge status (p=0.0346).

Other significant effect: Compared to females, males were less likely to have a non-routine discharge (OR=0.921, p<0.0001). The presence of severe PLE or less severe PLE was associated with decreased likelihood of having non-routine discharges. Black was 1.017 times more likely to have non-routine discharge than White. Compared to patients paid by other government entitlement programs, patients paid by Medicare or Medicaid had increased likelihood of having non-routine discharges. Comorbid depression was associated with a 18.3% increase in the odds of having non-routine discharges.

Non-significant effect: Kidney diseases did not have a significant effect on coronary atherosclerosis-related hospitalization. The discharge status did not differ between Hispanic and White and Asian and White. The logistic regression model has a c statistic 0.755, indicating good model fit.

Table 57: Logistic regression results of coronary atherosclerosis-related hospitalization discharge status

Variable	Odds Ratio	95% Confidence Interval		P value
Age	1.029	1.029	1.030	<0.0001
Male vs. Female	0.921	0.907	0.935	<0.0001
Race				
Black vs. White	1.017	0.991	1.043	<0.0001
Hispanic vs. White	0.906	0.880	0.933	0.0705
Asian vs. White	0.868	0.824	0.915	0.0032
Native American vs. White	0.756	0.685	0.836	<0.0001
Other vs. White	1.084	1.039	1.132	<0.0001

Payer type				
Medicare vs. Other	1.181	1.122	1.243	<0.0001
Medicaid vs. Other	1.145	1.081	1.213	<0.0001
Private vs. Other	1.045	0.993	1.101	0.0227
Self-pay vs. Other	0.870	0.815	0.930	<0.0001
No charge vs. Other	0.864	0.746	1.001	0.0083
Median zip code household income level				
Quartile 1 vs. Quartile 4	0.824	0.806	0.842	<0.0001
Quartile 2 vs. Quartile 4	0.866	0.848	0.885	<0.0001
Quartile 3 vs. Quartile 4	0.904	0.885	0.925	0.1677
PLE				
Less Severe vs. None	0.981	0.959	1.004	<0.0001
Severe vs. None	0.179	0.175	0.183	<0.0001
Kidney diseases				
Less Severe vs. None	1.006	0.897	1.127	0.3979
Severe vs. None	0.916	0.898	0.935	0.0031
Coronary atherosclerosis				
Severe vs. Less Severe	1.093	1.074	1.111	<0.0001
Depression (1 vs. 0)	1.183	1.153	1.213	<0.0001
Diabetes				
Type 1 vs. None	1.354	1.227	1.493	<0.0001
Type 2 vs. None	1.102	1.085	1.119	0.0346
APRDRG Severity				
1 vs. 0	0.458	0.325	0.646	<0.0001
2 vs. 0	0.716	0.508	1.008	<0.0001
3 vs. 0	1.486	1.055	2.095	<0.0001
4 vs. 0	5.242	3.712	7.403	<0.0001

5.5 Study results summary tables

This section presents the summary tables of the study results. The main findings were grouped into five summary tables: the effect of diabetes and complications on hospitalization cost and discharge status (Table 58 and Table 59); other significant variables in modeling hospitalization cost and discharge status (Table 60 and Table 61); generalized linear model fit test (modified park test) (Table 62). Tables 58 – 61 are based on effect estimates from the stratified matched cohort; while Table 62 includes both the original and the matched cohort results.

Table 58: The effect of diabetes and complications on hospitalization cost

Disease cohort	Comorbidities	Coefficient estimate	p-value	Adjusted mean hospitalization cost	95% CI of cost
Diabetes-related hospitalization	PLE (severe)	0.5073	<0.0001	$17,212	$16,610 - $17,835
	PLE (less severe)	0.0066	0.0667	$10,432	$10,072 - $10,806
	without PLE			$10,363	$10,000 - $10,740
	Kidney diseases (severe)	-0.0021	0.6266	$12,523	$12,112 - $12,948
	Kidney diseases (less severe)	-0.0240	0.0043	$12,252	$11,820 - $12,700
	without kidney diseases			$12,549	$12,128 - $12,985
	Coronary atherosclerosis (severe)	0.1145	<0.0001	$12,822	$12,377 - $13,283
	Coronary atherosclerosis (less severe)	-0.0150	0.0002	$11,264	$10,873 - $11,668
	without coronary atherosclerosis			$11,434	$11,035 - $11,848
Peripheral lower extremity (PLE) diseases-related hospitalization	Type 1 diabetes and Age <65	-0.0242	<0.0001	$14,611	$13,811 - $15,457
	Type 1 diabetes and Age ≥65	0.0203	0.5042	$15,276	$14,162 - $15,654
	Type 2 diabetes and Age <65	0.0475	<0.0001	$15,698	$14,966 - $16,466
	Type 2 diabetes and Age ≥65	-0.0035	0.5252	$14,918	$14,216 - $15,654
	without diabetes and	0.1316	<0.0001	$17,075	$16,269 - $17,921

	Age <65				
	without diabetes and Age ≥65			$14,969	$14,259 - $15,715
Kidney diseases-related hospitalization	Type 1 diabetes and Age <65	0.181	0.2660	$15,871	$15,326 - $16,435
	Type 1 diabetes and Age ≥65	0.0957	0.0002	$14,574	$13,746 - $15,451
	Type 2 diabetes and Age <65	0.0622	<0.0001	$14,094	$13,680 - $14,520
	Type 2 diabetes and Age ≥65	-0.0064	0.1663	$13,160	$12,770 - $13,561
	without diabetes and Age <65	0.1164	<0.0001	$14,879	$14,433 - $15,338
	without diabetes and Age ≥65			$13,244	$12,846 - $13,654
Coronary atherosclerosis-related hospitalization	Type 1 diabetes and Age <65	-0.0594	<0.0001	$15,818	$15,089 - $16,581
	Type 1 diabetes and Age ≥65	0.1016	0.0001	$18,580	$17,474 - $19,755
	Type 2 diabetes and Age <65	-0.0433	0.7473	$16,074	$15,540 - $16,626
	Type 2 diabetes and Age ≥65	-0.0165	<0.0001	$16,510	$15,955 - $17,084
	without diabetes and Age <65	-0.0251	<0.0001	$16,368	$15,821 - $16,935
	without diabetes and Age ≥65			$16,784	$16,218 - $17,370

Table 59: The effect of diabetes and complications on hospitalization discharge status

Diseases cohort	Comorbidities	Odds ratio	95% CI	P value
Diabetes-related hospitalization	Severe PLE vs. No PLE	1.494	1.465 – 1.522	<0.0001
	Less severe PLE vs. No PLE	1.221	1.204 – 1.239	0.9313
	Severe kidney diseases vs. No kidney diseases	0.959	0.946 – 0.973	0.1062
	Less severe kidney diseases vs. No kidney diseases	0.956	0.918 – 0.996	0.2400
	Severe coronary atherosclerosis vs. No coronary atherosclerosis	1.036	1.019 – 1.053	<0.0001
	Less severe coronary atherosclerosis vs. No coronary atherosclerosis	0.676	0.665 – 0.688	<0.0001
Peripheral lower extremity diseases-related hospitalization	Type 1 diabetes vs. No diabetes	1.370	1.248 – 1.505	<0.0001
	Type 2 diabetes vs. No diabetes	1.262	1.236 – 1.289	0.0024
Kidney diseases-related hospitalization	Type 1 diabetes vs. No diabetes	1.332	1.273 – 1.395	<0.0001
	Type 2 diabetes vs. No diabetes	1.202	1.185 – 1.219	0.0012
Coronary atherosclerosis-related hospitalization	Type 1 diabetes vs. No diabetes	1.354	1.227 – 1.493	<0.0001
	Type 2 diabetes vs. No diabetes	1.102	1.085 – 1.119	0.0346

Table 58: Significance patterns in generalized linear models for hospitalization cost

Variables	Diabetes-related hospitalization		Peripheral lower extremity diseases-related hospitalization		Kidney diseases-related hospitalization		Coronary atherosclerosis-related hospitalization	
	Coefficient	P value	Coefficient	P value	Coefficient	P value	Coefficient	P value
Sex (ref: Female)								
Male	0.0126*	<0.0001	-0.0025	0.5283	0.0205*	<0.0001	0.0765*	<0.0001
Race (ref: White)								
Black	-0.0200*	<0.0001	-0.0071	0.1750	0.0049	0.1889	-0.0378*	<0.0001
Hispanic	0.0642*	<0.0001	0.0487*	<0.0001	0.0498*	<0.0001	0.0553*	<0.0001
Asian	0.1087*	<0.0001	0.0934*	<0.0001	0.1378*	<0.0001	0.1224*	<0.0001
Native American	-0.0828*	<0.0001	-0.0675	0.0019	-0.0176	0.2562	0.0114	0.4040
Other	0.0954*	<0.0001	0.0990*	<0.0001	0.1460*	<0.0001	0.0699*	<0.0001
Payer (ref: Other)								
Medicare	-0.0975*	<0.0001	-0.0904*	<0.0001	0.0244	0.0462	-0.0775*	<0.0001
Medicaid	-0.0879*	<0.0001	-0.0404	0.0025	-0.0296	0.0249	-0.0866*	<0.0001
Private	-0.0406*	<0.0001	-0.0389	0.0020	0.1166*	<0.0001	0.0303	0.0001
Self-Pay	-0.1945*	<0.0001	-0.1212*	<0.0001	-0.1350*	<0.0001	-0.0776*	<0.0001
No charge	-0.1586*	<0.0001	-0.1325*	<0.0001	-0.1535*	<0.0001	-0.0245	0.2177
Income (ref: Quartile 4)								
Quartile 1	-0.1585*	<0.0001	-0.1568*	<0.0001	-0.1976*	<0.0001	-0.1248*	<0.0001
Quartile 2	-0.1209*	<0.0001	-0.1190*	<0.0001	-0.1546*	<0.0001	-0.0843*	<0.0001
Quartile 3	-0.0548*	<0.0001	-0.0561*	<0.0001	-0.0814*	<0.0001	-0.0432*	<0.0001
Short term complication (Yes vs No)	-0.2542*	<0.0001						
Depression (Yes vs No)	-0.0060	0.1415	0.0006	0.9216	-0.0242*	<0.0001	-0.0802*	<0.0001

Retinopathy (Yes vs No)	0.1019*	<0.0001						
APRDRG_Severity (ref: 0)								
1	01083	0.0128	-0.0473	0.6639	0.0114	0.8586	-0.1414	0.0635
2	0.2704	0.0012	0.0852	0.4339	0.0761	0.2298	0.1414	0.0635
3	0.5998*	<0.0001	0.3287	0.0025	0.3813*	<0.0001	0.6110*	<0.0001
4	1.3618*	<0.0001	1.1076*	<0.0001	1.2665*	<0.0001	1.3957*	<0.0001

Table 59: Significance patterns in logistic regression model for hospitalization discharge status

Variables	Diabetes-related hospitalization		Peripheral lower extremity diseases-related hospitalization		Kidney diseases-related hospitalization		Coronary atherosclerosis-related hospitalization	
	Odds ratio	P value	Odds ratio	P value	Odds ratio	P value	Odds ratio	P value
Age	1.032*	<0.0001	1.037*	<0.0001	1.039*	<0.0001	1.029*	<0.0001
Male vs. Female	0.998	0.6642	0.908*	<0.0001	0.894*	<0.0001	0.921*	<0.0001
Race								
Black vs. White	0.990*	<0.0001	1.296*	<0.0001	0.988*	<0.0001	1.017*	<0.0001
Hispanic vs. White	0.773*	<0.0001	0.931	0.1281	0.739*	<0.0001	0.906	0.0705
Asian vs. White	0.719*	<0.0001	0.790*	<0.0001	0.700*	<0.0001	0.868	0.0032
Native American vs. White	0.795	0.0029	0.783	0.0004	0.764	0.0008	0.756*	<0.0001
Other vs. White	0.926*	<0.0001	1.064	0.0013	0.951*	<0.0001	1.084*	<0.0001
Median Zip code household income								
Quartile 1 vs. Quartile 4	0.999	0.0320	1.015	0.0883	0.980	0.6208	0.824	<0.0001
Quartile 2 vs. Quartile 4	0.977	0.0068	1.000	0.9766	0.977	0.2710	0.866	<0.0001
Quartile 3 vs. Quartile 4	0.983	0.1531	0.987	0.1293	0.975	0.1734	0.904	0.1677
Payer type								
Medicare vs. Other	1.753*	<0.0001	1.442*	<0.0001	1.292*	<0.0001	1.181*	<0.0001
Medicaid vs. Other	1.551*	<0.0001	1.405*	<0.0001	1.104*	<0.0001	1.145*	<0.0001
Private vs. Other	1.140*	<0.0001	1.029	0.0161	0.882*	<0.0001	1.045	0.0227
Self-pay vs. Other	0.720*	<0.0001	0.636*	<0.0001	0.500*	<0.0001	0.870*	<0.0001
No charge vs. Other	0.645*	<0.0001	0.645*	<0.0001	0.428*	<0.0001	0.864	0.0083
Short term complication (Yes vs. No)	0.631*	<0.0001						
Peripheral lower extremity diseases								
Less severe vs. None	1.221	0.9313			1.215*	<0.0001	0.981*	<0.0001

Severe vs. None	1.494*	<0.0001			1.304*	<0.0001	0.179*	<0.0001
Kidney diseases								
Less severe vs. None	0.956	0.2400	0.981	0.8616			1.006	0.3979
Severe vs. None	0.959	0.1062	0.982	0.7844			0.916	0.0031
Coronary atherosclerosis								
Less severe vs. None	1.036*	<0.0001	0.919*	<0.0001	1.052*	<0.0001		
Severe vs. None	0.676*	<0.0001	0.715*	<0.0001	0.784*	<0.0001		
Diabetes type								
Type 1 vs. None			1.370	<0.0001	1.332*	<0.0001	1.354*	<0.0001
Type 2 vs. None			1.262	0.0024	1.202	0.0012	1.102	0.0346
Retinopathy (Yes vs. No)	0.994	0.6284						
Depression (Yes vs. No)	1.208*	<0.0001	1.410*	<0.0001	1.353*	<0.0001	1.183*	<0.0001
APRDRG_Severity								
1 vs. 0	0.357*	<0.0001	0.462*	<0.0001	0.383*	<0.0001	0.458*	<0.0001
2 vs. 0	0.568*	<0.0001	0.946*	<0.0001	0.534*	<0.0001	0.716*	<0.0001
3 vs. 0	1.125*	<0.0001	2.220*	<0.0001	0.929	0.2477	1.486*	<0.0001
4 vs. 0	3.175*	<0.0001	7.834*	<0.0001	3.222*	<0.0001	5.242*	<0.0001

Table 60: Results of modified Park test

Disease Cohort	Variables	Coefficient λ	Standard Error	P-value
Diabetes – Full	PLE	1.8843	0.0071	<0.0001
Diabetes – Matched	PLE	1.8280	0.0068	<0.0001
Diabetes – Full	Kidney diseases	2.2696	0.0083	<0.0001
Diabetes – Matched	Kidney diseases	1.9512	0.0109	<0.0001
Diabetes – Full	Coronary atherosclerosis	2.0602	0.0081	<0.0001
Diabetes – Matched	Coronary atherosclerosis	1.9614	0.0107	<0.0001
PLE – Full	Diabetes	1.6419	0.0077	<0.0001
PLE – Matched	Diabetes	1.6191	0.0093	<0.0001
PLE – Full	Diabetes type * age group	1.6343	0.0077	<0.0001
PLE – Matched	Diabetes type * age group	1.6243	0.0093	<0.0001
Kidney diseases – Full	Diabetes	1.9897	0.0070	<0.0001
Kidney diseases – Matched	Diabetes	1.9547	0.0089	<0.0001
Kidney diseases – Full	Diabetes type * age group	1.9607	0.0069	<0.0001
Kidney diseases – Matched	Diabetes type * age group	1.9310	0.0089	<0.0001
Coronary atherosclerosis – Full	Diabetes	1.7269	0.0049	<0.0001
Coronary atherosclerosis -- Matched	Diabetes	1.7885	0.0060	<0.0001
Coronary atherosclerosis – Full	Diabetes type * age group	1.7384	0.0049	<0.0001
Coronary atherosclerosis -- Matched	Diabetes type * age group	1.7917	0.0060	<0.0001

Chapter 6: Discussion

This study was a cross-sectional study with secondary data analysis of the 2010 to 2012 National Inpatient Sample. The primary objective of this study was to examine the association between the presence and severity of diabetes-related complications and diabetes-related hospitalization costs and health care utilization. The secondary objective of this study was to explore how the presence and type of diabetes influenced complications-related hospitalization costs and health care utilization. The two objectives were examined in four study cohorts: diabetes-related hospitalization cohort, peripheral lower extremity (PLE) diseases-related hospitalization cohort, kidney diseases-related hospitalization cohort, and coronary atherosclerosis-related hospitalization cohort. For each study cohort, a stratified matched cohort, based on distribution of age, sex, and race, was drawn from the data set. The analysis results were presented for both the full cohort and the matched cohort.

This chapter summarizes and discusses the study findings: the study results for each cohort are summarized and the findings from this study are discussed in the context of previous studies; the clinical and policy implications of the study results are presented; the strengths of this study and some additional limitations of this study are identified; and finally, several recommendations are provided for future research.

6.1 Summary of Study Results

6.1.1 Summary of study results on diabetes-related hospitalization

The final diabetes-related hospitalization cohort contained 804,192 discharge records: 213,560 with peripheral lower extremity diseases as comorbidity, 173,564 with

comorbid kidney diseases; 196,296 with coronary atherosclerosis as comorbidity; 406,762 without any of these three complications. The mean cost of diabetes-related hospitalization was $10,357 (SD: $13,696). Among patients with diabetes-related hospitalization, 67.9% had routine discharges, that is, discharge to home for additional care.

The analysis findings on the incremental impact of PLE and diabetes-related hospitalization cost suggest that severe PLE and less severe PLE increased diabetes-related hospitalization cost by 66.6% and 1.35% respectively. The adjusted mean diabetes-related hospitalization cost was $17,212, $10,432, and $10,363 for patients with severe PLE, less severe PLE, and without PLE respectively.

Comorbid kidney diseases were not found to be associated with an apparent increase in diabetes-related hospitalization cost. In the analysis based on the matched cohort, severe and less severe kidney diseases were associated with insignificant decreases in diabetes-related hospitalization cost ($p>0.0001$). The adjusted mean hospitalization cost was $12,523, $12,252 and $12,549 for hospitalized diabetes patients with severe kidney diseases, patients with less severe kidney diseases and patients without kidney diseases respectively.

Coronary atherosclerosis had a small incremental effect on diabetes-related hospitalization cost. The cost for hospitalized diabetes patients with severe coronary atherosclerosis was found to be 1.12 times the cost for hospitalized diabetes patients without coronary atherosclerosis. Hospitalization cost for patients with severe coronary atherosclerosis was $12,822; the cost for patients with less severe coronary

atherosclerosis was $11,264; and the cost for patients without coronary atherosclerosis was $11,434.

The three diabetes complications examined in this study influence diabetes-related hospitalization discharge status in different ways. The presence of severe PLE was associated with a 49.4% increase in the odds of having non-routine discharges compared to patients without PLE; the presence of less severe PLE was associated with a 22.1% increase in the odds of having non-routine discharges compared to patients without PLE. The presence of severe or less severe kidney diseases was not significantly associated with diabetes-related hospitalization discharge status (p=0.2400 and p=0.1062 respectively). Less severe coronary atherosclerosis was associated with a 3.5% increase in the odds of having non-routine discharges; while severe coronary atherosclerosis was associated with a 32.4% decrease in the odds of having non-routine discharges.

6.1.2 Summary of study results on peripheral lower extremity diseases-related hospitalization

The final peripheral lower extremity (PLE) diseases-related hospitalization cohort contained 219,752 discharge records. The prevalence of diabetes among patients with PLE-related hospitalization is higher than the prevalence of PLE among patients with diabetes-related hospitalization: 44.76% of the hospitalized PLE patients have diabetes as comorbidity; 26% of the patients with diabetes-related hospitalization have PLE (results 6.1.1). The mean PLE-related hospitalization cost was $15,004 (SD: $16,415). Among patients with PLE-related hospitalization, 57.0% were discharged to home; while 43.0% had non-routine discharges.

The presence of type 1 diabetes was associated with a 12% decrease in PLE-related hospitalization cost, while the presence of type 2 diabetes was associated with a 3.85% decrease in PLE-related hospitalization cost. The adjusted mean PLE-related hospitalization cost for patients without diabetes was $15,749. The mean PLE-related hospitalization cost for patients with type 2 diabetes was $15,142. The mean PLE-related hospitalization cost for patients with type 1 diabetes was $13,856. The association between diabetes and PLE-related hospitalization cost was modified by age. PLE-related hospitalization cost was highest among patients age below 65 years and without diabetes ($17,075). PLE-related hospitalization cost was comparable between patients less than 65 years of age with type 1 diabetes ($14,611), or with type 2 diabetes ($15,698), or patients aged 65 years or older with type 1 diabetes ($15,276), or with type 2 diabetes ($14,918), or without diabetes ($14,969).

Although the presence of diabetes did not have an overall significant effect on PLE-related hospitalization cost, diabetes was found to be associated with PLE-related hospitalization discharge status. PLE patients with diabetes were 1.37 times more likely to have a non-routine discharge compared to PLE patients without diabetes. The presence of type 2 diabetes was associated with greater odds (a 26.2% increase) of having non-routine discharges though the p-value was above 0.001.

6.1.3 Summary of study results on kidney diseases-related hospitalization

The final cohort of kidney diseases-related hospitalization contained 504,320 discharge records. The prevalence of diabetes among patients with kidney diseases-related hospitalization was also higher than the prevalence of kidney diseases among patients with diabetes-related hospitalization: 55.9% of the patients with kidney diseases-

related hospitalizations have diabetes comorbidity; 21.6% of the hospitalized diabetes patients have kidney diseases comorbidity. The mean kidney diseases-related hospitalization cost was $13,360 (SD: $17,859). 59.1% of the patients with kidney diseases-related hospitalization had routine discharges.

Type 1 diabetes was associated with a 5.7% increase in kidney diseases-related hospitalization cost, while type 2 diabetes was associated with a 2.5% decrease in kidney diseases-related hospitalization cost. The adjusted mean hospitalization cost for hospitalized kidney diseases patients with type 1 diabetes was $14,735. Kidney diseases patients with comorbid type 2 diabetes had adjusted mean hospitalization cost of $13,602. The hospitalization cost for kidney diseases patients without diabetes was $13,945.

The association between diabetes and kidney diseases-related hospitalization cost was also modified by age. The incremental cost of type 1 diabetes to kidney diseases-related hospitalization was $922 for patient below 65 years and $1,320 for patient age 65 years or older. Among patients below 65 years, the kidney diseases hospitalization cost for patients with type 2 diabetes was $785 lower than that for patients without diabetes. However, among patients age 65 years or older, the cost for patients with type 2 diabetes was only $84 lower than the patients without diabetes.

The presence of diabetes was found to influence kidney diseases-related hospitalization discharge status. The presence of type 1 diabetes was associated with a 33.2% increase in the odds of having non-routine discharges; while the presence of type 2 diabetes was associated with a 20.2% increase in the odds of having non-routine discharges. Comorbid PLE also increased the likelihood of having non-routine

discharges, while comorbid coronary atherosclerosis decreased the likelihood of having non-routine discharges.

6.1.4 Summary of study results on coronary atherosclerosis-related hospitalization

The coronary atherosclerosis-related hospitalization cohort contained 546,488 discharge records. Of all the hospitalized coronary atherosclerosis patients, 37.2% have diabetes as comorbidity. The mean coronary atherosclerosis-related hospitalization cost was $16,718 (SD: $16,962). Among hospitalized coronary atherosclerosis patients, 76.25% have routine discharges while 23.75% have non-routine discharges.

Diabetes was not found to add significantly to coronary atherosclerosis-related hospitalization cost. Type 2 diabetes was associated with a 2.1% decrease in coronary atherosclerosis-related hospitalization cost; type 1 diabetes was associated with a non-significant 1.5% decrease in coronary atherosclerosis-related hospitalization cost (p=0.3149). The adjusted mean coronary atherosclerosis-related hospitalization cost was $16,190 for patients without diabetes; $15,955 for patients with type 1 diabetes; and $15,859 for patients with type 2 diabetes. The association between diabetes and coronary-atherosclerosis related hospitalization cost was also modified by age. The incremental cost of type 1 diabetes was $1,796 among hospitalized coronary atherosclerosis patients age 65 years or older, while the cost for patients with type 1 diabetes comorbidity was $550 lower than patients without diabetes among those age below 65 years.

The type of diabetes (either type 1 or type 2) had a differential effect on coronary atherosclerosis-related hospitalization discharge status. Type 1 diabetes was associated with a 35.4% increase in the odds of having non-routine discharges, while type 2 diabetes

did not have any significant effect on coronary atherosclerosis-related hospitalization discharge status.

Taken together the findings of this study highlight the importance of peripheral lower extremity diseases as a key driver of diabetes-related hospitalization cost at the per episode level. Severe PLE adds $6,849 to a single diabetes-related hospitalization, which represents a 66% increase in diabetes related hospitalization cost.

The effect of kidney diseases and coronary atherosclerosis to diabetes-related hospitalization cost is not as apparent as that of PLE. Kidney diseases did not add significantly to diabetes-related hospitalization cost. Severe coronary atherosclerosis, however, is associated with a $1,388 incremental cost to diabetes-related hospitalization cost.

Overall diabetes is not consistently shown as a significant contributor to complications-related hospitalization cost. However, the interactions between diabetes type and age on complications-related hospitalization cost are noteworthy, which may indicate that specific subgroups are associated with increased health care cost and should receive attention. Furthermore, both type 1 and type 2 diabetes are associated with increased likelihood of having non-routine discharges after hospitalization, which may imply that diabetes could be associated with subsequent health care utilization for complications-related hospitalization.

Table 61: Comorbidities and hospitalization cost

Comorbidities	Diabetes-related hospitalization	PLE-related hospitalization	Kidney diseases-related hospitalization	Coronary atherosclerosis-related hospitalization
Type 1 diabetes	$12,043	$13,856	$14,735	$15,955
Type 2 diabetes	$12,562	$15,142	$13,602	$15,859
Without diabetes		$15,749	$13,945	$16,190
Severe PLE	$17,212	$21,014	$19,893	$18,411
Less Severe PLE	$10,432	$10,557	$11,923	$14,847
Without PLE	$10,363		$11,784	$14,987
Severe kidney disease	$12,523	$14,469	$14,263	$15,034
Less severe kidney diseases	$12,252	$15,168	$13,568	$16,175
Without kidney diseases	$12,549	$15,056		$16,846
Severe coronary atherosclerosis	$12,822	$15,406	$14,692	$21,321
Less severe coronary atherosclerosis	$11,264	$14,934	$13,745	$12,008
Without coronary atherosclerosis	$11,434	$14,362	$13,840	

6.2 Synthesis of findings with the literature

With regard to the descriptive statistics of comorbidities in each diseases cohort, the findings of this study are overall in line with existing studies and common knowledge. Comorbid diabetes is more prevalent among complications-related

hospitalization compared to the prevalence of complications among diabetes-related hospitalization. On the one hand, among patients with diabetes-related hospitalizations, 26.6% had PLE, 21.6% had kidney diseases and 24.3% had coronary atherosclerosis. On the other hand, comorbid diabetes was present in 44.8% of the PLE-related hospitalizations, 55.9% of the kidney diseases-related hospitalizations and 37.1% of the coronary atherosclerosis-related hospitalizations. These demographic findings reaffirm the fact that these three complications are important sequelae of diabetes.

Certain racial/ethnic characteristics in the study cohorts are consistent with the existing literature. Approximately half of the patients with kidney diseases-related hospitalization were from racial/ethnic minority groups like Black, Hispanic, Asian, Native American and so on. Around 33% of the kidney diseases-related hospitalization patients were Black. As mentioned previously, racial/ethnic minority groups carried an increased likelihood of developing kidney diseases, which was also demonstrated by the descriptive characteristics of this study sample. For patients with coronary atherosclerosis-related hospitalization, the majority was male (>60%) and White (>70%). This was also in line with the literature mentioned in the method section.

The diabetes-related hospitalization cost was slightly higher for males than females. Though the effect of sex had a significant p-value (<0.0001) because of the sample size, the adjusted mean hospitalization cost for males and females only had a small difference (~$100-$200) and the 95% confidence intervals overlap. This was consistent with the findings from Pennsylvania hospital inpatient database (Ma et al., 2014). In the PLE-related hospitalization cohort, the effect of sex on hospitalization cost was insignificant. The *Reduction of Atherothrombosis for Continued Health* (REACH)

registry also found that peripheral artery diseases-related hospitalization did not differ by gender (Mahoney et al., 2010). However, a study using NIS on diabetic foot ulcers found that the adjusted mean hospitalization charge was higher for males than females (Hicks et al., 2014). This discrepancy could be due to the difference in inclusion criteria in the Hicks study and this study. In the kidney diseases-related hospitalization cohort, cost for males was significantly higher for males than females by the p-value, but the confidence intervals of the adjusted mean hospitalization cost still overlap. However, the effect of sex on hospitalization cost was more apparent in the coronary atherosclerosis-related hospitalization cohort. The cost for males was 8% higher than the cost for females. The adjusted mean cost for males was $1,225 higher than the adjusted mean cost for females. This result is not surprising given the fact that coronary atherosclerosis is more prevalent in males.

Although increase in age was associated with higher diabetes-related hospitalization cost in the full study cohort, the age effect was diminished in the matched cohort when age was used as one of the stratum variables. The Ma et al. paper found a curvilinear relationship between age groups and hospitalization charge (Ma et al., 2014). Therefore it is reasonable not to draw the simple conclusion that aging increases diabetes-related hospitalization cost. In the PLE-related hospitalization cohort, the hospitalization cost was overall higher for younger patients (<65) than older patients (≥65). Similar results were also obtained in the Hicks et al. paper, which also showed that hospital inpatient care cost for patients with diabetic foot ulcers was highest for patients age 18-64 (Hicks et al., 2014). Though it is true that lower extremity diseases is more prevalent among older patients than younger patients, good diseases management among the

younger patients with lower extremity diseases should not be neglected because the younger patients could be potentially associated with higher inpatient care cost. In the kidney diseases-related hospitalization cohort, significantly higher hospitalization cost was also observed in the younger patients (<65) compared to the older patients (≥65). This result also indicates that younger patients with kidney disease should be monitored closely and should get optimal primary care to minimize the need for hospital inpatient care. Age did not demonstrate a consistent effect in the coronary atherosclerosis-related hospitalization cohort: in the model without interaction, older age is associated with a small decrease (0.24%) in hospitalization cost; however, in the interaction model (interaction between age and diabetes type), hospitalization cost is 1.03 times for older patients (≥65) than younger patients (<65).

This study is consistent with several previous studies on the importance of PLE as a driver of diabetes-related health care cost. A recent study using hospital discharge data from Pennsylvania found that peripheral circulatory disorders is associated with 38% increase in diabetes-related hospitalization charge ($p<0.0001$) and neurological manifestations of diabetes is associated with a 30% increase in diabetes-related hospitalization charge ($p<0.0001$) (Ma et al., 2014). In this dissertation study, peripheral vascular disorders and neuropathy are examined together as peripheral lower extremity diseases, which may explain some of the discrepancies in the percentage increase. Nonetheless, it is still reasonable to argue that the two results are comparable to a large extent. Another study focusing on a particular form of severe PLE – diabetic foot ulcers (DFU) – show that the increased annual health care cost of DFU is $11,710 for patients paid by Medicare and $16,883 for patients paid by private insurance respectively (Rice et

al., 2014). The cost estimate is higher than what this study finds, which is likely due to the fact that DFU cost is studied in a one year time frame instead of at episode level.

Although the studies citied highlighted PLE as a driver of diabetes-related health care cost, the importance of peripheral lower-extremity diseases was still largely neglected in the previous studies. In this extent, the study results are meaningful in that severe PLE was shown as a key cost driver to a diabetes-related hospital inpatient episode of care.

Unlike some previous studies, this study did not find a significant effect of kidney diseases comorbidity on diabetes-related hospitalization cost. A retrospective Germany study estimated that the costs related to nephropathy in diabetic patients were €1,332 (from the health insurance perspective) and €2,019 from the societal perspective on average in the year 2002 (Happich et al., 2008). Another study that compared the cost of managing diabetic nephropathy in the U.S. and the U.K. pointed out that the total cost per person with diabetic nephropathy is $3,735 per year in the U.S. and $2,672 per year in the U.S (Gordois et al., 2004). A U.S. claims data study found that the average total cost for patients with microvascular complications were $14,414 over 12 months; while that for patients without microvascular complications were $8,669 ($p<0.001$) (Pelletier et al., 2009). These studies studied the total costs attributed to nephropathy in a one year time frame; however, this dissertation study explored the incremental cost of kidney diseases at a single hospitalization episode of care level. This may explain some of the discrepancies with the previous studies. Furthermore, a major driver of kidney diseases-related health care cost – the cost of chronic dialysis – is billed in a separate payment system instead of being billed through the Inpatient Prospective Payment System (IPPS)

or Outpatient Prospective Payment System (OPPS). Therefore the cost for dialysis is not captured in the hospital inpatient charge and that may explain the discrepancy from previous studies. A European study found that the presence of microvascular complications increased hospitalization cost by 100% (Williams et al., 2002). However, in that particular study, nephropathy, neuropathy, and retinopathy are combined into a broad category as microvascular complications. It is not known from that study about the individual impact of kidney diseases. In addition, it is also unknown whether the dialysis cost is included in hospitalization cost or not in the Europe.

This study found only a small incremental impact of severe coronary atherosclerosis on diabetes-related hospitalization cost; however, most previous studies generally show cardiovascular diseases as a major component of diabetes expenditures. For instance, a study found that the annual health care expenses for diabetes patients with macrovascular complications are $5,119 higher than that for diabetes patients without macrovascular complications (Fu et al., 2009). Another study with 2000 data showed 52% of the total cost of diabetes complications was attributed to macrovascular complications (Caro et al., 2002). The presence of macrovascular complications increased hospitalization cost by 200% based on a Europe study (Williams et al., 2012). Several possible reasons may explain the discrepancy: First, the majority of previous studies were investigating total medical cost in a certain time frame and aggregating different component of total medical cost (outpatient visits, pharmacy cost, etc.); Second, although the European study was from episode of care perspective, cardiovascular complications and peripheral vascular complications were studied together as

macrovascular complications and diseases severity was not take into account in that study.

When studying complications-related hospitalization, comorbid diabetes does not always show a significant effect. In addition, the interaction between diabetes type and age could not be neglected when examining complications-related hospitalization cost. There are some interesting comparisons between this study results and previous study results. The total ulcer-related cost was found to be significantly higher for diabetes patients < 65 years compared to older diabetes patients ($16,390 vs. $11,925, p=0.02) in a study among diabetes patients with lower extremity ulcer episode using claims data (Stockl et al., 2004). This study also finds that the adjusted mean PLE-related hospitalization cost was higher for type 2 diabetes < 65 years ($15,698) than type 2 diabetes ≥ 65 years ($14,216). However, in this study, the PLE-related hospitalization cost was slightly higher for older type 1 diabetes patients ($15,276) than younger type 1 diabetes patients ($14,611). This is an important finding with the implication that diabetes type and age has to been taken into account for optimal disease management of patients with peripheral lower-extremity diseases.

With regard to coronary atherosclerosis-related hospitalization, an early study found that the average cost for patients with cardiovascular diseases and type 2 diabetes was $10,172; while that for patients with cardiovascular diseases only was $6,396 (Nichols et al., 2002). This dissertation study differs from previous studies in that type 1 diabetes is found to have a more apparent significant incremental cost to coronary atherosclerosis-related hospitalization among patients ≥ 65 years old; while the type 2

diabetes did not have a significant incremental cost for coronary atherosclerosis-related hospitalization cost in both the younger and the older patients.

In terms of kidney diseases-related hospitalization, hospitalization cost was highest for younger patients with type 1 diabetes. A previous study has shown that the onset of nephropathy among patients with type 1 diabetes is usually late compared to that among patients with type 2 diabetes. However, the potential longer duration of type 1 diabetes may be associated with elevated clinical and economic burden. Study by Dall et al. found that hospital inpatient care utilization ratio was much higher for type 1 diabetes patients with renal complications than type 2 diabetes patients with renal complications (Dall et al., 2010). However, the possible differential effect of type 1 and type 2 diabetes on complications-related health care utilization was largely neglected in the previous study. The findings from the Dall study and this study need to be confirmed by more ongoing studies. If this differential effect was confirmed, future policy making should address the diabetes type clearly and has corresponding strategy for each diabetes type.

Despite that the incremental cost of diabetes to complications-related hospitalization cost was not as apparent as the incremental cost of PLE to diabetes-related hospitalization cost, the overall inpatient burden of these three complications are still huge. For example, the mean and median cost for diabetes-related hospitalization (mean: $10,342; median: $6,847) was much lower than that for PLE-related hospitalization (mean: $15,004; median: $10,314), kidney diseases-related hospitalization (mean: $13,360; median: $8,313) and coronary atherosclerosis-related hospitalization (mean: $16,718, median: $12,232).

A unique finding of this study is that the factors that are associated with discharge status post diabetes-related hospitalization or complications-related hospitalization were examined in multivariate logistic regression model. Logistic regression model diagnostics show good overall model fit. Overall, PLE comorbidity is associated with more non-routine discharges for diabetes-related hospitalization; kidney diseases is not significantly associated with diabetes-related hospitalization discharge status; while coronary atherosclerosis's impact on diabetes-related hospitalization discharge status differs by severity – patients with less severe coronary atherosclerosis had increased likelihood of non-routine discharges while patients with severe coronary atherosclerosis had decreased likelihood of non-routine discharges. This result highlights the crucial role of PLE in driving subsequent health care cost and utilization after diabetes-related hospitalization discharge. Furthermore, the presence of either type 1 or type 2 diabetes is associated with more non-routine discharges for the three complications-related hospitalizations. This is also an important finding: although diabetes may not always impose a significant incremental cost to complications-related hospitalization, it could be associated with subsequent health care utilization after discharge.

6.3 Clinical and Policy Implications of the Study

This study explored the interplay between diabetes and its complications at the hospital inpatient level by analyzing the effect of complications on diabetes-related health care utilization and the effect of diabetes on complications-related health care utilization using the same hospital discharge data. The study results substantiate that the long-recognized complications of diabetes as a key driver of diabetes-related hospitalization cost. For example, comorbid severe PLE added around $7,000 to a diabetes-related

hospitalization. Based on CDC report, 688,000 hospital discharges with diabetes as first diagnosis were reported in 2009; 5.5 million hospital discharges with diabetes as any-listed diagnosis were reported in 2009. Taken together these figures, the total annual hospital inpatient cost attributed severe PLE could be enormous, even if just 10% of these hospitalized diabetes patients have such comorbidity. Furthermore, the complications are also associated with hospitalization discharge status, which will contribute to long-term health care utilization after discharge.

Therefore this study corroborates the importance of secondary prevention of complications among diabetes patients. Diabetes patients should be monitored more closely. Patients with diabetes should be expected to get HbA1c test, foot exams, eye exams, and cholesterol screenings on a regular basis. Special attention should be given to diabetes patients with other established risk factors for long-term complications, such as aging, smoking, obesity, low adherence rate, hypertension and dyslipidemia.

The findings of this study are in keeping with the recommendations from the American Diabetes Association's "Standards of Medical Care in Diabetes" (ADA, 2011). This clinical guideline provides detailed information regarding the diagnosis and care for diabetes. It has a section focused on management of diabetes complications, including cardiovascular diseases, nephropathy screening and treatment, retinopathy screening and treatment, neuropathy screening and treatment, and foot care. Specific strategies to achieve appropriate control of risk factors of developing complications among diabetes patients are included in this guideline. Clinical guidelines like this should be part of a curriculum taught to health care students (physicians, nurses, pharmacists) and should also be integrated into current clinical practice in measurable ways.

Furthermore, the findings related to severe peripheral lower extremity diseases support the message conveyed in the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for the management of patients with peripheral arterial disease (Hirsch et al., 2006). In this guideline, diabetes was regarded as one of the strongest risk factors for developing peripheral lower-extremity diseases. Recommended management of peripheral lower extremity disease include routine screening of peripheral artery diseases using ankle-brachial index (ABI) and monitoring patient's progression once early symptom was detected. Routine screening and close monitoring could potentially slow the progression of peripheral lower-extremity diseases to the severe form, which was found to be a cost driver to diabetes-related hospital inpatient care in this study.

There are clearly promising clinical and policy initiatives being implemented to incorporate measures of optimal care for diabetes. For example, in the state of Minnesota, clinical experience with a five component; all-or-nothing Optimal Diabetes Care (ODC) measure has been reported by clinic for eleven years. In that period of time, the statewide ODC rate has increased from 6% to 46% (http://www.mnhealthscores.org/diabetes-13184). Some clinics are achieving ODC rate > 70%. The five specific goals to reach include: blood pressure < 140/90mmHg; HbA1c < 8%; taking a statin as needed to manage cholesterol; being tobacco-free; taking an aspirin daily. These measures are all related to controlling HbA1C, blood pressure, and cholesterol, all of which contribute to the complications studied in this study. The ODC measure, however, does not include any component specifically related to screening and monitoring for lower-extremity diseases. It does include an emphasis on tobacco, which has been linked to lower-

extremity diseases. However, based on these findings, the potential to include a component such as screening of peripheral artery diseases using ABI should be considered.

The interactions between diabetes, peripheral lower extremity diseases, kidney diseases and coronary atherosclerosis are intricate and complicated. On the one hand, diabetes leads to the development of these long-term complications. On the other hand, cardiovascular complications of diabetes increase the risk of peripheral vascular disorders tremendously and verse versa; a recent study show that peripheral artery diseases influence prognosis to diabetic nephropathy. Early prevention and detection could potentially help reduce the incidence and prevalence of several of these long-term complications instead of just one of them. If early symptoms of long-term complications are observed, intervention should be adopted as early as possible to delay the progression of complications to a more severe form.

From the health care policy perspective, optimal diabetes disease management programs should be adopted nationwide. Previous studies have shown that implementation of diabetes diseases management program at health plan level is associated with decreased hospitalization rate and decreased per member per month cost (Rubin et al., 1998). These programs have also been found to lead to substantial improvements in costs and clinical outcomes in the short-term. The long-term effectiveness of disease management programs should be evaluated in future studies and be incorporated in policy making.

In additional to the overall population health, optimal diabetes care is also meaningful for the health plans performance. Several measures related to diabetes care are incorporated in the CMS star rating programs. These measures include: Diabetes Care – Eye exam; Diabetes Care – Kidney Disease Monitoring; Diabetes Care – Blood Sugar Controlled; Medication Adherence for Diabetes Medications. Like the ODC measure, there is no measure specific to screening of peripheral artery diseases. The CMS star ratings evaluate the quality of a Medicare plan on a scale of 1 to 5 stars from lowest to highest. Diabetes care is crucial to the payers. In addition, value based purchasing, accountable care organization, and alternative payment models are currently being developed and executed to tie payments to quality metrics and the cost of care. In this aspect, diabetes care and its outcomes is also relevant to the providers.

The findings from this study are also significant to both pharmacist professionals and the pharmacy profession. In-depth knowledge of diabetes and its complications will help pharmacists provide medication therapy management to diabetes patients. Furthermore, pharmacist also plays an indispensable role in the quality improvement of the overall health care system. Good management of diabetes largely depends on medication adherence to drug therapy in addition to behavioral risk factor modification. For these reasons, the clinical guidelines on management of diabetes and its complications should be integrated into the curriculum taught to pharmacist students. This will enable pharmacists to be aware of monitoring diabetes and complications progression when providing pharmaceutical care to patients. As stated previously, adherence to diabetes medications is one of the measures in the CMS star rating programs. Adherence to hypertension medications and adherence to statin are also CMS

star rating measures. Pharmacist can ensure that patients are provided counseling to better understand the importance of taking their prescribed drugs regularly and to have their diabetes under appropriate control, which has been found clinically to slow the progression of complications.

Therefore optimal diabetes care is significant for all the players of the health care system: the patients, the payers, and the providers. The findings of this study, along with the previous studies, could be used to execute strategies to improve and optimize diabetes care and to benefit the overall population health.

6.4 Strengths of the Study

This study has several strengths compared to existing studies. First, this study was based on a large and national representative hospital discharge sample. The total sample sizes in each study cohort ranged from 220,000 to 804,200. Furthermore, this is a national sample which represented more than 95% of the U.S. population. The sample sizes from previous studies were usually at a thousand or ten thousand level and the samples were based on a particular region or several hospitals. Therefore the study results could have better reliability in making inferences and better generalizability across the country.

Second, this study examined hospital inpatient care for diabetes and complications in two ways: the effect of complications on diabetes-related hospital inpatient cost and care utilization and the effect of diabetes on complications-related hospital inpatient cost and health care utilization. No previous study has conducted research like this. In examining the effect of complications-related health care utilization,

this study has novel findings on the potential differential effect of type 1 and type 2 diabetes on complications-related hospitalization cost and discharge status.

Third, this study includes hospitalization discharge status as secondary outcome and explored factors that are associated with hospitalization discharge status. Very few studies have looked at hospitalization discharge status in the past; however, hospitalization discharge status could be an indicator for subsequent health care utilization. In addition, discharge to nursing home or long-term care has been found to be associated with worse outcomes like increased re-hospitalization rates during follow-up. Therefore this study addressed a current gap in knowledge with regard to diabetes- and complications-related hospitalization discharge status.

Fourth, this study employs rigorous statistical methods in assessing diabetes- and complications-related hospital inpatient cost and health care utilization. The use of generalized linear model with gamma distribution and log link function has been established as a superior way to evaluate health care cost compared to simple linear regression with log transformed cost. What's more, this study also provided the effect estimates from a stratified matched sample in addition to the full sample. This could potentially help balance some of the unmeasured confounding factors and render the effect estimates to be more reliable.

6.5 Limitations of the Study

There are a number of limitations of the study that should be highlighted:

(1) This study sample consisted only of diabetes patients, peripheral lower extremity disease patients, kidney disease patients, and coronary atherosclerosis patients

who had been hospitalized during 2010 to 2012. Therefore the generalizability of this study is limited to only hospitalized patients. However, since hospital inpatient care is a major driver for medical costs attributed to diabetes, in-depth understanding of hospital inpatient cost and the incremental cost of complications improves our current knowledge on the economic burden of diabetes.

(2) Though the statistical inferences from this study have the advantage of being drawn based on large sample (n=220,000 to 804,200), the downside is that a very small difference can be significant for studies from large samples. This study used an adjusted p-value less than 0.0001. Even with this adjustment, some small differences were still statistically significant. In these circumstances, looking at the confidence interval of the effect estimate is recommended rather than looking at the effect estimate and p-value alone. Therefore, this study presents the confidence intervals of the adjusted mean cost and the odds ratio to supplement the significance testing.

(3) The study sample was restricted to hospitalizations for adult patients with diabetes (age $\geq$ 18 years) and female patients without gestational diabetes. Therefore the study results are not generalizable to hospitalizations among children or female patients with gestational diabetes. Patients with a principal or secondary diagnosis of cancer were also excluded from the final sample; therefore the study results may not be generalized to diabetes patients with cancer.

(4) It is widely known that health care cost varies by geographic locations in the U.S. Geographic differences are multifactorial and information to measure many of them are not available in the NIS dataset. The effect of geographic location was not completely accounted for in this study. This study proposed to use a generalized linear

mixed effects model to include a random intercept for geographic location; however, the generalized linear model did not converge due to the large sample size and the amount of variables in the study sample. Therefore, the accuracy of the incremental cost estimates from this study may be influenced by the unexplained geographic variation.

(5) This study used cost-to-charge ratio to calculate the hospitalization cost estimate. In the U.S., the hospital charge for care is different from the payment that a hospital receives from the payer (Medicare, Medicaid, private insurance, etc.), which is also different from the actual cost of the hospitalization. Furthermore, the use of cost-to-charge ratio provides an estimate of hospitalization cost, but the cost estimate may not necessarily represent the opportunity cost, which is the real cost in the economic sense. Despite this limitation, cost-to-charge ratio is considered the current industry standard and has been widely used to calculate the medical cost for policy evaluation and policy generation.

(6) As previously mentioned, this study relies on diagnosis codes and procedure codes for sample selection, cohort construction, and identification of complication. Coding errors may influence the reliability and validity of the study results. But it is important to keep in mind that the codes in the study records are discharge codes, which are different from admission codes. Some researchers suggest that admission codes carry greater concerns than discharge codes; therefore the codes included in this study could still be considered reliable to a large extent.

(7) Counter-intuitively, this study did not find a significant incremental cost of kidney diseases to diabetes-related hospitalization cost. In part, this may be due to hospital billing processes. Dialysis for patients with end-stage renal diseases is billed

within a separate payment system instead of the inpatient prospective payment system (IPPS) or outpatient prospective payment system (OPPS). However, it is important to note that the findings related to kidney diseases (i.e., no incremental cost difference attributable to kidney diseases) apply to the routine hospital costs reported in this hospital claims database.

(8) In examining disposition of patients after hospitalization, this study used a dichotomous variable for hospitalization discharge status as routine discharge (discharge to home without additional care) and non-routine discharge (discharge to home health care, a short-term hospital, skilled nursing facility, death, unknown destination, and against medical advice). There is not, however, a widely adopted recommendation for the classification of discharge status. A particular concern is "discharged to home health care," which while not facility-based may in fact involve care by health professionals in the home and represents an intermediate care step. Other classifications, for example, a trichotomous discharge status variable that recognizes the uniqueness of home health care may yield other findings.

(9) The classification of complications severity is based on diagnosis and procedure codes on a single hospitalization discharge record. There is no access to medical records to obtain a full diagnosis/diseases history of complications. For instance, if a patient had coronary artery bypass graft a year ago, he should be classified as having severe form of coronary atherosclerosis. However, there is no way to trace the patients' diseases history in this study. Therefore misclassification of complication severity may be present in the study and may influence some study findings.

(10) This study excluded high cost hospitalizations (cost > $1 million), but included all low cost hospitalizations in the statistical analysis. While these low cost hospitalizations could have an effect on the calculation of the mean, in reality, that effect is small. The percentage of patients with cost <$500 and cost <$1,000 was minimal: around 0.1% of the total patients had cost <$500 and 0.5% of the patients had cost <$1,000, leading to the conclusion that low cost hospitalizations most likely had no influence on the analysis findings.

(11) Though this study is a national representative sample, some hospitals (Veterans Administration hospital and Indian Health Service hospital) are excluded from the national inpatient sample. Therefore the study results may not be generalized to patients who received inpatient care from these hospitals.

(12) Although this study used a national representative sample, it is data based on the period of time from 2010 to 2012. Health care policy changes, advances in diabetes care, kidney diseases care, peripheral lower-extremity diseases care, along with new medication introductions after 2012 may influence the current clinical management of these diseases and potentially reduce the generalizability of the study findings. However, these aspects could not be reflected from this study.

6.6 Recommendations for Future Research

The findings from this study highlight the complex interactions between diabetes and its complications on hospital inpatient cost and health care utilization. On the one hand, diabetes complications, particularly peripheral lower extremity diseases, are associated with significantly higher hospitalization cost and subsequent health care

utilization at discharge. On the other hand, both type 1 and type 2 diabetes have been found to be associated with increased likelihood of non-routine discharges for the complications-related hospitalization. Differential effect of diabetes type by age on complications-related hospitalization cost has been observed for each of the three complications-related hospitalizations. These findings point out that good diabetes disease management programs need to incorporate secondary complication prevention and patients hospitalization history into care management planning. Early monitoring and detection could potentially reduce the incidence and prevalence of diabetes complications and reduce the long-term health care cost and utilization related to complications. There are several additional questions that could be addressed by future research:

First, there is a need for future studies focused on the younger population with diabetes. A growing number of younger persons are being diagnosed with diabetes, especially among racial/ethnic minority groups. These younger patients are likely to carry diabetes for a longer period of their lifetime and the risk of developing long-term diabetes increases considerably with the number of years that a patient has been living with diabetes. More studies are needed to examine the factors that are associated with health care cost and utilization among younger diabetes patients and to develop and improve good disease management programs for younger diabetes patients.

Second, contrary to previous studies, this study did not find a significant incremental cost of kidney diseases on diabetes-related hospitalization. This may be due to inpatient hospital billing procedures that do not capture inpatient hospital dialysis cost. Dialysis cost is billed through a separate billing system. A research study that includes this information is recommended to better understand the incremental cost of kidney

diseases to diabetes-related hospitalization cost. Therefore, even though this study did not find higher hospitalization cost associated with kidney diseases, the long-term economic burden of kidney diseases should not be neglected.

Third, this study is the first to address discharge status after diabetes or complications-related hospitalization. Further research should focus on the measurement of discharge status. As noted in the limitations, discharge status was included in analysis as a dichotomous variable. Other classification schemes should be considered in future studies.

Fourth, this study highlights the incremental cost of peripheral lower extremity diseases and coronary atherosclerosis to diabetes-related hospitalization. Future studies could illuminate the conditions that contribute most to the incremental cost difference. For instance, the procedure codes could be used to identify the common procedures that are cost drivers for peripheral lower extremity comorbidities.

Finally, the observation period for this study was 2010 to 2012. However, the health care arena is a dynamic one with health care policy changes, disease management changes, and innovations in pharmaceuticals that can have a dramatic effect on health care cost. This study should be updated on a periodic basis to ensure timeliness of the findings.

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Appendices

Appendix 1: Data Use Agreement for the Nationwide Databases from the Healthcare

Cost and Utilization Project Agency for Healthcare Research and Quality

This Data Use Agreement ("Agreement") governs the disclosure and use of data in the HCUP Nationwide Databases from the Healthcare Cost and Utilization Project (HCUP) which are maintained by the Center for Delivery, Organization, and Markets (CDOM) within the Agency for Healthcare Research and Quality (AHRQ). The HCUP Nationwide databases include the National (Nationwide) Inpatient Sample (NIS), Kids' Inpatient Database (KID), Nationwide Emergency Department Sample (NEDS), and Nationwide Readmissions Database (NRD). Any person ("the data recipient") seeking permission from AHRQ to access HCUP Nationwide Databases must sign and submit this Agreement to AHRQ or its agent, and complete the online Data Use Agreement Training Course at http://www.hcup-us.ahrq.gov, as a precondition to the granting of such permission.

Section 944(c) of the Public Health Service Act (42 U.S.C. 299c-3(c)) ("the AHRQ Confidentiality Statute"), requires that data collected by AHRQ that identify individuals or establishments be used only for the purpose for which they were supplied. Pursuant to this Agreement, data released to AHRQ for the HCUP Databases are subject to the data standards and protections established by the Health Insurance Portability and Accountability Act of 1996 (HIPAA) (P.L. 104-191) and implementing regulations ("the Privacy Rule"). Accordingly, HCUP Databases may only be released in "limited data set" form, as that term is defined by the Privacy Rule, 45 C.F.R. § 164.514(e). HCUP data may only be used by the data recipient for research which may include analysis and aggregate statistical reporting. AHRQ classifies HCUP data as protected health information under the HIPAA Privacy Rule, 45 C.F.R. § 160.103. By executing this Agreement, the data recipient understands and affirms that HCUP data may only be used for the prescribed purposes, and consistent with the following standards:

No Identification of Persons-The AHRQ Confidentiality Statute prohibits the use of HCUP data to identify any person (including but not limited to patients, physicians, and other health care providers). The use of HCUP Databases to identify any person constitutes a violation of this Agreement and may constitute a violation of the AHRQ Confidentiality Statute and the HIPAA Privacy Rule. This Agreement prohibits data recipients from releasing, disclosing, publishing, or presenting any individually identifying information obtained under its terms. AHRQ omits from the data set all direct identifiers that are required to be excluded from limited data sets as consistent with the HIPAA Privacy Rule. AHRQ and the data recipient(s) acknowledge that it may be

possible for a data recipient, through deliberate technical analysis of the data sets and with outside information, to attempt to ascertain the identity of particular persons. Risk of individual identification of persons is increased when observations (i.e., individual discharge records) in any given cell of tabulated data is less than or equal to 10. This Agreement expressly prohibits any attempt to identify individuals, including by the use of vulnerability analysis or penetration testing. In addition, methods that could be used to identify individuals directly or indirectly shall not be disclosed, released, or published. Data recipients shall not attempt to contact individuals for any purpose whatsoever, including verifying information supplied in the data set. Any questions about the data must be referred exclusively to AHRQ. By executing this Agreement, the data recipient understands and agrees that actual and considerable harm will ensue if he or she attempts to identify individuals. The data recipient also understands and agrees that actual and considerable harm will ensue if he or she intentionally or negligently discloses, releases, or publishes information that identifies individuals or can be used to identify individuals.

Use of Establishment Identifiers-The AHRQ Confidentiality Statute prohibits the use of HCUP data to identify establishments unless the individual establishment has consented. Permission is obtained from the HCUP data sources (i.e., state data organizations, hospital associations, and data consortia) to use the identification of hospital establishments (when such identification appears in the data sets) for research, analysis, and aggregate statistical reporting. This may include linking institutional information from outside data sets for these purposes. Such purpose does not include the use of information in the data sets concerning individual establishments for commercial or competitive purposes involving those individual establishments, or to determine the rights, benefits, or privileges of establishments. Data recipients are prohibited from identifying establishments directly or by inference in disseminated material. In addition, users of the data are prohibited from contacting establishments for the purpose of verifying information supplied in the data set. Any questions about the data must be referred exclusively to AHRQ. Misuse of identifiable HCUP data about hospitals or any other establishment constitutes a violation of this Agreement and may constitute a violation of the AHRQ Confidentiality Statute.

More information can be found here:

https://www.hcup-us.ahrq.gov/team/NationwideDUA.jsp

Appendix 2: University of Minnesota Institutional Review Board Approval

1511E79984 - PI Zhao - IRB - Exempt Study Notification

irb@umn.edu <irb@umn.edu> Wed, Dec 2, 2015 at 10:26 AM
To: zhao0282@umn.edu

TO : carls007@umn.edu, zhao0282@umn.edu,

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: 1511E79984

Principal Investigator: Ruizhi Zhao

Title(s):
Investigation of Hospital Inpatient Costs and Health Care Utilization for Patients with Diabetes and their Association with Diabetes Complications

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This e-mail confirmation is your official University of Minnesota HRPP notification of exemption from full committee review. You will not receive a hard copy or letter. This secure electronic notification between password protected authentications has been deemed by the University of Minnesota to constitute a legal signature.

The study number above is assigned to your research. That number and the title of your study must be used in all communication with the IRB office.

If you requested a waiver of HIPAA Authorization and received this e-mail, the waiver was granted. Please note that under a waiver of the HIPAA Authorization, the HIPAA regulation [164.528] states that the subject has the right to request and receive an accounting of Disclosures of PHI made by the covered entity in the six years prior to the date on which the accounting is requested.

If you are accessing a limited Data Set and received this email, receipt of the Data Use Agreement is acknowledged.

This exemption is valid for five years from the date of this correspondence

and will be filed inactive at that time. You will receive a notification prior to inactivation. If this research will extend beyond five years, you must submit a new application to the IRB before the study's expiration date. Please inform the IRB when you intend to close this study.

Upon receipt of this email, you may begin your research. If you have questions, please call the IRB office at (612) 626-5654.

You may go to the View Completed section of eResearch Central at http://eresearch.umn.edu/ to view further details on your study.

The IRB wishes you success with this research.

We value your feedback. We have created a short survey that will only take a couple of minutes to complete. The questions are basic, but your responses will provide us with insight regarding what we do well and areas that may need improvement. Thanks in advance for completing the survey. http://smallurl.com/exempt-survey