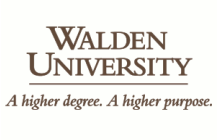

2015

The Association between Rheumatoid Arthritis and Type 2 Diabetes Mellitus

Magaly Perez Nieves
Walden University

Walden University

College of Health Sciences

This is to certify that the doctoral dissertation by

Magaly Perez Nieves

has been found to be complete and satisfactory in all respects,
and that any and all revisions required by
the review committee have been made.

Review Committee
Dr. Daniel Girdano, Committee Chairperson, Public Health Faculty
Dr. Frank Casty, Committee Member, Public Health Faculty
Dr. Mehdi Agha, University Reviewer, Public Health Faculty

Chief Academic Officer
Eric Riedel, Ph.D.

Walden University
2015

Abstract

The Association between Rheumatoid Arthritis and Type 2 Diabetes Mellitus

by

Magaly Perez Nieves

M.P.H., University of Puerto Rico, 1998

B.S., University of Puerto Rico, 1997

Dissetation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

Public Health

Walden University

August 2015

Abstract

A research report from the Centers for Disease Control and Prevention (CDC) indicated that more than 50% of people with diabetes mellitus (DM) in the United States (U.S.) also have arthritis. The diabetes population is disproportionately affected by arthritis, but there has been limited and inconsistent research to confirm the association between type 2 diabetes mellitus (T2DM) and rheumatoid arthritis (RA). The current study aimed to identify an association between T2DM and RA for noninstitutionalized U.S. adults between 1999 and 2012 using a nationally representative sample from the National Health and Nutrition Examination Survey (NHANES) database (n =31,488). A quantitative, cross-sectional investigation was conducted to determine if patients with T2DM had an increased prevalence of RA. The current study also sought to identify characteristics that could affect the association between both groups and the prevalence of cardiovascular disease (CVD) in this population. Prevalence and adjusted odds ratios (OR) using logistic regression were calculated. The results show evidence of a strong association between T2DM and concomitant RA. Prevalence of RA was significantly higher in participants with T2DM compare to those without T2DM. Important factors in this association were gender, ethnicity, education, disability, and work functioning. The prevalence of CVD and adjusted OR of association were doubled in participants with T2DM and RA when compared to participants who had just one of the conditions; the OR of association was quadrupled when compared to those without this comorbidity. This study may provide patients and health care providers with a better understanding of the need for management of both conditions in a interdisciplinary manner.

The Association between Rheumatoid Arthritis and Type 2 Diabetes Mellitus

by

Magaly Perez Nieves

M.P.H., University of Puerto Rico, 1998

B.S., University of Puerto Rico, 1997

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

Public Health

Walden University

August 2015

Dedication

I dedicate this dissertation to my family who has been of great support during the process of completing my degree. In particular to my husband Oscar who has been always supportive of my decisions; to my son, Miguel Angel, who at his little age was able to share his mom's time with this project and finally to my mother Maria who has been my biggest motivation.

Acknowledgments

I would like to express my appreciation to my committee chair Dr Daniel Girdano, who was constantly present and available to help during this long research process. Thanks for the advice and support throughout the application process and at all stages of my research. I really appreciate your knowledge but more your understanding and support on a daily basis. I would also like to thank my committee members, Dr Casty and Dr Agha, for your time, support, and advice reviewing my research. I would like to thanks all the anonymous reviewers at Walden University, including the IRB, at which this work has been accepted and presented. Great appreciation to Eli Lilly and company for their support in my development as a better professional.

As a special recognition, BIG THANKS to David Nelson, my statistician, NHANES database expert, and my friend. Thanks for sharing all your knowledge with me and responding to all my questions no matter how silly they were. Your deep knowledge of the field and presence continually proved to be a valuable asset. Thanks for all your advice during this process and for your spirit of adventure in regard to my research. Without your guidance this dissertation would not have been possible. I would also thank Kathy Ruiz for your help with proof reading, reviewing, and editing this work.

Finally and most importantly I would like to acknowledge my family. To my kids, David and Miguel Angel, for understanding every time I needed to share their time with school. To my husband, Oscar, who has encouraged and challenged me to complete this project. And finally to my mom, Maria Nieves, who is my major inspiration; there are not enough words to say THANK YOU. This work is dedicated to you.

Table of Contents

List of Tables

List of Figures

Chapter 1: Introduction to the Study

Background

The prevalence of diabetes has reached epidemic proportions worldwide; more than 347 million people, corresponding to almost 7% of the world's population, are estimated to live with diabetes (IDF, 2012; WHO, 2013a). The number is expected to grow to more than 552 million by 2030, corresponding to approximately 8% of the world's total population (IDF, 2012). Diabetes caused 4.8 million deaths and cost more than $471 billion in healthcare expenses in 2012 (IDF, 2012). In the United States, diabetes affects 25.8 million people of all ages, or approximately 8.3% of the U.S. population (CDC, 2011a). Several comorbidities have been related to diabetes, and some of them are considered complications of the same condition (ADA, 2013a). As part of the public health strategy, it is important to consider everything affecting health issues. For example, in case of diabetes, it is essential to work in a interdisciplinary manner to (a) identify emerging issues and opportunities, and (b) develop ways in which different components can work together to build upon each other's areas of expertise. This approach stimulates collaborations and helps ensure that health efforts are coordinated, not duplicated.

Arthritis is not widely recognized as comorbid with diabetes and is notconsidered as part of the potential difficulties that patients and care providers may encounter when managing diabetes (ADA, 2013a). Data from the CDC indicated that more than half of people with diabetes also suffer from arthritis; however, no clear evidence is available

that indicates an association between type 2 diabetes mellitus (T2DM) and rheumatoid arthritis (RA), one of the most common types of arthritis (CDC, 2008; CDC, 2010b).

The incidence and prevalence of RA are difficult to define, and changes in trends are difficult to predict. The prevalence of RA varies between 0.3% and 1% globally; it is more common in women and in developed countries. The World Health Organization (WHO) indicated that within 10 years of onset , at least 50% of patients in developed countries are unable to hold down a full-time job (Woolf & Pfleger, 2003; WHO, 2013b). An estimated 1.5 million people in the United States were affected by RA in 2007 (CDC, 2013a; Myasoedova et al., 2010).

Arthritis and other rheumatic conditions are the most common cause of disability among U.S. adults and have been for the past 15 years. Forty-two percent of adults with doctor-diagnosed arthritis report activity limitations due to arthritis (CDC, 2010b). Considering diabetes and the effect on disability, the National Health Interview Survey (NHIS) has found that disability affects an estimated 20–50% of patients with diabetes. In general, patients with diabetes report rates of disability that are substantially higher than those reported by the general U.S. population (CDC, 2011a). The consequences of disability are extensive, including increased absenteeism, lack of employment, lower income levels, limited access to health care services, decreased health status, and lower quality of life. Evidence also has indicated that DM and RA are equally associated with increased risk of cardiovascular disease (CVD; Kitas & Erb, 2003; Karanasos et al., 2012; Lindhardsen et al., 2010; Peters et al., 2009; Peters et al., 2010; Van Halm et al., 2009), which is identified as the major cause of death in the United States (CDC, 2011b).

However, no data are available that reflect how the prevalence of CVD is affected by the comorbidity of T2DM and RA.

Researchers have reported data that indicate a potential association between T2DM and RA; however finding an association between these two important conditions was not the main purpose for most of these investigations. Only a few studies have been conducted to evaluate the potential association between T2DM and RA, and results are not consistent. Simard and Mittleman concluded that there was no association between RA and DM; however, this study was limited because it included only people aged 60 years old and over and did not include the general population and it evaluated data only from 1988 to 1994 (Simard & Mittleman, 2007). Tentolouris et al. (2008) evaluated the presence of concomitant RA in patients with DM and followed studythem for at least 10 years, but was not able to reach any conclusions due to the relatively small cohort. Solomon et al. (2010a) examined the risk of DM in patients with RA : RA appeared to be associated with an increased risk of DM. However, this increased risk decreased with age. According to the authors, , this study needs replication. Dubreuil et al. (2012) evaluated the risk of incident DM in RA and found that the risk was significantly elevated only with increased body mass index (BMI) and smoking.

Data from other studies have demonstrated different results when an association between DM and RA is evaluated as an exploratory objective. Based on these studies, it is not clear how these important conditions are related, which is an important gap to assess in order to be able to manage this comorbidity adequately.

Since the literature has shown mixed results with small direct and indirect studies, the next logical step is to conduct a larger and more direct investigation to evaluate the association between T2DM and RA and potentially relevant characteristics. The current study included a cross-sectional evaluation with a bigger sample, considering all adult age ranges (over 20 years old) and using more recent data (19992012) from NHANES.

This study has implications for social change. This resulting data may give care providers and patients a better understanding of how to manage both conditions using an interdisciplinary approach. Results may also support the creation of adequate public health interventions for preventing arthritis in patients with diabetes and for managing modifiable lifestyle characteristics for both conditions.

This chapter covers the following topics: the problem and the research questions to be addressed in this investigation,. the theoretical foundation and a brief summary of the literature , the nature of the research, and the study's assumptions, limitations, scope, and significance.

Statement of the Problem

CDC data from 2008 has indicated that more than half of people with diabetes also suffer from arthritis in general; however, no association between T2DM and RA, a common type of arthritis, has been demonstrated (CDC, 2008). There are several reasons] why association could exist between these two conditions: (a) both conditions are linked to CVD (Stamatelopoulus et al., 2009b; Van Halm et al., 2009; Lindhardsen et al., 2010; Peters et al., 2009; Stamatelopoulos et al., 2009a); (b) systemic inflammation is one of the characteristics of RA (CDC, 2012a); at the same time it has been demonstrated that

these characteristics of inflammation predispose the development of insulin resistance and T2DM (Sattar et al., 2003); (c) markers of inflammation like C-reactive protein (CRP) and interleukin 6 predict T2DM (MacLennan, 2007); and (d) medications commonly used in RA, like glucocorticoids, are expected to contribute to insulin resistance, which increases the risk of developing T2DM (Wasko et al., 2011; Antohe et al., 2010; Antohe et al., 2012; Bili et al., 2011; Solomon et al., 2010b; Solomon et al., 2011; Sasaki et al., 2010; Yokota & Igaki, 2012).

Diabetes is a broadly recognized public health issue and, as part of a public health strategy to improve health, it is important to consider all related health issues and to investigate them in a interdisciplinary manner (ADA, 2013a; ADA, 2013b; ADA, 2014). RA is not widely recognized as a comorbidity of diabetes and thus is not managed as such (CDC, 2012a). The conclusions in the literature about the association between T2DM and RA are inconsistent (Simard and Mittleman, 2007; Tentolouris et al., 2008; Solomon et al., 2010a; Dubreuil et al., 2012; Bartels et al., 2012).

Purpose of the Study

The quantitative and cross-sectional study sought to clarify whether there is any association between T2DM and RA for noninstitutionalized U.S. adults between 1999 and 2012. It explored whether patients with T2DM (independent variable) had increased prevalence of RA (dependent variable) compared with patients without T2DM using a U.S. nationally representative sample, both with and without adjustment for potentially confounding factors. Logistic regression analysis was performed with the complex survey sampling methods utilizing sampling strata and taking surveys' weight into consideration

in order to be generalizable to the U.S. population. To mitigate confounding bias, covariates identified in the literature as potential confounders (gender, age, race/ethnicity, education level, and smoking status) were considered in this analysis. The adjusted odds ratios (ORs) for the association between T2DM and RA were estimated after adjusting for covariates.

Using a group of patients with RA, this study identified and described potential characteristics that could differentially affect the prevalence of T2DM. The characteristics or variables evaluated for this analysis were age, gender, race/ethnicity, education level, poverty level, disability, smoking status, blood pressure levels, BMI, lipid levels (high-density lipoprotein [HDL]/ low-density lipoprotein [LDL], total cholesterol [TC]), CRP, use of antirheumatic medications, and the presence of CVD.

Using a second group of patients with T2DM, this study identified and described potential characteristics that could differentially affect the prevalence of RA. The characteristics or variables evaluated for this analysis were age, gender, race/ethnicity, education level, poverty level, disability, smoking status, blood pressure levels, BMI, lipid levels (HDL/LDL, TC), presence of CVD, plasma glucose, and glycosylated hemoglobin (HbA1c).

Using a third group of patients with T2DM and concomitant RA, this study evaluated and compared the risk of CVD for three groups: T2DM with concomitant RA; RA without concomitant T2DM; and T2DM without concomitant RA. Logistic regression was performed to complete these analysis.

Research Questions and Hypotheses

This study sought to answer the following research questions by testing their associated hypotheses:

1. Do patients with T2DM have statistically significant increased prevalence of RA in comparison with patients without T2DM?

   $H_0$1: Patients with T2DM do not have a statistically significant increased prevalence of RA compared to patients without T2DM, after adjustment for potential confounders.

   H_A1: Patients with T2DM do have a statistically significant increased prevalence of RA compared to patients without T2DM, after adjustment for potential confounders.

2. What demographic, lifestyle, or clinical characteristics are significantly different for those patients with RA and T2DM in comparison with patients with RA but no presence of T2DM?

   Is there a difference in prevalence of RA based on the specific demographic, lifestyle, or clinical characteristics in patients with and without T2DM?

   $H_0$2a:

   - Patients with T2DM do not have a statistically significant different prevalence of RA compared to patients without T2DM based on specific demographic, lifestyle, or clinical characteristics.

H_A2a:

- Patients with T2DM do have a statistically significant different prevalence of RA compared to patients without T2DM based on specific demographic, lifestyle, or clinical characteristics.

Characteristics evaluated on this inquiry are demographic (age, gender, race/ethnicity, education level, and poverty level); lifestyle (disability, smoking status, and work functionality), and clinical (blood pressure levels, BMI, lipid levels [HDL/LDL, TC], CRP, use of antirheumatic medications, and presence of CVD).

3. What demographic, lifestyle, or clinical characteristics are significantly different for those patients with RA and T2DM in comparison with patients with T2DM but no presence of RA?

   Is there a difference in prevalence of T2DM based on the specific demographic, lifestyle, or clinical characteristics in patients with and without RA?

   $H_0$3a:

   - Patients with RA do not have a statistically significant different prevalence of T2DM compared to patients without RA based on specific demographic, lifestyle, or clinical characteristics.

   H_A3a:

   - Patients with RA do have a statistically significant different prevalence of T2DM compared to patients without RA based on specific demographic,

lifestyle, or clinical characteristics.

Characteristics evaluated on this inquiry are demographic (age, gender, race/ethnicity, education level, and poverty level); lifestyle (disability, smoking status, work functionality); and clinical (blood pressure levels, BMI, lipid levels [HDL/LDL, TC], presence of CVD, plasma glucose, and HbA1c).

4. Do patients with T2DM and concomitant RA have a statistically significant higher prevalence of CVD in comparison with patients with T2DM and no presence of RA and patients with RA and no presence of T2DM?

   H04a:

   - Patients with T2DM and concomitant RA do not have a statistically significant increased prevalence of CVD compared to patients with T2DM and no presence of RA and patients with RA and no presence of T2DM, after adjustment for potential confounders.

   H_A4a:

   - Patients with T2DM and concomitant RA do have a statistically significant increased prevalence of CVD compared to patients with T2DM and no presence of RA and patients with RA and no presence of T2DM, after adjustment for potential confounders.

Theoretical Foundation

This study used a theoretical framework based on the expanded chronic care model (ECCM) and the social ecological model (SEM). The first model, ECCM, shows an integrated effort to manage chronic disease, in an organized and multifaceted way, that

has been proven to work on better management of DM. Social and behavioral characteristics may also make an important contribution in the association between both conditions. The second model, SEM, highlight the important of evaluating multiple factors that could contribute to potential association. This model considers the complex interplay between individual, relationship, community, societal factors, and public policy. It helps address the factors that could influence the association between T2DM and RA. A discussion of these two theories is found in Chapter 2.

Rationale for a connection between DM and RA has been noted in prior research. First, it is known that cardiovascular risk is higher in both conditions, T2DM and RA. Second, inflammation plays an important role in both conditions. In RA, the immune system attacks joints, which creates ongoing inflammation, which in turn, produces increased markers, such as CRP, and these markers have been shown to be associated with DM (Schmidt et al., 1999; MacLennan, 2007; Sattar et al., 2003). On the other hand, inflammation is also associated with insulin resistance, which makes the body less responsive to insulin, thus increasing the risk of developing T2DM (Schmidt et al, 1999; Sattar et al., 2003). In addition, some treatments for RA, such as nonsteroidal, antiinflammatory medications (NSAIDs) and corticosteroids, could elevate blood glucose levels and thus increase the risk of diabetes; other drugs, such as tumor necrosis factor (TNF) inhibitors and hydroxychloroquine, are associated with a decreased risk of DM in patients with RA (Wasko et al., 2011; Antohe et al., 2010; Antohe et al., 2012; Bili et al., 2011; Solomon et al., 2010b; Solomon et al., 2011; Sasaki et al., 2010; Yokota & Igaki, 2012). A summary of the available data is discussed in the literature review.

Nature of the Study

This study employed a quantitative, cross-sectional design using a secondary analysis of data from the large nationally representative data set, the continuous NHANES. Data analysis was performed using SAS (version 9.2). Different groups from the diagram in Figure 1 were used to answer the three questions in this study.

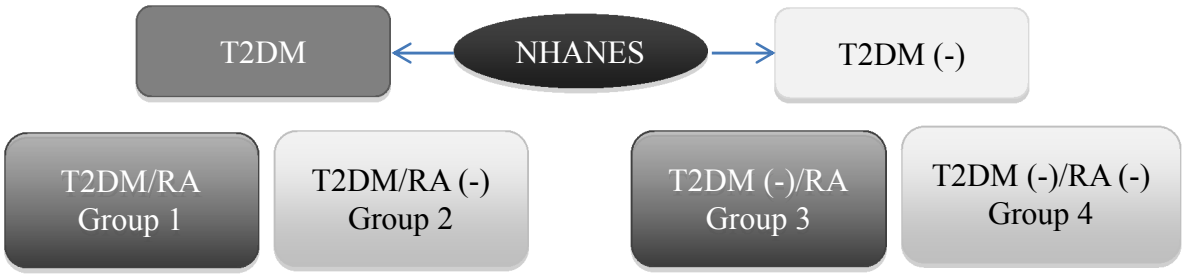

Figure 1. Study cohorts.

For Objective 1, it was aimed to evaluate if patients with T2DM do have a statistically significant increased prevalence of RA compared to patients without T2DM, after adjustment for potential confounders. The cross-sectional association between T2DM and RA was investigated using logistic regression with T2DM as the independent variable and RA as the dependent variable. A description of variables and crude and adjusted prevalence of RA for patients with and without T2DM was included. Adjusted ORs of RA were determined, considering the following potential confounders—age, sex, race/ethnicity, education, and smoking—as previously determined by Simard and Mittleman (2007).

For Objective 2, Groups 1 and 3 from the study group diagram (Figure 1) were used to identify patients with RA and both with and without T2DM. Logistic regression

was performed using RA as the dependent variable and T2DM as the independent variable in order to determine univariate ORs. . This analysis described potential characteristics that are statistically significantly different comparing prevalence of T2DM within RA in comparison with prevalence of T2DM within participants with no presence of RA.. The characteristics evaluated in this inquiry were demographic (age, gender, race/ethnicity, education level, and poverty level); lifestyle (disability, smoking status, and work functioning); and clinical (blood pressure levels, BMI, lipid levels [HDL/LDL, TC], plasma glucose, HbA1c, CRP, and the use of antirheumatic medications).

For Objective 3, Groups 1 and 2 in the study group diagram were used to identify patients with T2DM among patients with and without RA. Logistic regression was performed using T2DM as the dependent variable and RA as the independent variable to determine univariate ORs. This analysis described potential characteristics that are statistically significantly different comparing prevalence of T2DM within RA in comparison with prevalence of T2DM within participants with no presence of RA. Characteristics evaluated on this inquiry were demographic (age, gender, race/ethnicity, education level, and poverty level); lifestyle (disability, smoking status, and work functioning); and clinical (blood pressure levels, BMI, lipid levels [HDL/LDL, TC], CRP, use of antirheumatic medications, plasma glucose, and HbA1c).

For Objective 4, the analysis described and compared the prevalence rates of CVD among patients with T2DM and comorbid RA, patients with T2DM and without

RA, and patients with RA and without T2DM. This analysis included crude and adjusted prevalence of RA for all groups.

Using NHANES from the National Center for Health Statistics, RA and T2DM were identified using specific classifications for the target populations:

- RA: Included all patients 20 years and older with self-reported RA using an affirmative response to the RA-related question of the survey
- T2DM: Included all patients 20 years old and older with self-reported diabetes. To exclude type 1 diabetes mellitus (T1DM), all patients who reported receiving a physician's diagnosis before age 30 and who initiated insulin therapy within one year of diagnosis were excluded. Women reporting a diagnosis of diabetes during pregnancy were excluded.

The following covariates were evaluated in this study: 1) demographic characteristics including age, gender, race/ethnicity, education level, and poverty level; 2) lifestyle characteristics including smoking status, work functioning, and disability; 3) clinical characteristics including blood pressure levels, BMI, lipid levels (HDL/LDL and TC); rheumatic-related characteristics including CRP (inflammation) and use of antirheumatic medications; diabetes-related characteristics including plasma glucose and HbA1c; and finally presence of CVD.

Definitions

The primary variables and covariates are defined below.

Primary Variables

Diabetes mellitus (DM): DM is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Insulin is a hormone that regulates blood sugar. As an effect of DM, patients suffer hyperglycemia (high blood sugar levels) which leads to serious damage to different systems of the body. Some of the most common complications of diabetes are related to damage of the heart, blood vessels, eyes, kidneys, and nerves (USMLM, 2014; ADA, 2013a). There are different types of diabetes but for this study only T2DM is considered. T1DM, gestational diabetes (diabetes during pregnancy), and any other type of diabetes were excluded for the purpose of this study. Pre / bordenline diabetes was not considered for this analysis. The diagnosis, treatment, and burden of T2DM are discussed further in Chapter 2.

Rheumatoid arthritis (RA): RA is a chronic, systemic inflammatory disorder that may affect many tissues and organs, but principally attacks synovial joints. The process produces an inflammatory response of the synovium (synovitis) secondary to hyperplasia of synovial cells, excess synovial fluid, and the development of pannus in the synovium. This process often leads to the destruction of articular cartilage and ankylosis of the joints. Similar to DM, the cause of RA is unknown, but autoimmunity plays a pivotal role in both its chronicity and progression. RA is considered a systemic autoimmune disease that causes the body to produce cells that attack its own tissues. This results in inflammatory damage to the joints and surrounding muscle resulting in moderate

discomfort to severe pain, swelling, and redness (CDC, 2012a). The diagnosis, treatment, and burden of RA are discussed further in Chapter 2.

Covariables

Age: The risk of developing most types of arthritis including RA increases with age. The risk of T2DM increases with age especially after age 45, which is likely the result of less exercise, loss of muscle mass, and weight gain as people age.

Gender: Most types of arthritis are more common in women; 60% of all people with arthritis are women. In general, no significant gender difference has been found for diabetes.

Race/ ethnicity: Blacks, Hispanics, American Indians, and Asian-Americans are more likely to develop T2DM than whites. In general, no significant race or ethnic difference has been found for arthritis.

Education level: Mokdad et.al. (2001) identified that patients with DM having "less than a high school education" had the highest rate (13%) among the educational levels. Some literature has indicated that education level is an important marker of clinical status in RA. Risk factors such as smoking, inactivity, and medication regimen noncompliance are more prevalent in those patients who have a lower educational level (high school or less) compared with those classified with a higher education level (more than high school) (Callahan & Pincus, 1988).

Poverty level: The poverty levels set a minimum amount of gross income a family needs for food, clothing, transportation, shelter, and other necessities. In the United States, this level is determined by the Department of Health and Human Services.

Poverty level varies according to family size. The number is adjusted for inflation and reported annually in the form of poverty guidelines. Based on data from the Behavioral Risk Factor Surveillance System (BRFSS), people who make $15,000 or less are three times more likely to have diabetes than people who make $50,000 or more, regardless of race. Poverty is an important factor in DM because people with lower incomes are less able to afford healthy foods, may lack education on good nutrition, or simply have less access to healthy food options in their particular area. Another point to consider is inactivity or reduced work functioning, which is higher within patients with diabetes. Reduced work functioning negatively impact employment, which may lead to lack of insurance affecting access to medical care. Along the same lines, RA can cause disability and reduce productivity, which are also associated with unemployment, low poverty levels and lack of access to medical care (Lundkvist, 2008), .

Smoking: Smoking is a practice in which a substance is burned, and the smoke is tasted or inhaled. Currently the most common substance is tobacco in the form of cigarettes. There is plenty of evidence that shows that smoking cigarettes increases the risk of RA and DM, while quitting can reduce the risk.

Disability: A disability may be physical, cognitive, mental, sensory, emotional, developmental, or some combination of these. A disability may be present from birth or occur during a person's lifetime. The consequences of disability are extensive including increased absenteeism, lack of employment, lower income levels, limited access to health care services, decreased health status, and lower quality of life. Arthritis and other rheumatic conditions are the most common cause of disability among U.S. adults and

have been for the past 15 years (CDC, 2013a). Forty-two percent of adults with doctor-diagnosed arthritis report arthritis-attributable activity limitations (CDC, 2010b).

The NHIS has found that disability affects an estimated 20–50% of patients with diabetes including work disability. Patients with diabetes, in general, report rates of disability that are substantially higher than those reported by the general U.S. population (CDC, 2006; Mayfield, 1999; Aubert, R.,1995).

***Blood pressure levels and hypertension*:** Blood pressure is the pressure of the blood within the arteries. It is produced primarily by the contraction of the heart muscle. Systolic blood pressure (SBP) is defined as the highest arterial blood pressure of a cardiac cycle occurring immediately after the contraction of the left ventricle of the heart and diastolic blood pressure (DBP) is the lowest arterial blood pressure of a cardiac cycle occurring during passive rhythmical expansion of the heart. Its measurement is recorded by two numbers, and measurements are reported in millimeters of mercury (mmHg).

Hypertension: Hypertension is the elevation of blood pressure.

The following table reflects blood pressure categories defined by the American Heart Association (AHA).

Blood pressure category	Systolic mm Hg (upper #)		Diastolic mm Hg (lower #)
Normal	less than 120	and	less than 80
Prehypertension	120 – 139	or	80 – 89
High blood pressure (hypertension) Stage 1	140 – 159	or	90 – 99
High blood pressure (hypertension) stage 2	160 or higher	or	100 or higher
Hypertensive crisis (emergency care needed)	Higher than 180	or	Higher than 110

There is evidence in the literature that has indicated an association between hypertension and diabetes as well as its complications including micro- and macrovascular disease. RA, as well as DM, is associated with elevated risk of CVD, which is attributed to several potential factors including hypertension. Hypertension is highly prevalent and seems to be underdiagnosed and undertreated among patients with RA (Panoulas et al., 2008).

BMI, obesity, and overweight: BMI is defined as the individual's body weight divided by the square of his or her height. Thisuniversal formulaused in medicine produces a unit of measure of kg/m^2.

The CDC uses the following weight categories for adults based on BMI (body mass index) ranges.

Weight status	BMI
Underweight	Below 18.5
Normal	18.5 – 24.9
Overweight	25.0 – 29.9
Obese	30.0 and above

Obesity is a medical condition that is characterized by excessive accumulation and storage of fat in the body and is considered an independent risk factor for several chronic conditions including T2DM, RA, and CVD. Carrying excess pounds puts stress on joints, particularly on the knees, hips, and spine. Obese people have a higher risk of developing arthritis. Being overweight is a primary risk factor for T2DM. The more fatty tissue a person has the more resistant to insulin the cells become (AHA, 2013).

Lipid levels **(HDL/LDL and TC)**: Blood lipids (or blood fats) are lipids in the blood, either free or bound to other molecules. They are mostly transported in a protein capsule, and the density of lipids and type of protein determine the fate of the particle and its influence on metabolism. The concentration of blood lipids depends on intake and excretion from the intestine, and uptake and secretion from cells. Blood lipids are mainly fatty acids and cholesterol. Hyperlipidemia is the presence of elevated or abnormal levels of lipids and/or lipoproteins in the blood and is a major risk factor for CVD.

The 2001 National Cholesterol Education Program (NCEP) clinical guidelines for cholesterol testing and management are as follows:

Classification	Total cholesterol
Normal blood cholesterol	<200 mg/dl
Borderline-high cholesterol	200–239 mg/dl
High cholesterol	>240 mg/dl

HDL and LDL are two smaller of the five major groups of lipoproteins, which enable lipids like cholesterol and triglycerides to be transported within the water-based bloodstream.

In healthy individuals, about 30% of blood cholesterol is carried by HDL. Having large numbers of large HDL particles correlates with better health outcomes, and hence HDL is commonly called "good cholesterol." In contrast, having small amounts of large HDL particles is independently associated with atheromatous disease progression within the arteries. Studies have shown that higher levels of type-B LDL particles (as opposed to type-A LDL particles) promote health problems and CVD, and hence LDL is commonly called “bad cholesterol.”

***C-reactive protein (CRP)*:** CRP is a protein found in the blood, levels of which rise in response to inflammation. Measuring CRP level is a screen for infectious and inflammatory diseases. Rapid, marked increases in CRP occur with inflammation, infection, trauma and tissue necrosis, malignancies, and autoimmune disorders. Because there are a large number of disparate conditions that can increase CRP production, an elevated CRP level does not diagnose a specific disease. An elevated CRP level can provide support for the presence of an inflammatory disease, such as RA.

Use of Antirheumatic medications: A variety of medications is used to treat RA. When given early enough, some interrupt the progression of the disease by reducing inflammation and preventing joint damage. Others help relieve symptoms of joint stiffness and pain. The following drugs can be given alone or in combination: disease-modifying anti-rheumatic drugs (DMARDs); biologic response modifiers (a category of DMARDs); glucocorticoids; NSAIDs; and analgesics.

Plasma glucose: Glucose is the primary sugar that is made from the foods and beverages a person consumes. This glucose travels throughout the bloodstream to provide energy to cells in all regions of the body. Plasma glucose refers to the amount of this primary sugar that is found in the liquid portion of the blood. The fasting plasma glucose (FPG) test measures blood sugar levels and is one of the alternatives used to diagnose diabetes. This is a relatively simple and inexpensive test that identifies problems with insulin function. Measurements of plasma glucose are reported in milligrams per deciliter (mg/dL) or millimoles per liter (mmol/L).

General glucose targets specified in guidelines for management of T2DM in the United States are shown in the following table:

HbA1c	FPG	Postprandial glucose	Guideline authority	Reference
≤6.5%	<110 mg/dL)	≤180 mg/dL)	AACE	Garber et al., 2013
<6.5%	<7 mmol/L (<126 mg/dL)	<11.1 mmol/L (<200 mg/dL)	ADA	ADA 2014

Note: AACE = American Association of Clinical Endocrinologists; ADA = American Diabetes Association.

Plasma glucose is also important to identify episodes of hypoglycemia or low level of blood sugar, defined as blood glucose level lower than 70 mg/dL.

Glycated hemoglobin or glycosylated hemoglobin (hemoglobin A1c, HbA1c, A1C, or Hb1c): This is a form of hemoglobin that is measured primarily to identify the average plasma glucose concentration over prolonged periods of time. It is formed in a nonenzymatic glycation pathway by hemoglobin's exposure to plasma glucose. Normal levels of glucose produce a normal amount of glycated hemoglobin. As the average amount of plasma glucose increases, the fraction of glycated hemoglobin increases in a predictable way. This serves as a marker for average blood glucose levels over the previous months prior to the measurement.

The 2010 American Diabetes Association (ADA) Standards of Medical Care in Diabetes added the HbA1c ≥ 48 mmol/mol (≥6.5%) as another criterion for the diagnosis of glucose levels. High levels of HbA1c have been associated with CVD, nephropathy, and retinopathy. Monitoring HbA1c in patients with diabetes may improve outcomes. In general, the reference range (that is found in healthy people) is about 20 to40 mmol/mol (4–5.9%). The International Diabetes Federation and American College of Endocrinology recommend HbA1c values below 48 mmol/mol (6.5%) while American Diabetes Association recommends HbA1c values below 53 mmol/mol (7.0%) for most patients.

Cardiovascular disease (CVD): CVD is a group of disorders of the heart and blood vessels and include coronary heart disease: disease of the blood vessels supplying the heart muscle; cerebrovascular disease: disease of the blood vessels supplying the brain; peripheral arterial disease: disease of blood vessels supplying the arms and legs; rheumatic heart disease: damage to the heart muscle and heart valves from rheumatic fever, caused by streptococcal bacteria; congenital heart disease: malformations of heart

structure existing at birth; deep vein thrombosis and pulmonary embolism: blood clots in the leg veins, which can dislodge and move to the heart and lungs. Heart attacks and strokes are usually acute events and are mainly caused by a blockage that prevents blood from flowing to the heart or brain. The most common reason is a build-up of fatty deposits on the inner walls of the blood vessels. Strokes can be caused by bleeding from a blood vessel in the brain or by blood clots.

There are several studies that provide evidence of the increased cardiovascular risk in RA and DM. For RA, studies have found 1.5 to 2-fold increase in comparison with the general population. Potential reasons are risk factors associated with CVD as well as RA such as obesity, insulin resistance, hypertension, atherosclerosis, dyslipidemia (Stamatelopoulus et al., 2009b), and inflammation (Sattar et al., 2003). Cardiovascular risk in RA is increased to an extent comparable to the risk found in DM (Van Halm et al., 2009; Lindhardsen et al., 2010; Peters et al., 2009; Stamatelopoulos et al., 2009a). CVD has been identified as the major complication of DM and is the primary cause of early mortality among people with this condition. About 65% of patients with DM die from heart disease and stroke. Adults with DM are two to four times more likely to have heart disease or suffer a stroke than people without diabetes (NIH, 2007; CDC, 2011a). This was confirmed by a meta-analysis of 102 prospective studies in which it was concluded that patients with DM have about two-fold excess risk for a wide range of vascular diseases, independently from other conventional risk factors (Sarwar, 2010).

Sample weight: A fraction or selection of individuals from within a statistical population is used to estimate characteristics of the whole population. A sample weight is

used when a sample design does not give each individual an equal chance of being selected. In this case, each person is assigned with a sample weight to compensate for the unequal selection probability (e.g., for minority racial/ethnic population groups) and adjust for nonresponse. This strategy is used by NHANES to avoid bias when determining estimates of a nationally represented sample.

Assumptions

The sample used in NHANES was selected to represent the adult U.S. population. The information on the set of surveys utilized for the current study was collected in a consistent and appropriate manner by health care providers and interviewers. It is expected that all information collected in the survey is kept strictly confidential. NHANES is an ongoing program and the information collected contributes to annual estimates. Due to this reason, it is appropriate to accumulate data over several years to provide adequate estimates. It was assumed that the criteria selected to define T2DM and RA were accurate for both conditions, and data self- reported by patients was true.

Scope and Delimitations

The current study used data from the continuous NHANES to evaluate the association between T2DM and RA. The NHANES population represented a weighted, random sample of the civil, noninstitutionalized population of the United States. It is important to document that the population sample and the limitations of the database were applicable to the U.S. population and may have excluded generalizations (external validity) to other countries, especially with different health care systems. NHANES data captures one point in time (cross-sectional design), which provides almost no basis for

drawing conclusions about causality; thus, this study can be used only for correlation purposes. Additional prospective and longitudinal studies will be needed if a correlation is found in order to demonstrate causality between variables.

Limitations

The NHANES study does not have a specific question to determine the type of diabetes a patient has. Diabetes for the current study included any patient with T2DM based on patient's self-reported diabetes. To eliminate potential patients with T1DM, all patients who reported receiving a physician's diagnosis before age 30 and who initiated insulin therapy within 1 year of diagnosis were excluded. There is a small chance of misclassification which could over or underestimate the prevalence of T2DM. Women with a diagnosis of diabetes during pregnancy or evidence of gestational diabetes were excluded.

The design of this study has various limitations. First, due to the cross-sectional design, analysis was restricted to the association between DM and RA; no temporality or causality information, can be concluded. Second, both T2DM and RA have a high prevalence in the older population, which could bias prevalence. Adjustment by age was intended to mitigate this possibility.

The process of identifying diabetes and arthritis in the database could have lead to misclassification, considering the self-reporting from patients, which is considered another limitation. Someaspects of subject recruitmentcould erve to underestimate the prevalence of the disease in the population. For example, participants with severe disease in both cases could be missed because they were physically unable to see a doctor for

examination; along the same line, institutionalized people (e.g., those in nursing homes) are excluded from NHANES. In addition, patients without access to health care or those who were economically disadvantaged may not have had the opportunity to be diagnosed for conditions that require a specialist. Disability could also have minimized the number of patients considered for this survey.

Significance

Diabetes is a broadly recognized public health issue and, as part of a public health strategy to improve health, it is important to consider all related health issues and to investigate them in a interdisciplinary manner (ADA, 2013a; ADA, 2013b; ADA, 2014). RA is not widely recognized as a comorbidity of diabetes and thus is not managed as such (CDC, 2012a).

Among individuals with diabetes, comorbid RA might present an under recognized hurdle and at the same time is not managed as part of the potential difficulties that people may encounter when managing diabetes.

This study has implications for social change. This resulting data may give health care providers and patients a better understanding of how to manage both conditions using an interdisciplinary approach. Results may also support the creation of adequate public health interventions for preventing arthritis in patients with diabetes and for managing modifiable lifestyle characteristics for both conditions.

Summary

Data from the CDC indicates that more than 50% of all people in the United States with diabetes mellitus (DM) have some kind of arthritis (CDC, 2008). However,

there is no recognized association between T2DM and RA and for this reason these two conditions are not managed in a interdisciplinary manner.. The current study aimed to identify if any association existed between T2DM and RA for noninstitutionalized U.S. adults between 1999 and 2012 using a nationally representative sample from the NHANES. A quantitative, cross-sectional investigation was used to determine if patients with T2DM had increased prevalence of RA. At the same time, the current study sought to clarify which characteristics could differentially affect the association between both groups and the potential risk increased risk for of CVD when this comorbidity exists. With the complex survey methodology in mind, a logistic regression analysis was performed taking the complex survey methodology into consideration to analyze the U.S. population. The prevalence and adjusted odds ratios (OR) for the cross-sectional association between T2DM and RA was determined after adjusting for potential confounders. The study may provide patients and health care providers with a better understanding of how to manage both conditions in a interdisciplinary manner.

Chapter 1 introduced the problem along withthe approach for answering the research question. Chapter 2 provides an overview of the relevant literature. Chapter 3 includes a detailed description of the research methods. The results are discussed in Chapter 4. A summary of findings, conclusions, and recommendations for future investigation is included in Chapter 5.

Chapter 2: Literature Review

Introduction

The purpose of this chapter is to define the main variables for this investigation, DM and RA. In the first section of this chapter, the definition, diagnosis, burden, and treatment of DM and RA are discussed . Second, a description of the theoretical foundations and how they inform the current research are covered. Finally, the available research on DM and RA are discussed, including the following: the risk of CVD in both conditions; studies evaluating inflammation and markers of inflammation; research on the behavioral aspects of this issue; and a discussion of the few available studies that were developed in order to evaluate the association between DM and RA—the ultimate target of the literature review.

RA and DM are both disorders with unknown causality and similar risk factors. The association between these two conditions has not been clearly defined. Some studies on this association lack consistency or conclusions. The majority of the results found in the literature were based on studies that were not designed to assess this relationship. As indicated by Doran (2007), it is not clear whether there is an increased prevalence of DM in patients with RA or an increased prevalence of RA in patients with DM. This study sought to evaluate the cross-sectional association between T2DM and RA and to identify the characteristics that may be relevant in this association. This literature review will provide an overview of the effort that has been done in this area..

Literature Review Strategy

The following databases—limited to full text from 2008 to 2012—were used for the literature review: MEDLINE, EMBASE, ProQuest (dissertations) and Cochrane Collaborative. The keywords were limited to *diabetes* and *rheumatoid arthritis*. Seminal review articles were read when they offered reference lists to key articles. To avoid publication bias, three supplementary sources were used over the same time period to identify relevant articles: American Diabetes Association (ADA), European Association of the Study of Diabetes (EASD) and International Diabetes Foundation (IDF).

The following criteria were followed to select articles: (a) information was pertinent to any one of the research questions; (b) a full-text article was available and included a full description of the study design and methods used to assess the association between main variables; (c) the publication was available in English or Spanish; (d) general articles on T2DM or DM were included (all other specific types of DM were excluded); and (e) arthritis was limited to RA.

Diabetes Mellitus

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia (high levels of glucose in blood) of diabetes is associated with long-term damage, dysfunction, and failure of different organs including retinopathy (damage of the eyes), nephropathy (damage to the kidneys), neuropathy (issues with nerves), and CVD (problems with heart and blood vessels) (ADA, 2013a; UKPDS, 2000). There are different types of diabetes but for this study only T2DM is considered. T1DM,

gestational diabetes (diabetes during pregnancy), and any other type of diabetes will be excluded for the purpose of this study. Prediabetes will not be considered in this analysis.

The most common symptoms for diabetes are polyuria (excessive excretion of urine), polydipsia (continuous thirst), constant hunger, weight loss, vision changes, and fatigue. Symptoms are similar in all types of diabetes, but they are less marked in T2DM, which makes the disease difficult to diagnose. This delay on diagnosis may have critical consequences because the disease could exist for several years affecting systems in the body before awareness of the disease. T2DM was an adult disease until recently, but it is now also occurring in children due to changes in lifestyles and behaviors during the last decades.

Diagnosis of Diabetes

The ADA issued diagnostic criteria for DM based on one of four abnormalities: HbA1c, FPG, random elevated glucose with symptoms, or abnormal oral glucose tolerance test (OGTT) (ADA, 2013a).

Specific criteria for the diagnosis of diabetes are as follows:

1. HbA1c ≥6.5%. The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay.*

Or

2. FPG ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 hours.*

Or

3. 2-hours plasma glucose ≥200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

Or

4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dl (11.1 mmol/l).

* In the absence of unequivocal hyperglycemia, Criteria 1–3 should be confirmed by repeat testing.

Classifications of Diabetes

There are four classifications of diabetes: (a) T1DM; (b) T2DM; (c) gestational diabetes, and d) other. The first two categories include the vast majority of all patients with diabetes considering approximately 90–95% for T2DM and 5–10 % for T1DM. T2DM will be the main focus of this investigation. T1DM, gestational diabetes, and other types of diabetes are not included in the literature review for the purpose of this study.

Type 2 Diabetes Mellitus

This type of diabetes formerly called noninsulin-dependent or adult-onset is the most common among all cases with diabetes and includes individuals who have insulin resistance and usually have relative (rather than absolute) insulin deficiency. T2DM is a chronic condition in which insulin resistance disturbs the body's ability to properly metabolize carbohydrate, fat, and protein preventing the cells in the body from effectively accessing and utilizing blood glucose as a source of energy (CDC, 2013b; Ryden et al., 2007). This type of diabetes is a progressive disease that worsens with elevated blood glucose levels, and is a consequence of genetic predisposition, unhealthy diet, physical inactivity, and increasing weight (CDC 2013b; Ryden et al., 2007). There are many different causes of this form of diabetes, but the specific etiologies are not known. In these patients, autoimmune destruction of cells does not occur, and most patients are obese, and obesity itself causes some degree of insulin resistance. Patients who are not obese by traditional weight criteria may have an increased percentage of body fat distributed predominantly in the abdominal region. This form of diabetes frequently goes undiagnosed for many years because the hyperglycemia develops gradually, and at earlier

stages is often not severe enough for the patient to notice any of the classic symptoms of diabetes. T2DM symptoms may develop very slowly. In fact, a patient can have T2DM for years without knowing it, which increases the risk of developing micro- and macro vascular complications. The risk of developing T2DM increases with age, obesity, and lack of physical activity (ADA, 2013a).

Treatment of Diabetes

The 2009 Consensus Statement from the ADA and the EASD recommends that all diabetes management programs include, at diagnosis and throughout the management of T2DM, a lifestyle intervention strategy to promote weight loss and increase activity levels (Nathan et al., 2009). Such lifestyle programs, however, generally have limited long-term success in maintaining glycemic goals in patients with T2DM, thus requiring the need for medications to control glucose levels. Medications available to control diabetes are the following:

- Oral antidiabetic medications: biguanides (e.g., metformin); secretagogues (e.g., sulphonylureas); thiazolidinediones (e.g., glitazones); alpha-glucosidase inhibitors; meglitinides (e.g. repaglinide); dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g., sitagliptin, vildagliptin); and sodium glucose co-transporter-2 (SGLT-2) inhibitors (e.g., canagliflozin, dapagliflozin)
- Insulin: short-acting and rapid-acting (mealtime) insulin therapies; intermediate-acting and long-acting (basal) insulin therapies; and mixed insulin therapies

- Glucagon-like peptide-1 (GLP-1) analogs

Burden of Diabetes

The burden of diabetes is increasing globally, particularly in developing countries. The IDF estimated that approximately 371 million people worldwide have diabetes (including T1DM or T2DM) as of 2012. The number of cases is expected to grow to 552 million by the year 2030 (IDF, 2012). Diabetes increases the risk of cardiovascular and cerebrovascular disease. The risk of dying as a result of CVD in people with diabetes (primarily heart disease and stroke) is more than 50%. The overall risk of dying among people with diabetes is at least double the risk of people without diabetes (WHO, 2013a).

In the United States, diabetes affects 29.1 million people of all ages which constitute approximately 9.3% of the population. In 2010, diabetes was the seventh leading cause of death; and based on death certificate reports, diabetes contributed to 234,051 deaths in the United States (CDC, 2014).

Several important studies contributed to a greater understanding of DM and the implications of this condition including the DCCT, UK Prospective Diabetes Study (UKPDS), Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE), and Action to Control Cardiovascular Risk in Diabetes (ACCORD):

- The DCCT is a major clinical study conducted from 1983 to 1993 funded by the National Institute of Diabetes and Digestive and Kidney Diseases. The study showed that maintaining blood glucose levels as close to normal

as possible is associated with a decrease of micro- and macrovascular complications (DCCT, 1993; DCCT, 1996).

- The UKPDS is the largest randomized, multicenter trial for newly diagnosed patients with T2DM conducted from 1977 to 1997 in 23 UK clinical sites. This study concluded that a better control of blood glucose and/or blood pressure is associated with a reduction of diabetes complications. The results of this study indicated that improving glycemic control reduces the risk of microvascular disease by 25% ($p<0.05$). (UKPDS, 2000).
- The ADVANCE study suggests that a strategy of intensive glucose control may reduce the occurrence of micro- and macrovascular events, as patients in this study who received treatment targeting intensive control of glucose levels (HbA1c level < 6.5%) experienced a 10% relative reduction in the occurrence of major macro- and microvascular events (Patel et al., 2008).

Other studies, including the ACCORD study, that were presented at the ADA conference in 2008 conference have suggested that intensive control of blood glucose levels in T2DM might have no impact on the likelihood of death or CVD, or may even increase the risk of cardiovascular events and mortality. The ACCORD study concluded that the use of intensive therapy increased mortality and did not significantly reduce the occurrence of major cardiovascular events (Gerstein et al., 2008; Genuth & Ismail-Beigi, 2012).

Diabetes prevalence is increasing dramatically worldwide. The following factors are some of the causes for the elevated numbers: changes in lifestyle including poor nutrition and inactivity; demographic changes such as aging, which increase the high risk population; and better surveillance and interventions, which identify more cases (USDHHS, 2013). Diabetes is an important public health challenge but also has big implications on the economic aspect of health management. Based on the last analysis from the ADA, the estimated cost of diagnosed diabetes in 2012 is $245 billion, considering direct medical costs ($176 billion) and lack of productivity ($69 billion). The cost of diabetes care accounts for more than one in five health care dollars in the United States (ADA, 2013b, CDC, 2011a).

Rheumatoid Arthritis

RA is a chronic disease identified by inflammation including joint swelling, joint tenderness, and destruction of synovial joints, which lead to severe disability and premature mortality (Aletaha et al., 2010). It is an autoimmune disease, which means the body's immune system mistakenly attacks healthy tissue, and its cause is unknown. RA can occur at any age; however, it is more common in middle age. Women get RA more often than men. Infection, genes, and hormone changes may be linked to the disease.

RA usually affects joints on both sides of the body equally. Wrists, fingers, knees, feet, and ankles are the most commonly affected. The disease often begins slowly, usually with only minor joint pain, stiffness, and fatigue. One of the most common symptoms is morning stiffness, which could last more than one hour. In addition, joints may feel warm, tender, and stiff when not used for an hour. Joint pain is often felt on the

same joint on both sides of the body. Over time, joints may lose their range of motion and may become deformed. Other symptoms include chest pain when taking a breath (pleurisy); dry eyes and mouth (Sjogren syndrome); burning eyes, itching, and discharge; nodules under the skin (usually a sign of more severe disease); numbness, tingling, or burning in the hands and feet; and sleep difficulties.

Diagnosis of Rheumatoid Arthritis

There is no specific test that can confirm a diagnosis of RA. Most, but not all, patients with RA will have some abnormal test results. Two lab tests that often help in the diagnosis are: a) rheumatoid factor test; and b) anti-CCP antibody test. Other tests that may be done include: complete blood count; CRP; erythrocyte sedimentation rate; joint ultrasound or magnetic resonance imaging (MRI); joint x-rays; and synovial fluid analysis.

Treatment of Rheumatoid Arthritis

The key objectives when treating RA are to reduce pain, control inflammation, and delay or stop the progression of the disease. The treatment of RA is more than just medications--it a multifaceted group of elements including medications, occupational or physical therapy, exercise, and in some cases, surgery. It is important to identify the disease as early as possible and treat it aggressively to delay or stop the progression of joint damage.

The following treatments are commonly used for RA: NSAIDs; DMARDs; biologics; and steroids to treat severe RA or when symptoms flare. Surgery (joint replacement) is an option when joint pain and inflammation become intolerable or joints

simply refuse to function. NSAIDs reduce pain and inflammation but do not slow progression of RA. DMARDs help slow or stop the progression of disease by suppressing the immune system overall, but there is an increased probability of infection.

The newest and most effective treatments for RA are biologics that are genetically engineered proteins. They are designed to inhibit specific components of the immune system that play a pivotal role in inflammation, which is a key component in this condition. Biologic drugs are commonly used when previous drugs have failed to stop the inflammation of RA. It has been found that biologics may slow or even stop RA progression; however because biologics suppress the immune system, they also increase the risk of infection.

As previously mentioned for severe RA or when RA symptoms flare, steroids may be an option to ease the pain and stiffness of affected joints. They can be given as injections directly into an inflamed joint or can be taken as a pill. Potential side effects of long-term steroid use include high blood pressure, osteoporosis, and diabetes.

Burden of Rheumatoid Arthritis

The majority of population-based descriptive statistics on RA is available because of the Rochester Epidemiology Project (REC). REC was originally funded by the National Institute of General Medical Sciences in 1966 under the direction of Dr. Leonard T. Kurland. Based on this study, in 1995-2007, 41 per 100,000 people were diagnosed with RA each year. Incidence rose with age (e.g., 8.7 per 100,000 people among those aged 18-34 compared with 54 per 100,000 among those aged ≥ 85 years); and incidence peaked among people aged 65-74 years (89 per 100,000) (all estimates

age-adjusted to 2000 U.S. population). The prevalence of RA is believed to range from 0.5–1.0% in the general population. Prevalence estimates derived from 2001-2005 U.S. ambulatory health care system data estimated that 1.5 million U.S. adults have RA. The age-adjusted prevalence of RA among women was 7.7 per 1000 compared with 4.4 per 1000 among men (CDC, 2012a).

RA causes significant morbidity, disability, and mortality but also substantially decreases quality of life and productivity, which negatively impacts society as well as individual patients. RA impacts people of all ages but most heavily on people of working age (disease is most common after 40), and it is a major cause of sickness, absence, disability, and unemployment.

Similar to DM, RA has big economic implications for the population. Based on available literature, the total annual cost of RA in the United States is around $19.3 billion. According to Birnbaurm et al. (2010), 33% of the total cost is allocated to employers, 28% to patients, 20% to the government, and 19% to caregivers. Adding intangible costs of quality-of-life deterioration ($10.3 billion) and premature mortality ($9.6 billion), total annual societal costs of RA (direct, indirect, and intangible) increased to $39.2 billion (Birnbaum et al., 2010).

Theoretical Foundation

This study has a theoretic foundation based on the ECCM and the SEM. The first model shows an integrated effort to manage chronic disease using an organized and multifaceted approach that has been proven to improve management of DM and the

second one draws an important evaluation of multiple factors or characteristics that could contribute to the potential association.

Expanded Chronic Care Model

The ECCM was developed in 2003 by Barr et al. to improve the original model called ChroniccCare model (CCM). CCM was created by Dr. E. Wagner in 1996, in the United States, to support the care of patients with chronic disease and combine a number of approaches to improve the overall management of the diseases. This model provides a broader approach to the prevention and management of chronic diseases and focuses practice and efforts toward health outcomes for individuals, communities, and populations (Barr et al., 2003).

The original model combines elements of health promotion and population health including

- Self-Management – Implementing various approaches to enhance skills and capacities for personal health and wellness. Individuals are offered support by their health care provider and in the community to develop skills to improve their health.
- Decision Support – Using guidelines and standards to guide health care services. Health care providers use specific information to make appropriate decisions about health care and disease management.
- Delivery System Design – Organizing and coordinating health care services in ways that meet the needs of individuals to better prevent and manage chronic disease.

- Information Systems – Developing systems to collect information about health. The information can be used to make the case for new policies and programs, evaluate established programs, and support new ways of working to improve the quality of care.

The new model is integrated with the following components:

- Health System - Organization of Healthcare - Program planning that includes measurable goals for better care of chronic illness.
- Community Resources and Policies - Developing partnerships with community organizations that support and meet patients' needs.

Figure 2 and 3 includes figures 1 and 2 from Barr et al., 2003 to clearly show the enhancement of the model.

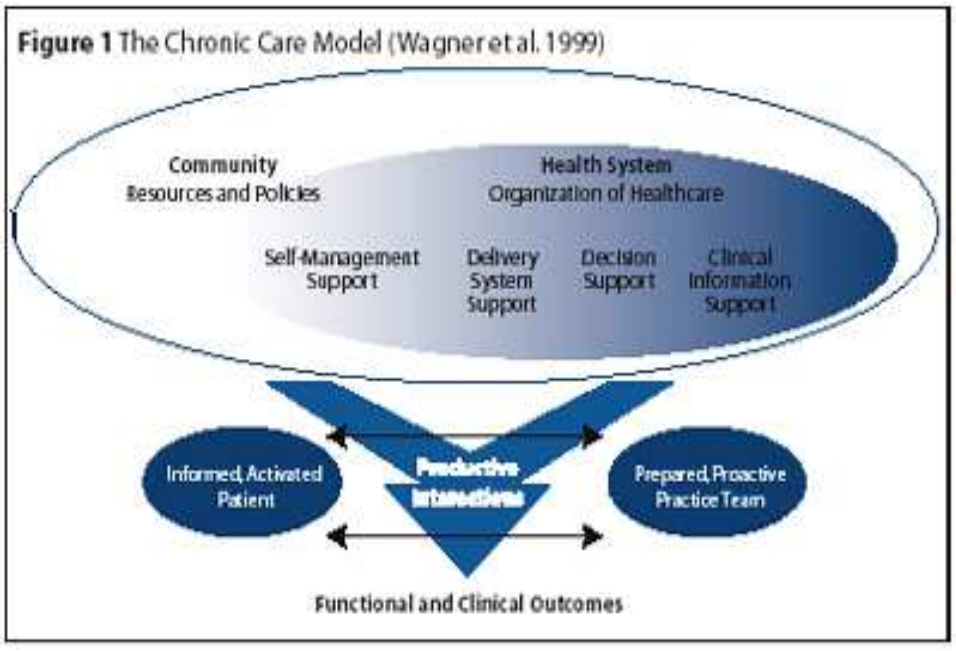

Figure 2. The chronic care model (reprinted with permission from Longwoods Publishing Corporation).

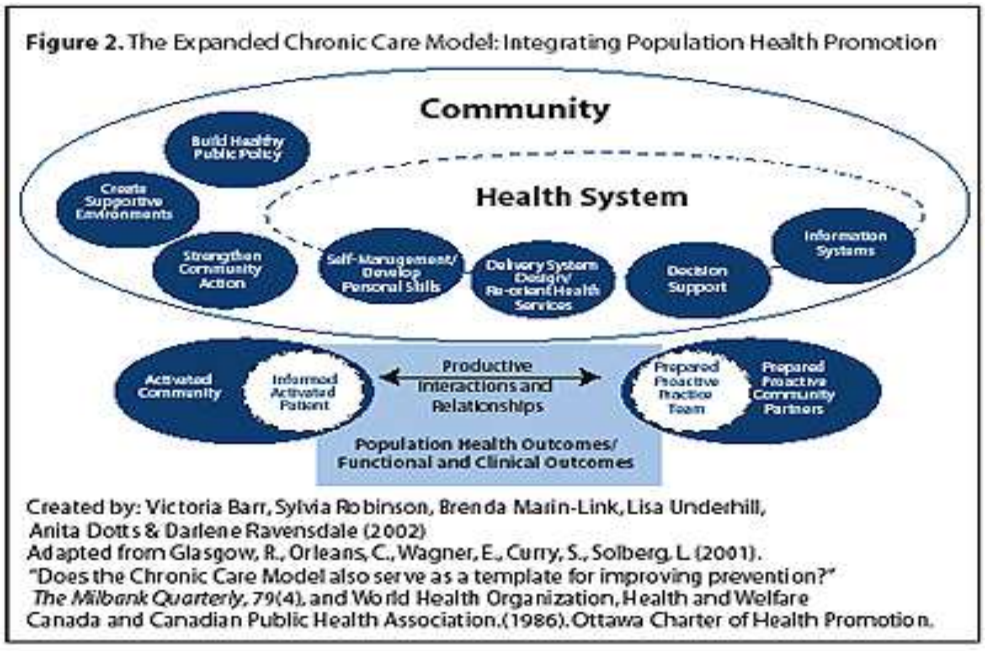

Figure 3. The expanded chronic care model (reprinted with permission from Longwoods Publishing Corporation).

The model is organized and brings multifaceted support for primary care teams that have been proven to positively affect care of patients with diabetes (Coleman et al., 2009; Nutting et al., 2007). The expanded version of the model incorporates other areas like population health promotion, recognition of the social determinants of health, and enhanced community participation, which bring a better management of chronic diseases (Barr et al., 2003).

Chronic disease is a major threat to the health of a population; this group of diseases is the most common cause of death and the most costly element to the health care system (WHO, 2013b). There are several factors contributing to the elevated prevalence of chronic disease including the high rates of modifiable risk factors, such as smoking, physical inactivity, unhealthy diets, and excess alcohol use. These risk factors

drive other intermediate risk conditions, such as high blood pressure, high blood sugar, excess body fat, and high blood cholesterol. In addition, mental and emotional stress may be important aspects in the development or progression of chronic disease. The age of the population is another point to consider in this topic because chronic diseases become more prevalent as people get older. There are many other factors that affect health including income level, education level, and employment status. It is clear that social, behavioral, economic, and environmental conditions influence a person's ability to maintain good health, prevent chronic disease, and manage the complications of the disease. Good health is necessary to maintain the labor force and to continue the well-being of individuals and the continued wealth of the world (Sullivan, S.,2011).

In order to better manage this hazard, a comprehensive and coordinated approach must be implemented to prevent complications and better manage progression of disease, which includes

- All parties working together, including individuals, the community, and health care providers (interdisciplinary approach)
- Support of individuals to become more engaged and active in managing their own health (better understanding of diseases and potential interactions between them to better manage health in general)
- Use of the most current evidence and guidelines to provide quality care in a coordinated, team-based approach with many disciplines working together (use current and correct information and standards to provide quality care)

- An increased focus on promoting health and preventing disease and the progression of disease

This model tries to achieve optimal health considering all of the determinants of health for chronic disease prevention and management. As previously explained in Chapter 1, association between T2DM and RA has not been demonstrated. The results of this study are essential to achieve different components of the model including self-management, interdisciplinary decision support, and delivery system to manage both chronic conditions (T2DM and RA) investigated in this research. Regardless of advances in treatment, research shows that patients frequently do not achieve targets nor get the care they want or need, thus a different approach is needed to achieve better outcomes (Sullivan, 2011).

This investigation intends to provide a better understanding of the association between T2DM and RA, which will help health care providers to incorporate it in their daily care practice but also will inform patients, health care systems, and government if action may be needed in this area. If appropriate, new guidelines or interventions could be created to better manage both conditions in a interdisciplinary approach and integrated decision support and to improve health outcomes as recommended per the model. This study will also describe characteristics that could be relevant for this association which will create the foundation for areas of intervention.

It has been well documented that this approach has been successful when applied to diabetes management (Vargas et al., 2007; Frei et al., 2010). Coleman et al. (2009) examined the evidence of this model's effectiveness by reviewing articles published since

2000 that used one of five key CCM papers as a reference. This review found that these studies suggest that redesigning care using the CCM leads to improved patient care and better health outcomes. Vargas et al. indicated that patients with diabetes experienced reduced risk of CVD; for every 48 patients who received care from a practice using this model, risk declined by one CVD event (Vargas et al., 2007). Other quality improvement evaluations based on the CCM have been published. All showed improvement on some process measures, and most also showed improvement on some intermediate outcome measures such as HbA1c, LDL cholesterol, and arterial pressure. The authors indicated that due to limitations in the study designs of these evaluations, it is difficult to conclude that these changes are the result specifically from CCM efforts.

It is clear that social, behavioral, and environmental conditions influence a person's ability to maintain good health, prevent chronic disease, and manage the complications of the disease. These characteristics may also have an important contribution in the association between both conditions (T2DM and RA). This leads to the second model contemplated in this research, which is the Social Ecological Model (SEM).

Social Ecological Model

This SEM was introduced in 1970s, formalized as a theory in the 1980s, and continually revised by Urie Bronfenbrenner. This model considers the complex interplay between individual, relationship, community and societal factors, and public policy.

The application of the SEM focuses on several goals: to explain the person-environment interaction, to improve people-environment transactions, to encourage

human growth and development in particular environments, and to improve environments, so they support expression of individual's system's natures. Knowing appropriate information to prevent illnesses or complications or to increase benefit, for example, a person should avoid an environment in which they may be more susceptible to have negative outcomes or try to incorporate some settings that are particularly conducive to a positive outcome or health benefits.

The SEM looks at multiple levels of influence on specific health behaviors including the following: individual, relationship, community and societal factors, and public policy (see Figure 4)

- Individual – Intrapersonal--individual's knowledge, demographics, attitudes, values, skills, behavior, self-concept, self-esteem
- Relationship – Interpersonal--social networks, social supports, families, work groups, peers, friends, neighbors norms, incentives, organizational culture, management styles
- Community/Society--community resources, organizational structure, communication networks, neighborhood organizations, folk practices, nonprofit organizations, informal and formal leadership practices
- Public policy--legislation, policies, taxes, regulatory agencies, laws

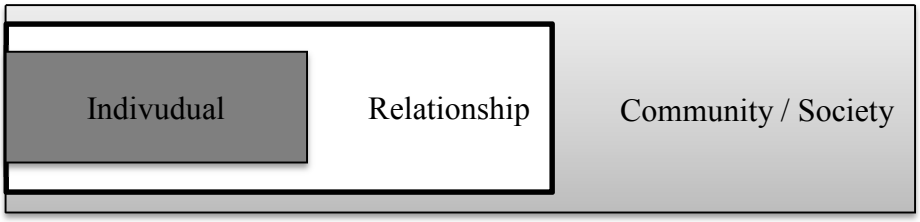

Figure 4. Social ecological model levels.

Multi-level interventions are considered the most effective in changing behavior. This investigation will help define and describe characteristics that could be relevant in the association between DM and RA. For diabetes, self-management education has been identified as "the cornerstone of care for all individuals with diabetes who want to achieve successful health-related outcomes" per the ADA and the National Standards for Diabetes Self-Management Education (Messing et al., 2004, page S143).

An ecological approach to self-management not only includes the individual but also integrates the patient characteristics with the services and support they receive from their social situation, which includes family, friends, worksites, organizations, and cultures; and the physical and policy environments of neighborhoods, communities, and governments. From this perspective, the individual should be aware of factors that help them with the initiation and maintenance of healthy behaviors or environments that improve health outcomes.

The current investigation in this document may identify and describe all potential characteristics relevant in the association between T2DM and RA. Social and behavioral characteristics to be evaluated in this case are race/ethnicity, education level, poverty level, disability, smoking status, and work functionality. The results from the study will enhance the understanding of these characteristics for RA and T2DM patients and the relationship to the potential association. Results of this investigation may be used as the foundation for future diabetes programs to facilitate potential interventions for patients with RA and T2DM.

Previous Research

In addition to the theoretical foundation discussed before, prior research also alluded to rationale that could connect DM and RA. First, it is known that cardiovascular risk is elevated in both conditions and several studies have evaluated and compared the risk for RA and DM. Second, the risk of inflammation plays a role in both conditions. In RA, the immune system attacks joints creating ongoing inflammation. Diseases with a relevant component of inflamation, like RA, increase markers of inflammation, like CRP, that have shown previous association with DM. On the other hand, inflammation is associated with insulin resistance; which impairs the body's ability to respond to insulin adequately, increasing the risk of developing T2DM. In addition, some treatment for RA like NSAIDs and corticosteroids could increase blood glucose levels increasing the risk of DM; while other treatments like TNF inhibitors and hydroxychloroquine were related with a decreased risk of DM in patients with RA

A review of the existing literature was conducted to find available research related to the potential association between T2DM and RA. Different studies designed to investigate other areas had noted a potential association between DM and RA but only few addressed the direct relationship between both conditions. Available research specific to this association is limited, and results are not clear or consistent to answer the question.

Cardiovascular Risk for RA and DM

The majority of the research available for DM and RA is related to the relationships between both conditions, independently, with the risk of CVD. Based on

literature relevant to RA, it has been demonstrated that RA is characterized by elevated cardiovascular morbidity and mortality; however, the reason is not clear (Kitas & Erb, 2003). Potential reasons are risk factors associated with CVD as well as RA including obesity, insulin resistance, hypertension, atherosclerosis, and dyslipidemia (Stamatelopoulus et al., 2009a). Other research indicates the increase of cardiovascular morbidity and mortality with RA could be related to systemic inflammation found in this condition (Sattar et al., 2003).

On the other hand, looking at diabetes, CVD has been identified as the major complication of diabetes and is the primary cause of early death among people with this condition. About 65% of people with diabetes die from heart disease and stroke. Adults with diabetes are 2 to 4 times more likely to have heart disease or suffer a stroke than people without diabetes (NIH, 2007).

It is recognized that both conditions, DM and RA, are connected with an increased risk of CVD. Several investigations have been performed to compare the potential risk of different elements of CVD in both RA and DM. The following section summarizes the information available in this area.

Karanasos et al. (2011) investigated if RA is associated with increased cardiovascular morbidity compared with DM. As a result, the authors found that RA patients in the absence of obstructive coronary artery disease (CAD) may display myocardial ischemia at similar levels to DM and higher than matched control subjects. Another publication from Karanasos et al (2012) shows a prospective evaluation of the possible presence of myocardial ischemia, by dobutamine stress-contrast

echocardiography in asymptomatic patients and comparison to patients with DM and a control group. Results showed that symptomatic patients with RA exhibited high myocardial ischemic burden which was comparable to patients with DM. It was found that myocardial ischemia was common in patients with no obstructive CAD. Positive stress result was found in 67% of RA patients, 78% of DM patients, and 31% of controls ($p<0.05$ for RA vs. control, $p<0.01$ for DM vs. control, p = NS for RA vs. DM).

Similarly, Zampeli et al. (2012) evaluated the presence of silent myocardial ischemia in patients with RA versus patients with DM. They found significant CAD in patients with positive stress ECHO results was more common in DM (50%) and controls (73%) than in RA patients (25%). The conclusions in this case could imply the presence of microvascular rather than coronary abnormalities as a result of elevated myocardial ischemic burden by dobutamine stress-contrast echocardiography in the absence of obstructive CAD exhibit by asymptomatic patients with RA.

Lindhardsen et al. (2010) completed a study to compare the incidence of myocardial infarction (MI) in patients with RA or DM using prescription claims, hospitalizations, and outpatient visits through individual-level-linkage nationwide administrative registers. The overall incidence rate ratio of a MI event after developing RA was increased to 1.61 (95% CI 1.42 to 1.83), which was comparable to the risk of MI after developing diabetes of 1.70 (95% CI 1.59 to 1.83). Aligned with previous investigations, the study found that the risk of MI is especially high among younger patients with RA. Similar to what has been found in DM, this study concluded that RA is an independent risk factor for MI.

A study was performed by Yazdanyar el al. (2012) to determine whether the risks of perioperative death and CV events among patients with RA differed from those among unaffected controls and patients with DM. The authors concluded that RA was not associated with adverse perioperative CV risk or mortality risk. In this research, the cases were classified by severity of risk (low-risk, intermediate-risk, or high-risk noncardiac procedure). Results showed 2.34% of patients with low risk had a composite CV event, and death occurred in the 2.34% of patients. For intermediate and high risk, the numbers were 0.51%, and 2.12% for composite CV event and 0.50%, and 2.59%, for death, respectively. Death was less likely in RA patients than in DM patients (0.30% versus 0.65%; $p< 0.001$) for patients undergoing an intermediate-risk procedure, but the difference in mortality rates among those undergoing low-risk versus those with high-risk procedures was not significant. Patients with RA were less likely to have a CV event than patients with DM for procedures of low risk (3.38% versus 5.30%; $p < 0.001$) and intermediate risk (0.34% versus 1.07%; $p < 0.001$). After evaluation using adjusted models, RA was not independently associated with an increased risk of perioperative death or a CV event.

A 3-year prospective study performed by Peters et al. (2009) indicates that the risk of CVD in RA was significantly elevated compared with the general population and comparable with the extent of the risk in T2DM. For this study, the incidence of CVD in patients with RA was 9% in comparison to 4.3% in the general population. The hazard ratio (HR) for patients without diabetes and with RA (2.16) was comparable with those with T2DM (2.40).

In a cross-sectional study evaluating the risk of CVD between DM and RA, it was concluded that the prevalence of CVD was elevated comparable with what is found in T2DM. Prevalence in the population without diabetes was 5% versus 12.4% found in the population with diabetes and 12.9% in the population with RA (Van Halm et al., 2009).

Stamatelopoulos et al. (2009a) concludes that atherosclerosis (vascular condition in which an artery wall thickens as a result of the accumulation of fatty materials such as cholesterol) is equal on the severity and frequency in patients with DM or RA. The study results reinforced the fact that CVD risk factors need to be addressed for patients with DM but also for patients with RA.

Yazdanyar et al. (2010) performed a cross-sectional analysis of the National Inpatient Sample of the HealthCare Utilization Projects using data from years 1998 to 2002 to compare the risk of perioperative cardiovascular outcomes in a hospital setting among patients with RA, DM, both conditions, and neither condition. The study results indicated that RA was not an independent predictor of perioperative cardiovascular events including acute MI, acute stroke, non-ST elevation MI (ST segment elevation indicates that a relatively large amount of heart muscle damage is occurring, because the coronary artery is totally blocked), and/or congestive heart failure with pulmonary edema. Conversely DM was associated with increased odds of cardiovascular outcomes across all surgical risk levels.

As indicated in the previous summary, there is substantial evidence for increased cardiovascular risk in RA comparable to what is found in DM. Some researchers have questioned if patients with DM and concomitant RA could have doubled cardiovascular

risk, but no data was found in this area. Do patients with T2DM have increased risk of RA in comparison with patients without T2DM? Is the risk of CVD in RA similar to the risk of CVD in T2DM because both conditions are related and because the risk factors or characteristics are similar? Is the risk of CVD a bigger concern for patients having both conditions?

Systemic Inflammation

Another area of interest in the relationship between RA and DM is the potential systemic inflammation that is present in RA including markers and how it could potentially link with insulin resistance. If inflammation can promote insulin resistance, the prevalence of the metabolic syndrome may be increased in patients with RA, which at the same time is indicative of increased risk for CVD. The potential role of insulin resistance as a cardiovascular risk factor in patients with inflammatory arthritis has been examined. Schmidt et al. (1999) found that markers of inflammation are associated with the development of diabetes in mid age adults reflecting the pathogenesis of T2DM. The authors of this study indicated that insulin resistance may help in the development of inflammation instead of being a consequence of high concentrations of inflammatory mediators (Schmidt et al., 1999).

MacLennan (2007) reported that arthritis and diabetes are characterized by high levels of CRP and interleukin-6 (II-6), markers of inflammation; however no association between both conditions was found.

Drug Therapies Affecting RA and DM

Treatment for both conditions has been investigated as potential positive and negative factors in this association. For RA, NSAIDs and corticosteroids are known for their negative effect in blood glucose levels which increase the risk of DM; while other drugs like TNF inhibitors and hydroxychloroquine were related with a positive risk decrease of DM in patients with RA (Wasko et al., 2011; Antohe et al., 2010; Antohe et al., 2012; Bili et al., 2011; Solomon et al., 2010b; Solomon et al., 2011; Sasaki et al., 2010; Yokota & Igaki, 2012).

Behaviors Affecting DM and RA

On the behavioral side, it is important to mention elements that could affect both conditions: physical activity, or the opposite, inactivity. Based on information from the ADA and the American College of Sports Medicine, physical activity could reduce blood glucose and risk factors for complications (e.g., obesity and hypertension) in persons with diabetes and could improve CVD outcomes. Considering RA, this is a very important factor because physical activity can decrease pain and improve functionality, mobility, mood, and quality of life for most adults with many types of arthritis including RA. Inactivity could negatively affect both conditions, RA and T2DM. Based on information from the BRFSS from 2005 to 2007, the prevalence of physical inactivity is higher for those patients with DM and RA (29.8%) in comparison with those who had only one or none of these two conditions (diabetes alone -21.0%). This association was independent of age, sex, or BMI (CDC, 2008).

Key Variables Literature Review and Methodology Concepts

Few studies were found that directly evaluate the question related to the association between T2DM and RA. First, an evaluation of the cross-sectional association between prevalent RA and DM among institutionalized U.S. civilians aged 60 years or older was completed by Simard and Mittleman in 2007. The authors performed a similar study design (cross-sectional investigation) to what was performed in this investigation using NHANES; however, they focused their study specifically on the elderly population and data used are dated (1988-1994). This study was not able to bring positive or negative evidence of a strong cross-sectional association between prevalent RA and DM. Only 144 participants were identified with RA, and there were 24 who also had prevalent DM (17%) compared with 16% (n = 815) of the 5152 participants without RA (p = 0.46). Using a logistic regression model controlling for age and sex, the odds ratio for the RA-DM association was 1.3 (95% CI 0.68 to 2.3). Results were not different after multivariate adjustment also controlling for race, smoking, and education. The authors indicated that the sample found was not enough for this investigation. The current study addresses the potential limitations of this study to achieve successful results.

Tentolouris et al. (2008) completed a prospective study to determine the presence of concomitant RA in consecutive DM patients who were regularly followed up for at least 10 years in an outpatient clinic setting. The results showed a prevalence of RA of 0.38% in all DM patients (3 patients with T1DM and 2 patients with T2DM) which was not significantly lower than that in the control group [0.65% (17 patients); p = 0.36]. This study was not able to make any valid conclusions due to the relatively small size of the

group. The authors indicated that if the RA prevalence persists at the 0.25% level using a larger DM data set, the difference from the general population would easily reach significance (i.e. Yate's χ 2 -test 4.44) when 1500 patients with T2DM are studied.

Solomon et al. (2010a) completed a retrospective study to examine the risk of DM among patients with RA, psoriatic arthritis or psoriasis (PsA/PsO), compared with nonrheumatic controls. In this case, the groups were assembled using linked healthcare utilization data from British Columbia, Canada. The incident rates (IRs) for DM among patients with RA was 8.6 per 1000 person-years (95% CI 8.5 to 8.7) and for nonrheumatic controls was 5.8 (95% CI 5.8 to 5.8). The adjusted hazard ratio (HR) for RA compared with nonrheumatic controls was 1.5 (95% CI 1.4 to 1.5). As per the study results, it is suggested that RA may be related to a higher risk of DM.

Dubreuil et al. (2012) evaluated the risk of incident DM in PsA and RA, in the UK general population (1986 and 2010), with adjustment for BMI and lifestyle factors. Age and sex matched HR for DM was 1.12 (95% CI 1.01 to1.25) in RA relative to the comparison groups. After adjustment for BMI, smoking, and alcohol use, this HR was attenuated substantially (1.00). With further adjustment for glucocorticoid use and comorbidity index, the HR was 0.94 (95% CI 0.84 to 1.06) in RA. The results of this study indicated that the risk of DM among patients with RA is significantly elevated only due to increased BMI and smoking. These results suggest that diabetes risk should not be attributed only to the presence of inflammatory disease.

This study concluded that risk of DM between patients with RA is significantly higher; however the results indicated that the reason for this is mostly due to increase in

factors such as BMI and smoking and not due to the factor of inflammation. Finally, Bartels et al. (2012) examined how the presence of RA affected HbA1c and lipid measurements in older adults (aged 65 or older) with DM using Medicare data. The main reason for this investigation was not the relation between RA and DM; however, it was included in the review to document important data related to the topic. Similar to Simard and Mittleman, the authors in this investigation concentrated their efforts on a specific population. In this case, only 2% of the DM population had comorbid RA (n = 5572). DM patients with comorbid RA were more likely than those without RA to have baseline CVD (such as 17% more congestive heart failure), diabetes-related complications including kidney disease (19% higher), lower extremity ulcers (77% higher), and peripheral vascular disease (32% higher). In adjusted models, DM patients with RA were less likely to receive recommended HbA1c testing (OR 0.84, 95% CI 0.80 to 0.89) than those without RA, but were slightly more likely to receive lipid testing (OR 1.08, 95% CI 1.01 to 1.16). Interestingly, for older adults with DM, the presence of comorbid RA predicted lower rates of HbA1c testing but slightly improved lipid testing.

As previously discussed in this literature review, other investigations have used the quantitative cross-sectional methodology to clarify this type of question. This study aims to evaluate the potential association between T2DM and RA including determination of crude and adjusted prevalence for the population. Cross-sectional and quantitative investigation is the appropriate methodology for this type of inquiry because this methodology can be used to describe the population, such as prevalence of an illness which is the main objective for this investigation. This is an evaluation of the population

at one point in time to capture and describe patients' characteristics, outcomes, and risk factors. Based on the inconsistency found in the literature so far on this topic, the design of the current study is adequate to determine potential association between these two diseases. The quantitative methodology of the current study is an appropriate way to test theories as an alternative of qualitative research, which is more relevant for new concepts with minimum research available. As previously mentioned, Simard and Mittleman (2007) used this methodology to investigate this relationship; however their study had some limitations that will be considered in this study. Several investigations have successfully used a cross-sectional methodology to determine prevalence of other conditions using representative U.S. data from NHANES. For example, this methodology and data source have been used to determine the prevalence of obesity in the United States (Ogden et al., 2012). Findings of this research include: more than one-third of adults and almost 17% of youth were obese in 2009–2010; there was no change in the prevalence of obesity among adults or children from 2007–2008 to 2009–2010; obesity prevalence did not differ between men and women; and adults aged 60 and older were more likely to be obese than younger adults. Another related investigation that successfully utilized this methodology was performed by Coresh et al. (2003) to determine the prevalence of Chronic Kidney Disease (CKD) in the U.S. population. The prevalence of CKD in the U.S. adult population was 11% (19.2 million), and prevalence was also determined by disease stage (Coresh et al., 2003).

Summary

Given the potential association with CVD, insulin resistance, high levels of inflammatory markers, and other behaviors such as inactivity, the question arises whether patients with DM have an increased risk of RA or have RA as comorbidity. This review of literature served as the basis for this potential association; however, there are no studies to date that have directly answered the question of the association between DM and RA in the general U.S. population. If these two important conditions are related, health care providers and patients should start managing both diseases on an interdisciplinary manner and combining efforts for the benefit of the patient.

Chapter 3 will define the research methods for this study including the definition of the population and variables to be evaluated. This next chapter will also describe the data to be used including procedures for recruitment, participation, and data collection.

Chapter 3: Research Method

Introduction

The purpose of this study was to determine if any association exists between T2DM and RA for noninstitutionalized U.S. adults between 1999 and 2012. This study also describes potential characteristics that may be important in understanding this comorbidity, including the potential high prevalence of CVD. Chapter 3 explains the methodology that was utilized to perform this investigation and answer the research questions.

This chapter explains the study design and includes a description of the study population, criteria for sample selection, definition of variables, and original data collection methodology. General information about the current data set and data analysis is described. The ethical protection of participants—including IRB review, privacy and patients' rights—are also discussed.

Research Design and Rationale

This quantitative, cross-sectional investigation explored whether patients with T2DM (independent variable) have increased prevalence of RA (dependent variable)—compared with patients without T2DM—using a U.S. nationally representative sample and adjusting for the following potential confounding factors, as evidenced in the literature review: gender, age, race/ethnicity, education level, and smoking status (Simard & Mittleman, 2007).

I sought to answer the following research questions by testing their associated hypotheses:

1. Do patients with T2DM have statistically significant increased prevalence of RA in comparison with patients without T2DM?

   $H_0$1:

   - Patients with T2DM do not have a statistically significant increased prevalence of RA compared to patients without T2DM, after adjustment for potential confounders.

   H_A1: with T2DM do have a statistically significant increased prevalence of having RA compared to patients without T2DM, after adjustment for potential confounders.

2. What demographic, lifestyle, or clinical characteristics are significantly different for those patients with RA and T2DM in comparison with patients with RA but no presence of T2DM?

   Is there a difference in prevalence of RA based on the specific demographic, lifestyle, or clinical characteristics in patients with and without T2DM?

   $H_0$2a:

   - Patients with T2DM do not have a statistically significant different prevalence of RA compared to patients without T2DM based on specific demographic, lifestyle, or clinical characteristics.

   H_A2a:

   - Patients with T2DM do have a statistically significant different prevalence of RA compared to patients without T2DM based on specific demographic, lifestyle, or clinical characteristics.

Characteristics evaluated on this inquiry are demographic (age, gender, race/ethnicity, education level, and poverty level); lifestyle (disability, smoking status, and work functioning), and clinical (blood pressure levels, BMI, lipid levels [HDL/LDL, TC], CRP, use of antirheumatic medications, and presence of CVD).

3. What demographic, lifestyle, or clinical characteristics are significantly different for those patients with RA and T2DM in comparison with patients with T2DM but no presence of RA?

   Is there a difference in prevalence of T2DM based on the specific demographic, lifestyle, or clinical characteristics in patients with and without RA?

   $H_0$3a:

   - Patients with RA do not have a statistically significant different prevalence of T2DM compared to patients without RA based on specific demographic, lifestyle, or clinical characteristics.

   H_A3a:

   - Patients with RA do have a statistically significant different prevalence of T2DM compared to patients without RA based on specific demographic, lifestyle, or clinical characteristics.

   Characteristics evaluated on this inquiry are demographic (age, gender, race/ethnicity, education level, and poverty level); lifestyle (disability, smoking status, and work functioning); and clinical (blood pressure levels,

BMI, lipid levels [HDL/LDL, TC], presence of CVD, plasma glucose, and HbA1c).

4. Do patients with T2DM and concomitant RA have a statistically significant higher prevalence of CVD in comparison with patients with T2DM and no presence of RA and patients with RA and no presence of T2DM?

$H_0$4a:

- Patients with T2DM and concomitant RA do not have a statistically significant increased prevalence of CVD compared to patients with T2DM and no presence of RA and patients with RA and no presence of T2DM, after adjustment for potential confounders.

H_A4a:

- Patients with T2DM and concomitant RA do have a statistically significant increased prevalence of CVD compared to patients with T2DM and no presence of RA and patients with RA and no presence of T2DM, after adjustment for potential confounders.

The current study proposed a secondary analysis of cross-sectional data from a large nationally representative data set, the continuous NHANES. Per definition, cross-sectional data is information collected at one time point or over a short period. This type of study provides information that is typically used to estimate the prevalence of the outcome of interest for a given population, and it is very useful to support public health planning and interventions. Information on individual characteristics, including exposure to risk factors, in conjunction with information about the outcome, may also be collected

in this type of study. Cross-sectional studies provide a snapshot of the outcome and the characteristics associated with it at a specific point in time, which is exactly the intended purpose of this investigation.

At this point, the researcher wants to describe a U.S. population with respect to an outcome and a set of risk factors. As previously mentioned in Chapters 1 and 2, studies performed so far are not clear whether there is an increased prevalence of DM in patients with RA or vice versa. The few studies that have been conducted to evaluate the potential association between DM and RA are not consistent. One study performed by Simard and Mittleman concluded no association between RA and DM. This study was in some areas limited because it did not include the general population (only people aged 60 years and older), and only data from 1988 to 1994 was evaluated (Simard & Mittleman, 2007). A study completed by Tentolouris et al. (2008) evaluated the presence of concomitant RA in patients with DM who were followed for at least 10 years. This study was not able to make any conclusions due to the relatively small cohort. Another study completed by Solomon et al. (2010a) examined the risk of DM in patients with RA between other conditions. As a result, RA appeared to be associated with an increased risk of DM; however this increased risk decreased with age. By author recommendation, this study needs replication. Dubreuil et al. (2012) evaluated the risk of incident DM in RA and found that the risk of DM among patients with RA is significantly elevated only due to increased BMI and smoking. Based on the inconsistency found in the literature to date on this topic, the design of this study may be able to clarify potential noncausal association between these two conditions. This quantitative methodology is an appropriate way to

test theories as an alternative of qualitative research, which is more relevant for new concepts with minimum research available.

As mentioned in Chapter 2, Simard and Mittleman used this methodology previously; however, the data was not sufficient to make any conclusions for their research. In this present study, the author is evaluating a larger sample including additional and more recent years to increase the power of the study, which was previously an issue and, thus, answer the question appropriately at this phase. In addition, the first three questions will also be analyzed considering the variable "age of diagnosis," which will exclude from the sample those diagnosed with RA before DM or vice versa as applicable. Prospective and longitudinal design could be a next step to confirm the results of this study; however time and budgets considerations need to be evaluated for this type of study design. The next possible approach (prospective and longitudinal research) also gives the opportunity to obtain and evaluate prospective data specific to particular elements that cannot be captured in this design (e.g., RA symptoms such as joint pain and potential association to glucose control over time).

Time and resources are not constraints in this current investigation. Using existing cross-sectional data, particularly from NHANES, has advantages: (a) inexpensive public database; (b) takes less time to conduct and no patients recruitment is requirement; (c) can estimate the prevalence of outcome of interest because the sample is from a nationally representative source; and (d) a variety of outcomes and risk factors can be assessed.

The crude prevalence of RA will be calculated for patients with T2DM and with no presence of T2DM. A logistic regression analysis will be performed taking surveys weight into consideration to generate estimates of the U.S. population. Covariates identified in the literature as potential confounders (gender, age, race/ethnicity, education level, and smoking status) will be considered to mitigate confounding bias during the analysis. The adjusted ORs for the association between T2DM and RA will be determined.

Using a group of patients with presence of RA among patients with and without T2DM, this study will identify and describe potential characteristics that could differentially affect the prevalence of RA within the groups. Characteristics to be evaluated on this inquiry are demographic (age, gender, race/ethnicity, education level, and poverty level); lifestyle (disability, smoking status, and work functioning) and clinical (blood pressure levels, BMI, lipid levels [HDL/LDL, TC], CRP, use of antirheumatic medications, and presence of CVD).

Using a second group of patients with the presence of T2DM among patients with and without RA, the study will also identify and describe potential characteristics that could differentially affect the prevalence of T2DM. Characteristics to be evaluated on this inquiry are demographic (age, gender, race/ethnicity, education level, and poverty level); lifestyle (disability, smoking status, and work functioning); and clinical (blood pressure levels, BMI, lipid levels [HDL/LDL, TC], presence of CVD, plasma glucose, and HbA1c).

Using the addition of a third group of patients with T2DM and concomitant RA, the study will evaluate and compare the prevalence of CVD for three groups (DM plus concomitant RA, RA with no T2DM, and T2DM with no RA) in comparison with individuals without any of these two conditions (no RA with no T2DM).

Additional analysis using logistic regression will be performed to adjust for all other potential covariates in the last three inquires. This technique attempts to reduce the bias due to confounding variables.

Considering the fact that no specific study concludes that there is a real association between DM and RA, this study will help to identify the possible association between DM and RA and any important elements to be considered for this association. The current study employs a quantitative, cross-sectional design using data from the large nationally representative data set, NHANES. Data analysis will be performed using SAS.

Methodology

Study Population

This study comprises adult (18 years and older) including patients with T2DM and concomitant RA, patients with T2DM and no presence of RA, and patients with RA and no presence of T2DM using NHANES data sets from 1999 to 2012.

Data Source and Sampling Procedure

The data source for this investigation is the continuous NHANES, which is one of the most important programs driven by the National Center for Health and Statistics (NCHS) as part of the CDC in the United States. The purpose of this effort is to maintain

continuous assessment of the health and nutritional aspects of adults and children in the United States (CDC, 2012b).

The NHANES program began in the early 1960s and has been conducted as a series of surveys focusing on different population groups or health topics. Since 1999, the survey became a continuous program aiming to cover a variety of measurements to describe and evaluate health and nutrition of the U.S. population. This data set offers the benefit of having interviews as well as physical examinations for better evaluation of health. Data collection includes: (a) the interview, which consists of demographic, socioeconomic, dietary, and health-related questions and (b) the examination component, which consists of medical, dental, and physiological measurements and laboratory tests (CDC, 2012c).

Benefits of conducting a secondary data analysis using NHANES are: (a) data is generalizable to a wider population, (b) low cost and time (because data are already collected), and (c) better statistical validity. Information gathered from this database has been used to influence policy and improve public health (CDC, 2012b).

The procedure NHANES uses to select participant is complex and multistage, and uses a probability sampling design. This process allows having a sample that is representative of the civilian, noninstitutionalized U.S. population. The sample does not include persons residing in nursing homes, members of the armed forces, institutionalized persons, or U.S. nationals living abroad.

As published by the CDC, the process of sampling used in NHANES consists of 4 stages that are described below (CDC, 2012b):

- Stage 1: Primary sampling units (PSUs) are selected. These are mostly single counties or, in a few cases, groups of contiguous counties with probability proportional to a measure of size (PPS).
- Stage 2: The PSUs are divided into segments (generally city blocks or their equivalent). As with each PSU, sample segments are selected with PPS.
- Stage 3: Households within each segment are listed, and a sample is randomly drawn. In geographic areas where the proportion of age, ethnic, or income groups selected for oversampling is high, the probability of selection for those groups is greater than in other areas.
- Stage 4: Individuals are chosen to participate in NHANES from a list of all persons residing in selected households. Individuals are drawn at random within designated age-sex-race/ethnicity screening subdomains. On average, 1.6 persons are selected per household.

The sampling design used by NHANES includes sample weights allowing for calculation of population-based estimates of variables (CDC, 2012b). This strategy decreases the opportunity of having selection bias and increases the reliability of the data analysis. This is due to the fact that NHANES oversamples limited populations such as elderly (60 years and older), African Americans, and Hispanics. Notably, beginning in 2007, a new sampling methodology was implemented; however this does not affect the analysis for the current study. As part of this change, NHANES oversampled different populations including:

- All Hispanics, not just Mexican Americans
- For each of the race/ethnicity domains, the 12-15 and 16-19 year age domains were combined and the 40-59 year age domains were split into 10-year age domains 40-49 and 50-59.

It is important to note that women were no longer oversampled.

The population evaluated in this survey consists of approximately 5000 persons from all ages in the United States every year. Considering the size of the U.S. population, the opportunity of being a participant of this program in more than one "2 year cycle" is minimal or almost null (CDC, 2012b). After 1999, NHANES includes a continuous design that brings flexibility to combine data or variables over several cycles. This gives the investigators the opportunity to evaluate rare conditions or to target small populations. In this way, researchers have the opportunity to study larger population size and also to include more variables without losing statistical power during data analysis due to these factors. Table 1 includes the description of this concept as it will be used in the current study:

Table 1.

Details of Continuous Design of the Data per Year

Survey cycle	Data collection years	Data processing years	Data release years	Analysis years
NHANES 1999-2000	1999-2000	2001-2002	2002	2002+
NHANES 2001-2002	2001-2002	2003	2004	2004+
NHANES 2003-2004	2003-2004	2005	2006	2006+
NHANES 2005-2006	2005-2006	2007	2008	2008+
NHANES 2007-2008	2007-2008	2009	2010	2010+
NHANES 2009-2010	2009-2010	2011	2012	2012+
NHANES 2011-2012	2011-2012	2013	2013	2013+

Selection Criteria and Power Analysis

NHANES has standardized procedures to access population groups that are challenging to recruit such as the elderly. RA and T2DM will be identified using specific criteria for the target population of adults 20 years old and older. The age of 20 year and older is selected because only participants over 20 years of age are approached to respond to the arthritis questions. For RA, it is considered all patients that have self reported RA with a positive response to arthritis and RA in the following questions: *Doctor ever said you had arthritis?* If so, *Which type of arthritis? rheumatoid arthritis?*

In case of diabetes, type of diabetes is not defined in continuous NHANES so a previously used algoritm is use to define T2DM population. Based on this algorithm, the first step is to identify patients 20 years old and older who self-report diabetes. As previously mentioned, the age of 20 year and older is selected because only participants

over 20 years of age are approached to respond to the arthritis questions. A participant is considered to have diabetes if he or she answered Yes to the question *ther than during pregnancy, have you ever been told by a doctor or healthcare professional that you have diabetes or sugar diabetes?* This method has been used in previous publications (Berkowitz, 2013; Heliovaara et al., 1993; Midthjell et al., 1992; Kehoe et al., 1994). To minimize inclusion of patients with T1DM, patients who were diagnosed before the age of 30 and initiated insulin within one year of diagnosis are excluded. This approach is in accordance with previous evaluations ofNHANES data (Koopman et al., 2005; Seligman, et al., 2007). Sensitivity of this measure has been reported to be more than 95% in previous NHANES analyses (Seligman et al., 2007), and specificity has been reported to be as high, at 97% (Kehoe et al., 1994). Participants with biochemical but not self-reported diabetes are not included because age at diagnosis could not be determined in these cases. Women reporting diagnosis of diabetes during pregnancy are excluded.

NHANES has the benefit of allowing researchers to use single or multilayer data sets. This is possible because surveys were conducted as a continuous annual survey with periodic releases every two years. To achieve a better sample size and optimize validity for this study, data from 1999 to 2012 is evaluated. It is generally accepted to use alpha of 0.05 and and power estimates of 0.80 to determine an appropriate sample size via power analysis. For the primary analysis of the association between T2DM and RA, the study has a power of 0.89 to detect an absolute risk diference of 1.5% (OR: 1.32) with two tailed test and alpha of 0.05. This calculation was performed using N-Query Advisor [PTT0U-1,nqa] (Machin & Campbell, 1987)

The approximate size of the total population of interest is 30,878 including approximately 329 participants with T2DM and concomitant RA; 2,366 participants with T2DM and no presence of RA; 1,183 participants with RA and no presence of T2DM; and 23,073 with neither condition.

The following section defines and explains the elements considered in the present study including definitions of primary variables and covariates. Definition of the problem and research questions were defined in previous sections of this chapter.

Study Variables

***DM*:** Patients with T2DM were identified based on the self-reporting of this condition through the following question: *Other than during pregnancy, have you ever been told by a doctor or healthcare professional that you have diabetes or sugar diabetes?* To minimize inclusion of patients with T1DM, patients who were diagnosed before the age of 30 and initiated insulin within one year of diagnosis are excluded. Participants with biochemical but not self-reported diabetes are not included because age at diagnosis could not be determined in these cases. Women reporting diagnosis of diabetes during pregnancy are excluded

***RA*:** Patients with RA were identified based on the self-reporting of this condition through the following questions: *Has a doctor or other health professional ever told {you/SP} that {you/s/he} . . .had arthritis? If so, Which type of arthritis was it? Rheumatoid arthritis?*

Age: Captured as the age when participant completed the survey. For the purposes of the study this variable is continuous.

Gender: Captured as a dichotomous categorical variable. Categories: *male* (0) and *female* (1).

Race/ethnicity: Captured as a categorical variable using the following categories: *Hispanic, Non-Hispanic White, Non-Hispanic Black,* and *Other* (including multiracial persons).

Education level: Captured as a continuous variable using the following categories: *at least ninth grade, 9- 11th grade, high school graduate, some college,* and *college graduate.*

Poverty level: Measured by the NHANES as *poverty income ratio (PIR)*. Continuous and binary categorical variable with PIR values below 1.00 considered as being below the official poverty threshold = *poor*, whereas PIR values of 1.00 or greater indicating income values above the poverty level = *not poor* as determined by the U.S. Bureau of the Census and updated annually for inflation with the Consumer Price Index (USCB, 2011).

Smoking: Categorical variable with the following classifications: never, past smoker (>6 months not smoking), and current smoker (≤6 months since last smoked).

Disability: Categorical variable with the following classification: *Yes* = evidence of mental or physical disability and *No* = No evidence of disability. Evidence of disability is operationally defined using Items 2–4 from the four-item CDC Measuring Healthy Days questionnaire. The Healthy Days scale was developed by a working unit from the CDC as a way to measure Health Related Quality of Life (HRQoL) in population surveys. The MOS SF-36 and the Quality of Well-Being scale were considered too long

for use in public health surveillance for phone interviews, so the three-item parsimonious Healthy Days approach was adopted. The three questions are listed below. Item 1 asks only about general health and therefore does not provide sufficiently specific data to measure disability.

- (2) Thinking about your physical health, which includes physical illness and injury, for how many days during the past 30 days was your physical health not good?
- (3) Now thinking about your mental health, which includes stress, depression, and problems with emotions, for how many days during the past 30 days was your mental health not good?
- (4) During the past 30 days, for about how many days did poor physical or mental health keep you from doing your usual activities, such as self-care, work, school or recreation?

Items 2, 3 and 4 each report a range of 0 to30 days when health was not good or activity was limited. Items 2 and 3 are frequently tallied together and a score of any days when physical or mental health was not good up to a total of 30 days is calculated, because activity limitations can be from physical or mental health. Mean number of unhealthy days for persons in the general public were reported as ranging from 5.1 at age 40 to 6.7 days at age 75 or greater. No disability is recorded for 0 to 13 days, but 14 to 30 days is recorded as disability for questions two through four. The same operational definition of disability for Physical, Mental and Activity will be used in this study: 0 to 13 days = no disability and 14 to 30 days = disability. Disability for several chronic

diseases is monitored at the state and territory level by the BRFSS using the CDC HRQOL-4 in population surveys. Reliability and validity have been well established during the extensive use of this scale in state and national health monitoring through the BRFSS. The same definition was used independently for mental and physical disability.

Work functioning: Categorical variable with the following classification: *Yes* = inability to work and *No* = No evidence of inability to work using the following question: Does a physical, mental or emotional problem now keep you from working at a job or business?

Blood pressure levels: BP as two continuous variables namely *systolic BP* and *diastolic BP*.

Hypertension: Captured as a categorical variable (*Yes* or *No*).

BMI: Height and weight measurements were obtained using standardized techniques and equipment. BMI will be calculated using the following formula: BMI = weight (kg)/height^2 (m^2).

Obesity: This variable was used as a categorical variable using the following classification: BMI of < 25 kg/m^2 = *normal*, 25 to 29 kg/m^2 = *overweight,* and $\geq$ 30 kg/m^2 = *obese*

Lipid levels (HDL, LDL, and TC): For the current study, HDL, LDL, and TC were assessed as continuous variables considering recommendations from the AHA (AHA, 2014). Considering HDL cholesterol, higher levels are better. Low HDL cholesterol puts you at higher risk for heart disease. People with high blood triglycerides usually also have lower HDL cholesterol. In case of the LDL or better known as bad

cholesterol; a low LDL cholesterol level is considered good for your heart health. However, your LDL number should no longer be the main factor in guiding treatment to prevent heart attack and stroke, according to new guidelines from the American Heart Association. A total cholesterol score is calculated using the following equation: HDL + LDL + 20 percent of your triglyceride (most common type of fat in the body) level. A total cholesterol score of less than 180 mg/dL is considered optimal.

CRP*:* Continuous variable. CRP level was measured directly from serum using latex enhanced nephelometry.

Use of antirheumatic medications*:* Categorical variable with the following classification:

- *Antirheumatics (*including biologic response modifiers): *Yes* = number of patients with any evidence of use of antirheumatics including biologics; *No* = no evidence
- *Glucocorticoid: Yes* = number of patients with any evidence of use of Glucocorticoids; *No* = no evidence
- *Analgesics*: Yes = number of patients with any evidence of use of analgesics; No = no evidence

Plasma glucose*:* Continuous variable. Measures are fasting.

HbA1c*:* Continuous variable.

CVD*:* Categorical variable with the following classification: *Yes* = evidence of any congestive heart failure, coronary heart disease, angina, angina pectoris, and heart

attack; *No* = no evidence of congestive heart failure, coronary heart disease, angina, angina pectoris, and heart attack.

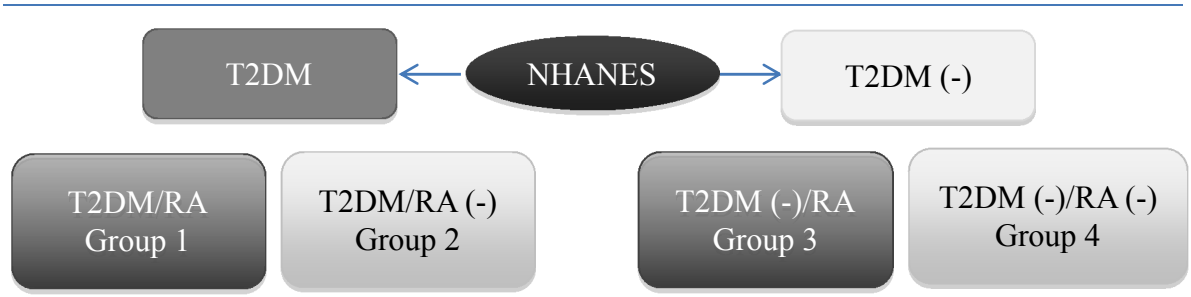

Figure 5. Study groups diagram.

Data Analysis

All statistical analyses are "design-based" so the complex survey sampling design is utilized in SAS procedures such as SURVEYFREQ, SURVEYMEANS, and SURVEYLOGISTIC. For Objective 1, the analysis investigates the cross- sectional association between T2DM and RA using a logistic regression with T2DM as the independent variable and RA as the dependent variable. Adjusted OR of RA is determined considering the following confounding: age, sex, race/ethnicity, education, and smoking as previously determined by Simard and Mittleman (2007).

For Objective 2, Groups 1 and 3 from the study group diagram (Figure 5) are used to identify patients with the presence of RA among patients with and without T2DM. Logistic regression was performed using RA as the dependent variable and characteristics of T2DM as the independent variable to determine univariate ORs. This analysis describes potential characteristics that are statistically significantly different comparing prevalence of RA within T2DM in comparison with prevalence of RA within participants

with no presence of T2DM. Characteristics evaluated on this inquiry are demographic (age, gender, race/ethnicity, education level, and poverty level); lifestyle (disability, smoking status, and work functioning); and clinical (blood pressure levels, BMI, lipid levels [HDL/LDL, TC], CRP, use of antirheumatic medications, and presence of CVD).

For the Objective 3, Groups 1 and 2 from the study group diagram (figure 5) are used to identify patients with the presence of T2DM between patients with and without RA.. Logistic regression was performed using T2DM as the dependent variable and characteristics of RA as the independent variable to determine univariate ORs. This analysis describes potential characteristics that are statistically significantly different comparing prevalence of T2DM within participants with RA and prevalence of T2DM within participants with no presence of RA. Characteristics evaluated on this inquiry are demographic (age, gender, race/ethnicity, education level, and poverty level); lifestyle (disability, smoking status, and work functioning); and clinical (blood pressure levels, BMI, lipid levels [HDL/LDL, TC], presence of CVD, plasma glucose, and HbA1c).

This study uses chi square test to evaluate nominal, ordinal, and categorical variables; this statistical test is commonly used to compare observed data with data expected to be obtained according to a specific hypothesis. The chi-square test evaluates the null hypothesis**,** which states that there is no significant difference between the expected and observed result. For continuous variables with interval and ratio level data, t-tests will be used. *t*-tests are tests for statistical significance that can be used in several different types of statistical tests: (a) to test whether there are differences between two groups for the same variable, based on the mean (average) value of that variable for each

group; (b) to test whether a group's mean (average) value is greater or less than some standard; (c) to test whether the same group has different mean (average) scores on different variables.

Due to the amount of covariates to be considered in Objectives 3 and 4 and the potential correlation between each, it is possible to confront an issue of multi-colliniarity in the regression model. Collinearity is a data problem that has the consequences of resulting in large standard errors. To minimize this problem, it was decided to obtain a sample considering several years of the NHANES data set (1999-2012). More data can produce more precise parameter estimates (with lower standard errors), as seen from the formula in variance inflation factor for the variance of the estimate of a regression coefficient in terms of the sample size and the degree of multicollinearity. Another remedy for this phenomenon is redefining or eliminating variables. Then, variable clustering could be used in this case, which may result in the dropping of nonimportant or redundant variables to produce a model with better significant coefficients.

For Objective 4, the analysis describes and compares the prevalence rates of CVD among patients with T2DM and comorbid RA, patients with T2DM and no presence of RA, and patients with RA and no presence of T2DM. Logistic regression is used to assess the interaction of RA and T2DM combined (independent variables) to determine if there is association to CVD (dependent variable). This model is used with and without the covariates listed previously.

Threats to Validity

The current study proposes to use data from the continuous NHANES to evaluate the association between T2DM and RA. The population studied in the continuous NHANES represents a weighted, random sample of the civil, noninstitutionalized population of the United States. It is important to document that the population sample and limitations of the database will be applicable to U.S. population and may exclude generalizations (external validity) to other countries especially with different health care systems. NHANES data captures one point in time (cross-sectional design), which provides almost no basis for drawing conclusions about causality; thus it is also important to document that, as part of the limitations of this design, this study can only be used for correlation. Additional prospective and longitudinal studies will be further needed if correlation is found in order to demonstrate causality between variables.

Ethical Considerations

It was important to anticipate ethical issues that may be associated with the present study and be proactive in protecting participants' privacy and rights. This study was conducted to clarify a question within the literature using NHANES data. Because data were already collected, the study could not be affected by a personal influence. This study constituted a secondary analysis of data and thus I had no access to personal data and at the same time was not able to be in contact with participants. This fact eliminates any potential opportunity of coercion.

All NHANES plans, procedures, and progress were reviewed and approved by the IRB for the NCHS on a periodic basis.

Before any procedure was completed or data were collected, the participant read and voluntary signed an appropriate informed consent (previously reviewed and approved by the IRB). In addition to the process followed by NHANES to protect participants' privacy and rights, the IRB at Walden University reviewed and approved the current investigation. The IRB approval number was 02-21-14-0123975.

Summary

Chapter 3 provided the methodology proposed to perform this quantitative, cross-sectional investigation. The primary objective of this investigation is to identify if there is any association between T2DM and RA for noninstitutionalized U.S. adults between 1999 and 2012 using a nationally representative sample from the NHANES. The current study is intended to determine if patients with T2DM have increased prevalence of RA. At the same time, the current study helps clarify which characteristics could differentially affect the relationship between both groups and evaluate the potential increased prevalence for CVD when this comorbidity exists. The results of the current study may provide patients and care providers with a better understanding of the needs to manage both conditions. Data analysis is performed using SAS software.

Results and findings from the study are presented in Chapter 4.

Chapter 4: Results

Introduction

The purpose of this study was to clarify if any association exists between T2DM and RA for noninstitutionalized U.S. adults between 1999 and 2012. A quantitative, cross-sectional design was used to investigate the potential association and to identify characteristics that differentially affect the odds of association between groups. Finally, the study evaluated the prevalence of CVD when this comorbidity exists. The purpose of this chapter is to present results and findings of the study.

Using existing data, the analysis was performed after adjusting for potential confounding factors (age, gender, ethnicity, education, and smoking status). The following hypotheses were tested to achieve the objectives of the study:

Hypothesis 1: Patients with T2DM do have a statistically significant increased prevalence of having RA compared to patients without T2DM.

Hypothesis 2: Patients with T2DM do have a statistically significant different prevalence of RA compared to patients without T2DM, based on specific demographic, lifestyle, or clinical characteristics.

Hypothesis 3: Patients with RA do have a statistically significant different prevalence of T2DM compared to patients without RA, based on specific demographic, lifestyle, or clinical characteristics.

Hypothesis 4: Patients with T2DM and concomitant RA do have a statistically significant increased prevalence of CVD compared to patients with T2DM and no presence of RA and patients with RA and no presence of T2DM.

Chapter 4 provides a characterization of the study population and summarizes the results of the analyses for the previously described investigation.

Analyses

The investigation used the continuous NHANES Data, from 1999 to 2012,. in which 71,917 U.S. noninstitutionalized individuals participated in this survey. Of those, 68,705 completed both the interview and the examination portions, yielding overall response rates of 96%. Of this number, 36,071 who were at least 20 years old were asked RA survey questions. As part of the criteria for this study, any females with evidence of pregnancy were excluded from the sample (3,850); this decreased the sample to 32,221. Of that number, 3,689 participants self-reported diabetes. After applying study selection criteria for diagnosed T2DM (see Chapter 3), 3,572 adult participants with diagnosed T2DM were used in the current study. Similarly, 8,601 reported having some type of arthritis in general and 1,705 participants met the criteria for diagnosed RA (see Figure 6).

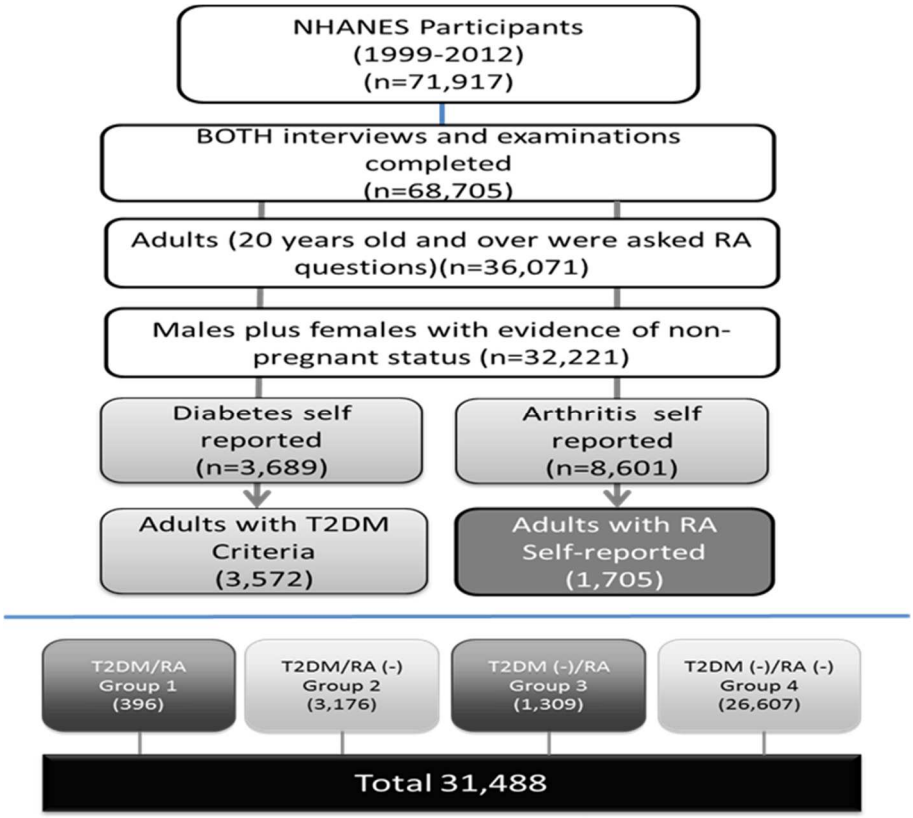

Figure 6. Study population.

Tables 2 through 7 (shown later in this chapter) presents the socio-demographic and health-related characteristics of study participants in the 1999 to 2012 NHANES data sets. As presented in Figure 6, the population consisted of four groups; participants with evidence of T2DM and RA (n = 396 patients); participants with evidence of RA but no T2DM (n = 1309); participants with evidence of T2DM but no evidence of RA (n = 3176); and participants with no evidence of T2DM nor RA (n = 26,607). Differences between the cohorts were assessed by F-tests and t-tests for continuous variables, and chi-square statistics for categorical variables. The primary hypothesis of the current study (Objective 1) was tested at two-tailed $p < 0.05$. All bivariate were considered exploratory

in nature. The overall p-value (Groups 1 = 2 = 3 = 4) was examined first; only if overall p-value was significant, then additional pairwise p-values were evaluated. If no significant in overall test; pairwise p-values were not considered. All statistical analyses utilized SAS version 9.2 (SAS Institute) SURVEY procedures that accounted for the complex survey characteristics of NHANES, such as strata, weighting, and clustering of observations.

Demographic Characteristics

Table 2 describes the demographic characteristics evaluated in the research including age, gender, race/ethnicity, education level, and poverty level.

Table 2.

Demographic Characteristics of Population by T2DM and RA Status

		Group 1 TD2M+/RA+	Group 2 TD2M+/RA-	Group 3 TD2M-/RA+	Group 4 TD2M-/RA-
Variable	Level	Mean or PCT (95% CI)	Mean or PCT (95% CI)	Mean or PCT (95% CI)	Mean or PCT (95% CI)
Gender	M	40.40 (34.7-46.1)	54.57 (52.4-56.77)	46.45 (43.1-49.8)	53.30 (52.7-53.9)
Gender	F	59.60 (53.9-65.3)	45.43 (43.2-47.6)	53.55 (50.2-56.9)	46.70 (46.1-47.3)
Age at screening		64.26 (62.3-66.2)	60.64 (60.0-61.3)	57.13 (56-58.3)	44.61 (44.1-45.1)
Ethnicity	All Hispanic	12.06 (7.8-16.3)	14.50 (11.6-17.4)	8.54 (6.2-10.9)	13.17 (11.4-14.9)
Ethnicity	NH White	57.07 (49.5-64.6)	62.54 (59.1-66.0)	72.71 (69.3-76.1)	70.93 (68.6-73.2)
Ethnicity	NH Black	25.52 (20.3-30.7)	15.44 (13.0-17.9)	14.64 (12.3-17.0)	10.40 (9.2-11.6)
Ethnicity	Other	5.35 (2.0-8.7)	7.52 (5.9-9.2)	4.11 (2.6-5.6)	5.50 (4.9-6.4)
Education	Less than 9th grade	19.50 (13.7-25.3)	14.05 (12.5-15.6)	9.60 (7.8-11.4)	5.96 (5.5-6.4)
Education	9-11th grade	21.18 (16.2-26.6)	16.79 (15.1-18.5)	17.52 (14.8-20.3)	12.13 (11.4-12.9)
Education	HS grad/equivalent	27.84 (21.3-34.4)	25.58 (23.32-28.0)	29.73 (26.5-33.0)	24.32 (23.4-25.3)
Education	Some college	24.60 (18.4-30.7)	26.77 (24.3-29.2)	29.28 (25.6-32.9)	30.65 (29.7-31.6)
Education	College grad	6.87 (3.4-10.4)	16.80 (14.7-19.0)	13.87 (11.1-16.6)	26.93 (25.4-28.5)
Poverty index ratio		2.19 (2.0-2.4)	2.62 (2.5-2.7)	2.62 (2.5-2.8)	3.02 (3.0-3.1)

Note: F = female; Grad = graduate; HS = high school; M = male; N = no; NH = non-Hispanic; PCT = percent; Y=yes.

Table 3.

Significance of Differences Among Groups for Demographic Characteristics of Population by T2DM and RA Status

Variable	1=2=3=4 pVal 1	1 v 2 pVal 2	1 v 3 pVal 3	1 v 4 pVal 4	2 v 3 pVal 5	2 v 4 pVal 6	3 v 4 pVal 7
Gender	<.0001	<.0001	0.0695	<.0001	<.0001	0.2736	0.0002
Age at screening	<0.0001	0.00054	<0.000	<0.0001	<0.0001	<0.000	<0.0001
Ethnicity	<.0001	0.0005	<.0001	<.0001	<.0001	<.0001	<.0001
Education level	<.0001	0.0012	0.0002	<.0001	0.0032	<.0001	<.0001
Poverty index ratio	<0.0001	<0.0001	0.0006	<0.0001	0.90075	<0.000	<0.0001
Smoking status	<.0001	0.4802	0.0658	0.0008	<.0001	<.0001	<.0001
Physical disability	<.0001	0.0021	0.0024	<.0001	0.8131	<.0001	<.0001
Mental disability	<.0001	0.0336	0.2635	<.0001	0.2069	<.0001	<.0001
Disability	<.0001	0.0033	0.0104	<.0001	0.9247	<.0001	<.0001

Note: pVal = p value; chi-square test was used to evaluate nominal, ordinal, and categorical variables. For continuous variables with interval and ratio level data, t-tests was used; Groups numbers based on table 2.

Gender: Those groups with participants with positive evidence to RA were predominantly females (T2DM and RA: 59.6% [95% CI: 53.9% - 65.3%; $p < .0001$]; RA and no T2DM: 53.6% [95% CI: 50.3% - 56.9%; $p < .0001$]) in comparison with those with negative evidence of RA (T2DM [-] and RA [-]: 46.7% (95% CI: 46.1% -

47.3%; $p < .0001$); RA [-] and T2DM [+]: 45.4% (95% CI: 43.2% - 47.6%; $p < .0001$), which is consistent with the literature available related to RA.

Age: Participants with T2DM and no RA tended to be older (60.6 [95% CI: 59.9 – 61.3; $p < .0001$) than participants with RA and no T2DM (57.1 [95% CI: 56.0 – 58.3; $p < .0001$]); however, participants with both conditions combined were found to be even older (64.3 [95% CI: 62.3 – 66.1; $p < .0001$]) than those with only one condition or those with no evidence of RA or T2DM (44.6 [95% CI: 44.1 – 45.1; $p < .0001$]).

Education: Participants with lower level of education ("less than a high school education") were more likely to have evidence of disease (T2DM and RA [40.7% (95% CI: 34.3% -47.1%; p < .0001)], T2DM alone [30.8% (95% CI:28.7% – 33.0% ; $p < .0001$)], and RA alone [27.1% (95% CI:23.9% – 30.4% ; $p < .0001$)]) versus the group of participants with no evidence of T2DM or RA (18.1% (95% CI: 17.1% – 19.1%; $p < .0001$)). Education was not significantly different between individual diseases or even comparable to those with both conditions. See Figure 7.

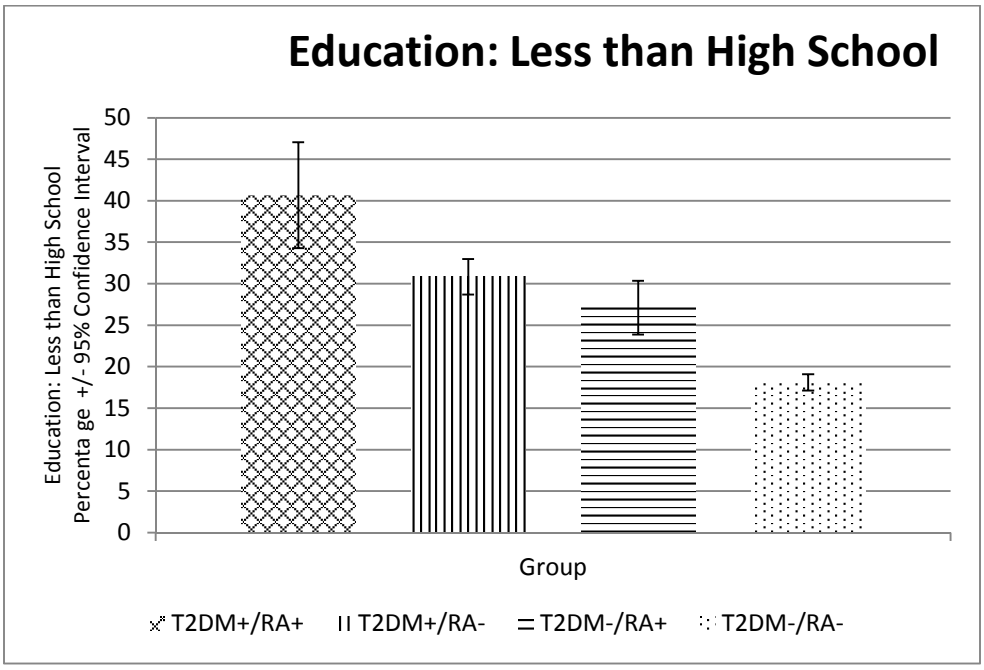

Figure 7. Distribution of patients with "less than high school" education by diabetes and RA status in the United States (1999 – 2012).

Race / Ethnicity: The proportion of non-Hispanic black participants was higher in the group with this comorbidity (25.5% [95% CI: 20.3% – 30.7%; p <.0001]) than the group with only T2DM or only RA (15.4% [95% CI: 13.0% – 17.9%; p <.0001]); 14.6% (95% CI: 12.3% – 17.1% ; p <.0001), respectively). No significant difference was found in participants with this comorbid conditions within Hispanics or non-Hispanic whites. See Figure 8, 9, and 10.

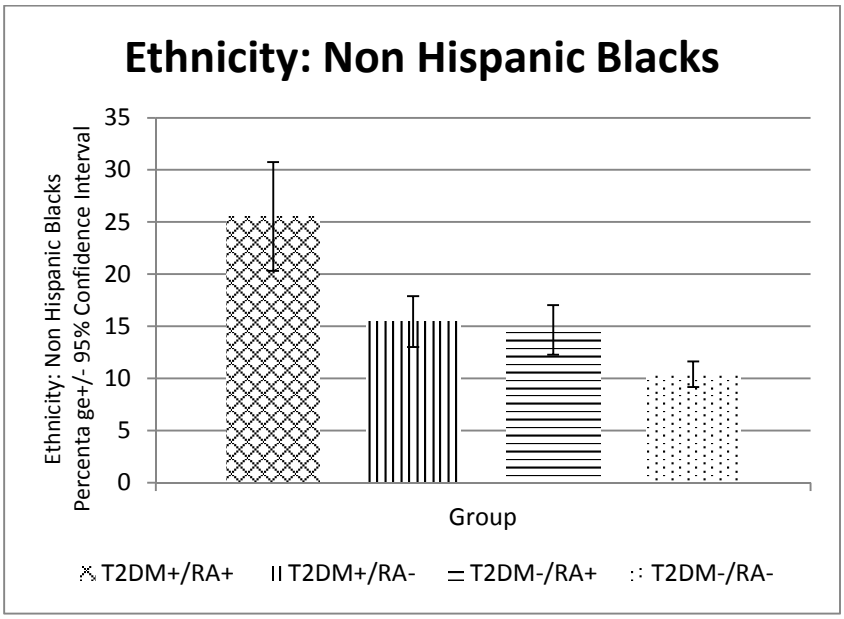

Figure 8. Distribution of patients by ethnicity (non-Hispanics Blacks) among patients by diabetes and RA status in the United States (1999-2012).

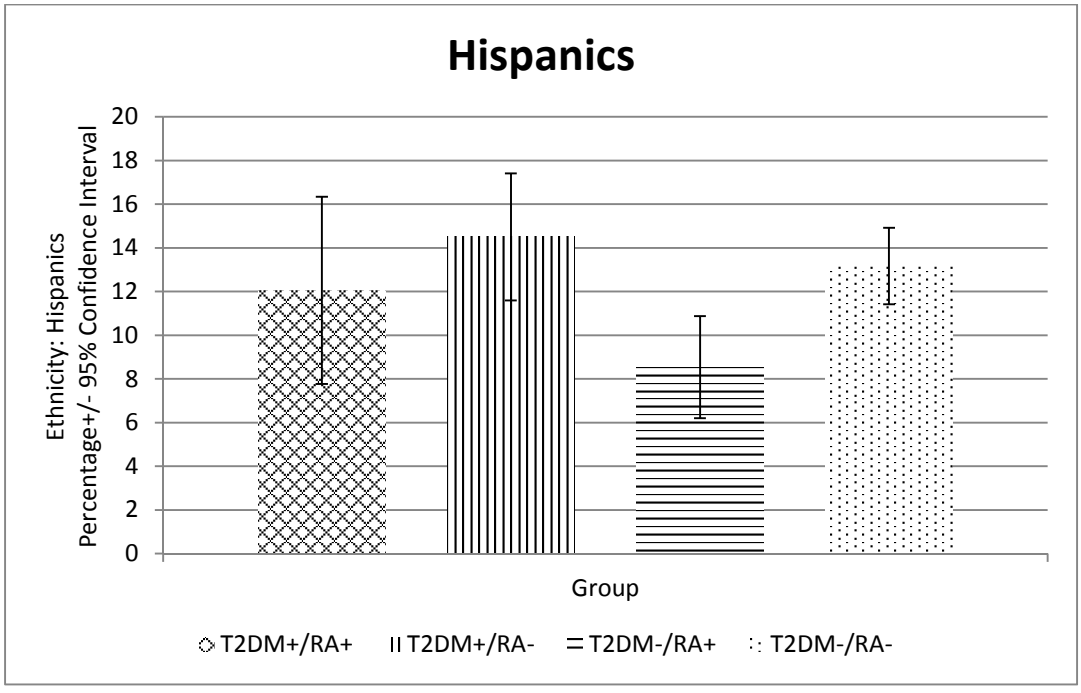

Figure 9. Distribution of patients by ethnicity (Hispanics) among patients by diabetes and RA status in the United States (1999 – 2012).

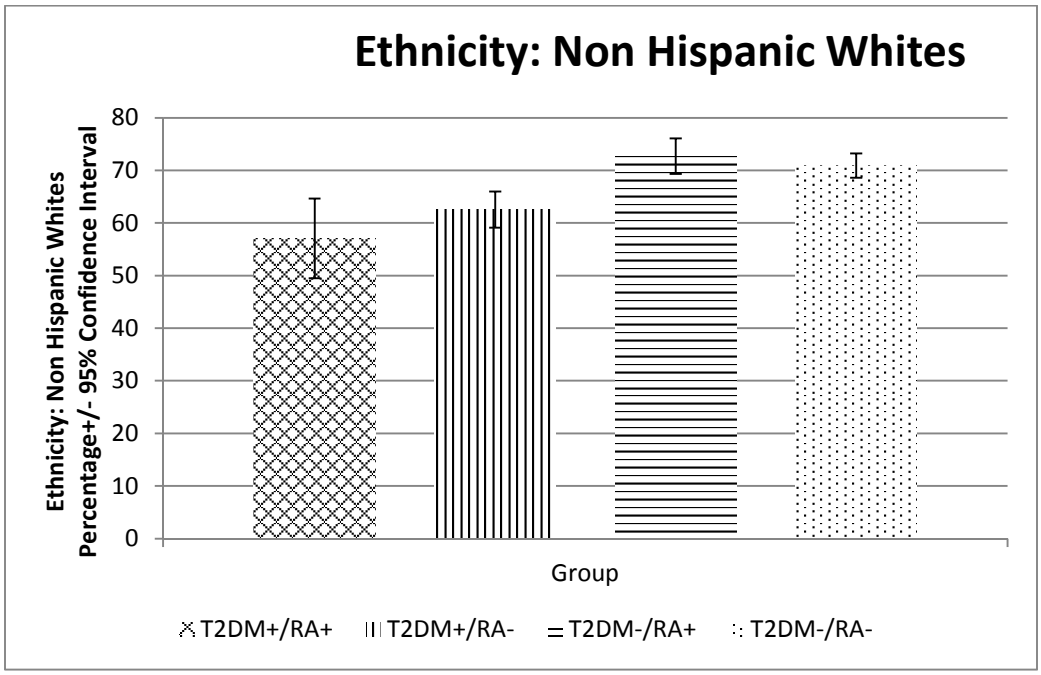

Figure 10. Distribution of patients by ethnicity (non-Hispanics Whites) among patients by diabetes and RA status in the United States (1999 – 2012).

PIR: Income relative to the poverty index on the group of this comorbidity was lower (2.2 [95% CI: 2.0 – 2.4 ; p <.0001]) than those with only 1 condition (T2DM alone: 2.6 [95% CI: 2.5 – 2.7 ; p <.0001]; RA alone: 2.6 [95% CI: 2.5 – 2.8 ; p <.0001]); similar in those with only one condition; and higher in those participants with no evidence of RA or T2DM.

Lifestyle Characteristics

Tables 4 and 5 describes the lifestyle characteristics evaluated in the research including smoking status, disability and work functioning.

Table 4.

Lifestyle Characteristics of Population by T2DM and RA Status: Bivariate and Multivariate Analysis

Variable	Level	Group 1 TD2M+/RA+ Mean or PCT (95% CI)	Group 2 TD2M+/RA- Mean or PCT (95% CI)	Group 3 TD2M-/RA+ Mean or PCT (95% CI)	Group 4 TD2M-/RA- Mean or PCT (95% CI)
Smoking status	Nonsmoker	44.24 (37.1-51.4)	48.20 (45.9-50.5)	38.43 (34.8-42.1)	52.80 (51.6-54.0)
Smoking status	Past Smoker	33.95 (26.5-41.5)	33.58 (31.5-25.7)	30.78 (27.7-33.9)	21.52 (20.7-22.4)
Smoking status	Current Smoker	21.81 (15.1-28.5)	18.22 (16.6-19.8)	30.79 (27.3-34.4)	25.68 (24.7-26.6)
Physical disability	Y	26.50 (20.9-32.1)	17.56 (15.7-19.5)	17.97 (14.8-21.1)	7.63 (7.1-8.1)
Physical disability	N	73.50 (67.9-79.1)	82.44 (80.6-84.3)	82.03 (78.9-85.2)	92.37 (91.9-92.9)
Mental disability	Y	19.46 (13.4-25.5)	13.47 (11.6-15.3)	15.63 (12.6-18.7)	9.42 (8.9-9.9)
Mental disability	N	80.55 (74.5-86.6)	86.53 (84.7-88.4)	84.37 (81.3-87.4)	90.58 (90.1-91.1)
Disability	Y	17.45 (11.7-23.2)	10.32 (8.6-12.0)	10.45 (8.2-12.7)	3.68 (3.3-4.0)
Disability	N	82.55 (76.8-88.4)	89.68 (88.0-91.4)	89.55 (87.3-91.8)	96.32 (96.0-96.7)
Work functioning	N	55.78 (48.6-63.0)	73.36 (70.9-75.9)	71.88 (67.9-75.9)	91.46 (90.7-92.3)
Work functioning	Y	44.22 (37.0-51.4)	26.64 (24.2-29.1)	28.12 (24.1-32.1)	8.54 (7.7-9.4)

Table 5

Significance of Differences Among Groups for Demographic Characteristics of Population by T2DM and RA Status

Variable	1=2=3=4 pVal 1	1 v 2 pVal 2	1 v 3 pVal 3	1 v 4 pVal 4	2 v 3 pVal 5	2 v 4 pVal 6	3 v 4 pVal 7
Smoking status	<.0001	0.4802	0.0658	0.0008	<.0001	<.0001	<.0001
Physical disability	<.0001	0.0021	0.0024	<.0001	0.8131	<.0001	<.0001
Mental disability	<.0001	0.0336	0.2635	<.0001	0.2069	<.0001	<.0001
Disability	<.0001	0.0033	0.0104	<.0001	0.9247	<.0001	<.0001
Work functioning	<.0001	<.0001	<.0001	<.0001	0.5106	<.0001	<.0001

Note: pVa l= p value; chi-square test was used to evaluate nominal, ordinal, and categorical variables. For continuous variables with interval and ratio level data, *t*-tests was used; Groups numbers based on table 4.

Smoking: Smoking cigarettes is a factor associated with T2DM as well as RA. Interestingly, based on the study results, the proportion of current smokers was lower within those participants with positive diagnosis to T2DM and RA (21.8% current smokers [95% CI: 15.1% - 28.5%; p<.0001]), particularly within those with only T2DM (18.2% [95% CI:16.6% – 19.8% ; p <.0001]) compare with those participants with compare with those participants with no T2DM or RA (25.68% [95% CI:24.7% – 26.6% ; p <.0001]). However, considering the past smokers, participants with positive diagnosis of both conditions had a higher likelihood of having been past smokers (34.0% [95% CI: 26.5% – 41.5% ; p < .0001]) or individual diseases (T2DM alone: 33.6% [95% CI: 31.5%

- 35.7% ; $p < .0001$]); RA alone: 30.8% (95% CI: 27.7% - 33.9% ; $p < .0001$]) in comparison to those with no T2DM or RA (21.5% [95% CI: 20.7% - 22.4% ; $p < .0001$]). See Figure 11.

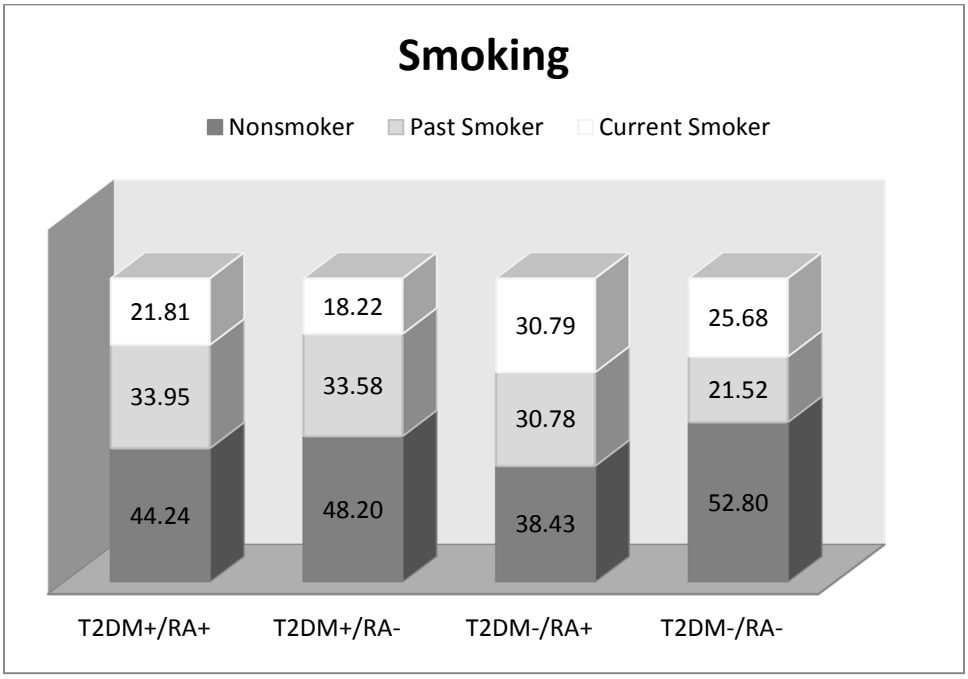

Figure 11. Distribution of patients by "smoking status" among patients by diabetes and RA status in the United States (1999–2012).

Disability: A significant proportion of participants with T2DM and RA report disability. In the current study, disability was defined based on how many days during the past 30 days your physical or mental health was not good preventing you from doing your usual activities, such as self-care, work, school, or recreation. Refer to Chapter 3 for a complete definition of disability. The proportion of participants with physical disability in participants with positive evidence of RA alone and positive evidence of T2DM alone was higher than the normal population but similar between individual diseases (17.6% [95% CI:15.7% – 19.5% ; $p < .0001$]; 18.0% [95% CI: 14.9% – 21.1%; $p < .0001$]);

however, the proportion of physical disability in participants with both conditions was significantly higher (26.5% [95% CI: 20.9% – 32.1%; $p < .0001$]). It was found that mental disability is more prevalent in participants with RA alone (15.6% [95% CI: 12.6% – 18.7% ; $p < .0001$]) versus participants with T2DM alone (13.5% [95% CI: 11.7% – 15.3% ; $p < .0001$]); however, the proportion of mental disability was significantly higher in participants with both conditions (19.5% [95% CI:13.4 – 25.5 ; $p < .0001$]) In general, participants with both conditions (T2DM and RA) had higher probabilities of being physically and mentally disabled (17.5% [95% CI: 11.7% – 23.2%; $p < .0001$]) versus participants with T2DM alone (10.3% [95% CI: 8.6% – 12.0%; $p < .0001$]) or participants with RA alone (10.5% [95% CI: 8.2% – 12.7%; $p < .0001$]). See Figure 12, 13 and 14.

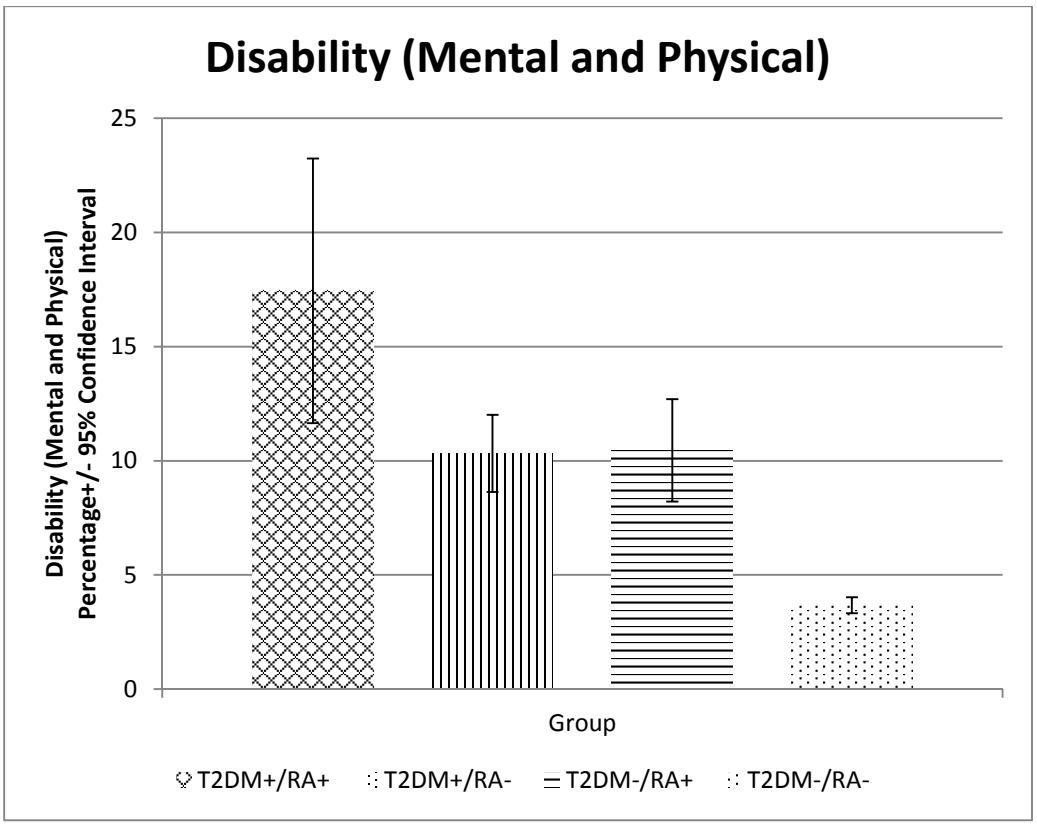

Figure 12. Distribution of patients by general disability (mental & physical) among patients by diabetes and RA status in the United States (1999–2012).

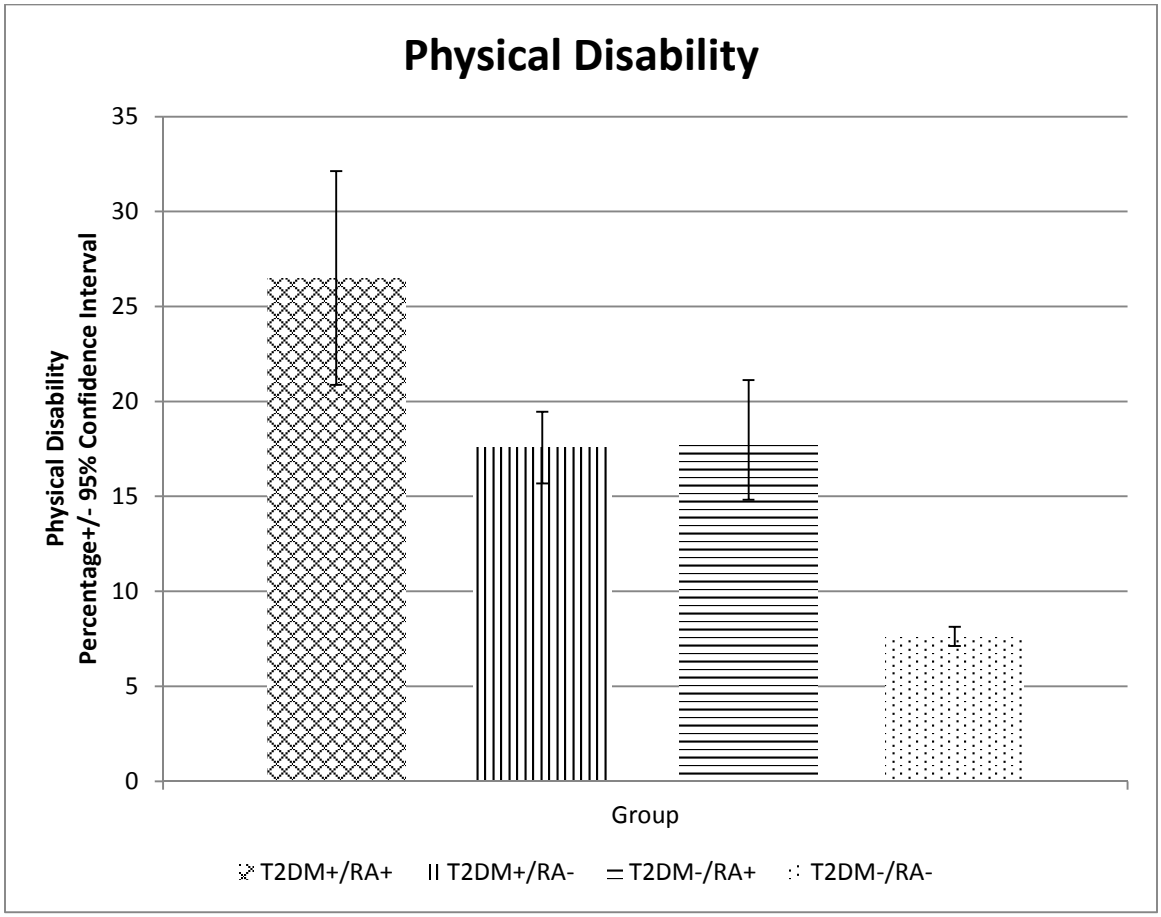

Figure 13. Distribution of patients by physical disability among patients by diabetes and RA status in the United States (1999–2012).

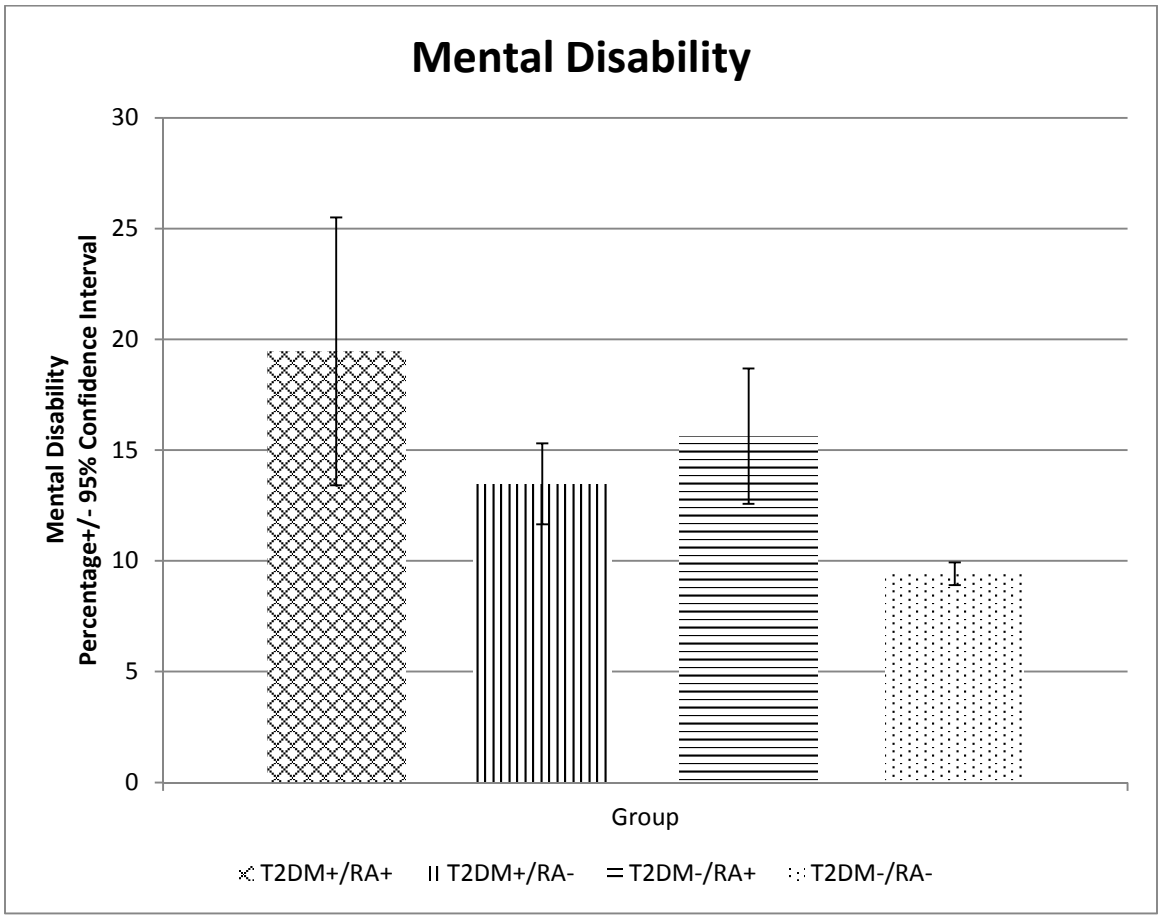

Figure 14. Distribution of patients by mental disability among patients by diabetes and RA status in the United States (1999–2012).

Work Functioning: As an important factor to consider related to the previous characteristic (disability), this study also evaluated the ability to work. Similarly, the proportion of participants that was not able to work was higher within the group of participants with both conditions combined (44.2% [95% CI: 37.0% – 51.4%; p <.0001]) versus the group of participants with presence of only one of the conditions; 26.6 % (95% CI: 24.2% – 29.1%; p < .0001), and 28.1% (95% CI: 24.3% – 32.1%; p < .0001) for T2DM and RA, respectively. In comparison, the group of participants with no evidence

of any of these diseases, the inability to work was only 8.5% (95% CI: 7.7% – 9.4%; $p <$ .0001). See Figure 15.

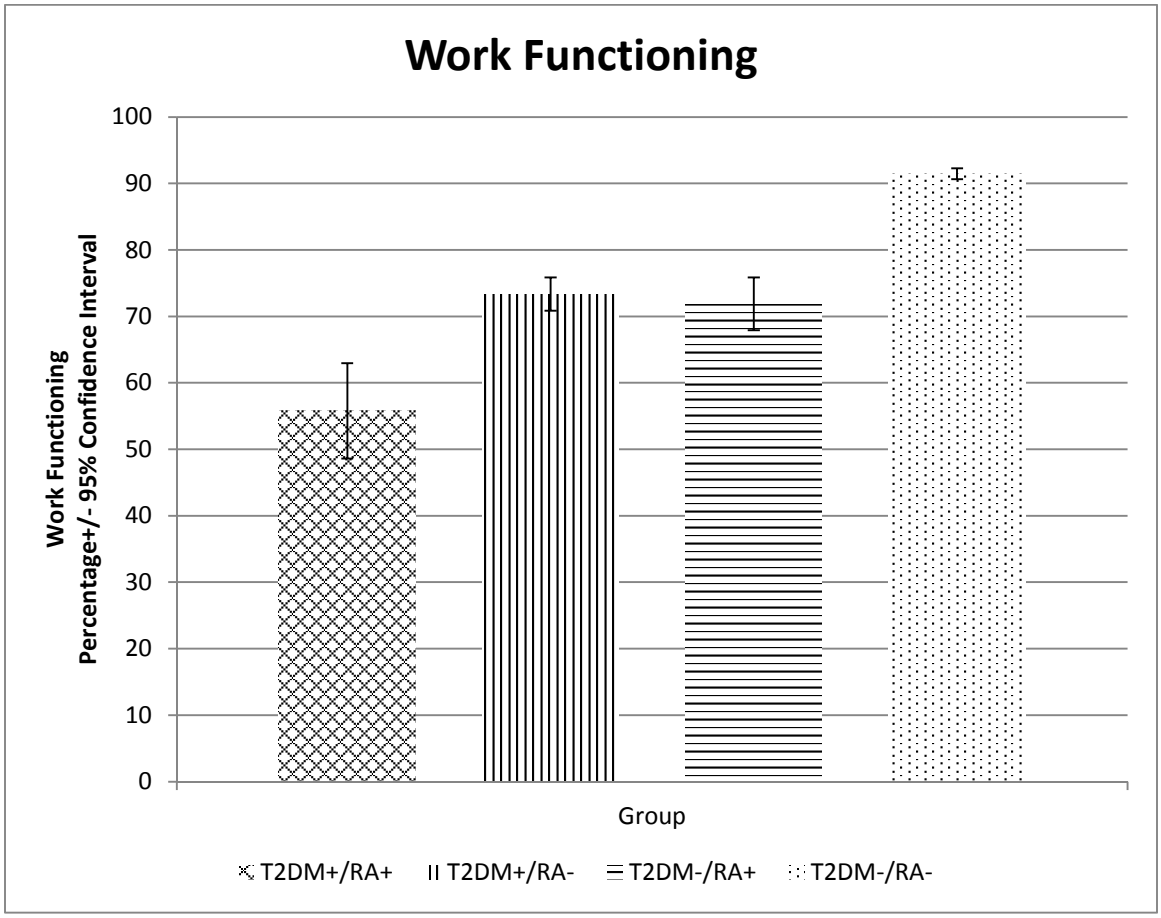

Figure 15. Distribution of patients by work functioning among patients by diabetes and RA status in the United States (1999 – 2012).

Clinical Characteristics

Clinical characteristics evaluated in the present investigation were: hypertension, blood pressure levels, BMI, lipid levels (HDL/LDL, TC), CRP, glucose, HbA1c, and the use of some medications commonly used to treat arthritis. Tables 6 and 7 describe the clinical characteristics assessed in the research.

Table 6.

Clinical Characteristics of Population by T2DM and RA Sstatus: Bivariate and Multivariate Analysis

Variable	Level	Group 1 TD2M+/RA+ Mean or PCT (95% CI)	Group 2 TD2M+/RA- Mean or PCT (95% CI)	Group 3 TD2M-/RA+ Mean or PCT (95% CI)	Group 4 TD2M-/RA- Mean or PCT (95% CI)
BMI		32.38 (31.5-33.2)	32.38 (32.0-32.8)	29.06 (28.5-29.6)	27.92 (27.8-28.1)
Obesity classification	Normal weight	16.29 (11.9-20.7)	13.82 (12.2-15-4)	28.65 (245.5-31.9)	35.03 (34.0-36.1)
Obesity classification	Overweight	25.03 (19.7-30.3)	27.86 (25.7-30.0)	32.21 (29.2-35.2)	34.94 (34.1-35.8)
Obesity classification	Obese	58.68 (52.2-65.1)	58.32 (55.6-61.0)	39.14 (35.7-42.6)	30.04 (29.2-31.0)
Hypertension	Normal	28.42 (22.3-34.5)	26.78 (24.4-29.1)	35.42 (31.6-39.2)	47.66 (46.6-48.7)
Hypertension	Prehypertension	45.41 (39.1-51.7)	50.97 (48.3-53.6)	48.50 (44.9-52.1)	44.62 (43.6-45.6)
Hypertension	Hypertension	26.17 (20.8-31.5)	22.25 (20.3-24.2)	16.08 (13.7-18.5)	7.72 (7.3-8.1)
Systolic blood pressure		131.97 (129.7-134.2)	132.00 (131.0-133.0)	128.01 (126.5-129.6)	121.67 (121.3-122.1)
Diastolic blood pressure		63.98 (61.3-66.7)	68.76 (68.0-69.6)	70.51 (69.4-71.6)	71.31 (71.0-71.7)
HDL		46.63 (44.9-48.4)	47.16 (46.5-47.8)	52.92 (51.7-54.1)	52.47 (52.1-52.8)
LDL		106.59 (97.37-115.8)	105.32 (102.6-108.0)	118.60 (114.8-122.4)	118.00 (117.1-118.9)
Total cholesterol		191.33 (184.6-198.0)	191.67 (188.9-194.5)	202.73 (199.4-206.0)	198.46 (197.7-199.2)
Glucose		149.64 (142.0-157.3)	158.13 (153.6-162.6)	101.15 (99.6-102.7)	98.54 (98.1-99)
HbA1c		7.08 (6.9-7.3)	7.32 (7.2-7.4)	5.48 (5.4-5.5)	5.36 (5.35-5.37)

(table continues)

Variable	Level	Group 1 TD2M+/RA+ Mean or PCT (95% CI)	Group 2 TD2M+/RA- Mean or PCT (95% CI)	Group 3 TD2M-/RA+ Mean or PCT (95% CI)	Group 4 TD2M-/RA- Mean or PCT (95% CI)
CRP		0.75 (0.60-0.91)	0.56 (0.52-0.60)	0.59 (0.54-0.65)	0.38 (0.37-0.40)
Analgesics	N	83.11 (77.8-88.4)	91.70 (90-.2-93.2)	85.89 (83.7-84.1)	95.93 (95.6-96.3)
Analgesics	Y	16.89 (11.6-22.2)	8.30 (6.8-9.8)	14.11 (11.9-16.2)	4.07 (3.7-4.4)
Antirheumatic drugs	N	97.76 (96.6-98.9)	99.96 (99.9-100)	96.25 (96.7-97.8)	99.85 (99.8-99.9)
Antirheumatic drugs	Y	2.24 (1.1-3.4)	0.04 (0-0.1)	3.75 (2.2-5.3)	0.15 (0.1-0.2)
Glucocorticoids	N	94.39 (91.2-97.6)	97.38 (96.6-98.1)	93.69 (92.1-95.3)	98.74 (98.6-98.9)
Glucocorticoids	Y	5.61 (2.5-8.8)	2.63 (1.9-3.4)	6.31 (4.7-7.9)	1.26 (1.1-1.4)

Table 7.

Significance of Differences Among Groups for Demographic Characteristics of Population by T2DM and RA Status

Variable	1=2=3=4 pVal 1	1 v 2 pVal 2	1 v 3 pVal 3	1 v 4 pVal 4	2 v 3 pVal 5	2 v 4 pVal 6	3 v 4 pVal 7
BMI	<0.0001	1	<0.000	<0.0001	<0.0001	<0.000	<0.0001
Obesity classification	<.0001	0.4448	<.0001	<.0001	<.0001	<.0001	<.0001
Hypertension	<.0001	0.2396	0.0005	<.0001	<.0001	<.0001	<.0001
Systolic blood pressure	<0.0001	0.97822	0.004	<0.0001	0.00015	<0.000	<0.0001
Diastolic blood pressure	<0.0001	0.00065	<0.000	<0.0001	0.00138	<0.000	0.10921
HDL	<0.0001	0.58266	<0.000	<0.0001	<0.0001	<0.000	0.43366
LDL	<0.0001	0.80551	0.0173	0.01786	<0.0001	<0.000	0.75905
Total cholesterol	<0.0001	0.92953	0.0045	0.03891	<0.0001	<0.000	0.01236
Glucose	<0.0001	0.06572	<0.000	<0.0001	<0.0001	<0.000	0.00155
HbA1c	<0.0001	0.02179	<0.000	<0.0001	<0.0001	<0.000	<0.0001
CRP	<0.0001	0.02092	0.0716	<0.0001	0.43273	<0.000	<0.0001
Analgesics	<.0001	0.0001	0.3396	<.0001	<.0001	<.0001	<.0001
Antirheumatic drugs	<.0001	<.0001	0.1235	<.0001	<.0001	0.1576	<.0001
Glucocorticoid	<.0001	0.0151	0.7038	<.0001	<.0001	<.0001	<.0001

Note: pVal = p value; chi-square test was used to evaluate nominal, ordinal, and categorical variables. For continuous variables with interval and ratio level data, t-tests was used; Groups numbers based on Table 6.

Body Max Index (BMI). BMI was assessed as a continuous and also categorical variable. As a continuous variable, BMI was higher in those participants with the presence of T2DM. This was similar between those participants with or without RA (T2DM and RA [32.4 (95% CI: 31.5 – 33.2 ; p <.0001)]; T2DM with no RA [32.4 (95% CI: 32.0 – 32.9; p <.0001)]). However; BMI was lower in the group of participants with RA alone or participants with no presence of RA or T2DM (29.1 [95% CI: 28.5 – 29.6; p <.0001] and 27.9 [95% CI: 27.8 – 28.1 ; p <.0001], respectively). Participants with T2DM and RA had similar BMI as those with T2DM alone.

Using weight classification based on BMI levels (categorical variable), where normal weight was defined as BMI of 25 kg/m2 or less; overweight as BMI of 25 to 29.9 kg/m2, and obesity as BMI of 30 kg/m2 and above, it was found that the proportion of obese participants was higher in the group of participants with presence of T2DM with or without RA (58.7% [95% CI: 52.2% – 65.1%; p < .0001], 58.3% [95% CI: 55.6% – 61.0% ; p < .0001], respectively) than those with presence of RA alone (39.1% [95% CI: 35.7% – 42.6% ; p < .0001]) or no presence of RA or T2DM (30.0% [95% CI: 29.2% – 31.0% ; p < .0001]). See Figure 16.

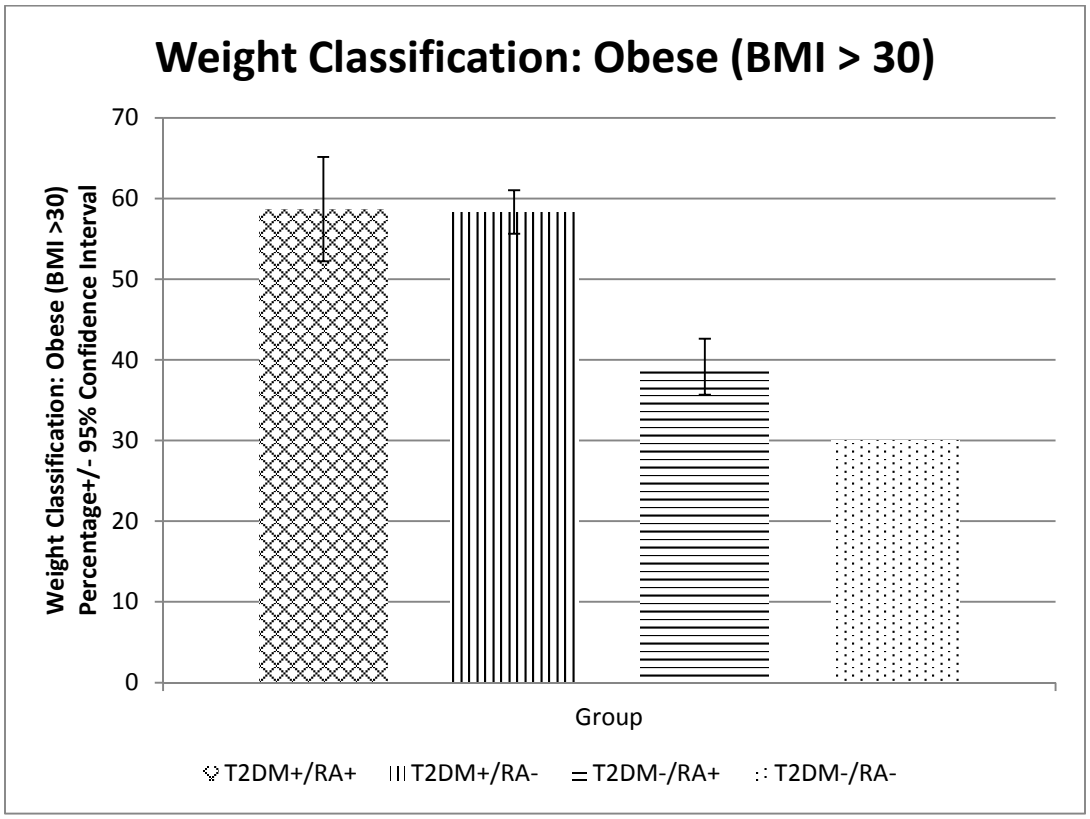

Figure 16. Distribution of obese patients (BMI >30) among patients by diabetes and RA status in the United States (1999 – 2012).

The cardiovascular marker profile was very similar between participants with T2DM and RA versus T2DM and no RA, yet they differed with RA and no T2DM (and the group of no RA or T2DM).

Hypertension/Blood Pressure: Consistent with the literature, hypertension is highly predominant in participants with T2DM and comorbid RA (26.2% [95% CI: 20.8% – 31.5%; $p < .0001$]) as well as in participants with T2DM alone (22.3 [95% CI: 20.3% – 24.2% ; $p < .0001$]) in comparison with participants with no T2DM or participants with negative evidence of this comorbidity (7.7% [95% CI:7.3% – 8.1% ; $p < .0001$]). There was no significant difference in the proportion of participants with

hypertension between the group of participants with T2DM and RA in comparison with T2DM and no RA; however, participants with only RA (16.1% [95% CI: 13.7% – 18.5%; $p < .0001$]) were less likely to have hypertension in comparison to those with only T2DM or with those participants with both conditions. The proportion of hypertension within participants with RA alone (16.1% [95% CI: 13.7% – 18.5%; $p < .0001$]) was significantly higher in comparison with participants with no evidence of RA or T2DM (7.7% [95% CI: 7.3% – 8.1% ; $p < .0001$]). See Figure 17.

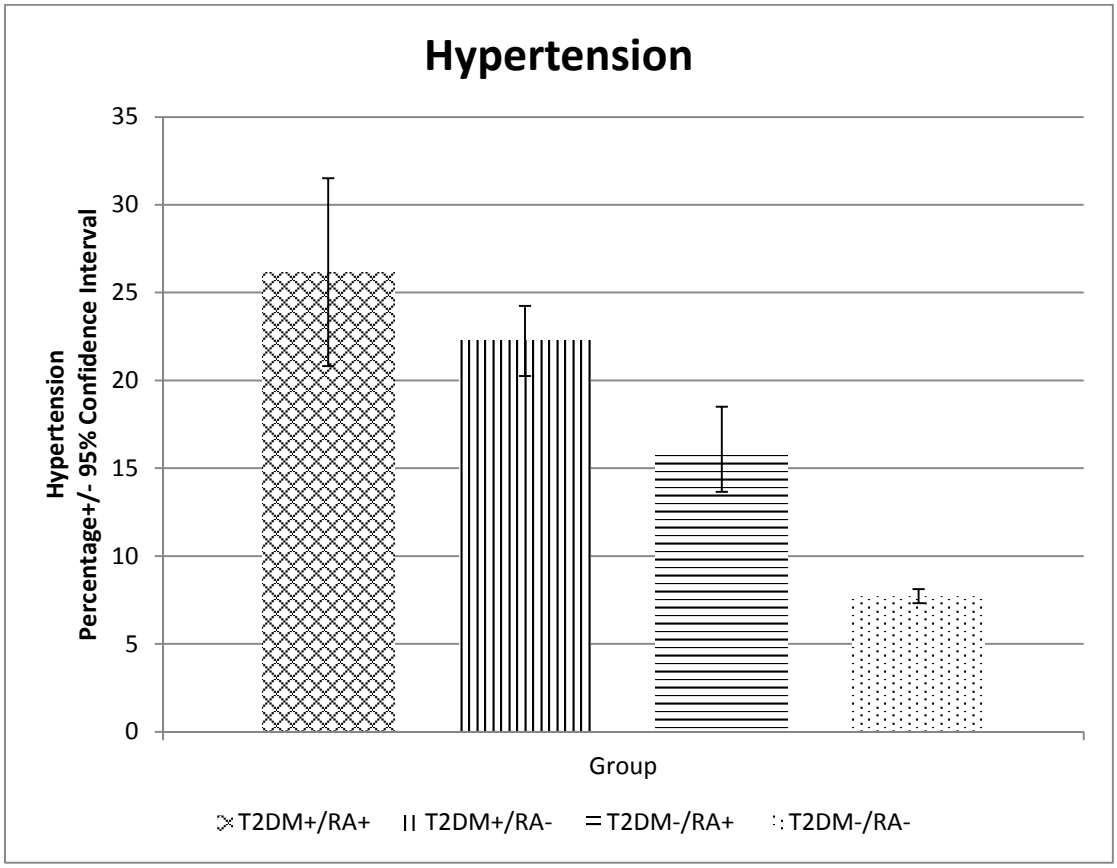

Figure 17. Distribution of patients with hypertention among patients by diabetes and RA status in the United States (1999 – 2012).

The average systolic blood pressure for participants with T2DM and RA as well as participants with T2DM and no RA was 132 (95% CI: 129.7 -134.2; $p < .0001$) and 132 (95% CI: 131.0 – 133.0; $p < .0001$), respectively; for participants with RA and no T2DM was128 (95% CI: 126.5 - 130 ; $p < .0001$); and for participants with no presence of RA or T2DM was122 (95% CI: 121.3 – 122.1 ; $p < .0001$). The average diastolic blood pressure for participants with T2DM and RA was 64 (95% CI: 61.3 – 66.7; $p < .0001$); for participants with T2DM and no RA was 69 (95% CI: 68 – 70 ; $p < .0001$); for participants with RA and no T2DM as well as for participants with no presence of RA or T2DM was 71 (95% CI: 69.4 – 71.6 ; $p < .0001$) and 71 (95% CI: 71 – 71.7; $p < .0001$), respectively.

Lipids: TC was more elevated in participants with RA alone (202.7 [95% CI: 199.4 – 206.0 ; $p < .0001$]) in comparison with participants with both conditions, T2DM and RA, and participants with T2DM alone (191.3 [95% CI: 184.6 – 198.0 ; $p < .0001$] and 191.7 [95% CI: 188.9 – 194.5 ; $p < .0001$], respectively).

Glucose/HbA1c: The mean glucose was more elevated in those participants with T2DM alone (158.1 [95% CI: 153.6 – 162.6 ; $p <.0001$]) and participants with both conditions (149.6 [95% CI: 142.0 – 157.3 ; $p < .0001$]) versus those participants with no evidence of T2DM (101.2 [95% CI: 99.6 – 102. 7; $p < .0001$]). Similar patterns were found with HbA1c with a mean value of 7% for participants with T2DM versus a mean value of approximately 5% for participants with no evidence of T2DM. No difference was found in glucose for those with this comorbidity.

CRP levels were similar within patients with T2DM (.56 [95% CI: 0.52 – 0.6; $p < 0.0001$]) and RA alone (.59 [95% CI: 0.54 – 0.65; $p < 0.0001$]); however, higher among patients with both conditions (.75 [95% CI: 0.60 – 0.91; $p < 0.0001$]) and lower than those participants with no evidence of RA or T2DM (.38 [95% CI: 0.37 – 0.40; $p < 0.0001$]).

Among all included participants (n = 31,488), the prevalence of T2DM was 7.6% (95% CI: 7.2% - 8.0% ; p < .0001) and the prevalence of RA was 4.0% (95% CI: 3.7% - 4.3% ; p < .0001). For the primary objective of the present study, the analysis investigated the cross-sectional association between T2DM and RA using a logistic regression with T2DM as the independent variable and RA as the dependent variable. The analysis included a description of variables and crude and adjusted prevalence of RA for patients with and without diabetes. Adjusted ORs of RA were determined considering predetermined confounding factors based on previous research including age, sex, race/ethnicity, education, and smoking. Prevalence of T2DM was also calculated using the same analysis. Results af these analysis is shown in Tables 8 to 11.

Table 8.

Prevalence of RA Within U.S. Patients with T2DM; Patients with No Diagnosis of T2DM; and the General Population

T2DM	RA	Frequency	Percent	Std error	95% CI		p-value
					Lower	Upper	
T2DM (+)	RA (+)	396	9.0144	0.5806	7.88	10.15	<0.0001
T2DM (-)	RA (+)	1309	3.6222	0.1433	3.34	3.90	
All	RA (+)	1705	4.034	0.1411	3.76	4.31	

Note: (+) = positive; (-) = negavive

Table 9.

Odd Ratios of RA from Multivariate Llogistic Regression Model

Variable		Odds Ratio	OR 95% CI		p-value
			Lower	Upper	
Diabetes	T2DM vs not T2DM	1.450	1.229	1.711	<.0001
Gender	F vs M	1.302	1.147	1.479	<.0001
Age	Per 1 year increase	1.040	1.035	1.044	<.0001
Ethnicity	All Hispanic vs Other	0.879	0.616	1.256	<.0001
	NH black vs other	1.671	1.159	2.408	
	NH white vs other	1.004	0.701	1.438	
Education	9-11th grade vs some College	1.213	0.979	1.501	<.0001
	College graduate vs some College	0.564	0.452	0.703	
	High school Grad/equivalent vs some College	1.115	0.924	1.346	
	Less than 9th grade vs some college	1.212	0.932	1.575	
Smoking Status	Current smoker vs past smoker	1.368	1.139	1.643	<.0001
	Nonsmoker vs past smoker	0.730	0.616	0.865	

Table 10.

Prevalence of T2DM within U.S. patients with RA; Patients with No Diagnosis of RA; and the General Population

RA Status	T2DM	Frequency	Percent	Std error	95% CI		p-value
					Lower	Upper	
RA (+)	T2DM (+)	396	17.0646	1.0717	14.96	19.17	<0.0001
RA (-)	T2DM (+)	3176	7.2401	0.2067	6.83	7.65	
All	T2DM (+)	3572	7.6365	0.2049	7.23	8.04	

Table 11.

Odd Ratios of T2DM from Multivariate Logistic Regression Model

Variable		Odds Ratio	OR 95% CI		p-value
			Lower	Upper	
Diabetes	RA vs not RA	1.450	1.229	1.711	<.0001
Gender	F vs M	1.302	1.147	1.479	<.0001
Age	Per 1 year increase	1.040	1.035	1.044	<.0001
Ethnicity	All Hispanic vs other	0.879	0.616	1.256	<.0001
	NH black vs other	1.671	1.159	2.408	
	NH white vs other	1.004	0.701	1.438	
Education	9-11th grade vs some college	1.213	0.979	1.501	<.0001
	College graduate vs some college	0.564	0.452	0.703	
	High school grad/equivalent vs some college	1.115	0.924	1.346	
	Less than 9th grade vs some college	1.212	0.932	1.575	
Smoking status	Current smoker vs past smoker	1.368	1.139	1.643	<.0001
	Nonsmoker vs past smoker	0.730	0.616	0.865	

The prevalence of RA among participants with T2DM was 9.0% (95% CI:7.9% - 10.2% ; p <.0001), which was significantly higher than the prevalence of RA among those participants without T2DM (3.6% [95% CI:3.3% - 3.9%; p < .0001]). See Figure 18. Considering the prevalence of T2DM among participants with and without RA, the difference was significantly higher with a prevalence of 17.1% (95% CI: 15.0% - 19.2% ; p <.0001) for those participants with RA versus 7.2% (95% CI: 6.8% – 7.7% ; p <.0001) among those without RA (OR 2.64; 95% CI [2.24, 3.10]; p < .0001). See Figure 19. The adjusted ORs for the cross-sectional association between RA and T2DM were 1.45 (95% CI 1.29, 1.71; p < .0001). The results of the current study demonstrated that there was a

strong association between RA and T2DM after adjusting for potential confounders as shown in Tables 8 through 11.

The distribution of the dependent and independent variables are presented in the figure below including both prevalence of RA (Figure 18) among participants with T2DM and no evidence of T2DM and also prevalence of T2DM (Figure 19) among participants with RA and no evidence of RA. Prevalence of individual diseases in the general population is shown in both figures for illustration purposes.

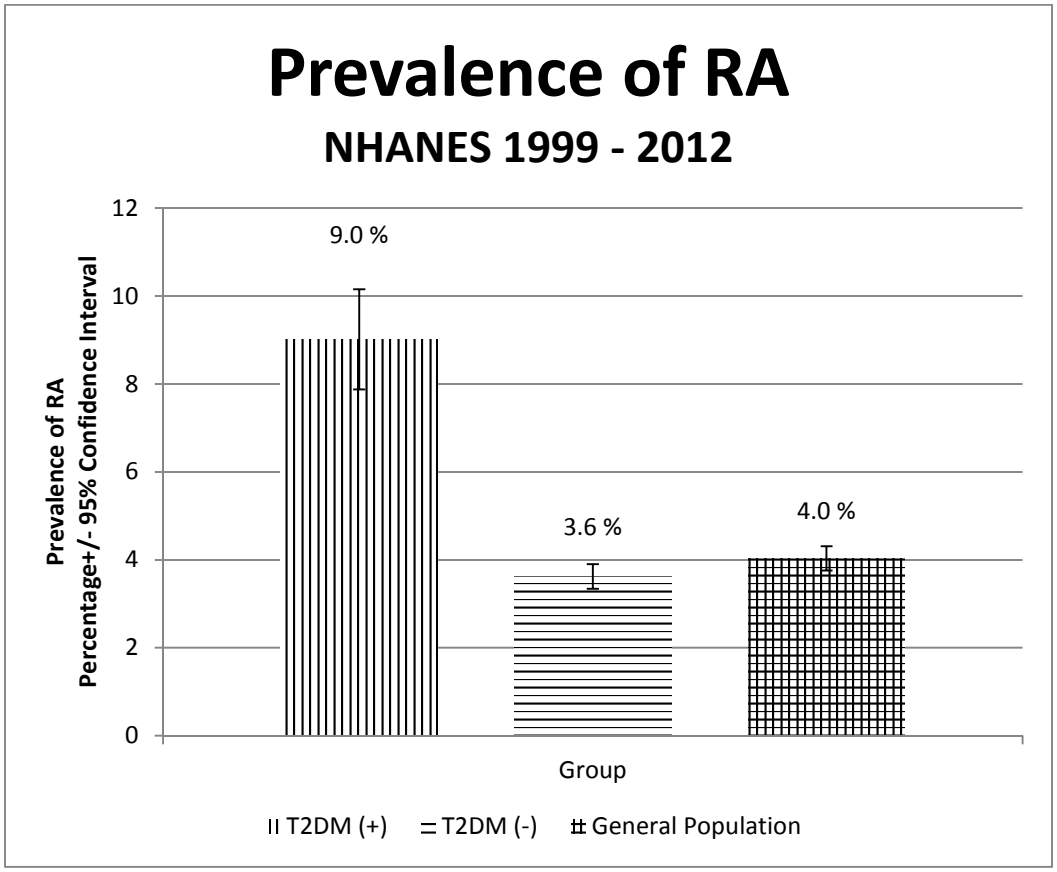

Figure 18. Prevalence of RA among U.S. patients with T2DM; patients with no diagnosis of T2DM; and the general population; NHANES 1999- 2012.

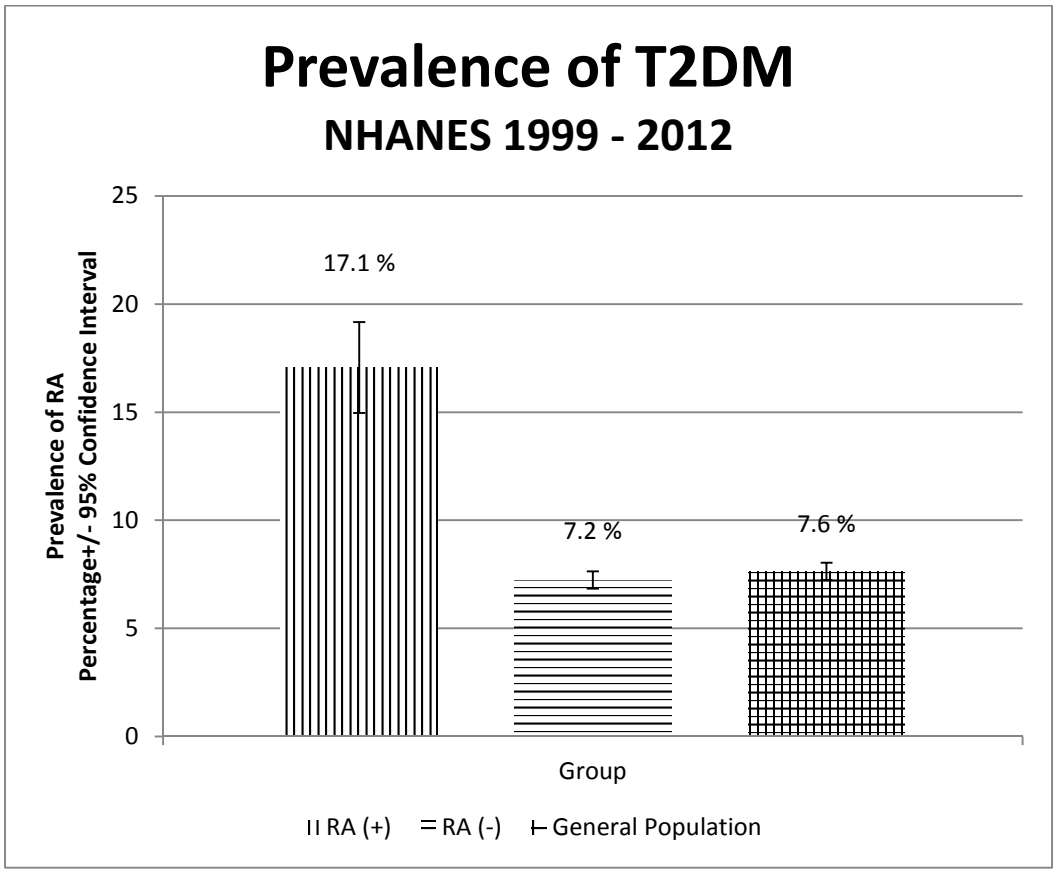

Figure 19. Prevalence of T2DM within patients with RA; patients with no diagnosis of RA; and the general population; NHANES 1999 – 2012.

The next two hypotheses evaluated potential demographic, lifestyle, or clinical characteristics that affect the odds of association of T2DM or RA within the population groups. To evaluate the hypothesis and achieve objectives, chi-square tests were performed to evaluate nominal, ordinal, and categorical variables. The chi-square test evaluates the null hypothesis, which states that there is no significant difference between the expected and observed result.

The secondary objective for the investigation was to identify what demographic, lifestyle, or clinical characteristics are significantly associated with increased odds of RA

by comparing prevalence of RA within T2DM in comparison with prevalence of RA within participants with no presence of T2DM. To achieve the objective, participants were identified within the subgroup of the presence of RA between participants with and without T2DM. A logistic regression was performed using RA as the dependent variable, which produced univariate odds. This analysis described characteristics that were potentially statistically significantly different in prevalence of RA within patients with T2DM in comparison with prevalence of RA within participants with no presence of T2DM. The following characteristics were evaluated: demographic (age, gender, race/ethnicity, education level, and poverty level); lifestyle (disability, smoking status, and work functioning) and clinical (blood pressure levels, BMI, lipid levels [HDL/LDL, TC], CRP, and use of antirheumatic medications.

Table 12 represents the ORs for RA within the group of participants with T2DM and within those with no presence of T2DM. Table 3 shows that females, with or without a diagnosis of T2DM, have increased odds of having RA ($p < 0.0001$; OR: 1.77; 1.32 respectively). This result was expected because it is well know that females in the general population are more likely to have concomitant RA. Regarding ethnicity, increased odds of RA among non-Hispanic blacks and decreased RA odds among all Hispanics were consistent between T2DM and non-T2DM. In addition, both T2DM and non-T2DM showed decreasing odds of RA as education level increased, as did increasing income relative to the poverty index.

Though significant in both groups, increasing age had a larger impact on increasing odds of RA in the non-T2DM group (OR: 1.04 per year; 95% CI: 1.04-1.05; *p*

< 0.0001) compared to the T2DM group (OR: 1.02 per year; 95% CI: 1.01-1.03; p = 0.0007).

Smoking Status: Also, smoking status appeared to be more associated with RA among non-T2DM group than the T2DM group. For instance, past smokers in the non-T2DM group had 1.97 (95% CI: 1.64-2.35; $p < 0.0001$) greater odds of RA compared to the same odds for the T2DM group of 1.10 (95% CI: 0.77-1.57; $p = 0.59$).

Disability: In view of disability, mental and physical disabilities were evaluated and as expected, for both the T2DM and non-T2DM groups, lack of physical and mental disabilities were associated with lower odds of having RA. Those with reduced work functionality were also associated with RA diagnosis, but this had greater impact on the non-T2DM group 4.19 (95% CI: 3.35-5.23; $p < 0.0001$) compared to the T2DM group of 2.18 (95% CI: 1.62-2.95; $p < 0.0001$).

Obesity: Compared to normal weight, obese individuals had 1.59 greater odds (95% CI: 1.33-1.91; $p < 0.0001$) of having RA if they are non-T2DM, whereas no such relationship was seen with T2DM (OR: 0.85; 95% CI: 0.59-1.23; $p = 0.40$). The same relationship was observed with higher average systolic blood pressure, higher fasting glucose, and higher HbA1c levels, which were associated with greater odds of RA in the non-T2DM group, but was not statistically related to RA among the T2DM group.

Table 12.

Univariate Odds Ratio of RA

Variables	Overall				Within T2DM Subgroup				Within non-T2DM Subgroup			
	OR Estimate	Lower 95% CI for OR	Upper 95% CI for OR	p-value	OR Estimate	Lower 95% CI for OR	Upper 95% CI for OR	p-value	OR Estimate	Lower 95% CI for OR	Upper 95% CI for OR	p-value
Gender	1.377	1.211	1.565	<.0001	1.772	1.379	2.279	<.0001	1.316	1.14	1.518	0.0002
Age at screening	1.041	1.037	1.045	<.0001	1.021	1.009	1.033	0.0007	1.041	1.037	1.045	<.0001
All Hispanics vs NH white	0.692	0.564	0.849	0.0004	0.911	0.649	1.278	0.5895	0.633	0.509	0.787	<.0001
NH black vs NH white	1.538	1.347	1.757	<.0001	1.812	1.347	2.436	<.0001	1.373	1.195	1.578	<.0001
Other vs NH white	0.769	0.548	1.079	0.1283	0.781	0.378	1.611	0.5027	0.729	0.5	1.063	0.1009
Educ 9-11th grade vs less than 9th grade	0.844	0.677	1.052	0.1319	0.908	0.585	1.411	0.6692	0.897	0.694	1.159	0.4059
Educ college grad vs less than 9th grade	0.281	0.223	0.353	<.0001	0.295	0.162	0.535	<.0001	0.32	0.243	0.422	<.0001
Educ HS grad/ Equivalent vs less than 9th grade	0.699	0.576	0.848	0.0003	0.784	0.494	1.245	0.3021	0.759	0.602	0.958	0.0202
Educ some college vs less than 9th grade	0.544	0.437	0.679	<.0001	0.662	0.421	1.04	0.0733	0.594	0.454	0.775	0.0001
Poverty index ratio	0.844	0.811	0.877	<.0001	0.823	0.745	0.908	0.0001	0.86	0.822	0.899	<.0001
Poverty line at or below line vs above line	1.327	1.117	1.576	0.0013	1.276	0.958	1.699	0.0954	1.308	1.073	1.594	0.0079
Current smoker vs nonsmoker	1.549	1.312	1.829	<.0001	1.304	0.856	1.985	0.2163	1.648	1.375	1.974	<.0001
Past smoker vs nonsmoker	1.862	1.578	2.197	<.0001	1.102	0.772	1.573	0.5942	1.965	1.641	2.354	<.0001
Physical disability (y vs n)	0.379	0.313	0.458	<.0001	0.591	0.419	0.832	0.0026	0.377	0.302	0.471	<.0001
Mental disability (y vs n)	0.553	0.455	0.673	<.0001	0.645	0.429	0.969	0.035	0.561	0.446	0.707	<.0001
Disability (y vs n)	0.33	0.265	0.411	<.0001	0.545	0.359	0.827	0.0043	0.327	0.254	0.421	<.0001
Work functioning (y vs n)	4.086	3.351	4.981	<.0001	2.183	1.617	2.948	<.0001	4.188	3.354	5.229	<.0001

(table continues)

	Overall				Within T2DM Subgroup				Within non-T2DM Subgroup			
Variables	OR Estimate	Lower 95% CI for OR	Upper 95% CI for OR	p-value	OR Estimate	Lower 95% CI for OR	Upper 95% CI for OR	p-value	OR Estimate	Lower 95% CI for OR	Upper 95% CI for OR	p-value
BMI	1.03	1.02	1.039	<.0001	1	0.981	1.019	1	1.027	1.016	1.038	<.0001
Obesity vs normal weight	1.664	1.407	1.969	<.0001	0.853	0.591	1.232	0.3976	1.593	1.33	1.909	<.0001
Overweight vs normal weight	1.135	0.977	1.318	0.0969	0.762	0.526	1.104	0.1506	1.127	0.951	1.336	0.1671
Hypertension vs normal	2.743	2.226	3.381	<.0001	1.109	0.762	1.612	0.5894	2.804	2.227	3.531	<.0001
Prehypertension vs normal	1.435	1.21	1.702	<.0001	0.84	0.599	1.176	0.3096	1.462	1.219	1.754	<.0001
Systolic blood pressure	1.016	1.013	1.019	<.0001	1	0.994	1.006	0.9782	1.017	1.013	1.021	<.0001
Diastolic blood pressure	0.99	0.984	0.995	0.0002	0.982	0.973	0.991	<.0001	0.995	0.989	1.001	0.0964
HDL	0.999	0.995	1.003	0.667	0.997	0.987	1.008	0.5877	1.002	0.997	1.006	0.4246
LDL	1	0.997	1.002	0.7474	1	0.993	1.007	0.9403	1.001	0.998	1.004	0.6691
Total cholesterol	1.002	1	1.003	0.0458	1	0.997	1.003	0.9301	1.002	1.001	1.004	0.0071
Glucose	1.005	1.004	1.007	<.0001	0.998	0.995	1	0.0841	1.006	1.003	1.009	<.0001
HbA1c	1.241	1.19	1.295	<.0001	0.915	0.843	0.993	0.0325	1.312	1.219	1.412	<.0001
CRP	1.203	1.155	1.252	<.0001	1.146	1.027	1.279	0.0146	1.198	1.147	1.252	<.0001
Use of analgesics (1 vs 0)	3.73	3.087	4.507	<.0001	2.246	1.452	3.472	0.0003	3.871	3.138	4.776	<.0001
Use of antirheumatics (1 vs 0)	24.829	15.014	41.06	<.0001	53.76	7.04	410.513	0.0001	25.333	14.782	43.415	<.0001
Use of glucocorticosteroids (1 vs 0)	4.784	3.587	6.379	<.0001	2.205	1.152	4.218	0.0169	5.269	3.852	7.207	<.0001

The results in this case indicated that the following characteristics were important in the association between T2DM and RA: gender, ethnicity, education, disability, and work functioning.

Contrary to the second objective, for the third objective, the investigation used participants within the subgroup of the presence of T2DM among patients with and without RA to identify what demographic, lifestyle, or clinical characteristics are significantly associated with increased odds of T2DM by comparing prevalence of T2DM within participants with RA and prevalence of T2DM within participants with no presence of RA. Similarly, a logistic regression was performed using T2DM as the dependent variable and univariate ORs were determined. The analysis described potential characteristics that were statistically significantly different in prevalence of T2DM within patients with RA in comparison with prevalence of T2DM within participants with no presence of RA. Characteristics evaluated were demographic (age, gender, race/ethnicity, education level, and poverty level); lifestyle (disability, smoking status, and work functioning); and clinical (blood pressure levels, BMI, lipid levels (HDL/LDL, TC), presence of CVD, plasma glucose, and HbA1c).

Table 13 represents the ORs for T2DM within the group of participants with RA and those with no presence of RA. The trends were very similar to Table 12. Among the RA population, significant association of age, work functioning, obesity, hypertension, prehypertension, and systolic blood pressure were found in the T2DM group, but the odds were less than the non-RA population.

Table 13.

Univariate Odds Ratio of T2DM

	Overall				Within RA Subgroup				Within non-RA Subgroup			
Variables	OR Estimate	Lower 95% CI for OR	Upper 95% CI for OR	p-value	OR Estimate	Lower 95% CI for OR	Upper 95% CI for OR	p-value	OR Estimate	Lower 95% CI for OR	Upper 95% CI for OR	p-value
Gender	1.01	0.926	1.101	0.8249	0.781	0.597	1.022	0.0716	1.053	0.96	1.154	0.2729
Age at screening	1.054	1.052	1.056	<.0001	1.033	1.021	1.045	<.0001	1.054	1.052	1.057	<.0001
All Hispanics vs NH white	1.257	1.091	1.448	0.0015	1.799	1.284	2.52	0.0006	1.249	1.083	1.441	0.0022
NH Black vs NH white	1.772	1.578	1.99	<.0001	2.221	1.649	2.991	<.0001	1.683	1.489	1.903	<.0001
Other vs NH white	1.538	1.243	1.902	<.0001	1.659	0.783	3.516	0.1863	1.551	1.237	1.943	0.0001
Educ 9-11th grade vs less than 9th grade	0.584	0.502	0.681	<.0001	0.595	0.357	0.992	0.0465	0.588	0.504	0.685	<.0001
Educ college grad vs less than 9th grade	0.252	0.209	0.304	<.0001	0.244	0.124	0.479	<.0001	0.265	0.219	0.32	<.0001
Educ HS grad/ equivalent vs less than 9th grade	0.441	0.376	0.516	<.0001	0.461	0.276	0.77	0.0031	0.446	0.378	0.528	<.0001
Educ some college vs less than 9th grade	0.364	0.312	0.425	<.0001	0.414	0.248	0.689	0.0007	0.371	0.314	0.437	<.0001
Poverty index ratio	0.853	0.828	0.879	<.0001	0.832	0.749	0.925	0.0007	0.862	0.836	0.888	<.0001
Poverty line at or below line vs above line	1.218	1.075	1.38	0.0019	1.173	0.839	1.64	0.3497	1.202	1.058	1.367	0.0049
Current smoker vs nonsmoker	0.784	0.698	0.88	<.0001	0.615	0.397	0.952	0.0294	0.778	0.689	0.878	<.0001
Past smoker vs nonsmoker	1.681	1.514	1.866	<.0001	0.958	0.662	1.387	0.8209	1.709	1.532	1.908	<.0001
Physical disability (yes vs no)	0.387	0.338	0.444	<.0001	0.608	0.433	0.852	0.0039	0.388	0.331	0.454	<.0001
Mental disability (yes vs no)	0.656	0.564	0.763	<.0001	0.767	0.479	1.227	0.2686	0.668	0.571	0.781	<.0001
Disability (yes vs no)	0.332	0.277	0.398	<.0001	0.552	0.345	0.884	0.0134	0.332	0.276	0.399	<.0001
Work functioning (yes vs no)	3.865	3.333	4.481	<.0001	2.026	1.519	2.703	<.0001	3.886	3.314	4.558	<.0001

(table continues)

	Overall				Within RA Subgroup				Within non-RA Subgroup			
Variables	OR Estimate	Lower 95% CI for OR	Upper 95% CI for OR	p-value	OR Estimate	Lower 95% CI for OR	Upper 95% CI for OR	p-value	OR Estimate	Lower 95% CI for OR	Upper 95% CI for OR	p-value
BMI	1.089	1.082	1.096	<.0001	1.065	1.042	1.088	<.0001	1.09	1.083	1.097	<.0001
Obese vs normal weight	4.765	4.14	5.485	<.0001	2.637	1.785	3.894	<.0001	4.922	4.246	5.705	<.0001
Overweight vs normal weight	1.966	1.705	2.267	<.0001	1.366	0.893	2.09	0.1501	2.022	1.746	2.341	<.0001
Hypertension vs normal	4.941	4.335	5.63	<.0001	2.028	1.364	3.015	0.0005	5.13	4.463	5.897	<.0001
Prehypertension vs normal	1.976	1.754	2.226	<.0001	1.167	0.836	1.63	0.3648	2.032	1.791	2.306	<.0001
Systolic blood pressure	1.025	1.023	1.027	<.0001	1.009	1.003	1.015	0.0027	1.026	1.024	1.028	<.0001
Diastolic blood pressure	0.983	0.98	0.987	<.0001	0.975	0.965	0.984	<.0001	0.985	0.981	0.989	<.0001
HDL	0.974	0.971	0.978	<.0001	0.973	0.963	0.983	<.0001	0.975	0.971	0.978	<.0001
LDL	0.987	0.985	0.99	<.0001	0.987	0.979	0.996	0.0034	0.987	0.985	0.99	<.0001
Total cholesterol	0.996	0.994	0.997	<.0001	0.993	0.988	0.998	0.0099	0.996	0.994	0.998	<.0001
Glucose	1.053	1.047	1.06	<.0001	1.058	1.044	1.072	<.0001	1.052	1.046	1.059	<.0001
HbA1c	7.509	6.403	8.805	<.0001	8.35	4.946	14.096	<.0001	7.352	6.232	8.673	<.0001
CRP	1.201	1.147	1.258	<.0001	1.131	1.001	1.279	0.0489	1.195	1.14	1.254	<.0001
Use of analgesics (1 vs 0)	2.15	1.758	2.629	<.0001	1.237	0.798	1.916	0.3417	2.132	1.714	2.653	<.0001
Use of antirheumatics (1 vs 0)	0.848	0.494	1.456	0.5496	0.588	0.298	1.161	0.1261	0.279	0.042	1.855	0.1865
Use of glucocorticosteroids (1 vs 0)	2.032	1.536	2.688	<.0001	0.882	0.46	1.689	0.7048	2.108	1.555	2.859	<.0001

The purpose of the fourth objective was to determine the prevalence of CVD among participants with comorbid T2DM and RA in comparison to participants with T2DM and RA independently and those with no evidence of T2DM or RA. The prevalence and adjusted ORs for the prevalence of CVD in participants with comorbid T2DM and RA was determined after adjusting for potential confounders (age, gender, ethnicity, education, and smoking status). Logistic regression assessed the interaction of RA and T2DM (independent variables) to determine if therelationship to CVD (dependent variable) has a multiplicative effect on odds of CVD (significant interaction) or whether their combination acts as two independent risk factors (nonsignificant interacton).

Table 14.

Prevalence of CVD Within U.S. Patients by T2DM and RA Status; NHANES 1999-2012

CVD Status	T2DM	Freq.	Percent	95% CI		p-value
				Lower	Upper	
CVD (+)	T2DM(+)/RA(+)	165/396	43.3971	36.22	50.57	<0.0001
	T2DM(+)/RA(-)	947/3169	28.9474	26.81	31.09	
	T2DM(-)/RA(+)	303/1305	21.3305	18.52	24.14	
	T2DM(-)/RA(-)	2294/26581	6.45262	6.07	6.83	
	All	3709/31451	8.7681	8.26	9.28	

Note: Freq. = frequency.

Table 15.

Odd Ratios of CVD from Multivariate Logistic Regression Model

	Variable	Odds ratio	OR 95% CI		p-value
			Lower	Upper	
Diabetes	T2DM+/RA+ vs T2DM-/RA-	4.737	3.508	6.397	<.0001
	T2DM+/RA- vs T2DM-/RA-	2.898	2.564	3.276	

	T2DM-/RA+ vs T2DM-/RA-	2.091	1.769	2.471	
Gender	F vs M	0.701	0.629	0.780	<.0001
Age	Per 1 year increase	1.075	1.071	1.079	<.0001
Ethnicity	All Hispanic vs other	0.645	0.485	0.858	<.0001
	NH Black vs other	0.969	0.725	1.294	
	NH White vs other	1.025	0.791	1.328	
Education	9-11th grade vs some college	1.333	1.129	1.574	<.0001
	College graduate vs some college	0.724	0.632	0.830	
	High school grad/ equivalent vs some college	1.041	0.910	1.191	
	Less than 9th grade vs some college	1.309	1.091	1.569	
Smoking Status	Current smoker vs past smoker	1.182	1.030	1.356	<.0001
	Nonsmoker vs past smoker	0.689	0.607	0.783	

Among all participants (n = 31,488), the prevalence of CVD was 8.8% ± 0.3%. The prevalence of CVD among participants with comorbid T2DM and RA was 43.4% ± 3.7%, which was significantly higher than the prevalence of CVD among those participants with T2DM alone (28.95% ± 1.1%) and among those participants with RA alone (21.3 ± 1.4%). Prevalence and adjusted ORs for T2DM and RA independently were consistent with previous research. Prevalence of CVD among participants with no evidence of T2DM or RA was 6.5% ± 0.2. The adjusted OR of CVD in participants with comorbid T2DM and RA was 4.74 (95% CI 3.51, 6.40; $p < .0001$) while the ORs for T2DM and RA independently were 2.90 (95% CI 2.56, 3.28; $p < .0001$) and 2.09 (95% CI 1.77, 2.47; $p < .0001$), respectively. The results of this study demonstrated that the ORs of CVD among participants with comorbid T2DM and RA is approximately two times the possibility of having CVD when participants have one of these conditions and about four times the possibility of having CVD in comparison with those not having any

of these conditions. CVD is definitely an important factor to consider when managing participants with comorbid T2DM and RA. See Figure 20 for the distribution of the prevalence of CVD in participants with T2DM and RA as well as the prevalence of CVD in the individual diseases. Prevalence of CVD in the general population is shown for demonstration purpose.

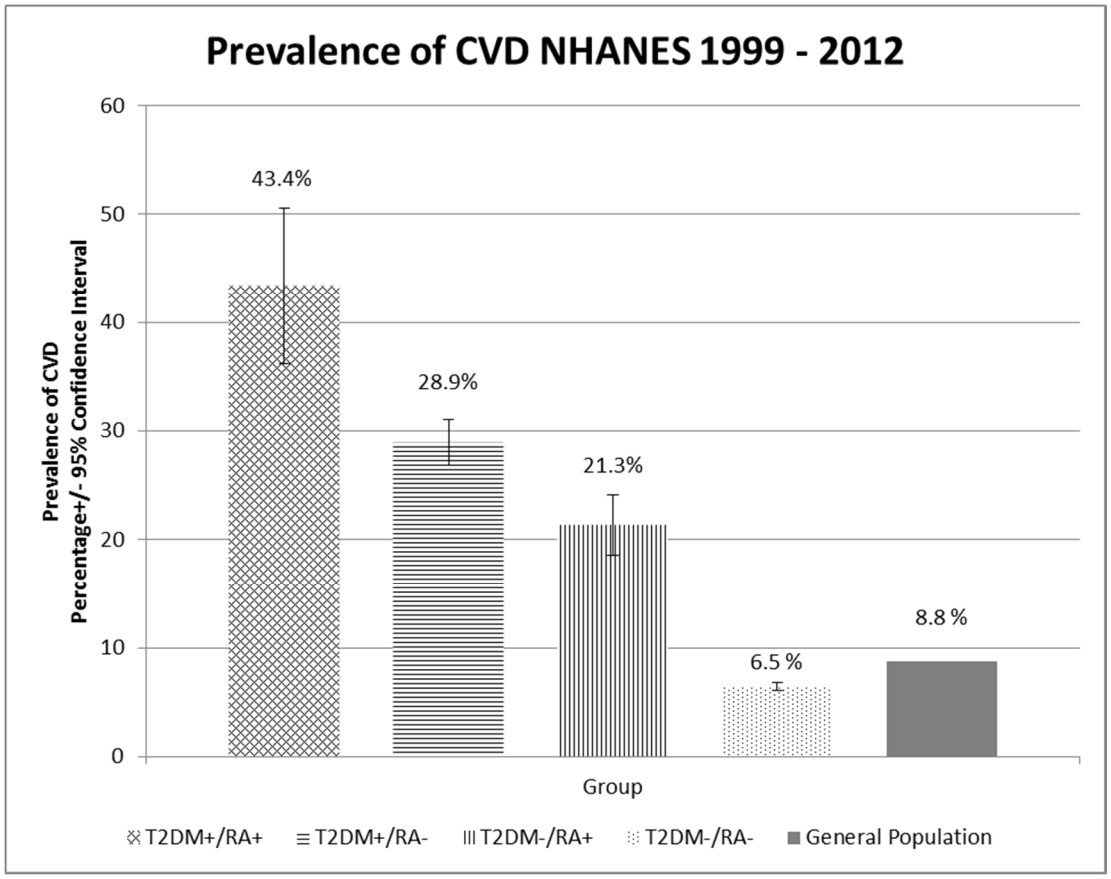

Figure 20. Prevalence of CVD among patients by diabetes and RA status in the United States (1999 – 2012).

Summary

The statistical analyses of the current study data supported Hypotheses 1 through 4. These analysis included univariate, bivariate, and multivariate assessments of adults

within the different groups: (a) T2DM and RA; (b) T2DM and no presence of RA; (c) RA and no presence of T2DM; and (d) no presence of T2DM nor RA using NHANES data from1999 to 2012. The results supported a significant association between comorbid T2DM and RA. Prevalence of RA was significantly higher for those participants with T2DM in comparison with the prevalence of RA in participants with no evidence of T2DM. In addition, the prevalence of T2DM was higher in participants with RA versus participants with no evidence of RA. The adjusted OR for the cross-sectional association between RA and T2DM were 1.45 (95% CI: 1.23, 1.71; $p < .0001$). The results of this study demonstrated a strong association between RA and T2DM, and that the prevalence of CVD among participants with this comorbidity (T2DM and RA) was higher than those having individual diseases and even higher comapared to the general population. The ORs of CVD among participants with comorbid T2DM and RA was two times the posibility when having one of these conditions and four times the possibility when not having any of these conditions. CVD is an important factor to consider when managing patients with comorbid T2DM and RA.

Chapter 5 helps understand study findings; discusses their importance to current literature, and presents conclusions. This next chapter also discusses the social change implications of the study results and conclusions, the limitations of the current study, and further recommendations for future research in this area.

Chapter 5: Discussion, Conclusions, and Recommendations

Introduction

Evidence shows that the population of patients with diabetes is disproportionately affected by arthritis in general; however, there is no recognized association between T2DM and RA. Up to this point, the available research has been unclear about the existence and nature of the association between T2DM and RA. This is why health care providers do not consider this comorbidity as part of the management of these two individual diseases. Because these two conditions have several factors in common, it is important to understand whether they are related and whether they should be managed in a interdisciplinary manner to achieve better patient outcomes. The present study was performed on a nationally representative sample to clarify the relationship between T2DM and RA, and to assess potential demographic, lifestyle, and clinical factors that could be relevant.

Using six 2-year data sets (data from 1999 to 2012) from the continuous NHANES, the present study examined the cross-sectional association between T2DM and comorbid RA. Statistical analysis was used to assess the prevalence and adjusted ORs for this association after adjusting for the following confounders: age, gender, ethnicity, education, and smoking status. The 1999-2012 data sets—which were used to assess the primary study hypotheses—allowed for assessments of a higher statistical power (N = 31,488) compared to previous research. The combined data set was used to compare differences between participants with both T2DM and RA; with T2DM and no presence of RA; with RA and with no presence T2DM; and without either diagnosis. The results

demonstrated that there was a strong association between RA and T2DM after adjusting for potential confounders. It was found higher prevalence of RA in participants with T2DM in comparison with those without T2DM and the general population as well as higher prevalence of T2DM in participants with RA. Relevant factors in this cross-sectional association between T2DM and RA were gender, ethnicity, education, obesity, hypertension, disability, and work functioning.

Using the same methodology, the study also investigated the prevalence of CVD, which is a primary cause of death in the United States, in participants with the comorbidity (T2DM and RA). The prevalence of CVD among participants with comorbid T2DM and RA is approximately two times the prevalence of having CVD when participants have only one of these conditions and about four times the prevalence of having CVD in comparison with those not having any of these conditions. Previous research indicated that the prevalence of CVD was similar in patients with T2DM and RA independently; which was higher than the prevalence of CVD in the general population. The current study reinforced previous research but also demonstrated that the prevalence of CVD is even higher in participants with T2DM and comorbid RA in comparison with those participants having only one of these diseases. Until now, no data have been available that evaluated the prevalence of CVD in patients with presence of both conditions.

Summary and Interpretation of Findings

T2DM and RA

The present study results indicated that the prevalence of RA in participants with T2DM was higher than those participants without evidence of T2DM. It is important to note the importance of adjustment for the different potential confounders (age, gender, ethnicity, education, and smoking status) while evaluating the association between these two conditions. After adjustment, the ORs of the association changed; however, the OR of association remained statistically significant supporting strong association between the dependent and independent variable. The finding persisted after controlling for potential confounders. Previous research has suggested a potential association between T2DM and RA; however, the majority of the research was not designed to investigate this specific association and thus the results were not enough strong to make conclusions. Only a few studies have been conducted to investigate this specific association and most had limitations that don't allow making conclusions on this topic. One of the most relevant studies in this area was performed by Simard and Mittleman (2007). The results showed no association between RA and DM. Their study was somewhat limited because it did not include the general population, but only people aged 60 years old and over and only evaluated data from 1988 to 1994. The current study went beyond the work done by Simard and Mittleman using a larger and more representative including all adults (18 years old and older) sample along with better power . The current study analysis was adjusted by age to mitigate any bias in this area. Tentolouris (2008) also evaluated the risk of RA in T2DM previously in a 10-year longitudinal study and noticed that the risk

of RA was associated with T2DM; however, the sample was too small to make conclusions. The current study complements the previous longitudinal research made by Tentolouris supporting the association between T2DM and RA. In another study, Solomon looked at this association from a different perspective evaluating the risk of T2DM in patients with RA. He found an association; however, he established that the work needed replication before making any conclusion. As part of the current study, the prevalence of T2DM in participants with RA was also evaluated as well as the OR for this association, and it was found that prevalence of T2DM was higher in participants with RA than in participants without RA or also in comparison with the prevalence in the general population. The authors also notice this association decreased with age, a variable that was adjusted in the current research as previously mentioned.

Another study in this area was completed by Dubreuil et al. in 2012 where the authors evaluated the risk of incident diabetes in PsA and RA in the general population, with adjustment for BMI and lifestyle factors. This research used electronic medical records database representative of the UK general population. As a result, it was found that the risk of incident DM in RA was significantly elevated, but only due to BMI and smoking. In the current study, smoking was included as one of the variables used for adjustment. BMI was added to the adjustment and the OR of the association between T2DM and RA remains strong (OR: 1.3; 95% CI: 1.1 to 1.5, $p > 0.006$). There is additional indirect research data related to this comorbidity; however, the main purpose of the research was not to evaluate this association and thus results might only be used to generate hypotheses but not to make conclusions.

Recently Jiang, et al published a new study that investigated this association using a meta-analysis to explore the risk of DM in RA patients. The conclusion of such study indicates that RA is associated with increased risk of DM, including T1DM and T2DM which support the results of the current research (Jiang et al., 2015).

Important Factors or Characteristics

The current study also evaluated potential demographic, lifestyle, and clinical characteristics or factors that could be relevant in this association using a nationally representative sample.

Demographic characteristics. The demographic characteristics evaluated in the research were age, gender, race/ethnicity, education level, and poverty level.

Age: It is well known, that the risk of developing arthritis (most types of arthritis including RA) increases with age. The risk of T2DM increases with age especially after age 45 probably because people tend to exercise less, lose muscle mass, and gain weight as they age. As expected, results of the study indicated that participants with T2DM and comorbid RA were older than those with only one of the diseases. The mean age of participants with T2DM alone was higher than those with only diagnosis of RA and at the same time much higher than those with no evidence of T2DM or RA.

Gender: Taking gender in consideration, it is known that most types of arthritis are more common in women because 60% of all people with arthritis are females. In general, no significant difference has been found by gender for diabetes. In the general population for the study, the proportion of participants by gender were almost even (51% female: 49% male); however, when participants were segregated by presence of disease it

was found that participants with diagnosis of RA (with or without T2DM) were more likely to be female. This was more pronounced in the case of participants with RA with comorbid T2DM.

Race and ethnicity: Based on previous literature, blacks, Hispanics, American Indians, and Asian-Americans are more likely to develop T2DM than whites. In general, no significant difference has been found by race or ethnicity for arthritis. The study results showed a significant difference in the proportion of non-Hispanic blacks within this comorbidity. The proportion of non-Hispanic blacks was higher in the group with this T2DM and RA than the group with only RA or only T2DM suggesting that this particular ethnicity is more affected by the combination of these two conditions.

Education: Some literature indicates that education level is an important marker of clinical status in RA (Callahan & Pincus, 1988). Previous research on diabetes has suggested that "less than a high school education" had the highest rate among the educational levels for patients with DM (Mokdad et al., 2001). It is important to consider that risk factors such as smoking, inactivity, and medication regimen noncompliance are more prevalent in those patients who have a lower educational level (high school or less) compared with those classified with higher education level (more than high school). The results of this study supported previous research because the proportion of participants with "less than a high school education" were significantly higher in participants with both conditions (T2DM and RA). This confirmed that patients with lower level of education ("less than a high school education") are likely to be sicker than those with higher education.

Poverty: As indicated in previous chapters, the poverty levels set minimum amount of gross income a family needs for food, clothing, transportation, shelter, and other necessities. PIR values below 1.00 considered as being below the official poverty threshold (poor), whereas PIR values of 1.00 or greater indicating income values above the poverty level. Poverty is an important factor in DM because poor people are less able to afford basic elements like healthy food to manage their disease. Both T2DM and RA are possible causes for disability and unemployment, which lead to lack of productivity and are related to low poverty levels. The study results indicated that the PIR is similar in participants with T2DM or RA independently; however, it decreased with the combination of both conditions and increased with no evidence of RA or T2DM. The results suggested that lower poverty status is associated with increased sickness.

Lifestyle Characteristics. Factors related to patients' lifestyle that were evaluated in this investigation were smoking, disability, and work functioning.

Smoking Status: There is plenty of evidence that relates both DM and RA with smoking. Smoking cigarettes increases the risk of RA and DM; while quitting smoking can reduce the risk. The data from the present research indicated that smoking status appeared to be more associated with RA among the non-T2DM group than the T2DM group. For instance, past smokers in the non-T2DM group had greater odds of RA compared to the same odds for the T2DM group. The finding suggested that more patients with T2DM stop smoking after the diagnosis.

Disability: Disability is an important factor to consider because arthritis and other rheumatic conditions are the most common cause of disability among U.S. adults. Forty-

two percent of adults with doctor-diagnosed arthritis report arthritis-attributable activity limitations. The NHIS has found that disability affects an estimated 20–50% of patients with diabetes. Previous literature has established that patients with diabetes, in general, report rates of disability that are substantially higher than those reported by the general U.S. population (CDC, 2006; Mayfield, 1999; Aubert, 1995). In the current study, we corroborated that both physical and mental disabilityare significantly higher for those participants with RA alone and also with T2DM, which is consistent with the information available up to this point. In addition to this, it was noted that disability is even more marked in those participants that carry both conditions. This affects both physical and mental disability but is more relevant with physical disability.

Work Functioning: Similarly, looking into work functioning, the results followed the same direction with a significant proportion of participants with T2DM and comorbid RA reporting inability to work. This statement was also applicable to participants with the individual diseases with rates higher than in the general population and lower than participants with the comorbidity of T2DM and RA. Intyerestingly, those with reduced work functionality were associated with RA diagnosis, but this had greater impact on the non-T2DM group compared to the T2DM group. Further work would be required to determine whether the impact is less on the T2DM group because their work functionality is already decreased due to their DM.

After evaluating demographic and lifestyle characteristics, it is important to mention the importance of socio economic status (SES) of these patients. SES primarily constitutes material and financial resources (e.g., income/wealth [PIR]), occupation

(disability and work functioning), and knowledge (e.g., education levels), all of which either act independently or in combination to influence health. The combination of all these elements is important to evaluate in a multifactorial manner while treating diseases like T2DM and RA and could be even more cumbersome when managing combinations of diseases. The effect of SES could affect the ability to effectively manage disease and also patients' motivation to achieve adequate health.

Clinical characteristics. Clinical characteristics evaluated in this investigation were hypertension, blood pressure levels, BMI, lipid levels (HDL/LDL, TC), CRP, glucose, HbA1c levels, and the use of some medications commonly used to treat arthritis.

The study evaluated the blood pressure levels as a continuous variable and hypertension as a categorical variable considering the following categories**:** normal, prehypertension, and hypertension. Previous research indicated that there is association between hypertension and diabetes as well as its complications including micro- and macrovascular disease. RA, as well as DM, has evidence of association with elevated risk of CVD, which is attributed to several potential factors including hypertension. Hypertension is highly prevalent but seems to be underdiagnosed and undertreated among patients with RA (Panoulas et al., 2008). The present study clearly demonstrated that hypertension is highly predominant in participants with T2DM and comorbid RA as well as in participants with T2DM in comparison with participants with no T2DM. Participants with only RA were less likely to have hypertension in comparison to those with only T2DM; however, the proportion was significantly increased in comparison with participants with no evidence of RA or T2DM.

The current study also evaluated BMI as a continuous variable and as a categorical variable based on the following weight categories: normal, overweight, and obese. BMI is considered an independent risk factor for both T2DM and RA. It is well documented that obese people have a higher risk of developing arthritis, and being overweight is a primary risk factor for T2DM. The study results supported the above statement since BMI was higher in those participants with the presence of T2DM; with RA or without RA versus those with RA alone or participants with no presence of RA or T2DM. It was found that participants with T2DM and RA have the same BMI as those with T2DM alone, which could indicate that T2DM is highly affected by increased BMI. BMI for participants with RA alone was significantly lower in comparison with those with presence of T2DM but significantly higher in comparison with those with no presence of these two diseases. The findings suggested that obesity is a significant factor in both conditions with a higher relevance on those with presence of T2DM. The results following the weight categories confirmed the previous statement based on BMI indicating that there is more obesity in participants with presence of T2DM with or without RA; however participants with RA alone are significantly more obese than those with no without presence of RA or T2DM.

Lipids were not found to be significantly different within these groups; except for TC, which was higher in those participants with positive RA.

Inflammation is an important element to consider in the potential relationship between T2DM and RA. One of the methods used to assess inflammation is using CRP in which elevated levels can provide support for the presence of inflammation. The study

found no significant difference in CRP between participants with T2DM and comorbid RA in comparison with those participants with individual diseases; however the CRP levels for all groups (T2DM and RA, T2DM alone, and RA alone) were significantly higher than those without evidence of disease (T2DM or RA). The levels of CRP were not significantly higher in participants with both conditions in comparison with those with individual diseases (T2DM and RA).

Plasma glucose and HbA1c are elements to consider for the diagnostic of diabetes and to assess glycemic control. Plasma glucose is also important to identify episodes of hypoglycemia or hyperglycemia. As expected, the study results indicated that participants with positive diagnosis of T2DM have higher glucose and HbA1c levels. Interestingly, but not significant, it was found that participants with both conditions have slightly better glycemic control based on glucose and HbA1c levels than those with only T2DM. This could be based on better patient control and disease management as comorbidities increased. Some treatments of RA are known to affect glucose levels. In those participants with no presence of T2DM, there was a small but significant difference between those with or without RA that could be related to the use of the previously mentioned drugs. The study also evaluated the use of some of these treatments: (a) antirheumatic drugs including biologic response modifiers; (b) glucocorticoids; and (c) analgesics. As expected, the results indicated that participants with positive diagnosis to RA (with or without T2DM) have a higher use of these drugs; however, participants with positive diagnosis of T2DM use these types of medication more than the general population.

CVD in participants with T2DM and comorbid RA.

As previously described in Chapter 2, there is a substantial amount of evidence for the increased cardiovascular risk in RA which is comparable to what is found in T2DM; however, there were no data available that describe the prevalence of CVD in patients with T2DM and comorbid RA. Potential factors associated with CVD and RA are obesity, insulin resistance, hypertension, atherosclerosis, dyslipidemia (Stamatelopoulos et al., 2009a), and inflammation (Sattar et al., 2003). CVD has been identified as the major complication of diabetes and is the primary cause of early death among people with this condition (NIH, 2007). It is recognized that both conditions, DM and RA, are connected with an increased risk of CVD.

The current investigation evaluated the prevalence of CVD in participants with T2DM and concomitant RA and found that the prevalence and ORs of association of CVD among participants with comorbid T2DM and RA is approximately two times the possibility of having CVD when participants have one of these conditions and about four times the possibility of having CVD in comparison with those not having any of these conditions or those in the general population. As previously mentioned, there are several investigations evaluating the risk of CVD in these individual diseases (T2DM and RA) and comparing the risk between the two disesase. The present study supported previous research finding a similar prevalence of CVD between both diseases; however, it exceeded previous research by demonstrating that CVD is even higher in those participants with this comorbidity of T2DM and RA.

Conclusion

In conclusion, the present study provides evidence supporting a strong association between T2DM and concomitant RA. Prevalence of RA is significantly higher in participants with T2DM in comparison with those with no diagnosis of T2DM. Important factors in common in this association are gender, ethnicity, education, disability, and work functioning, which significantly increase the OR of association for RA in participants with diagnosed T2DM.

Finally, prevalence of CVD and adjusted OR of association are double in participants with T2DM and comorbid RA in comparison with participants with just one of the conditions andfour times higher if compared with those with no comorbidity or with the general population.

Significance of the Study

The current study is the first one assessing the relationship between T2DM and RA using continuous NHANES data. A previous study assessed this relationship using NHANES III (not continuous data) and it was limited to elderly (65 years and older); In contrast, the current study included participants 20 years old and older and covered 12 years of data (1999-2012), which increased the sample size while improving the power of the study. Using this type of data set gave the study the strength of representativeness of the data since study participants constituted a large nationally representative sample of noninstitutionalized adults. The NHANES data set also allowed for the collection and assessments of a wide range of known confounding variables, which were controlled for

during the analysis, as well as sampling methodology that allowed accounting for special populations that are not normally considered in other database studies.

These strengths address some limitations found in previous studies, including sample size, potential confounding and selection bias due to failure to control for important factors, and nonrandom sampling. The sampling strategy used by NHANES decreases the opportunity of having selection bias and at the same time increases reliability of the data analysis. The continuous design brings flexibility to combine and analyze data over several cycles of two years increasing sample size.

The current study adds new hypotheses related to the association between T2DM and RA that warrant further investigation in prospective and longitudinal studies that could demonstrate causality. The study findings also support and reinforce the results of several previous studies on the prevalence or risk of CVD in patients with T2DM and RA independently; however, it is the first study to investigate the prevalence of CVD in patients with T2DM and comorbid RA. Along the same line, additional research is needed in this area to understand important factors in this comorbidity (T2DM, RA, and CVD) and to investigate potential causality.

Limitations

This is secondary analyses of cross-sectional data (data captured in one point in time), which does not allow determination of temporality of the association between T2DM and RA; therefore, no causal relationships conclusion should be made in this case. The primary objective of the study was to determine prevalence, thus the design was appropriate for the purpose. However, ideally once an association is shown, the next step

is to understand the nature of the association; and the current study cannot make any determination in this matter. In order to mitigate this limitation, additional analysis was performed taking in consideration the date from diagnosis for RA and T2DM, which gives the opportunity to understand the proportion of participants who reported diagnosis of T2DM before RA or vice versa in those participants with diagnosis of both conditions. The same analysis was performed with CVD to understand this variable within the last objective of the study (prevalence of CVD in participants with T2DM and comorbid RA).

Because the NHANES collects data from noninstitutionalized individuals, it may exclude some population groups at higher risk for both T2DM and RA, including residents of institutionalized settings (e.g., nursing homes) and persons of lower socioeconomic status without a home or home address. It may also exclude generalizations (external validity) to other countries especially with different health care systems. To mitigate potential selection bias, the present study findings are generalized to noninstitutionalized adults with T2DM and RA in the United States. Also because T2DM as well as RA are known to lead to mental and physical disability, a subset of disabled patients may not be included in the study and conclusions regarding this population are not be possible.

The diagnosis of RA and T2DM were self-reported by participants, which may lead to underreporting of diagnoses and misclassification bias; however, previous studies have found consistency between self-reported data on diabetes and data that were confirmed via medical records.

Another limitation related to the diagnosis of T2DM is that there is no defined variable for T2DM and thus a previously documented algorithm was used to identify patients with T2DM from all patients with diabetes. T1DM was operationally defined as an age of onset less than 30 years and receiving insulin treatment within a year after diagnosis; which resulted in the exclusion of a considerable number of persons with diabetes. The possibility that some of these individuals may have been patients with T2DM should be considered; however, use of this definition is supported by previous studies as previously stated. Future longitudinal studies or with specific diabetes diagnosis (T2DM or T1DM) are recommended to complement these findings.

Implications for Social Change and Recommendations for Action

The current study has several implications for social change. Considering the clinical perspective, this study supports that a different attention is needed from health care providers while managing patients with T2DM and concomitant RA; in particular, considering the elevated probability of having CVD, which is primary cause of death in the United States. The findings add to the evidence suggesting that there is a strong association between T2DM and RA. Furthermore, this study added characterization and identification of specific differences between patients with T2DM and RA; T2DM and no RA; RA and no T2DM; and those with no disease with regard to demographic, lifestyle, and clinical factors. The findings may aid health care providers (e.g., endocrinologists, diabetes educators, and nurses), especially busy primary care physicians (PCPs), to characterize and identify a population that could be at high risk for having one disease, which will facilitate targeted screening, early detection, and treatment of the second

disease or vice versa. Also, for those patients that already have both diseases, the HCP in particular the PCP, that in many cases manage all diseases in a interdisciplinary manner, may use a different approach that could address all patients' needs.

The findings provide evidence that ethnicity is an important factor to consider, as shown by a significantly higher proportion of non-Hispanics lacks with positive diagnosis of T2DM and comorbid RA when compared to those with individual diseases or no presence of either of the two diseases. Additionally age (older patients); gender (highly in females), and education (less educated people) are important factors to consider while attending to patients at risk of this comorbidity.

The present study results suggest CVD is highly prevalent in patients with T2DM and comorbid RA. With the caveat that it is not possible to determine causality, it is important for health care providers to grant additional importance to the cardiovascular risk in patients with this comorbidity of T2DM and RA. This study further emphasizes the need for effective screening and early diagnosis of CVD in this population.

By strengthening current evidence, these findings can serve as input for policy and/or decision makers, which may to help inform policies to improve patients' health. Based on this and further data, screening and targeted public health intervention approaches could be implemented in particular to manage these diseases in a multifactorial or interdisciplinary manner as supported by the CCM.

From a research standpoint, current study findings indicate strong association between T2DM and RA and highlight potential factors to consider in this association; however, additional research is needed to understand the nature of this association; which

disease could predict the other one and also which factors could be predictors versus consequences of the interaction between these comorbidites. Longitudinal data is needed to understand all factors that could affect this association and also recognize the multilevel environment that could affect the individual support as well as the organizational (provider – community) perspective considering the SEM theory.

As future studies are designed to examine the relationship between T2DM and RA, the mediating effects of factors like disability and work functioning need to be taken into consideration in addition to known potentially confounding factors (age, gender, ethnicity, education, and smoking status). Further longitudinal studies are needed to determine causal relationship that could help identify groups at risk for the appropriate prevention and/or interventions.

The findings also demonstrate that patients with T2DM and comorbid RA are more likely to have CVD. It is important to characterize patients with evidence of T2DM, RA, and comorbid CVD and how they differ with those patients with CVD and only one of these conditions (T2DM and RA). Once potential predictors are defined, it is possible to create interventions for disease detection and treatment as well of management of complications in an appropriate and timely manner. Longitudinal studies are needed to understand temporal association between these diseases and to understand possible predictors or links between causatives precursors. Additional research may help inform HCPs how to manage these diseases in a interdisciplinary manner following the CCM.

References

American Diabetes Association. (2013a). Living with Diabetes. Retrieved from http://www.diabetes.org/living-with-diabetes/?loc=GlobalNavLWD

American Diabetes Association. (2013b). Economic costs of diabetes in 2012. *Diabetes Care,* 36(4), 1033-46.

American Diabetes Association. (2014). Standards of medical care in diabetes—2014. *Diabetes Care,* 37(Supplement 1), S14-80.

American Heart Association. (2013). Obesity Information. Retrieved from http://www.heart.org/HEARTORG/GettingHealthy/WeightManagement/Obesity/Obesity-Information_UCM_307908_Article.jsp

American Heart Association. (2014). What your cholesterol means. Retrieved from http://www.heart.org/HEARTORG/Conditions/Cholesterol/AboutCholesterol/What-Your-Cholesterol-Levels-Mean_UCM_305562_Article.jsp

Antohe, J., Bili A., Sartorius, J.A., Kirchner, H.L., Morris, S.J., Dancea, S., et al….,Chester, M. (2010). Tumor necrosis factor-inhibitors and reduced risk of developing diabetes in patients with rheumatoid arthritis. *Arthritis and Rheumatism*, 62, 1442.

Antohe, J.L., Bili, A., Sartorius, J.A., Kirchner, H.L., Morris, S.J., Dancea, S., Wasco, M.C. (2012). Diabetes mellitus risk in rheumatoid arthritis: Reduced incidence with anti-tumor necrosis factor alpha therapy. *Arthritis Care and Research*, 64, 215-221.

Aletaha, D., Neogi, T., Silman, A.J, Funovits, J., Felson, D.T., Bingham, C.O. 3rd,

Birnbaum, N.S., … Hawker, G. (2010). 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum*, Sep;62(9), 2569-81.

Aubert, R. (1995). Diabetes in America. National Institute of Health. National Institute of Diabetes and Digestive and Kidney Disease. *NIH Publication* 95-1468.

Barr, V., Robinson, S., Marin-Link, B., Underhill, L., Dotts, A., et al. (2003). Chronic Care Model: An integration of Concepts and Strategies from Population Health Promotion and Chronic Care Model. *Hospital Quarterly,* 7(1), 73-82.

Bartels C.M., Saucier J.M., Thorpe C.T., et al. (2012). Monitoring diabetes in patients with and without rheumatoid arthritis: a Medicare study. *Arthritis Research and Therapy*, 14(4), doi:10.1186/ar3915.

Berkowitz, A.A., Meigs, J.B. & Wexler, D.J. (2013). Age at type 2 diabetes onset and glycaemic control: results from the National Health and Nutrition Examination Survey (NHANES) 2005–2010. *Diabetologia*, 56, 2593–2600.

Birnbaum, H., Pike, C., Kaufman, R., Marynchenko, M., Kidolezi, Y., & Cifaldi, M. (2010). Societal cost of rheumatoid arthritis patients in the US. *Current Medical Research and Opinion*, Jan;26(1), 77-90

Bili, A., Sartorius, J., Kirchner, H., Morris, S., Ledwich, L. (2011). Hydroxychloroquine Use and Decreased Risk of Diabetes in Rheumatoid Arthritis Patients. *JCR: Journal of Clinical Rheumatology*, 17, 115-120.

Callahan, L.F., & Pincus, T. (1988). Formal education level as a significant marker of clinical status in rheumatoid arthritis. *Arthritis Rheumatology*, 31(11), 1346-57.

Centers for Disease Control and Prevention. (2006) Prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitation - United States, 2003-2005. *MMWR,* 55, 1089-92.

Center for Disease Control. (2008). CDC Morbidity and Mortality Weekly Report (*MMWR*) (2008) Arthritis as a Potential Barrier to Physical Activity Among Adults with Diabetes --- United States, 2005 and 2007. *MMWR*, 57(18), 486-489. Retrieved from http://www.cdc.gov/mmwr/preview/mmwrhtml/ mm5718a3.htm?scid=mm5718a3_e

Center for Disease Control. (2010a) CDC - Arthritis - Physical Activity for Arthritis – Factsheet Retrieved from http://www.cdc.gov/arthritis/pa_factsheet.htm

Center for Disease Control. (2010b). CDC Morbidity and Mortality Weekly Report (*MMWR*) (2010) 42% of adults with doctor-diagnosed arthritis report arthritis-attributable activity limitations. *MMWR*, 59(39), 1261-1265. Retrieved from http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5939a1.htm?s_ cid=mm5939a1

Center for Disease Control and Prevention. (2011a). National Center for Chronic Disease Prevention and Health Promotion National Diabetes Fact Sheet, 2011. Retrieved from http://www.cdc.gov/diabetes/pubs/pdf/ndfs_ 2011.pdf

Centers for Disease Control and Prevention. (2011b). National Center for Health Statistics (2011). Leading Causes of Death in US. Retrieved from http://www.cdc.gov/nchs/fastats/lcod.htm

Centers for Disease Control and Prevention (CDC). (2012a). Rheumatoid Arthritis, 2012.

Retrieved from http://www.cdc.gov/arthritis/basics/rheumatoid.htm

Centers for Disease Control (CDC). (2012b). National Health and Nutrition Examination Survey (NHANES). About the NHANES. Retrieved March 5, 2012, from the U.S. Department of Health and Human Services (USDHHS), the National Center for Health Statistics (NCHS) database from http://www.cdc.gov/nchs/nhanes.htm

Centers for Disease Control (CDC). (2012c). NHANES: Questionnaire or Examination Protocol, or Laboratory Protocol). Department of Health and Human Services (USDHHS). Retrieved from http://www.cdc.gov/nchs/nhanes/nhanes_questionnaires.htm

Center for Disease Control (CDC). (2013a). Arthritis-Related Statistics. Retrieved from http://www.cdc.gov/arthritis/data_statistics/arthritis_related_stats.htm

Center for Disease Control (CDC). (2013b). Diabetes Public Health Resource. Retrieved from http://www.cdc.gov/diabetes/

Center for Disease Control (CDC). (2014). National Diabetes Statistics Report, 2014. Retrieved from http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf

Coleman K., Austin, B.T., Brach, B., & Wagner, E.H. (2009). Evidence On The Chronic Care Model In The New Millennium *Health Affairs*, 28(1), 75-85 Retrieved from http://content.healthaffairs.org/content/28/1/75.full.html

Coresh, J., Astor, B.C., Greene, T., Eknoyan G., & Levey, A.S. (2003). Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis*, 41, 1-

12.

Diabetes Control and Complications Trial (DCCT). (1993). The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med,* 329(14), 977–86.

Diabetes Control and Complications Trial (DCCT) Research Group. (1996). The absence of a glycemic threshold for the development of long-term complications. The perspective of the DCCT. *Diabetes, 45*, 1289-1298.

Doran, M. (2007). Rheumatoid Arthritis and Diabetes Mellitus: Evidence for an Association? *The Journal of Rheumatology*, 34, 460-461.

Dubreuil, M., Rho, Y., Man, A., Zhu, Y., Zhang, Y., Love, T., (2012). The risk of diabetes in psoriatic arthritis and rheumatoid arthritis: 2614. *Arthritis & Rheumatism*, 64, S1107-S1108.

Frei, A., Chmiel, C., Schläpfer, H., Birnbaum, B., Steurer, J., & Rosemann, T. (2010). The Chronic CARe for diAbeTes study (CARAT): a cluster randomized controlled trial. *Cardiovascular Diabetology,* 9, 23.

Garber, A.J, Abrahamson M.J., Barzilay J.I., Blonde L., Bloomgarden Z.T., Bush M.A., Dagogo-Jack S., … Davidson M.H.; American Association of Clinical Endocrinologists. (2013). AACE comprehensive diabetes management algorithm *Endocr Pract*, Mar-Apr;19(2), 327-36.

Genuth, S., & Ismail-Beigi, F. (2012). Clinical Implications of the ACCORD Trial. *The Journal of Clinical Endocrinology & Metabolism,* January;97(1), 41-48.

Gerstein, H.C., Miller, M.E., Byington, R.P., Goff, D.C. Jr., Bigger, J.T., et al. (2008). The Action to Control Cardiovascular Risk in Diabetes Study Group 2008 Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med,* 358, 2545–2559.

Heliovaara, M., Aromaa, A., Klaukka, T., Knekt, P., Joukamaa, M., & Impivaara O. (1993). Reliability and validity of interview data on chronic diseases. The Mini-Finland Health Survey. *J Clin Epidemiol,* 46, 181–191.

International Diabetes Federation (IDF). (2012). Diabetes Atlas. Retrieved from http://www.idf.org/diabetesatlas

Jiang, P., Li, H., Li, X., (2015). Diabetes mellitus risk factors in rheumatoid arthritis: a systematic review and meta-analysis. Clin Exp Rheumatol. 2015 Mar-Apr;33(1):115-121

Karanasos, A., Felekos, I., Aggeli, C., Zampeli, E., Protogerou, A., Stefanadis, C., et al. (2011). Myocardial ischemia in asymptomatic patients with rheumatoid arthritis: A comparative study with diabetes mellitus. *Arthritis and Rheumatism,* 63(10 SUPPL. 1).

Karanasos, A., Toutouzas, K., Aggeli, C., Felekos, I., Tsiamis, E., Sfikakis, P., et al. (2012). Rheumatoid arthritis is associated with high ischemic burden, comparable to diabetes mellitus, but in the absence of obstructive coronary disease. *Circulation*, 126(21 SUPPL. 1)

Kehoe, R.,Wu, S.Y., Leske, M.C., & Chylack, L.T. Jr. (1994). Comparing selfreported and physician-reported medical history. *Am J Epidemiol,* 139, 813–818.

Kitas, G.D., & Erb, N. (2003). Tackling ischemic heart disease in rheumatoid arthritis.

Rheumatology 42, 607–13.

Koopman, R.J., Mainous, A.G. 3rd, Diaz, V.A., & Geesey, M.E. (2005) Changes in age at diagnosis of type 2 diabetes mellitus in the United States, 1988 to 2000. *Annual Family Medicine*, 3, 60–63

Lindhardsen, J., Gislason, G.H., Ahlehoff, O., Madsen, O.M., & Hansen, P.R. (2010). The risk of myocardial infarction is similar in rheumatoid arthritis and diabetes - A nationwide cohort study. *European Heart Journal,* 31, 148.

Lundkvist, J., Kastäng, F., & Kobelt, G. (2008). The burden of rheumatoid arthritis and access to treatment: health burden and costs. *European Journal Health Economics*. 8 Suppl. 2, S49-60.

Machin, D., & Campbell, M.J. (1987). *Statistical Tables for design of Clinical Trials.* Oxford: Blackwell Scientific Publications.

MacLennan, W. J. (2007). Rheumatoid arthritis and diabetes. *Age & Ageing*, 36(5), 486.

Mayfield, J.A., Deb, P. & Whitecotton, L. (1999). Work disability and diabetes. *Diabetes Care,* 22(7): 1105-1109.

Mensing, C., Boucher, J., Cypress, M., Edd, M., Mulcahy, K., Barta, P., … , Adams, C. (2004) National Standards for Diabetes Self-Management Education. *Diabetes Care*, Volume 27, Supplement 1, January 2004 Page S143

Midthjell, K., Holmen, J., Bjorndal, A., & Lund-Larsen, G. (1992). Is questionnaire information valid in the study of a chronic disease such as diabetes? The Nord-Trondelag Diabetes Study. *J Epidemiol Community Health,* 46, 537–542.

Mokdad, A.H., Ford, E.S., Bowman, B.A., Dietz, W.H., Vinicor, F., Bales, V.S., &

Marks, J.S. (2003). Prevalence of Obesity, Diabetes, and Obesity-Related Health Risk Factors, 2001. *JAMA*, 289(1):76-79.

Myasoedova, E., Crowson, C.S., Kremers, H.M., Therneau, T.M., & Gabriel, S.E. (2010). Is the incidence of rheumatoid arthritis rising?: results from Olmsted County, Minnesota, 1955-2007. *Arthritis Rheumatology*, 62(6), 1576-82.

National Institute of Health (NIH). (2007). The link between diabetes and cardiovascular disease. Retrieved from http://ndep.nih.gov/media/CVD_FactSheet.pdf

Nathan, D.M., Buse, J.B., Davidson, M.B., Ferrannini, E., Holman, R.R., Sherwin, R., & Zinman B.; American Diabetes Association; European Association for Study of Diabetes. (2009). Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*, 32(1), 193-203.

Nutting, P.A., Dickinson, W.P., Dickinson LM, et al. (2007). Use of chronic care model elements is associated with higher-quality care for diabetes. *Ann Fam Med*. 2007; 5:14–20.

Ogden, C. L., Carroll, M. D., Kit, B.K., & Flegal, K.M. (2012). Prevalence of obesity and trends in body mass index among U.S. children and adolescents, 1999-2010. *Journal of the American Medical Association*, 307(5), 483-490.

Panoulas, V.F., Metsios, G.S., Pace, A.V., John, H., Treharne, G.J., Banks, M.J., & Kitas, G.D. (2008). Hypertension in rheumatoid arthritis. *Rheumatology (Oxford),* 47(9), 1286-98.

Patel, A., MacMahon, S., Chalmers, J., Neal, B., Woodward, M., Billot, L., Harrap, S., … Williams. B. (2007). Effect of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet,* 370, 829-840.

Patel, A., MacMahon, S., Chalmers, J., Neal, B., Billot, L., Woodward M., Marre M., … Travert F. (2008). Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *New England Journal of Medicine,* 358(24), 2560-72.

Peters M.J.L., Van Halm V.P., Voskuyl A.E., Smulders Y.M., Boers M., Lems W.F., et al. (2010). Rheumatoid arthritis increases the risk of cardiovascular diseases as strongly as diabetes mellitus. *Nederlands Tijdschrift voor Geneeskunde,* 154(17), 801-806.

Peters, M.J., Van Halm, V.P., Voskuyl, A.E., Smulders, Y.M., Boers M., Lems W.F., Visser M., Stehouwer C.D., Dekker J.M., Nijpels G., Heine R., Dijkmans B.A., Nurmohamed, M.T. (2009). Does rheumatoid arthritis equal diabetes mellitus as an independent risk factor for cardiovascular disease? A prospective study. *Arthritis Rheum*, 61(11), 1571-9.

Ryden, L., Standl, E., Bartnik, M., Van Den Berghe, G., et al. (2007). Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes

(EASD). *Eur Heart J,* 28(1), 88-136.

Sarwar, N., Gao, P., Seshasai, S.R., Gobin R., Kaptoge, S., Di Angelantonio, E., Ingelsson, E., … Danesh J. (2010). Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet,* 26;375(9733), 2215-22.

Sasaki, T., Hiki, Y., Nagumo, S., Ikeda, R., Kimura, H., Yamashiro, K., et al. (2010). Acute onset of rheumatoid arthritis associated with administration of a dipeptidyl peptidase-4 (DPP-4) inhibitor to patients with diabetes mellitus. *Diabetology International,* 1, 90-92.

SAS Institute Inc. (2008). *SAS/Stat 9.2 user's guide: Introduction to power and sample size analysis.* Cary, NC: SAS Institute Inc.

SAS Institue Inc. (n.d.). *SAS Annotated Output: Proc Logistic*. Retrieved from http://www.ats.ucla.edu/stat/sas/output/sas_logit_output.htm.

Sattar, N., McCarey, D.W., Capell H., & McInnes, I.B. (2003) Explaining how "high-grade" systemic inflammation accelerates vascular risk in rheumatoid arthritis. *Circulation,* 108(24), 2957-63.

Schmidt, M.I., Duncan, B.B., Sharrett, A.R., et al. (1999). Markers of inflammation and prediction of diabetes mellitus in adults (Atherosclerosis Risk in Communities Study): a cohort study. *Lancet,* 353, 1649-52.

Seligman, H.K., Bindman, A.B., Vittinghoff, E., Kanaya, A.M., Kushel, M.B. (2007). Food insecurity is associated with diabetes mellitus: results from the National Health Examination and Nutrition Examination Survey (NHANES) 1999-2002. *J*

Gen Intern Med, 22, 1018–1023.

Simard, J.F., & Mittleman, M.A. (2007). Prevalent rheumatoid arthritis and diabetes among NHANES III participants aged 60 and older. *J Rheumatol,* 34, 469-73.

Solomon, D., Love, T., Canning, C., & Schneeweiss, S. (2010a). Risk of diabetes among patients with rheumatoid arthritis, psoriatic arthritis and psoriasis. *Annals of the Rheumatic Diseases,* 69, 2114-2117.

Solomon, D.H., Massarotti, E.M., Garg, R., Canning, C., Liu J., & Schneeweiss S. (2010b). Systemic immunosuppressives and the risk of diabetes in rheumatoid arthritis (RA) and Psoriatic Arthritis (PsA). *Arthritis and Rheumatism*, 62, 339.

Solomon, D., Massarotti, E., Garg, R., Liu, J., et al. (2011). Association Between Disease-Modifying Antirheumatic Drugs and Diabetes Risk in Patients With Rheumatoid Arthritis and Psoriasis. *JAMA*, 305, 2525-2531.

Stamatelopoulos, K.S., Kitas, G.D., Papamichael, C.M., Chryssochoou, E., Katsiari, C.G., Georgiopoulos G., et al. (2009a). Preclinical atherosclerosis is of similar severity in rheumatoid arthritis and diabetes mellitus despite differential impact of traditional risk factors and systemic inflammation. *Arthritis and Rheumatism*, 60, 941.

Stamatelopoulos, K., Kitas, G, Papamichael, C., Chryssohoou, E., Kyrkou, K., Georgiopoulos, G., et al. (2009b). Atherosclerosis in Rheumatoid Arthritis Versus Diabetes: A Comparative Study. *Arteriosclerosis, Thrombosis & Vascular Biology,* 29, 1702-1708.

Sullivan, S. (2011). Department of Health and Community Services. Improving Health

Together: A Policy Framework for Chronic Disease Prevention and Management in Newfoundland and Labrador. Chronic Disease Policy Framework.

Tentolouris, N., Arapostathi, C., Voulgari, C., Grammatikou, S., Andrianakos, A., & Sfikakis, P. (2008). The effect of diabetes mellitus on the prevalence of rheumatoid arthritis: a case-control study. *Diabetic Medicine,* 25(8), 1010-1011

United Kingdom Prospective Diabetes Study (UKPDS) Group. (2000). Association of glycemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): A prospective observational study. *British Medical Journal,* 321, 405-412.

United States Census Bureau (USCB). (2011). The Research SUPPLEMENTAL POVERTY MEASURE: 2011 Retrieved from http://www.census.gov/prod/2012pubs/p60-244.pdf

United States Department of Health and Human Services (USDHHS). (2013). Healthy people 2020. Retrieved from http://www.healthypeople.gov/2020/default.aspx

United States Medical Library of Medicine (USMLM). (2014). Diabetes. National Center for Biotechnology Information, U.S. National Library of Medicine. Retrieved from http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002194/

Van Halm, V.P., Peters, M.J., Voskuyl, A.E., Boers, M., Lems, W.F., Visser, M., Stehouwer, C.D., … Nurmohamed MT. (2009). Rheumatoid arthritis versus as a risk factor for cardiovascular disease: a cross-sectional study, the CARRE Investigation. *Ann Rheum Dis.* 68(9), 1395-400.

Vargas, R.B., Mangione, C.M., Asch, S., et al. (2007). Can a chronic care model

collaborative reduce heart disease risk in patients with diabetes? *J Gen Intern Med*, 22, 215–222.

Wasko M.C., Kay J., Hsia E.C., & Rahman M.U. (2011). Diabetes mellitus and insulin resistance in patients with rheumatoid arthritis: risk reduction in a chronic inflammatory disease. *Arthritis care & research,* 63(4), 512-521.

Woolf, A. D., & Pfleger, B. (2003). Burden of major musculoskeletal conditions. Special Theme – Bone and Joint Decade 2000 –2010 Bulletin of the World Health Organization 2003, 81 (9).

World Health Organization (WHO). (2013a). Media Center Diabetes Fact Sheet # 312 Updated March 2013. Retrieved from http://www.who.int/mediacentre/factsheets/fs312/en/

World Health Organization (WHO). (2013b). Chronic diseases and health promotion. Retrieved from http://www.who.int/chp/topics/rheumatic/en/

Yazdanyar, A., Wasko, M.C., Kraemer, K.L., & Ward M.M. (2010). Hospital-based surgical procedures and the risk of perioperative cardiovascular events: A comparison study of rheumatoid arthritis and diabetes mellitus using the National Inpatient Sample of the HealthCare cost and Utilization Project. *Arthritis and Rheumatism,* 62, 1039.

Yazdanyar, A., Wasko, M., Kraemer, K. & Ward, M. (2012). Perioperative all-cause mortality and cardiovascular events in patients with rheumatoid arthritis: Comparison with unaffected controls and persons with diabetes mellitus. *Arthritis & Rheumatism,* 64, 2429-2437.

Yokota, K., & Igaki, N. (2012). Sitagliptin (DPP-4 inhibitor)-induced rheumatoid arthritis in type 2 diabetes mellitus: A case report. *Internal Medicine*, 51, 2041-2044

Zampeli, E., Karanasos, A., Felekos, I., Aggeli, C., Stefanadis, C., Toutouzas, K., et al. (2012). Silent myocardial ischaemia without angiographically significant coronary artery disease in rheumatoid arthritis versus diabetes. *Rheumatology*, 51, i17.

Zhang, W., & Anis, A. (2011). The economic burden of rheumatoid arthritis: beyond health care costs. *Clin Rheumatol*. 30 Suppl, 1, S25-3

Appendix A: Copyright Permission