2014-12-08

# Exploring a Diabetic Registry for Cardiovascular Risk Factors

Mary C. Anziano PhD
*University of San Diego*

UNIVERISTY OF SAN DIEGO

Hahn School of Nursing and Health Science

DOCTOR OF PHILOSOPHY IN NURSING

# Exploring a Diabetic Registry for Cardiovascular Risk Factors

by

Mary C. Anziano

A dissertation presented to the
FACULTY OF THE HAHN SCHOOL OF NURSING AND HEALTH SCIENCE
UNIVERSITY OF SAN DIEGO

In partial fulfillment of the

Requirements for the degree

DOCTOR OF PHILOSOPHY IN NURSING

December 8, 2014

Dissertation Committee

Ann Mayo, RN; DNSc; FAAN Chairperson
Cynthia Connelly, RN; PhD; FAAN
Linda Urden, RN; DNSc; CNS, NE-BC, FAAN

## ABSTRACT

Background: Cardiovascular disease is the leading cause of death in the United States. There were over 18 million people diagnosed with diabetes in 2002. These disease processes together combine for significant health burden on society (American Diabetes Association, 2008). The purpose of the study was to describe the relationship between select demographics, and clinical characteristics to determine risk factors for cardiovascular disease in a diabetic population.

Methods: A retrospective descriptive study was conducted using a diabetic registry database containing patients diagnosed with diabetes from January 1, 2011 to December 31, 2012. Study variables included age, gender, socio-economic status, glycosylated hemoglobin levels (HgbA1c), micro-albumin levels, and low density lipoprotein levels (LDL). Descriptive and inferential statistics were conducted using SPSS Windows version 22.

Results: For the total cases (N=292) age ranging 35 years to 97 years, 57% female, the analysis revealed only one independent variable, gender, demonstrated a relationship with the dependent variable, LDL ($r$ =.138; $p$ =>0.009). For the regression analysis, combined variability of the independent variables (age, gender, socio-economic status, HgbA1c, and micro-albumin) accounted for only three percent variance in the dependent variable ($p$ =0.134). The overall model was not a good fit to the sample data.

Conclusions: The diabetic registry used for this study was designed to meet regulatory and accreditation requirements and as such had limited categories of data. The practicality of using a database for research has benefits, but can also impose significant

limitations. In this study the data categories were limited, possibly accounting for the lack of model fit. However, the findings did indicate a premise for future research using a diabetic registry if changes could be made to collect more categories of data such that the findings could provide full characterization of the sample and generalizability of the findings.

**Blank Page/Copyright**

## Dedication

I would like to dedicate this dissertation to my many wonderful patients that I have known and cared for throughout my 25 years as a nurse. They have inspired me to continue my education in the pursuit of better care for patients.

To my sons Thomas and Christopher Anziano, I would not know my way in the world without having you both in my life. The first day I met you Tommy, over 28 years ago, we struggled together with the challenges of your birth. It was during this time I decided to become a nurse. Thank you my love! To my Christopher, you have always been a wonderful inspiration since the first time I saw your lovely face and heard your loud scream. Thank you my love! It is my hope that you both will find your way in healthcare and derive the same feelings of hope, love and inspiration in your journey as I have.

**Acknowledgements**

I would like to express my gratitude to my dissertation chair, Ann Mayo, RN, DNSc, FAAN, for her tireless guidance and support through this challenging academic process. Her nursing expertise and attention to academic precision are beyond reproach. Additionally, her commitment and dedication to her students is unrelenting as is her desire for our success. I admire her deeply for her devotion to nursing; it is inspiring.

I would also like to thank Dr. Cynthia Connelly and Dr. Linda Urden as dissertation committee member. Their support and expertise was paramount in this project. Dr. Patricia Roth the USD PhD Nursing program director, has been kind and provided guidance over the many years it has taken to achieve this goal. It is my hope that I can inspire other nurses in achieving professional goals as I have been inspired by Drs. Mayo, Connelly, Urden and Roth.

I would also like to acknowledge and thank the ARCS Foundation, San Diego Chapter, for their support, interest, and dedication to the work of nurse scientists. Their commitment to nursing scientific endeavors has allowed doctoral students to complete work that helps the entire healthcare community.

I would also like to thank Sandra Monroy for her assistance in understanding and accessing the diabetic registry. She extracted the data for this project in her "extra time" and I greatly appreciate it. To my medical assistant and friend, Tamara Tiewater, thank you very much for listening to my worries and struggles with this project. You are amazing! To my sisters, Anna Stanbrough and Jaime Cloo, without your daily encouragement and support this project would not be done. Thank you both, so very much!

Thank you to Carol Scimone for her timely and prudent assistance with this dissertation. Lastly, to my former patient and now friend, Cynthia Stukey, your support and guidance not only as an individual with diabetes, but a constant friend, allowed this journey. I sincerely appreciate the many times you listened to my troubles. I thank you so very much my dearest friend, Cynthia.

## Table of Contents

## List of Tables

## List of Figures

## List of Appendices

# Chapter One

# INTRODUCTION

## *Overview of the Problem*

Cardiovascular disease (CVD) is a significant health problem in the United States. It affects more than 70 million people and accounts for approximately 40% of all deaths in the United States (Pal, 2006). In 2005 the estimated cost of care for CVD was $393.5 billion (Pal, 2006; Veazie et al., 2005). Heart disease was the leading cause of death in 2010, cerebrovascular disease ranked 4$^{th}$ (Murphy, 2013). Physiologic risk factors for CVD include elevated low density lipoprotein levels (LDL), blood pressure, obesity and diabetes. Behavioral risk factors include diet, exercise and tobacco abuse (Cooper et al., 2000; Pearson et al., 2002). Elevated LDL levels are an independent risk factor for CVD and lowering levels of LDL has significantly reduced the risk of CVD (Pearson et al., 2002). Diabetes is also an independent risk factor for CVD. There is a strong association between CVD and diabetes. Individuals with diabetes have two to four times greater heart disease death rates and two to four times greater death rates from stroke then non-diabetic individuals with CVD (Garg & Bakris, 2002; Grundy et al., 1999; Kvan, Pettersen, Sandvik, Reikvam, & Investigators, 2007; Stern, 1995). Because those individuals with

CVD and diabetes have a higher mortality rate when compared to non-diabetic individuals, studying the contributors to CVD in individuals with diabetes is an important research topic (Liu et al., 2005). Therefore, an investigation determining associations between specific bio-markers for CVD and diabetes, in a diabetic population, could be beneficial in the long term for improving patient care.

## ***Background of the Problem***

### *Cardiovascular Disease*

Cardiovascular disease (CVD) is a disease process that occurs in the arteries and veins of the vascular system and heart. This disease occurs most commonly from build-up of plaque in vessel walls and endothelial inflammation (Pearson et al., 2002). Structural problems from birth defects, genetic predisposition, and history of illicit drug abuse are also contributing factors in the development of CVD as well. Regardless of underlying pathology, this disease process causes heart attacks, heart failure, strokes, aneurysms, and decreased peripheral arterial blood flow that can lead to amputations of limbs. The morbidity and mortality of CVD increases two to four fold in individuals with diabetes compared to individuals without diabetes making diabetes a significant risk factor in developing CVD (Garg & Bakris, 2002; Kvan et al., 2007).

### *Diabetes*

Diabetes mellitus (DM) is a metabolic disorder characterized by elevated circulating glucose levels in the blood caused by either lack of production of insulin by the pancreas or resistance of insulin at the cellular level. Either the loss of production of insulin or resistance of insulin at the cellular level, are the determining factors when making the diagnosis of diabetes. Diabetes mellitus type 1 (DM 1) is characterized by the

loss of insulin producing cells of the pancreas, the islets of Langerhans. The underlying pathology of DM 1 is either immune-mediated, idiopathic or traumatic and accounts for approximately 10% of all cases of diabetes (Lambert & Bingley, 2002). Diabetes mellitus type 2 (DM 2) is far more prevalent and accounts for approximately 90% of all cases of diabetes

Diabetes mellitus 2 is characterized by two defects: insulin resistance and impaired insulin secretion. This disrupts the communication of insulin target tissues and the beta cells. The result in Type 2 diabetes is characterized by diminished peripheral insulin action, increased hepatic glucose production and impaired insulin secretion. Unlike DM 1 there are known risk factors in the development of DM 2. Obesity is considered to be greatest risk factor (Scheen, 2003). More likely, it is the combined effects of obesity, genetics, and poor diet that culminate in the diagnosis of DM 2 (Stern, 1995).

Cardiovascular disease (CVD) is highly correlated with both types of diabetes. It is interesting to note that elevated LDL levels in individuals with diabetes and individuals without diabetes are predictive of an increase in mortality from CVD in both populations. However, the diabetic population has a much higher mortality rate from CVD than individuals without diabetes (Bucala et al., 1994; Liu et al., 2005; Stern, 1995). There is a third disease process to consider when discussing CVD and diabetes. Renal disease is also considered to have a significant relationship with CVD and diabetes. However, it is not known if it precedes the other conditions or occurs as a result of CVD and DM (Bucala et al., 1994; Lane, 2004; Stehouwer & Smulders, 2006).

*Renal Disease*

Renal disease can be described as either acute kidney injury (AKI) or as chronic kidney disease (CKD). The AKI disease process can result from a variety of physiologic insults that include ischemic injury, cardiovascular surgery, sepsis, and radiocontrast administration. It occurs in approximately 5% of hospitalized patients. However, the occurrence increases to 15-30% for those considered high risk patients. The high risk patients are those who have had cardiovascular surgery and those patients that are septic. It is interesting to note that this high risk group is more likely to develop CKD. It is believed this is due to the improved mortality in this population, thus making this population at risk for advancing to CKD (Singh, Ricksten, Bragadottir, Redfors, & Nordquist, 2013). The development of CKD is more insidious and risk factors include not only AKI but also hypertension and diabetes.

Chronic Kidney Disease (CKD) is staged based on renal function values that include glomerular filtration rate (GFR) and albuminuria. As GFR decreases, urine protein levels increase. The more inverse this relationship becomes determines the stage of CKD with stage 1 being mild and stage 5 being end stage renal disease (ESRD). While the exact mechanism that causes low GFR and an increase in urine albumin levels is not known, it is believed to be related to renal oxygenation and hemodynamics. Specifically, the impairment of oxygen balance that causes hypoxia and cellular starvation induce disturbances in extracellular matrix production, deposition of collagen and fibrosis (Singh et al., 2013). Renal oxygenation and hemodynamic problems are found in individuals with hypertension and diabetes and are highly correlated with CVD. It is this association

that makes a renal marker such as micro-albumin level useful in determining the relationship between a known CVD marker such as LDL (Garg & Bakris, 2002).

***Problem Statement***

Cardiovascular disease (CVD) is the leading cause of mortality in the United States (Murphy, 2013). It is responsible for approximately 40 % of all deaths in the United States. This exceeds the next five leading causes of death combined (Veazie et al., 2005). Diagnosing and treating CVD in the United States is estimated to cost billions annually (Pal, 2006). There is an increase in mortality for those with CVD who also have diagnosis of DM (Grundy et al., 1999; Stern, 1995). Diabetes is also a significant health problem in the United States with more than 18 million diagnosed in 2002 (Engelgau et al., 2004) and costing more than $174 billion in 2007 (American Diabetes Association, 2008). These disease processes together combine for significant health and economic burden on society (American Diabetes Association, 2008). Using LDL as a bio-marker for coronary artery disease (CAD) has been established (Holvoet et al., 2001). It is also known that lower LDL levels equate to less risk of developing CVD (Pearson et al., 2002). The gap in the research that there has yet to be an identified relationship of micro-albumin, HgbA1c and LDL in a diabetic population (Hinzmann, Schlaeger, & Tran, 2012). Therefore, a study to investigate the relationships of these variables using a diabetic population could be beneficial in determining CVD risk factors in this population.

***Purpose of Study***

The purpose of this retrospective descriptive data-based study will be to investigate the relationship between HgbA1c, micro-albumin levels, select demographics

(age, gender, socio-economic status), and low density lipoprotein levels. The cases for this study will be drawn from a clinical database. To ensure that all cases in the database have a diagnosis of diabetes the sample will be chosen from a diabetic registry data bank. This study will use data to determine if the independent variables of age, gender, socio-economic status, HgbA1c and micro-albumin have a significant relationship with the dependent variable, LDL.

***Conceptual Framework***

The variables for this study can be categorized as follows: demographics, clinical characteristics and a primary clinical marker for CVD risk. The demographic variables will include age, gender and socio-economic status. The clinical characteristic variables will include HgbA1c, and micro-albumin. The LDL variable will be the outcome variable representing a primary clinical marker for CVD. See Figure 1.

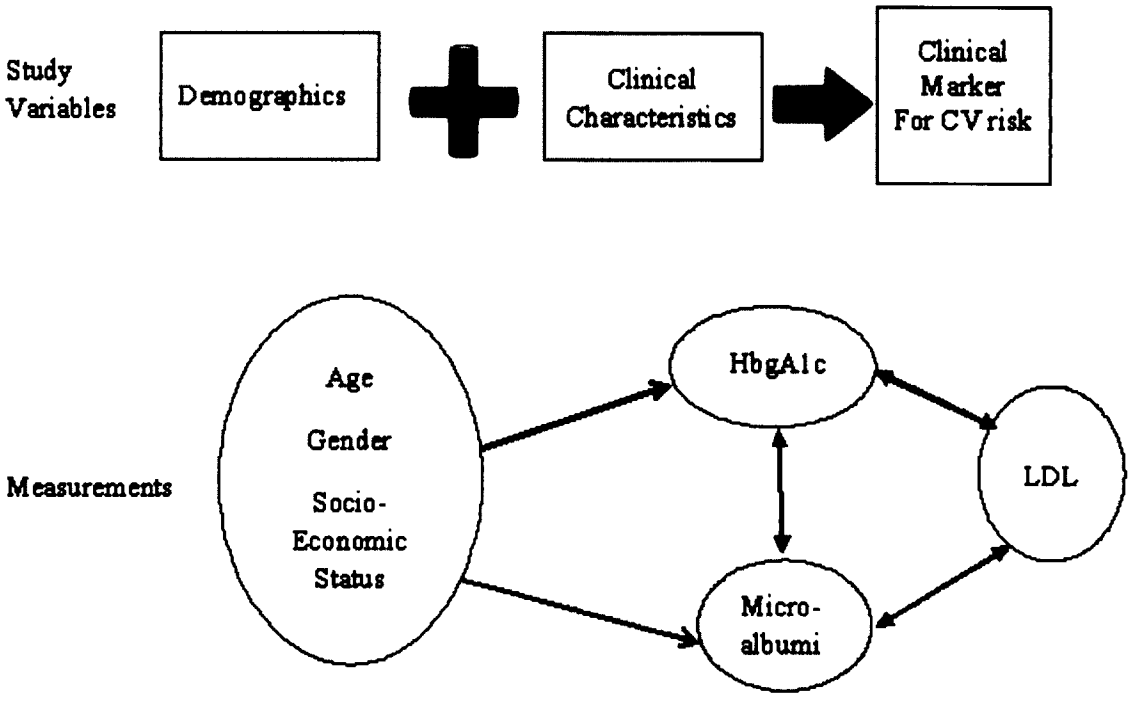


**Figure 1:** ***Conceptual Framework***

***Study Design***

This study will consist of a retrospective descriptive correlation design using de-identified data. The data are housed within a California health care organization's diabetic registry and will span from January 1, 2011 to December 31, 2012. All de-identified data that will be abstracted for investigation will have at least one numerical entry for each of the following: HgbA1c, micro-albumin, and LDL. Each case will include select demographics specifically age, gender and socio-economic status. No cases will have missing data.

***Study Aims***

Aim1: To describe HgbA1c levels, micro-albumin levels, LDL levels and select demographics (age, gender, socio-economic status).

Aim 2: To determine if there is a relationship between LDL levels and HgbA1c levels.

Aim 3: To determine if there is a relationship between LDL levels and micro-albumin levels.

Aim 4: To determine if there is a relationship between LDL levels and select case demographics (age, gender, socio-economic status).

Aim 5: To determine the degree of variability in LDL levels accounted for by HgbA1c levels, micro-albumin levels and select case demographics (age, gender, socio-economic status).

***Implications for Nursing***

Cardiovascular disease (CVD) is a significant health problem and nurses are vital in assisting patients in improving their cardiovascular health (Veazie et al., 2005). This

study will determine if there are relationships among select variables. This project will determine the relationship between select demographics, laboratory tests and LDL as a biomarker for CVD in a diabetic population. The findings from this study can be used by nurses to target clinical indicators for improvement, ultimately improving the cardiovascular health in this patient population.

### *Conclusion*

This chapter presented a discussion and overview of the issues related to cardiovascular disease. The discussion provided background information on cardiovascular disease, diabetes and renal disease. The patient population for this study was determined. Also a framework was provided that conceptualizes the relationship between the variables for this study. Lastly, the significance of the study was discussed. The review of the literature, in Chapter Two, will provide further insight into the necessity of this study.

## Chapter Two

## REVIEW OF THE LITERATURE

### *Introduction*

This chapter will review the literature that is relevant to the investigation of the relationships between the variables in this study. The conceptual framework for this study will describe the predicted relationship among the variables. There will be a discussion of the literature that supports the necessity of this study. This discussion will include a review of relevant research in cardiovascular disease and the use of glycosylated hemoglobin levels, micro-albumin levels and select demographics (age, gender, socioeconomic status) in cardiovascular research.

### *Conceptual Framework*

The variables for this study can be categorized as follows, demographics, clinical characteristics and a primary clinical marker for cardiovascular risk. The demographic variables will include age, gender and socio-economic status. The clinical characteristic variables will include glycosylated hemoglobin levels (HgbA1c), and micro-albumin. The low density lipoprotein (LDL) variable will be the outcome variable representing a primary clinical marker for cardiovascular disease (CVD). See figure 1.

***Cardiovascular disease:***

Cardiovascular disease (CVD) has been the leading cause of death worldwide since 1990 (Veazie et al., 2005). However, CVD was identified as a significant health risk prior to 1990. The National Heart Institute (NHI) noticed there was an increase in death from CVD in the early 1900s. In an ambitious attempt to learn more about CVD, the National Heart, Lung, and Blood Institute (NHLBI) partnered with Boston University to develop the Framingham Heart Study (FHS). The objective of this population-based prospective family cohort study was to identify common risk factors in a population that had no obvious symptoms of CVD or history of stroke or a heart attack at the time of enrollment. The population for the study was recruited from Framingham, Massachusetts and involved over 5,000 men and women. Data collected every two years included medical and lifestyle history, laboratory tests and physical examinations. From this original cohort it was learned that smoking, low levels of activity, high cholesterol level, high blood pressure, electrocardiogram abnormalities including atrial fibrillation, were associated with increased risk of heart disease and strokes ("Framingham Heart Study,"). In 1971, a second generation cohort was enrolled. This cohort included adult children of the original cohorts and was known as the Offspring cohort. The Third Generation cohort, enrolled in 2002, is the grandchildren of the Original cohort.

In her 2010 article, Caroline S. Fox describes the current state of knowledge obtained from the Framingham Heart Study. She evaluates diabetes as a risk factor for CVD and demonstrated an increased association of diabetes and CVD over the years of the FHS. Lastly, she offered suggestions for future research.

Fox, (2010), reported that early on in the FHS that diabetes was recognized as a risk factor for CVD and was associated with a 2-4 fold increased risk of myocardial infarction, peripheral arterial disease, congestive heart failure, increased mortality and stroke. Also discovered was that diabetes was a much stronger risk factor for CVD in woman than in men. Furthermore, because the FHS followed the same individuals over time the increase in incidence of diabetes in this population could be reliably determined. The incidence of diabetes doubled from 1970 to 1990 and this was most noted in obese individuals. But this information does not clearly explain how the incidence of diabetes will affect the rates of CVD (Fox, 2010).

In order to understand the increase in incidence of diabetes in the FHS and the unchanged relative risk of diabetes as a CVD risk factor, further investigation was done using a statistical metric known as attributable risk. This metric determines the impact of a given risk factor on a disease outcome. Applying this metric to the FHS data for the years 1952-1974 revealed a 5.4% attributable risk of CVD due to diabetes. The attributable risk metric was also applied to FHS data for the years 1975-1998 and the number increased to 8.7% for this time period. This indicated that the risk of CVD due to diabetes has increased in the FHS population. Fox, (2010), further noted during these times 1952-1974 and 1974-1998 that other key CVD risk factors such as hypertension either decreased or remained stable. She concluded that diabetes is a significant risk factor for CVD in the FHS population. She encouraged further research that would determine risk factors for CVD that may be more specific for diabetes (Fox, 2010).

The FHS is the longest running population based study in the world and has provided significant epidemiological information about heart disease, hypertension,

diabetes, diet, exercise, cigarette smoking, and medications such as aspirin. Some limitations of FHS include its tendency to overestimate risk factors; particularly, trying to generalize risk factors to populations that are not similar to the FHS participants. The FHS participants are mostly Caucasian middle class adults. This makes it difficult to generalize results to individuals who do not resemble the FHS participants. Regardless of these limitations, the FHS has provided valuable data about CVD and serves as a valuable data bank for future research.

Another interesting population based prospective study, The Hoorn Study, was developed to investigate the prevalence and determinants of glucose tolerance and cardiovascular risk factors in a randomly selected population in the Netherlands. The population from which the sample was drawn for this study came from Caucasian males and females aged 50-70 years, who lived in the Dutch community of Hoorn from 1989 to 1992. The data collected included, age, gender, health history including hypertension and diabetes, renal function (GFR, creatinine, micro-albumin), and various other markers associated with CVD such as C-reactive protein. Glucose tolerance in this population was based on the mean of two oral glucose tolerance test and participants were stratified into normal glucose tolerance, impaired glucose tolerance, and non-insulin-dependent diabetes mellitus. The total population of the Hoorn cohort was 2,484 participants (Jager et al., 1998).

In 2002, Henry et al., used a stratified random sample of all individuals from the initial Hoorn Study cohort to investigate the association of mildly impaired renal function and CVD (Henry et al., 2002). At baseline this population of 631 individuals had mean age of 64 years old, 52% were woman, 55% had hypertension and 27% had type 2

diabetes, meaning that 73% of population either had normal glucose tolerance or had impaired glucose tolerance. Renal function was estimated in this population by microalbuminuria and glomerular filtration rate. At 10.2 years follow-up, there were 117 deaths; 50% were from CVD and were highly associated with impaired renal function. This population based prospective study revealed that there was a 26% increase of death from CVD when the renal function marker, GFR was decreased (Henry et al., 2002). While this study, much like the FHS, has limitations due to its population base of Caucasian participants, it does demonstrate an association between CVD and renal function. This study also did not discuss the 73% of its population that had either normal glucose tolerance or had impaired glucose tolerance. However, this was not stated as a purpose for this study, but given that its population was from the original Hoorn cohort, the data were available but was not discussed.

Unfortunately, more recent investigations have not fully demonstrated how cellular dysfunction and inflammatory activity can predict CVD. The association between renal disease and heart disease is present and thought to be related to these underlying cellular processes (Levey et al., 1998; Stehouwer et al., 2002). Holvoet et al., in 2001 concluded that LDL is a sensitive biomarker for coronary artery disease (CAD) (Holvoet et al., 2001). It therefore, would be reasonable to use LDL as a marker for CVD in this study. What remains to be found is a valid and reliable biomarker that can represent renal function such as micro-albumin, and if a relationship exists between such a biomarker and a known CVD marker such as LDL.

***Micro-albumin Levels:***

Micro-albumin levels, also termed microalbuminuria, are an increased excretion of albumin in the urine. Higher levels of micro-albumin have been associated with age, gender and race. Specifically, there is a higher prevalence in females and non-Hispanic blacks (Weir, 2007). Micro-albumin can predict CVD mortality and is considered an independent risk factor for CVD even with adjustment for hypertension (Tagle, Acevedo, & Vidt, 2003). In individuals with diabetes, micro-albumin is the earliest clinical sign that indicates vascular damage in the kidneys and it is believed that it is reflective of vascular damage throughout the body (Weir, 2004).

Hillege et al. (2001), determined that elevated micro-albumin levels in the general population were independently associated with increased CVD morbidity (Hillege et al., 2001). This was a cross-sectional cohort study done in the Netherlands. It prospectively investigated the natural course of microalbuminuria and the relationship between CVD and renal disease. Participants were asked to submit an early morning urine sample and answer a questionnaire that determined their current health and health history. The results revealed increased levels of micro-albumin in individuals with diabetes, hypertension, and hyperlipidemia. Also significant was advanced age, male gender, smoking and history of myocardial infarction and stroke. However, when adjustments were made for high risk groups (individuals with diabetes, hypertension, and hyperlipidemia), the researchers found that elevated micro-albumin levels were associated with increased morbidity in the general population. Limitations of this study include the misclassification that can occur with self-reported histories. Also, its cross-sectional

design limits the ability to causally relate cardiovascular risk factors, albuminuria and cardiovascular morbidity.

In their study, Arnlov et al., (2005), investigated a sub sample of middle-aged non-diabetic and non-hypertensive individuals from the FHS (Arnlov et al., 2005). It was determined that urinary albumin excretion, even at low levels, was predictive of CVD. This suggested that low levels of micro-albumin may be significant in predicting CVD in all populations. However, in individuals with diabetes, this association is greater with higher predictive values for CVD (Weir, 2004).

Weir, (2004), discusses in his review article the importance of micro-albumin and its predictive benefits in individuals with type 2 diabetes for determining renal disease and CVD. Approximately 28% of individuals with type 2 diabetes have micro-albuminuria. Twenty to forty percent of these individuals, without specific interventions, will progress to nephropathy and end-stage-renal disease. Weir, (2004), argues that this figure would likely be higher were if not for the fact that many of these individuals with diabetes die from myocardial infarctions or strokes before progression to advanced renal disease can occur. Therefore, the association of elevated micro-albumin and CVD likely indicates vascular problems throughout the body. A near linear relationship between raising micro-albumin levels and myocardial infarction and stroke in individuals with diabetes indicates that micro-albumin is a very significant marker for CVD in this population (Weir, 2004).

Valmadrid, Klein, Moss and Klein, (2000), concluded that there was higher mortality from CVD when micro-albumin levels were elevated (Valmadrid, Klein, Moss, & Klein, 2000). Their population based study used a prospective cohort of 840

individuals with diabetes from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR). Participants provided urine samples during the 1984-1986 examination period. Of the 840 individuals with diabetes, 54.8% had normal urine samples, 24.8% had microalbuminuria and 20.5% had gross proteinuria. At the 12 year follow-up, 364 deaths had occurred from cardiovascular disease. Higher mortality from CVD was noted in individuals with diabetes that had microalbuminuria and proteinuria as compared to those individuals with diabetes that had normal urine samples. They concluded that microalbuminuria and gross proteinuria are associated with mortality from CVD.

The pathologic mechanism for the association between micro-albumin and CVD is not fully known. There is, however, an association and as a result of this relationship, micro-albumin can be a useful predictor of CVD in research studies. Although, Valmadrid et al., (2000), concluded that cardiovascular death rates in diabetics are much higher when there is microalbuminuria and gross proteinuria, they did not demonstrate how these levels affect individuals prior to death. It would be beneficial to have a study using a diabetic population to determine if there is an association between a biomarker for renal function, such as micro-albumin, and a biomarker for CVD, such as LDL, prior to death. For this study, micro-albumin will be an independent variable and its relationship with CVD biomarker LDL will be determined in a diabetic registry population.

***Glycosylated Hemoglobin Levels***

Glycosylated hemoglobin (HgbA1c) levels represent the average glucose levels over two to three months prior to the blood draw. This is a routine test ordered for

individuals with diabetes at least yearly and more frequently when the diagnosis of diabetes is new or glycemic control has not been achieved. Levels <5.6% for most individuals with diabetes is considered within the normal range (Nathan et al., 2008). However, in older adults (greater than 65), there are increased risks of side effects from such tight glycemic control. This is likely from changes in body fat composition and the decline of renal and hepatic function associated with the aging process. Therefore, individuals with diabetes who are over 65 years old are at increased risk for hypoglycemia and complications from hypoglycemia, such as changes in cognition and balance, that can result in falls and diabetic coma. The recommendation is a HgbA1c of 7.0% (Nathan et al., 2008; Stark Casagrande, Fradkin, Saydah, Rust, & Cowie, 2013). This is interesting to note because research has demonstrated that even a 1% increase in HgA1c increases CVD risk and could be a contributing factor to the increased risk of CVD with aging (Khaw et al., 2004).

Khaw, Wareham, Bingham, Luben, Welch & Day (2004), investigated the association of HgA1c, CVD and mortality in adults (Khaw et al., 2004). In this prospective population study completed in Norfolk, United Kingdom, 5, 570 women and 4, 662 men were 45-79 years of age. In the 6 year follow-up, all-cause mortality and CVD was significantly predicted by HgbA1c levels. It was determined that lower threshold levels for diabetes, such as 5.0% in men and 6.0% in women, could predict increased risk for CVD Furthermore, a 1% increase in HgA1c was found to be significant in predicting CVD and mortality in men when >5.4% and in women when > 6.0%.

In a study that investigated the nature of the relationship of HgbA1c levels and cardiovascular events in chronic heart failure, Gerstein, Swedberg, Carlsson, et al., (2008), demonstrated that HgbA1c is an independent progressive risk factor for cardiovascular mortality and morbidity (Gerstein et al., 2008). Of 2,412 participants, 907 individuals had diabetes. The sample for this study was drawn from the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program. Inclusion criteria for the study included having had at least one HgbA1c reading during the 34 month study. Data analysis revealed that in individuals with symptomatic chronic heart failure, the HbgA1c was found to be strongly associated with risk factors for cardiovascular events regardless of the presences of diabetes. In this study, cardiovascular mortality and morbidity increased by approximately 25% for every 1% increase in the level of HgbA1c (Gerstein et al., 2008).

There is evidence that HgbA1c is associated with CVD even at non-diabetic levels. However, the nature of this association between glycosylated hemoglobin and cardiovascular disease is not fully known. This study will extract HgbA1c values from a diabetic registry to determine the degree of association for this study's CVD biomarker, LDL.

***Summary***

This chapter reviewed the literature that are relevant to the investigation of the relationships between the variables. The conceptual framework for this study described the predicted relationships among the variables. The relevant research in cardiovascular disease and the use of glycosylated hemoglobin levels, micro-albumin levels and select

demographics (age, gender, socioeconomic status) was discussed. The methodology for this investigation will be discussed in Chapter Three.

## Chapter Three

## METHODOLOGY

### *Introduction*

The purpose of this retrospective descriptive data-based study was to investigate the relationship between glycosylated hemoglobin levels (HgbA1c), micro-albumin levels, select demographics and low density lipoprotein levels (LDL). The data were extracted from a diabetic registry data bank from a Central California health care organization. This chapter will present the research design and methodology that was used in the investigation. There will also be a discussion addressing the protection of human subjects.

### *Setting and Database*

This study used data collected from a Central California health maintenance organization (HMO). This HMO provides primary health care to people living in Kern County. Kern County is the eleventh most populated county in the state of California with over 860,000 people. The county's main sources of economic growth are from the agricultural industry and the extraction of petroleum. Also important to Kern County's economic viability is the aviation, space and military industry.

Therefore, the majority of this HMO's population is derived from individuals working in agricultural, petroleum and military industries (kerncounty.com).

This HMO's diabetic registry was used as the database for this study. The registry was developed to track healthcare information for the HMO's population of diabetic patients. The data collected included demographic and clinical information. The demographic data included the individual's date of birth, gender, and zip code. Not included was the individual's ethnicity, as this information is not consistently recorded in this HMO's patient's health history. Consistently collected clinical information included laboratory values for glycosylated hemoglobin levels (HgbA1c), micro-albumin levels and low density lipoprotein levels (LDL). Additional clinical information collected included yes/no responses to the following: A foot exam completed, including monofilament testing, and by which type of provider; diabetic eye exam, and blood pressure measurement. Some of this additional clinical information is inconsistently collected and recorded in the registry.

This data are automatically input into the database on a daily basis from the electronic medical record (EMR). The information was captured by diagnosis codes, laboratory claim reports and laboratory results for each individual in the diabetic registry. Once a patient was added to the diabetic registry their EMR is tagged to copy over information into the registry. New imputed information was reviewed bimonthly by the systems developer. The systems operator confirmed that inputted information was accurate for patient, diagnosis, lab values, and all other clinical data. For those HMO patients who do not have a medical record, the information was entered manually into the registry. The data in this diabetic registry were stored and retrieved for healthcare

regulatory and accreditation purposes. It has not been used as a database for research purposes in the past (Monroy, 2013).

***Research Design***

This study used a retrospective descriptive correlation design using de-identified data previously collected from patients. Data were housed within a health care organization's diabetic registry and spanned from January 1, 2011 to December 31, 2012. All de-identified data that were to be abstracted for investigation will have at least one numerical entry for all of the following, HgbA1c, micro-albumin, and low density lipoprotein levels. Each case included select demographics; specifically, age, gender and socio-economic status. No cases with missing data were used in this study. The study design that was chosen supported the investigation of associations between the variables. As background, retrospective design works with large sample sizes and therefore, lends itself well to data abstraction from registries from which a large number of cases can be obtained. There is also the benefit of time efficiencies, as the data have already been collected and stored in a databank For this study, data abstraction and analysis will allow the associations, or lack thereof, between the independent and dependent variables to be revealed. The independent variables for this study included HgbA1c levels, micro-albumin levels, and select demographics (age, gender, socio-economic status). The dependent variable was the LDL levels.

***Study Aims***

Aim 1: To describe HgbA1c levels, micro-albumin levels, LDL levels and select demographics (age, gender, socio-economic status).

Aim 2: To determine if there was a relationship between LDL levels and HgbA1c levels.

Aim 3: To determine if there was a relationship between LDL levels and micro-albumin levels.

Aim 4: To determine if there was a relationship between LDL levels and select case demographics (age, gender, socio-economic status).

Aim 5: To determine the degree of variability in LDL levels accounted for by HgbA1c levels, micro-albumin levels and select case demographics (age, gender, socio-economic status).

***Dependent Variable***

The dependent variable, LDL, is one of the five major groups of lipoproteins that enable transport of fat molecules and cholesterol into artery walls. Specifically, LDL is a very large molecule that can transport numerous fat molecules and cholesterol into the artery wall. These fat molecules and cholesterol are retained in the wall by arterial proteoglycans and macrophages that engulf the LDL particles causing the formation of plaque. It is this buildup of plaque that can result in heart attack, peripheral vascular disease, and stroke (Krauss, 1995). Numerous studies have identified LDL as a predictive value in the development of heart disease (Niskanen, Turpeinen, Penttila, & Uusitupa, 1998).

The LDL is a numerical value that is obtained via a laboratory blood test. It is part of a lipid profile panel and is obtained on nearly all patients with diabetes or others who have risk factors for heart disease. This makes the LDL readily available for use in

research studies (Howard, et. al., 2000). Low density lipoprotein levels (LDL) for each case were downloaded from the database

***Independent Variables***

The independent variables, HgbA1c and micro-albumin, are laboratory values that provide information about diabetes and urine protein levels. The HgbA1c is a blood test used to ascertain glycemic control in a diabetic. The value of the HgbA1c is determined by exposure to plasma glucose with higher values indicating increased blood glucose levels. This lab value has become the standard of care in determining how well diabetics are managing their blood glucose levels over a period of months (Nathan et al., 2008). Nearly all patients with diabetes that are followed by health care professionals regularly will have at least one to four HgbA1c values done within a year (Stark Casagrande et al., 2013). Also, part of the laboratory test for patients with diabetes includes a urine test to check protein levels.

Micro-albumin is a urinary laboratory test that indicates how much protein (albumin) the kidneys are excreting. This is done as a random urine test. Increased levels of micro-albumin indicate that there is high permeability for albumin in the renal glomerulus, meaning a higher risk that renal injury occurring (Andersen et al., 2000).

Demographic data were downloaded for each case and included age, gender and zip code (proxy for socio-economic status) for each case. Age was measured in years and was interval data. Gender was measured as male or female and was categorical level data. The zip code was used as a proxy for socio-economic status (Geronimus & Bound, 1998) and was categorical level data.

*Inclusion and Exclusion Criteria*

Inclusion criteria: Cases that had a recorded diagnosis of diabetes and at least one value for each of the following: LDL level, HgbA1c level and micro-albumin level from the time period of January, 1 2011 to December 31, 2012.

Exclusion Criteria: All cases for the time period of January 1, 2011 to December 31, 2012 that did not have values for LDL level, HgbA1c level, or micro-albumin level entered into the diabetes registry were excluded from the study. No child cases (under 18 years), expired cases, or cases of those who were no longer members of the HMO at the time of the data extraction were used. Also all cases that did not have electronic medical records were excluded.

***Data Retrieval Procedures***

The diabetic registry of a health care organization in Central California was used for this study. Permission was obtained to utilize the organization's database for this study (see Appendix B). Per organizational protocol, the organization's data manager used study inclusion and exclusion criteria to extract the data. A preliminary data query by the data manager estimated the number of cases that meet the inclusion and exclusion criteria was to be just over 880 cases (Monroy, 2013). The following data were extracted into an Excel spreadsheet: HgbA1c levels, micro-albumin levels, select demographics (age, gender, socio-economic status) and LDL levels.

***Sample Size, Power and Significance***

It is important to establish the sample size necessary for the statistical analysis with considerations of power, population effect size, and level of significance (Huck, 2008). For the purposes of this study, the alpha level was set at.05. This equated to a

0.95 % probability and is equivalent to a 95% confidence level in order to decrease the chances of committing a type I error, a false positive claim. The power of the significance test was the probability of rejecting the null hypotheses when the null hypotheses is false, considered a type II error, a false negative claim. Next, for this study an acceptable level of power was .80 and was utilized to determine the sample size (Huck, 2008). Effect size was considered next. When choosing an effect size, researchers decide how small a difference they are willing to accept and still find the results worthwhile (Huck, 2008). For this study the effect size that was determined to be clinically significant was .25.

This study involved several different analyses. Each type of analysis required a different sample size and of these analyses, the multiple regression required the most conservative sample size to detect a significant model. With the alpha set at .05, to achieve a power of .80 and an effect size .25, the minimum sample size of 57 was determined based on A-priori sample size calculator. However, a sample size of 300 was chosen as a reasonable sample to be representative of the database ("Bayes's Theorem ", 2013). Once all inclusion and exclusion criteria were met, cases were randomized to obtain a sample size of 300 cases by using a random sample calculator.

***Data Analysis***

The data were transferred from an Excel spreadsheet into SPSS Windows version 22 for analysis. The following analyses were used to address each aim: descriptive statistics, Pearson *r,* and multiple regression. The analysis for each aim are explained.

Aim 1: To describe HgbA1c levels, micro-albumin levels, LDL levels and select demographics (age, gender, socio-economic status). Descriptive statistics will be conducted to describe the independent and dependent variables. This included frequency

and percentages for categorical data and means, standard deviation, and ranges for continuous data.

The following aims were addressed by using the Pearson *r* correlation to determine the relationships between these interval data variables. Aim 2: To determine if there was a relationship between mean LDL, levels and HgbA1c levels. Aim 3: To determine if there was a relationship between mean LDL levels and micro-albumin levels. Aim 4: To determine if there was a relationship between mean LDL levels and select case demographics (age, gender, socio-economic status).

Multiple regression will be utilized to address Aim 5. Aim 5: To determine the degree of variability in LDL levels accounted for by HgbA1c levels, micro-albumin levels and select case demographics (age, gender, socio-economic status).

***Multiple Regression***

This study sought to determine if there were significant relationships between the independent variables and the dependent variable and to what degree the variation in the dependent variable was explained by the independent variables. As background, regression analysis is used when the primary purpose of a study is to describe relationships among independent variables and account for variability in a dependent variable. Regression analysis results can be displayed using scatter plots where the points on the plot represent the results. The X-axis is the independent variable and the dependent variable is the Y-axis. The spread of the points on the plot determines the magnitude of relationship among the variables. The strength of these relationships determines the amount of variation in the Y variable as explained by the X variable. Demonstrating strong relationships between variables using regression analysis was the

goal of the study and so several important factors were considered (Mertler & Vannatta, 2005).

Important factors to consider in regression analysis include the slope of the regression line, where the points are scattered around the line and the point that the regression line crosses the Y-axis. Once these factors are considered, a regression equation can be calculated. However, multicollinearity must be addressed as part of an analysis. Multicollinearity occurs when there are moderate to high intercorrelations among the independent variables. This can result in overlapping information, limiting the size of multiple correlation and increasing the variance of regression coefficients, resulting in an unstable equation. To prevent problems with multicollinearity in this study, a tolerance test was performed to measure the collinearity among the independent variables. If there is a problem with multicollinearity, it can be managed by either deleting one of the problematic variables or by combining them to create a single construct. Lastly, sample size needs to be considered. For a reliable equation, the sample size ($n$) should be greater than/equal to 104 plus dependent variable/predictor ($k$). Other factors such as power, population effect size and level of significance also must be considered when determining sample size for analysis as described above (Mertler & Vannatta, 2005).

***Limitations of the Study***

Several limitations were anticipated. Most significant to note was that there was no ethnic information for this databank population. This makes it very difficult to generalize the results of this study to other populations. The zip code was used proxy for socio-economic status. While all cases had at least one value for each clinical variable, it

was anticipated that some cases might have numerous values collected over a range of time. While mean scores were used for study analysis; there was a possibility of overestimation of the relationships among the variables. Lastly, it was known that such disease specific databank registries designed to meet regulatory and accreditation requirements generally have limited numbers of variables restricting researchers from fully characterizing the cases.

***Protection of Human Subjects***

A retrospective data analysis has low risk for harm to human subjects. It was anticipated that informed consent would not be required because there was no contact with human subjects; the researcher only used data extracted from a diabetic registry. Anonymity was addressed as follows: The data manager extracted the cases from the diabetic registry and insured that all data were de-identified prior to providing the data to the investigator. Confidentiality of the de-identified data were important to the health care organization; therefore, only aggregate data were reported in the results. No individual case data or raw data were included in any reports. For the purposes of analysis, raw case data resided on the investigator's password protected computer. Data extraction occurred after receiving study level of oversight determination from the institutional review board (IRB) of the University of San Diego. The level of oversight was exempt. The health care organization did not have an IRB.

***Conclusion***

This chapter explored the methodology for this investigation with rationales for sampling and sample size. The dependent and independent variables were defined for this study. The inclusion and exclusion criteria for the study cases were explained as were the

data collection and data analysis procedures. Lastly, there was a discussion addressing the protection of human subjects. Results of the analysis are discussed in Chapter Four.

# Chapter Four

## STUDY RESULTS

The purpose of this study was to investigate the relationship between glycosylated hemoglobin levels (HgbA1c), micro-albumin levels, select demographics (age, gender, socio-economic status), and low density lipoprotein levels (LDL) in a diabetic population. The cases for this study were drawn from a diabetic registry. In this chapter, study results will be presented, including sample characteristics. The descriptive profile analysis of the sample will be presented. The results for each research aim will be explained.

### *Community Characteristics*

This study used data collected from a Central California Health Maintenance Organization (HMO). This HMO provides primary health care in Kern County. There are over 860,000 people living in Kern County making it the eleventh most populated county in California. The county's main sources of economic growth are from agricultural and petroleum industries. Also well represented in Kern County economics are the educational, transportation, and military industries. The largest ethnic groups in Kern

County, as reported by City-Data.com (2014), are Hispanic at close to 51%, White at nearly 37%, and Black, at approximately 5%.

***HMO Characteristics***

The HMO used for this study was established in Kern County over 30 years ago and is affiliated with a nationally recognized network of physicians. Their mission is to prioritize patient satisfaction and education in all medical and service activities. They achieve their mission by offering numerous locations for healthcare services throughout the county. They provide patient education and are also involved in local healthcare charity events for cancer, women's health, cardiovascular health, and child health care programs. There are five campuses that house the HMO providers located in Kern County. Also, throughout the county there are numerous private practice physician offices that are affiliated with the HMO through the physician network. As a result of their association with the physician network, their HMO patients have more choices for healthcare throughout the entire county of Kern, website 10/11/14. Several years ago the HMO developed a diabetic registry to track healthcare information for regulatory and accreditation requirements (Monroy, 2013). It was this data bank that was used for this study.

***Diabetic Registry***

The data collected included demographic and clinical information. The demographic data included the individual's date of birth, gender, and zip code. Clinical information included laboratory values for HgbA1c, micro-albumin, and LDL. Additional information in the registry was inconsistently collected and therefore, was not used for this study.

***Sample***

The inclusion criteria for each case was: a) a diagnosis of diabetes, b) at least one value for each of the following: LDL level, HgbA1c level, and micro-albumin level from the time period of January 1, 2011 to December 31, 2012. The exclusion criteria for this study were cases under 18 years of age, expired cases, cases who were no longer members of the HMO at the time of the data extraction, and cases that did not have an electronic medical record. There were 883 cases that met the inclusion criteria for this study. The minimum sample size of 57 was determined based on A-priori sample size calculator. However, a sample size of 300 was chosen as a reasonable sample to be representative of the database ("Bayes's Theorem", 2013). A random sample calculator determined the 300 cases that were used to represent this study's population.

Micro-albumin levels for eight cases were three standard deviations from mean. Further investigation of these eight cases revealed that they were univariate outliers. As univariate outlier, this meant that the other variables for these eight cases were within the normal distribution for the other variables (Katz, 2006; Mertler & Vannatta, 2005). The final population size used for this study was 292 cases for all variables except median income that had eleven cases with missing data (n=281).

***Descriptive Findings***

Aim 1: Describe HgbA1c levels, micro-albumin levels, LDL levels and select demographics (age, gender, socio-economic status). Descriptive statistics were computed to describe these variables and included frequency and percentages for categorical data and means, standard deviation, and ranges for continuous data.

The mean age for this sample was 73 ±12 years old. Mean income was $48,264 ±$16,700 per year, mean HgbA1c was 7.0 ±1.3 mg/dl, and mean LDL of 95.2 ±30 mg/dl. The majority of the sample was female (n= 165; 57%) with the only significant difference between females and males being the LDL means (male 90.0 vs. female 99.0; t= -2.436, $p = 0.015$). Table 1 summarizes the descriptive statistics for the continuous data variables.

Table 1. *Descriptive Statistics: Age, Median Income, HgbA1c, Micro-albumin, and LDL*

| | | |
|---|---|---|
| Age (n=292) | M = 73<br>SD = 12 | Range<br>35 – 97 |
| Income (n=281) | M = 48,264<br>SD = 16,700 | Range<br>29,910 – 96,322 |
| HgbA1c mg/dl (n=292) | M = 7.0<br>SD = 1.3 | Range<br>5.3 – 13.5 |
| Micro-albumin mg/dl (n=292) | M = 49.1<br>SD = 86.9 | Range<br>0.4 – 630.6 |
| LDL mg/dl (n=292) | M = 95.2<br>SD = 30.0 | Range<br>27.0 – 313.0 |

***Correlations***

Aims 2 and 3 were to determine if there was a relationship between LDL levels and the other two laboratory values of HgbA1c and micro-albumin, respectively. Aim 4 was to determine if there was a relationship between LDL levels and select case demographics. Pearson *r* correlation and point biserial (run in SPSS as Pearson *r*) statistics were used to determine any relationships between the dependent variable and

the independent variables. The Pearson *r* correlations are significant if *p* values are equal to or lesser than 0.05 (Field, 2005).

Aim 2: Determine if there was a relationship between LDL levels and HgbA1c levels. Results indicated there was not a statistically significant relationship, $r = .019, p > 0.376$.

Aim 3: Determine if there was a relationship between LDL levels and micro-albumin levels. Results indicated there was not a significant relationship, $r = -.010, p > 0.435$.

Aim 4: Determine if there was a relationship between LDL levels and select case demographics (age, gender, socio-economic status as measured by median income). Results indicated there was not a significant relationship between LDL and age or with LDL and median income: Age $r = -.072, p > 0.111$. Median income $r = .056, p > 0.177$. There was a statistically significant relationship between LDL level and gender, $r = .138$ and $p > 0.009$.

Aim 5 will be addressed by discussing the regression analysis.

***Regression***

Aim 5: Determine the degree of variability in LDL levels accounted for by HgbA1c levels, micro-albumin levels, and select case demographics. A two- model regression analysis was conducted using a block design. Model 1 (gender as the only independent variable) revealed an *R* value of 0.138; $R^2$ value of 0.019; $p = 0.020$. The A-priori identified complete model, with all of the independent variables, revealed the study data did not fit the model: *R* value of .173; $R^2$ value of 0.030; $p = 0.134$. While the $R^2$ value for these independent variables accounted for three percent of the variation of

LDL levels, the model was not significant. Ninety seven percent (97%) of the variability in LDL level was unaccounted for in the specified model. The possible reasons for this finding will be further discussed in Chapter Five.

***Summary of Results***

The results presented in this chapter included a descriptive profile analysis of the sample population and results of the research aims. This analysis revealed there was only one independent variable (gender) that demonstrated a relationship with the dependent variable. However, gender only accounted for 1.9% of the variance in the dependent variable. The combined variability of the independent variables in this study accounted for only three percent variance in the dependent variable and was not statistically significant. This indicated the overall model was not a good fit. There will be a discussion of the analysis and an interpretation of the results in Chapter Five.

## Chapter Five

## DISCUSSION OF FINDINGS

The purpose of this study was to investigate cardiovascular risk factors in a diabetic population. A retrospective study was conducted using a diabetic registry from a Health Maintenance Organization (HMO). The consistently collected data from this diabetic registry was analyzed to determine if there were any relationships between the independent variables and the dependent variable. The results determined the independent variables, glycosylated hemoglobin levels (HgbA1c), micro-albumin levels, and select demographics (age, socio-economic status) with the exception of gender, did not reveal any significant relationship to the dependent variable, low density lipoprotein levels (LDL). This chapter will present a summary of findings and limitations of this study. Lastly, implications for nursing practice and future research will be presented.

### *Sample Demographic Characteristics*

The demographic variables for this study included age, gender, and socio-economic status. The sample had a mean age of 73 years with more females than males.

This is a fairly consistent finding with other cardiovascular disease studies and findings associated with diabetes. Regitz-Zagrosek, Lehmkuhl and Weickert in their 2006 review of gender and cardiovascular disease noted that women develop cardiovascular disease later in life and also live longer that men. They state age affects woman and men differently. Men develop metabolic problems such as hyperlipidemia and diabetes at a younger age then women but women will have a higher prevalence of these disease processes later in life, living longer with these diseases. Regitz-Zagrosek et al., 2006, suggest the link may be hormone related, however, further research is indicated. Zip codes with data linked to median income were used as a proxy for socio-economic status (Geronimus & Bound, 1998). The sample mean median income was $48,264 (range $30,909 to $96,322). Financially, for this study's sample, this was slightly lower than the national median income of $51,939 US census Bureau, website Sept 2014. There is evidence that lower income levels are associated with risk factors for both diabetes and CVD in the United States (Kanjilal et al, 2006). It is believed that individuals with lower income levels have less access to care and likely more complications associated with the disease process when compared to individuals with higher income (Bonow, Smaha, Smith, Mensah, & Lenfant, 2002).

Interestingly, for this dissertation study, results did not reveal an association between median income and the marker for cardiovascular disease marker, LDL. This may very likely be because this study's sample was drawn from an HMO and as a result, his sample had access to healthcare. For other populations in Kern County that are not associated with an HMO this might be a different finding.

***Sample Clinical Characteristics***

Clinical variables for this study included HgbA1c, micro-albumin, and LDL. The mean HgbA1c for this sample was 7.0mg/dl. The recommended level for most individuals with diabetes is considered within the normal range when the HgbA1c level is below <5.6mg/dl (Nathan et al., 2008). However, based on the mean age of 73 years for this study's sample, a HgbA1c level of 7.0mg/dl is considered within the normal range as there are significant risk for hypoglycemia in individuals with diabetes over 65 years old (Nathan et al., 2008; Stark Casagrande, Fradkin, Saydah, Rust, & Cowie, 2013).

Based on national recommendations for the general population (not individuals with diabetes), the LDL goal is <99mg/dl (ADA, 2013). However, a sample of diabetic patients was used for this study. The national goal for individuals with diabetes with more than one risk factor for cardiovascular disease (which would include diabetes) is a LDL of <70mg/dl (ADA, 2013). Therefore, this sample had at least one known risk factor for cardiovascular disease (ADA, 2013). Due to the limited number of data topics contained in the diabetic registry used for this study, determining if other risk factors existed was not possible. Therefore, a mean LDL of 95.2 may be an elevated level in this sample population if it could have been determined that the patients had more than one risk factor.

The micro-albumin level mean (49.1 mg/dl) for this study's sample was above normal for both the general population and for individuals with diabetes (Hillege et al., 2001). While not significant, of interest was that the mean values for females (53mg/dl) were nearly 10mg/dl higher than males micro-albumin levels (44.2mg/dl). Other findings are mixed regarding this association between micro-albumin and gender. The current

study's finding is consistent with a literature review using data from the National Health and Nutrition Examination Survey (NHANES) (Weir, 2007). The review revealed a higher prevalence of micro-albumin levels associated with female gender. However, a different study reported a higher prevalence of micro-albumin levels was associated with male gender (Hillege et al., 2001). It was recommended that these findings be further investigated to determine the extent of the relationships (Hillege et.al, 2001;Weir, 2007). This current study demonstrated with this sample, although not generalizable due to lack of significance, that females had higher micro-albumin levels compared to males.

## Associations with LDL Levels in the Sample

No significant associations, with the exception of gender to LDL levels, were found between the independent variables and the dependent variable in this study. Specifically, the independent variables of age, median income, HgbA1c levels, and micro-albumin levels were not significantly associated with the dependent variable, LDL. The relationship of gender with LDL levels will be discussed next. Then the possible reasons for the lack of association among the remaining variables and LDL levels will be discussed.

### *Gender and LDL Association*

For this study, only one variable, gender, was found to be correlated with the dependent variable, LDL $r$ =.138, $p$>0.009. Gender in this study revealed the following mean LDL levels: males 90.0 ± 26.5 mg/dl, vs. females 99.0 ± 32.0 mg/dl, t =-2.436, $p$ = 0.015. Holvoet et al., in 2001 concluded that LDL levels were a sensitive biomarker for coronary artery disease (CAD) in men and women. They compared LDL levels to the Global Risk Assessment Scoring (GRAS) that was developed to by the American College

of Cardiology and the American Heart Association as a guide for primary prevention of CAD. The GRAS scoring is based on age, high density lipoprotein levels (HDL), total cholesterol levels, diabetes, smoking, systolic blood pressure. Holvoet et al., (2001) determined that LDL levels alone were a sensitive marker of CAD in their study; with LDL level having a 76% positive predictive value compared to GRAS that had only a 20% positive predictive value in predicting CAD. They further found the positive predictive value of the LDL marker was higher in females (81%) than in males (55%). This indicates that LDL is better for predicting CAD than GRAS for females.

This dissertation study did find a correlation between gender and LDL levels. It also found higher LDL levels in females when compared with males. However, gender only accounted for 1.9 % of variance in the regression model, while all the independent variables combined accounted for 3% of the variance. This indicated that 97% of variance could not be accounted for in this regression model for this study. This will be discussed further in the next section.

***Regression Analysis***

In this study, a regression analysis was conducted using an A-priori model to determine which independent variables (age, gender, median income, HgbA1c levels, and micro-albumin levels) would contribute to a significant amount of variance in the dependent variable, LDL. However, the sample data did not fit the regression model. The possible reasons for this will be discussed next.

According to a number of authors when results do not reveal relationships that were anticipated, it is recommended that sample size should be re-evaluated (Field, 2005; Huck 2008; Mertler & Vannatta, 2005). Based on the alpha (.05), power (.80), effect size

(.25), and the method of analysis (multiple regression), minimum sample size of 57 was determined to be sufficient to detect relationships in this study. However, because a relatively large sample was available, a sample size of 300 was chosen as a reasonable sample size to be representative of the database ("Bayes's Theorem", 2013). There were eight cases that had micro-albumin levels that were determined to be three standard deviations from the mean for that study variable and were therefore removed (Katz, 2006; Mertler & Vannatta, 2005). Thus, the final sample size for this study was 292. The sample size was determined to be of adequate size, being well over the minimum calculated sample size of 57.

The study findings only determined a three percent variance in the LDL value; meaning that 97% of variance was unaccounted for with this model. There are three possible reasons for non-significance of variance in a model. These include; 1) no linear relationship at the bivariate analysis level; 2) problems with outlier data points; and 3) missing explanatory variables.

The first reason for data not fitting an A-priori regression model is there is actually no linear relationship at the bivariate analysis level among the variables. Field (2005) explains that correlation between variables is demonstrated when the mean for one variable increases or decreases the as mean for the other does so as well. This relationship can be either positive or negative. No correlation between the variables indicates a lack of a linear relationship (Field, 2005). In this study there was only one pair of variables that demonstrated a significant bivariate relationship and that was between gender and LDL.

Second, there can be a problem with outlier data points. If there are data points that are over three standard deviations from the mean, is can change the regression line

such that there is no line or that the line is pulled positively or negatively away from the main data points (Field, 2005; Mertler & Vannatta, 2005). In this study, there was a univariate outlier that was managed and therefore this would not likely explain the lack of data-to-model fit in this study.

Finally, the third possible reason that this study's data did not fit the model was that the "true" explanatory variables were not included in the study. Retrospective studies using clinical databases can have limited data available to utilize as research variables as this study most likely demonstrated. However, population-based retrospective studies that have used large databases designed for longitudinal research, such as the Framingham Heart Study (FHS) databank have been successful in determining relationships among numerous variables. This is likely due to the numerous choices of variables that researchers have when using such large databases such data typically includes medical and lifestyle history, laboratory tests and physical examinations. Researchers have successfully used the FHS data bank to discover many of the risk factors for heart disease and strokes including smoking, high blood pressure, low levels of activity, high cholesterol levels, and electrocardiogram abnormalities (Dawber, 1960; Kannel, Dawber, Kagan, Revotskie, & Stokes, 1961; Kannel, 1967; Wolf, Kannel, & McNamara, 1970).

This study used a diabetic registry that was designed to track health care information for regulatory and accreditation requirements (Monroy, 2013). This was problematic because the categories of data that were available for use within this diabetic registry were limited. This will be further discussed in the limitations section.

***Limitations of the Study***

This section will discuss the use of proxy data, data that was inconsistently collected, and data categories that were not part of the database. All three of these situations can be limitations in research studies.

First, using proxy data can impose limitations in research. This study used zip code as a proxy for median income. Geronimus and Bound in their 1998 study, investigated using zip codes to better identify the economic status of individuals to be used in healthcare research. They compared this to detailed lengthy government surveys over a 20-year period. It was concluded that the use of zip codes is less costly and does give an accurate economic assessment of a given population. However, other information collected by zip code, such as education and ethnicity are less accurate (Geronimus & Bound, 1998). This study used zip code as a proxy for median income and it did provide financial information about the sample that was fairly consistent with national numbers for median income.

Second, some types of data included in the database were so inconsistently collected they could not be included in this study. The data inconsistently collected in this diabetic registry included; 1) blood pressure measurement; 2) diabetic foot exam; 3) monofilament test for sensation in the feet; and 4) diabetic eye exam. These categories of data could not be used in this study because the collection of this information in the data bank was sparse.

Finally, the most significant limitation of this study may have been the very limited availability of categories of data in the HMO's database. For example race and ethnicity were not included in this database. Examples of clinical data categories not

captured included; 1) high density lipoprotein levels; 2) age at diagnosis of diabetes; 3) diabetic medication history (none, oral, insulin, or both oral and insulin); 4) smoking history; 5) health history information such as: heart attack, cerebral vascular accident, renal disease, and dialysis. Having additional demographics and clinical data available for use in this study would have assisted in better characterizing the sample and may have provided additional variables to explain more variance in the model.

This study was missing valuable data that would have helped not only to define the study sample but may also have allowed the findings to be generalized beyond this study. In summary, this disease specific databank as designed to meet regulatory and accreditation requirements and as such had limited numbers of useful variables restricting full characterization of the sample and generalizability of the findings.

## Implications for Nursing

### *Nursing Practice*

Cardiovascular disease (CVD) is a significant health problem and nurses are vital in assisting patients in improving their cardiovascular health (Veazie et al., 2005). Although there was only one significant finding in this study, the study may provide useful information for nurses. As an example, it is known that the sample drawn from this diabetic registry had HgbA1c levels that met American Diabetic Association recommendations (ADA, 2013). On the other hand, the LDL levels in this sample population are likely too high and should be closer to 70 mg/dl instead of 95.2 mg/dl. This is because it is very likely that many of the individuals in this diabetic registry have other cardiovascular risk factors. This is useful information for nurses. Nurses should look beyond just HgbA1c levels and utilize evidence-based guidelines as interventions to

lower the LDL level in patients with diabetes. Ongoing monitoring by nurses of both HgbA1c levels and LDL levels are important in order to maintain cardiovascular health, as well as overall health.

The mean micro-albumin levels for this sample were above normal. Normal levels for micro-albumin are 0-17 mg/dl for the general population. Differences in these levels can be related to the measure utilized by different laboratories. However, any level over 20 mg/dl should be considered elevated (Stehouwer & Smulders, 2006). On the other hand, micro-albumin levels for individuals with diabetes have yet to be determined but when evidence is eventually available, the recommended levels will likely be lower than 10mg/dl (Weir, 2007).

Elevated micro-albumin levels are considered to be reflective of renal damage as well as CVD (Levey et al., 1998; Stehouwer & Smulders, 2006; Lane, 2004). Garg and Bakris, in their 2002 review of the literature, determined that patients with elevated micro-albumin levels also had higher blood pressure levels. They discussed that even micro-albumin levels of 28-30mg/dl were associated with higher blood pressure readings when compared to micro-albumin levels that were <20mg/dl. They recommend further research to investigate if micro-albumin can be used to as a clinical marker for blood pressure control, as well as for renal disease.

Considering the association of elevated micro-albumin levels and blood pressure measurement, interventions by nurses to lower blood pressure in this diabetic registry population may also help lower the micro-albumin levels. By adding blood pressure measurements to diabetic registries and trending those measurements over time, nurses would be able to recommend interventions that may assist individuals with diabetes in

lowering their blood pressure. Nurses would be able to achieve this goal by providing diet, exercise, and medication management education to this diabetic registry population.

***Research***

A number of subsequent research studies can be recommended to continue this study's line of inquiry. These include further expansion of the study conceptual framework to include more variables, changing the dependent variable to a different variable reflective of CVD. This study used a conceptual framework to predict the possible relationships among the variables. See figure 1. An expanded version of this basic framework may be useful in future nursing research. First, the demographic measurements could be expanded to include race and ethnicity. With different rates of diabetes occurring among different races and ethnicities, it is important to investigate the relationship among all of the framework variables in the context of race and ethnicity. Second, the clinical characteristics could be expanded to additional measurements such as blood pressure and HDL levels.

A different biomarker for cardiovascular disease may be a prudent next step. A better clinical marker for cardiovascular risk might be micro-albumin levels. There is a demonstrated relationship between elevated micro-albumin levels and increased risk of CVD (Arnlov et al., 2005). Weir (2004) describes that micro-albumin is the earliest clinical sign of vascular damage in the kidneys and it is believed it is reflective of vascular damage throughout the body.

Changing the biomarker for CVD to micro-albumin and adding additional variables may be beneficial in better determining cardiovascular risk factors in a diabetic population. Fox (2010) describes the current state of knowledge obtained from the

Framingham Heart Study (FHS). She evaluated diabetes and CVD in the FHS population and concluded there was an association between the two disease processes. She argued for further research that would determine risk factors for CVD that may be more specific for diabetes (Fox, 2010).

## Summary

The purpose of this study was to investigate cardiovascular risk factors in a diabetic population. A Health Maintenance Organization's diabetic registry was used as the data source. With the exception of gender and low density lipoprotein levels. the results did not reveal any significant relationships among the variables. The most likely reason for this result was the limited types of data available from the diabetic registry that could be used as categories of data. Although this particular data bank was limited because it was developed specifically to track health care information for regulatory and accreditation requirements, it could be redesigned in order to be used in future research studies. All data would need to be collected on a consistent basis and data categories expanded. This data bank would likely be very useful in investigating cardiovascular risk factors in a diabetic population with appropriate changes.

## Conclusion

Cardiovascular disease is a significant national health problem. It affects millions of people and is the leading cause of death in the United States. The estimated cost of care is over $393.5 billion annually (Pal, 2006; Veazie et al., 2005). The problem was so significant in the early 20$^{th}$ century that the National Heart Institute and the National Heart, Lung, and Blood Institute partnered with Boston University in an ambitious project. The goal was to determine common cardiovascular risk factors in a population

that had no obvious symptoms of cardiovascular disease at the time of enrollment. This population-based prospective family cohort study, the Framingham Heart Study, has been instrumental in obtaining valuable data about cardiovascular disease. Their ground-breaking discoveries include identifying that cigarette smoking, low levels of activity, high cholesterol levels, high blood pressure, and electrocardiogram abnormalities are associated with increased risk of heart disease and strokes. Numerous researchers have used this data bank to investigate many aspects of cardiovascular health and how other disease processes such as cancer and diabetes can compound the effects of cardiovascular complications.

Fox (2010), reported early on in the Framingham Heart Study, that diabetes was recognized as a risk factor for cardiovascular disease. In her report she cited a two to four fold increased risk of heart attack, peripheral arterial disease, congestive heart failure, stroke and increased mortality associated with diabetes. She encouraged further research to determine risk factors for cardiovascular disease that may be more specific for diabetes (Fox, 2010).

In this dissertation study a disease registry was used to determine cardiovascular risk factors in a diabetic population. The results revealed an association between gender and the cardiovascular biomarker for this study, low density lipoprotein levels. However, the association contributed to small variance in the regression model. It has been discussed in this chapter that there were limited numbers of data categories in the diabetic registry available to explain a substantial amount of variance in the proposed model. This may be encouraging in terms of laying the groundwork for future research. More comprehensive diabetic registries may be used in the future to determine cardiovascular

risk factors and by doing so, would contribute valuable clinical information about how cardiovascular disease and diabetes are related and launch innovations in improving clinical care for patients with diabetes.

## References

American Diabetes Association. (2008). Economic costs of diabetes in the U.S. in 2007. *Diabetes Care, 31*(3), 596-615. doi: 10.2337/dc08-9017

American Diabetes Association. (2013). Standards of medical care in diabetes. *Diabetes Care, 31(Suppl 1)*, S11-S66. doi: 10.2337/dc13-S011

Andersen, S., Blouch, K., Bialek, J., Deckert, M., Parving, H. H., & Myers, B. D. (2000). Glomerular permselectivity in early stages of overt diabetic nephropathy. *Kidney International, 58*(5), 2129-2137. doi: 10.1111/j.1523-1755.2000.00386.x

Arnlov, J., Evans, J. C., Meigs, J. B., Wang, T. J., Fox, C. S., Levy, D., . . . Vasan, R. S. (2005). Low-grade albuminuria and incidence of cardiovascular disease events in nonhypertensive and nondiabetic individuals: the Framingham Heart Study. *Circulation, 112*(7), 969-975. doi: 10.1161/circulationaha.105.538132

Bayes's Theorem (2013) *Encyclopædia britannica.*

Bonow, R.O., Smaha, L.A., Smith, Jr., S.C., Mensah, G.A., Lenfant. (2002). World Heart Day 2002: The international burden of cardiovascular disease: Responding to the emerging global epidemic. *Circulation*, 106(13), 1602-1605.

Bucala, R., Makita, Z., Vega, G., Grundy, S., Koschinsky, T., Cerami, A., & Vlassara, H. (1994). Modification of low density lipoprotein by advanced glycation end products contributes to the dyslipidemia of diabetes and renal insufficiency. *Proeedings of the National Academy of Sciences of the United States of America, 91*(20), 9441-9445.

City-Data.com. Kern County, California demographcs. Retrieved September 27, 2014 from www.city-data.com/county/Kern_County-CA.html.

Cooper, R., Cutler, J., Desvigne-Nickens, P., Fortmann, S. P., Friedman, L., Havlik, R., . . . Thom, T. (2000). Trends and disparities in coronary heart disease, stroke, and other cardiovascular diseases in the United States: findings of the national conference on cardiovascular disease prevention. *Circulation, 102*(25), 3137-3147.

Dawber, T.R. (1960). Summary of recent literature regarding cigarette smoking and coronary heart disease. *Circulation*, 22, 164-166.

Engelgau, M. M., Geiss, L. S., Saaddine, J. B., Boyle, J. P., Benjamin, S. M., Gregg, E. W., . . . Venkat Narayan, K. M. (2004). The Evolving diabetes burden in the United States. *Annals of Internal Medicine, 140*(11), 945-950. doi: 10.7326/0003-4819-140-11-200406010-00035

Field, A. (2005). *Discovering statistics using SPSS (2nd ed.)*. Thousand Oaks, CA: Sage.

Fox, C. S. (2010). Cardiovascular disease risk factors, type 2 diabetes mellitus, and the Framingham Heart Study. *Trends Cardiovasc Med, 20*(3), 90-95. doi: 10.1016/j.tcm.2010.08.001

Framingham Heart Study. Retrieved April 6, 2014, from www.framinghamheartstudy.org

Garg, J. P., & Bakris, G. L. (2002). Microalbuminuria: marker of vascular dysfunction, risk factor for cardiovascular disease. *Vasc Med, 7*(1), 35-43.

Geronimus, A. T., & Bound, J. (1998). Use of census-based aggregate variables to proxy for socioeconomic group: evidence from national samples. *American Journal of Epidemiology, 148*(5), 475-486.

Gerstein, H. C., Swedberg, K., Carlsson, J., McMurray, J. J., Michelson, E. L., Olofsson, B., . . . Investigators, C. P. (2008). The hemoglobin A1c level as a progressive risk factor for cardiovascular death, hospitalization for heart failure, or death in patients with chronic heart failure: an analysis of the Candesartan in heart failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program. *Archives of Internal Medicine, 168*(15), 1699-1704. doi: 10.1001/archinte.168.15.1699

Grundy, S. M., Benjamin, I. J., Burke, G. L., Chait, A., Eckel, R. H., Howard, B. V., . . . Sowers, J. R. (1999). Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation, 100*(10), 1134-1146.

Henry, R. M., Kostense, P. J., Bos, G., Dekker, J. M., Nijpels, G., Heine, R. J., . . . Stehouwer, C. D. (2002). Mild renal insufficiency is associated with increased cardiovascular mortality: The Hoorn Study. *Kidney International, 62*(4), 1402-1407. doi: 10.1111/j.1523-1755.2002.kid571.x

Hillege, H. L., Janssen, W. M., Bak, A. A., Diercks, G. F., Grobbee, D. E., Crijns, H. J., . . . Prevend Study, G. (2001). Microalbuminuria is common, also in a nondiabetic, nonhypertensive population, and an independent indicator of cardiovascular risk factors and cardiovascular morbidity. *Journal of Internal Medicine, 249*(6), 519-526.

Hinzmann, R., Schlaeger, C., & Tran, C. T. (2012). What do we need beyond hemoglobin A1c to get the complete picture of glycemia in people with diabetes? *International Journal of Medical Sciences, 9*(8), 665-681. doi: 10.7150/ijms.4520

Holvoet, P., Mertens, A., Verhamme, P., Bogaerts, K., Beyens, G., Verhaeghe, R., . . . Van de Werf, F. (2001). Circulating oxidized LDL is a useful marker for identifying patients with coronary artery disease. *Arteriosclerosis, Thrombosis, and Vascular Biology, 21*(5), 844-848.

Howard, B. V., Robbins, D. C., Sievers, M. L., Lee, E. T., Rhoades, D., Devereux, R. B., . . . Howard, W. J. (2000). LDL cholesterol as a strong predictor of coronary heart disease in diabetic individuals with insulin resistance and low LDL: The Strong Heart Study. *Arteriosclerosis, Thrombosis, and Vascular Biology, 20*(3), 830-835.

Huck, S. W. (2008). *Reading statistics and research* (5th ed.). Boston, MA: Pearson.

Jager, A., Kostense, P. J., Nijpels, G., Heine, R. J., Bouter, L. M., & Stehouwer, C. D. (1998). Microalbuminuria is strongly associated with NIDDM and hypertension, but not with the insulin resistance syndrome: the Hoorn Study. *Diabetologia, 41*(6), 694-700. doi: 10.1007/s001250050970

Kanjilal, S., Gregg, E.W., Cheng, Y.J., Zhang,P., Nelson, D.E., Mensah, G., & Beckles, G.L. (2006). Socioeconomic status and trends in disparities in 4 major risk factors for cardiovascular disease among US adults, 1971–2002. *Archives of Internal Medicine,* 166(21), 2348–2355.

Kannel, W.B. (1967). Habitual level of physical activity and risk of coronary heart disease: the Framingham Study. *Canadian Medical Association Journal*, 96 (12), 811-812.

Kannel, W.B., Dawber, T.R., Kagan, A., Revotskie, N., Stoke,s J.I. (1961). Factors of risk in the development of coronary heart disease – six year follow-up experience. The Framingham Study. *Annals of Internal Medicine*, 55, 33-50.

Katz M.H. (2006). *Multivariable Analysis. A practical guide for clinicians (2nd ed.).* New York, NY: Cambridge University Press.

Khaw, K. T., Wareham, N., Bingham, S., Luben, R., Welch, A., & Day, N. (2004). Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. *Annals of Internal Medicine, 141*(6), 413-420.

Krauss, R. M. (1995). Dense low density lipoproteins and coronary artery disease. *American Journal of Cardiology, 75*(6), 53B-57B.

Kvan, E., Pettersen, K. I., Sandvik, L., Reikvam, A., & Investigators, I. S. (2007). High mortality in diabetic patients with acute myocardial infarction: cardiovascular co-morbidities contribute most to the high risk. *International Journal of Cardiology, 121*(2), 184-188. doi: 10.1016/j.ijcard.2006.11.003

Lambert, P., & Bingley, P. J. (2002). What is type 1 diabetes? *Medicine, 30*(1), 1-5. doi: http://dx.doi.org/10.1383/medc.30.1.1.28264

Lane, J. T. (2004). Microalbuminuria as a marker of cardiovascular and renal risk in type 2 diabetes mellitus: a temporal perspective. *Renal Physiology - American Journal of Physiology, 286*(3), F442-450. doi: 10.1152/ajprenal.00247.2003

Levey, A. S., Beto, J. A., Coronado, B. E., Eknoyan, G., Foley, R. N., Kasiske, B. L., . . . Wright, J. T., Jr. (1998). Controlling the epidemic of cardiovascular disease in chronic renal disease: what do we know? What do we need to learn? Where do we go from here? National Kidney Foundation Task Force on Cardiovascular Disease. *American Journal of Kidney Disease, 32*(5), 853-906.

Liu, J., Sempos, C., Donahue, R. P., Dorn, J., Trevisan, M., & Grundy, S. M. (2005). Joint distribution of non-HDL and LDL cholesterol and coronary heart disease risk prediction among individuals with and without diabetes. *Diabetes Care, 28*(8), 1916-1921.

Mertler, C. A., & Vannatta, R. A. (2005). *Advanced and Multivariate Statistical Methods* (3rd ed.). Glendale, CA: Pyrczak Publishing

Monroy, S. (2013). [Personal Communication].

Murphy, S. L., Jiaquan, X., Kochanek, K.D. (2013). Deaths: Final Data for 2010. National Vital Statistics Reports,. *61*(4), 1-3. Retrieved from www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_04.pdf

Nathan, D. M., Kuenen, J., Borg, R., Zheng, H., Schoenfeld, D., Heine, R. J., & Group, A. c.-D. A. G. S. (2008). Translating the A1C assay into estimated average glucose values. *Diabetes Care, 31*(8), 1473-1478. doi: 10.2337/dc08-0545

Niskanen, L., Turpeinen, A., Penttila, I., & Uusitupa, M. I. (1998). Hyperglycemia and compositional lipoprotein abnormalities as predictors of cardiovascular mortality in type 2 diabetes: a 15-year follow-up from the time of diagnosis. *Diabetes Care, 21*(11), 1861-1869.

Pal, S. (2006). Prevalence of cardiovascular disease. *US Pharmacist., 31*(2).

Pearson, T. A., Blair, S. N., Daniels, S. R., Eckel, R. H., Fair, J. M., Fortmann, S. P., . . . Taubert, K. A. (2002). AHA Guidelines for primary prevention of cardiovascular disease and stroke: 2002 update: consensus panel guide to comprehensive risk reduction for adult patients without coronary or other atherosclerotic vascular

diseases. American Heart Association Science Advisory and Coordinating Committee. *Circulation, 106*(3), 388-391.

Regitz-Zagrosek,V., Lehmkuhl, E., Weickert, M.O. (2006). Gender differences in the metabolic syndrome and their role for cardiovascular disease. *Clinical Research in Cardiology*, Mar;95(3), 136-47.

Scheen, A. J. (2003). Pathophysiology of type 2 diabetes. *Acta Clinica Belgica, 58*(6), 335-341.

Singh, P., Ricksten, S.-E., Bragadottir, G., Redfors, B., & Nordquist, L. (2013). Renal oxygenation and haemodynamics in acute kidney injury and chronic kidney disease. *Clinical and Experimental Pharmacology and Physiology, 40*(2), 138-147. doi: 10.1111/1440-1681.12036

Stark Casagrande, S., Fradkin, J. E., Saydah, S. H., Rust, K. F., & Cowie, C. C. (2013). The prevalence of meeting A1C, blood pressure, and LDL goals among people with diabetes, 1988-2010. *Diabetes Care, 36*(8), 2271-2279. doi: 10.2337/dc12-2258

Stehouwer, C. D., Gall, M. A., Twisk, J. W., Knudsen, E., Emeis, J. J., & Parving, H. H. (2002). Increased urinary albumin excretion, endothelial dysfunction, and chronic low-grade inflammation in type 2 diabetes: progressive, interrelated, and independently associated with risk of death. *Diabetes, 51*(4), 1157-1165.

Stehouwer, C. D., & Smulders, Y. M. (2006). Microalbuminuria and risk for cardiovascular disease: analysis of potential mechanisms. *Journal of the American Society of Nephrology, 17*(8), 2106-2111. doi: 10.1681/ASN.2005121288

Stern, M. P. (1995). Diabetes and cardiovascular disease. The "common soil" hypothesis. *Diabetes, 44*(4), 369-374.

Tagle, R., Acevedo, M., & Vidt, D. G. (2003). Microalbuminuria: is it a valid predictor of cardiovascular risk? *Cleveland Clinic Journal of Medicine, 70*(3), 255-261.

Valmadrid, C. T., Klein, R., Moss, S. E., & Klein, B. E. (2000). The risk of cardiovascular disease mortality associated with microalbuminuria and gross proteinuria in persons with older-onset diabetes mellitus. *Archieves of Internal Medicine, 160*(8), 1093-1100.

Veazie, M. A., Galloway, J. M., Matson-Koffman, D., LaBarthe, D. R., Brownstein, J. N., Emr, M., . . . American Heart, A. (2005). Taking the initiative: implementing the American Heart Association guide for improving cardiovascular health at the community level: healthy people 2010 heart disease and stroke partnership community guideline implementation and best practices workgroup. *Circulation, 112*(16), 2538-2554. doi: 10.1161/CIRCULATIONAHA.105.169179

Weir, M. R. (2004). Microalbuminuria in type 2 diabetics: an important, overlooked cardiovascular risk factor. *Jounal of Clinical Hupertention, 6*(3), 134-141; quiz 142-133.

Weir, M. R. (2007). Microalbuminuria and cardiovascular disease. *Clinical Journal of the American Society of Nephrology, 2*(3), 581-590. doi: 10.2215/CJN.03190906

Wolf, P.A., Kannel, W.B., McNamara, P.M. (1970). Occult impaired cardiac function, congestive heart failure, and risk of thrombotic stroke: The Framingham Study. *Neurology*, 20 (4), 373.

# Appendix B


May 19, 2014

To Whom It May Concern:

Mary Anziano, FNP-C has permission to use the Diabetic Registry Data Bank of BFMC/HPN for research purposes.

This may be done with the following stipulations:

1. The identities of participants in the Diabetic Registry Data Bank will be de-identified.
2. The research proposal will be reviewed and approved by the University of San Diego's Institutional Review Board.

Please feel free to contact me with any questions or concerns. I may be reached at (661) 331-2747.

Sincerely,

Debbie Zamiora
Risk Management

cc: Carol Sorrell, C.O.O.

DZ/hp