DEVELOPMENT OF CARDIOVASCULAR DISEASE RISK SCORE BY ADDING A BODY COMPOSITION ASSESSMENT

By

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To my mom, dad, brother and grandfather

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LIST OF ABBREVIATIONS

AHA	American Heart Association
ACC	American College of Cardiology
ADA	American Diabetes Association
AUC	Area Under Curve
ASCVD	Atherosclerotic cardiovascular disease
ASSIGN	ASsessing cardiovascular risk using SIGN guidelines
BIA	Bioelectrical Impedance Analysis
BMI	Body Mass Index
CACS	Coronary Artery Calcium Score
CDC	Center for Disease and Prevention Controls
CRF	CardioRespiratory Fitness
CVD	Cardiovascular Disease
CHD	Coronary Heart Disease
CT	Computed Tomography scan
DXA	Dual-energy X-ray Absorptiometry scan
FHS	Framingham Heart Study
FHS-OS	Framingham Heart Study-Offspring Study
HDL-C	High-Density Lipoprotein Cholesterol
IL-1	Interleukin-1
MESA	Multi-Ethnic Study of Atherosclerosis
MRI	Magnetic Resonance Imaging
NFL	National Football League
NHLBI	National Heart, Lung and Blood Institute
NHANES	National Health and Nutrition Examination Survey

NIDDK	National Institute for Diabetes, Digestive, and Kidney Diseases
NWO	Normal Weight Obesity
ROC	Receiver Operating Characteristics
SAD	Sagittal Abdominal Diameter
TNF-α	Tumor Necrosis Factor-α
TOS	The Obesity Society
USPSTF	United States Preventive Services Task Force
WC	Waist Circumference
WHR	Waist-to-Hip Ratio
WtoHR	Waist-to-Height Ratio
WHO	World Health Organization
%BF	Percentage of Body Fat

Abstract of Dissertation Presented to the Graduate School
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Cardiovascular disease has been a top leading cause of mortality in the United States (US). In order to assess cardiovascular disease (CVD) risk, the risk score was developed in the late 1990s to decrease CVD prevalence and mortality. It is an affordable and effective tool to estimate future CVD risk in clinical settings. However, to take into account obesity epidemic, some risk scores have adopted Body Mass Index (BMI) into their model. Recent studies have found that BMI may cause misclassification of people who fall in the normal weight and moderate overweight range. Therefore, the purpose of this study was to develop a CVD risk score by adding a body composition assessment for adults ages 44 and older.

This study used the Multi Ethnic Study of Atherosclerosis (MESA) dataset, collecting asymptomatic population data with diverse races and ethnicities (n=5,483). It was randomly divided into two datasets of equal size. One dataset was used to create the risk score, and the other used to validate the model. As a result, the risk model included eight classical CVD risk factors: age, sex, systolic blood pressure, hypertensive medication, diabetes, total cholesterol, high-density lipoprotein cholesterol

(HDL-C), and smoking. The quartile of waist-to-hip ratio (WHR) was used as the optimal body composition assessment. By using Cox proportional hazards regression with a 10 year follow-up period, non-invasive and affordable risk scores were derived with moderately good performance. Scores of risk factors have been established based on hazard ratios. This risk score was validated (AUC, 0.746). Specifically, the model showed better predictive accuracy in the normal weight and the overweight population (AUC, 0.771).

This developed CVD risk score may contribute to improving health care professionals' decision making when providing treatment, particularly for populations who may be misclassified as healthy or unhealthy as a result of their BMI score. Moreover, given the estimated potential CVD risk, it may assist in effectively managing the heath of this population.

CHAPTER 1
INTRODUCTION

Cardiovascular disease (CVD) has been a top leading cause of death and a primary reason for high economic burden in the United States (US) for decades. Several risk factors such as hypertension, diabetes and smoking for developing CVD have been identified. Obesity, in particular, is considered a primary risk factor associated with CVD due to substantial prevalence and the strong association of chronic diseases. Obesity is typically defined by body mass index (BMI, kg/m^2), which is a simple equation of weight divided by height squared. However, since body weight reflects several body compositions such as fat, bone mass, muscle mass or body water, BMI alone may not accurately assess the true amount of body fat. Thus, the use of BMI alone may misclassify populations at low risk as being intermediate risk in reality such as normal weight with excessive fat or overweight with lower fat. Misclassification disrupts accurate CVD risk estimation. For instance, people with normal weight who have excessive fat are prone to suffer from metabolic syndrome, prediabetes or diabetes. To improve predictive accuracy of risk estimation, a variety of body composition factors (i.e., waist circumference and grip strength) has paid more attention. Body composition assessments are a simple, non-invasive, and lower cost method to measure body fat. These assessments have been shown to play important roles in stratifying populations who fall into the borderline of normal weight and obesity. This in turn allows for improvements in population stratification with enhanced predictive accuracy.

Risk score is a practical tool to estimate the potential risk of CVD development. It provides objective evidence of current health states to patients and it enhances health

care provider's decision making in clinical settings. Developed in 1970, the Framingham risk score (FRS) is the initial CVD risk score. Current risk scores include several common demographics (i.e., age and sex) and biomarkers (i.e., systolic blood pressure, total cholesterol and diabetes). Obesity-related factors such as BMI or waist circumference are not commonly included in risk scores. Many researchers have attempted to include specific biomarkers to the FRS; however, there is limited evidence that supports including body composition factors in risk estimation. Therefore, the proposed study aims to identify the optimal body composition assessment in CVD risk estimation and develop CVD risk score with a chosen body composition assessment. The goals of the proposed study are to: 1) determine an optimal body composition assessment to predict CVD risk; 2) develop the CVD risk score by adding a selected body composition assessment; and 3) test validation of the risk model, and to examine improvement of predictive accuracy in normal weight and overweight populations who would be at intermediate risk of CVD.

CHAPTER 2
LITERATURE REVIEW

Cardiovascular Disease (CVD)

Cardiovascular disease (CVD) is defined as disorders of the heart and blood vessels that can cause a heart attack or stroke (American Heart Association, 2014). Specifically, Atherosclerosis, a blood clot or plaque that blocks the blood flow to the heart or to the brain, can damage the brain cells or the heart muscle which may result in death. Coronary heart disease (CHD), arrhythmia, heart attack and stroke are all forms of CVD (D'Agostino et al., 2008).

CVD has been a top leading cause of death in the United States since 1969 (Ma, Ward, Siegel, & Jemal, 2015). While its rate decreased to about 65.7% between 2011 and 2013, a recent study reported the total number of CVD related deaths increased in 2011 to 2014 (Ma et al., 2015; Sidney et al., 2016). The prevalence of CVD was projected to reach more than 40% of the US population by 2030 (American Heart Association, 2016; Heidenreich et al., 2011). Furthermore, CVD was associated with a vast economic burden. Total direct medical costs of CVD were expected to double to $818.1 billion and the total costs of CVD was projected to reach $1 trillion in 2030 (Heidenreich et al., 2011). With healthcare having reached $3.2 trillion in the US in 2015, the growth of CVD costs will continue to be a burden for the US economy.

To combat the increased threat of CVD in public health, the American Heart Association (AHA) established "The 2020 Impact Goal" to reduce the number of CVD and stroke deaths by 20 percent by the year 2020 (Roger et al., 2011). AHA recommends seven effective approaches called as "Life's Simple 7" to improve cardiovascular health. The approaches for CVD prevention included metabolic

biomarkers such as normal range of blood pressure (below 120/80mmHg), cholesterol (below of 170mg/dL), weight (below of 25kg/m^2), blood glucose (less than 100mg/dL); having a non-smoking status (never smoked or having quit for 12 months or longer); lifestyle interventions such as regular physical activity (150 minutes per week for moderate-intensity activity or 60 minutes per week for vigorous-intensity activity); and healthy diet (eat 4 to 5 components of nutrition) (Lloyd-Jones et al., 2010). These recommendations and approaches were established based on common CVD risk factors.

Risk factors for CVD, such as metabolic biomarkers and demographics, were identified using the Framingham Heart Study (FHS) (Black, 1992; Kennel, O'Agustino, & Betanger, 1968). Starting in the late 1970s, FHS recruited 5,127 participants, ages 30 to 62 in Framingham, Massachusetts in 1948. Researchers have examined participants' health every two years for more than 30 years (Black, 1992). Using epidemiological results, this research study contributed identifying several CVD risk factors. To become CVD risk factors, they must meet criteria. Specifically, these risk factors should be statistically associated with CVD regardless of age, gender or race. The associations also should be proven by experimental studies with biological sense and the factors must be a contributor of increased risk of developing CVD (Black, 1992). Therefore, several major risk factors were selected and have been widely used to estimate risk of CVD. The following section will present a current list of risk factors.

Risk Factors

Demographics

Demographics are non-modifiable factors. CVD risk increases with age. More than a third of CVD mortality was attributed to older adults over 65 years of age (Alan S.

Go et al., 2014). Older adults were also more likely to develop chronic diseases, which may result in increased risk of CVD (Alan S Go et al., 2014; Menke, Casagrande, Geiss, & Cowie, 2015). Since nothing can delay aging to prevent CVD, it needs to pay more attention to healthy aging with diet and maintaining fitness.

Gender is another predictor of CVD. Incident rates of CHD in men were three times higher than in women and CHD mortality among men was five times greater compared to women's mortality rates (Jousilahti, Vartiainen, Tuomilehto, & Puska, 1999). According to Jousilahti and colleagues, most risk factors were observed lower risk for women whereas high smoking rates was shown in men (Jousilahti et al., 1999). Moreover, research indicated that estrogen, the primary female sex hormone, may play a protective role and thus gender differences might be a strong predictor of CVD (Stampfer & Colditz, 1991).

Lastly, race and ethnicity were also considered to be a major risk factor of CVD. In 2010, African-American men had the highest CVD death rates (369.2 per 100,000 person), followed closely by African-American women (260.5 per 100,000 person) (Alan S. Go et al., 2014). Among non-Hispanic African-American adults ages 20 and older, 46% of men and 48% of women had CVD. This same group saw 46,081 male and 47,130 female CVD related deaths in 2011 (American Heart Association / American Stroke Association, 2015). The primary reason for CVD health disparities was the high prevalence of hypertension and diabetes as risk factors. Forty-four percent of African-American adults have hypertension in 2010 and almost 22% had diabetes in 2012 (Alan S Go et al., 2014; Menke et al., 2015).

Cholesterol

High cholesterol is the total cholesterol greater or equal to 240mg/dL. High-density lipoprotein cholesterol (HDL-C) of lower than 40mg/dL is known to be one of primary predictors of CVD (National Heart, Lung, and Blood Institute, 2002). Hyperlipidemia is a form of high blood lipids over the body and fat-type lipids may accumulate in the vessels, blocking blood circulation. Approximately 31.9 million US adults had higher total cholesterol in 2010 (Go et al., 2014). Moreover, lower level of HDL-C was associated with higher CVD mortality (Wilson, Abbott, & Castelli, 1988)

High blood pressure.

High blood pressure is an independent risk factor for CVD. High blood pressure was determined by measured blood pressure that is greater or equal to 140mmHg of systolic blood pressure or greater or equal to 90mmHg of diastolic blood pressure (Chobanian et al., 2003; Alan S Go et al., 2014). Over 70% of people who had CVD was attributable to high blood pressure (Go et al., 2014), and more than 28% of US adults had hypertension in 2010 (Egan, Zhao, & Axon, 2010; Yoon, Burt, Louis, & Carroll, 2012). Although over half of people with high blood pressure are controlled, it is still major contributor of CVD (Egan et al., 2010).

Diabetes.

Diabetes is defined as a group of metabolic diseases cause by abnormal glucose level of greater or equal to 6.5 % of HbA1c level or greater or equal to 126 mg/dL of fasting plasma glucose level (American Diabetes Association, 2010). While diabetes was independently associated with complications such as nephropathy, retinopathy or peripheral neuropathy, many epidemiological studies found that diabetes was highly associated with CVD and CVD mortality (American Diabetes Association, 2010; Hu et

al., 2001; Wei, Gaskill, Haffner, & Stern, 1998). The mortality rate of patients with diabetes was 4.7 times greater than patients without diabetes (Wei et al., 1998). The prevalence of diabetes had steadily increased among US adults, to a rate of 12.3% in 2012, and as such, should be considered a major risk factor for CVD (Menke et al., 2015). As a result, AHA included diabetes as a major risk factor for CVD in its clinical guideline (Goff et al., 2014).

Smoking

Smoking is a modifiable behavioral risk factor of CVD. According to the Centers for Disease Control and Prevention (CDC), smoking accounted for 32.7% of deaths from CVD among adults over 35 years of age in the US (Centers for Disease & Prevention, 2008). The relationship between smoking and CVD is that chemicals in tobacco may cause blood vessels to swell or be inflamed; these damaged vessels may result in CVD (CDC, 2014).

Obesity

Obesity is a strong predictor of CVD. Obesity is defined as excessive or abnormal body fat accumulation over the body (World Health Organization, 2016). It is typically measured by Body Mass Index (BMI, kg/m^2). The World Health Organization (WHO) established clinical BMI cut points of 18.5 kg/m^2 for normal, 25 kg/m^2 for overweight, and 30 kg/m^2 for obesity in order to classify populations based on BMI associations and mortality (World Health Organization, 1995). As BMI and mortality present J-shaped association, obesity itself is associated with higher mortality rate (Adams et al., 2006). Obesity was caused by a combination of genetic, community environmental and behavioral factors. For genetic factors, a specific gene defect can result in the disruption of physiological pathways to control the development of obesity,

which in turn, may results in obesity (Farooqi & O'Rahilly, 2006). Community environment also caused the development of obesity. For example, a lack of access to a physical activity related facility such as a gym and an increasing amount of time spent in a car may induce a sedentary lifestyle, which was associated with high prevalence of obesity (Frank, Andresen, & Schmid, 2004; Gordon-Larsen, Nelson, Page, & Popkin, 2006). Lastly, a lack of physical activity or excessive fat intake may disrupt one's energy balance. When energy intake was greater than energy consumption, extra fat accumulates in the organs and can lead to common chronic diseases (Heymsfield & Wadden, 2017; Larsen et al., 2014).

Obesity was closely linked to high mortality and several chronic diseases such as hypertension, diabetes, dyslipidemia, nonalcoholic fatty liver disease, chronic kidney disease (Adams et al., 2006; Black, 1992; Heymsfield & Wadden, 2017; Jensen et al., 2014). Individuals who were obese showed a greater risk of developing hypertension as a result of the increases in blood pressure and volume (Lavie, Milani, & Ventura, 2009; Wilson, D'agostino, Sullivan, Parise, & Kannel, 2002). They also had seven times higher odds of developing diabetes and two times higher odds of developing high cholesterol compared to people with normal weight (Mokdad et al., 2003). The prevalence of obesity continues to increase. The most recent trend study reported that prevalence of obesity has doubled since 1980, with a prevalence rate of 37.7% in men and 40.4% in women in 2014 (Flegal, Kruszon-Moran, Carroll, Fryar, & Ogden, 2016). In an attempt to seize this trend, the United States Preventive Services Task Force (USPSTF) recommends adults who have a BMI of 30kg/m^2 or greater be provided with counseling or behavioral interventions for weight loss (U.S. Preventive Services Task Force., June,

2012). Contrastingly, recent studies have found protective effect of obesity and worse prognosis of heart attack in population with normal weight. This arises from the use of BMI only when defining obesity.

Physiological mechanism between body fat and CVD. Abnormal or excessive body fat accumulation is a primary cause of metabolic disorders. The physiological system stores nutrient surplus as a form of fat tissue around the abdomen, organs, skeletal muscle or tissues (Heymsfield & Wadden, 2017). This fat tissue controlled amount of fat according to energy-balance needs (Tchkonia et al., 2013). Excessive body fat accumulation called to obesity occurs when energy intakes exceeded energy consumption. Especially, sedentary lifestyle has been epidemic and people were less likely to consume their energy.

Cumulative body fat elevates proinflammatory cytokines such as tumor necrosis factor (TNF) α and interleukin (IL)-1 (Heymsfield & Wadden, 2017). They were produced by fat tissue and play roles in regulating infection, immune response and inflammation (Dinarello, 2000). Increase of proinflammatory cytokines disrupts impaired insulin signaling and elevated insulin resistance (Heymsfield & Wadden, 2017). This abnormal process eventually may cause diabetes and CVD.

Body fat depots were associated with CVD risk factors. It is well-documented that abdominal obesity played a significant role in the increase of insulin resistance and CVD (Barreira et al., 2012). In addition, to date, visceral fat, which is observed underneath subcutaneous fat and around organs has been paid attention as a risk factor of CVD. One study found that visceral fat located around the organs can cause inflammation around organs and can consequently cause hypertension and insulin resistance

(Fontana, Eagon, Trujillo, Scherer, & Klein, 2007). Particularly, since visceral fat stores lipids, increased visceral fat was associated with insulin resistance (Katsuki et al., 2003). In addition, accumulation of excessive visceral fat around kidney increased abdominal pressure and it can cause hypertension (Hall et al., 2010).

Likewise, the primary cause of obesity induced CVD risk factors and CVD was body fat instead of body weight. Therefore, accurate measurement of body fat needs to be considered when predicting CVD risk.

Misclassification of BMI

BMI is widely used to define excessive body fat, or obesity. Preliminary studies have shown that BMI was highly correlated to percentage of body fat (%BF) and cardiovascular mortality (Gómez-Ambrosi et al., 2012; Ortega, Lavie, & Blair, 2016). Body weight includes the weight of organs, bones, waters, muscles and fats and thus the use of BMI only may misclassify the population placed at borderline between the normal and overweight range. Body weight cannot measure the pure fat that determines obesity. An early report of a WHO expert committee previously addressed concerns of the use of BMI only when defining obesity (World Health Organization, 1995). The report noted that clinical cut offs were arbitrarily chosen based on association between BMI and mortality (World Health Organization, 1995). Therefore, BMI is not a perfect proxy of obesity measurement. Other studies have found that prevalence of obesity measured by BMI alone was different from prevalence of true obesity defined by body fat percentage. In one study, one third of men were misclassified as obese due to different contributors of body weight such as muscle mass and muscle density (Pasco et al., 2014). Similarly, Gomez-Ambrosi and colleagues found in their study that the majority of people categorized as overweight based on BMI were actually obese when

using body fat percent (Gómez-Ambrosi et al., 2012). Additional studies have found using BMI alone misclassified populations at risk of mobility impairments, cardiometabolic diseases, and CVD (Peterson, Al Snih, Stoddard, Shekar, & Hurvitz, 2014; Silventoinen, Magnusson, Tynelius, Batty, & Rasmussen, 2009). According to Peterson and colleagues, about 17% of individuals with high body fat percent who were misclassified as normal BMI (usually referred as low risk) showed higher prevalence of metabolic syndrome (Peterson et al., 2014). For example, while most Asians were shown to be normal weight, they were more likely to have diabetes and CVD (Kim et al., 2014; Raji, Seely, Arky, & Simonson, 2001). Multiple studies suggested lower cut offs of BMI for the Asian population (Barba, Cavalli-Sforza, Cutter, & Darnton-Hill, 2004). These arguments indicated that the use of BMI only to define obesity may not be the best proxy in predicting CVD risk.

An example of BMI misclassification can be seen in professional athletes. One study demonstrating CVD risks in National Football League (NFL) players found that professional football players had lower prevalence of CVD risk factors (i.e., impaired fasting glucose, smoking, and dyslipidemia) compared to healthy men of similar age; however, the study found that more than half of the professional football players were obese based on BMI alone (Tucker et al., 2009). In addition, as opposed to conventional deteriorated effect of obesity, the obesity paradox explained the ironic protective effect of obesity defined by BMI. The obesity paradox explained better prognosis or lower mortality rate of overweight or obesity patients with known CVD compared to individuals who have normal BMI (Asgari et al., 2016; Curtis et al., 2005; Lavie et al., 2016; Oreopoulos et al., 2008). While one meta analysis argued that the

protective effect of obesity attenuated with mortality (Wang et al., 2015), other studies still advocated for the benefits of obesity among individuals with heart failure or coronary artery disease (Curtis et al., 2005; Oreopoulos et al., 2008; Romero-Corral et al., 2006; Shakiba, Soori, Mansournia, Nazari, & Salimi, 2016). Meanwhile, regardless of having any type of CVD, people with normal weight abdominal obesity had twice higher mortality than people with overweight or obesity (K. R. Sahakyan et al., 2015). This inverse relationship also can be found in inpatient mortality where patients who were obese showed a slightly longer length of stay (Fonarow et al., 2007).

Obesity Paradox and Normal Weight Obesity. Prognosis of patients with overweight classification or obesity is also associated with the obesity paradox. Patients receiving hemodialysis showed improved survival over 5 years (Kalantar-Zadeh et al., 2010) and patients who received percutaneous coronary interventions with coronary artery disease had greater 5-year survival compared to normal weight patients (Hastie et al., 2010). In addition, being metabolically healthy or not may play an important role in increased CVD risk regardless of being overweight or obese. Individuals who were metabolically healthy were individual whose metabolic biomarkers, such as glucose level, blood pressure, cholesterol level and insulin resistance, were placed within normal range. A growing body of evidence has shown that people with normal weight who were metabolically unhealthy had greater risk of CVD than people with overweight or obesity who were metabolically healthy (Artham, Lavie, Milani, & Ventura, 2008; Voulgari et al., 2011). This evidence indicates obesity defined by BMI may require a question of independent risk factor of CVD risk assessment.

Normal weight obesity (NWO) refers to individuals who fall in the normal range of BMI (18.5kg/m^2-25kg/m^2) and who have excessive body fat (Romero-Corral et al., 2009). Preliminary studies found that people with NWO showed higher prevalence of metabolic syndrome and higher mortality rate (Batsis et al., 2013; Romero-Corral et al., 2009; Shea, King, Yi, Gulliver, & Sun, 2012). About 18% of the population with normal weight had prediabetes and its trend of prediabetes in normal weight had significantly increased (Mainous, Tanner, Jo, & Anton, 2016). Furthermore, adults with normal BMI who had sedentary lifestyle were more likely to have prediabetes or diabetes (Mainous, Tanner, Anton, Jo, & Luetke, 2017). Despite the risk of misclassification of the use of BMI shown by several studies, people at normal BMI were usually neglected in chronic disease screening guidelines offered by the USPSTF. For instance, diabetes screening is recommended people aged between 40 to 70 years old who are overweight or obesity defined by BMI (U.S. Preventive Services Task Force, 2015). The screening guideline recommends providing intensive behavioral counseling to adults who are overweight or obese measured by BMI and who have CVD (U.S. Preventive Services Task Force, 2014). This indicates that people who are placed at borderline of BMI and who are at high risk of any type of chronic disease may miss an opportunity to receive appropriate healthcare recommendations to prevent the onset of chronic diseases. Therefore, the use of BMI alone may miss people at low risk who would be at intermediate high risk of CVD development.

Body Composition Assessments

A body composition assessment is used to quantify current body composition that affects physical functions and health states. It has played an important role particularly in sports medicine, because some weight-sensitive sports such as boxing or

rhythmic gymnastics requires to frequently monitoring body weight and subtle changes in body mass which can result in a competitive advantage (Ackland et al., 2012). Moreover, the assessment can provide essential guidelines for training and nutrition to athletes due to the strong correlation to body composition (Nana, Slater, Hopkins, & Burke, 2013). Monitoring body composition allows for population stratification of those at risk of disease.

Recent studies have shown that body composition assessments contributed to identifying populations at high risk for chronic diseases (Mainous, Tanner, Anton, & Jo, 2015, 2016; Mainous, Tanner, Jo, et al., 2016). Among populations with normal BMI, lower grip strength was associated with hypertension, prediabetes and diabetes (Mainous et al., 2015; Mainous, Tanner, Anton, et al., 2016). This indicates that body composition assessments may stratify populations at risk who are typically neglected in health examination.

Body composition assessments are a convenient and non-invasive measurement in risk assessment. While its costs may vary depending on type of techniques, it is relatively inexpensive and can be easily used in any healthcare setting. To date, there is no “gold standard” assessment. While BMI is widely used to identify obese populations in several risk assessments, it is not included in current CVD risk assessment. Wilson and colleagues have shown that BMI was a significant factor in CVD risk prediction (Wilson et al., 2008). However, as aforementioned, BMI only assessments may misclassify people who fall into the borderline between normal and overweight BMI who may be at risk for CVD. As substitutes, diverse body compositions have been considered as a risk factor for several chronic diseases. However, body composition

assessments have been controversial in identifying people at high risk of developing CVD and have not been widely utilized with respect to risk estimation in routine clinical settings.

Numerous body composition assessments have been proposed in clinical settings. Some require simple measurements using a scale or tapeline, whereas others demand expertise and a high-technique laboratory machine such as computed tomography (CT) scans, dual-energy x-ray absorptiometry (DXA) scans, bioelectrical impedance analysis (BIA), or magnetic resonance imaging (MRI). Despite their accuracy in measurement, these machines are extremely expensive for the purpose of measuring body composition and estimating CVD risk in asymptomatic populations. Furthermore, a lack of health insurance coverage may be a barrier in utilizing these machines. The proposed study will propose the use of inexpensive and non-invasive body composition assessments. The following section will provide details about the different types of body composition assessments.

Waist Circumference (WC)

Waist circumference (WC) is a strong indicator of abdominal obesity (Pouliot et al., 1994; Karine R Sahakyan et al., 2015). It was highly correlated with body fat mass and percentage of body fat (Barreira et al., 2012). Research has shown that waist circumference was significantly associated with CVD incidence and mortality, although the results were varied between sex (Aune et al., 2016; De Koning, Merchant, Pogue, & Anand, 2007). Specifically, for every 1cm increased in WC, there was an associated 2% increase in the relative risk of CVD (De Koning et al., 2007). Several studies have reported that WC was a better predictor for mortality and CVD risk factors than BMI (Kartheuser et al., 2013). Since 1988, the mean WC for men went from 96.0cm to

100.4cm and from 89.0cm to 94.0cm for women (Li, Ford, McGuire, & Mokdad, 2007). At the same time, the prevalence of abdominal obesity significantly increased to 42.2% in men and 61.3% in women (Li et al., 2007). Among several indices of abdominal obesity, WC was the preeminent indicator of body fat mass (Barreira et al., 2012).

WC is a simple and portable measurement of abdominal obesity by using a line tape. An examiner marks the midpoint between the lower ribs and the iliac crest and the line tape is brought around the waist following a normal exhale (Sampaio, Simões, Assis, & Ramos, 2007). This method may be prone to measurement error depending on the examiner's skill and it is not able to estimate whole body fat.

Waist-to-Hip Ratio (WHR)

Waist-to-hip ratio (WHR) is also a common indicator of the relative accumulation of abdominal fat (Consultation, 2008). In fact, unlike WC, WHR has a higher correlation to fat distribution and is relatively lower correlated with body fat mass compared to WC (Barreira et al., 2012). However, WHR was better suited in identifying individuals at higher risk of developing obesity-associated health complications (Smith, 2016). Furthermore, Koning's meta-study confirmed that WHR was a stronger predictor of CVD events compared to WC (De Koning et al., 2007). These findings can be seen in the case of the NFL players. Whereas most players were placed within the obesity range as defined by BMI, their mean WHR was lower than cut off point for obesity; this may explain lower risk of mortality and favorable risk factors (Tucker et al., 2009).

WHR is computed by WC and hip circumference. Hip circumference is measured by using the line tape similar to measuring the WC. An examiner measures at the widest circumference point around the hip (Sampaio et al., 2007). The WHO provided

clinical cut off points of 0.90 in men and 0.85 in women (World Health Organization, 2008).

Waist-to-Height Ratio (WtoHR)

Waist-to-height ratio (WtoHR) is an indicator of abdominal obesity (Ashwell & Gibson, 2016). It played a role in predicting diabetes (MacKay, Haffner, Wagenknecht, D'agostino, & Hanley, 2009) and it contributed to identifying early health risks among people who are considered normal weight (Ashwell & Gibson, 2016). It was also associated with higher risk of cardiometabolic risk factors (Ashwell & Gibson, 2016). Specifically, people with normal weight with an unhealthy WtoHR were observed as having a high risk of prediabetes (Mainous, Tanner, Jo, et al., 2016). Since WtoHR was highly correlated with body fat mass and percentage body fat, it may alter BMI (Barreira et al., 2012). A meta-study found that WtoHR was a better indicator of cardio-metabolic risk factors than BMI or WC (Ashwell & Gibson, 2016). Consistent cut off points have not been established in clinical settings.

CVD Risk Score

CVD risk score is a tool used to estimate future risk of CVD within 10 years or a lifetime. The given scores allow patients to know their current CVD risk status. Using these risk scores, healthcare providers, in particular physicians, are able to recommend timely and appropriate health care services and can provide health management services to patients for the next step in screening (Koopman & Mainous, 2008). In clinical settings, risk assessments showed effectiveness in reducing CVD risk and prescribed statin was dramatically increased (Artac, Dalton, Majeed, Car, & Millett, 2013). Another advantage of CVD risk scores is that it can lead to improved patient-physician communication and the scores may lead to better clinical decision making by

physicians (Koopman & Mainous, 2008). In Europe, CVD guidelines have recommend the use of risk score models in health examinations as a prevention strategy since 1994 (Pyörälä, De Backer, Graham, Poole-Wilson, & Wood, 1994). Risk score played a role in stratifying patients into different risk levels (Koopman & Mainous, 2008). Healthcare providers can take advantage of patient classifications in determining the level of treatment and identify priority groups who need preventive services.

Several CVD risk evaluations have been developed for different cohort populations. For example, the Framingham risk score (FRS) was developed for non-Hispanic Whites (Lloyd-Jones et al., 2004), the Reynolds risk score for women (Ridker, Buring, Rifai, & Cook, 2007), the QRISK for general population in England (Hippisley-Cox et al., 2007), the Assessing cardiovascular risk using SIGN guidelines (ASSIGN score) for Scottish populations (Tunstall-Pedoe, Woodward, Tavendale, A'brook, & McCluskey, 1997), the SCORE model for the general population in Europe (Conroy et al., 2003) and the Atherosclerotic cardiovascular disease (ASCVD) risk score used for US populations (Goff et al., 2014). The FRS was the original CVD score and most assessments developed derived from the FRS. Thus, risk scores shared common factors such as demographics (i.e., age and sex) and metabolic biomarkers (i.e., systolic blood pressure, HDL-C, and diabetes), while a few variables differ. For instance, QRISK and ASSIGN scores included social deprivation factors in order to reduce health inequality in CVD risk (Hippisley-Cox et al., 2007; Tunstall-Pedoe et al., 1997). The FRS and the ASCVD focused on metabolic biomarkers (Goff et al., 2014; Lloyd-Jones et al., 2004). The ASCVD included race to take into account genetic effect and it also considered several biomarkers such as C-reactive protein, apolipoprotein B,

family history in population classification. (Lloyd-Jones et al., 2010). Finally, the Reynolds risk score's main focus was on women (Ridker et al., 2007).

Existing scores have proven their validation by applying their measures to other populations and by comparing the other scores. For example, QRISK, developed in England, was showed valid CVD scores among UK's primary care population and it compared scores with the FRS and the ASSIGN (Hippisley-Cox et al., 2007). The ASCVD was verified among a contemporary US population (Muntner et al., 2014). To derive estimated risk score, these evaluations assign a specific value on each risk factor based on statistical probability and estimates the sum of these scores (Sullivan, Massaro, & D'Agostino, 2004; Wilson et al., 1998). Chapter 2 will articulate how to calculate the risk score.

Framingham Risk Score (FRS)

FRS derived from the Framingham Heart Study in 1998 and it was the first measurement of CVD risk estimation among adults (Wilson et al., 1998). This score included eight traditional risk factors: age, sex, diabetes, smoking status, measured systolic blood pressure, history of diagnosed hypertension, total cholesterol and HDL cholesterol (D'Agostino et al., 2008; Wilson et al., 1998).

The FRS was initially created for non-Hispanic White populations, and as such was considered to be less valid in predictive power in regards to race and ethnicity. However, recent studies have verified the validity and reliability of the score in diverse populations (D'Agostino Sr, Grundy, Sullivan, & Wilson, 2001), with men only in the US (J. Gander, 2014), with men only in the UK (P. Brindle et al., 2003), older populations (Rodondi et al., 2012) and populations with different socioeconomic status (P. M. Brindle et al., 2005). Specifically, the biggest concern that the FRS derived from white

dominant population was solved with good performance of the model in multi-ethnic groups (D'Agostino Sr et al., 2001). In addition, C-index, which measures discrimination of risk scores among older adults between the ages of 70 and 79, was not significantly different from the original FRS (p=.54) and thus, the FRS was valid in older adults as well (Rodondi et al., 2012). However, the FRS has limitations in stratifying populations who fall into the blind spot of risk because of an absence of obesity-related factors in the model.

Adding a New Indicator

Adding new indicators to the risk assessment might contribute to improving accuracy of risk estimation. Numerous studies have suggested adding novel biomarkers such as C-reactive protein, coronary artery calcium score (CACS), ankle brachial index and genetic markers to the risk model (Albert, Glynn, & Ridker, 2003; Collaboration, 2008; Greenland, LaBree, Azen, Doherty, & Detrano, 2004). Including ankle brachial index to the FRS reclassified 19% of men and 36% of women into risk categories (Collaboration, 2008) and combined models with CACS and the FRS showed improvement of predictive risk among asymptomatic populations (Greenland et al., 2004). Similarly, adding innovative markers to existing models may allow for prediction with enhanced accuracy and may contribute to better patient classification.

Adding many risk factors to the model, however, is not necessary to enhance predictive accuracy. There are two aspects of predictive accuracy. The first is a reliable prediction and the second is discrimination (Harrell, Lee, Califf, Pryor, & Rosati, 1984). As several factors were involved in the model, there might be a complex effect of interactions among these factors. It may not be able to reproduce a reliable prediction. Furthermore, the ability of a model classify patients by the outcome is called as

discrimination (Harrell et al., 1984). However, if there was an interaction effect, the quality of a model may be deteriorated. According to the parsimonious principle, least number of factors that are strongly associated with the outcomes would be appropriate to include in the model (Ridker et al., 2007).

As previously mentioned, adding new innovative biomarkers to existing models has been shown to predict CVD risk with similar predictive ability (Albert et al., 2003; Collaboration, 2008; Greenland et al., 2004). Unfortunately, despite the importance of body composition to date, few studies include body composition component in CVD risk model. Furthermore, there is no gold standard estimator and existing risk scores do not reflect obesity-related mechanism by excluding body composition assessments. Therefore, this proposed study will use the FRS to develop risk scores with improved predictive accuracy.

Specific Aims

The goals of the proposed study were: 1) to determine the optimal body composition assessment to predict CVD risk, 2) to develop CVD risk score by assigning numeric value to each variables, and 3) to test validation of the developed CVD risk model and improvement of predictive accuracy in normal weight and overweight populations.

Aim 1. Select an Optimal Body Composition Assessment

The proposed study identifies an optimal body composition assessment to predict CVD risk. Candidates with body composition assessments were chosen based on preliminary studies (Ashwell & Gibson, 2016; De Koning et al., 2007). Each body composition is evaluated to meet the assumption of survival analysis and multicollinearity tests. Several models including each qualified body composition

assessment from assumption tests and multicollinearity tests are specified. After comparing specified models in regards to predictive accuracy, the final model with the highest capability of prediction was chosen.

> H_1: The model with an optimal body composition assessment will predict CVD risk with better predictive accuracy compared to the reference model without a body composition assessment.

Aim 2. Develop the Final Risk Score

Once the best fit model with the optimal body composition assessment was identified, numerical values will be assigned to each level of variables according to the Hazard Ratio (Mainous et al., 2007).

Aim 3. Test a Validation of Developed Model and Improvement of Predictive Accuracy in Normal Weight and Overweight Populations

The risk score tests two hypotheses. Prior to the test of the first hypothesis, the study report prevalence of BMI misclassification among normal weight and overweight populations derived from a national representative dataset. This result gives a robust rationale for focusing on normal weight and overweight populations. The National Health and Nutrition Examination Survey (NHANES) for years between 1999 and 2006, was used.

This was followed by a validation test of the developed model with the selected body composition assessment. In addition, the improvement of predictive accuracy of the final model was examined in individuals who are normal weight and overweight by using the second group from the Multi-Ethnic Study of Atherosclerosis (MESA).

> H_2: The developed model will be validated in different populations.
>
> H_3: The developed model will show greater predictive accuracy in normal weight and overweight populations compared to the overall population.

CHAPTER 3
METHODS

Data

This study used the Multi-Ethnic Study of Atherosclerosis (MESA) to develop a CVD risk score. The MESA was designed to identify a variety of risk factors as well as subclinical diseases defined as noninvasively detected diseases by the National Heart, Lung and Blood Institution (NHLBI) in July of 2000 (Bild et al., 2002). The MESA is capable of investigating pathophysiology of CVD and subclinical CVD progress such as conditions of the aorta and coronary arteries, and thus can be used in identifying new CVD risk factors and assessing CVD risk as a prevention strategy (Bild et al., 2002).

The MESA derived from a population-based cohort sample composed of 6,814 men and women equally between the ages of 44 and 84 who were free of CVD at baseline. Participants were recruited from six US field centers beginning in 2000, and risk factors and subclinical disease indicators were measured repeatedly for five times with follow-up periods of up to 12 years (Bild et al., 2002). A strength of this cohort is in its racial and ethnic diversity. The population of the cohort was approximately 38% White, 28% African-American, 22% Hispanic, and 12% Asians (National Heart, Lung, and Blood Institute, 2012). This diversity in race and ethnicity allows generalizability of the developed risk score model. This in turn may enhance clinicians' decision making regardless of racial and ethnic differences for CVD prevention in routine clinical settings. Furthermore, the MESA data consists of several body composition factors such as waist circumference, hip circumference, total body fat (kg) and body surface area. These components can examine the impact of the use of body composition and consequently,

it allows for better selecting of an optimal body composition assessment for the development of a CVD risk model.

The MESA was divided into two groups of equal sample size randomly - group 1 and group 2. Group 1 was used to develop a risk score and identify an optimal body composition assessment. Group 2 was used in a validation test of the developed model. Figure A-1 illustrates the flow chart of the final sample size.

The National Health and Nutrition Examination Survey (NHANES) was used to report prevalence of BMI misclassification in the US for adults 44 and older who corresponds to the study population when developing a model. The NHANES is a large, national representative, cross-sectional dataset using a complex stratified multistage probability cluster sample design. The survey design with weighting variables and allows for population estimates calculations. NHANES includes both interviews and standardized physical examinations such as urine, blood analysis and body composition examination. As such, it can assess the health and nutritional status of the non-institutionalized US population (National Health And Nutrition Examination Survey).

The data has been collected annually since the early 1960s. Participants were recruited at the county level. Health interviews were completed in participants' homes and health examinations were conducted in mobile health centers. Data was released after it was cleaned, de-identified, edited, reviewed via a disclosure review board, and finalized. It is now a publicly available data set (National Health And Nutrition Examination Survey, 2014). The NHANES consists of a variety of body composition assessments such as BMI, WC and sagittal abdominal diameter. It includes Dual-energy X-ray Absorptiometry (DXA) data which is widely adopted to measure accurate

body fat mass and bone density, and can identify true body fat mass. The current study used the data for the years of 1999 to 2006. Although the most recent data exists, the data used in this study is the most recent data with a whole body DXA which measures percent body fat (%BF). %BF captures the most accurate body fat mass and excessive fat mass.

Participants

Participants were US adults ages 44 and older who were free of any type of CVD events such as a heart attack, angina, heart failure, resuscitated cardiac arrest and stroke or transient ischemic attack (TIA) at baseline and who have had procedures related to CVD (e.g. CABG, angioplasty, valve replacement, pacemaker or defibrillator implantation or heart surgeries). This specific population was ideal for establishing primary CVD preventive care strategy. Participants who did not have all risk factors (i.e., age, sex, systolic blood pressure, treatment of hypertension, diabetes, total cholesterol, HDL-C and smoking) and who missed at least one of body composition assessments (i.e., waist circumference, waist-to-hip ratio, and waist-to-height ratio and BMI) were excluded.

Outcomes

The primary outcome of the study was the time to the first event of CVD, including nonfatal myocardial infarction, resuscitated cardiac arrest, definite angina, probable angina, stroke, and CVD death. CVD death included stroke death, CHD death, other atherosclerotic death, and other CVD-related death (National Heart, Lung, and Blood Institute, 2012). The outcomes were collected from multiple sources including death certificates, medical records from hospitalizations, autopsy reports, and interviews with participants or physicians, relatives or friends (Bild et al., 2002).

Independent Variables

Eight of the classic risk factors and seven non-invasive body composition assessments were included in the risk score model. All risk factors were modified into categorical variables based on the FRS (Wilson et al., 1998). Table 3-1 illustrated with details.

Risk Factors

For demographics, age was categorized as follows: 44-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75 and older. Sex was used as coded (i.e. men and women). Race or ethnicity factor was excluded.

Hypertension definition followed the initial FRS definition established based on the seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure (Chobanian et al., 2003). Hypertension treatment was a binary variable asking for use of antihypertensive medication. The study sample was limited to individuals who did not use antihypertensive medications. Independently, systolic blood pressure (SBP) was classified into four groups at cut offs of lower than 130, 130-139,140-159 and 160 mm Hg or greater. Diastolic blood pressure (DBP) was categorized into four levels: lower than 85, 85-89, 90-99 and 100 or greater. Systolic blood pressure was defined using four levels: 1) normal (SBP<130mmHg), 2) high blood pressure (SBP: 130-139 mmHg), 3) hypertension stage I (SBP:140-159 mmHg), and 4) hypertension stage II-IV (SBP≥160mmHg).

Total cholesterol and HDL-C were also considered. They were modified into categorical variables based on the third report of the National Cholesterol Education Program (NCEP) (National Heart, Lung, and Blood Institute, 2002). For total cholesterol, cut offs were lower than 160 (4.14mmol/L), 160-199 (2.60-3.36mmol/L), 200-239 (3.37-

4.14mmol/L), 240-279 (6.22-7.24mmol/L) and 280 mg/dL or greater (7.25mmol/L or greater). Thresholds for HDL-C were less than 35 (less than 0.90mmol/L), 35-44 (0.91-1.16mmol/L), 45-49 (1.17-1.29mmol/L), 50-59 (1.30-1.55 mmol/L), and 60 or greater (1.56mmol/L or greater).

Diabetes was a dichotomous variable. People who have ever been diagnosed with diabetes by a doctor or who were under treatment with insulin was categorized as diabetes. People whose blood glucose level measured by fasting plasma glucose (i.e., normal<126mg/dL, 7.0mmol/L) or Hemoglobin A1c of less than 6.5% (48mmol/mol) was defined as normal, and diabetes was defined to people whose blood glucose level of greater or equal to 126mg/dL (7.0mmol/L) or HbA1c of greater than 6.5% (48mmol/mol) (American Diabetes Association, 2016).

Smoking status was categorized into two groups: non-smokers who have never smoked in their lifetime or who have quit smoking for more than 12 months; and current smokers, those who smoked regularly in past 12 months (Wilson et al., 1998). Table 3-1 presents the description of how to operate risk factors for the risk score.

Body Compositions

Seven different body composition assessments were selected on the list of potential variables for the risk score. As can be seen in Table 3-2, four typical body composition assessments were modified into categorical variables with varying cutoffs. Clinical cutoffs used are indicative of most adopted cutoffs in clinical settings and research. For instance, WC and WHR were recoded based on widely adopted clinical cut points. Sex-specific thresholds for WC are 88cm (35 inch) for women and 102cm (40 inch) for men (World Health Organization, 2008). In WHR, cut offs are 0.90 for men and 0.85 for women (World Health Organization, 2008). WtoHR does not have

established universal cut-points. Thus a widely adopted threshold, 0.5, was chosen based on the literature (Ashwell & Gibson, 2016). To account for the potential impact of data distribution of the data, tertile and quartiles were used in developing the model.

Integrated body composition assessments with BMI were also considered. Zhu and colleagues initially used a combination of WC and BMI to examine CVD risk factors and resulted in better performance when using the combined assessments rather than using a single BMI (S. Zhu et al., 2004). Integrated body composition may take into account abdominal obesity which is significantly associated with chronic diseases and effect of regional fat on CVD risk. Therefore, the study used integrated body composition assessments (i.e., WC, WHR and WtoHR) with BMI. Table 3-3 illustrates the classification of integrated assessments.

Table 3-1. Description of Operation for CVD Risk Factors

Variable		Operation	Clinical Range
Demographics	Age (year-old)	Categorical	44-49 50-54 55-59 60-64 65-69 70-75
	Sex	Dichotomous	Men Women
Risk Factors	Hypertension Medication	Dichotomous	Yes No
	Systolic Blood Pressure (SBP, mm Hg)	Categorical	lower than 120 120-129 130-139 140-159 ≥160 mm Hg or greater
	Total Cholesterol (mg/dL, mmol/L)	Categorical	<200 (<3.36mmol/L) 200-239 (3.37-4.14mmol/L) 240-279 (6.22-7.24mmol/L) 280 mg/dL or greater (7.25mmol/L or greater)
	High-Density Lipoprotein Cholesterol (HDL-C) (mg/dL, mmol/L)	Categorical	less than 35 (less than 0.90mmol/L) 35-44 (0.91-1.16mmol/L) 45-49 (1.17-1.29mmol/L) 50-59 (1.30-1.55 mmol/L) 60 or greater (1.56mmol/L or greater).
	Diabetes	Dichotomous	Diabetes: Diagnosed diabetes or abnormal glucose level (FPG>=126mg/dL,7.0mmol/L or HbA1c>=6.5%, 48mmol/mol) Non-diabetes: FPG<126mg/dL,7.0mmol/L HbA1c<6.5%, 48mmol/mol
	Smoking Status	Dichotomous	Yes No

Table 3-2. Description of Sex-Specific Cutoffs of Body Composition Assessments

Body Composition Assessment	Criteria		Cutoffs	
			Men	Women
Body Mass Index (BMI, kg/m^2)	Clinical	Underweight	<18.5	
		Normal	18.5-24.9	
		Overweight	25.0-29.9	
		Obese	>30.0	
	Tertile (%)	33	25.77	25.33
		67	29.40	30.52
	Quartile (%)	25	24.80	24.25
		50	27.53	27.64
		75	30.34	32.24
Waist Circumference (WC, cm)	Clinical		102 (40 inch)	88 (35 inch)
	Tertile (%)	33	94	88.5
		67	103.5	102
	Quartile (%)	25		
		50	91.3	85
		75	98.5	95.5
		50	106.5	106.4
		75		
Waist-to-Hip Ratio (WHR)	Clinical		0.9	0.85
	Tertile (%)	33	0.93	0.86
		67	0.98	0.94
	Quartile (%)	25	0.92	0.84
		50	0.96	0.90
		75	1.00	0.96
Waist-to-Height Ratio (WtoHR)	Clinical		0.9	
	Tertile (%)	33	0.54	0.55
		67	0.59	0.64
	Quartile (%)	25	0.53	0.53
		50	0.57	0.60
		75	0.61	0.67

Table 3-3. Description of Classification of Integrated Body Composition Assessments Combining with BMI

Integrated Body Composition Assessments		Classification				
			BMI			
			Underweight	Normal	Overweight	Obese
BMI & WC	WC	Normal	+	+	+	-
		Obese	-	+	+	+
BMI & WHR	WHR	Normal	+	+	+	-
		Obese	-	+	+	+
BMI & WtoHR	WtoHR	Normal	+	+	+	-
		Obese	-	+	+	+

Statistical Analysis

The statistical analyses were performed using SAS 9.4 (Copyright © 2013 by SAS Institute Inc., Cary, North Carolina) and SUDAAN 11.0 (Cary, North Carolina). The dataset was randomly divided into two groups of equal size. The first group was used to create a risk score and the second group was used to test a validation of the model. First, the descriptive analysis of baseline characteristics for the study population was given using Chi-square tests to examine significant differences in risk factors and the CVD incidents. Prevalence of CVD was presented. Next, several statistical analyses such as c-statistics, Receiver Operating Characteristics (ROC) curves and Hosmer-Lemeshow chi-square tests were performed to estimate discrimination, calibration and goodness-of-fit. Prevalence of BMI misclassification was analyzed. Specific statistics strategies are described as follows.

AIM 1. Select an Optimal Body Composition Assessment.

> H_1: The model with an optimal body composition assessment will predict CVD risk with better predictive accuracy compared to the reference model without a body composition assessment.

Seven body composition assessments were selected based on preliminary studies. Out of seven, four individual measurements were used as an individual measurement; 1) body mass index (BMI, kg/m^2), 2) waist circumference (WC, inch), 3) waist-to-hip ratio (WHR) and 4) waist-to-height ratio (WtoHR). They were modified as categorical variables according to clinical cutoffs, tertile and quartile, as shown in Table 3-2 (World Health Organization, 1995, 2008). In addition, three measurements were integrated forms of body composition assessments with BMI in order to improve classification among normal weight and overweight population who are typically misclassified by the use of BMI only; 5) BMI & WC, 6) BMI & WHR and 7) BMI &

WtoHR. Among WC, WHR and WtoHR, they are highly correlated theoretically and statistically so that these were not transformed as an integrated form. These integrated assessments were also operated as categorical variables based on clinical cutoffs. Table 3-3 described integrated assessments.

In order to choose an optimal body composition assessment, several tests were performed using Group 1. First, bivariate analyses were performed to test significant difference between body composition assessments and the CVD incidents. A statistically significant variable was eligible to test proportionality assumption for Cox proportional hazards analyses. Second, proportionality assumption test of each assessment was performed. Proportional hazards assumption test used Schoenfeld residuals. This test focused on correlation of residuals of variables and time. Specifically, when the correlation of body composition assessment and the time to CVD event is not significant, the assumption was met. It indicated that the body composition assessment did not change over the time to the first CVD event. Lastly, multicollinearity test was conducted. A body composition assessment should not be significantly correlated with conventional risk factors. If a correlation between new factor and existing factors exist, it may cause a discrepancy in estimated coefficients. Multicollinearity can be detected by using variance inflation factors (VIF). A VIF showed how much the existence of correlation between additional factor and existing factors inflates the estimated coefficient. When the VIF is statistically significant, it indicated that multicollinearity does not significantly affect the estimation. These process determined candidates of an optimal body composition assessment for development of CVD risk score.

Several adjusted Cox proportional hazards models including different qualified body composition assessments were specified and analyzed. The reference model containing eight typical CVD risk factors without any body composition assessments was initially analyzed. Following by, models including each selected body composition assessment were analyzed. C-statistics and the area under a curve (AUC) were used to compare discrimination of each model and Hosmer-Lemeshow Chi-square tests were performed to test calibration and goodness-of-fit of the model (Demler, Paynter, & Cook, 2015).

Discrimination represents the ability of the prediction model to distinguish population into two groups - who have the outcomes of interests and who do not have the outcomes (Harrell, Lee, & Mark, 1996). To test discrimination, a c index which is widely used measurement of predictive discrimination was computed in each model. The c index assesses predictive accuracy derived from predictors in a model and it generates probability of how concordant predictions and actual observed outcomes are (Harrell et al., 1996). If the predicted survival time to CVD event is longer for person who actually have never had CVD event in lifetime, the predicted value is concordant with the outcome. A range of the c index value is from .5 which means no predictive discrimination to 1.0 that means perfect discrimination with the outcome (Harrell et al., 1996).

The ROC curve is another technique to present a plot of the tradeoff between sensitivity and specificity at cut off points (Zhu, Zeng, & Wang, 2010). Two curves are drawn-the first curve is 45 degree of diagonal that indicates 50% of sensitivity and 50% of specificity, and the other curve is the predicted curve derived from the proposed

model. The fact that the predicted curve comes to closer to the diagonal curve indicates less accurate of the model, whereas cut off point reaches to the upper left corner of the plot called as perfect classification (Zhu et al., 2010). Given the ROC curve, the Area Under Curve (AUC) indicated predictive accuracy (Zou, O'Malley, & Mauri, 2007). A range of the AUC is between 0 to 1.0. If the AUC is below .5, the model has worse predictive accuracy whereas 1.0 of the AUC indicates perfect accuracy (Zou et al., 2007). The model which had the highest value in c-statistics was chosen as the final risk score model. ROC curves were presented as figures in Appendix.

AIM 2. Develop the Final Risk Score.

To develop a risk score, scores was developed based on adjusted Hazard Ratios of the variables (Mainous et al., 2007). Specifically, numeric points were assigned to each level of the variable. If HR of a certain level of the variable was not significant, it scored as zero.

AIM 3. Test a Validation of Developed Model and Improvement of Predictive Accuracy in Normal Weight and Overweight Population

Prior to the test for validation of the developed model, the prevalence of BMI misclassification was reported by using the NHANES for the years of 1999-2006. The NHANES is the large nationally representative dataset and it allows population estimates of the US population. Particularly, the dataset contains body fat percentage (%BF) measured by the DXA and it allowed to capture true excessive body fat mass. Thus BMI classified population who are normal weight and overweight and %BF identified excessive %BF in each BMI group. Using weighting variable, chi-square test was performed to examine prevalence of BMI misclassification in the US adults aged 44

and older. It gave a robust rationale of following a validation test focusing on normal weight and overweight population.

H_2: The developed model will be validated in different population.

A validation test of the developed model was performed in group 2. C-statistics and the ROC curve were computed and the Hosmer-Lemeshow statistics was also conducted to test calibration and goodness-of-fit.

H_3: The developed model will show greater predictive accuracy in normal weight and overweight population compared to overall population.

The final model was designed to improve predictive accuracy in population at low risk who would appropriately be classified as intermediate high risk. This misclassified population was normal weight and overweight population. Thus, to assess improvement of predictive accuracy in these populations, c-statistics and the AUC for discrimination and the Hosmer-Lemeshow statistics for goodness-of-fit were performed only within normal weight and overweight population in group 2.

CHAPTER 4
RESULTS

The aims of this dissertation were to identify an optimal body composition assessment and to develop a CVD risk score by adding a selected body composition assessment. This study also performed a validation test of the developed risk score in different population and in subpopulation of normal weight and overweight populations only. Simultaneously, the study provided prevalence of BMI misclassification at the population level and gave a rationale for focusing on normal weight and overweight populations. As the main purpose of the use of the body composition assessment was to improve patient classification for those who may be underestimated or overestimated because of BMI misclassification, and this study conducted additional validation test within normal BMI and overweight populations. The findings are presented in four sections, including the results of the descriptive analysis for the study sample and the results of the three aims.

Descriptive Analyses

Total sample sizes were 5,483 from the MESA and 5,595 (representing 55,642,860 US adults) from the NHANES. The MESA sample was randomly divided into two groups of equal sizes. Group 1 (n=2,741) was used to for create the risk score and group 2 (n=2,742) was used for a validation test. Table 4-1 summarizes the comparison of risk factors profile between group 1 and group 2. Both groups showed similar prevalence of CVD (group 1 = 6.8% vs. group 2 = 6.6%, p=0.78). Group 1 was more likely to have men, current smokers, individuals who took hypertension medication and had diabetes; these proportions were not significantly different from group 2. The means of age, systolic blood pressure and HDL-C were slightly higher in group 1,

whereas total cholesterol was lower in group 2. All risk factors except total cholesterol were not significantly different between group 1 and group 2.

Table 4-2 presents the baseline characteristics of risk factors of group 1. Of group 1, 6.8% (n=187) had CVD, a mean age of 61.5 years (MESA), and ranged between 44 and 84 years of age. Individuals with CVD were significantly older than individuals without CVD ($p<.01$). Gender was equally distributed, with men more likely to have CVD than women. The majority of the study population were never smokers (87.5%) and out of the current smokers, 9.7% had CVD. Less than 10% of group 1 had systolic blood pressure over 160mmHg, and they showed the highest likelihood of having CVD. Total cholesterol was not statistically significant in different levels of CVD ($p=.76$). Individuals in group 1 who had diabetes were twice more likely to have CVD ($p<.01$).

Table 4-3 illustrates the baseline prevalence of CVD in each body composition assessment. The mean BMI was 28.26kg/m^2 (SD=5.37) and the majority was overweight (39.4%). Prevalence of CVD was highest in those who were obese (7.3%); however, it was not statistically significant in BMI ($p=.53$). According to tertile and quartile cutoffs, highest ranks showed the highest prevalence of CVD but they were not statistically significant (tertile $p=.44$; quartile $p=.16$). In WC, the mean WC was 97.74cm (SD=14.19). More than half had abdominal obesity according to clinical cutoffs and regardless of any cutoffs, individuals with higher WC showed higher likelihood of having CVD. In WHR and WtoHR, the means were 0.92 (SD=0.08) and 0.59 (SD=0.09), respectively. The majority was obese according to both assessments. Results showed

that the higher WHR or WtoHR were, they were more likely to have CVD. Prevalence of CVD was significantly different in all levels of both assessments.

Integrated assessments with BMI allowed estimating more accurately the prevalence of obesity and CVD in normal weight and overweight populations. Combined BMI and WC showed 20.1% of the sample was classified as overweight while not having abdominal obesity. Particularly, of the overweight population, the proportion of abdominal obesity was slightly lower than normal WC (19.3%). In the normal weight population, 3.8% had abdominal obesity and showed higher CVD prevalence than overweight populations with normal WC (11.5% vs. 6.3%). However, this combined measurement was not statistically significant in CVD (p=.11). In contrast, combined BMI and WHR, and combined BMI and WtoHR showed higher prevalence of normal weight obesity. Of normal the weight population,16.6% were obese based on combined BMI and WHR, and 17.2% were obese according to combined BMI and WtoHR. These proportions were significantly higher than those for the normal weight population with normal range of WHR (p<.01) or WtoHR (p<.01). Normal weight obesity populations showed four times greater likelihood of having CVD than overweight populations having normal range of WHR or WtoHR.

Development of Risk Score

Aim 1. Select an Optimal Body Composition Assessment

Seven body composition assessments were considered as a candidate for CVD risk factor. Body composition assessments involved in the study are described in detail in Table 3-2 and Table 3-3. To determine an optimal body composition assessment, the proportionality assumption test between the body composition assessments and the time to the first CVD event and multicollinearity test between typical risk factors and the

body composition assessments were performed. As can be seen in Table 4-4, none of the body composition assessments were statistically significant with the time to the first CVD event and this indicates that these assessments were assumed to be independent of time. Therefore, all body composition assessments met the proportionality assumption according to the Schoenfeld residuals test. In the multicollinearity tests, variance inflation factors (VIFs) of all body composition assessments were greater than 1, and the quartiles of WHR was the only statistically significant variable (p=.01). This means that the quartiles of WHR was not correlated with the other typical risk factors. Therefore, the quartiles of WHR were selected as the optimal body composition assessment to predict CVD risk in adults. The higher WHR was, the higher the risk of having CVD. With this, individuals who fell in the 4th quartile of WHR were 1.86 times as likely to have CVD.

With the selected body composition assessment, the final model was specified. The final model was compared with the reference model which included only eight typical CVD risk factors. Table 4-5 describes the hazard ratios of each risk factor and c-statistics for discrimination and Hosmer-Lemeshow chi-square test for calibration and goodness-of-fit. Overall, hazard ratios of typical risk factors were similar in both models. The final model showed slightly greater c-statistics and the result of Hosmer-Lemeshow test was not statistically significant (p=0.45). Thus, we failed to reject the null hypothesis that predicted CVD events were not significantly different from the observed events. Also there was no significant lack of fit for the final model. That is, the final model could predict the CVD risk successfully. The ROC curves were plotted in Figure B-1. The AUC of the reference model was 0.757 and the AUC of the final model with the quartiles of

WHR was 0.763. However, as a result of the chi-square test, the final model was not significantly different from the reference model (p=.13).

Aim 2. Develop the Final Risk Score

The final risk score was specified with the quartiles of WHR. Numeric scores were determined based on hazard ratios. As can be seen in Table 4-6, the total score is 24 points and minimum score is zero. If HR of a level of variables was not statistically significant, that level was scored as zero. For instance, all levels of HDL-C were not significant and all levels were scored zero. For the quartile of WHR, a score of 4th quartile was 2. That is, men who have greater than 1.00 or women who have greater than 0.96 had 2 points.

Aim 3. Test a Validation of the Developed Model and Improvement of Predictive Accuracy in Normal Weight and Overweight Populations

Prevalence of BMI misclassification in US adults was shown in Table 4-7. The unweighted sample size was 5,595 representing 55,642,860 US adults aged 44 and older. Of normal weight populations, 65.6% of US adults who had excessive %BF were misclassified as healthy. Moreover, although 8.4% of the overweight population had normal %BF, they were considered to be unhealthy. Women who were normal weight (70.4%) were likely to have excessive %BF and the majority of men who were overweight showed normal range of %BF (96.2%). Thus, a substantial proportion of US adults, particularly normal weight populations, was misclassified according to the BMI.

To assess the performance of the developed risk score, two validation tests were conducted. First, the risk score was validated in remaining random split of the data, group 2 (n=2,742). Since group 2 presented similar characteristics as group 1 (See Table 4-1), it represented an appropriate study sample for a validation test. The final

model was validated as moderately good performance (AUC, 0.746) and its calibration was not significant (p=.24) (See Table 4-8 and Figure C-1). We failed to reject the null hypothesis that states there is no significant difference between observed events and predicted events of the outcome.

The developed risk score was tested in normal weight and overweight populations only. Results showed better goodness-of-fit in normal weight and overweight populations (AUC, 0.771), as shown in Table 4-8 and Figure D-1. The Hosmer-Lemeshow test also failed to reject the null hypothesis that indicated there is no significant difference between observed and predicted events of the outcome in normal weight and overweight populations. In conclusion, the developed risk score performed better in normal weight and overweight populations.

Table 4-1. Comparison of Characteristics between Group 1 and Group 2

Factor	Group 1	Group 2	p-value
Sample size	2741	2742	
CVD prevalence	6.8	6.6	.78
Age (years)	61.5	61.4	.87
Male (%)	50.3	49.7	.70
Current smoking (%)	50.6	49.4	.74
Systolic Blood Pressure (mmHg)	133.6	133.3	.61
Hypertension Medication (%)	51.5	48.5	.09
Total Cholesterol (ml/dL)	193.5	194.9	.17
HDL- Cholesterol (ml/dL)	51.2	50.7	.23
Diabetes Mellitus (%)	51.9	48.1	.31

Table 4-2. Baseline Profile of CVD Risk Factors of Study Population from Group 1 of the Multi-Ethnic Study of Atherosclerosis (MESA) (n=2,741)

Predictors	Total Population	Cardiovascular Disease Event (%)		p-value
		Yes	No	
Sample size	2741	187	2554	<.01
Age (Mean, year-old)*	61.5	67.1	61.1	<.01
Gender*				
Male	47.8	9.4	90.6	<.01
Female	52.2	4.5	95.5	
Smoking status*				
Never smoker	87.5	6.4	93.6	.03
Current smoker	12.5	9.7	90.4	
Systolic blood pressure (mmHg)*				
<130	45.5	4.3	95.8	<.01
130-139	21.7	5.7	94.3	
140-159	24.1	10.3	89.7	
≥160	8.8	13.3	86.7	
Hypertension Medication*				
No	62.9	5.0	95.0	<.01
Yes	37.1	9.9	90.1	
Total Cholesterol (mg/dL)				
<200	60.6	6.8	93.3	.76
200-239	30.2	6.6	93.4	
≥240	9.2	7.9	92.1	
High-Density Lipoprotein Cholesterol (HDL-C)* (mg/dL)				
<35	21.2	9.5	90.5	<.01
35-59	55.0	6.8	93.2	
≥60	23.8	4.4	95.6	
Diabetes*				
No	88.0	6.0	94.0	<.01
Yes	12.0	12.8	87.2	

* Statistically significant at .05

Table 4-3. Baseline Characteristics of Body Composition of Group 1 from the Multi-Ethnic Study of Atherosclerosis (MESA) (n=2.741)

Variable		Total Population	Cardiovascular Disease Event (%)		p-value
			Yes	No	
BMI					
Clinical Cutoffs	Underweight	0.5	0.0	100.0	.53
	Normal	29.1	6.0	94.0	
	Overweight	39.4	7.1	92.9	
	Obese	31.0	7.3	92.7	
Tertile	1st	33.4	6.1	93.9	.44
	2nd	34.6	6.8	93.3	
	3rd	32.0	7.6	92.4	
Quartile	1st	25.8	5.1	94.9	.16
	2nd	24.8	6.8	93.3	
	3rd	25.5	7.6	92.4	
	4th	23.9	7.9	92.1	
Waist Circumference					
Clinical Cutoffs*	Normal	47.4	5.8	94.2	.04
	Abdominal Obesity	52.6	7.8	92.2	
Tertile*	1st	33.4	4.1	96.0	<.01
	2nd	34.3	8.1	91.9	
	3rd	32.4	8.3	91.7	
Quartile*	1st	25.8	3.8	96.2	<.01
	2nd	24.8	6.8	93.2	
	3rd	25.2	8.5	91.5	
	4th	24.2	8.3	91.7	
Waist-to-Hip Ratio (WHR)					
Clinical Cutoffs*	Normal	23.8	3.1	96.9	<.01
	Obesity	76.2	8.0	92.0	
Tertile*	1st	33.2	4.5	95.5	<.01
	2nd	34.3	6.2	93.8	
	3rd	32.5	9.9	90.1	
Quartile*	1st	26.2	3.8	96.2	<.01
	2nd	25.9	5.9	94.1	
	3rd	24.0	7.2	92.9	
	4th	24.0	10.8	89.2	
Waist-to-Height Ratio (WtoHR)					
Clinical Cutoffs*	Normal	14.1	2.6	97.4	<.01
	Obese	85.9	7.5	92.5	
Tertile*	1st	33.4	4.3	95.7	<.01
	2nd	33.4	7.3	92.7	
	3rd	33.3	8.9	91.1	
Quartile*	1st	26.9	3.5	96.5	<.01
	2nd	25.8	6.9	93.1	

Table 4-3. Continued

Variable		Total Population	Cardiovascular Disease Event (%)		p-value
			Yes	No	
Waist-to-Height Ratio (WtoHR)					
Quartile	3rd	23.1	8.2	91.8	
	4th	24.2	9.1	90.9	
BMI & WC					
Underweight		0.5	0.0	100.0	.11
Normal & normal		25.3	5.2	94.8	
Normal & obese		3.8	11.5	88.5	
Overweight & normal		20.1	6.3	93.7	
Overweight & obese		19.3	8.0	92.1	
Obese		31.0	7.3	92.7	
BMI & WHR*					
Underweight		0.5	0.0	100.0	<.01
Normal & normal		12.5	2.9	97.1	
Normal & obese		16.6	8.3	91.7	
Overweight & normal		7.8	2.8	97.2	
Overweight & obese		31.6	8.2	91.8	
Obese		31.0	7.3	92.7	
BMI & WtoHR*					
Underweight		0.5	0.0	100.0	.02
Normal & normal		11.9	2.8	97.3	
Normal & obese		17.2	8.3	91.7	
Overweight & normal		1.7	2.2	97.8	
Overweight & obese		37.7	7.4	92.7	
Obese		31.0	7.3	92.7	

* Statistically significant at .05

Table 4-4. Results of Proportionality Assumption Test with Body Composition Assessments and the Time to the First CVD Event in Group 1 Using the Multi-Ethnic Study of Atherosclerosis (n=2,741)

Body Composition Assessments	Proportionality p-value	VIF VIF	VIF p-value
BMI			
Clinical Cutoffs	0.52	1.15	0.62
Tertile	0.52	1.13	0.77
Quartile	0.53	1.15	0.51
WC			
Clinical Cutoffs	0.51	1.21	0.07
Tertile	0.53	1.12	0.16
Quartile	0.54	1.13	0.20
WHipR			
Clinical Cutoffs	0.53	1.12	0.28
Tertile	0.52	1.13	0.12
Quartile*	0.53	1.14	0.01
WHeightR			
Clinical Cutoffs	0.53	1.09	0.33
Tertile	0.53	1.13	0.21
Quartile	0.54	1.15	0.11
BMI&WC	0.51	1.16	0.92
BMI&WHipR	0.52	1.17	0.84
BMI&WHeightR	0.53	1.16	0.78

* Statistically significant at .05

Table 4-5. Results of Comparison of CVD Risk Models Using Cox Proportional Hazard Regressions

Predictor	A (Reference model)		B (Quartile of WHR)	
	HR	95% CI	HR	95% CI
Age (years)				
<50	1.00	Referent	1.00	Referent
50-54	3.31	0.94-11.63	3.20	0.91-11.26
55-59	7.09	2.15-23.40	6.72	2.03-22.19
60-64	5.97	1.76-20.20	5.45	1.61-18.49
65-69	11.59	3.57-37.58	10.70	3.29-34.77
>=70	12.41	3.85-39.97	11.25	3.48-36.31
Sex				
Male	1.97	1.42-2.73	2.07	1.49-2.87
Total Cholesterol (mg/dL)				
<200	1.00	Referent	1.00	Referent
200-239	1.34	0.97-1.87	1.31	0.94-1.83
>=240	1.75	1.08-2.86	1.74	1.07-2.83
HDL-C (mg/dL)				
<40	1.27	0.90-1.78	1.79	0.84-1.67
40-59	1.00	Referent	1.00	Referent
>=60	0.73	0.48-1.12	0.77	0.50-1.19
Systolic Blood Pressure (mmHg)				
<130	1.00	Referent	1.00	Referent
130-139	0.91	0.58-1.41	0.88	0.57-1.36
140-159	1.58	1.09-2.30	1.54	1.06-2.24
>=160	2.04	1.29-3.24	1.96	1.23-3.10
Anti-Hypertension Medication				
Yes	1.39	1.03-1.89	1.37	1.01-1.87
Diabetes				
Yes	1.70	1.19-2.43	1.56	1.09-2.24

Table 4-5. Continued

Predictor	A (Reference model)		B (Quartile of WHR)	
	HR	95% CI	HR	95% CI
Smoking				
Current Smoker	2.12	1.44-3.12	2.09	1.42-3.08
WHR quartile				
1st	-	-	1.00	Referent
2nd	-	-	1.21	0.74-1.98
3rd	-	-	1.33	0.82-2.15
4th	-	-	1.82	1.15-2.89
c statistics	0.757		0.763	
Hosmer-Lemeshow Chi-square	0.07		0.45	
Chi-square	Referent		0.13	

* Statistically significant at .05
** Statistically significant at .01

Table 4-6. Scoring on the Final Risk Model

Factor	HR	95% CI	Points
Age (years)			
45-49	1.00	-	0
50-54	3.20	0.91-11.26	0
55-59	6.72	2.03-22.19	7
60-64	5.45	1.61-18.49	5
65-69	10.70	3.29-34.77	11
70-74	11.25	3.48-36.31	11
Gender			
Female	1.00	-	0
Male	2.07	1.49-2.87	2
Systolic Blood Pressure			
<130	1.00	-	0
130-139	0.88	0.57-1.36	0
140-159	1.54	1.06-2.24	2
>=160	1.96	1.23-3.10	2
Hypertension Medication			
No	1.00	-	0
Yes	1.37	1.01-1.87	1
Total Cholesterol			
<200	1.00	-	0
200-239	1.31	0.94-1.83	0
>=240	1.74	1.07-2.83	2
HDL-C			
<40	1.79	0.84-1.67	0
40-59	1.00	-	0
>=60	0.77	0.50-1.19	0
Diabetes			
No	1.00	-	0
Yes	1.56	1.09-2.24	2
Smoking Status			
No	1.00	-	0
Yes	2.09	1.42-3.08	2
Waist-to-Hip Ratio (WHR)			
1st	1.00	-	0
2nd	1.21	0.74-1.98	0
3rd	1.33	0.82-2.15	0
4th	1.82	1.15-2.89	2

Table 4-7. Summary of Body Mass Index Misclassification in US Adults aged over 44 and Older Using National Health and Nutrition Examination Survey (NHANES), 1999-2006 (unweighted n=5,595, weighted n=55,642,860)

		Prevalence of misclassification BMI	
		Normal weight	Overweight
% Body fat	Normal	34.4	8.4
	Obese	65.6	91.6

Table 4-8. Summary of a Validation Test in Group 2 and Subpopulation of Normal weight and Overweight population only in Group 2 Using the Multi Ethnic Study of Atherosclerosis (MESA)

	Group 2 (n=2,742)	Normal weight and overweight population (n=1,815)
Discrimination		
c statistic	0.746	0.771
Calibration		
Hosmer-Lemeshow chi-square statistics	0.24	0.76

CHAPTER 5
DISCUSSION

Discussion

This study developed the CVD risk score by adding the quartiles of WHR. We found that the quartile of WHR was a significant and the optimal predictor of CVD risk estimation. Adding the quartiles of WHR resulted in better performance while the improvement was not statistically significant from the reference model which excluded the quartile of WHR. The developed risk score was validated in group 2 with moderately good performance. It especially showed greater improvement of performance particularly among normal weight and overweight populations.

This study is valuable in the sense of improvement of performance in normal weight and overweight populations who are usually misclassified by the use of BMI only. This study provided additional clinical value to the typical CVD risk score by integrating the optimal body composition assessment. Furthermore, it may suggest an alternative assessment to define obesity when considering CVD in clinical settings.

Body Composition Assessment

The developed risk score selected WHR as the optimal body composition assessment in CVD risk assessment. Its selection was validated with the preliminary study that WHR played a significant role in predicting CVD and mortality (Cameron et al., 2012). Moreover, to date, of 363 existing CVD risk scores, 29% selected BMI as a predictor. To our knowledge, this is the first study that equipped WHR to the risk score and resulted in better performance to predict CVD risk. Adding WHR is innovative approach to account for current obesity trend. In 2012, more than half of US adults had abdominal obesity and its prevalence has significantly increased since 1999 (Ford,

Maynard, & Li, 2014). Abdominal obesity was strongly associated with CVD risk rather than total body fat (Myint, Kwok, Luben, Wareham, & Khaw, 2014). The risk of abdominal obesity resulted in twice the risk of mortality in normal weight populations (Karine R Sahakyan et al., 2015). Therefore, a proxy considering abdominal obesity became a critical role in CVD risk estimation. In addition, hip circumference also played a role as an independent factor in CVD risk and mortality (Heitmann, Frederiksen, & Lissner, 2004; Lissner, Björkelund, Heitmann, Seidell, & Bengtsson, 2001). Epidemiological studies have shown that hip circumference was associated with CVD incidents and mortality and it was correlated with abdominal obesity (Cameron et al., 2012; Heitmann et al., 2004). To account for the association of hip circumference with CVD, the WHR may account for body fat accumulation over the body compared to waist circumference only. In addition, since only 33.7% of normal weight population had abdominal obesity, abdominal obesity may not be commonly observed in normal weight population (Mainous et al., 2016). With this reason, the use of waist circumference may miss normal weight individual with excessive body fat again. However Ramsaran and Maharaj showed that WHR was associated with normal weight obesity population (Ramsaran and Maharaj, 2017). Therefore, the WHR may capture body fat accumulation over the body with improved accuracy particularly in normal weight population and it may contribute to enhancing CVD risk estimation.

Normal weight obesity defined by %BF (e.g., 25% of men and 32% of women) integrated with BMI (18.5-24.9kg/m^2) in middle-aged adults may be associated with sarcopenia in older adults. Sarcopenia represents age-associated loss of muscle mass (Stenholm, Harris, Rantanen, Visser, Kritchevsky & Ferrucci, 2009). It may cause

physical function impairment and poor health states in older adults (Stenholm et al., 2009). If adults in middle age who are currently normal weight obese maintain excessive body fat during their lifetime without exercise, they will be likely to have higher rates of abnormal CVD risk and mortality (Batsis et al., 2013). Such individuals, particularly because they have normal range of BMI, are likely to miss an opportunity to receive preventive care on time. Thus, their CVD risk may go untreated and place them at greater risk of adverse CVD outcomes. Furthermore, CVD risk factors including hypertension and diabetes were associated with sarcopenia (Chin et al., 2013; Han, 2017). Schrager and colleagues articulated that inflammatory markers such as CRP, IL-18 were associated with excessive body fat as well as muscle strength (Schrager et al., 2007). These inflammatory markers may elevate CVD risk factors and individuals with sarcopenic obesity may be more likely to present CVD. Moreover, more than 20% of US older adults had sarcopenia, and its prevalence is projected to increase (Batsis et al., 2013). Therefore, normal weight obesity as a potential factor of sarcopenia should be paid attention to prevent CVD in older adults.

Creating risk score is a complex process of consideration with clinical significant and statistical significance. The developed risk score incorporated categorical forms of predictors. Categorical form is easy and simple way to classify populations at risk on the basis of clinical guidelines. Clinicians use clinical cutoffs of a categorical factor to inform patients to achieve for preventing chronic disease risk. However, statistics-wise, categorical form of a predictor is not frequently used because of the principle of statistical significance. For instance, the initial FRS attempted to include BMI as a categorical form and simultaneously, BMI was excluded due to no statistical significance

(Wilson et al., 1998). The updated risk score, however, added BMI as a significant predictor to the risk model and BMI was incorporated as a continuous form (Wilson et al., 2008). QRISK, which is widely used in the UK also adopted BMI by including interaction term of BMI and age whereas the ASCVD risk score excluded BMI due to non-significance (Goff et al., 2014; Hippisley-Cox et al., 2007). This indicates that the form of a predictor played a critical role in determining risk factor in risk assessment. Although statistical significance should be considered when meeting the assumption of regression analysis, it calls into question how to deal with a gap between a statistical significance and a clinical significance in selecting a risk score in risk score.

Limitation In Terms of a Body Composition Assessment. This study has some limitations in regards to body composition assessments. First, the current study selected quartiles of WHR as a threshold instead of most adopted cutoffs. Some epidemiological studies found that quartiles of WHR showed more accurate power to predict CVD and mortality compared to BMI (Myint et al., 2014; Sokol et al., 2016). This approach, however, may raise concern about inconsistent cutoffs in different populations. Lear and colleagues argue that cutoffs of WHR associated with CVD risk factors were different in racial and ethnic groups (Lear, James, Ko, & Kumanyika, 2010). More specifically, Asians who were likely to have higher visceral fat and higher risk of CVD showed lower cutoffs of WHR than European and Caucasians (Lear et al., 2010). Also recent epidemiological studies reported significant association of a high risk for chronic diseases with lower BMI in Asians and suggest race-specific BMI cutoffs based on an association of chronic disease risk (Raji et al., 2001). To take into account race-specific physiological characteristics, the current study used a longitudinal dataset

composed of diverse ethnic participants. This reduced bias when determining cutoffs of quartiles. Further efforts would be needed to establish reliable clinical cutoffs of WHR with diverse population-based datasets.

Second, this study selected non-invasive and conventional body composition assessments as a proxy for obesity; they are also unable to directly measure the amount of body fat. Using high-technic equipment such as BIA or DXA allows for the most accurate body fat mass measurements. These techniques have not been adopted for use in clinical settings because of the high costs for the sole purpose of screening and absence of health insurance coverage by most health insurers. This study showed a substantial proportion of normal weight populations were classified as healthy on the basis of %BF. WHR may miss some populations with true excessive body fat. In future study, %BF may play a critical role to capture true excessive body fat over the body and contribute to identifying obese population who has true excessive body fat. By adding %BF to the risk score, the score will estimate more accurate risk score for population who are normal weight obesity population or overweight population who are usually misclassified by non-invasive measurement. Thus, a cost-effective body composition assessment which is able to measure accurate body fat mass is needed. Appropriate health care reimbursement policies are also needed. Future research should apply more accurate body composition assessments to predict CVD risk.

Risk Factors

This study used eight typical CVD risk factors that have been used in most risk scores. To date, in addition to the WHR, there have been several attempts to investigate the effect of variety body composition types on CVD. A recent exploratory study revealed that neck circumference was positively associated with CVD risk factors

(Preis et al., 2010). Neck circumference represented upper body subcutaneous fat which is associated with insulin resistance and high LDL-C (Koutsari, Snozek, & Jensen, 2008). While it may be a novel marker of CVD, weak correlations of less than .50 with total cholesterol, LDL-C and glucose should be considered to be a significant CVD risk factor (Ben-Noun & Laor, 2003). Other studies focused on sagittal abdominal diameter (SAD) when considering CVD risk (Kahn et al., 2014; Pouliot et al., 1994; Sampaio et al., 2007). SAD represented a simple non-invasive measurement of visceral fat located around the organs (Zamboni et al., 1998). Visceral fat has been paid attention as a critical cause of systemic inflammation and was significantly associated with CVD (Fontana et al., 2007; Mahabadi et al., 2009). Individuals with high visceral fat showed 1.83 times higher odds of stroke (Mahabadi et al., 2009). Thus, in order to reflect the risk of visceral fat, future risk score can be developed by adding SAD. As mentioned above, a direct body fat measurement would be the best way to assess CVD with improved accuracy. While %BF is a representative surrogate of body fat mass, it requires a technician and high technique machines such as MRI and CT. Future accessible and cost effectiveness measurement of body fat mass may be a key in measuring CVD risk in the future.

Some physiological biomarkers have been added to the CVD risk score. Cardiorespiratory Fitness (CRF) is defined as the ability of the circulatory and respiratory system to supply oxygen as energy source during physical activity (Caspersen, Powell, & Christenson, 1985). It has been discussed as a key factor of CVD and mortality in the light of “fat but fit” theory (Blair et al., 1995; Hainer, Toplak, & Stich, 2009). Regardless of obesity, improved CRF was associated with reduced

mortality rate about 44% in men (Blair et al., 1995). With this advantage, Gander and colleagues recently proposed updating the FRS by adding CRF (J. C. Gander et al., 2017). In addition, Greenland and colleagues added coronary artery calcium score (CACS) to the FRS (Greenland et al., 2004). CACS is the measurement of cumulative calcium on the artery that causes ASCVD and higher CACS was associated with twice higher risk of ASCVD than (Keelan et al., 2001). It is noted that these risk scores contributed to emphasizing the importance of physiological markers in predicting CVD risk.

Lifestyle factors were also considerable risk factors of CVD. The fact that lifestyle factors were modifiable prior to the CVD occurrence is an advantage in prevention for asymptomatic populations. Physical activity has been an increased focus because of the increase in sedentary lifestyles. According to Mainous and colleague, individuals with abnormal blood glucose were less likely to perform exercise despite normal weight (Mainous et al., 2017). To take into account the significance of lifestyle factors, Chiuve and colleague created a lifestyle-based prediction model and incorporated CVD risk score to examine the association between lifestyle factors and CVD risk factors (Chiuve et al., 2014). They considered dietary factors and seven behavioral factors (i.e., exercise, sleep duration, sedentary lifestyle, smoking, alcohol, BMI and WC) and found that unhealthy lifestyles were significantly associated with elevated risk of CVD (Chiuve et al., 2014; Gooding et al., 2017). Levesque and colleagues also created a simpler lifestyle risk score and showed that a high risk lifestyle score significantly increased elevated CVD risk factors (Levesque, Poirier, Despres, & Almeras, 2017). Healthy lifestyle affects body compositions and it may be a key in obesity prevention. Therefore,

on the basis of current physical activity and nutrition guidelines, it would be worth considering that healthy lifestyle factors can be integrated to the CVD risk score.

Limitation In Terms of Risk Factors. This study has a limitation in terms of selecting risk factors. The developed risk score is the use of typical CVD risk factors without considering new biomarkers and lifestyle factors. As mentioned above, modifiable behavioral risk factors have been shown to prevent CVD and were effective in predicting elevated CVD risk (Chiuve et al., 2014; Gooding et al., 2017). Other research has taken into account socioeconomic status, such as poverty, as a risk factor and has provided insights for prevention strategies using a societal approach (Hippisley-Cox et al., 2007). Recent study has attempted to add genetic factors to the risk score (Knowles et al., 2017). It is important to consider the diverse dimensions of CVD prevention as a key role in improving predictive accuracy.

Risk Score

This study developed a new CVD risk score by adding a body composition assessment to improve decision making for clinicians. Previous studies have investigated socioeconomic characteristics and physiological features of high CVD risk populations by using CVD risk score (Gulliford et al., 2017; Patel, Taksler, Hu, & Rothberg, 2017; Robinson, Jackson, Wells, Kerr, & Marshall, 2017). Robinson and colleagues found that many primary care physicians used estimated CVD risk score when making a decision (Robinson et al., 2017). Use of CVD risk score in primary care setting played a significant role in identifying high risk populations who were unaware of their CVD risk because of missed opportunities to undergo health check (Gulliford et al., 2017). This showcased the value of the developed risk score in identifying populations with elevated CVD risk who did not get CVD risk estimates at primary care settings

because of their healthy body weight ranges. Moreover, by using the non-invasive body composition assessment, the use of the improved risk score may provide an opportunity to check the potential for CVD risk in a primary care clinical setting. There might be some challenges to use the risk score in primary care setting. Unless the risk score is not required to use in primary care setting, patients may not estimate their risk without physician's suggestion. According to Gulliford and colleagues, given an opportunity to estimate their CVD risk by a primary care physician, most patients at high risk ended up recognizing their CVD risk (Gulliford et al., 2017). Moreover, it is unknown that primary care physicians would widely utilize body composition assessments in addition to BMI in primary care setting. Especially, while the WHR was adopted to the current risk score, it may not be universally adopted in primary care setting. To date, limited studies have investigated the use of CVD risk score and the use of body composition assessments when providing treatment at primary care settings. Therefore, additional studies should investigate the use of risk score in health care settings and evaluate the impact of risk score on CVD prevention care.

The developed risk score showed moderately good ability to predict CVD compared to the other risk scores. For instance, AUC of the original FRS was .75 and AUC of the updated risk score with BMI developed by Wilson and colleagues was .81 (Wilson et al., 1998; 2008). The lowest AUC was the risk score with CACS developed by Greendland and colleagues and it was .68 (Greenland et al., 2004). In addition, when the CRF was added to the FRS, the AUC was .80 (Gander et al., 2017). AUC of the most recent risk score developed by the ACA/AHA was .71 (Muntner et al., 2014).

Therefore, based on these results of goodness-of-fit, the developed risk score with the quartile of WHR was proved to perform moderately good.

The developed CVD risk score has common points to metabolic syndrome. Metabolic syndrome is defined as presence of at least three CVD risk factors including insulin resistance/hyperglycemia, abdominal obesity, hypertension and dyslipidemia (American Heart Association, 2016b). To diagnose metabolic syndrome, the WHO, the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III and International Diabetes Federation (IDF) released comprehensive criteria (Huang, 2009). Mostly, they provided clinical thresholds of each CVD risk factors (e.g., waist circumference, triglcerides, HDL-C, blood pressure and fasting glucose) and counted a number of occurrences of these metabolic disorders. When people who had more than three metabolic disorders, they are diagnosed to metabolic syndrome (Huang, 2009). There are some similarities between metabolic syndrome criteria and the CVD risk score used in this study. First, the purpose of both methods is to classify patients who are at low/high risk of chronic disease. Second, both utilize an adiposity measurement; the criteria of metabolic syndrome adopted waist circumference and the current developed risk score used the WHR. They considered the impact of excessive body fat accumulation on CVD risk factors. On the other hand, there are some differences. While they both used a body composition assessment, metabolic syndrome focuses on abdominal obesity instead of body fat accumulation over the body. The current developed risk score used the WHR and it may consider total body fat accumulation. Thus, it will contribute classifying misclassified population particularly, normal weight population. Next difference is risk estimation. The CVD risk score estimates risk by

weighing a level of each risk factor while metabolic syndrome simply counts numbers of risk factors. The risk score provides more accurate potential risk estimates and healthcare providers may suggest effective treatment or preventive care services. Lastly, the outcomes are different. Metabolic syndrome diagnoses metabolic disorders that significantly link to CVD. It does not provide how much potential risk of CVD people have. The risk score, however, directly provides CVD risk estimates. It helps not only to classify population at low, intermediate and high, but also to provide objective evidence to initiate appropriate preventive care service.

The developed risk score may incorporate clinical guidelines for preventive care. Current clinical guidelines use risk score as a criteria when recommending preventive care services. The most recent ACC and AHA guideline suggest a clinical threshold of 7.5% of 10-year CVD risk for initiation of statin treatment (Goff et al., 2014). The USPSTF recommends a routine lipid screening and CVD risk assessment for individuals with an estimated 10-year CVD risk of 10% or greater (USPSTF, 2016). These efforts may encourage the use of CVD risk score in clinical settings and may result in clinicians using this tool when delivering care. However, both guidelines used the ASCVD risk score that did not include a body composition assessment and may miss some populations with elevated CVD risk. Since these guidelines focus on individuals at high risk of typical CVD risk factors, some people who are at intermediate risk may miss an opportunity to assess their CVD risk. Consequently, they may miss an opportunity to receive preventive care services in advance. A consequence of missing those opportunity can elevate CVD incidents. Additionally, as presented above, the clinical thresholds were not consistent between the two guidelines. More studies are

needed to provide sufficient evidence to establish universal cutoffs by using the updated risk score.

Limitation In Terms of Risk Score. Performance of the developed risk score was not statistically significant with the reference model which excluded the quartiles of WHR whereas the predictive accuracy was slightly improved. It was corresponding to the initial FRS that attempted to add categorical form of BMI to the risk score (Wilson et al., 1998). Despite multiple evidences of significant association between BMI and CVD, BMI did not play a significant role when added to the risk score. Likewise, although some epidemiological studies have shown that WHR was significantly associated with CVD and CVD risk factors (De Koning et al., 2007; Myint et al., 2014), adding the WHR did not improve the predictive accuracy significantly. To account for statistical significance, further study may examine invisible relationship between the WHR and CVD risk factors and reflect this relationship when updating the risk score.

The developed risk score focused on middle age of adults over the age of 44 who were the target population for primary CVD preventive care services (USPSTF, 2016). Middle-age adults showed elevated risk of chronic disease and CVD (Egan et al., 2010; Menke et al., 2015). Particularly, they had the highest prevalence of obesity in the US (Flegal et al., 2016). As a result, the majority of risk scores, including the current risk score were created by focusing on this population. However, some studies have argued the optimal timing of estimating CVD risk is for the purpose of prevention (Gooding et al., 2017; Liu et al., 2012; Shah et al., 2016). As previously stated, even though this middle age group has been focused on as a high-risk group, CVD risk estimation in middle age may be too late in preventing CVD risk. The prevalence of obesity in US adolescents

has jumped to 20.6% and its prevalence in young adults between the ages of 20 and 39 has reached 34.3% in 2014 (Flegal et al., 2016; Ogden et al., 2016). These younger populations are a potential high risk group for premature CVD risk. Thus, it is recommended that obesity prevention strategy for young adults to combat increase CVD prevalence. Several studies suggest healthy lifestyle interventions through young adulthood (Gooding et al., 2017; Liu et al., 2012; Shah et al., 2016). Higher fitness levels and maintaining healthy lifestyles in young adulthood have been found to be strongly associated with lower risk of CVD (Liu et al., 2012; Shah et al., 2016). Furthermore, the most recent USPSTF guideline include that primary care physicians can offer behavioral counseling to individuals who are not overweight or obese and who do not have any CVD risk factors (e.g., diabetes, hypertension and dyslipidemia) for CVD prevention treatment (Grossman et al., 2017; U.S. Preventive Services Task Force, 2012). While this population has a small net benefit from behavioral counseling, it is a valuable opportunity to modify current lifestyle habits in order to maintain a healthy lifestyle and prevent CVD risk (Grossman et al., 2017). Further risk score should also reflect these changes and need to be updated for young adults. Additional studies should investigate an optimal timing to estimate CVD risk score for the purpose of prevention.

Next, an external validation test of the model was not performed. The current study performed an internal validation test using a random split of the dataset. While it proves an accurate predictive accuracy of the model in different study populations, it still lacks generalizability in applying this risk estimation to other population groups. The developed risk score was created from middle age adults. It may underestimate the risk

of CVD for young adults. Therefore, the developed risk score needs to be tested in diverse populations including young adults.

Implication

Cardiovascular Disease (CVD) risk score is a pragmatic tool for both asymptomatic population and healthcare providers. For healthcare providers, it may improve clinical decision making. For asymptomatic population, it allows examine their potential CVD risk and receive preventive care services before the onset of CVD. Particularly, it can be used in primary care setting in which is a gateway of health care. Primary care physicians may provide appropriate preventive care in a timely manner and people can save costs for seeking a cardiologist.

The proposed model may contribute to classifying populations at low risk who would be intermediate high CVD risk because of BMI misclassification. This population has been neglected in receiving appropriate health care or disease prevention strategies such as screening or timely counselling on time because they are not a target population in clinical guidelines. Thus, the developed risk score may contribute in classifying populations previously neglected from the CVD risk assessments. Also, current clinical guideline may need to expand the target population for CVD screening.

Lastly, focusing on the body composition assessment can contribute to updating current healthcare policy. In 2016, The US Equal Employment Opportunity Commission (EEOC) issued a new rule about Employer Wellness program offered by the Affordable Care Act. The wellness program offers health promotion and chronic disease preventive care services to employers with subsidies. However when participants fail to meet a certain outcome such as normal weight, they will be penalized about 30% of costs of health insurance coverage. The strategy of adding the WHR as a substitute for BMI may

contribute to classifying population with enhanced performance and prevent unfair penalty.

CHAPTER 6
CONCLUSION

This study developed a non-invasive and affordable CVD risk score for populations aged 44 and older by adding the quartiles of WHR as the optimal body composition assessment. The risk score included eight classical risk factors (age, sex, diabetes, hypertension medication, systolic blood pressure, total cholesterol, HDL-C and smoking) and the quartiles of WHR. It was designed to improve predictive accuracy particularly for normal weight and overweight populations who were usually misclassified by the use of BMI only and who were neglected in receiving appropriate preventive care. As obesity becomes epidemic in public health, obesity-related measurement may play a key role in CVD risk assessment. Thus, adding WHR may be advantageous for primary care physicians when assessing CVD risk and may provide more accurate CVD risk estimations. WHR is a stronger predictor of CVD than BMI, and it may account for abdominal obesity which has also become epidemic in the US (De Koning et al., 2007; Ford et al., 2014). Therefore, the developed risk score may contribute to accounting for most recent trend of obesity in US adults and providing scientific evidence to establish efficient health promotion strategy to prevent CVD risk. The developed risk score may also aid clinicians, specifically primary care physicians, in predicting future CVD risk with objective evidence and improve overall decision making.

APPENDIX A
FLOW CHART OF STUDY POPULATION

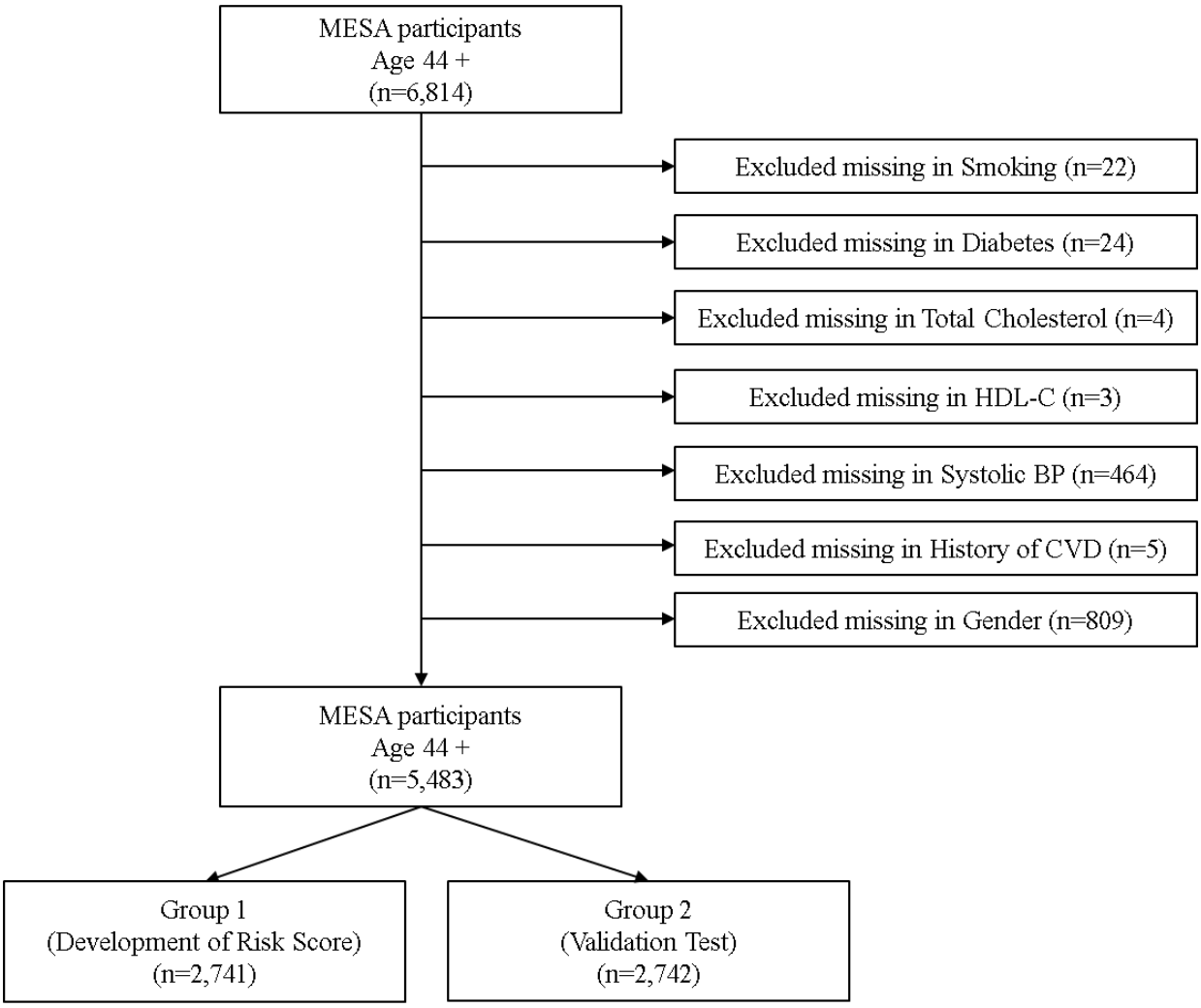

Figure A-1. Flow Chart of the Multi Ethnic Study of Atherosclerosis (MESA) with Exclusion Criteria Presenting the Final Sample Size

APPENDIX B
AREA UNDER THE CURVE OF THE FINAL MODEL

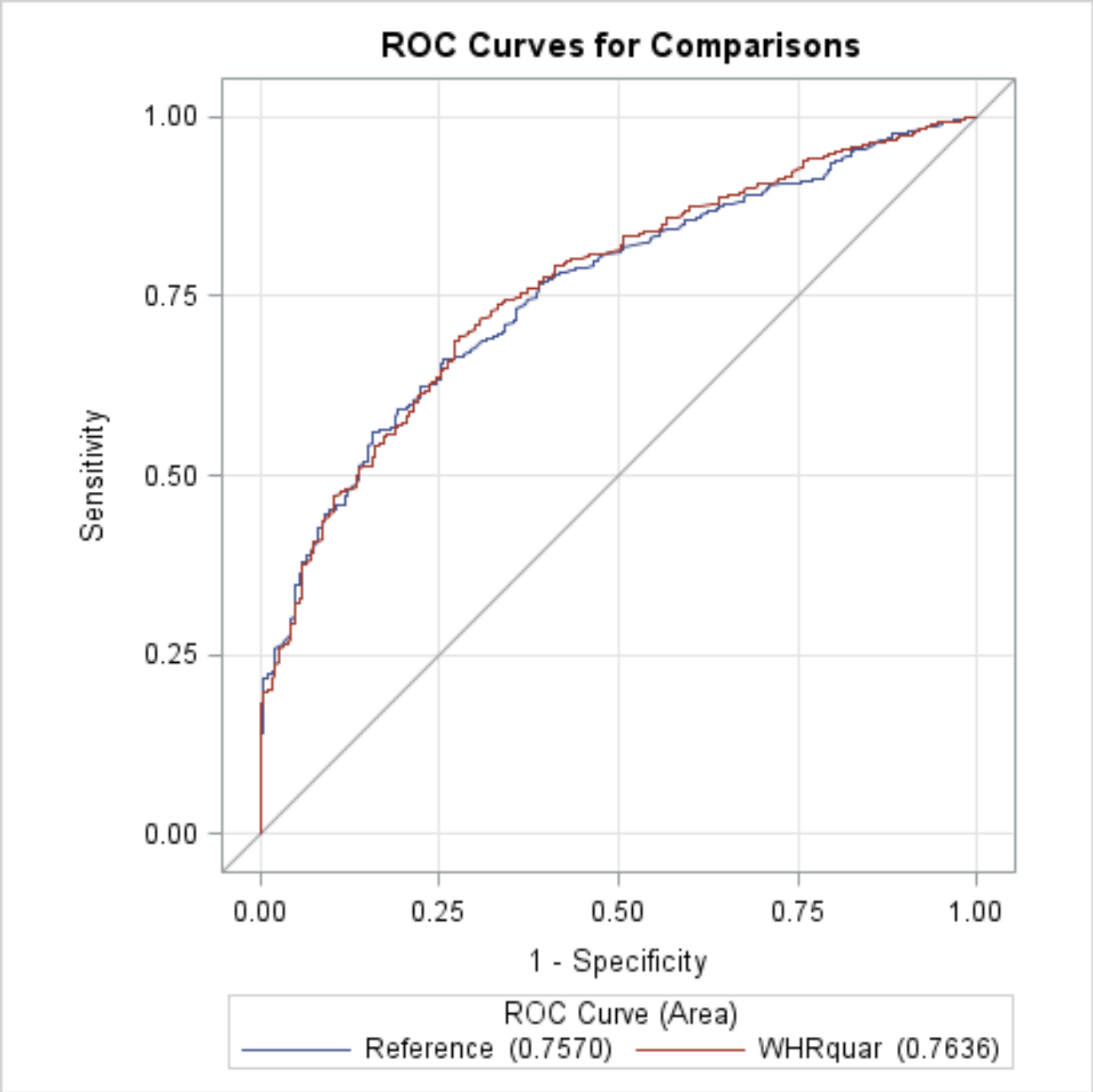

Figure B-1. Areas Under the Curve (AUC) comparing the predictive ability of the reference model ("Reference") compared to the models with selected body composition assessment ("WHRquar": Quartile of Waist-to-Hip Ratio) in Group 1 (n=2,741)

APPENDIX C
AREA UNDER THE CURVE OF THE VALIDATION TEST

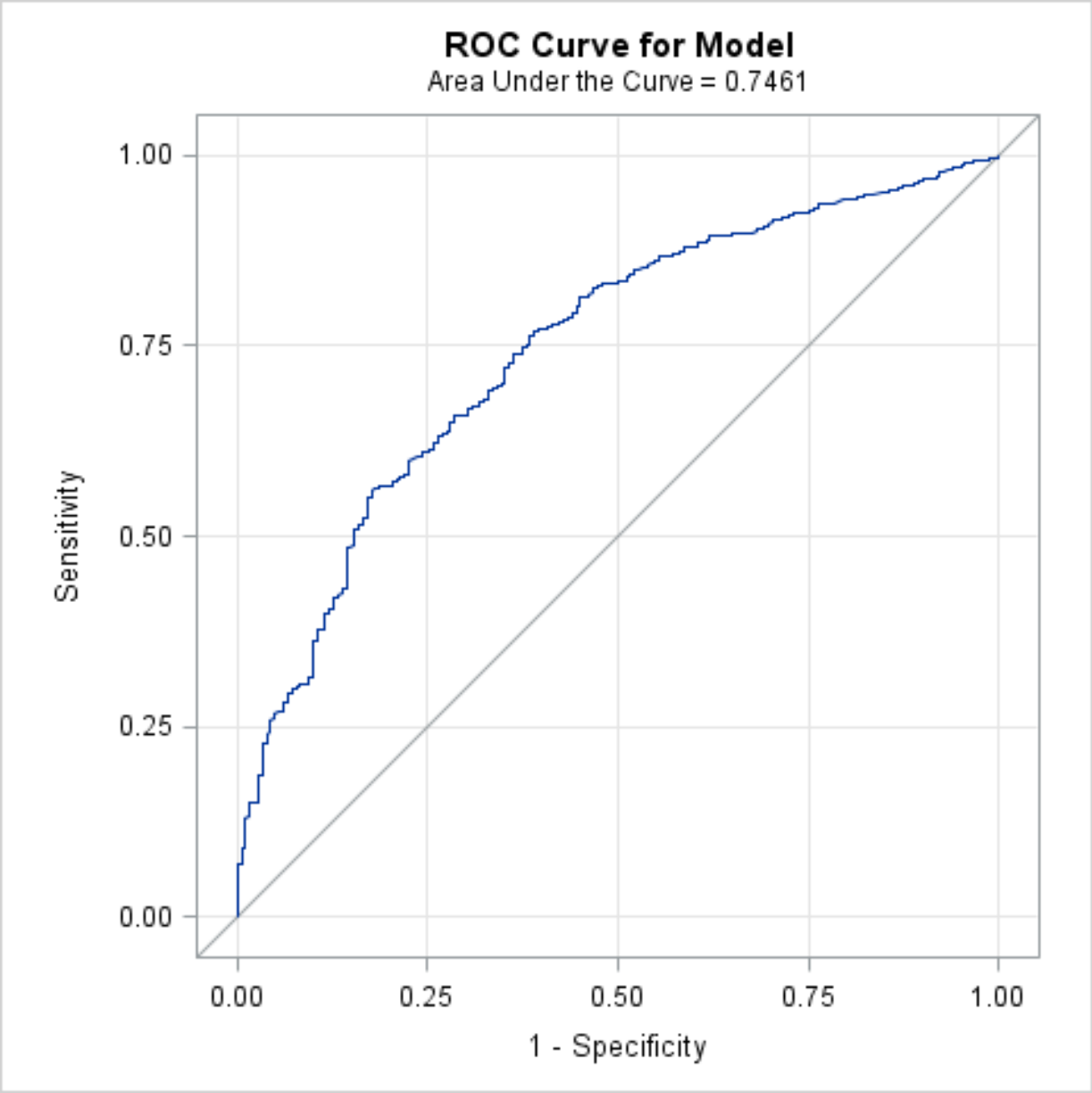

Figure C-1. Area Under the Curve (AUC) of the Validation Test in Group 2 (n=2,742, p= .24).

APPENDIX D
AREA UNDER THE CURVE IN NORMAL WEIGHT AND OVERWEIGHT POPULATION

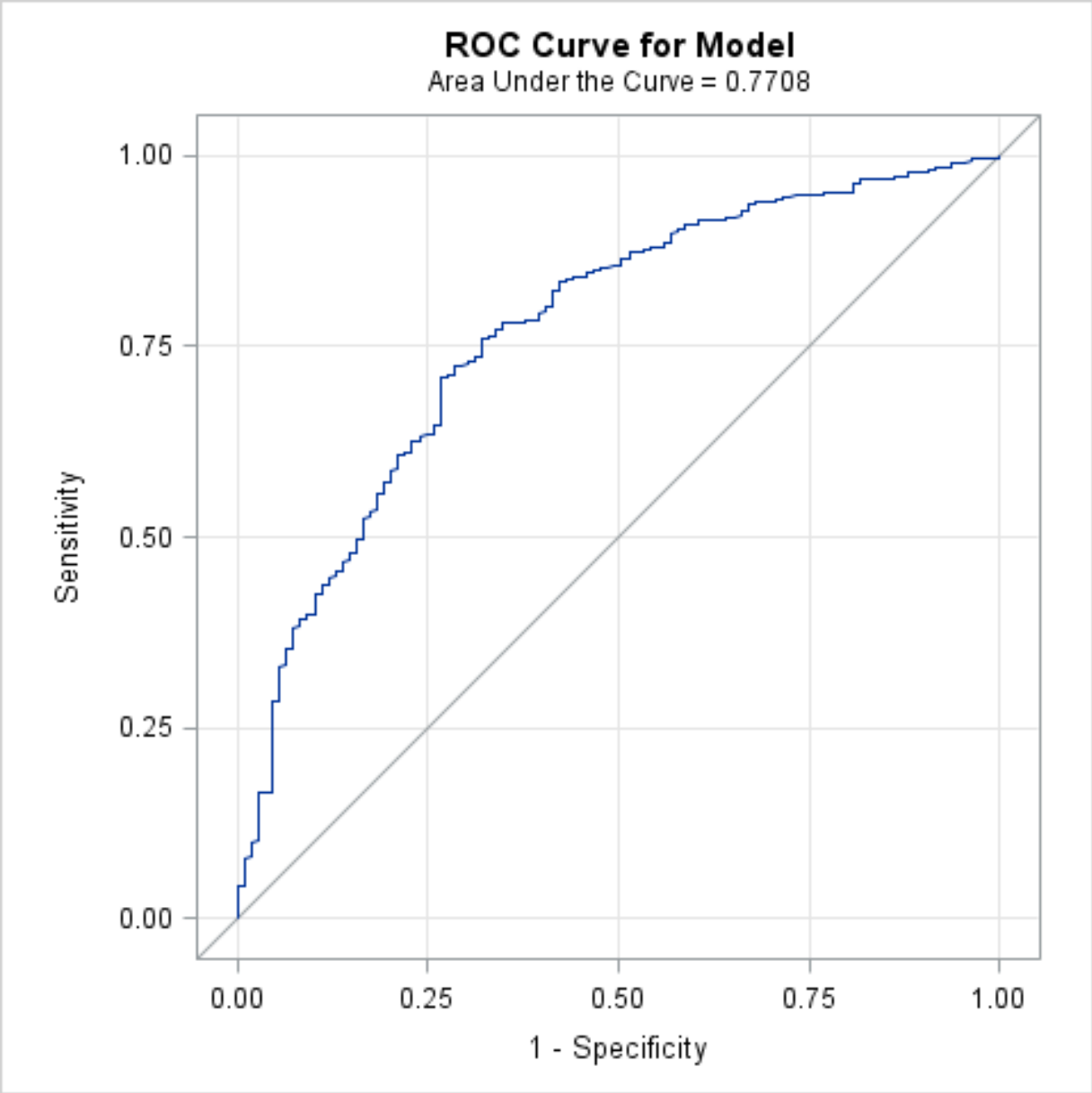

Figure D-1. Area Under the Curve (AUC) of the Final Model in Normal Weight and Overweight Population in Group 2 (n=2,742, p= .76).

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BIOGRAPHICAL SKETCH

Ara Jo was born in Seoul, Republic of Korea. She had diverse education backgrounds. She had Bachelor of Economics and Exercise Science at Ewha Womans University. After graduation, she moved to the US and she received her master's degree in sport management at Florida State University. After finishing her master's degree, she decided to study health services research at the Department of Health Services Research, Management and Policy. Her research interests stemmed from these broad backgrounds. During her PhD program, her primary research focused on preventive care services for chronic diseases such as screening and lifestyle intervention and body composition assessments.