THE EFFECTS OF WEIGHT LOSS AND AEROBIC EXERCISE ON 10-YEAR AND LIFETIME ASCVD RISK CALCULATED USING THE POOLED COHORT EQUATIONS

by

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BACKGROUND: Atherosclerotic Cardiovascular Disease (ASCVD) is the leading cause of morbidity and mortality in the United States. The American Heart Association (AHA) and American College of Cardiology (ACC) developed the Pooled Cohort Equations (PCE) to estimate10-year and lifetime ASCVD risk. Exercise and hypocaloric diets reduce ASCVD risk scores by decreasing blood pressure and cholesterol. However, there are currently no data on the magnitude of change in ASCVD score from a lifestyle intervention. METHODS: twenty-four overweight and obese adults (Age: 46.5 $\pm$ 10.5 yrs.; Weight: 95.5 $\pm$ 12.7 kg; BMI: 34.4 $\pm$ 3.4 kg/m^2) participated in 10 weeks of supervised aerobic exercise while participating in an OPTIFAST weight loss program to achieve clinically significant weight loss ($\geq$7% body weight). Body composition was measured using a whole-body DEXA scan. Cardiorespiratory fitness was measured using the modified balke protocol. The OPTIFAST program was ~800 kcals per day of total meal replacement consumed as shakes, bars, and soups. By week 8, participants increased their daily intake to 1300-1500 kcals and could replace two products with

whole foods per day. Participants were also encouraged to attend weekly behavioral classes to assist with dietary compliance. The weekly aerobic exercise volume began at 300 MET min per week and increased by 50 MET min each week until 700 MET min each week was reached. 10-year and lifetime ASCVD risk scores were calculated using the PCE. RESULTS: At baseline, participants had a mean 10-year ASCVD risk of 3.0% and a mean lifetime risk of 32.8%. Following the intervention, there was a mean decrease in body weight (-8.4 kg, -9.9 %, $p<0.001$), systolic BP (-9.1 mmHg, $p<0.001$), diastolic BP (-5.7 mmHg, $p<0.001$), total cholesterol (-15.1 mg/dL, $p<0.001$), low-density lipoproteins (-7.8 mg/dL, $p<0.006$), and high-density lipoproteins (-2.4 mg/dL, $p<0.038$). There were also reductions in 10-year (-0.6%, $p<0.001$) and lifetime ASCVD risk (-8.1%, $p<0.006$) after the intervention. Changes in ASCVD risk were associated with changes in systolic BP ($r=0.481$, $p<0.017$) and diastolic BP ($r=0.64$, $p< 0.001$), but not lipid values. No associations were observed between the change in 10-year or lifetime ASCVD risk in body composition or fitness variables. CONCLUSION: Our results suggest a combined weight loss and aerobic exercise program elicited a large change in lifetime scores, but not in 10-year ASCVD scores. Future research should investigate the impact of lifestyle interventions on participants in populations with high ASCVD risk at baseline.

The Effects of Weight Loss and Exercise on 10-year and Lifetime ASCVD Risk Calculated Using the Pooled Cohort Equations

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2. American Heart Association (AHA)
3. American College of Cardiology (ACC)
4. Pooled Cohort Equations (PCE)
5. High-density lipoprotein (HDL)
6. Low-density lipoprotein (LDL)
7. Coronary heart disease (CHD)
8. Cardiovascular disease (CVD)
9. Body mass index (BMI)
10. Waist-to-hip ratio (WHR)
11. Blood pressure (BP)
12. American College of Sports Medicine (ACSM)
13. Systolic blood pressure (SBP)
14. Diastolic blood pressure (DBP)

Chapter I: Introduction

Atherosclerotic Cardiovascular Disease (ASCVD) represents the leading cause of mortality and morbidity in the United States, particularly among older Americans. The incidence of ASCVD events increases dramatically with each decade of life after 45 years of age in all sex and racial/ethnic groups.[1] ASCVD is defined by the American Heart Association (AHA) and the American College of Cardiology (ACC) as acute coronary syndromes, myocardial infarction, stable or unstable angina, arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease of atherosclerotic origin, as well as heart failure and atrial fibrillation.[2] ASCVD has a long progression meaning it can occur over a lifetime. Symptoms that can occur with ASCVD can include plaque rupture, thrombosis, ischemia, and myocardial infarction. These symptoms will cause a resultant decrease in blood supply that will affect almost every organ in the body.[3] It is important to have a screening tool for ASCVD to determine who is at an increased risk of ASCVD so treatment and prevention can begin.

Since ASCVD has such a long progression, clinical screening practices are essential to reduce future adverse outcomes. This is important as until recently ASCVD could only be observed in late stages.[2] Screening for ASCVD risk stratification in primary prevention involves screening risk in an individual who does not have ASCVD. ASCVD risk remains the foundation of primary prevention with risk stratification of 10-year risk and lifetime risk. The AHA advocates for estimating 10-year ASCVD risk because it enables matching of the intensity of preventive interventions to the patient's absolute risk, to maximize anticipated benefit and minimize potential harm from overtreatment.[2]

Before the 10-year ASCVD risk equations were developed guidelines for CVD risk were based on 30-year risk.[2] In the 2013 AHA/ACC guidelines on the Assessment of Cardiovascular

Risk, a Work Group was put together to create a new set of equations that would predict 10-year ASCVD risk. These equations were called the Pooled Cohort Equations (PCE).[4] In order for the Work Group to derive these equations, they used data from community-based cohorts of adults, with adjudicated endpoints for CHD death, nonfatal myocardial infarction, and fatal or nonfatal stroke.[4] The Work Group used state-of-the-art statistical methods to derive and internally validate the PCE, which provide sex and race-specific estimates of the 10-year risk of ASCVD for African American and Caucasian men and women 40 to 79 years of age. The variables that statistically merit inclusion in the risk assessment equations are age, sex, race, systolic and diastolic blood pressure, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, history of diabetes, smoker status, and medication treatments. The calculator developed to assess ASCVD risk is called the ASCVD Risk Estimator +, which can be found on the ACC website. Many of the variables in the ASCVD risk calculator are positively associated with obesity.[5]

Obesity is a major underlying risk factor for the development of ASCVD, however, the mechanisms underlying this relationship are not fully understood. The prevalence of obesity and development of ASCVD typically have a clustering of major and emerging risk factors. This clustering is called metabolic syndrome.[6] Many clinicians could link obesity to an increased risk of ASCVD because many of the variables in the ASCVD risk calculator are increased by obesity.[7] These variables include hypertension, hypercholesterolemia, and hyperglycemia. There are also emerging risk factors that are not present in the calculator like atherogenic dyslipidemia, insulin resistance, pro-inflammatory state, and prothrombotic state that obesity effects that can increase the likelihood of an ASCVD event. The treatment of ASCVD has commonly been statins. Statins are a medication that targets cholesterol which is a component of the calculator.

Since the PCE were developed, there has not been any study done on lifestyle intervention and how that could affect ASCVD risk. This is important because it could give patients and clinicians different treatment options when it comes to the prevention of ASCVD. One that does not include taking medications. By investigating the effects of a combined intervention of diet and exercise utilizing the PCE on 10-year and lifetime ASCVD risk, this study will contribute to the knowledge needed to effectively design interventions of diet and exercise for improving ASCVD risk in overweight and obese individuals.

Purpose:

The primary purpose of this study is to investigate the effect of weight loss and aerobic exercise on estimated 10-year and lifetime ASCVD risk. Secondly, this study will evaluate potential physiological mediators, such as body composition, weight loss, aerobic fitness, insulin, glucose, and cholesterol levels on improvements in ASCVD risk score. For this present study, data will be utilized from the Prescribed Exercise to Reduce Recidivism After Weight Loss pilot (PREVAIL-P) study.

Hypothesis:

The ASCVD risk score will improve following the combined diet and aerobic exercise intervention. Secondly, weight changes, aerobic fitness, body composition, insulin, glucose, and cholesterol levels will serve as mediators for the improvement of the ASCVD risk score.

Delimitations:

This present study included participants from Greenville, NC, and surrounding areas. It looked at overweight or obese class 1 and 2 (25-39.9 kg/m^2) individuals between the ages of 30-65 years of age. The OPITFAST weight loss program was used for the diet and exercise intervention.

Supervised aerobic exercise sessions on a treadmill were performed. The duration of the combined intervention was 10 weeks.

Chapter II: Review of Literature

Atherosclerotic Cardiovascular Disease

Atherosclerosis is characterized by the thickening of the arteries walls, a process that progresses slowly and silently over decades.[3] Symptoms generally occur in the late stages of disease and are usually caused by the gradual narrowing of the arterial lumen, which is associated with progressive plaque progression. The clinical manifestation of atherosclerosis over time can include plaque rupture, thrombosis, ischemia, and myocardial infarction. The resultant decrease in blood supply can affect almost any organ, although coronary heart disease (CHD) and stroke are the most common consequences.[3]

According to the National Center for Biotechnology Information about 610,000 people (1 out of every 4 deaths) will die of cardiovascular disease annually. Coronary heart disease is the leading cause of death in the Western world killing over 370,000 people annually. On average, about 735,000 Americans have a myocardial infarction every year. Out of these 525,000 have an initial attack, and 210,000 have a recurrent attack. It has been reported that 75% of acute myocardial infarctions occur from plaque rupture and the highest incidence increases beyond age 50. This higher prevalence of atherosclerosis in men compared to women is attributed to the protective function of estrogens, which is lost after menopause. Stroke from any cause represents the fifth leading cause of death and the major cause of serious long-term disability in adults in the United States. It is reported that nearly 795,000 people suffer every year in the U.S resulting in about 140,323 deaths. The major form of stroke, ischemic stroke is due to atherosclerotic cardiovascular disease. These statistics exhibit what CVD does in terms of mortality and morbidity and why there needs to be a screening tool for the assessment of CVD.

Screening for ASCVD

Screening for cardiovascular disease risk factors and risk stratification for atherosclerosis of ASCVD is an important component of primary prevention meaning patients without ASCVD. According to the AHA recommendations for the assessment of ASCVD risk remains the foundation of primary prevention. The AHA and the ACC defines ASCVD as acute coronary syndromes, MI, stable or unstable angina, arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease of atherosclerotic origin, as well as heart failure and atrial fibrillation.[2] ASCVD has remained the leading cause of mortality and major morbidity in developed countries since the 20th century, particularly among older individuals. ASCVD has increased exponentially in the last few decades due to the aging population. ASCVD starts at a young age and will progress throughout life however, the incidence of ASCVD events increase significantly after 45 years of age in all sex and racial/ethnic groups.[1] Since the disease progresses slowly, it has provided an opportunity to diagnose the disease before any symptoms occur, but until recently only advanced ASCVD could be observed.[3]

The AHA/ACC recommendations include ASCVD screening for adults 40 to 75 years of age, clinicians should routinely assess traditional cardiovascular risk factors and calculate the 10-year risk of ASCVD by using the pooled cohort equation (PCE). For adults 20 to 39 years of age, it is reasonable to assess traditional ASCVD risk factors at least every 4 to 6 years. In adults at borderline risk (5% to <7.5% 10-year ASCVD risk) or intermediate risk (≥7.5% to <20% 10-year ASCVD risk), it is reasonable to use additional risk enhancing factors to guide decisions about preventive interventions. In adults at intermediate risk or selected adults at borderline risk with risk-based decisions uncertain, it is reasonable to measure a coronary artery calcium score

to guide clinician-patient risk discussion. For adults 20 to 39 years of age and for those 40 to 59 years of age who have <7.5% 10-year ASCVD risk, estimating lifetime or 30-year ASCVD risk may be considered.[2]

Estimated ASCVD Risk as a Screening Tool

In the 2013 ACC/AHA Guidelines on the Assessment of Cardiovascular Risk, the workgroup decided to develop a new set of equations called the Pooled Cohort Equations (PCE). These equations were used to estimate the 10-year and lifetime risk of developing a first ASCVD event.[4] The workgroup used the best available data from community-based cohorts of adults, with adjudicated endpoints for CHD death, nonfatal myocardial infarction, and fatal or nonfatal stroke. These cohorts included participants of both African American and Caucasian backgrounds with at least 12 years of follow-up. Only black and Caucasian racial groups were included because other racial/ethnic groups had insufficient data to be included in the final analysis. The final pooled cohorts included participants from several large studies that were racially and geographically diverse. These studies included the Atherosclerosis Risk in Communities (ARIC) study, the Cardiovascular Health Study, and the Coronary Artery Risk Development in Young Adults (CARDIA) study, combined with applicable data from the Framingham Original and Offspring Study cohorts.[4]

The Work Group used state-of-the-art statistical methods to derive and internally validate the PCE, which provides sex and race-specific estimates of the 10-year risk of ASCVD for black and Caucasian men and women 40 to 79 years of age. The variables that statistically merit inclusion in the risk assessment equations are age, sex, race, systolic and diastolic blood pressure, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein

(LDL) cholesterol, history of diabetes, smoker status, and medication treatments. On the American College of Cardiology website, the risk calculator can be found to assess ASCVD risk.[4]

ASCVD Risk Guidelines

Current clinical guidelines advocate for the calculation of 10-year ASCVD risk at an initial visit to establish an initial reference point for a patient's ASCVD risk. The calculator is also used as a screening tool to estimate the potential impact of different interventions on patient risk and reassess ASCVD risk at follow-up visits to examine the need for increased prevention. Follow-up risk incorporates the change in patients' ASCVD risk factors over time to track if they changed from initial and follow-up values to determine the new ASCVD risk. The risk can be used to help clinician-patient discussions on risk and risk-lowering interventions. The 10-year risk for ASCVD is categorized as low-risk (<5%), borderline risk (5% to 7.4%), Intermediate risk (7.5% to 19.9%), and high risk (≥20%). In patients with a low 10- year ASCVD risk score, primary prevention is consuming a healthy diet and exercising. Medication is not recommended unless LDL is greater than or equal to 190 mg/dL. With borderline risk, the use of a statin medication may be recommended if certain conditions or risk enhancers are present. These conditions may increase the risk of heart disease or stroke.

When the ASCVD risk is calculated, there are certain conditions called ASCVD risk enhancers, which can increase ASCVD risk. These enhancers include a family history of early-onset ASCVD, continually elevated LDL greater than or equal to 160 mg/dL, chronic kidney disease, metabolic syndrome, preeclampsia or premature menopause, inflammatory diseases, South Asian ancestry, and continually elevated triglycerides greater than or equal to 175 mg/dL. When using the ASCVD Risk Calculator it will have fields required to populate to calculate 10-

year ASCVD risk for patients. Once all the fields are populated the risk will be automatically calculated. It will calculate the patient's current 10-year ASCVD risk, the lifetime ASCVD risk, and what the optimal ASCVD risk should be for age, sex, and race. After the patient risk is calculated, there will be an option to look at different therapies that could have an impact on the risk score. For example, if a patient had a high blood pressure that resulted in a high-risk score, this option will advise on different therapy options that would try to decrease the risk score by lowering blood pressure.

Obesity and ASCVD Risk

Obesity is a major underlying risk factor for the development of ASCVD in the general population. Whereas both anthropometric measures of overall obesity like body mass index (BMI), central obesity (waist circumference), and waist-to-hip ratio (WHR) are strongly linked to ASCVD.[7] The relationship is stronger for WHR than for overall obesity.[7] A large scale study with N=27,098 participants from 52 countries showed that there is a graded and highly significant association between WHR and MI (OR 1.59-1.97; $p<0.0001$) even after adjustment for other ASCVD risk factors.[8]

Obesity can be called an underlying risk factor for ASCVD because it raises the risk for ASCVD through other risk factors including hypercholesterolemia, hypertension, and hyperglycemia. There are also emerging risk factors like atherogenic dyslipidemia, insulin resistance, pro-inflammatory state, and prothrombotic state. The relationship between obesity to major and emerging risk factors varies, depending on the genetic and acquired characteristics of the individual. Most obese persons who develop ASCVD typically have a clustering of major and emerging risk factors. This clustering would be called metabolic syndrome.[6] Hu et al describes the relationship between obesity phenotypes such as hypertension and hyperlipemia on

ASCVD risk.[9] This is important because the association between obesity and ASCVD has two different aspects. Obesity is generally accepted as an independent risk factor for many cardiovascular diseases; however, in some groups, the long-term prognoses for obese patients with ASCVD are often better than for lean patients. This paradox has been shown to exist in undergoing coronary intervention, hypertension, heart failure, and even the general population. Despite the strong association between obesity and ASCVD (r=0.61),[10] the mechanisms underlying this relationship are not well understood. Understanding the connection between obesity and ASCVD is complicated by a plethora of possibilities. Obesity acts on so many metabolic pathways, producing so many potential risk factors, that is virtually impossible to differentiate between the more important and less important. The possibilities for confounding variables are enormous. This complexity provides a great challenge for basic and clinical research.[6]

According to the Nurse Health study results, it is suggested that obesity with metabolic syndrome in all groups has the highest risk of ASCVD.[9] Obesity and metabolic syndrome are risk factors for ASCVD, and their additive effects may further increase the risk of ASCVD. Different factors such as the elevated risk of complications associated with obesity such as type 2 diabetes, hyperlipidemia, and hypertension increase the risk of ASCVD. Cytokines secreted by adipose tissue (e.g., tumor necrosis factor, interleukin 6, and fibrinogen activation inhibitors), increased heart and blood flow load by adipose tissue, insulin resistance, and lipid toxicity would increase the risk of ASCVD in obesity. After looking at a sample of 10,826 individuals aged 40-79 years of age the study suggested that ASCVD risk is also higher in patients with obesity and normal metabolic status compared to patients with normal weight and metabolic syndrome, indicating that abnormal metabolic state has a greater impact on ASCVD than obesity, which

may be associated with the mechanism of the obesity paradox. Current investigations on the obesity paradox suggested that obesity may have some benefits. The above benefits may offset the adverse effects of obesity. Therefore, obese individuals without metabolic syndrome may be obese and relatively healthy. Studies have confirmed that endothelial function with obesity may still be normal.[11] Obese insulin sensitive individuals had a favorable metabolic profile compared to the obese insulin-resistant group. The state of healthy obesity may be unstable and affected by lifestyle and may progress to metabolic syndrome, which increases the risk of ASCVD.

According to an analysis using CARDIA study data,[12] obesity is positively associated with many ASCVD risk factors including hypertension and diabetes as well as clinical CVD events and raises the risk for future ASCVD in young and middle-aged adults. The study population looked at 5115 healthy adults who were recruited from the general population from 1985-1986. There have been seven follow-up examinations after baseline with 72% of the surviving cohort attending the 2010-2011 examinations. Of the 3672 participants attending the 2000-2001 examinations, participants who were aged 40 years or less were excluded. The average 10-year ASCVD risk increased from 2.0% in 2000-2001 to 4.6% in 2010-2011, as the average age increased from 42.8 to 52.7 years. The 10-year change in ASCVD risk scores was significantly higher for men (3.1%-6.8%) than women (1.1%-3.1%). By 2010-2011, 57.5% of black men were found to have a 10-year ASCVD risk score of 7.5% or more. The proportion of middle-aged black women (17.4%) with a 10-year ASCVD risk score of 7.5% or more was higher than those for white men (14.7%) and women (1.6%).

However, results from other studies incorporating body mass index (BMI) in ASCVD risk prediction models are equivocal.[4] The Framingham Heart Study, a study composed predominately of White participants, observed a weak independent association between BMI and

CVD events (p=0.04) which was lost when other CVD risk factors were updated every 4 years.[13] ASCVD and obesity are disproportionately high among middle-aged blacks than whites[14] with the adverse health effects of obesity especially elevated for black women. The CARDIA study is important because it discusses the differences between races and ASCVD risk which is a variable in the ASCVD risk calculator. In this community-based sample, it was observed that a significantly greater proportion of blacks were observed to have higher obesity prevalence and 10-year ASCVD risk than whites. Black women had the highest prevalence of obesity with a greater proportion of them having a 10-year ASCVD risk of 7.5% or more compared to white men and women. Although BMI trends were positively associated with a 10-year change in ASCVD risk scores by 33%, it explained very little variance in risk score trends in all race-sex groups, possibly due to its influence being largely mediated through risk factors already included in the risk score equation. The findings of this study do not downplay the importance of obesity as a modifiable risk factor for ASCVD as obesity predicts diabetes, hypertension, and dyslipidemia. The present study estimated risk score trends, not incident events, and longitudinally assessed BMI was not significantly associated with changes in 10-year ASCVD estimated risk trends. Some possible explanations for the discrepancies in results include differences in risk prediction models used to estimate 10-year ASCVD risk which has differing covariates, the functional form for modeling obesity, and variations in the population sampled, as well as CVD events of interest. The omission of diabetes from some risk predictions may have resulted in obesity contributing to ASCVD risk prediction because obesity is a strong predictor of diabetes.[15] As seen in the CARDIA study[12] and the collaborative analysis of 58 prospective studies,[16] when the relation between diabetes and other ASCVD risk factors associated with obesity is adequately accounted for, the independent predictive ability of obesity on ASCVD is

attenuated. This idea is supported by results from the ARIC study[17] in which the addition of BMI alone to the base prediction model minimally improved ASCVD risk prediction.

ASCVD Intervention

There are several clinical strategies to treat or prevent CVD, but statins have demonstrated significant clinical benefits in reducing CVD by lowering LDL.[18] In Taiwan, following the Third Report of the National Cholesterol Education Program, and the 2003 and 2009 Taiwan clinical guidelines for dyslipidemia, patients with hyperlipidemia were considered at high risk for a CV event, and statins are generally the most frequently used first-line therapy for patients with hyperlipidemia.[19] The 2013 ACC/AHA guidelines for the treatment of blood cholesterol to reduce ASCVD in adults suggest that statin medications reduce ASCVD events in primary and secondary prevention.[20] The 2013 ACC/AHA guidelines suggest that medications for the treatment of cholesterol are most used. it is acknowledged that lifestyle is the foundation for cholesterol reduction efforts. This includes a heart-healthy diet, regular exercise, avoidance of tobacco, and maintenance of healthy body weight.[20] Cholesterol is one factor in the ASCVD risk calculator that can be controlled by medication. Another factor is hypertension.

Blood pressure (BP) control is a recommended component of ASCVD risk reduction.[21] Elevated blood pressure represents a significant risk factor for ASCVD. Obesity is a risk factor for ASCVD because hypertension is elevated by obesity. The AHA 2020 Strategic Plan defined a normal blood pressure as <120/<80 mm/Hg and defined 80-89 mm/Hg diastolic and 120-139 mm/Hg systolic as prehypertension and >140 mm/Hg as hypertension (Rippe & Angelopoulos, 2014). Blood pressure medications help control hypertension, which in turn would lower ASCVD risk. Just like cholesterol, The Joint National Commission recommends that lifestyle

interventions such as regular aerobic exercise, limiting salt intake, maintenance of proper healthy weight, and not smoking cigarettes should be the cornerstone of any antihypertensive regimen.[21] The American College of Sports Medicines (ASCM) position stance on exercise and hypertension states, that hypertension is one of the most common medical disorders that is associated with an increased all-cause and CVD mortality. Lifestyle modifications are advocated for the prevention, treatment, and control of hypertension, with exercise being an integral component. Exercise programs that primarily involve endurance activity prevent the development of hypertension and lower blood pressure (BP) in adults with normal BP and those with hypertension.[22]

Hypertension and dyslipidemia are both elevated in obese individuals (Brown et al., 2000). This is important because obese individuals are likely to have an increased risk of ASCVD.[12] Some studies have assessed mortality based on body fat and lean mass rather than BMI or weight alone, and they have suggested that subjects losing body fat rather than lean mass have a lower mortality.[5] This suggests that losing weight along with exercise could be a frontline therapy when it comes to preventing and treating ASCVD.

Effects of Weight Loss and Exercise on ASCVD Risk

The most popular treatments for ASCVD at the present time are the use of statins to treat hyperlipidemia and anti-hypertensive medications to treat hypertension. In some cases, if the patient's ASCVD risk score is elevated above a healthy level, the clinician might suggest the use of aspirin to help with thinning the blood, so it flows easier through the occluded arteries. In the ASCVD calculator, there are modifiable and non-modifiable variables.

The non-modifiable variables in the ASCVD risk calculator outweigh the modifiable variables. The first of the non-modifiable variables is age. There has been vast research on the effects of aging and CVD incidence. The reason age is a risk for CVD is according to[23] there are two major age-related predictors for future CVD diagnosis and are the main contributors to the development of CVD in older adults. They are arterial stiffness and endothelial dysfunction. The next non-modifiable risk is race/ethnic background. A study looking at the racial/ethnic inequities in the associations of allostatic load CVD specific mortality found that racial/ethnic heterogeneity of the association of allostatic load scores with all cause-mortality ($p=0.005$) and with CVD (0.007). They observed that allostatic load scores were on average 2.2 for blacks compared to 2.05 for white.[24] The last non-modifiable risk for ASCVD is sex. According to it is evident that male age-adjusted CVD mortality (79.6%) is higher than female mortality (20.4%) throughout life.[25] However, as women increase in age their age-specific CVD mortality increases more rapidly than their male counterparts. This is due to the women being post-menopausal. Although the non-modifiable risk factors of CVD are very important to understand, it is more important to look at the modifiable risks so that clinicians can come up with viable prevention and treatment options.

The modifiable risk factors that will be most affected by exercise and weight loss will be blood pressure and cholesterol. High BP is a major health problem in the U.S, affecting more than 50 million people. Although high BP is among the most common reasons for outpatient visits, control is often inadequate. BP can be lowered using anti-hypertensive medications, but these are not effective for everyone, may be costly, and result in adverse effects that may reduce adherence to the medications.[26] The main behavioral interventions recommended to reduce BP are exercise and the Dietary Approaches to Stop Hypertension (DASH) diet. Weight loss is also

recommended for BP reduction in overweight/obese individuals. According to (Bacon et al., 2004) there is a reduction in systolic blood pressure (SBP) and diastolic blood pressure (DBP) by 12.5 mmHg and 7.9 mmHg respectively in overweight/obese patients when a combined exercise and weight-loss intervention is introduced.

Cholesterol is split up into three parts. High-density lipoproteins (HDL), low-density lipoproteins (LDL), and total cholesterol (TC). Presently dyslipidemia is most treated using drug therapy, although nonpharmacological therapies have become more apparent because of the safety and concerns using medications. The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) recommends the use of lifestyle therapies, which include a combination of diet and exercise modifications, in place of drug treatments for patients who fall into an intermediate range of CHD risk.[27] Low saturated diets combined with exercise lowered TC, LDL, and triglyceride levels by 7-18, 7-15, and 4-18% respectively, while increasing HDL by 5-14%. These findings suggest that combination lifestyle therapies are an effective means of improving cholesterol levels and should be implemented in place of drug therapies.[28]

There is one more modifiable risk factor for ASCVD and that is smoking. Although smoking is not affected by weight loss and exercise, smoking is the most preventable cause of CVD morbidity and mortality than any other risk factor.[29] Smoking cessation is probably the most effective preventive measure that can be taken. The beneficial impact of smoking cessation on the overall risk of CHD is twice that gained by controlling either hyperlipidemia or hypertension.[29]

The ASCVD risk calculator considers all the non-modifiable risk factors and all the modifiable risk factors before calculating 10-year and lifetime ASCVD risk, The main

modifiable risk factors that should be focused on are BP and cholesterol. Out of all the variables in the calculator, BP and cholesterol are the only two that can be affected by a combined intervention of weight loss and exercise.

Summary

Many studies examine the use of medications on the reduced risk of ASCVD, but to my knowledge, there are not any studies that examine the combined effects of weight loss and exercise on the ASCVD risk score using the pooled cohort equations. This could be important because we don't yet know the ASCVD reduction associated with combined lifestyle intervention and who might benefit the most. There is extensive literature that shows weight loss and exercise can affect both hypertension and dyslipidemia. This is important because high blood pressure and high cholesterol are two major modifiable components of the PCE that can be affected by treatments. My research project will look at a combined lifestyle intervention of diet and exercise for the prevention of ASCVD instead of using medications to reduce the risk of developing ASCVD.

Chapter 3 Methods

The purpose of this study was to investigate the changes in ASCVD risk from baseline through weight loss and to assess any impact of potential physiological mediators on the changes of ASCVD following the weight loss intervention. The data for this study was obtained from the Prescribed Exercise to Reduce Recidivism After Weight Loss pilot (PREVAIL-P) study. The primary purpose of the PREVAIL-P study was to evaluate the amount of aerobic exercise and its effects on weight maintenance following clinically significant weight loss.

Participants:

The PREVAIL-P study recruited 39 participants from the Pitt County, North Carolina area by way of email sent to ECU employees, newspaper advertisements, Facebook advertisements, a PREVAIL study website, and various information posted around Vidant Health. The participants that were eligible for the PREVAIL-P study are both men and women between the age of 30-65 years. The participants were classified as overweight, class 1 obese, or class 2 obese making their BMI 25-40 kg/m^2. Participants was excluded if the presence of significant CVD or other diseases, diagnosis of type 1 or 2 diabetes or fasting blood glucose ≥126 mg/dL, systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥100 mmHg.

Participant Screening

Initial screening for eligibility was performed via an online survey and telephone interview. The survey and interview were used to determine base eligibility on the inclusion and exclusion criteria. If eligibility was determined, an orientation visit was scheduled with study staff to further discuss eligibility, discuss pertinent information about participation in the study, and answer any participant questions. When the participant was deemed eligible for the study informed consent was signed saying that they were willing to participate in the study. Additional

information was also obtained from participants including a medical history questionnaire, study surveys, and potential barriers to the study. Clinical measures of height, weight, and resting blood pressure were gathered. The participants returned for a follow-up visit where they received a metabolic blood draw, which was reviewed by a physician for medical clearance. Once cleared by a physician the participant completed a VO_2 max test and body composition that was assessed using the DEXA.

***Primary Outcome Measurements*:**

The primary outcome measures of this study were the change in 10-year and lifetime ASCVD risk scores from baseline to after clinically significant weight loss $\geq 7\%$. ASCVD risk was evaluated using the online ASCVD Risk Estimator Plus (Figure 1) on the ACC website. Participants were measured weekly using a level beam scale (Health O Meter Professional, McCook, IL) and recorded to the nearest tenth of a kg. Weight measurements were performed before the participant's exercise session.

Secondary Outcome Measurements

The secondary outcome measurements were collected at baseline and the end of the weight loss phase. The assessments that were chosen for secondary measurements were cardiorespiratory fitness (VO_2 max), body composition, weight, blood pressure and an array of blood measures (lipids, glucose, insulin).

Outcome Measure Visit

Body Composition: Two forms of body composition were taken here. The first will be a waist circumference measurement. It was evaluated using a Gulick tape measure at the natural waist. Three measurements were taken, and the results were averaged together. A whole-body dual-energy x-ray absorptiometry (DEXA) (Hologic, Horizon A Marlborough, MA) was completed to

calculate fat mass, lean mass, and visceral fat. The participant was positioned in the center of the table in a supine position. In this position, the participant had their arms to the side with thumbs facing upward and feet turned in a pigeon-toed position. If the participant was too wide for the scanning area, they were positioned so that the entire right side of the body is scanned. The DEXA software estimated the left side that is missing from the scan by using the right side that was scanned.

Maximal Exercise Test: The maximal test measured pre- and post-intervention was used to determine the participants' heart rate range for the exercise sessions and to determine the participants' cardiorespiratory fitness. VO_2 max was tested using a modified Balke treadmill (Trackmaster 425, Carefusion, Newton Kansas) protocol. The respiratory gases (VO_2, VCO_2) and ventilation was measured continuously using a True Max 2400 Metabolic Measurement Cart (Parvomedics, Salt Lake City, Utah) to determine cardiorespiratory fitness. The treadmill test began with a speed of 2.0 mph at a grade of 0.0%. for the first two minutes. After the first two minutes, the speed increased to 3.0 mph and a grade of 2.5% for the next two minutes. The grade increased by 2.5% every two minutes until volitional fatigue was achieved. ECG reports from baseline exercise testing were cleared by the supervising physician prior to the beginning of exercise sessions to ensure there was no contraindications to exercise.

Weight: A weigh-in occurred at baseline and at the conclusion of the intervention to determine how much weight was lost. Each participant should have fasted for 12 hours before the weigh-in. All participants were required to wear a hospital gown during the weigh-in to ensure that clothes do not add extra weight.

Blood Pressure: Pulse wave velocity was used to assess blood pressure levels at baseline and at the end of the intervention. The participant was to refrain from any large meals and caffeine at

least two hours before the test. They were also encouraged to avoid any vigorous exercise and vasoactive medications for at least 12 hours. Testing was performed in a quiet and temperature-controlled room. The blood pressures were taken using a SphygmoCor XCEL (Itasca, IL). The participant was rested for five minutes before taking the resting blood pressures. Three measurements were taken then averaged together.

Blood Measures: Blood measures that were collected are lipids, glucose, and insulin. The lipids that were measured are total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very-low-density lipoprotein (VLDL). The blood sample was taken with the subject in a fasted state, and it was obtained through venipuncture. LabCorp's clinical laboratory analyzed the blood sample.

OPTIFAST Weight Loss Program

Weight loss was obtained using the OPTIFAST diet, which is a very low-calorie diet run by VIDANT Wellness Clinic. The OPTIFAST diet was used to help participants reach clinically significant weight loss so that their ASCVD risk could be calculated. The diet used meal replacements (e.g., shakes, bars, soups) that were portion-controlled and nutritionally balanced. Since the diet was a low-calorie diet, it was medically supervised to ensure participants were staying healthy. The OPTIFAST diet coincided with supervised exercise training at East Carolina University in the Fitness, Instruction, Testing, and Training (FITT) building.

At the beginning of the program, participants received a nutrition assessment, to help the dietitian/nutritionist gauge the types of food they regularly ate and how often they ate those foods. VIDANT Wellness Clinic has over 10 years of experience delivering this intervention. The dietitians that delivered the intervention are certified by Nestle. The PREVAIL-P study provided the resources to cover the cost of the program. The first two weeks of the 10-week

program consisted of a full meal replacement to get the participants acclimated to the diet. Each product provided 160-170 kilocalories, 14 g protein, 3 g total fat, 0 trans-fat, around 20 g carbohydrate, 220 mg sodium, 470 mg potassium, <1 g lactose, and 10-30% of the RDI for vitamins and minerals. Each day, 5 products from the diet was consumed (approximately 800-820 kilocalories). At week 8, participants were able to eliminate two products per day, allowing them to reach a daily caloric intake of 1300-1500 kilocalories. The food that they ate came off the Healthy Food Exchange List. During the last two weeks of the program, participants could be completely off the OPTIFAST products and eat all self-prepared food. If desired participants could consume 1 to 2 products per day.

The participants attended a weekly class at VIDANT Wellness Clinic to get assistance in increasing compliance with the diet and helping them meet their weight loss goal. The class size was expected to be approximately 20-25 participants, but it was a rolling class, meaning the participants could enter the program at any week and still receive the full program. The classes (Figure 2) that were taught are Identifying Eating Cues, Triggers, and Eating Style, Where are the Calories? Reading Food Labels; Strategies for Portion Control; Motivation to Change; Relaxation Techniques; Effects of Stress on Body Weight; Exercise Update; Mindful Eating and Emotional Eating; Eating Out, Special Occasions; Cooking Quick and Light. At the beginning of each meeting, the participants completed a weigh in and filled out a questionnaire provided by Nestle regarding the food they ate over the previous week. The questionnaire also discussed the amount of fluid the participant drank, and if any physical changes occurred. When all the participants had finished with the questionnaire, they begin the discussion on the assigned topic. At the end of the session, participants were allowed to ask questions to the dietitian or each other.

Exercise Training

The exercise training portion of the program was combined with the OPTIFAST diet to help participants elicit a greater magnitude of weight loss. The sessions took place at ECU in the FITT building using a treadmill. The ramp protocol (Figure 3) was used for exercise trainings. All the participants started at the same amount of exercise 300 MET minutes per week. Each week 50 MET minutes were added until a total of 700 MET minutes per week was met. This took about 2-3 sessions per week depending on how long the participant exercised on the treadmill per session. To determine the length of each exercise session, the 700 MET minutes was divided into however many days the participant wanted to exercise per week (2-3 days/week). Exercise adherence was quantified in the amount of MET minutes exercised divided by the amount each participant was required to do. Exercise compliance was defined as the amount of exercise sessions attended by the amount of sessions required.

In the first exercise session each week, the participant completed a weigh in using a calibrated scale. After the participant had weighed in, the supervising staff member took resting blood pressure and got a resting heart rate. During the exercise session heart rate was monitored and collected continuously (every second) using the Zephyr Bioharness 3 HR monitors (Medtronic Annapolis, MD). The session began with a 5-minute warm-up, then they went right into their exercise bout. When the exercise session had concluded, the study staff member obtained another resting blood pressure and heart rate, to make sure the participant was in a good state to leave. The average heart rate needed to be collected for the exercise with warm-up and cool-down omitted from the average. The average heart rate for the entire session was exported into the OmniSesnse 5.0 (Medtronic Annapolis, MD) software program. Mean heart rate, total

energy expenditure, rating of perceived exertion, MET minutes exercised, and total exercise time was be entered into the study database, for future use.

The speed and grade the participants exercised at was estimated using the heart rate/VO_2 relationship established from their baseline maximal test. Participants were required to exercise at the heart rate range associated with 50%-75% of their VO_2max. Submaximal testing occurred periodically to improve the accuracy of the exercise-related energy expenditure. Submaximal tests were used to steady-state exercise at the same intensity as the training sessions. A correction factor was obtained (actual energy expenditure/predicted energy expenditure) during the submaximal test to account for individual variability in prediction equations for energy expenditure.

Statistical Analysis

All baseline participant characteristics was compiled. Continuous data (weight, aerobic fitness, body composition, BMI, insulin, glucose, and cholesterol levels) that is collected was presented in means and standard deviations. All categorical data (age, sex, race/ethnicity) is presented using percentages. The baseline correlations for the ASCVD risk subscales is computed using Pearson Correlation. Paired T-tests was used to test the changes in ASCVD risk score, cardiorespiratory fitness, body composition, weight, and blood measures from pre- to post-intervention. Change in body composition, fitness, weight, insulin, glucose, or cholesterol levels was compared to ASCVD risk score (10-year ASCVD and lifetime ASCVD). To investigate potential mediators in response to the ASCVD risk score, a linear regression analysis with stepwise elimination was used. Variables that were entered into the regression model were changes in body composition, fitness, weight, and changes in cardiometabolic levels such as insulin, glucose, and cholesterol. All variables were entered into the regression analysis at the

same time. This study was intent to treat so participants were not excluded if they did not meet weight loss goal. Participants that did not adhere/comply to exercise sessions withdrew from the study.

Chapter IV: Results

Baseline characteristics of the study participants (N=36) are displayed in (Table 1). The sample had a mean (SD) age of 46.5 (10.5) years, a mean weight of 95.5 (12.7) kg, and a mean BMI of 34.2 (3.4) kg/m^2. The sample was 80.6% female and 19.4% male. The sample consisted of 55.6% Caucasian, 36.1% black, 2.8% Asian, 2.8% American Indian or Alaskan Native, and 2.8% mixed race. Smoking status for the sample was 74.3% were never smokers and 25.7% are former smokers. Out of the former smokers, 2.8% quit 6 months-1.5 years before the beginning of the study. The former smokers that quit 1.5-2.5 years before the study was 2.8%. The number of participants that quit 3.5-5 years before the study was 2.8%. Out of the former smokers, 16.7% quit more than 5 years before the start of the study. For baseline 10-year and lifetime ASCVD, the sample had a mean score of 3.0% (3.0) and 32.8% (13.7) respectively.

Table 2 presents the mean changes in the outcome variable from the weight loss and aerobic exercise intervention. We observed a significant reduction in body weight with a range of 4.0 to 19.8 kg, with a percent weight loss of 9.3%. There was also a significant reduction in percent fat mass, overall body fat percentage, and lean mass ($p<0.001$). We also observed a significant decrease in waist circumference of 8.4 cm ($p<0.001$). For cardiometabolic levels, there was a significant decrease in total cholesterol ($p<0.001$), LDL ($p<0.006$), and a decrease in HDL ($p<0.038$). We also had significant reductions in fasting insulin and glucose levels ($p<0.001$). For cardiorespiratory fitness, a significant increase was observed in relative fitness ($p<0.001$); however, no significant change was observed in absolute fitness ($p>0.05$).

The primary purpose of this study was to investigate the effect of weight loss and aerobic exercise on estimated 10-year and lifetime ASCVD risk. We observed significant reductions in both 10-year and lifetime ASCVD risk (Table 2). Weight loss and exercise reduced 10-year

ASCVD risk by 0.6% ($p<0.001$; Figure 4) and lifetime ASCVD risk by 8.1% ($p<0.006$; Figure 5). The hypothesis for my primary outcome measure was met because weight loss and exercise did reduce 10-year and lifetime ASCVD risk.

The secondary purpose of this study was to investigate the physiological mediators of change in 10-year and lifetime ASCVD risk. We did that by analyzing Pearson correlations (Table 3) against change in 10-year and lifetime ASCVD risk. We found that change in 10-year ASCVD risk was positively correlated with both SBP and DBP. Change in lifetime ASCVD risk was positively correlated with change in total cholesterol. However, we wanted to test the independent association of change against change in 10-year and lifetime ASCVD risk. We ran linear regression analysis to test this. As displayed in Table 4, changes in SBP and DBP were the main predictors of improvements in 10-year ASCVD risk (model $r^2=0.74$; Figure 6). We also saw that change in HDL (model $r^2=0.20$; Figure 7) and age (model $r^2=0.06$; Figure 8) were predictors of change for 10-year ASCVD risk. Lifetime ASCVD risk independent association of change was with change in total cholesterol ($r^2=0.35$; Figure 9).

Chapter V: Discussion

The primary finding of the present study is that a weight loss and aerobic training intervention resulted in a significant, but minimal change in 10-year ASCVD risk (0.6%). However, the intervention produced a larger change in lifetime ASCVD risk (8.1%). Secondly, improvements in 10-year ASCVD risk were associated with changes in SBP and DBP along and changes in total cholesterol were predictors for changes in lifetime ASCVD. These findings have clinical implications for overweight and obese individuals, who often have higher ASCVD risk compared to lean adults.[6,9] To our knowledge, this is the first study to investigate the impact of a combined intervention of weight loss and aerobic exercise on estimated ASCVD risk.

Obesity is a major underlying risk factor for ASCVD. It increases the risk because it raises other risk factors such as hypercholesterolemia, hypertension, and hyperglycemia.[6] The PCE are used to stratify patients based on ASCVD risk in clinical settings. These equations advanced the field of cardiovascular risk stratification from the Framingham risk calculations as risk estimates by using data from racially and ethnically diverse populations allowing for more accurate risk calculations. While it is assumed that there would be a risk reduction in ASCVD due to lifestyle-based interventions, the magnitude of this reduction has not been previously quantified. Clinically significant weight loss is known to reduce variables utilized in the calculator for ASCVD including SBP and DBP along with total cholesterol, LDL, and HDL.[30,31]

In the intervention aspect of our study, we observed clinically significant weight loss (9.3%) and reduction in SBP (-9.1 mmHg), DBP (-5.7 mmHg), total cholesterol (-15.1 mg/dL), LDL (-7.8 mg/dL), and HDL (-2.4 mg/dL). However, despite these beneficial changes, we observed a significant, but small reduction in 10-year ASCVD risk (0.6%). A potential rationale for why we did not observe a greater magnitude reduction is that our sample had a low

baseline10-year ASCVD risk (3.0%). Specific constraints of the research study contributed to their low ASCVD risk at baseline including that the sample was relatively young (46.5 yrs.), non-smokers, and non-diabetic. Additionally, while some participants presented with dyslipidemia and hypertension, a portion of the sample was either medicated for this condition (thus presenting with normal values) or had normal cholesterol and blood pressure values. Thus, the combination of the aforementioned factors may have contributed to the participants having a low 10-year ASCVD risk at baseline, which could have resulted in our small reduction of 10-year ASCVD risk. We observed a more meaningful decrease in lifetime ASCVD risk (8.1%).

In our analysis, we also evaluated potential predictors for change in ASCVD outcome measures to inform what factors that might have the most impact on risk. The linear regression model for 10-year ASCVD risk found that independent factors were associated with reductions in SBP, DBP, and HDL along with age. In my study we observed the lowering of total cholesterol after weight loss and exercise. According to a study on the effects of exercise training on traditional lipid profiles, reductions in body weight following aerobic exercise result in a substantial decrease in total cholesterol and LDL with significant improvements in HDL levels (Gordon et al., 2014). A potential issue with my study is that we saw a slight reduction of HDL, yet the change of HDL was in the linear regression analysis. This could be due to the substantial decrease in the total lipid pool therefore decreasing HDL slightly (-2 mg/dL). However, it is likely the health benefits of the small decrease in HDL are outweighed by the significant reduction in the total lipid profile. For lifetime ASCVD risk, changes in total cholesterol were the main factor that reduced lifetime ASCVD risk. We added other variables into the equation, but only total cholesterol was included in the linear regression model. In our results, we found that reductions in blood pressure were major factors in reducing 10-year ASCVD risk. This may

represent potential targets for intervention that are specifically focused on improving ASCVD risk through lifestyle intervention. According to the ACSM Position Stance on exercise and hypertension they advocate for lifestyle modification on the treatment and prevention of hypertension, with exercise being an integral component.[22]

A potential issue with the PCE is that a measure of physical activity or fitness, which are independent predictors of CVD are not included as variables. For example, a 1 MET increase in fitness has been associated with a 15% reduction in CVD risk from a recent meta-analysis independent of other risk factors.[33] In our study, we had improvements in physical fitness by METS and Relative VO_2peak. We improved VO_2peak by +2.4 mL/kg/min and improved our METS by +0.7, which is a main measure of fitness used in epidemiological studies. This could mean that when evaluating the change in ASCVD involving exercise there may be an underestimation of potential improvement in the intervention in our program since cardiorespiratory fitness can be improved in programs with aerobic exercise training. Importantly, several studies have demonstrated an inverse relationship between cardiorespiratory fitness and generally cardiovascular mortality and despite the strong association between fitness and ASCVD risk, there are no long-term risk prediction tools available that incorporate measured fitness.[34] The PCEs like many other risk prediction tools have decided to leave out fitness which is a known ASCVD risk factor. The exclusion of fitness has been partially explained by many organizations because an essential mechanism through which exercise influences its cardioprotective effects were thought to be a modification of traditional and novel risk factors.[35] The association between higher levels of physical activity and lower ASCVD rates could explain up to 59% of the activity-related reduction in ASCVD risk.[36] A study wanted to improve the accuracy of the pooled cohort equations by studying whether cardiorespiratory fitness could be

used to improve the accuracy of the risk model. The study found that higher fitness was associated with a significant 21% lower risk to develop the study endpoint. Each one-unit increase in baseline METS was associated with a 5% lower risk to develop the study endpoint. Continuous net reclassification improvement analysis showed an overall improvement of 11% in the accuracy of classification when fitness was added to the ASCVD risk model.[37] The addition of fitness to the pooled cohort ASCVD risk could significantly improve the accuracy of the model.[35,37]

The present study has several strengths. First, the sample was racially diverse, consisting of 36% African American. Secondly, all exercise sessions were supervised by study staff where heart rate and RPE were monitored throughout the session. The amount of exercise a participant completed was strictly monitored and tracked. Our sample had an adherence of 95.2% $\pm$ 7.5 and a compliance (attendance rate) of 93.7% $\pm$ 8.3 The diet consisted of the OPTIFAST diet, which was medically supervised at Vidant Wellness Center to enhance the ability to achieve clinically significant weight loss. Lastly, the PCEs were used to assess 10-year and lifetime ASCVD risk which has been validated by the ACC and AHA.

This study also has several limitations. First, there are limitations regarding the sample used in the study. There was an underrepresentation of men with 80.6% of the sample being female. The sample was overweight/class I obese, so the findings are not generalizable to those of normal weight or a higher BMI class. Age of our sample was also a limitation since we did not have older adult who have a higher baseline risk. Another limitation is that the 10-year risk at baseline was low, which could have contributed to a smaller reduction. It is also important to note that the data was gathered from a weight maintenance study, for which getting participants

to clinically significant weight loss was the first component of the study. Since the data for the present study came from the weight loss component of that study, there is no control group.

In conclusion, a combined OPTIFAST weight loss and aerobic exercise training program may lead to reductions in both 10-year and lifetime ASCVD risk using the pooled cohort equations. The public health implications of these findings include new potential clinical interventions to improve 10-year and lifetime ASCVD risk. Future studies should investigate the impact of exercise on ASCVD risk during weight maintenance, the influence of strength training on improved ASCVD risk, and the inclusion of fitness into ASCVD prediction models.

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Tables and Figures

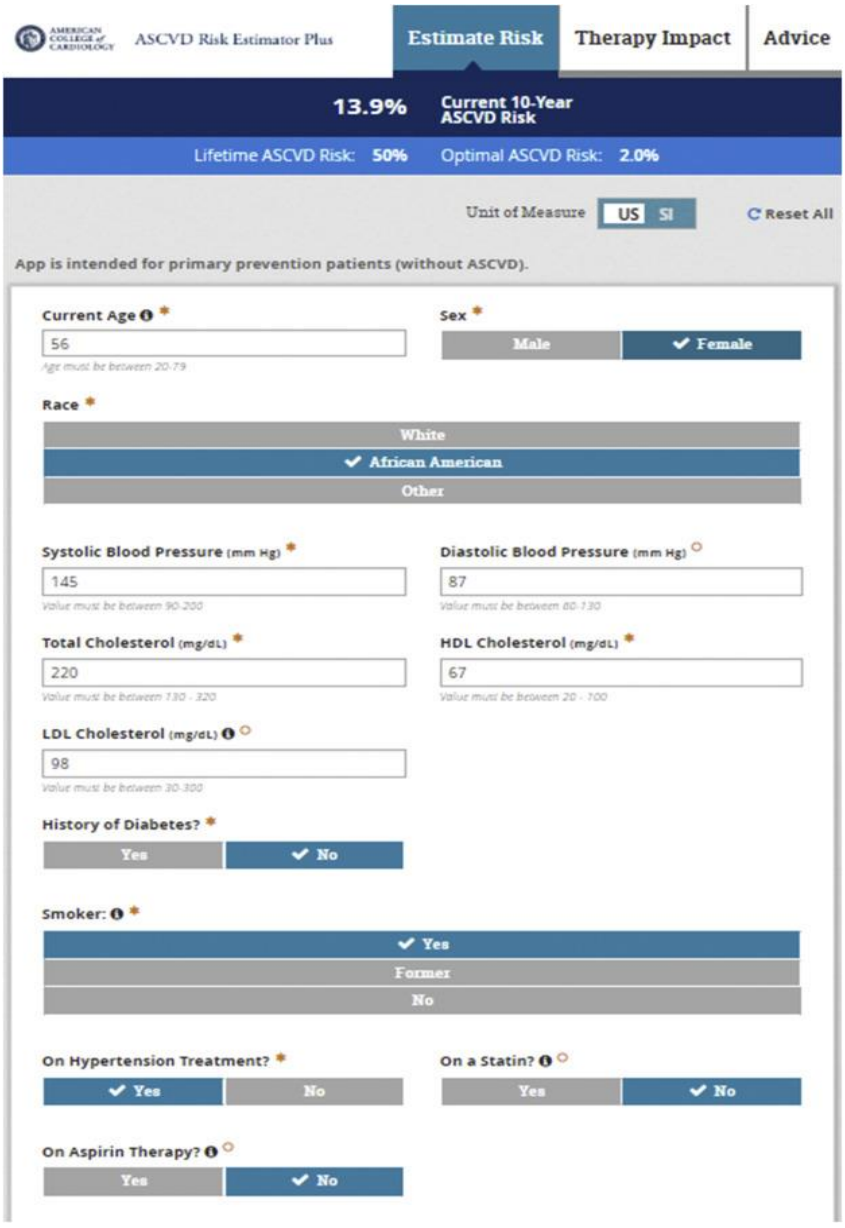


Figure 1: ASCVD Risk Estimator Plus on the ACC website

DIDACTIC CONTENT FOR OPTIFAST CLASS SCHEDULE	
WEEK 1	Product Info/Program Logistics/Goal Setting – RD & Behaviorist
WEEK 2	Motivation to Change - Behaviorist
WEEK 3	Importance of Self-Monitoring - RD
WEEK 4	Exercise Update – Exercise Specialist
WEEK 5	Identifying Eating Cues, Triggers, and Eating Style? - RD
WEEK 6	Where are the calories? / Food Label Reading - RD
WEEK 7	Mindful Eating/Emotional Eating - Behaviorists
WEEK 8	Relaxation Techniques – Mind Body Staff
WEEK 9	Eating Out/Special Occasions/Cooking Quick and Lite - RD
WEEK 10	Effects of Stress on Body Weight - Behaviorist

Figure 2: Didactic content for the OPTIFAST lifestyle education classes

	Exercise amount
Week 1	300 MET min.
Week 2	350 MET min.
Week 3	400 MET min
Week 4	450 MET min.
Week 5	500 MET min.
Week 6	550 MET min.
Week 7	600 MET min.
Week 8	650 MET min.
Week 9-10	700 MET min.

Figure 3: Aerobic exercise progression from week 1 to week 10

Variable	Mean (S.D.)
Age (Years)	46.5 (10.5)
Have you ever been diagnosed with type 1 or 2 diabetes (%)	
No	100.0
Yes	0.0
Sex, (%)	
Female	80.6
Male	19.4
Race, (%)	
Caucasian	55.6
African American	36.1
Asian	2.8
American Indian or Alaskan Native	2.8
Mixed Race	2.8
Please choose overall smoking status (%)	
Former	25.7
Never	74.3
If former smoker, how long did you quit smoking (%)	
6 months-1.5 years ago	2.8
1.5-2.5 years ago	2.8
3.5-5 years ago	2.8
More than 5 years ago	16.7
Statis (%)	
Not on Statin Therapy	97.2
On Statin Therapy	2.8
Are you currently on aspirin therapy? (%)	
No	97.1
Yes	2.9
Variable	**Baseline Mean (S.D.)**
Weight (kg),	95.5 (12.7)
BMI, (kg,m^2)	34.2 (3.3)
Waist Circumference, (cm)	98.0 (9.4)
Body Fat, (%)	41.5 (5.7)
Peripheral SBP, (mmHg)	123.0 (13.4)
Peripheral DBP, (mmHg)	77.7 (9.2)
Glucose, (mg/dL)	96.3 (9.7)
Insulin, uIU/mL	18.0 (10.7)
Cholesterol, Total (mg/dL)	187.0 (30.2)
LDL, (mg/dL)	112.9 (27.4)

HDL, (mg/dL)	52.5 (12.8)
Absolute VO_{2peak}, (L/min)	2.00 (0.50)
Relative VO_{2peak}, (mL/kg/min)	21.4 (4.1)
METs	6.1 (1.2)
Estimated METs	8.4 (1.2)
10 Year ASCVD	3.0 (3.0)
Lifetime ASCVD	32.8 (13.7)

Table 1. Baseline participant characteristics. Continuous variables are displayed in mean (SD) and categorical variables are summarized in % (n). BMI: Body Mass Index, VO_{2peak}: Maximal Oxygen Consumption. SBP: Systolic Blood Pressure. DBP: Diastolic Blood Pressure. LDL: Low-density lipoprotein. HDL: High-density lipoprotein.

Variable	Total Δ Mean (S.D.)	95% CI Lower	Upper	p-value
Weight (kg), (%)	-9.3 (3.1)	-10.4	-8.3	0.001
BMI, (kg,m^2)	-3.3 (1.4)	-2.8	-3.7	0.001
Waist Circumference, (cm)	-8.4 (5.0)	-6.7	-10.1	0.001
Body Fat, (%)	-2.1 (1.8)	-1.5	-2.7	0.001
Peripheral SBP, (mmHg)	-9.1 (15.1)	-5.8	-12.4	0.001
Peripheral DBP, (mmHg)	-5.7 (6.2)	-3.6	-7.8	0.001
Glucose, (mg/dL)	-11.2 (8.0)	-8.5	-13.9	0.001
Insulin, (uIU/mL)	-8.9 (13.4)	-4.2	-13.6	0.001
Cholesterol, Total (mg/dL)	-15.1 (19.1)	-8.6	-21.6	0.001
LDL, (mg/dL)	-7.8 (16.1)	-2.4	-13.3	0.006
HDL, (mg/dL)	-2.4 (6.7)	-0.14	-4.7	0.038
Absolute VO_{2peak}, (L/min)	+0.023 (0.15)	-0.03	0.07	0.358
Relative VO_{2peak}, (mL/kg/min)	+2.4 (1.5)	1.9	3.0	0.001
METs	+0.7 (0.4)	0.55	0.85	0.001
Estimated METs	+0.8 (0.9)	0.51	1.2	0.001
10 Year ASCVD	-0.6 (0.6)	-0.80	-0.30	0.001
Lifetime ASCVD	-8.1 (12.4)	-13.6	-2.6	0.006

Table 2: Change scores from baseline to 10-week follow-up. Presented as mean change with 95% confidence intervals

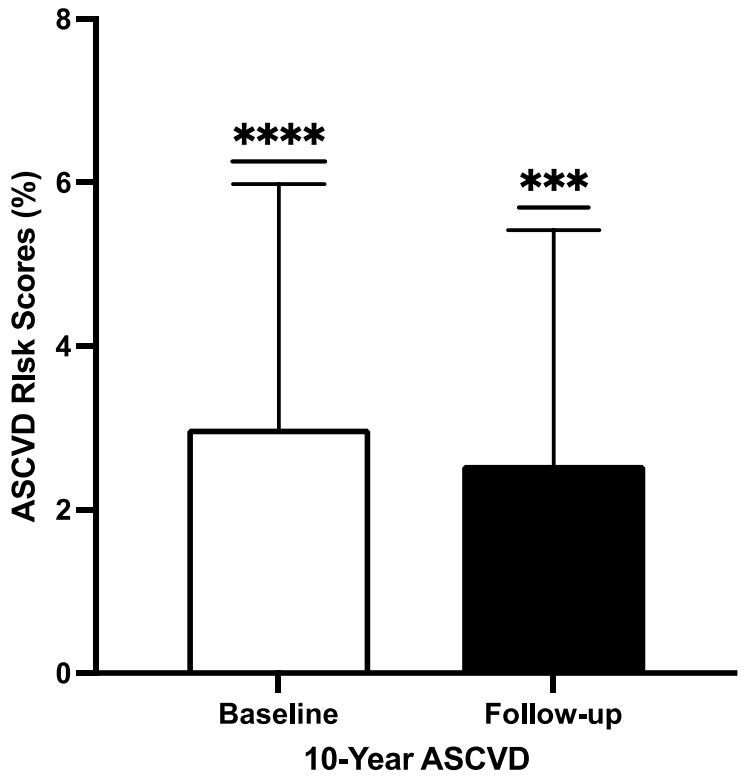


Figure 4: Change in 10-year ASCVD risk with 95% CI from baseline to follow-up.

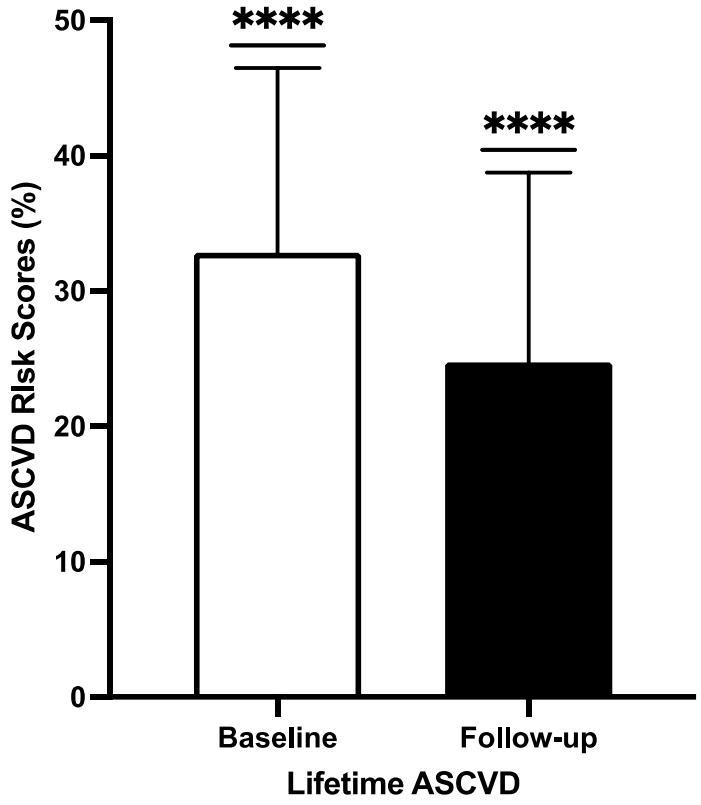


Figure 5: Change in lifetime ASCVD risk with 95% CI from baseline to follow-up.

	Δ 10-Year ASCVD		Δ Lifetime ASCVD	
	r	p	r	p
Δ Systolic Blood Pressure	**0.799**	**< 0.001**	0.248	0.265
Δ Diastolic Blood Pressure	**0.474**	**< 0.001**	-0.108	0.632
Δ Total Cholesterol	-0.099	0.645	**0.476**	**0.025**
Δ HDL	-0.066	0.760	0.017	0.941
Δ LDL	-0.120	0.567	0.420	0.052
Δ Glucose	-0.211	0.321	0.322	0.144
Δ Insulin	**-0.438**	**0.041**	**-0.499**	**0.025**
Δ Weight	0.325	0.121	0.086	0.703
Δ BMI	-0.009	0.966	-0.096	0.671
Δ Waist Circumference	0.217	0.310	0.382	0.079
Δ % Fat Mass	0.325	0.121	-0.130	0.565
Δ Visceral Fat Volume	0.040	0.854	0.134	0.551
Δ Visceral Fat Area	-0.101	0.637	0.239	0.283
Δ Absolute Fitness	-0.251	0.237	0.106	0.640
Δ Relative Fitness	-0.341	0.104	-0.037	0.871
Δ Estimated METs	0.062	0.775	0.002	0.992
Δ METs	-0.340	0.104	-0.037	0.871
Age	-0.373	0.073	0.110	0.625

Table 3: Pearson correlations between systolic blood pressure, diastolic blood pressure, cardiometabolic levels, body composition, fitness, age and improvements in 10-year and lifetime ASCVD risk.

10-Year ASCVD Linear Regression Model				
Variable	Standardized Coefficient β	T value	Variable r^2	p-value
Δ SBP (mmHg)	0.752	5.108	0.57	<0.001
Δ DBP (mmHg)	-0.629	-3.454	0.17	<0.001
Δ HDL (mg/dL)	-0.351	-3.531	0.20	0.002
Age	-0.255	-3.154	0.06	0.006
Lifetime ASCVD Linear Regression Model				
Variable	Standardized Coefficient β	T value	Variable r^2	p-value
Δ Total Cholesterol (mg/dL)	0.589	3.094	0.347	0.006

Table 4: Linear regression models for 10-year and lifetime ASCVD.

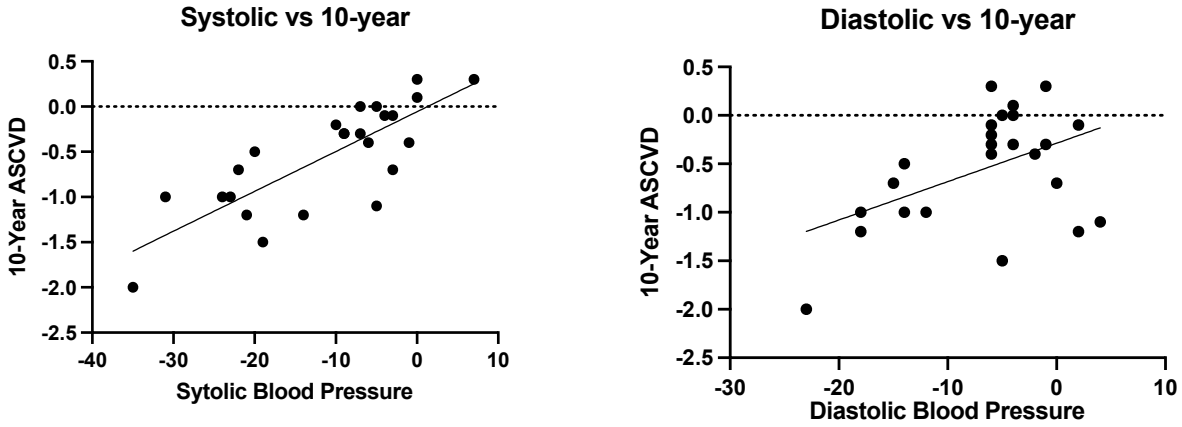


Figure 6: Scatter plots displaying the correlation between change in systolic and diastolic blood pressure against change in 10-year ASCVD.

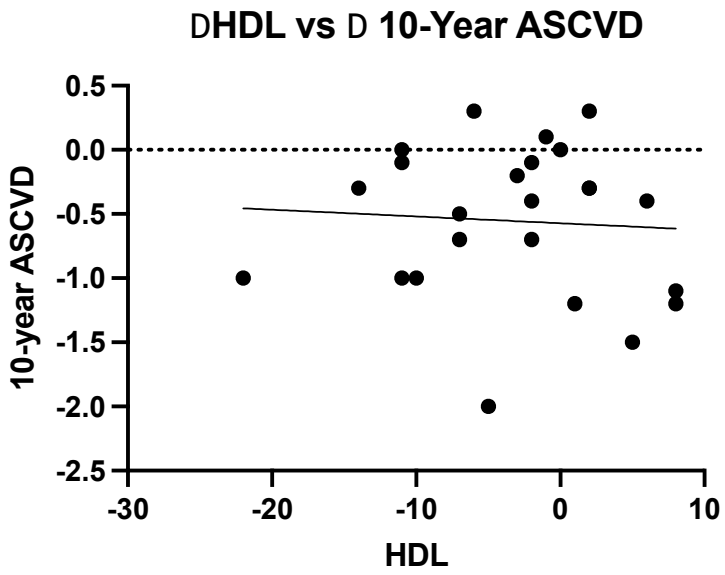


Figure 7: Scatter plots displaying the correlation between change in HDL against change in 10-year ASCVD.

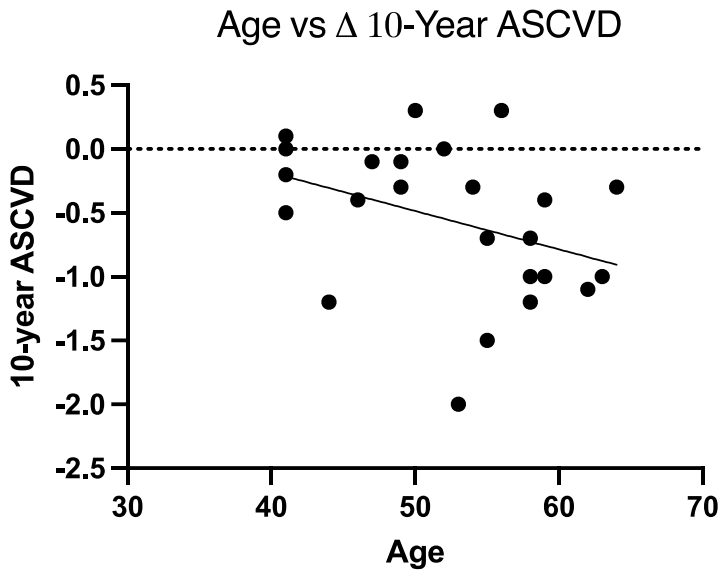


Figure 8: Scatter plots displaying the correlation between age against change in 10-year ASCVD.

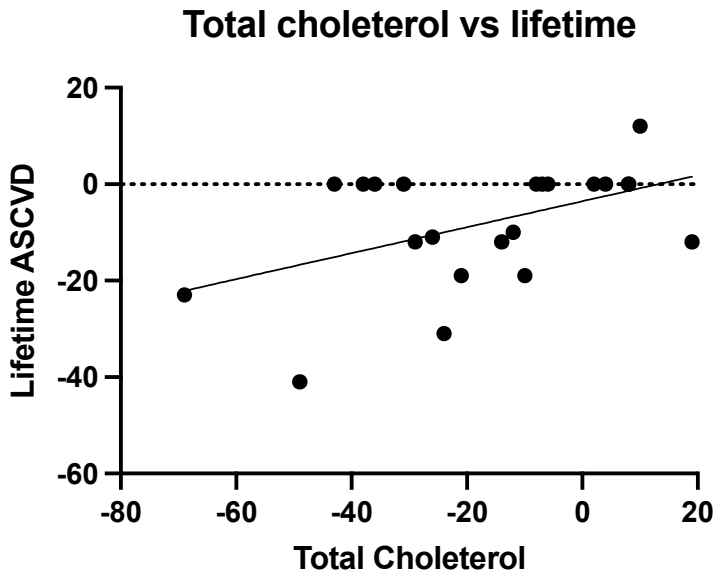


Figure 9: Scatter plots displaying the correlation between change in total cholesterol against change in lifetime ASCVD.

Appendix: IRB Approval Letter

EAST CAROLINA UNIVERSITY
University & Medical Center Institutional Review Board
4N-64 Brody Medical Sciences Building· Mail Stop 682
600 Moye Boulevard · Greenville, NC 27834
Office **252-744-2914** · Fax **252-744-2284** ·
rede.ecu.edu/umcirb/

Notification of Continuing Review Approval: Expedited

From: Biomedical IRB
To: Damon Swift
CC:

Anna Huff
Date: 10/26/2020
Re: CR00008847
UMCIRB 18-001904
PREVAIL-P

The continuing review of your expedited study was approved. Approval of the study and any consent form(s) is for the period of 10/19/2020 to 10/18/2021. This research study is eligible for review under expedited category # 8c. The Chairperson (or designee) deemed this study no more than minimal risk.

As the Principal Investigator you are explicitly responsible for the conduct of all aspects of this study and must adhere to all reporting requirements for the study. Your responsibilities include but are not limited to:

1. Ensuring changes to the approved research (including the UMCIRB approved consent document) are only initiated with UMCIRB review and approval except when necessary to eliminate an apparent immediate hazard to the participant. All changes (e.g. a change in procedure, number of participants, personnel, study locations, new recruitment materials, study instruments, etc.) must be prospectively reviewed and approved by the UMCIRB before they are implemented;

2. Ensuring that only valid versions of the UMCIRB approved, date-stamped informed consent document(s) are used for obtaining informed consent (consent documents with the IRB approval date stamp are found under the Documents tab in the ePIRATE study workspace);

3. Promptly reporting to the UMCIRB all unanticipated problems involving risks to participants and others;

4. Applying for continuing review and receive approval of continuation of the study prior to the study's current expiration date. Application for continuing review should be submitted no less than 30 days prior to the expiration date. Lapses in approval (i.e. study expiration) should be avoided to protect the safety and welfare of enrolled participants and liability to the University; and

5. Submission of a final report when the study meets the UMCIRB criteria for closure. Study approval should not be allowed to expire simply because the study is completed, rather the UMCIRB should be formally notified of study completion via the final report process.

The approval includes the following items:

Document	Description
Compensatory Health Beliefs Scale.doc(0.01)	Surveys and Questionnaires
compensatory health beliefs scale.pdf(0.01)	Surveys and Questionnaires
Dr. Swift's letter of intent for IRB review.pdf(0.01)	Additional Items
Food Cravings Questionnaire-State(0.02)	Surveys and Questionnaires
Food frequency Questionnaire(0.01)	Surveys and Questionnaires
Food-Craving Inventory(0.03)	Surveys and Questionnaires
Light Scanner Protocol(0.01)	Study Protocol or Grant Application
PDF of study website(0.01)	Recruitment Documents/Scripts
PREVAIL-EMAIL recruitment (0.01)	Recruitment Documents/Scripts
PREVAIL-P Consent Study 1-Clean(0.04)	Consent Forms
PREVAIL-P-Consent-Study-2-Clean(0.01)	Consent Forms
Retrospective VAS(1).docx(0.01)	Surveys and Questionnaires
SF-36(0.01)	Surveys and Questionnaires
Study 1- Recruitment(0.03)	Recruitment Documents/Scripts
Study 2 Flyer (0.03)	Recruitment Documents/Scripts
Study protocol (0.04)	Study Protocol or Grant Application
Three Factor Eating Questionnaire(0.02)	Surveys and Questionnaires
Web-screener(0.01)	Recruitment Documents/Scripts
Weight Efficacy Life-Style Questionnaire (0.02)	Surveys and Questionnaires
Weight Stigma questionnaire(0.02)	Surveys and Questionnaires

For research studies where a waiver or alteration of HIPAA Authorization has been approved, the IRB states that each of the waiver criteria in 45 CFR 164.512(i)(1)(i)(A) and (2)(i) through (v) have been met. Additionally, the elements of PHI to be collected as described in items 1 and 2 of the Application for Waiver of Authorization have been determined to be the minimal necessary for the specified research.

The Chairperson (or designee) does not have a potential for conflict of interest on this study.

East Carolina University

Hello, Damon Swift

Compare

- 1 - Study Personnel & Funding
  - 1 Study Identification
  - 1.1 Study Staff Roles and Responsibilities
  - 1.2 IRB Researcher Training Records
  - 1.3 Funding Sources
  - *1.31 Industry Sponsor Information*
  - 1.32 Federal Government Sponsored Studies
  - *1.33 Non-Profit Sponsored Studies*
  - *1.34 State or Local Government*
  - *1.35 Other University or College*
  - *1.36 Internally Funded (ECU)*
  - 1.4 Conflict of Interest
  - 1.43 Sponsored Programs & Conflict of Interest
  - 1.5 Study Locations
  - *1.51 Multi-Site Coordination Center*
  - *1.53 External IRB*
- 2 - Study Objectives & Design
  - 2.0 Required Reviews

You Are Here: PREVAIL-P

Reading: UMCIRB 18-001904

Go to forms menu | Print | Help

Study Identification Information

This is the first step in your Human Research Application. You will automatically be guided to the appropriate page views needed to complete your submission. If a question is not applicable to your study, you may state this as your response. Please read the help text located on the right side of the page throughout this application.

1.0 * **Study Name (Short):**
PREVAIL-P

The short study name is limited to 255 characters.

2.0 **Study Name (Long):**
Prescribed Exercise to Reduce Recidivism After Weight Loss

Most other text boxes do not have any limits on number of characters.

3.0 * **Summary of Research in Lay Terms:**
The Prescribed Exercise to Reduce Recidivism After Weight Loss pilot (PREVAIL-P) study will evaluate the effect of aerobic exercise training amount on weight maintenance following after a significant weight loss. Study participants will lose about 7-10% of their body weight and be assigned to exercise at physical activity guidelines or weight maintenance guidelines.

The lay summary should be no more than 400 words and should include the following:
Background/Purpose of Study
Description of Subjects/Participants
Research Methods/Procedures

4.0 * **Principal Investigator:**
Damon Swift

Use the "select" or "add" button to choose from a list of individuals for each applicable role.

5.0 **Faculty Investigator** (Serving as the responsible individual in the oversight of the research study when the PI is a student, resident, fellow or visiting faculty.)

Faculty Investigator IRB Certification Renewal Deadline:

6.0 **Study Coordinator or Contact Individual:**
Anna Huff

7.0 **Contact Individual(s) (if different from Study Coordinator or Principal Investigator):**

Last Name	First Name	Organization Profile	IRB Certification Renewal Deadline

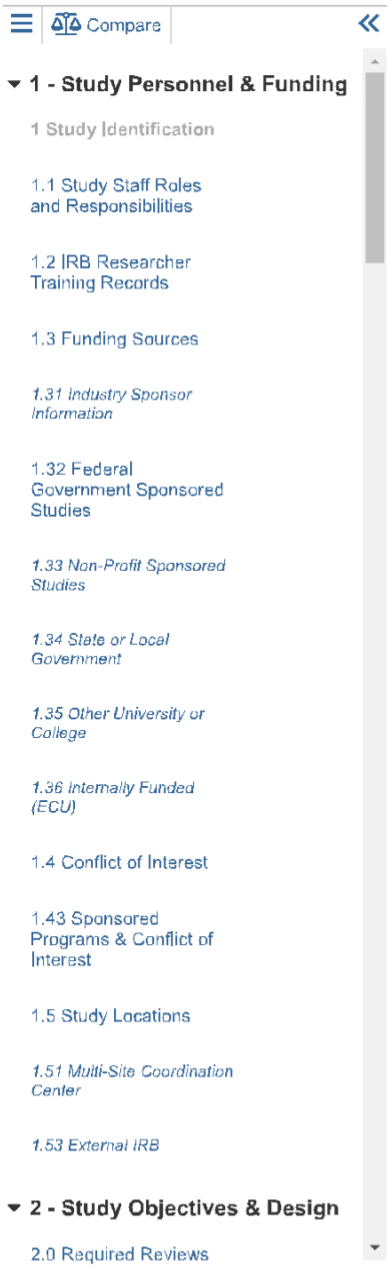
There are no items to display

*People added here **will** be able to **edit** the study.*

Clicking the "Add" button allows you to choose individuals that are already registered within ePIRATE. This function will not add individuals that have not registered in ePIRATE yet.

8.0 **Sub-Investigators:**

Last Name	First Name	Organization	Profile	IRB Certification Renewal Deadline
Anderson	Brianna	Kinesiology, Department of	Brianna Anderson's Profile	3/31/2022



Last Name	First Name	Organization	Profile	IRB Certification Renewal Deadline
Barefoot	Savanna	Kinesiology, Department of	Savanna Barefoot's Profile	9/2023
Bartlett	Allison	Kinesiology, Department of	Allison Bartlett's Profile	7/18/2022
Beyl	Robbie	Other Organization/Institution	Robbie Beyl's Profile	9/20/2021
Boone	Paige	Kinesiology, Department of	Paige Boone's Profile	9/5/2022
Brophy	Patricia	East Carolina Diabetes and Obesity Institute (ECDOI)	Patricia Brophy's Profile	3/20/2022
Brown	Taylor	Kinesiology, Department of	Taylor Brown's Profile	9/21/2021
Carels	Robert	Psychology, Department of	Robert Carels's Profile	7/18/2023
Charlton	Sarah	Kinesiology, Department of	Sarah Charlton's Profile	8/21/2022
Clark	Angela	East Carolina Diabetes and Obesity Institute (ECDOI)	Angela Clark's Profile	7/12/2021
Davis	Emily	Kinesiology, Department of	Emily Davis's Profile	1/12/2022
Dubis	Gabriel	East Carolina Diabetes and Obesity Institute (ECDOI)	Gabriel Dubis's Profile	8/27/2023
Feffer	Andrew	Kinesiology, Department of	Andrew Feffer's Profile	1/17/2022
Garner	Zoe	Kinesiology, Department of	Zoe Garner's Profile	1/13/2023
Gosney	Ryan	Kinesiology, Department of	Ryan Gosney's Profile	1/11/2023
Grammer	Emily	Kinesiology, Department of	Emily Grammer's Profile	7/2/2023
Hearne	Joshua	Kinesiology, Department of	Joshua Hearne's Profile	7/20/2022
Hiller	Kayleigh	Kinesiology, Department of	Kayleigh Hiller's Profile	7/23/2022
Holland	Kyle	Kinesiology, Department of	Kyle Holland's Profile	1/5/2023
Holsinger	Jourdyn	Kinesiology, Department of	Jourdyn Holsinger's Profile	7/15/2021
Houmard	Joseph	Kinesiology, Department of	Joseph Houmard's Profile	5/1/2023
Howell	Harrison	Kinesiology, Department of	Harrison Howell's Profile	8/12/2022