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The Effect of Depression, Inflammation and Sleep Quality on Risk for Cardiovascular Disease

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by

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LIST OF ABBREVIATIONS

ACC	American College of Cardiology
ACS	Acute Coronary Syndrome
AHA	American Heart Association
AHRQ	The Agency for Healthcare Research and Quality
AIS	Acute Ischemic Syndrome
AMI	Acute Myocardial Infarction
BP	Blood Pressure
BMI	Body Mass Index
CABG	Coronary Artery Bypass Graft Surgery
CDC	Center for Disease Control and Prevention
CHD	Coronary Heart Disease
CI	Confidence Interval
CES-D	Center for Epidemiologic Studies Depressive Symptoms Scale
CRP	C-reactive Protein
CVA	Cerebrovascular Event
CVD	Cardiovascular Disease
DEP S	Depressive Symptoms
DM	Diabetes Mellitus
FRS	The Framingham Risk Score

HDL	High Density Lipoprotein
Hs-CRP	High Sensitivity C-reactive Protein
Heart SCORE	Heart Strategies Concentrating on Risk Evaluation
IHD	Ischemic Heart Disease
IL-6	Interleukin-6
LDL	Low-density Lipoprotein
MACE	Major Adverse Cardiac Event
MI	Myocardial Infarction
NSTEMI	Non-ST-elevation Myocardial Infarction
OR	Odds Ratio
RERI	Relative Excess Risk Due to Interaction (RERI)
RRTW	The Reynolds Risk Tool for Women
STEMI	ST Elevation Myocardial Infarction
TG	Triglycerides
USPSTF	The US Preventive Services Task Force
WHO	World Health Organization

ABSTRACT

Background

Cardiovascular disease (CVD) remains the number one killer even after years of advances and preventative measures. Identifying and reducing modifiable risk factors is a health care priority. CVD Risk assessments are calculated using several traditional risk factors including age, gender, race, blood pressure, cholesterol, history of diabetes, and smoking to estimate a persons' risk of developing CVD (heart disease or stroke) in the next 10-years. In addition to the traditional risk factors for CVD, there is increasing evidence of metabolic disorders, depressive symptoms, inflammation and sleep quality posing a greater risk for CVD. However, these factors are not included in the current risk prediction models including the Framingham Risk Score, Reynolds Risk Score, and Pooled Cohort Risk Equations. Therefore, this study examined the effect of depressive symptoms, inflammation, and sleep quality on the independent risk for CVD.

Objective

The primary objective of this study was to evaluate the independent relationships between traditional cardiac risk factors, depressive symptoms, inflammation, and sleep quality, on long-term risk of major adverse cardiovascular events (MACE). The secondary objective was to evaluate whether gender modifies the relationships between depressive symptoms, inflammation, and sleep quality on long-term risk of MACE.

Design

A secondary analysis was conducted on data obtained from the Longitudinal prospective cohort study Heart Strategies Concentrating on Risk Evaluation (Heart SCORE) conducted by the University of Pittsburgh. The ongoing Heart SCORE study has been prospectively examining cardiovascular disease (CVD) risk factors and CVD events on an initial cohort of 2,000 enrolled adults ages 45 to 75 at study entry. A Cox proportional-hazard model was used to evaluate the relationship between traditional risk factors as well as independently and collectively for depressive symptoms, inflammation and sleep quality and risk of MACE. Models were reanalyzed adding gender as an interaction term and in stratified analyses to evaluate whether gender modifies the relationships between sleep quality, depressive symptoms, and inflammation and long-term risk of MACE.

Results

The participants (N= 1,895) included in this study were, 1256 females (66%), 639 males (34%), ranging from 45 to 75 years of age with a median age of 60 years, 42% Blacks, 55% Whites and 3% other race. Six percent, (*n* =113) of the participants experienced a major cardiac event during a mean of nearly 10 year follow up. Results indicated that men as compared with women with high levels of interleukin-6 had particularly high risk for CVD, as defined by two separate definitions of MACE, MACE1: Hazard Ratio (HR) 3.44 vs. 1.72 for males and females, respectively, MACE6: HR 2.51

vs. 1.69 for males and females, respectively. These results suggest the high inflammation in men is strongly associated with future risk of CVD. The addition of depressive symptoms to the initial traditional risk factor model was associated with a modest increase in the risk of both definitions of MACE (HR range from 1.20 to 1.68) with similar results observed by gender. Sleep quality/Insomnia was not associated with long-term risk of MACE overall or when evaluated separately by gender.

Conclusion

Primary prevention with early identification of potential modifiable risk factors is a key strategy in planning interventions to reduce the risk of CVD. Results from this study suggest that depression and inflammation (e.g. IL-6) should be studied in other populations to estimate their independent predictive value in risk stratification. Whereas sleep quality was not associated with long-term risk of CVD in this analysis, future studies should consider the use of objective measures of sleep quality, such as actigraphy in addition to standard use of self-report measures and sleep diaries.

CHAPTER ONE:

INTRODUCTION

Cardiovascular disease (CVD) is the number one cause of death worldwide, with an estimated cost of $316 billion per year (Benjamin et al., 2018). Cardiovascular disease is a broad term used to include any ailment of the heart and vascular system (Center for Disease Control and Prevention, CDC, 2018). The Agency for Healthcare Research and Quality (AHRQ) has elevated cardiovascular disease prevention and treatment as national priority in the National Quality Strategy (AHRQ, 2014). The Million Hearts Campaign initiative aims to prevent one million heart attacks and strokes over a 5-year period with an objective to identify and spread better models of care delivery and payment (Benjamin et al., 2018).

Although several multivariable risk estimation scores and equations have been derived and published, there are inherent limitations of using the existing scores (Goff et al., 2014). In addition, data are sparse on the use and impact of absolute risk scores in clinical practice in primary-prevention settings to determine absolute risk score for varying populations of the United States (Goff et al., 2014). Risk factor determination using the existing CVD risk assessment models may predict the incidence of CVD events and mortality. However, many experts believe that there is a need to identify and add novel risk markers in short- and long-term risk assessment to determine outcomes in all racial/ethnic groups, and across the age spectrum, and in women and men (Lin et

al., 2018). The short- and long-term risk assessment in diverse groups will guide providers to offer a more personalized approach to patient behavioral and motivating interventions, change and adherence to therapy for improving risk factor levels, and clinical outcomes (Lin et al., 2018).

The US Preventive Services Task Force (USPSTF) recently published recommendations regarding the use of non-traditional risk factors in CVD risk assessment (Curry et al., 2018). The focus of the most recent recommendations was on the ankle-brachial index (ABI), high-sensitivity C-reactive protein (hsCRP) level, and coronary artery calcium (CAC) score (Benjamin et al., 2018; Curry et al., 2018; Lin et al., 2018). When endorsing change of health benefits, potential harms and cost are considered. Although, the impact of these risk factors was not consistent nor significant enough to recommend reform from current practice, the potential benefits were recognized and may be considered in a more personalized approach for prevention and treatment (Benjamin et al., 2018; Curry et al., 2018; Lin et al., 2018).

Evidence is also emerging that other non-traditional risk factors such as depressive symptoms and sleep quality may increase susceptibility and aid in subsequent prediction for CVD (Alcantara & Davidson, 2014; Sands-Lincoln et al., 2013). In general, most cohort studies that assessed risk calibration with the use of novel markers found that adding one of the non-traditional risk factors improved calibration and potentially better preventive care (Curry et al., 2018). Therefore, using existing data set from Heart Strategies Concentrating on Risk Evaluation (Heart

SCORE) study, this secondary data analysis focused on examining the contribution of a few key non-traditional risk factors, on predicting long-term risk of CVD.

Background of the Problem

National and worldwide initiatives in the development of risk assessment tools have resulted in improved treatment guidelines, including use of medications and invasive interventions that have played significant roles in the reduction of CVD mortality (Benjamin et al., 2018). Traditionally, prevention and management of CVD begins with an assessment to identify the presence of cardiac risk factors (Benjamin et al., 2018; Curry et al., 2018). The risk factors are conditions that, on average, make a person more likely to develop a disease. Such risk factors for CVD are categorized into modifiable or non-modifiable risk factors. Modifiable risk factors for CVD include: high blood pressure, diabetes, hypercholesterolemia, obesity, sedentary lifestyle, smoking, uncontrolled stress, and unhealthy dietary habits (Benjamin et al., 2018). Age, family history of early heart disease and menopause for women are risk factors that cannot be changed to reduce the likelihood of CVD, and thus, are termed non-modifiable risk factors (Benjamin et al., 2018).

Primary care providers are responsible for identifying modifiable risk factors and management of preventive interventions including education and life-style changes (AHRQ, 2014). However, studies have used different stratum and risk calibration approaches to determine risk (Curry et al., 2018). In this regard, although the addition of some non-traditional risk scores improved calibration, there is inconsistent evidence as to the benefits of basing therapeutic strategies on some of the non-traditional risk

factors for patients; for example, adding statin therapy for patients with elevated hsCRP levels (Ridker et al., 2008). As clinical practice moves toward a single threshold (algorithm) for treatment, this concern may no longer be relevant in clinical decision making. The USPSTF recommends including more information on the differences between commonly used CVD risk assessment tools, as well as population distribution of risk (Curry et al., 2018).

History of Cardiac Risk Assessment

The original CVD risk assessment was developed for adults between the ages of 30 to 62 at the time of first examination, and with no history of heart attack or stroke. These assessments were derived from participants enrolled in the Framingham Heart Study, which began in 1948 (Kannel, 1976). The Framingham Heart Study, along with other important large studies, such as the Seven Countries Study and the Nurses' Health Study, provided the information now known about cardiac risk including healthy lifestyle such as healthy diet and regular exercise (Kannel, 1976). Additionally, greater knowledge about the differences in cardiovascular risk between men and women were gleaned from these studies. The first risk prediction equations demonstrated the potential amplified risk when having multiple risk factors such as, hypertension, elevated total cholesterol, decreased HDL, smoking, glucose intolerance, and left ventricular hypertrophy, versus one risk factor (O'Donnell & Elosua, 2008).

The CVD Risk assessments are calculated using several factors including age, gender, race, blood pressure, cholesterol, history of diabetes, and smoking to estimate

a persons' risk of developing CVD (heart disease or stroke) in the next 10-years. The overall goals of these tools are to assist not only clinicians, but also patients, in understanding risk and monitoring over time and quantifying potential benefits of preventative therapies (Benjamin et al., 2018; Curry et al., 2018; Lin et al., 2018).

The Framingham Risk Score

The Framingham Risk Score (FRS) assessment is a well-known and widely accepted tool, developed from the knowledge gained in the long-term Framingham Heart Study. The FRS uses a simple point score to provide 10-year estimates of myocardial infarction or cardiac mortality (Hermansson & Kahan, 2018). The first Framingham risk score was introduced in 1976 and identified risk factors successful at predicting 10-year risk for CVD. This study validated non-modifiable risks such as age, gender, family history and previous history of cardiac problems and modifiable risk factors including smoking, diabetes, hyperlipidemia, and hypertension (Hermansson & Kahan, 2018; Kannel,1976). The Tool was updated in 2002 with the addition of dyslipidemia, and in 2008 with the addition of diabetes as a major risk factor (Hermansson & Kahan, 2018). The FRS tool has been questioned for its generalizability to the general American population, as it was developed and tested on a primarily White male population.

Reynolds Risk Score for Women

The Reynolds Risk Score for Women (RRSW) was developed to overcome the drawback from FRS with gender-specific assessment. The RRSW includes assessing activity, lifestyle, and diet, and includes a measure of the inflammatory marker C-

Reactive Protein (CRP) (Goff et al., 2013). The RRSW was developed from findings of a large study with over 24,000 healthy non-diabetic women. These women were followed over 10 years and monitored for the development of a major cardiac event (Ridker et al., 2007).

Reynolds Risk Score for Men

The Reynolds Risk Score for men was developed based on a study following over 10,000 healthy non-diabetic men over 10 years. Like the women's tool, the addition of High Sensitive C-Reactive protein (hsCRP) and family history of a major event prior to the age of 60 years of age was added to the model improving predictability of CVD in men (Ridker et al, 2008).

Pooled Cohort Equations Risk Estimator

Through collaborative efforts of the AHA, National Heart, Lung and Blood Institute (NHLBI) and The American College of Cardiology, the Pooled Cohort Equations Risk Estimator tool was developed to better predict the 10-year risk of developing atherosclerotic cardiovascular disease (ASVCD) and how that risk may change over time as preventative measures are initiated (Goff et al., 2013). Attention was taken to include various races and gender within this study (Goff et al, 2013). The Pooled cohort screen is presently recommended as the standard of practice for risk screening. Unlike the Reynolds score but similar to the FRS, the Pooled Cohort Equations tool includes diabetes as a risk factor, highlights the large burden of disability from non-fatal cardiac events and provide separate equations for non-White populations. Yet, given the increased evidence that inflammation plays a crucial role in

the process of atherogenesis, the Pooled Cohort Equations do not include CRP or other inflammatory markers in risk calculation (Held et al., 2017; Joseph et al., 2017).

Many developing countries have developed CVD risk scores specific for their region such as the Canadian CVD guideline (Anderson et al., 2012); The European Society of Cardiology uses the Systemic Coronary Risk Evaluation (SCORE) risk charts (Perk et al., 2012); The UK National Institute for Health and Care Excellence uses the QRISK3 risk tool; and The Scottish Intercollegiate Guidelines Network (SIGN) uses the ASSIGN risk score to determine the 10-year risk of a CVD events (National Institute for Health and Care Excellence (NICE), 2014). These risk assessments tool do not include non-traditional risk scores such as hsCRP (Scottish Intercollegiate Guidelines Network (SIGN),2017).

The above-mentioned risk scores are algorithms that enable health care providers and patients to estimate 10-year and lifetime risks for atherosclerotic CVD to provide preventive services to minimize the risk (Bell & Saraf, 2014). Unfortunately, there is insufficient data to reliably predict risk for those less than 40 years of age or greater than 79 years of age (Curry et al., 2018). Also, evidence is emerging on the association of metabolic disease, depressive symptoms, and sleep quality that increases CVD risk, and these are not included in the above risk prediction tools, thereby warranting further studies. Thus, this secondary analysis aimed to examine the value of these non-traditional risk factors in risk prediction.

Problem

Despite a wide range of educational programs, national campaigns, increased funding and improved screening tools, CVD continues to have very high mortality and burden of disability on society. Nearly half of all Americans (44%) have at least one of the three key risk factors for heart disease: high blood pressure, high cholesterol, or smoking (Benjamin et al., 2018). Moreover, the growing obesity epidemic is associated with unhealthy diet, high blood pressure and a dramatic rise in Type 2 diabetes (Benjamin et al., 2018).

Over the past 2 decades, considerable progress has been made in the reduction of CVD related deaths, with a decrease of nearly 3.79% from 2000 to 2011 (Sidney et al., 2016). However, the decline flattened around 2011 and remains flattened today (Mensah et al., 2017; Sidney et al., 2016). The annual rate of decline for CVD mortality between 2000-2011 was 3.79 percent, while the same measures from 2011-2014 were only less than one percent (Sidney et al., 2016). The current risk reductions recommendations are based mostly on the risk assessment with the Framingham Risk Score or Pooled Cohort Equations. Quality studies comparing traditional risk assessment with traditional risk assessment together with novel markers such as cytokines are needed to measure the potential impact of adding nontraditional risk factors on clinical decision thresholds and patient outcomes (Shaima, Vinayaga-Moorthi & Kutty-Shaheen, 2016).

Purpose

Depressive symptoms have been linked to CVD and CVD mortality (Lahtinen et al., 2018; Lawes et al., 2018). Additionally, persons with high levels of inflammatory markers and altered sleep quality have also been identified as being at a higher risk of CVD (Dhar & Barton, 2016). These modifiable risk factors are not traditionally screened for and may contribute to both primary and secondary prevention for cardiac disease aimed at reducing risk for CVD and limiting complications, mortality, and disability, including among those who have experienced a major adverse cardiac event.

The purpose of this secondary data analysis was to evaluate the predictive ability of depressive symptoms, inflammation, and sleep quality on CVD risk. An additional clinical question was to determine, if screening for these non-traditional modifiable risk factors during routine exams, may allow for primary prevention measures that may reduce risk of CVD. This included evaluation overall and by gender.

Specific Aims:

1. To prospectively evaluate the independent relationships between traditional cardiac risk factors, depressive symptoms, inflammation, and sleep quality, on long-term risk of major adverse cardiovascular events (MACE).

2. To prospectively evaluate whether gender modifies the relationships between depressive symptoms, inflammation, and sleep quality on long-term risk of MACE.

Definition of Terms

For purposes of this study, the following terms are defined:

Cardiovascular Disease

Cardiovascular disease (CVD) is a global term that refers to conditions that involve the heart and vascular system. This includes a diagnosis of congenital malformations of the heart and/or vasculature, hypertension, arrhythmias or irregular electrical activity of the heart, valvular heart disease and ischemic heart disease or arthrosclerosis (Benjamin et al., 2018). For this study, persons with congenital malformations were not included.

Major Adverse Cardiac Event

Major adverse cardiac event (MACE) is a composite endpoint commonly used in research, yet without a standard definition (Kip et al., 2008). The Heart SCORE study employed 6 different definitions for MACE. To illustrate a lack of standard definition and end points for MACE, deJung et al. (2017) defined "CVD events" as admission for heart failure, ischemic cardiovascular events, and cardiac death. In a dissimilar manner, Nejatian et al. (2017) defined MACE as a hospital stay with an MI, unplanned revascularization including percutaneous coronary intervention, coronary artery bypass surgery and all-cause mortality (deJung et al., 2017; Nejatian et al., 2017). Within the current analysis, two of the six definitions of MACE were examined, as defined below.

MACE1. MACE1 includes, all cardiac deaths, acute myocardial infarction, (AMI), cerebral vascular accident (CVA), acute ischemic syndrome (AIS) and any coronary revascularization procedure.

MACE6. MACE6 includes all deaths**,** acute myocardial infarction, (AMI), cerebral vascular accident (CVA), acute ischemic syndrome (AIS).

Atherosclerosis

Atherosclerosis, also known as atherosclerotic heart disease (ASHD), involves a buildup of plaque inside arteries leading to a narrowing and stiffening of the vasculature. The plaque is made up from cellular waste, fatty deposits, calcium, and fibrin (Benjamin et al., 2018). Vascular narrowing slows the flow of oxygenated blood and increases the risk of blood clot formation. Additionally, plaque can break away from the arterial wall, increasing risk for a thrombus or obstructed blood flow (Benjamin et al., 2018). Atherosclerosis increases risk of organ failure due to diminished oxygenated blood flow.

Ischemic Heart Disease

Ischemic heart disease is a condition in which buildup of plaque within the walls of the coronary arteries causes narrowing within the size and compliance of the vasculature creating an obstructed blood flow. The reduced blood flow results in reduced oxygenation or ischemia to the heart muscle and organs (Benjamin et al., 2018).

Cardiac Events

Cardiovascular events include the diagnosis of death related to cardiac disease, myocardial infarction, acute ischemic syndrome, cerebral vascular accident (ischemic), and ischemic heart disease requiring revascularization or opening of the arteries to increase blood flow. Ischemic heart disease and cardiovascular events are of interest for this study.

Myocardial Infarction (MI)

The most common cause of an MI is atherosclerosis that has led to a complete blockage of blood flow to an area of the heart (Benjamin et al., 2018). Additional terminology includes ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI). These terms are based on presentation of a MI on an electrocardiogram (ECG) (Kumar & Cannon, 2009; Senter & Francis, 2009).

Revascularization

Revascularization refers to any medical procedure employed to restore blood flow to the heart. There are several procedures that may fall under this term. Angioplasty includes procedures done without open surgery by accessing arteries through the skin such as percutaneous transluminal coronary angioplasty (PTCA) and arterial stenting. Additionally, coronary artery bypass (CABG) is a surgical procedure to restore blood flow to the heart, falling under the revascularization term (Thygesen, Alpert & Harvey 2007).

Cerebral Vascular Accident

Cerebral vascular accident (CVA), which is also referred to as a stroke, is a condition that occurs when blood flow to the brain is obstructed and the brain is without enough oxygen resulting in death of brain cells. There are 2 categories of stroke based on etiological classifications of CVA, including ischemic and hemorrhagic strokes (Benjamin et al., 2018; Speranza et al., 2000).

Acute Ischemic Stroke

Acute Ischemic Stroke (AIS) is caused from narrowing or obstruction of blood flow from atherosclerosis or an obstruction caused from a blood clot to the brain. It may be transient as from a spasm or a clot that breaks free or minimal blood flow resulting in hypoxia to the brain tissue usually without permanent damage; this is referred to as a transient ischemic accident (TIA) (Benjamin et al., 2018; Kidwell & Warach, 2003; NIHLBI, 2018).

Hemorrhagic Stroke

Hemorrhagic stroke is caused from bleeding in the brain that may cause pressure and/or loss of blood flow to the brain, resulting in damage or death to brain cells (NIHLBI, 2018).

Diabetes

Diabetes Mellitus, commonly known simply as diabetes, is a disease in which the body's ability to produce or respond to the hormone insulin is impaired, resulting in abnormal metabolism of carbohydrates and elevated levels of glucose in the blood and urine (Shoback & Gardner, 2011). It is considered a chronic metabolic disorder in which the blood glucose is higher than the acceptable rages of 80-130 mg/dL. This hyperglycemic state is a result of pancreas inability to control blood glucose levels.

Type I Diabetes

Type I diabetes is the result of ineffective secretion of insulin by the pancreas, with about 5-10% of all diabetics being type I (American Diabetes Association (ADA), 2018). Treatment includes daily administration of insulin.

Type II Diabetes

Type II diabetes is a failure of the pancreas to compensate for a resistance of the insulin by the cells resulting in hyperglycemia. Diabetes affects more than 30 million people in the United States, and approximately 90% of all cases are classified as Type II (ADA, 2010).

Gestational Diabetes

Gestational diabetes is often temporary and occurs during pregnancy. With this condition, the body is unable to maintain blood glucose levels within an acceptable range. Persons having gestational diabetes have an increased risk of developing Type II diabetes later in life (ADA, 2010; International Diabetes Foundation (IDF), 2018).

Depressive Symptoms

Symptoms of depression vary, but include loss of interest or pleasure, loss of energy, fatigue, sleep problems, and changes in appetite. Depressive symptoms have been linked to physiological changes such as increased inflammatory markers and is therefore relevant to this study (Dannehl et al., 2014). Sometimes, symptoms that look like depression are not really depression. Depressive symptoms range in seriousness from mild, temporary episodes of sadness to severe, persistent depression. Clinical depression is the more-severe form of depression, also known as major depression or

major depressive disorder. Clinical depression is a treatable serious medical illness according to the American Psychiatric Association (APA, 2015). This paper includes persons with depressive symptoms, rather than a diagnosis of clinical depression.

InInterleukin-6 (IL-6)

Interleukin-6 is a measure of inflammation that has an expected value in the general population of approximately 1-5 pg/ml. Secretion of IL-6 occurs as an acute phase inflammatory response and plays a role in the process that leads to atherosclerosis. IL-6 triggers the liver to produce the inflammatory marker C-reactive protein (CRP) (Yudkin, Kumari, Humphries & Mohamed, 2000).

C-reactive Protein (CRP)

C-reactive protein is produced in the liver and adipocytes and is a part of the acute phase inflammatory response (Martinez & Gonzalez- Juanatey, 2009). CRP is a non-specific indicator of elevated inflammation that may occur secondary to stress, infection, cancer, CVD, rheumatoid arthritis, and trauma (Yudkin, Kumari, Humphries & Mohamed, 2000).

Highly Sensitive C-Reactive Protein (hsCRP)

Similar to CRP, hsCRP measures more specifically blood vessel CRP and is a more specific measure with respect to risk of atherosclerosis. Current recommendations for evaluating cardiovascular risks suggest the use of hsCRP. However, this assessment may not be cost effective as a high level of accuracy requires multiple laboratory measurements, 2 weeks apart, and with the average of the readings used to estimate potential cardiac risk (CDC, 2018).

Quality of Sleep (Insomnia)

Sleep is the natural periodic suspension of consciousness during which the powers of the body are restored (Harvey Stinson, Whitaker Moskoviz & Virk, 2008). Insomnia refers to habitual sleeplessness or inability to sleep. Quality of sleep is measured as insomnia, assessed as the ability to fall asleep or sleep latency, duration of sleep and functional ability upon awakening. Quality of sleep has been linked to work related injuries and errors, perceived quality of life, as well as physical illness including increased inflammatory markers, diabetes, and cardiovascular disease. Research has suggested that sleep of less than six-hours or poor quality of sleep (sleep apnea, for example), increases risk for experiencing a cardiac event (Barger et al., 2017).

Traditional Risk Factors for CVD

A risk factor refers to something that increases health risk or susceptibility. Below are definitions of several conditions that have been accepted as traditional risk factors for CVD (Goff et al., 2014; Lin et al.,2018)

Hypertension

Hypertension refers to abnormally high arterial blood pressure that is usually indicated by an adult systolic blood pressure of 120 mm Hg or greater or diastolic blood pressure of 80 mmHg or greater (James et al., 2014; Whelton et al., 2017). Systolic blood pressure represents the pressure exerted against arterial walls with each heartbeat. This is the upper number on the blood pressure reading. The newest guidelines recommend systolic blood pressure to be < 120 mm Hg. Diastolic blood

pressure, the lower number of the reading, represents the pressure exerted against the arterial walls between heartbeats. Consistent readings over guideline-specific recommended levels are consistent with a diagnosis of hypertension (Whelton et al., 2017).

Metabolic Syndrome

Metabolic syndrome is a cluster of conditions which include elevated blood pressure, high blood sugar, excess body fat around the waist, low HDL (i.e. good cholesterol) and high triglyceride levels. The higher number of these factors and having at least 3 of the factors (definition of metabolic syndrome) increases future risk of CVD (Zimmet, Alberti & Shaw, 2005).

Body Mass Index

Body mass index (BMI) is a person's weight in kilograms divided by the square of height in meters (kg/m^2). A BMI greater than 25 indicates overweight; greater than 30 is classified as obese (WHO, 2014).

Central Obesity or Abdominal Obesity

Central obesity is defined as excessive adipose in the abdominal area and is an independent predictor of CVD. Measures in women greater than 89 centimeters and men greater than 102 centimeters portend higher risk for CVD (Canoy et al., 2013).

Dyslipidemia

Elevation of plasma cholesterol and triglycerides (TG) and low High-Density lipoprotein (HDL) cholesterol levels are defined as dyslipidemia, and contribute to the development of atherosclerosis (Bear, 2017). Although low HDL levels predict cardiovascular risk in the overall population, the increased risk may be caused by other factors, such as accompanying lipid and metabolic abnormalities, rather than the HDL level itself. Etiology for dyslipidemia can be primary (genetic), or secondary and caused by poor lifestyle or dietary practice, as well as some disease conditions (Goff et al., 2014).

Triglycerides (TRIG)

Triglycerides carry unused fat cells to be stored and used for energy later. Elevated triglycerides have long been considered a risk factor for CVD, and optimal levels are less than 150 mg/dL (Baer, 2017; Goff et al., 2014). Elevated triglycerides in diabetes increases the risk of CVD (Goff et al., 2014).

High Density Lipoprotein (HDL)

Low, serum HDL cholesterol is strongly associated with risk factors for CVD. This cholesterol is often referred to as the “good” cholesterol as it works to transport fat out of the arteries. Anti-inflammatory and antioxidant effects of high HDL levels reduce endothelial damage and are favorable in preventing CVD (Goff et al., 2014). Recommended values for women are greater than 55mg/dL and men greater than 45mg/dL (CDC, 2017; Smith et al., 2017).

Low density Lipoprotein (LDL)

Low-density lipoprotein is often referred to as the bad cholesterol. Although not listed as a component of the metabolic syndrome, elevated LDL plays a key role in the development of atherosclerosis and is strongly associated with CVD. Recommended levels for LDL are less than 130 mg/dL, however, more recent guidelines are emphasizing lower numbers (<100 mg/dL). These values vary among agencies with newer guidelines recommending target values based on risk analysis and comorbidities (Baer, 2017; Pallazola et al., 2018).

Significance to Nursing

In the campaign against CVD, primary prevention with early identification of potential modifiable risk factors is key in planning interventions to reduce occurrence of the disease. CVD has become our Nations' costliest chronic disease and will continue to be the most burdensome disease that Americans will face in the coming decades. Thus, expenses associated with CVD are expected to soar in coming years. Therefore, identifying the degree to which depressive symptoms, inflammation, and sleep quality influence development of CVD may support changes in how routine screenings are conducted to better inform and manage CVD risk. This study aimed to address the gap in knowledge that exists for the optimal development of appropriate screenings and preventative measures to prevent cardiovascular disease.

CHAPTER TWO:

REVIEW OF LITERATURE

Scientific evidence supports a strong relationship between a person's lifestyle and risk for developing or dying from CVD. The World Health Organization (WHO) estimates that over 75% of premature CVD is preventable and risk factor amelioration can help reduce the growing CVD burden among both individuals and healthcare providers (Curry et al., 2018; Roth et al., 2017). While a general estimation of the relative risk for CVD can be approximated by counting the number of traditional risk factors present in a patient, a more precise estimation of the absolute risk for a first CVD event is desirable when making treatment recommendations for a specific individual.

This chapter presents the supporting evidence on the effects of traditional risk factors for CVD including; age, race, gender, obesity, smoking, diabetes, hypertension, and hyperlipidemia and the risk for developing CVD including the occurrence of a major adverse cardiac event (MACE). In addition, literature supporting evidence of interaction with demographic variables, as well as evidence on the non-traditional and potentially modifiable risk factors of depressive symptoms, inflammation, and sleep quality and their relationship to risk for CVD are discussed.

Traditional Risk Factors For CVD

Age Gender and Race as Risk For CVD

Age is an independent “non-modifiable” risk factor for CVD and confers heightened risk until the approximate age of 70 years when the risks start to level off (Dhingra & Vasan, 2012). Aging is associated with a decline in cellular regeneration, respiratory capacity, skeletal muscle decline, reduction in hormones, and a weakened and often chronically alarmed immune system (Barzilai, Huffman, Muzumdar, & Bartke, 2012). Aging increase ones’ risk for hypertension, visceral adiposity, insulin resistance, and atherosclerosis, all considered risk factors for CVD (Lopez-Candales, Hernandez-Bergos, Hernandez-Suarez & Harris, 2017; Mosca, Barrett-Connor & Wenger, 2011). Previous literature has used the term “heart age” to distinguish from chronological age. Heart age estimates a person’s age based on the presence of cardiac risk factors. For example, a 45-year-old obese, diabetic individual with hyperlipidemia and hypertension would be “older” in heart age than a 50-year-old non-smoker non-diabetic, who is overweight by about 10 pounds, and with normal blood pressure and cholesterol levels (Hirsch, Wits, Li, & Soliman, 2018; Yang et al., 2015). The CDC reports that the average American male has a heart age nearly 8 years and women 5.4 years greater than their true years of age (Hirsch et al., 2018; Yang et al., 2015). Chronological age is not modifiable but reducing modifiable risk factors could lower an individual’s heart age.

Prior to reaching age of 45-years, men have a higher rate of hypertension, increased arterial stiffness and endothelial dysfunction and nearly double the risk for CVD compared to women (Mosco, Barrett-Connor & Wenger, 2011; Benjamin et al., 2018*).* Cardiovascular disease develops, on average, 7 to 10 years later in women than in men (Maas & Appelman, 2010). As women start to age into the sixties, the rates start to even out for women, and those with comorbidities may have a higher risk for CVD than men (Benjamin et al., 2018; Mosco et al., 2011;). These differences could be related to female hormones that reduce with age and then cease during menopause. It has been thought that estrogen may have protective components. Rat studies have found estrogen to have a significant effect in epithelial homeostasis, anti-fibrotic effects, vasodilatation, and a reduction in oxidative stress, all factors directly related to the development (or lack thereof) of atherosclerosis (Lorga et al., 2017). Additionally, women who experience premature menopause, having lost the protection of estrogen before the age of 40, have been found to have a shorter life (Rocca et al., 2012; Sabbag et al., 2017).

Physiologically, women with CVD react differently and have poorer outcomes then men. Women often present with atypical complaints when experiencing an MI and have a higher risk of mortality (Sabbag et al., 2017). Symptoms do not always include the crushing chest pain, shortness of breath easily recognized as a potential cardiac event. Women complaints can be vague, including, fatigue, diaphoresis, and nausea (Mehta et al., 2016; Sabbag et al., 2017). These presentations contribute to delay in

medical evaluation and/or misdiagnoses, as women have been found to have higher rates of Global Registry of Acute Coronary Events (GRACE) score ≥140 (19% vs 12%, p = .007) (Sabbag et al., 2017). Moreover, revascularization procedures may be less likely to be successful in women who may have less complete blockages (Merz & Chang, 2016; Mehta et al., 2016). Additionally, revascularization procedures have increased bleeding complications thought to be related to increased platelet aggregation in women (Maas & Appelman, 2010; Mehta et al., 2016). These differences in presentation with MACE place women at a higher risk for misdiagnosis, delay of treatment, including invasive interventions, and death (Maas & Appelman, 2010; Mehta et al., 2016; Merz & Chang, 2016).

Historically, CVD risk factors are seen disproportionately in racial and ethnic populations (Kurian & Carderelli, 2007). An awareness of the disparities of CVD risk factors by race and ethnicity may guide clinicians to develop culturally sensitive educational, interventional and prevention programs aimed at risk factors prevalent within these populations. Blacks have been considered at higher risk for CVD. An analysis using subject data from both The Mediators of Atherosclerosis in South Asians Living in America study and The Multi-Ethnic Study of Atherosclerosis study reported Blacks to have more than double the risk for developing atherosclerotic CVD after all adjustments, compared to whites, HR 2.23, 95% CI [1.51, 3.30] (Kullo et al., 2007; Rifai et al., 2018). Hypertension, diabetes, obesity, and atherosclerosis have a higher prevalence at an earlier age in the Black population (Carnethon et al, 2017). According

to the American Heart Association (AHA), deaths rates for CVD are 270.6 per 100,000, for Non-Hispanic White Males compared with, 356.7 for Non-Hispanic Black males and 183.8 for Non-Hispanic White females and 246.6 for Non-Hispanic Black females (Benjamin et al., 2018). Cardiovascular related death rates are consistently higher among Blacks.

Despite this increased rate of mortality in the Black population, Blacks have paradoxically been found to have favorable lipid profiles in comparison to Whites. Racial differences in lipoprotein levels have previously been reported in the Heart SCORE study. For blacks compared to whites, the breakdown is as follows. Blacks had higher HDL cholesterol levels compared to Whites. Both Black men and Black women had fewer small dense LDL particles than their White counterparts (Aiyer, et al., 2007; Kullo et al., 2007). Similar findings are reported by Gaillard and Osei, (2016), that women with an elevated risk of obesity and many with prediabetes were analyzed for racial differences. Blacks with prediabetes were more obese (BMI 38.8 $\pm$ 6.7 kg/m2 than White 36.0 $\pm$5.4 kg/m2). Also, Blacks had lower triglycerides levels (84.4 $\pm$47.9 mg/dL) than Whites (125 $\pm$55.5 mg/dL). Moreover, this study reported higher HDL cholesterol levels and higher small sized LDL cholesterol in Black women (Gaillard & Osei, 2016).

Diabetes as a Risk For CVD

Diabetes has long been considered a “cardiovascular risk equivalent” and people with diabetes have 2 to 4 times increased risk of CVD morbidity and mortality than individuals without diabetes (Bertoluci & Zorzanelli, 2017). Younger diabetics such as men under the age of 35 years and women under 45 years without a raised LDL cholesterol level (more than 100 mg/dL), normotensive with no past cardiac history or obesity may not be at a greater risk. It was suggested in determining preventive measures, that the need for statin medication should make use of a more individualized approach (Bertoluci & Zorzanelli, 2017). The Cardiovascular Health study sought to explore differences by gender and race in risk for CVD. Compared to non-diabetics, a significant increased risk for CVD was established for Black, diabetic women HR 2.15, 95% CI [1.43, 3.23] and Black diabetic men HR 1.48, CI 95% CI [0.92, 2.39]. Interaction between diabetes, gender, and CVD was not significant (Vimalananda et al., 2014).

Diabetes has been long linked to CVD. Among those with Type II diabetes, 75% or greater of all hospitalizations and more than 50 % of deaths, are related to CVD (Benjamin et al., 2018). Diabetics, especially persons with Type II tend to be more overweight and have a more sedentary lifestyle in comparison to those without diabetes (Dokken, 2008). However, not everyone with diabetes is the same and differences in medical and family history, gender, race, and age influence risk. The AHA/ACC have suggested that diabetics be stratified for risk based on presence of comorbidities (Goff et al., 2014).

The physiological changes associated with diabetes, elevated blood glucose, and inflammatory responses place the diabetic individual at greater risk for atherosclerosis, which is a major component to CVD. Vascular endothelium lines the entire circulatory system and is responsible for maintaining blood vessel tone including vasodilation and constricting, and prevents thrombogenesis and inflammation (Rajendran et al.,2013). When blood sugars rise, the normal homeostasis and function of the endothelium is altered, and an inflammatory response releasing free radicals leads to the oxidized LDL. Diabetics often have an increased low-density lipoprotein (LDL) but smaller in size (Dokken, 2008). The smaller LDL are more likely to become oxygenized. In the effort of leukocytes and macrophages to destroy the oxidized LDL, foam cells occur and attach to the vascular wall along with LDL cells that lead to atherosclerosis. The effected endothelium is also responsible for platelet activation which is important in clot formation. This alteration in the endothelium may lead to platelet aggregation increasing the risk of blood clots forming (Dokken, 2008: Rajendran et al., 2013).

The prevalence of depression has been reported as two-fold in diabetics compared to non-diabetics (Anderson, Freedland, Clouse, & Lustman, 2001; Badescu et al., 2016). Furthermore, diabetics with depression have a much higher rate of atherosclerosis and have been reported to have a 50% increased mortality rate, and 40% increased rate of CVD over those without depression (van Dooren et al., 2013). These alarming findings support the concern for those with the combined effect of having diabetes and depressive symptoms being at a greater risk for developing CVD.

The connection between diabetes, hyperglycemia, and atherosclerosis is an obvious risk for CVD. Maintaining glucose control through diet, exercise, and taking medications as prescribed is imperative for a diabetic to limit these devastating effects. Poor medication compliance in diabetes has been shown to increase mortality by 45% and risk of a cardiac event by 41% (Kim et al., 2018).

Smoking as a Risk for CVD

Smoking is a modifiable independent risk factor for CVD. According to the Surgeon General's Report, smoking is a major cause of CVD and is responsible for one in every five deaths (Benjamin et al., 2018). Those who smoke as few as five cigarettes a day and nonsmokers, with exposure to secondhand smoke, experience an increased risk for CVD compared to nonsmokers (Benjamin et al., 2018). Smoking has a profound physiological effect and is estimated to shorten one's life by 10 years (Jha et al., 2013; McBride, 1992).

A brief explanation of the pathology of a cigarette will shed light on the effects of smoking and the development of CVD. Upon inhaling a cigarette, the nicotine, numerous chemicals and free radicals are not freely accepted, and an acute immune response is activated. The resulting response results in the release of hormones including adrenaline and noradrenaline (Powell, 1998). These hormones promote vasoconstriction, as well as an increase in heart rate and blood pressure (Gordan, Gwathmey & Xie, 2015; McBride, 1992). Simultaneously the immune response leads to

build up of oxidized LDL and foam cells attaching to the endothelium wall (Al-Delaimy et al., 2002; Messner & Bernhard, 2014; Morris et al., 2015). This inflammatory response within the endothelium was also described as a response high glucose levels in diabetics. The elevated heart rate and blood pressure increases oxygen demand. However, the oxygen carrying erythrocytes have absorbed carbon monoxide (CO) inhaled from the cigarette (Powell, 1998). The CO binds with the oxygen, resulting in the erythrocytes carrying carboxyhemoglobin and unable to transport the needed oxygen (Powell, 1998). To compensate for the need of oxygen, the body releases additional erythrocytes to transport the oxygen. The excess of erythrocytes referred to as erythrocytosis increases the viscosity of the blood which may slow movement through veins and arteries and may impede capillary flow completely (Sopori, 2002). Additionally, the immune system also initiates platelet aggregation increasing the risk of clot formation (Sopori, 2002).

A meta-analysis combining 25 separate cohort studies of the CHANCES consortium evaluated risk for CVD mortality and events in relation to smoking (Mons et al., 2015). Cox proportional hazard regression indicated that the risk was elevated for current smokers HR 2.07, 95% CI [1.82, 2.36] and former smokers HR 1.37, 95% CI [1.25,1.49]. Similarly, risk for cardiac events for current smokers HR 1.98, 95% CI [1.75, 2.25] and for former smokers HR 1.18, 95% CI [1.06, 1.32] were elevated (Mons et al., 2015).

Smokers were reported to lose 10 years off their lifespan however, if they quit smoking prior to the age of 34 years, recalculated survival analysis indicated life expectancy nearly identical to a non-smoker, gaining back 9 years of life. If one does not stop smoking until after the age of 34 years, they will still regain 4-6 years of life (Jha et al., 2013). Thus, it is never too late to quit smoking. Smoking cessation has significant benefits including a reported 36% reduction in CVD mortality seen over a 2-year period for those who quit smoking after having an MI (Rigotti & Clair, 2013). Actual benefits of quitting will be affected by how much one smoked on average per day and for how many years. After quitting smoking, risk for CVD drops drastically for the first 4 years, and then slows beyond that. (Bullen, 2014; Dresler et al., 2006).

In summary smoking has a profound effect on endothelial function. The constricted vasculature is lined with epithelium that has now has waste products attached to its walls, impeding blood flow, and a dysfunctional ability to cause vasoconstriction or dilatation (McBride, 1992). The blood is now thicker and sticky with an excess of platelets and erythrocytes and reduced oxygen (Powell, 1998). One can visualize how 20-40 cigarettes a day can significantly add to atherosclerosis, blood clots or complete occlusions, and as a causal basis for ischemic heart disease.

Hypertension as a Risk for CVD

Hypertension is quantitatively the most important traditional risk factor for premature CVD; it is more common than cigarette smoking, dyslipidemia, and diabetes

and accounts for an estimated 47% of all ischemic heart disease events globally (Wong et al., 2012). Among a large sample of subjects with a diagnosis of hypertension and either high Framingham Risk Score (FRS) (>20%), 23% or with prior CVD 32% ; almost two-thirds of hypertensive males 61% were found to be in the high-risk CVD groups compared to 49% of the females ($p < 0.001$) (Wong et al., 2012). This study also reported that Hispanics with a diagnosis of hypertension were less likely to be at higher risk than other ethnicities ($p < 0.05$) (Wong et al., 2012).

Racial differences in blood pressure have long been reported with Blacks having a higher prevalence and incidence of hypertension, as documented by AHA statistics obtained from 2009-2012. Indeed, an alarming 44.9% of adult Black men and 46.1% Black women have been diagnosed with hypertension compared to an overall rate of 32.6% for the entire US adult population (Mozaffarian et al., 2016). In contrast, The Systolic Blood Pressure Intervention Trial (SPRINT) looked at treatment modalities for hypertension as well as racial differences. Systolic BPs in this study were not significantly different among the different racial groups of Non-Hispanic White, Non-Hispanic Black and Hispanics (Still et al., 2018). This result varies from that reported by AHA that Non-Hispanic Black have more hypertension and death rates more than 30% higher than the general population (Still et al., 2018). In a study of high-risk veterans that included 23,955 men and 1,010 women and assessment of three risk factors that predispose to CVD (diabetes, hypertension, and hyperlipidemia), average BP was reported higher among Blacks comparative to whites. Black female veterans after age

adjustment had estimated mean systolic BPs of 136.3 mmHg as compared to 133.5 mmHg among white female veterans ($p < .01$). Mean diastolic BPs for black females were 82.4 mmHg versus 78.9 mmHg for white females ($p < 0.01$) (Goldstein et al. 2014). Large variations between studies was noted. It is necessary to continue monitoring for age, gender and racial differences. When evaluating population-wide blood pressure variation, it is important to include treatment modalities. In addition, future studies using age-adjusted models, models assessing relative risks compared to others of same age, and models including thorough assessments of target organ damage and ambulatory 24-hour blood pressure are needed to tighten the knowledge gap in elucidating differences among different ages, races, and gender.

Obesity as a Risk for CVD

As the prevalence of obesity continues to rise in the United States, the rate of CVD and associated complications will also increase. The obesity epidemic has the potential to reduce further gains in the US life expectancy, largely through an adverse effect on CVD mortality (Benjamin et al., 2018). The CVD risks associated with obesity are often assessed using the body mass index and central or abdominal obesity.

Body Mass Index as a Risk for CVD

Body Mass Index (BMI) is a measure of not only height and weight but also overall body mass. BMI is a preferred measure when looking at risk factors as it correlates with overall body fat, which is often linked with risk for heart disease (CDC,

2013). The calculation is based on a formula weight/height^2 (kg/m^2). A healthy BMI is (25 kg/m^2), increasing BMI is considered a key component to the metabolic syndrome (Zimmet, Alberti & Shaw, 2005). A number of studies have documented the association between obesity and cardiovascular disease (CVD) risk factors (Freedman, Khan, Serdula, Galuska, & Dietz, 2002; Gregg et al., 2005).

Central Obesity as a Risk for CVD

Central obesity is when body fat is disproportionately distributed in the abdominal area, with some describing it as having a pear shape. Central obesity has been found to be more predictive of mortality than an elevated BMI (Coutinho et al., 2013). For example, men with a normal BMI (this study used $\leq$ 22 kg/m^2 as normal), but with central obesity compared to men with an elevated BMI and no central obesity were at twice the risk for mortality, HR 2.42, 95% CI, [1.30, 4.53]. This study had comparable results among women, with central obesity being the most predictive factor for mortality (Sahakyan et al., 2015).

Lipid Levels and Risk for CVD

Dyslipidemia is a term that refers to elevation of plasma cholesterol, triglycerides (TRIGs), or both, or high LDL cholesterol or a low HDL cholesterol level that contributes to the development of atherosclerosis. Dyslipidemia is recognized as a prominent risk factor for CVD (Miller, 2009). Current guidelines focus on lowering LDL with a statin in both primary and secondary prevention, and a consensus statement by Pallazola et al.

(2018) reports discordance between established guidelines and global practices. The authors who reviewed five guidelines reported differences among major guideline committees and recommended addressing beyond risk estimation and aggressive management of moderate- to high-risk patients and the need for a unified guideline (Pallazola et al., 2018). Therefore, understanding the association between the levels of these lipids and CVD risks are important.

Triglycerides (TRIG) as Risk for CVD

Despite three decades of research, the controversy regarding the relationship between triglycerides and risk of CVD persists. Although, earlier cohort studies reported a univariate association between TRIG and CVD, this association was no longer statistically significant after adjustment for either total cholesterol (TC) or LDL cholesterol (Di Angelantonio et al., 2009). Cardiovascular risk was evaluated in a large cohort study of American Indians (N= 3216) over 17 years. This study reported that elevated TRIG in combination with low HDL increased the risk for developing CVD by 1.32-fold 95% CI [1.06. 1.64], and having diabetes increased this risk by 1.54% (Lee et al., 2017). After adjusting for covariates, a different study compared those with TRIG levels less than 100 mg/dL to those with greater than 500 mg/dL, with those with greater than 500 mg/dL being at greater than 60% higher risk of death over 22-years (Klempfer et al., 2016).

The Framingham Heart Study found that both genders were at a significantly greater risk for developing CVD if there LDL cholesterol level was greater than 160 mg/dL compared to those with an LDL less than 130 mg/dL, HR 1.74, 95% CI [1.36,2.24] for men and HR 1.68, 95% CI [1.17, 2.40] for women (Wilson et al., 1998). Similarly, in the Atherosclerosis Risk in Communities (ARIC) study, with a study population of over 12,000 middle aged men and women, the risk of coronary heart disease was significantly related to LDL levels. In fully adjusted models including age race smoking systolic blood pressure and diabetes the HR for elevated LDL for women was significant for men (HR 1.43) and women (HR 1.24) without any previous history of CVD (Sharrett et al., 2001). Thus, elevated LDL is an indication for aggressive treatment for primary prevention of CVD.

High Density Lipoprotein (HDL) as Risk for CVD

Desired levels of HDL cholesterol in men are >40 mg/dL and in women are >50 mg/dL (CDC, 2017). HDL, often referred to as the good cholesterol, is considered an independent risk (protective) factor for CVD (Toth, 2004). It is responsible for transporting excess fat and cholesterol and has anti-inflammatory properties reducing endothelial cell changes and decreases platelet aggregation. Low levels of high-density lipoprotein cholesterol (HDL; <40 mg/dL) are associated with increased risk of cardiovascular events (Toth, 2004). The cardioprotective functions of HDL include antioxidative, anti-inflammatory, anti-apoptotic, anti-thrombotic, vasodilatory, anti-infectious and antidiabetic activities (Hagstrom et al., 2016). The TRILOGY Acute

Coronary Syndrome trial evaluated HDL level as a dichotomous variable-very low (<30 mg/dL) vs, higher (≥30 mg/dL) and reported similar rate for a composite endpoint with essentially no risk difference between groups HR 1.13, 95% CI [0.95, 1.34] for MI and stroke. However, risks for cardiovascular death HR 1.42, 95% CI [1.13, 1.78] and all-cause death HR 1.36, 95% CI [1.11, 1.67] were higher in patients with very low baseline HDL (Hagstrom et al., 2016).

Low-Density Lipoprotein (LDL) as Risk for CVD

Elevated LDL is an indication for primary prevention of CVD. The rationale for activities focused on LDL reduction is based upon epidemiologic data documenting a continuous, positive, graded relationship between LDL concentration and CVD events and mortality (Leef, Bluementhel, & Martin, 2018; Wallis et al. 2000). Earlier evidence from The Framingham Heart Study demonstrated that men and women were >1.5 times more likely to develop clinically significant coronary artery disease if their LDL was >160 mg/dL compared to a reference population with LDL <130 mg/dL (Wilson et al., 1998). Similarly, in the Atherosclerosis Risk in Communities (ARIC) study, the risk of an incident coronary heart disease event was elevated by approximately 40% for every 39 mg/dL incremental increase in LDL (Sharrett et al., 2001).

Non-Traditional Risks For CVD

Depressive symptoms as a Risk for CVD

Major depression and depressive symptoms are commonly underdiagnosed and undertreated in patients with CVD (Celano & Huffman, 2011). Studies have found depression and its associated symptoms to be major risk factors for both the development of CVD and increased mortality post myocardial infarction (Silverman, Herzog, & Silverman, 2018). Furthermore when cardiac disease and major depression present together, the prognosis is worse (Celano & Huffman, 2011; Mehta et al., 2016)

The Enhancing Recovery in Coronary Heart Disease (ENRICHD) trial among patients who had recently suffered a myocardial infarction (MI), reported a diagnosis of depressive symptoms in 74% of the cohort (Carney et al., 2004). Depressive symptoms were associated with an included increased risk of CVD mortality HR of 1.57, 95% CI [1.06, 2.33], p=0.03 in a cross-sectional survey of 1,569 subjects (Ivanovs et al., 2018). Likewise, depressive symptoms evaluated among 1,928 persons with known coronary artery disease had an alarming effect. Depressive symptoms were measured by the Depression Scale (DEPS), a 10 item self-rating depression scale. Those in the highest quartile of depression at baseline were 4 times at risk for cardiac related death compared to those in the lowest group, HR 4.0, 95% CI [1.5, 10.5], p< 0.0001. The third highest quartile was also significantly elevated compared to the lowest HR 2.3, 95% CI [1.3, 4.1], p <0.05. This study concluded that depression had a significant effect on

cardiac related deaths, but not deaths unrelated to cardiac disease (Lahtind et al., 2018).

Findings from the Maine-Syracuse Study, (N=970) persons were measured for depressive symptoms using both the CES-D and the Zung self-rating depression scale (Crichton, Elias, & Robbins, 2016). Significant findings included an association between risk for metabolic syndrome and CES-D, OR 1.79; p=1.79 and the Zung depression score OR 1.71; p<0.01. Alarming was the use of antidepressants which seemed to increase the risk of Met S compared to persons not taking antidepressants OR 2.22; p<0.001 (Crichton et al., 2016). On the other hand, a smaller study conducted in Singapore included adults aged 21-50 years with major depression presently on antidepressant medications compared to non-depressed controls and non-medicated persons with depression (Ho et al., 2018). Persons taking antidepressants had significantly higher elevated blood pressure, elevated IL-6 and lower HDL, when compared to the non-depressed control group. Researchers suggested screening for depression severity be added to the Framingham equation so not to miss major risks for developing CVD (Ho et al., 2018). This study did not identify a benefit to medications nor identify the medications used to treat depression. They reported an interaction between TRIG and severity of depression.

Although evidence has strongly indicated that depression and/or depressive symptoms may significantly affect the risk of CVD, the effect may differ within different populations. Rates of depression are nearly twice as high in women compared to men

(Vaccarino & Bremner, 2016; WHO, 2017, CDC, 2012). Women diagnosed with depression have a higher incidence of cardiovascular disease (Lichtman et al., 2008; Mehta et al., 2016), and poorer outcomes post cardiac event, including higher rates of death over those without depressive symptoms (Celano & Huffman, 2011; Mehta et al., 2016; Rutledge et al., 2006). A large study, (*N*=13,000) examined participants over a 2-year span for effects of depression, measured with Beck's Depression Inventory, and the risk for CVD. Those with depression were at 2 times higher risk for CVD; Men (*n*=6392), OR 2.14, CI 1.78, 2.56]; and women, (*n*=7153), OR 2.03, 95% CI [1.70, 2.43] (Piwonski, Piwonska, & Sygnowska, 2014).

Depression may affect different age groups differently. A Swedish study included people aged 25 to 64 with the diagnosis of depression, and those 25 to 79 hospitalized with nonfatal CVD (*n* = 1,767). The results indicated a strong association between depression and CVD, and those diagnosed with depression under the age of 40 were at twice the risk for CVD compared to the older ages RR 2.17, 95% [CI 1.5, 3.03]. Those over the age of 70 years at the onset of depressive symptoms experienced no significant risk for CVD (Sundquist, Li, Johansson, & Sundquist, 2005).

Collectively, the evidence indicates that depression and/or depressive symptoms are a strong risk factors for CVD across various populations. Depression can lead to unhealthy eating habits, poor sleep quality, a decrease in physical activity, and elevated inflammation, all of which may lead to atherosclerosis (Stapelberg, Neumann, Shum, McConnell, & Hamilton-Craig, 2011).

Inflammation and Inflammatory Markers as Risk for CVD

Aging is associated with dysregulated immune and inflammatory responses. Inflammation has been suggested to be one of the mechanisms underlying the pathogenesis of several age-associated diseases disease including CVD (Libby, 2006) and obesity and diabetes (Shoelson, Herrero, & Naaz, 2007).

Age related effects of inflammation include overall low-grade inflammation due to cumulative tendencies. The stress that an individual has experienced throughout life builds up and scars generating more inflammation. It is thought that healthy persons may experience some of these aging changes as early as age 55 years (Lopez-Candales, Hernandez-Bergos, Hernandez-Suarez & Harris, 2017). Chronic inflammation increases the risk for developing atherosclerosis, Alzheimer's disease, and insulin resistance (Barzilai, Huffman, Muzumdar, & Bartke, 2012).

Gender differences were reported in a small pilot study seeking to evaluate gender differences in persons experiencing an acute myocardial infarction (AMI). Results found levels of IL-6 to be elevated significantly in men versus females. Patients were tested after hospitalization on day 3 post diagnosis of a NSTEMI and on day 5 post diagnosis of a STEMI. This study concluded a significant association between inflammatory markers IL-6 and CRP in men more so than women with a MI (Siennicka et al., 2018). The English Longitudinal Study of Ageing Study sought to evaluate the combined effect of both inflammation and depression. In men, the effect was highly

significant HR 3.89, 95% CI [2.04, 7.44]; *p*= 0.001 while in women a significant risk was not reported. Men with elevated inflammation and normal levels of symptoms of depression had elevated risk HR 2.43, 95% CI [1.59, 3.71]; *p*<0.001, whereas women were not at significantly higher risk HR 0.92, 96% CI [0.59, 1.44]; *p*=0.715 (Lawes, Demakakos, Steptoe, Lewis, & Carvalho, 2018).

The inflammatory processes described within effects of diabetes and smoking illustrate some of the physiological changes that occur when exposed to an inflammatory process. Normal inflammatory marker levels can be valuable in ruling out disease conditions. Conversely, an elevated inflammatory marker may indicate a higher probability of a condition being present or identifies the risk of being exposed to a specific disease condition. Various measures of inflammatory markers have been associated with higher risk of CVD (i.e. High sensitive C-reactive protein (hsCRP) and IL-6) being the most commonly reported (Chuang, Chih-Hung & Fang, 2014).

Inflammatory markers such as IL-6 and CRP have both been predictive of cardiac events. A prospective study over a six-year span followed over 900 male physician participants with no history of CVD. At the end of the study, 202 participants had experienced a myocardial infarction. Participants with IL-6 levels in the highest quartile had a 38% higher risk compared to those in the lower range, with a relative index of 2.3 times that of those in the lower quartile (Ridker, Rifaai, Stampfer & Hennekens, 2000). Similar findings were seen in a Japanese study (*N* =121) in which fifty percent of the participants experienced a new cardiac event within a three-year

span. In this study, baseline IL-6 was found to be an independent predictor of MACE with those in the highest quartile of IL-6 compared to those in the lowest quartile HR 3.33, 95% CI [1.63, 6.81] (Nishida et al., 2011). In this study after controlling for other variables, IL-6 was the better predictor of CVD, as hsCRP was not predictive (Nishida et al., 2011). Likewise, hsCRP and IL-6 were associated with CVD mortality and all-cause mortality, HR 2.15 and HR 2.11 respectively in the STABILITY study. However, after adjustments Il-6 remained the stronger predictor and hsCRP was no longer significant (Held et al., 2017).

IL-6 has also been shown to be an independent predictor of CVD mortality after MI. Specifically, when IL-6 was measured 6 hours after first symptoms of an MI and patients were followed for 3 years to monitor mortality, those who had the highest reading of IL-6 had the highest mortality and cardiac events, as indicated by Kaplan–Meier plots (X^2 14.13, p=0.0002) (Fan et al., 2011). This study recommended the possibility of treating with inflammation with medications such as tocilizumab to reduce the levels of IL-6 and to prevent atherosclerosis (Fan et al., 2011).

Evidence in recent years has demonstrated an association between elevated inflammatory markers and increased risk for CVD and mortality (Held et al., 2017; Nishida et al., 2011). Although the etiology of the inflammation may vary greatly, early detection and identification may allow for treatment or interventions to reduce the inflammation and thus potentially reduce risk of CVD.

Strong relationships seem prevalent among depression, CVD, and inflammation. Studies are mixed whether the relationships may be bidirectional. What comes first inflammation or depression, CVD, or depression? A meta-analysis by Howren, Lamkin and Suls (2009) suggested a positive association between depression and inflammation among patients with cardiac disease. Elevated inflammatory markers have been shown to be predictors of heart disease and have been linked to both CVD and depression (Danesh, et al., 2004; Dixon et al. 2008; Empana et al., 2005; Manev et al., 2008; Taylor, Aizenstein & Alexopoulos, 2013). A direct causal path from depression and CVD has been suggested after adjusting for inflammatory markers (Empana et al., 2005). A Malaysian study conducted among more than 400 persons noted bidirectional effects between depression and CVD. Depressive symptoms increased inflammatory markers leading to CVD, and an increased rate of CVD led to increased depression (Tajfard et al., 2014).

The joint effect of depression and/or depressive symptoms, inflammation and CVD have been reported in a number of studies. Men with both elevated C-Reactive Protein (CRP) with the presence of depressive symptoms had an increased risk of CVD related death HR 3.89, 95% CI [2.04, 7.44] (Lawes et al., 2018), whereas those with normal CRP and depressive symptoms had no significant increased risk for CVD (HR 1.50, 95% CI [0.63, 3.6]; p= 3.61 (Lawes et al., 2018). An Iranian study conducted on more than 462 persons also noted significant associations between depressive symptoms and inflammatory markers IL-6, IL-8 (p <0.05) and depressive symptoms.

These researchers concluded an interaction between depressive symptoms and CVD that was probably mediated by the inflammatory processes (Tajfard et al., 2014).

Sleep Quality/ Insomnia as Risk for CVD

Previous research suggests that poor sleep quality, sleep disorders, and insomnia increase the risk for CVD (Covassin & Singh, 2016). Key search words included sleep, insomnia, sleep disorders, hypertension, diabetes, obesity, heart disease, cholesterol, age, race, and gender Sleep is a potentially modifiable risk factor in the fight against CVD. Sleep quality has been associated with increased risk of many health conditions including CVD (Covassin & Singh, 2016). Although, sleep quality may vary among individuals, the duration of sleep, time taken to fall asleep, one's ability to stay asleep and daytime sleepiness or inability to stay awake have been significantly associated with the risk for CVD (Hoevenaar-Blom, Spijkerman, Kromhout, van den Berg, & Verschuren, 2011). Therefore, a review of current studies on sleep and CVD risk was conducted to shed light on the connection.

Changes in sleep patterns are common complaints in older people. Age related differences include sleep that is less consolidated, with increased interruptions. Change in sleep cycles including the Rapid eye movement (REM) cycle occurs earlier in sleep cycles compared to younger persons. There is evidence supporting that for every decade of an age they lose about 10-minutes of sleep. (Edwards, O'Driscoll, Ali, Jordan, Trinder & Malhotra, 2010). Aging is characterized by changes in both sleep and

circadian rhythms. Many older adults find their circadian rhythm has been moved forward. Changes in body temperature and hormonal secretions regulated by the circadian rhythm such as melatonin and morning rise of cortisol seems to come at an earlier time. Older persons tend to rise earlier than their younger counterparts (Dijk et al., 2000). Although occasional sleep complaints may not be associated with age, older adults experience chronic sleep difficulties more often than by younger adults. A similar poll of 1500 older Americans (aged 55+) found that 67% reported trouble sleeping and that only one in eight had discussed these problems with their physicians (Lamberg, 2003). It would be fair to say that older persons are at a greater risk for health-related problems for which may affect sleep (Edwards et al., 2010)

Sleep complaints may also vary within different races. Results from the Multi-Ethnic Study of Atherosclerosis (MESA) have Black men sleeping the shortest duration, and White women the longest. Black men complain of daytime sleepiness the most. None of the differences however were significant (Chen et al., 2015)

Cardiovascular disease may be affected by sleep quality in a number of ways. A study with over 20,000 participants found those with shortened sleep of less than six hours had a slightly higher risk of developing coronary vascular disease after controlling for relevant lifestyle factors such as smoking, exercise, and alcohol consumption HR 1.23, 95% CI [1.04, 1.45]. Also, this study reported that the risk for CVD decreased with longer sleep, eight hours HR 0.87, 95% CI [0.74, 1.02] and for those with more than nine hours of sleep HR 0.77, 95% CI [0.58,1.02] (Hoevenaar-Blom, Spijkerman, Kromhout, van den Berg, & Verschuren, 2011). Sleep quality measured with a single

question (Do you usually rise feeling rested?) combined with short duration of sleep demonstrated a significant increase in CVD risk for CVD HR 1.79, 95% CI [1.24, 2.58]; p<.05 (Hoevenaar-Blom et al., 2011).

The above evidence was supported in The Women's Health Initiative Observational Study Participants (N=86,329) of female participants, aged 50 to 79. This study results found those with elevated insomnia scores had and elevated risk for CVD (38%). Upon evaluating duration those with less than five hours and more than ten hours of sleep to have an increased risk for CVD with age and race adjusted models however in fully adjusted models, no statistical significance for less than 5 hours of sleep was appreciated (Sands-Lincoln et al., 2013). However, upon testing for interaction, those with both insomnia symptoms and longer sleep duration, slept greater than 10 hours had nearly double the risk for CVD, HR 1.93, 95% CI [1.06, 3.51]; $p<0.1$ (Sands-Lincoln et al., 2012). These results support the thought that quality of sleep influences the risk for CVD, increasingly so when duration and insomnia symptoms of bother, are both present.

Sleep quality can be affected by depression and or depressive symptoms. Persons with poor sleep quality were nearly 10 times more likely to have depression compared to those without symptoms in a community-based sample of 772 participants (Taylor, Lichstein, Durrence, Reidel & Bush, 2005). Sleep quality, measured by Pittsburgh Sleep Quality Index (PSQI), and depression and anxiety, measured by the Hospital Anxiety and Depression Scale (HADS) were measured on patients hospitalized

with a variety of cardiovascular related diseased (N=1071). Among patients hospitalized with a cardiac event, 43% percent of patients reported poor sleep quality. Sleep quality after adjustments for covariates was a significant risk factor for depression in this group HR 1.09, 95% CI [1.03, 1.15]; p=0.002 (Matsuda et al, 2017). Additionally, a test for interaction by gender, sleep and depression revealed differences among gender, women with poor sleep quality where at a much higher risk for depression compared to men; women OR 1.34, 95% CI [1.22, 1.48]; p<0.001, Men OR 1.17, 95% CI [1.12, 1.23]; p=0.017 interaction (p=0.008) (Matsuda et al., 2017).

There have been significant associations reported between increased inflammatory markers and sleep quality. Those with interrupted sleep or sleep of extremely short or long duration have been associated with increased levels of CRP and IL-6 (Mullington, Simpson Meier-Ewert & Haak, 2010). Shift workers, those with circadian rhythm disorders, and those with reported shortened sleep or poor sleep quality, have also been identified as having elevated markers (Kudielka, Buchtal, Uhde & Wust, 2007; Patel et al., 2009). Furthermore, insomnia appears to be associated with hypercortisolemia and a daytime shift of IL-6 and TNFα secretory patterns, conditions that may lead to multiple health problems including visceral obesity, insulin resistance, hypertension, and osteoporosis that, in turn, may affect longevity (Vgontzas et al., 2003). Smoking has been associated with sleep quality. Common reported difficulties in smokers include, sleep latency, duration with frequent awakening daytime sleepiness (Wetter & Young, 1994).

Summary

Current evidence suggests the modifiable risk factors depression and or depressive symptoms, inflammation, and quality of sleep, play a role in the development of CVD. Studies collectively have found depression and or depressive symptoms to increase one's risk for CVD by approximately 1.5 times or more. The exact link as to how depression would increase a person's risk is not fully known and may be the effect of many components. Depression and or depressive symptoms effects an individuals' diet, activity, sleep patterns and may also result in an inflammatory response. The link from inflammation and CVD is strong and may be related to the direct impact on atherosclerosis, increased blood pressure as well as link to diabetes. However, the direct causes of increased inflammation are multiplicative. Among the inflammatory markers frequently used in predicting CVD, IL-6, CPR and hsCRP were reported to be most predictive of CVD. Though evidence supports an association between sleep and CVD risk, Sleep quality is not a consistent predictor of CVD. Furthermore, the etiology of sleep difficulties is not always clear.

Despite evidence supporting the influence of depression, inflammation and sleep on CVD, uncertainties remain. Therefore, supporting, this secondary analysis of the data from The Heart Strategies Concentrating on Risk Evaluation study to evaluate the predictive effect of depressive symptoms, inflammation, and sleep quality on the risk for developing a major adverse cardiac event.

CHAPTER THREE:

METHODS

Chapter III presents the study design, rationale, sample and setting, and measures utilized from the Heart Strategies Concentrating on Risk Stratification study (Heart SCORE). This chapter also provides the aims and rationale of this secondary analysis. The analytic plan includes the specific variables that were considered, and methods used for statistical analyses of the data.

Study Design

This study is a secondary analysis of the data obtained from the Heart Strategies Concentrating on Risk Evaluation (Heart SCORE), a longitudinal prospective cohort study conducted over a 14-year period. The ongoing Heart SCORE study has been prospectively examining cardiovascular disease (CVD) risk factors and CVD events on an initial cohort of 2,000 enrolled adults ages 45 to 75 at study entry. The data collection was started in 2003 is still active with data obtained up to November 2017 for this analysis (Bambs et al.,2011**).** The current study explores the predictive relationship between the modifiable risk factors, depressive symptoms, inflammation, and quality of sleep, on the risk of developing cardiovascular disease.

Sample and Setting

As referenced above, the Heart SCORE study includes 2000 adults ranging from the ages of 45 to 75 years, who were living within the greater Pittsburgh, Pennsylvania area at the time of enrollment. The original aims of the study were to improve risk stratification and identify racial disparities within a population (Bambs et al., 2011). To meet the aims of the study, a priority was placed on oversampling of minorities to include approximately equal representation of White and Black subjects to permit stratified analyses by race in relation to risk of CVD. The specific target recruitment goals included 2,000 participants, 50% Black, 1,000 participants with low CVD risk, as measured by the Framingham risk score, 1,000 with intermediate or elevated risk, and 200 with established CVD. Recruitment strategies included mailings, referrals, and advertisements. To meet approximate proportional representation from Black communities, local organizations and church groups were targeted (Bambs et al., 2011).

Rationale for the Primary Study

The Heart SCORE study was designed with the aim of improving risk stratification, including identification of mechanisms associated with racial disparities for population differences in CVD (Bambs et al, 2011). To achieve this goal, after a baseline evaluation, subjects underwent annual visits which included measurements of traditional and emerging CVD risk factors, tabulation of adverse events and assessments of subclinical atherosclerosis.

Rationale for Secondary Analysis

This secondary data analysis sought to make use of this large longitudinal study to investigate the extent to which depressive symptoms, inflammation, and sleep quality are independently associated with risk of experiencing a major adverse cardiac event. To meaningfully lower the incidence of CVD and decrease mortality and disability, it is imperative to identify potentially modifiable risk factors. Depressive symptoms, inflammation, and sleep quality have been mentioned in numerous studies as having potential predictive value for risk of development of CVD. These suggested relationships provided the rationale for examination of the Heart SCORE data, a large community-based cohort study with long-term follow-up.

Protection of Human Subjects

The University of Pittsburgh Institutional Review Board (IRB) approved the Heart SCORE study to ensure that the privacy and rights of the participants were protected. Participants in the Heart SCORE study were informed of any risks including the time commitment for the longitudinal data collection. Written informed consent was obtained from all participants. All data obtained was de-identified before transfer for analysis. Approval from the Institutional Review Board at the University of South Florida was obtained (Appendix A).

Exclusion Criteria of the Heart SCORE Study

The Heart SCORE study excluded persons with major comorbidities, those in poor health, or those with life expectancies less than five years. Additionally, participants had to agree to participate in annual follow up exams. Those with previous major cardiac events could be enrolled into the study.

Exclusion Criteria for Secondary Analysis

This secondary analysis excluded study subjects with a history of major adverse cardiac event (MACE) prior to the baseline data collection. This included myocardial infarction, cerebrovascular accident, or coronary revascularization. Additionally, persons with missing outcome data were excluded. The original study collected data on 2,000 persons, of which, 105 were eliminated under the exclusion criteria for this secondary analysis, resulting in a final N=1895.

Outcome Variables of the Current Secondary Analysis

The present analysis defined CVD and cardiovascular events as Major Adverse Cardiovascular Events (MACE) using two closely related definitions.

Major Adverse Cardiac Event (MACE1) was defined as a diagnosis of at least one of the following; cerebral vascular accident, acute ischemic syndrome, myocardial infarction, coronary revascularization procedure, or experiencing cardiac death during the duration of the study.

Major Adverse Cardiac Event (MACE6) was defined as diagnosis of one of the following; cerebral vascular accident, acute ischemic syndrome, myocardial infarction, or death from any cause during the duration of the study.

Predictor Variables of the Current Secondary Analysis

Depressive Symptoms/ CES-D Scale

The Heart SCORE study recognized the contribution of psychosocial health to the physiological development of CVD. In this regard, the Center for Epidemiologic Studies-Depression Scale (CES-D) was used as a measure of depressive symptoms. The CES-D is a highly reliable tool with good reported internal consistency (alpha coefficient of >0.85) designed to identify depressive symptoms rather than to diagnose depression (Fischer, 2009; Smarr & Keefer, 2011). The items are scored on a scale of 0-3, with 0 indicating no symptoms and a 3 representing a greater severity of symptoms. Traditionally, a score of 16 or higher is consistent with a diagnosis of depression (Radloff, 1977). The total CES-D score can range from 0-60. Within Heart SCORE, total scores ranged from 0-51, with a mean of 7, and 10 was at the 75th percentile. Only 12% of the respondents had a value of 16 or greater at baseline. For the present analysis, the data was divided into tertiles consisting of 3 groups of equal participants, based on ranked values of the CES-D score and were coded as follows: Group 0 (CES-D, 0-4); Group 1 (CES-D > 4-9); Group 2 (CES-D > 9).

Inflammation/IL-6

The inflammatory response has been associated with multiple aspects of CVD, most importantly atherosclerosis. The Heart SCORE study included several measures of inflammatory biomarkers. Biomarkers that are frequently studied and associated with CVD include both C-reactive protein (CRP) and interleukin-6 (IL-6). These markers are associated with an acute phase stress reaction and systemic inflammation and have shown consistent independent relationships with CVD (Langenberg, Bergstrom, Scheidt-Nave, Pfeilschifter, & Barrett-Conner, 2006; Pearson et al., 2003).

In Heart SCORE, both, CRP and IL-6 were measured fasting with a venous blood draw using standard laboratory technique at the University of Pittsburg Medical Center clinical laboratory, at baseline. IL-6, with CRP measured as milligrams per deciliter (mg/dL) and IL-6 measured as picograms per milliliter (pg/ml) (Bambs et al., 2011). Due to high correlation of these measures, IL-6 was selected as the primary measure of inflammation. Results of IL-6 were highly skewed to the right, ranging from (0.038 to 48.27 pg/ml). Therefore, a natural log transformation was also considered. The median IL-6 value was 1.708 with 95% of participants having a value less than 5.7 pg/ml. A plot of frequency of MACE6 by half unit of IL-6 seemed to show a continual increase of events from 0 until about 2 pg/ml (the 60^{th} -70^{th} percentiles), and then a leveling off until passing the 95^{th} percentile.

Hence, for ease of interpretation, the data was divided into tertiles, containing equal number of participants based on ranked values of IL-6. Tertile cut-points were

(1.245 pg/ml and 2.28 pg/ml). Initial models indicated the risk of MACE (either 1 or 6) was similar for the second and third tertiles of IL-6. Therefore, the later tertiles were combined. Thus, IL-6 was treated as a dichotomous variable with the cut point at the 33.3rd percentile (1.245 pg/ml).

Sleep Quality / Insomnia Scale

Sleep quality was measured by The Insomnia Symptom Questionnaire (ISQ). This included assessment of symptoms of insomnia experienced over the last month as an overall measure of sleep quality. This 13-question self-report survey is widely used to assess for sleep disorders and reportedly has a high Cronbach-α coefficient of 0.89 indicating good internal consistency (Okun et el., 2009). The proposed algorithm for scoring the scale and identifying someone as having insomnia is as follows. (1) The participant indicates trouble falling asleep, trouble waking during the night or sleep that is unrefreshing (items 1, 2 or 5) frequently or always; (2) The participant has the problem(s) indicated in (1) for 4 weeks or longer and (3) the participant indicates that s/he has one or more daytime sequelae (items 6-13), “quite a bit,” or “always” (Okun et al., 2009).

Within Heart SCORE, this tool was administered as a self-report and many participants who indicated symptoms of insomnia did not answer the questions about duration. Consequently, three new categories for sleep quality were defined: (1) Participants who did not indicate difficulty falling asleep, difficulty staying asleep, or sleep that is unrefreshing as frequently or always: (items 1, 2 or 5); (2) Participants who

did indicate trouble falling asleep, trouble waking during the night, or sleep that is unrefreshing as frequently or always, (items 1, 2 or 5) but did not select "quite a bit" or "always" for any daytime sequelae; and (3) Participants who indicated trouble falling asleep, trouble waking during the night or sleep that is unrefreshing as frequently or always, and reported having one or more daytime sequelae (items 6-13), as "quite a bit," or "always".

Covariates

Demographics

Age, gender, and race were included as covariates in every model. Race included White, Black, and Other. Less than 4% of respondents self-classified themselves as other. Statistical analysis of this population proved difficult and is often marked non-determinant in tables or excluded from statistical analysis.

Smoking

Subjects were asked about smoking history. Self-reported use of cigarettes was categorized as; current, former, and never a smoker. Smoking history was included in all models as a categorical variable with two indicator variables representing current or former smoker. The number of cigarettes smoked per day, number of years smoked, and the number of years since quitting smoking were not available for analysis.

Diabetes Mellitus

During the baseline screening process, subjects were asked to complete self-report questionnaires. The questionnaire included a self-report of having diabetes, yes or no? Are you being treated for diabetes, yes or no? Diabetes was entered all models as a dichotomous variable.

Glucose

Baseline fasting venous glucose level, with standard analytical techniques were entered as a continuous variable (Bambs et al., 2011).

Use of Antihypertensive Medications

Subjects were asked if diagnosed with hypertension, yes or no, and are you currently taking medications for hypertension yes or no? Use of antihypertensive medications was entered as a dichotomous variable.

Systolic Blood Pressure (SBP)

Systolic blood pressure was included as a continuous variable for analysis. Blood pressures were obtained following the AHA gold standard within the Heart SCORE study. Subjects were seated, with legs uncrossed for a minimum of 5 minutes prior to taking the blood pressure. Experienced nurses using a manual sphygmomanometer took the blood pressures. The blood pressures were taken with the appropriated sized cuff and recorded twice, with a resting five minutes between readings. The average of

the two readings was recorded as the sample blood pressure. Equipment was subject to routine calibration and was replaced when reliable performance was not assured (ACC/AHA, 2017, Bambs et al., 2011).

Obesity

The Heart (SCORE) study included measures for BMI, skin fold tests, waist circumference and waist to hip ratio. The present analysis included continuous measures of BMI (kg/m2) and waist circumference in centimeters as covariates.

Cholesterol

High-density lipoprotein (HDL). was included in the initial models.

Triglycerides (TRIG). was included in initial models.

Statin Medications as determined from the question: Are you presently taking a “statin” medication? Yes or No, by a self-report questionnaire,

The laboratory lipid panel was obtained while participants were fasting for no less than six hours and after resting for a period no less than fifteen minutes prior to blood draw. The initial baseline lab studies of high-density lipoprotein (HDL), triglycerides (TRIG), and low-density lipoprotein (LDL) were measured using standard laboratory procedures. Follow up testing was completed using the Vertical Auto Profile test (VAP) method. These 3 lipid measures were included in initial models and entered as continuous measures. In addition, patients were asked if they were presently taking a

lipid lowering medication classified as a “statin’ medication? This was included as a dichotomous measure as a covariate

Statistical Analysis

The statistical analysis was guided by the aims of the study;

Aim 1

To prospectively evaluate the independent relationships between traditional cardiac risk factors, depressive symptoms, inflammation, and sleep quality, on long-term risk of MACE1 and MACE6.

Initially, univariate analysis of traditional risk factors for CVD were examined for association with MACE1 and MACE6 by use of Cox proportional hazards regression. This approach led to the selection of a final set of traditional risk factors to be included in all models. The variables that were screened included BMI, waist circumference, diabetes mellitus, systolic BP and use of hypertensive medications, HDL, TRIG, use of lipid-lowering agents, and glucose. Through stepwise selection, a variable was retained for future models based on the Wald Chi-Squared test, and the association with either MACE1 or MACE6 with selection *p*-values set at 0.2. The Wald Chi-Squared Test is used to test the null hypothesis that the effect from the predictor variable is 0. A significant *p*-value from a Wald Chi-Squared Test rejects the null, indicating a significant effect of the variable on the outcome of interest (Tabachnick, & Fidell, 2007). Retained

variables are subsequently indicated in Table 2, ad race was included in all models irrespective of statistical significance due to presumed biological relevance.

Once the set of traditional risk factors was identified, separate Cox Proportional hazard models were fit adding in (separate models) the three novel risk factors of interest: depressive symptoms, IL-6, and insomnia. The use of Cox proportional hazards regression was chosen because it can accommodate both continuous and categorical predictor variables and is able to provide individual effects known as hazard ratios (HR) for multiple predictors simultaneously. However, with the use of this method, there are a few assumptions that must be considered (Tabachnick, & Fidell, 2007).

1.) Independence between individual subjects.

2.) Multiplicative relationship between hazard and predictors.

3.) The hazard ratio is constant (i.e. proportional) over the time tested.

4.) The hazard ratio represents a 1 unit of change in risk of the outcome of interest holding all other predictors constant.

Aim 2

To prospectively evaluate whether gender modifies the relationships between depressive symptoms, inflammation, and sleep quality on long-term risk of MACE.

To determine whether the effects of IL-6, depressive symptoms and insomnia in predicting MACE1 or MACE6 differed between males and females, three additional models were run: Interaction Models 1-3 included the interaction term(s) between gender with depressive symptoms, gender with IL-6 and gender by insomnia, respectively. P-values from the interaction terms were examined to evaluate potential effect modification. In addition, in stratified analyses, respective hazard ratios for depressive symptoms, IL-6, and insomnia were summarized for males and females, respectively.

CHAPTER FOUR:
DATA ANALYSIS

This chapter provides a descriptive summary of the data obtained from the Heart Score Study and presents the data analysis based on the specific aims of this study.

The most recent follow-up data, including information on major cardiac events, was collected as of November of 2017 and covers a mean of 9.9 years. Table 1. provides summary statistics on the participants and variables of interest in this study. Continuous variables are tested with student *t*-tests and presented as mean and standard deviation, while categorical variables are presented as frequencies and percentages and were analyzed with Chi-Square tests.

Descriptive Statistics

The participants upon entrance into the study included 1,256 females (66%), 639 males (34%), ranging from 45 to 75 years of age with a median age of 60 years. Race, provided by participants as a self-report, was nearly equally represented with Blacks 42% (*n*=799), Whites 55% (*n*=1047), and Other 3% (*n*=49). Participants were followed for the development of a major adverse cardiac event (MACE). Six percent, (*n* =113) of the 1,895 participants experienced a cardiac event as defined by the MACE1 criteria.

Table 1*. Descriptive Statistics of the Sample*						
	MACE1			**MACE6**		
	Yes (n=113)	**No (n=1782)**	***p*-value**	**Yes (n=160)**	**No (n=1735)**	***p*-value**
Age Mean/SD	62.81±7.42	58.63 ± 7.41	<0.001	63.23±- 7.46	58.47± 7.35	<0.001
%Female	55 (48.67)	1201 (67.40)	<0.001	76 (47.50)	1180 (68.01)	<0.001
Race			0.835			0.180
White	64 (56.64)	983 (55.16)		85 (53.13)	962 (55.45)	
Black	47 (41.59)	752 (42.20)		74 (46.25)	725 (41.79)	
Other	2 (1.77)	47 (2.64)		1 (0.63)	48 (2.77)	
BMI kg/m2	30.56±6.33	30.01±6.36	0.380	30.26± 6.51	30.02±6.35	0.656
Waist (CM)	99.78±15.56	95.59±15.12	0.005	99.16±16.23	95.54 ±15.04	0.005
Smoking			0.216			0.001
Current smoker	15 (13.27)	177 (10.02)		29 (18.24)	163 (9.47)	
Former smoker	52 (46.02)	730 (41.31)		67 (42.14)	715 (41.55)	
Never smoker	46 (40.71)	860 (48.67)		63 (39.62)	843 (48.98)	
Diabetes Mellitus	24 (21.43)	157 (8.86)	<0.001	29 (18.24)	152 (8.81)	<0.001
Systolic Blood Pressure (mmHg)	144.2±20.72	135.7±19.35	<0.001	142.8±20.08	135.6±19.37	<0.001
BP meds	59 (52.21)	700 (39.39)	0.007	79 (49.38)	680 (39.31)	0.013
HDL	53.44±13.00	57.99±15.00	0.002	55.18 ±14.86	57.94±14.91	0.027
Triglycerides	126.5 ±58.57	122.9±76.70	0.623	126.2± 80.34	122.8±75.31	0.596
Statin meds	30 (26.55)	336 (18.91)	0.046	36 (22.50)	330 (19.08)	0.294
Glucose	105.4±32.23	98.27±25.32	0.004	104.0 ±24.06	98.22±25.94	0.007
IL-6			<0.001			<0.001
Lowest tertile	17 (17.17)	568 (34.30)		27 (19.15)	558 (34.57)	
Upper two tertiles	82 (82.83)	1088 (65.70)		114 (80.85)	1056 (65.43)	
DEP S /CES-D	7.00± 7.62	6.84±7.98	0.838	7.04±7.23	6.84±8.03	0.744
Dep S			0.791			0.274
Low CES-D	38 (33.63)	641 (36.42)		48 (30.38)	631 (36.79)	
Mid CES-D	35 (30.97)	544 (30.91)		54 (34.18)	525 (30.61)	
High CES_D	40 (35.40)	575 (32.67)		56 (35.44)	559 (32.59)	
Sleep Quality						
Insomnia			0.981			0.688
None/low freq.	64 (64.54)	991 (60.57)		93 (63.70)	962 (60.35)	
Hi freq./low day	22 (21.15)	356 (21.76)		28 (19.18)	350 (21.96)	
Hi freq./hi day	18 (17.13)	289 (17.67)		25 (17.12)	282 (17.69)	

Ŧ insomnia complaints include Trouble falling asleep, trouble with waking during the night and unrefreshing sleep. For those with complaints, day time problems are assessed. *Note*. ***, **, * denotes significant, p=<0.001, p<=0.01, p<=0.05, respectively. B denotes significance is borderline or close to significant, 0.05 =<p<0.1 Depressive symptoms (DEP S)

The rate of MACE1 was 9% for males, 4% for females, and by race, 6% for whites, 6% for blacks, and 4% for other. Nine percent, (*n*=160) of the 1,895 participants developed CVD as defined by MACE6. The rate of MACE was 13% for males, 6% for females, and by race, 8% for whites, 9% for blacks, and 2% for other.

Analysis for AIM 1

Independent relationships between traditional predictor variables and the outcome variables of MACE are seen in Table 2, as determined by stepwise selection (Model 1 for MACE 1 and Model 2 for MACE 6). Thus, each model thereafter was adjusted for established cardiovascular risk factors consisting of gender, race, diabetes, smoking, systolic blood pressure, and HDL cholesterol. Cox proportional hazard models were fit with the purpose of evaluating relationships between the above-

Table 2. ***Stepwise Selection Traditional Risk factors***

	MACE1	Selected	MACE6
Parameter	*p*-value		*p*-value
N=	113	1782	160
Age (years)	<.0001	XXX	<.0001
Gender	0.028	XXX	0.0002
Race	0.737	XXX	0.1286
Diabetes	0.004	XXX	0.0018
Smoking	0.148	XXX	<0.0001
Waist in (cm)	0.292		0.4247
BMI (kg/m2)	0.354		0.8124
HDL mg/dL	0.077	XXX	0.6336
Triglycerides (mg/dL)	0.289		0.4221
Use of Statin med	0.673		0.918
Systolic BP (mm Hg)	0.022	XXX	0.072
Antihypertensive meds	0.750		0.669
Glucose mg/dL	0.876		0.790

mentioned traditional risk factors, and then the novel risk factors of interest which included depressive symptoms, inflammation, and sleep quality. This approach was used for estimating long-term risk of either MACE1 or MACE6. These models are provided to illustrate the *p*-value criteria used for inclusion of covariates, realizing that race was included uniformly due to presumed biological importance. The models provided the basis for subsequent entry of the novel predictors of interest to estimate the independent relationship with risk of MACE.

Effect of Traditional Risk Factors for CVD

Table 3 shows the hazard ratios with 95% confidence intervals, for the traditional risk factors on developing MACE. As age increases by one year, the estimated adjusted higher risk for developing CVD was approximately 7% for MACE1 and 9% for MACE6. Males were at significantly higher risk of MACE with adjusted hazard ratios of 1.80 and 2.20 for MACE1 and MACE 6, respectively (i.e. approximately 2-fold higher risk overall).

Independent Effect of Diabetes and Traditional Risk for CVD

Having diabetes more than doubled the risk for the development of MACE for both MACE1, HR 2.34, 95% CI [1.46, 3.77], and MACE6 HR 2.10, 95% CI [1.37, 3.20] categories (see Table 3). Race was not associated with risk of development of CVD within this population group.

Table 3. ***Effect of Traditional Risk Factors on Risk for CVD***						
	MACE1			**MACE6**		
Parameter	Hazard Ratio	95% HR Confidence Interval	Sig	Hazard Ratio	95% HR Confidence Interval	Sig
Age (years)	1.072	[1.043, 1.102]	<.0001	1.089	[1.064, 1.115]	<.0001
Gender			0.003			<.0001
Female	(Reference)			(Reference)		
Male	1.804	[1.214, 2.681]		2.196	[1.565, 3.082]	
Race						
White	(Reference)			(Reference)		
Black	0.902	[0.601, 1.353]		1.224	[0.873, 1.717]	
Other	0.568	[0.139, 2.328]		0.181	[0.025, 1.309]	
Diabetes	2.344	[1.459, 3.767]	.0004	2.096	[1.372, 3.201]	.0006
Smoking						
Non- Smoked	(Reference)			(Reference)		
Current Smoker	1.813	[0.993, 3.309]	0.05	2.641	[1.645, 4.242]	<.0001
Former Smoker	1.084	[0.722, 1.626]		0.937	[0.658, 1.334]	
High-Density Lipoprotein (mg/dL)	0.987	[0.972, 1.001]	0.07	0.998	[0.985, 1.009]	
Syst Blood Pressure (mm Hg)	1.013	[1.004, 1.023]	0.007	1.009	[1.001, 1.017]	0.03

Independent Effect of Smoking and Traditional Risk Factors for CVD

The effect of being a smoker was highly significant ($p<0.0001$). Those who smoke were 1.8 times more likely to develop MACE1 than non-smokers and 2.6 times greater risk for developing CVD as defined by MACE6 see (Table 3). Persons reporting having been former smokers had risks near that of a nonsmoker with no significant increase in risk.

Independent Effect of High-Density Lipoprotein (HDL) and Traditional Risk for CVD

HDL cholesterol was not associated with future risk of MACE1 or MACE yet was in the direction of higher values being associated with overall lower risk -- see Table 3.

Independent Effect of Systolic Blood Pressure and Traditional Risk Factors on Risk for CVD.

Higher systolic blood pressure was statistically associated with a higher risk of both MACE1 and MACE6 classifications of CVD. The hazard ratio represents a 1 unit of change (Tabachnick, & Fidell, 2007). By extension, a 10-mm Hg increase in systolic blood pressure increased the risk of MACE1 by approximately 13%.

Independent Effect of Depressive Symptoms and Traditional Risk Factors on Risk of CVD

When adding the novel predictor of depressive symptoms (see Table 4) into the model with the traditional risk factors, there was evidence of mild to moderate increase in the risk of CVD. Specifically, the middle and higher tertiles of depressive symptoms suggested an increase in the risk of MACE1 by 21% and 43%, respectively. These did not achieve statistical significance. However, the middle and higher tertiles of depressive symptoms was statistically associated with a higher risk of MACE6 with adjusted hazard ratio estimates of 1.65 and 1.68, respectively.

Table 4*. Traditional Risk Factors Adding Depressive Symptoms (CES-D) on MACE*

	MACE1			MACE6		
Parameter	Hazard Ratio	95% HR Confidence Interval	Sig	Hazard Ratio	95% HR Confidence Interval	Sig
Age (years)	1.075	[1.046, 1.105]	<0.0001	1.095	[1.069, 1.122]	<.0001
Gender						
Female	(Reference)			(Reference)		
Male	1.89	[1.264, 2.817]	0.0019	2.35	[1.665, 3.323]	<.0001
Race						
White	(Reference)			(Reference)		
Black	0.91	[0.607, 1.366]		1.219	[0.866, 1.715]	
Other	0.57	[0.140, 2.343]		0.19	[0.026, 1.367]	
Diabetes	2.33	[1.452, 3.749]	0.0005	2.162	[1.415, 3.303]	0.0004
Smoking						
Non- Smoker	(Reference)			(Reference)		
Current Smoker	1.72	[0.938, 3.148]	0.079	2.554	[1.582, 4.125]	
Former Smoker	1.08	[0.722, 1.624]		0.935	[0.654, 1.335]	
High-Density Lipoprotein (mg/dL)	0.99	[0.973, 1.00]	0.082	0.997	[0.985, 1.009]	
Systolic Blood Pressure (mm Hg)	1.01	[1.003, 1.022]	0.010	1.009	[1.000, 1.017]	0.042
DEP S / (CES-D)						
CES-D, Low (0-4)	(Reference)			(Reference)		
CES-D, Mid (>4-9)	1.21	[0.757, 1.919]	0.430	1.648	[1.107, 2.454]	0.013
CES-D, Higher (>9)	1.43	[0.906, 2.259]	0.124	1.678	[1.116, 2.522]	0.012

Note. ***, **, * denotes significant, p=<0.001, p<=0.01, p<=0.05, respectively. B denotes significance is borderline or close to significant, 0.05 =<p<0.1 Depressive symptoms (DEP S)

Independent Effect of Inflammation and Traditional Risk Factors on Risk for CVD

When adding the novel predictor of IL-6, hazard ratio estimates for the traditional risk factors were only nominally attenuated. Specifically, age, gender, diabetes, smoking, and systolic BP all remained significant risk factors. Importantly, the effect of an elevated IL-6 on risk of developing CVD was substantial for both MACE1, HR 2.45, 95% CI [1.41, 4.25]; *p*= 0.001 and MACE6 HR 2.1, 95% CI [1.36, 2.28]; *p*=<0.001 (see Table 5). These results indicated that high inflammation is a strong, independent risk factor for long-term risk of MACE.

Table 5. ***Traditional Risk Factors adding Inflammation (IL-6) on MACE***

	MACE1			**MACE6**		
Parameter	Hazard Ratio	95% HR Confidence Interval	Sig	Hazard Ratio	95% HR Confidence Interval	Sig
Age (years)	1.077	[1.046, 1.109]	<.0001	1.090	[1.063, 1.117]	<.0001
Gender			0.004			<.0001
Female	(Reference)			(Reference)		
Male	1.85	[1.206, 2.844]		2.39	[1.666, 3.454]	
White	(Reference)			(Reference)		
Black	0.815	[0.523, 1.270]		1.137	[0.790, 1.633]	
Other	0.576	[0.140, 2.370]		0.181	[0.025, 1.309]	
Diabetes	1.931	[1.139, 3.274]	0.014	1.569	[0.973, 2.531]	0.064
Never Smoked	(Reference)			(Reference)		
Current Smoker	1.968	[1.067, 3.630]	0.030	2.629	[1.615, 4.282]	0.0001
Former Smoker	0.921	[0.593, 1.429]		0.834	[0.571, 1.218]	
High-Density Lipoprotein (mg/dL)	0.99	[0.975, 1.006]	0.2220 .	0.999	[0.986, 1.012]	
Systolic Blood Pressure (mm Hg)	1.012	[1.001, 1.022]		1.009	[1.001, 1.018]	0.039
Inflammation IL-6						
IL-6 (pg/ml) (low)	(Reference)			(Reference)		
IL-6 (pg/ml) (Higher)	2.445	[1.407, 4.248]	0.001	2.111	[1.357, 3.285]	0.0009

Independent Effect of Sleep Quality / Insomnia on Risk for CVD

The inclusion of mild or more severe insomnia was not statistically associated with risk of either MACE1 or MACE6 beyond the influence of traditional risk factors (see Table 6).

Table 6. ***Traditional Risk Factors adding Sleep Quality (Insomnia) on MACE***

	MACE1			MACE6		
Parameter	Hazard Ratio	95% HR Confidence Interval	Sig	Hazard Ratio	95% HR Confidence Interval	Sig
Age (years)	1.077	[1.046, 1.109]	<.0001	1.093	[1.066, 1.121]	<.0001
Gender			0.001			<.0001
Female	(Reference)			(Reference)		
Male	1.998	[1.31, 3.021]		2.404	[1.686, 3.429]	
Diabetes	2.303	[1.396, 3.800]	0.001	2.202	[1.288, 3.173]	0.002
Smoking						
Non- Smoker	(Reference)			(Reference)		
Current Smoker	2.136	[1.154, 3.953]	0.015	3.063	[1.838, 5.023]	<.0001
Former Smoker	1.076	[0.702, 1.649]		0.971	[0.668, 1.410]	
High-Density Lipoprotein(mg/dL)	0.987	[0.972, 1.002]	0.08	0.996	[0.984, 1.009]	
Syst Blood Pressure (mm Hg)	1.010	[1.00, 1.021]	0.043	1.008	[0.999, 1.016]	0.091
Sleep Quality- Measured by Insomnia Scale (IS)						
IS (No symptoms)-1	(Reference)			(Reference)		
IS (Mild) -2	1.031	[0.633, 1.677]		0.914	[0597, 1.400]	
IS (Daytime bother)-3	1.197	[0.704, 2.038]		1.189	[0.751, 1.881]	

Note. ∓ Sleep Quality/insomnia complaints 1. include Trouble falling asleep, trouble with waking during the night and unrefreshing sleep. For those with complaints, day time problems are assessed. Blood Pressure (BP)

Collective Effect of Traditional and Novel Risk Factors

When both traditional and all three novel risk factors were considered, adjusted hazard ratios tended to be attenuated to a small extent (see Table 7). Nonetheless, with this full set of risk factors, older age, male gender, diabetes, current smoker, and high inflammation remained strong independent risk factors for both MACE1 and MACE6.

Depressive symptoms in the upper tertile indicated a higher adjusted risk for MACE6 but not for MACE1. The estimated independent effect of high IL-6 was substantial with adjusted hazard ratios of 2.77 and 2.34 for MACE1 and MACE6, respectively

Table 7. ***Effect of Traditional Risk Factors adding, Depressive Symptoms, Inflammation and Sleep Quality***

	MACE1			MACE6		
Parameter	Hazard Ratio	95% HR Confidence Interval	Sig	Hazard Ratio	95% HR Confidence Interval	Sig
Age (years)	1.087	[1.054, 1.122]	<.0001	1.100	[1.070, 1.131]	<.0001
Female	(Reference)			(Reference)		
Male	2.141	[1.36, 3.364]	0.001	2.799	[1.897, 4.131]	0.001
White	(Reference)			(Reference)		
Black	0.812	[0.513, 1.298]		1.111	[0.754, 1.637]	
Other	0.337	[0.046, 2.45]		(Non-determinant)		
Diabetes	1.915	[1.101, 3.330]	0.021	1.558	[0.963, 2.59]	0.08
Never- Smoked	(Reference)			(Reference)		
Current Smoker	2.147	[1.138, 4.048]	0.018	2.849	[1.699, 4.777]	<0.0001
Former Smoker	0.891	[0.562, 1.411]		0.855	[0.572, 1.278]	
HDL (mg/dL)	0.991	[0.975, 1.008]		01.00	[0.986, 1.014]	
Systolic BP (mm Hg)	1.008	[0.997, 1.019]		1.007	[0.998, 1.017]	
CES-D, Low (0-4)	(Reference)			(Reference)		
CES-D, Mid (>4-9)	1.109	[0.659, 1.864]		1.465	[0.941, 2.280]	0.090
CES-D, Higher (>9)	1.276	[0.730, 2.218]		1.63	[1.009, 2.651]	0.046
I-6 (pg/ml) (low)	(Reference)			(Reference)		
IL-6 (pg/ml) (Higher)	2.767	[1.536, 4.98]	0.0007	2.339	[1.119, 3.775]	0.005
Sleep Quality- Measured by Insomnia Scale (IS)						
IS (No symptoms)-1	(Reference)			(Reference)		
IS (Mild) -2	1.031	[0.633, 1.677]		0.914	[0597, 1.400]	
IS (Daytime bother)-3	1.197	[0.704, 2.038]		1.189	[0.751, 1.881]	

Note. High-Density Lipoprotein (HDL), Interleukin-6 (IL-6), Depressive symptoms (DEP S) / measured by CES-D

Data Analysis Aim 2 -The Effect of Gender

Analysis was conducted to prospectively evaluate whether gender modifies the relationships between sleep quality, depressive symptoms, and inflammation and long-term risk of MACE. Summary statistics on the participants and variables separated by gender is presented in Table 8a for females and Table 8b for males. Student t-tests are reported for continuous variables, presented as mean and standard deviation.

Categorical variables were analyzed with Chi-Square tests and presented as frequencies and percentages. In comparing the overall gender specific summary statistics, no significant differences were identified. To examine the effects of gender on the relationships between depressive symptoms inflammation and insomnia symptoms, models were run to test for interaction with gender.

Effect of Gender and Depressive Symptoms on Risk for CVD

Table 9 provides results from three tests for the effect of gender. The first model shown demonstrates a joint model where the variables gender and depressive symptoms are combined (multiplied) in relation to predicting MACE (i.e. Females with high depressive symptoms). Wald chi-square test for these tests were not significant. However, this approach to investigating effect modification is often underpowered and inconclusive, in part, because joining these variables results in less precision and a large (e.g. four-fold) increase in the variance for the interaction term.

Table 8a.
Descriptive Statistics of Participants by Gender (Females)

	MACE1			MACE6		
FEMALES	Yes	No	p-value	Yes	No	p-value
Parameter	n=55	n=1201		n=76	n=1180	
Age M/SD	62.65 ± 7.81	58.55 ± 7.40	<0.001	63.79 ± 7.64	58.40 ± 7.33	<0.001
%Female	55 (48.67)	1201 (67.40)	<0.001	76 (47.50)	1180 (68.01)	<0.001
Race			0.976			0.674
White	30 (54.55)	642 (53.46)		38 (50.0)	634 (53.73)	
Black	24 (43.6)	533 (44.38)		37 (48.68)	520 (44.07)	
Other						
BMI kg/m2 M/SD	30.15 ± 6.32	30.19 ± 6.71	0.966	29.71 ± 589	30.22± 6.74	0.519
Waist in cm	94.68 ±15.88	93.69±15.43	0.648	95.51±15.88	93.68±15.42	0.658
Smoking			0.868			0.377
Current smoker	6 (10.91)	108 (9.07)	0.01	10 (13.16)	104 (8.89)	
Former smoker	21 (38.18)	485 (40.72)		27 (35.53)	479 (40.94)	
Never smoker	28 (50.91)	598 (50.21)		39 (51.32)	587 (50.17)	
Diabetes		109 (9.13)	0.008	15 (19.74)	105 (8.98)	<0.002
Systolic Blood Pressure (mmHg)	142.8 ±19.18	135.3±20.09	0.007	142.0±19.23	135.2±20.10	0.004
Hypertensive meds	30 (54.55)	487 (40.58)	0.040	39 (51.32)	478(40.54)	0.064
HDL	57.98 ±12.45	61.51±14.99	0.086	60.70±13.56	61.39±14.98	0.699
Triglycerides	134.3 ±63.57	120.2±75.39	0.172	123.3±63.46	120.7±75.63	0.771
Statin medication	13 (23.64)	217 (18.08)	0..298	18 (23.68)	212 (17.98)	0.213
Glucose	106.4±40.27	96.94±24.93	0.008	104.5±25.73	96.91. ±25.7	0.014
IL-6			0.067			0.031
Lowest tertile	9 (18.00)	336 (30.08)		12 (17.91)	333 (30.27)	
Upper two tertiles	41 (82.00)	781 (69.92)		55 (82.09)	767 (69.73)	
Depressive symptoms			0.138			0.214
CES-D, Low (0-4)	13 (23.64)	391 (32.97)		18 (24.00)	386 (33.10)	
CES-D, Mid (>4-9)	16 (29.09)	384 (32.38)		25 (33.33)	375 (32.16)	
CES-D, Higher (>9)	26 (17.27)	411 (34.65)		32 (42.67)	405 (34.73)	
Sleep Quality- Measured by Insomnia Scale (IS)			0.502			0.999
IS (No symptoms)-1	24 (50.00	639 (58.14)		38 (57.58)	625 (57.82)	
IS (Mild) -2	12 (25.00)	246 (22.38)		15 (22.73)	243 (22.48)	
IS (Daytime bother)-3	12 (2500)	214 (19.47)		13 (19.70)	213 (19.70)	

Note. 'Insomnia Category 1. Low frequency of or no complaints, 'Insomnia Category 2. High frequency of complaints, low bother Insomnia Category 3. High Frequency of complaints, high bother. Blood Pressure (BP)

Table 8b. ***Descriptive Statistics of Participants by Gender (Males)***

MALES	**MACE1**			**MACE6**		
Parameter	Yes *n*=58	No *n*=581	p-value	Yes *n*=84	No *n*=555	p-value
Age Mean/SD	62.97 ± 7.09	58.79 ± 7.46	<0.001	62.71 ± 7.30	58.63 ± 7.41	<0.001
Race			0.976			0.674
White	34 (58.62)	341(58.69)		47 (55.95)	328 (59.10)	
Black	23 (39.66)	219 (37.69)		37 (44.05)	205 (36.94)	
Other	1	21		0	22	
BMI kg/m2 M/SD	30.94 ± 6.38	29.63 ± 5.56	0.095	30.76 ±7.03	29.60± 5.40	0.081
Waist in cm	104.5 ±13.76	99.57 ±13.62	0.009	103.3 ± 15.48	99.54 ± 13.35	0.021
Smoking			0.107			0.001
Current smoker	9 (15.52)	69 (11.98)		19 (22.89)	59 (10.71)	
Former smoker	31 (53.45)	245 (42.53		40 (48.19)	236 (42.83)	
Never smoker	18 (31.03)	262 (45.49)		24 (28.92)	265 (46.46)	
Diabetes Mellitus	13 (22.81)	48 (8.30)	<0.001	14 (16.87)	47 (8.51)	0.016
Systolic BP (mmHg)	145.5 ±22.17	136.8 ±17.68	0.001	143.4 ±20.91	136.7 ±17.71	0.002
Takes BP meds	29 (50.00)	213 (36.92)	0.051 B	40 (47.62)	202 (36.66)	0.054
HDL	49.14 ±12.10	50.70 ± 12.13	0.35	50.27 ± 14.29	50.60 ±11.78	0.816
Triglycerides	119.1 52.88	128.4±79.1	0.379	12.87±93.16	127.74.50	0.881
Statin medication	17 (29.31)	119(20.62)	0.125	18 (21.43)	118(21.42)	0.998
Glucose	104.4 ± 22.43	101.0 ± 25.90	0.333	133.6 ± 21.52	101. ± 26.16	0.387
IL-6			<0.001			<0.001
Lowest tertile	8 (16.33)	232 (43.04)		15 (20.27)	225 (43.77)	
Upper two tertiles	41 (83.67)	307 (56.96)		59 (79.73)	289 (56.23)	
Depressive symptoms			0.138			0.214
CES-D, Low (0-4)	25 (43.10)	250 (43.55)		30 (36.14)	245 (44.63)	
CES-D, Mid (>4-9)	19 (32.76)	160 (27.87)		29 (34.94)	150 (27.32)	
CES-D, Higher (>9)	14 (24.14)	164 (28.57)		24 (28.92)	154 (28.05)	
Sleep Quality- Measured by Insomnia Scale (IS)			0.661			0.624
IS (No symptoms)1	40 (71.43)	352 (65.55)		55 (68.75)	337 (65.69)	
IS (Mild) -2	10 (17.86)	110 (20.48)		13 (16.25)	107 (20.86)	
IS (Daytime bother)3	6 (10.71	75 (13.97)		12 (15.00)	69 (13.45)	

Note. 'Insomnia Category 1. Low frequency of or no complaints, 'Insomnia Category 2. High frequency of complaints, low bother Insomnia Category 3. High Frequency of complaints, high bother. Blood Pressure (BP)

The next test for effect modification by gender is a stratified model. In other words, genders are separated for analysis. This model illustrates females with higher depressive symptoms have nearly double the risk for MACE1 (HR=1.95) and MACE6 (HR=1.82).

Table 9*. Gender by Depressive Symptoms Interaction on MACE*

	MACE1			**MACE6**		
Parameter	Hazard Ratio	95% HR Confidence Interval	Sig	Hazard Ratio	95% HR Confidence Interval	Sig
DEP S p-values						
Gender X Mid (CES-D)			0.686			0.905
Gender x High (CES-D)			0.185			0.704
DEP S**– Female**						
(CES-D) Low (0-4)	(Reference)			(Reference)		
(CES-D) Mid (>4-9)	1.376	[0.661, 2.865]	0.69	1.703	[0.919, 3.157]	NS
(CES-D) Higher (>9)	1.957	[0.999, 3.834]	0.06	1.820	[1.000, 3.312]	0.04 *
DEP S- Male						
(CES-D) Low (0-4)	(Reference)			(Reference)		
(CES-D) Mid (>4-9)	1.131	[0.616, 2.075]	NS	1.621	[0.961, 2.734]	0.07
(CES-D) Higher (>9)	1.035	[0.532, 2.014]	NS	1.551	[0.885, 2.727]	0.124
Gender by DEP S						
Female x Low (CES-D)	(Reference)			(Reference)		
Male x Low (CES-D)	2.50	[1.265, 4.979]	**	2.533	[1.368, 4.687]	**
Female x Mid (CES-D)	1.376	[0.661, 2.856]	NS	1.703	[0.919, 3.157]	B
Male x Mid (CES-D)	2.838	[1.370, 5.880]	**	4.105	[2.211, 7.622]	***
Female x High (CES-D)	1.957	[0.999, 3.834]	*	1.820	[1.000, 3.312]	*
Male x High (CES-D)	2.597	[1.192, 5.658]	*	3.935	[2.050, 7.553]	***

Note. ***, **, * denotes significant, p=<0.001, p<=0.01, p<=0.05, respectively. B denotes significance is borderline or close to significant, 0.05 =<p<0.1 Depressive symptoms (DEP S)

Therefore, females with depressive symptoms within the highest tertile of (CES-D) scores are at an increased risk for developing CVD compared to females with low levels of depressive symptoms. For men, depressive symptoms were not a significant predictor of MACE, however the hazard ratios were >1 indicates a suggestion of depression being associated with risk of MACE in males. The third analysis created indicator variables for combinations of gender and tertiles of depression. Males at every level (i.e. irrespective of level of depressive symptoms) had a higher risk of MACE as compared to women. Overall, results indicated that depressive symptoms were associated with higher risk of MACE in both genders, while not significantly different between genders.

Table 10. ***Gender by IL-6 Interaction on MACE***

	MACE1			**MACE6**		
Parameter	Hazard Ratio	95% HR Confidence Interval	Sig	Hazard Ratio	95% HR Confidence Interval	Sig
Gender x IL-6 Interaction			0.208			0.368
Effect of IL-6 High x Low						
Among Females	1.717	[0.822, 3.586]	NS	1.688	[0.893, 3.193]	NS
Among Males	3.441	[1.529, 7.744]	**	2.506	[1.383, 4.541]	**
Gender x IL-6 Combination						
Low IL-6 x Female	(Reference)			(Reference)		
Low IL-6 x Male	1.036	[0.380, 2.822]	NS	1.740	[0.793, 3.816]	NS
High IL-6 x Female	1.717	[0.822, 3.586]	NS	1.688	[0.893, 3.193]	NS
High IL-6 x Male	3.564	[1.662, 7.639]	**	4.360	[2.258, 8.416]	***
RERI Male IL-6 Interaction	3.564-1.036-1.717+1 = 1.811		0.29	4.360 -1.740-1.688+1 =1.932		0.026 *

Note. ***, **, * denotes significant, p=<0.001, p<=0.01, p<=0.05, respectively. B denotes significance is borderline or close to significant, 0.05 =<p<0.1

Effect of Gender on Inflammation /IL-6

As indicated in stratified analysis in Table 10, the effect of high IL-6 on long term risk of CVD was substantial and was higher in males than in females. Specifically, for MACE1, a high IL-6 in males resulted in an adjusted hazard ratio of 3.56 in males 95% CI [1.66, 7.64] as compared to an adjusted hazard ratio of 1.72 in females, 95% CI [0.82, 3.59]. Corresponding estimates for the MACE 6 definition were 4.36 in males 95% CI [2.26, 8.42] compared to 1.69 in females, 95% CI [0.89, 3.19]. Although these apparent gender differences did not reach statistical significance in the formal test of interaction, the evidence indicated that high IL-6 is a strong independent risk factor for long-term risk of CVD, particularly in males.

The calculation of the relative excess risk due to interaction (RERI) computed by the delta method is shown at the bottom of Table 10 (Li & Chambless,2007). The RERI for being male and having high IL-6 was 1.81 for MACE1 and 1.93 for MACE6, indicating a near double of risk among males.

Effect of Gender on Sleep Quality

Sleep quality measured by Insomnia questionnaire on all three categories of sleep quality was not a significant risk factor for MACE for either gender (Table 11). The differences in the ratios for males and females did not reach statistical significance (all interaction *p*-values were greater than 0.15). Moreover, for males, hazard ratio estimates for long-term risk of CVD in relation to insomnia were below the null value of

1.0, thereby indicating no increased risk. For females, hazard ratios associated with insomnia were only nominally above the null value of 1.0, again, indicating essentially no exceed risk of CVD.

Table 11. ***Gender by Sleep Quality Interaction on MACE***

	MACE1			MACE6		
Parameter	Hazard Ratio	95% HR Confidence Interval	Sig	Hazard Ratio	95% HR Confidence Interval	Sig
Interaction p-values						
Gender x Insomnia 2			0.183			0.251
Gender x Insomnia-3			0.204			0.917
Among Females						
Category 1	(Reference)			(Reference)		
Category 2	1.477	[0.736, 2.964]	NS	1.191	[0.652, 2.177]	NS
Category 3	1.668	[0.830, 3.354]	NS	1.175	[0.609, 2.265]	NS
Among Males						
Category 1	(Reference)			(Reference)		
Category 2	0.756	[0.377, 1.519]	NS	0.720	[0.893, 3.193]	NS
Category 3	0.811	[0.340, 1.934]	**	1.233	[0.650, 2.339]	***
Gender x Insomnia						
Insomnia 1 x Female	(Reference)			(Reference)		
Insomnia 1 x Male	2.609	[1.540, 4.418]	***	2.623	[1.691, 4.069]	***
Insomnia 2 x Female	1.477	[0.736, 2.964]	NS	1.191	[0.652, 2.177]	NS
Insomnia 2 x Male	1.973	[0.925, 4.208]	B	1.889	[0.986, 3.619]	B
Insomnia 3 x Female	1.668	[0.830, 3.354]	NS	1.175	[0.609, 2.265]	NS
Insomnia 3 x Male	2.115	[0.849, 5.265]	NS	3.234	[1.653, 6.328]	***

Note. 'Insomnia Category 1. Low frequency of or no complaints, 'Insomnia Category 2. High frequency of complaints, low bother Insomnia Category 3. High Frequency of complaints, high bother. '***, **, * -HR is significant, p=<0.001, p<=0.01, p<=0.05, respectively. B - HR is borderline or close to significant, 0.05 =<p<0.1

Summary

In summary, depressive symptoms were associated with a modest long-term risk of CVD in both males and females. High inflammation (IL-6) was associated with substantially higher long-term risk of CVD, particularly in males. Insomnia was not predictive of risk of CVD in this study. In conclusion, it would be suggested that depressive symptoms and inflammation may be considered in the future as screening targets for risk of CVD.

CHAPTER FIVE:
DISCUSSION

Chapter Five includes a synthesis of the study results, discussion and implications for nursing practice and recommendations for future research. The purpose of this study was to assess the effects of depressive symptoms, inflammation, and quality of sleep on the risk for developing cardiovascular disease (CVD), while additionally testing for differences among gender. The goal was to determine if any of these factors should be considered for use in the future for routine preventative screening for CVD risk.

Traditional Risks for CVD

This secondary analysis included a well-represented sample including, 66% females and 34% males with a mean age of 61 years and range from 47-75 years of age. Age was a significant predictor of MACE, which would be expected based on previously published studies. Increasing age has an increased effect on many risk factors for CVD such as central obesity, blood pressure, hyperlipidemia, insulin resistance, inflammation, and endothelial dysfunction (Dhingra & Vasan, 2012; Lopez-Candales et al., 2017; Yang et al., 2015). Men in this study were at nearly two-times the risk for MACE. This supports previous findings with men being at a greater risk than women for CVD within similar middle-aged populations (Maas & Appelman, 2010; Mosco, Barrett-

Connor & Wenger, 2011; Benjamin et al., 2018). However, it has been reported that differences among the genders decrease as age increases (Maas & Appelman, 2010; Mehta et al., 2016; Mosco, Barrett-Connor & Wenger, 2011; Benjamin et al., 2018). While many studies have had underrepresentation of Blacks, by purposeful oversampling, this study included 46% Blacks. Race was not a significant independent predictor of the development of CVD within this population group.

The traditional risk factors evaluated were consistent with previous research. The effect of smoking doubled the risk for developing MACE in this population. Our findings support previous studies including a meta-analysis of 25 studies among varying populations (Mons, et al., 2015). Despite the relatively small number of diabetics within the Heart SCORE cohort (9%), nearly every model tested yielded a significant effect from diabetes. Studies looking at the effect of diabetes on CVD have reported a 2-fold risk of CVD when compared to non-diabetics (Anderson et al., 2001; Badescu et al., 2016; Ivanos et al., 2018). These findings are consistent with our findings with diabetics being at 2.3 times the risk for MACE1 and 2.08 for MACE6. Despite several studies supporting the association between lower levels of HDL cholesterol and higher levels of triglycerides being predictive of long-term CVD risk (Klempfer et al., 2016; Miller, 2009), the present analysis found only minimal evidence for these relationships.

Systolic blood pressure was associated with risk for CVD in this analysis which is consistent with evidence of systolic blood pressure being a main predictor of CVD in a number of studies (Goldstein et al., 2014; Wong et al., 2012). Controlling blood pressure

at even a small range has been found to be beneficial in reducing these risks (Whelton et al., 2017).

Novel Risk Factors

Previous literature suggests that several novel risk factors, including depressive symptoms, inflammation, and sleep quality may influence the risk for having a major adverse cardiac event. Additionally, prior research suggests these factors affect outcomes and risk of mortality among those who have already developed CVD (Celano & Huffman, 2011; Mehta et al., 2016; Rutledge et al., 2006).

The effect of depressive symptoms was of considerable interest in the present analysis, particularly with respect to potential recommendations for both primary and secondary prevention of CVD. The addition of depressive symptoms to the initial traditional risk factor model increased the risk for MACE by more than 1.5 times, with estimates generally similar between men and women. Mixed results regarding an effect of gender and depressive symptoms have been reported. Evidence indicates a higher prevalence of depressive symptoms in women than in men (Vaccarino & Brenner, 2016). Despite the higher prevalence rates, the effects of depressive symptoms on MACE did not significantly differ between genders (Vaccarino & Brenner, 2016). The present findings support similar findings reported by Ivanovs et al. (2018), where depressive symptoms were a significant predictor in a sample of 1,500 persons HR

1.57, 95% CI [1.06, 2.33]; *p*= 0.03, and significant predictor of cardiac related death HR 3.2, 95% CI [1.2, 8.9]; *p*=0.025 (Ivanovs et al., 2018; Lahtind et al., 2018).

Inflammation, as measured with IL-6, was strongly associated with increased long-term risk of MACE among participants in the Heart Score cohort, especially in men. High inflammation has been associated with higher risk for cardiovascular events and death post event (Held et al., 2017; Nishida et al., 2011; Riker et al., 2000). The present finding of a particularly substantial risk of MACE in men in relation to high inflammation does not appear to have been widely reported in the literature.

Insomnia was not associated with long-term risk of CVD in this study. However, persons with difficulty falling asleep, staying asleep, and having daytime bother have been identified to be at higher risk for developing CVD in other studies (Hoevenaar-Blom et al., 2011).

Strengths and Limitations, Recommendations

The Heart SCORE data set provided a plethora of data and the advantages of having longitudinal follow-up of risk of cardiovascular events over time. The commitment by study participants to follow through for over 10 years helped to ensure validity of the data. The study sample ages, gender, and racial mix were fairly balanced among the participants which helps to aid in generalizability of results.

Study limitations include the overall good health of this community-based study population and hence relatively low rates of MACE. The population group was obtained

from a community population with similar backgrounds and relatively similar social economic status and lifestyles. Although there was racially nearly equal representation between whites and blacks, results from this population may not be generalizable to a larger population or compared to the US population. Possible reasons for this potential lack of generalizability included that this group was self-selected, mostly insured, had a relatively low rate of smokers (13%) that was than the national average (14.5%) (Benjamin et al., 2018).

Another limitation to this study is that the cut points chosen for depressive symptoms did not reflect standard cut points used for screening. In this analysis, the effect of depressive symptoms was significant at the highest tertile of depressive symptoms, (CES-D) Higher (>9), This range for the highest tertile represents relatively low scores as compared to the CESD score greater than 16 that indicates the presence of depressive symptoms consistent with depression (Radloff, 1997; Fischer, 2009). The lower cut points were chosen due to the sparse numbers of persons within the range of depressive symptoms consistent with a diagnosis of depression. Specifically, in this population, depressive symptoms were low; the mean CES-D score for women was (8.0) and the mean score for men was (5.6). Larger samples sizes and populations with an increased risk for CVD have been found to have increased prevalence of depression (Piwonski, Piwonska, & Sygnowska, 2014).

The inflammatory markers, including both CRP and IL-6, were only drawn at baseline. Using one value to predict long-term outcomes (i.e. CVD) may yield

difficulties related to the causes of elevation from a single measurement. Both markers are acute phase reactions, such as a recent illness or injury, and thus, an elevated IL-6 value from a single measurement may not be indicative of chronic inflammation. It would be suggested that IL-6 be measured annually to assess for chronicity of high inflammation.

Sleep quality was not associated with long-term risk of CVD. However, data collection for this measure was not optimal. Specifically, there was a great deal of missing data with this instrument, including missing data on duration of the problem. Completing multiple self-reports on follow up visits may lead to response fatigue, resulting in missing data and inaccurate responses (O'Reilly, 2017).

Implications for Nursing Practice

In summary, the purpose of this study was to estimate long-term risk of CVD in relation to novel factors including depressive symptoms, inflammation, and quality of sleep. Based on findings from this study, there are no firm global recommendations regarding changes to screening processes for CVD risk. However, evidence from this study showed that depressive symptoms were generally predictive of CVD in both men and women. Therefore, because depression is associated with poorer outcomes and mortality after a significant cardiovascular event, it is suggested that health providers, when considering an individualized patient centered approach, maintain a keen awareness of persons most likely to be at risk. Most screening tools for depressive

symptoms are available for free and involve a minimum time investment. In addition to standard risk evaluation such as the Pooled Cohort Risk Equations, providers may wish to screen for depressive symptoms in selected individuals as part of preventative healthcare visits.

Inflammation was highly predictive of long-term risk of CVD, especially in men. Therefore, like depressive symptoms, screening for inflammation should be considered on an individual basis. Screening with a laboratory test for IL-6 may prove to be a valuable tool in the prediction of CVD, especially in men.

Although not evident in this study, the literature suggests that insomnia with long duration and high symptoms of bother are associated with risk of CVD (Sands-Lincoln et al., 2012). Additional evidence is needed in this area to support routine screening for insomnia. The use of quantitative measures such as sleep actigraphy in addition to the self-reported insomnia score may yield more accurate data.

It is recommended that the findings from this study and previous studies be considered, when conducting risk assessments. A keen awareness of the effects of these novel risks factors allows for individualized approached for health screenings and educational opportunities for persons at risk.

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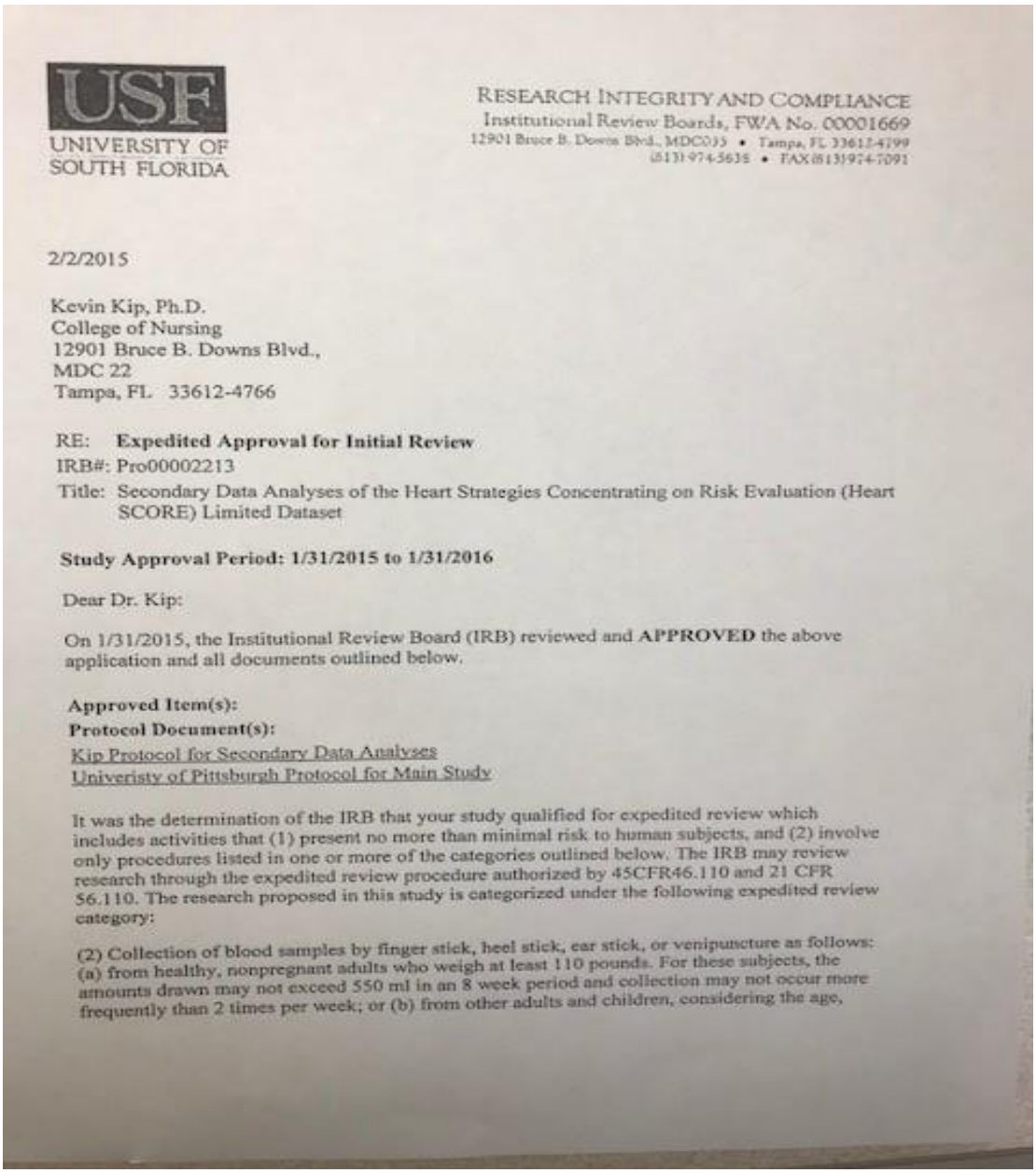
APPENDIX A:

INSTITUTIONAL REVIEW BOARD APPROVAL



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RESEARCH INTEGRITY AND COMPLIANCE
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2/2/2015

Kevin Kip, Ph.D.
College of Nursing
12901 Bruce B. Downs Blvd.,
MDC 22
Tampa, FL 33612-4766

RE: **Expedited Approval for Initial Review**
IRB#: Pro00002213
Title: Secondary Data Analyses of the Heart Strategies Concentrating on Risk Evaluation (Heart SCORE) Limited Dataset

Study Approval Period: 1/31/2015 to 1/31/2016

Dear Dr. Kip:

On 1/31/2015, the Institutional Review Board (IRB) reviewed and **APPROVED** the above application and all documents outlined below.

Approved Item(s):
Protocol Document(s):
Kip Protocol for Secondary Data Analyses
Univeristy of Pittsburgh Protocol for Main Study

It was the determination of the IRB that your study qualified for expedited review which includes activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the categories outlined below. The IRB may review research through the expedited review procedure authorized by 45CFR46.110 and 21 CFR 56.110. The research proposed in this study is categorized under the following expedited review category:

(2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows: (a) from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or (b) from other adults and children, considering the age,

Appendix A (continued)

weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

(4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing.

(7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

Your study qualifies for a waiver of the requirements for the informed consent process as outlined in the federal regulations at 45CFR46.116 (d) which states that an IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent, or waive the requirements to obtain informed consent provided the IRB finds and documents that (1) the research involves no more than minimal risk to the subjects; (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects; (3) the research could not practicably be carried out without the waiver or alteration; and (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation.

As the principal investigator of this study, it is your responsibility to conduct this study in accordance with IRB policies and procedures and as approved by the IRB. Any changes to the approved research must be submitted to the IRB for review and approval by an amendment.

We appreciate your dedication to the ethical conduct of human subject research at the University of South Florida and your continued commitment to human research protections. If you have any questions regarding this matter, please call 813-974-5638.

Sincerely,

V Jorgensen MD

E. Verena Jorgensen, M.D., Chairperson
USF Institutional Review Board