C-REACTIVE PROTEIN AND EXERCISE INTENSITY IN AFRICAN AMERICANS

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Racial health disparities have been shown in Cardiovascular Disease (CVD) with African Americans having a substantially greater risk compared to Caucasian Americans. One potential factor explaining racial differences in CVD may be increased levels of systemic inflammation in African Americans compared to Caucasians. Epidemiological studies have shown that CRP (a marker of systemic inflammation) is an independent risk factor for cardiovascular mortality[6,7], and is higher in African Americans compared to Caucasians. In addition to the elevated CRP levels, African Americans have increased levels of obesity and lower cardiorespiratory fitness compared to Caucasians. Although results have been inconsistent in studies related to exercise interventions to improve CRP levels, many studies have had primarily Caucasian participants and/or have used different intensities of aerobic training.

PURPOSE: The purpose of the present study was to determine the effects of moderate and high intensity aerobic exercise training on CRP in obese African-American men and women.

METHODS: The present study was a randomized-controlled trial of 60 obese and overweight African American men and women (body mass index of 25–45 kg/m^2), 35-65 years. Participants were randomized to the moderate intensity (MOD-INT; n = 20), high intensity (HIGH-INT; n = 20), or non-exercise control group (n = 20) for a 24-week intervention. The moderate intensity group participated in aerobic exercise at 50% of their VO_2 max, and the high intensity group participated in aerobic exercise at 75% of their VO_2 max. Participants completed a 12-hour fasted blood draw at the East Carolina Heart Institute. A venous blood sample of a total of 21 mL

of blood was drawn by the study nurse pre and post exercise intervention. Blood samples were sent to a clinical laboratory (LabCorp Inc., Burlington, NC) for a complete analysis of metabolic, lipid, insulin level measures, CRP, and blood chemistries. The serum separator tube was sent to LabCorp for measurement of C-reactive protein.

RESULTS: There were 11 participants in the control group, 10 participants in the moderate intensity exercise group, and 13 in the high intensity exercise group. There were no significant differences between the randomization groups for age, gender, weight, BMI, waist circumference, body fat percentage, glucose, insulin, and CRP ($p > 0.05$). We did not observe significant change in CRP levels among study groups in the MOD or the HIT group compared to the CON in obese African-American adults ($p=1.00$). The association between exercisers and change in CRP and fat-mass approached a significant change ($r=-0.379$, $p=0.07$). The HIGH-INT group had a larger increase in VO_2 max (ml•kg•min; L/min) ($p<0.05$) compared to the CON group. Also, there was a significant relationship between the CON group and MOD intensity group in estimated METs ($p<0.01$). Data for changes in clinical risk factors between participants based on change in CRP are shown in Table 2. There were no significant changes found in CRP for any clinical risk factors between non-responders and responders ($p>0.05$).

CONCLUSION: In conclusion, we observed that neither moderate or high intensity aerobic decreased systemic inflammation levels in obese African Americans. Secondly, CRP was not improved with a change in fat-mass in exercisers. Future research could allow for the analysis of both Caucasian and African Americans, allowing for a more direct comparison between the two races for the intervention variables measured. Also, it could entail an interval training aerobic group, as well as a resistance training exercise group to elucidate further comparisons in

intervention variables. Lastly, future studies may want to combine dietary and exercise to potentially lower CRP to a greater extent than exercise alone.

C-reactive Protein and Exercise Intensity in African Americans

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Chapter I: Introduction

The leading cause of mortality in both men and women in the United States is cardiovascular disease (CVD)[1,2]. Elevated systemic inflammation plays a central role in the pathophysiology of CVD, which represents a proinflammatory state[3]. CRP, a protein synthesized in the liver, increases in response to excess chronic inflammation[4]. Previous research shows elevated CRP levels are a predictive marker of inflammation and a key factor in the development of CVD[4,5]. Epidemiological research suggests high levels of CRP is an independent risk factor for both cardiovascular events and cardiovascular disease mortality[6,7]. Specifically, recent data indicates that every increase in 1.10 mg/L of CRP is associated with a 2- fold increase in CVD mortality[8]. Thus, CRP is a biomarker predictive of CVD[6–8].

Of note, African Americans have a higher rate of CVD risk factors compared to Caucasians. This difference in CVD risk factors between races may be attributed to higher levels of obesity amongst African Americans[9]. In addition to the increased prevalence of obesity in African Americans, previous literature demonstrates higher CRP levels in African American subjects, which may impose an increased risk for future CVD events[10,11]. It has been concluded that significant race differences exist in the population distribution of CRP[10]. Thus, interventions that reduce CRP in African Americans may have a favorable impact on cardiovascular disease risk and health disparities.

While CRP has been shown to be a risk factor for CVD, previous research has also discovered that higher levels of CRP are closely associated with the presence of obesity[10]. The accumulation of an excessive amount of fat is associated with the release of pro-inflammatory cytokines and subsequently increased CRP levels[12]. Cross-sectional studies have suggested that elevated CRP levels are more prevalent in obese individuals compared to non-obese[13–15].

According to a study conducted through The National Health and Nutrition Examination Survey, obese women were 4.8 times more likely to have clinically elevated CRP levels of >1 mg/L compared to normal-weight women, and obese men were 6.2 times more likely to have elevated CRP levels compared to normal-weight men[13]. Obesity continues to be a key factor in CVD, and a potential factor in elevated CRP levels.

Exercise training has been recommended by the American Heart Association (AHA) and the American College of Sports Medicine to reduce cardiovascular disease and has been shown to be an effective strategy to reduce systemic inflammation. According to the AHA, decreased physical activity is the fourth risk factor for atherosclerotic heart disease[16]. Recent data has shown that low cardiorespiratory fitness is associated with higher levels of CRP and cardiovascular mortality[17,24]. While research has shown fitness levels are inversely associated with cardiovascular mortality, studies investigating the effect of exercise intervention on CRP levels have mixed results. Although many studies conclude that a variety of aerobic training does improve CRP concentration levels, there is a gap of research supporting the effect of specific exercise intensity in CRP concentrations. Vigorous intensity exercise increases aerobic fitness more effectively than moderate intensity exercise, therefore, it is logical to investigate the efficacy of varying aerobic exercise intensities on subsequent changes in CRP levels [20].

Obese individuals with low cardiorespiratory fitness are more likely to have higher CRP level, as well as a higher risk for CVD. A lifestyle modification such as an increase in exercise is associated with improved CRP levels. However, little data exists directly comparing moderate to high intensity exercise training on CRP levels in obese adults and no studies exist, to our knowledge, in African Americans. Thus, a study comparing aerobic exercise training intensity on CRP in obese African Americans will provide valuable knowledge to the field. may add more

input on how to lower CRP levels due to the potential decrease in fat loss from aerobic exercise training.

Purpose

The purpose of this study is to determine the effects of moderate and high intensity aerobic exercise training on CRP in obese African American men and women.

Hypothesis

The levels of CRP in obese African American will decrease with high intensity aerobic exercise training compared to moderate intensity exercise training.

Delimitations

The present study includes the demographic of sedentary, obese African American aged 35-65 years, and moderate and high intensity aerobic exercise training on a treadmill.

Limitations

The use of sedentary, obese, African Americans, aged 35-60 years limits the generalizability of results to other ethnicities, age groups, and BMI classifications. Results cannot be inferred regarding other intensities of exercise due to the exercise intervention consisting of a moderate and vigorous intensity. The use of a treadmill also limits generalizability to other exercise training modalities.

Operational Definitions

1. CVD: Cardiovascular disease
2. CRP: C-reactive protein
3. CRF: Cardiorespiratory fitness
4. VO_2 max: maximal aerobic capacity, expressed in absolute (L/min) or relative values (ml/kg/min)

Chapter II: Review of Literature

In the United States, cardiovascular disease (CVD) is the leading cause of mortality in both men and women[1,2]. Underlying the pathophysiology of cardiovascular disease is elevated systemic inflammation, which represents the presence of a systemic proinflammatory state [3]. It is believed inflammation is triggered by excess low-density lipoprotein (LDL) cholesterol, lipocytes, and other cellular toxins within the blood stream[21,22]. LDL cholesterol proceeds to collect in the damaged area of the arterial wall, causing fatty streaks[21]. A chemical reaction causes oxidization of the LDL fatty streaks, signaling white blood cells known as monocytes to travel to the damaged site[21]. The monocyte converts into a macrophage, attempting to digest the cholesterol molecules[21]. Foam cells, macrophages with large amounts of oxidized lipids, begin to accumulate, forming plaque within the blood vessels and inhibiting blood flow[21]. The arterial wall thickens as plaque accumulates, driving the formation of atherosclerosis[21]. Furthermore, the accumulation of fibrous plaque formation augments an individual's susceptibility for a myocardial infarction[21,22]. The progression of atherosclerotic plaque is associated with increased production of proinflammatory cytokines[22]. Cytokines, a group of proteins secreted by cells of the immune system, act as chemical messengers to regulate natural defense mechanisms to symptoms such as inflammation[22,23]. During elevated systemic inflammation, a protein produced in the liver called C-reactive protein (CRP) will increase in response to excess inflammation[4]. Furthermore, studies have shown that the elevated concentration of CRP is a predictive marker of inflammation which underlies the development of CVD[4,5].

CRP and CVD risk

A protein synthesized in the liver called C-reactive protein (CRP) will increase in response to excess inflammation[4]. Previous research has shown that elevated levels of CRP is a predictive marker of inflammation[4,5]. Research supports this potential marker of vascular inflammation as a key pathogenic factor in the development of atherosclerosis, increasing the risk for CVD[6,7]. According to the AHA[24], those with CRP levels >3mg/L are categorized at a high risk for CVD. Much of the epidemiological research suggests that high levels of CRP is an independent risk factor for not only cardiovascular events, but mortality[6,7].

One study by Bahadursingh et al.[6] evaluated hospital patients (N=300) of Cross Crossing Medical Centre emergency department receiving routine cardiovascular assessment. Cases were divided into two groups. One group of patients with a cardiovascular event and the second group of patients were controls, those without a cardiovascular event[6]. Thirty-three percent of 89 subjects with CVD had higher CRP levels (>0.8 mg/L)[6]. The risk of CVD associated with an elevated CRP (> 0.8 mg/L) was generated through the calculation of odds ratios[6]. The results of this study indicated that a patient with high CRP levels had 1.8 times greater risk of CVD compared to a patient with normal CRP levels (>0.8 mg/L)[6]. Thus, this study concluded that there is an association between increased CRP levels and a high risk for CVD [6].

To further support the association between CRP and CVD, Cozlea et al.[7] evaluated the relationship between CRP levels and global CVD risk in patients (N=100) with cardiovascular risk factors in high risk regions of Europe[7]. The authors assessed the risk of CVD in each subject utilizing the systematic coronary risk evaluation (SCORE) chart, which estimates the risk of a fatal atherosclerotic events occurring in the next 10 years (low risk <1%, moderate risk 1-4%, high risk 5-9%, and very high risk ≥10%)[7]. The SCORE diagram assesed differet parameters

such as gender, age, smoker/non-smoker status, plasma cholesterol levels, and systlic blood pressure values[7]. Normal values for CRP in this study was classified as <10 mg/L[7]. All patients (n=100) in the study, both men and women, were categorized into two groups based on the measured CRP levels[7]. Patients were divided into two groups: Group A patients (n=50) with CRP levels <10 mg/L, and group B patients (n=50) with CRP levels of ≥10 mg/L[7]. Following the comparison of the SCORE values, 90% of the patients in Group A (<10 mg/L) were low to moderate risk for CVD, while 80% Group B (≥10 mg/L) were high to very high risk for CVD[10]. The CRP levels of Group B significantly correlated to a high risk of CVD following a 2x2 Chi square test (p=0.0001) [7] Given the results, the authors concluded that a CRP level over 10 mg/L is correlated with an over 4% risk of developing a fatal CVD in the next 10 years[7]. The incorperation of CRP in the CVD risk stratification can allow for the improvement of risk statification[7]. The inclusion of CRP in CVD screen may improve the accuracy of screening for CVD.

Building on this, Jeppesen et al.[8] investigated the relationship between CRP and CVD via analysis of 2,357 Danish men and women from the general population. The age of subjects ranged from 41-72 years, and all were without major symptoms of CVD at baseline[8]. The study had a median follow up of 9.4 years and found that CRP was an independent predictor of CVD as 1.33 (CI: 1.14-1.55) (P<0.001) in the fully adjusted model (e.g.risk factors unrelated to metabolic syndrome – age, sex, smoking habit and total cholestoral value)[8]**.** Per every increase in 1.10 mg/L of CRP was associated with a 95% increase in CVD[8]. The primary finding of this study was that the level of CRP was a significant risk factor in the development of future CVD[8].

Based on the current data, several research studies indentified that CRP is an independent risk factor of CVD[6–8]. The integration of CRP into the risk stratifications for CVD may prove to

be valuable in order to improve the effectiveness of risk classifications for CVD[10]. While CRP has been named to be an independent risk factor for CVD, previous research has also discovered that higher levels of CRP are closely associated with the presence of obesity[10].

CRP in African Americans (Racial Differences)

It is reported that African American's have a higher risk of CVD compared to Caucasians. This may be due, in part, to higher levels of obesity amongst African Americans[9]. Nearly 30% of Caucasian Americans adults are considered obese, in comparison to 45% of African American adults[25]. Additionally, the prevalence of obesity is 66% percent in African American females, compared to Caucasian American females at 47%[25]. However, there is a lack of research comparing CRP levels between African American and Caucasian Americans. Khera et al.[10] conducted a study to determine whether there are race and gender differences in CRP levels. CRP was measured in 2,749 Caucasian and African American subjects participating in the Dallas Heart Study, ages 30-65[10]. African American participants had higher CRP levels compared to white subjects (median, 3.3 vs. 1.8 mg/L; $p < 0.001$)[10]. Following an adjustment for cardiovascular risk factors, estrogen and statin use, and BMI, a CRP level >3 mg/L was more prevalent in Caucasian women (OR 1.6; 95% CI, 1.1 to 2.5) and African American women (OR 1.7; 95% CI, 1.2 to 2.6) but not in African American men (OR 1.3; 95% CI, 0.8 to 1.9)[10] when compared with Caucasian males. The authors concluded that significant race and gender differences exist in the population distribution of CRP[10].

An additional study, the Study of Women's Health Across the Nation (SWAN), conducted a multiethnic cross-sectional analysis in 3,154 women, without any known CVD[11]. The study population was 47.4% white, 27.7% African American, 8.5% Hispanic, 7.7% Chinese,

and 8.6% Japanese. Hedgepeth et al.[11] observed that African American women had the highest median CRP levels (3.2 mg/L), followed by Hispanic women (2.3 mg/L). The African American ethnicity was associated with CRP concentrations >3 mg/L, typically associated with high risk of CVD, following adjustment for age, socioeconomic status, BMI, and other risk factors (OR 1.37; 95% CI, 1.07-1.75) [11]. CRP concentrations varied among ethnic groups, with the highest levels among African American women[11]. Several interpretations from the studies above can be made; however, it is clear that higher CRP levels in African American subjects may impose an increased risk for future CVD events[10,11]. African American subjects indeed have a greater prevalence of cardiovascular risk factors, and higher CRP levels seem to be linked to this risk[10,11]. Since research in the area of racial differences in CVD risk factors is newly emerging, further research is needed to focus within the African American race to confirm the high prevalence of CRP levels as a main CVD risk factor[,11]. The racial differences in inflammation levels may directly contribute to the association of higher CVD mortality in African American subjects[10].

Obesity and Systemic Inflammation

The increased prevalence of obesity, an atherosclerotic CVD risk factor, has become a worldwide epidemic [26]. Currently, more than 50% of US adults are overweight, while 20% of adults are obese[17]. Another study focusing on the prevalence of obesity in the United States concluded that obesity was more prevalent in 32.2% among adult men and 35.5% among adult women[27]. Obesity is defined as having a body mass index (BMI) ≥30 kg•m$_2$ or waist girth >102 cm (40 in) for men and >88 cm (35 in) for women[28]. It is the accumulation of an excessive amount of fat that potentially interferes with the preservation of optimum health[12]. The excess

lipids within the adipose tissues release inflammatory mediators, such as cytokines tumor necrosis factor α and interleukin 6 (IL-6)[12]. The accumulation of cytokines and subsequent inflammation stimulates the body to synthesize CRP[12].

Previous studies have concluded that high CRP levels are more prevalent in obese individuals compared to non-obese[13–15]. A clinical trial that evaluated CRP levels within obese young adults, aged 17-39 years, found higher BMI associated with higher CRP concentrations compared to young adults with normal BMI[13]. For example, Visser et al.[13] followed 16,616 men and nonpregnant women over the age of 17 in the National Health and Nutrition Examination Survey[13]. Following the study, obese women were 4.8 times more likely to have clinically elevated CRP levels of >1 mg/L compared to normal-weight women, and obese men were 6.2 times more likely to have elevated CRP levels compared to normal-weight men[13]. Also, waist-to-hip ratio was positively associated with elevated CRP levels for both men and women[13]. For 1-SD increase in waist-to-hip ratio, men were 1.41 times and women were 1.21 times more prone to have elevated CRP levels[13].

Furthermore, Santos et al.[15] evaluated the association between CRP levels and metabolic syndromes in 957 subjects, ages 18-92 years[15]. Questionnaires were presented assessing social, demographic, behavioral, and clinical measures[15]. Anthropometrics and fasting blood samples were also collected[15]. Subjects were excluded if CRP levels measured ≥10 mg/L due to the potential indication of other clinically relevant inflammatory conditions[15]. Results showed higher adjusted mean levels of CRP (2.34 mg/L vs 1.36 mg/L, $P < 0.001$) in adults with metabolic syndrome compared to those without metabolic syndrome[15]. An increase in metabolic syndrome features was associated with an increase in mean CRP levels (0.97 to 3.18 mg/L)[15]. A higher prevalence for metabolic syndrome and high levels of CRP were present in older subjects,

former alcohol drinkers, and sedentary indivduals[15]. Additionally, significantly higher mean CRP levels were found in subjects with central obesity (2.45 mg/L vs. 1.24 mg/L, P<0.001), hypertriglyceridemia (2.17 vs 1.32 mg/L, P<0.001), high fasting glucose (1.96 vs 1.112 mg/L, P<0.001), and high blood pressure (1.76 mg/L vs. 1.12 P<0.001) compared to non-obese individuals[15]. Although there are numerous reasons for high levels of CRP, studies suggest it corresponds strongly with central obesity due to the excess inflammation[13,15]. A prominent theme contributing to obesity amongst individuals is the abundance of visceral adipose tissue.

Previous research suggests the visceral fat depot is a stronger contributor to CRP levels in individuals compared to other parameters of obesity[13,29,30]. Excess visceral adiposity potentially results in a proinflammatory condition, therefore, resulting in a low grade systemic inflammation, which further augmenting individual risk for CVD[31]. Faber et al.[30] hypothesized that visceral adipose tissue contributes to systemic inflammation of CRP. In 2,410 patients with vascular diseases, visceral and subcutaneous adipose tissue were analyzed through ultrasonography[30]. The association between fat measurements and CRP levels were measured using linear regression anaylsis[30]. For one-standard deviation increase of visceral fat, CRP levels increased by 0.10 mg/L (0.07-0.12) in men and 0.11 mg/L (0.15-0.19) in women[30]. Faber et al.[30] found visceral fat thickness to be the strongest contributor of systemic CRP levels in patients with vascular diseases. Since IL-6 is a key stimulator in the production of acute phase proteins, such as CRP, and visceral adipose releases more IL-6 compared to subcutaneous adipose tissue,[12,13] this may explain the observed trend of the relationship between high BMI and CRP in obese individuals[13].

Fitness and CRP

The improvement of exercise endurance and cardiorespiratory fitness has been an important focus to reduce CVD events[16]. In fact, the American Heart Association ranks decreased physical activity as the fourth risk factor for atherosclerotic heart disease[16]. Research concludes that cardiorespiratory fitness level is inversely associated with cardiovascular mortality and levels of CRP[17,24].

Aronson et al.[17] conducted a cross-sectional study in which levels of CRP were lower with increasing levels of cardiorespiratory fitness. Subjects (n=1,640) with metabolic syndrome were assessed for cardiovascular risk factors at the Rambam Center for Preventative Medicine[17]. The authors found for every one-unit increase in metabolic equivalents (METs), the adjusted geometric mean value of CRP decreased by 0.058 mg/L (95% confidence interval [CI] 0.038 to 0.078)[17]. The adjusted geometric mean CRP value in subjects who were in the upper fitness quartile compared with subjects in the lower fitness quartile was 1.48 versus 0.93 mg/L in subjects without metabolic syndrome (p= 0.01)[17]. Results indicated that subjects with metabolic syndrome who maintain a high fitness level have lower CRP concentrations compared to those with a low fitness level[17]. The results of the study indicate that something related to the physiological adaptations of being more fit appears to regulate CRP concentrations independent of other components of metabolic syndrome and other influencers of CRP levels[17].

Aronson et al.[32] conducted an additional study investigating the association between physical fitness and CRP. In a cross-sectional study, physical fitness was assessed in 892 adults based on fitness levels determined by the Bruce protocol maximal treadmill test[32]. After adjustment for age, gender, body mass index, smoking habit, presence of diabetes and hypertension, CRP levels decreased with increasing quartiles of fitness (p for trend <0.0001)[32]. Subjects in the highest fitness quintile had significantly lower adjusted odds of having high (>3

mg/L) CRP levels (odds ratio 0.53; 95% CI 0.39-0.71) compared to those in the lowest fitness quintile[32]. Aronson et. al[32] concluded that CRP concentration levels decrease consistently with increasing levels of cardiorespiratory fitness.

The Aerobics Center Longitudinal Study was an epidemiological study in which the association between cardiorespiratory fitness and CRP were examined. Church et al.[19] assessed 722 non-Hispanic, white males in the Cooper Clinic in Dallas, TX[19]. The geometric mean CRP levels and an odds ratio of elevated CRP across 5 levels of cardiorespiratory fitness was assessed[19]. Following full adjustment of the geometric mean across fitness quintiles, 49% of the men in the lowest fitness quintile have higher CRP value compared to 16% of the men in the highest fitness quintile[19]. There is a significant relationship for prevalence of high CRP values across the fitness quintiles ($p<0.001$)[19]. Patients with the highest fitness quintile (odds ratio of 0.17, 95% confidence interval 0.08 to 0.37) have the lowest risk of high CRP value compared to those in the lowest fitness quintile[19]. From these results, Church et al.[19] concluded that cardiorespiratory fitness levels were inversely associated with CRP levels. Furthermore, CRP values were significantly greater in the lowest fitness categories compared with higher fitness categories within overweight and obese individuals[19]. Low cardiorespiratory fitness has been proposed as a significant CVD risk factor that could be improved through a focus in lifestyle intervention, thus improving risk stratification[18]. These findings suggest that an assessment of cardiorespiratory fitness may improve the accuracy of risk prediction[18]. Furthermore, it supports another health benefit of fitness[18].

Exercise Training and CRP

Recent studies have examined the effects of obesity and high levels of CRP in lifestyle

interventions, such as an increase in physical activity and exercise training to decrease the risk of atherosclerotic CVD[33,34]. Stewart et al.[35] examined the effects of an exercise training program on CRP in postmenopausal women. Subjects (N=464) consisted of sedentary, overweight/obese, postmenopausal women with elevated systolic blood pressure (120.0 to 159.9 mm Hg)[35]. The subjects were randomized into 1 of 4 groups: a non-exercise control or 1 of 3 aerobic exercise groups; the aerobic exercise groups had an exercise energy expenditure of 4, 8, or 12 kcal/kg/week (KKW), respectively, for 6 months at training intensity of 50% of VO_2 peak[35]. Of the 464 participants, 427 returned for follow-up testing (92.0%)[35]. Results showed there were no differences in median CRP change between any of the groups ($p=0.6$)[35]. However, there was a decrease in CRP levels across quartiles of change in weight[35]. The mean CRP change, adjusted for baseline CRP and group randomization, was significantly ($p<0.02$ for each) different in the 4th quartile (most weight loss) compared to the 1st, 2nd, and 3rd quartiles of weight[35]. The 4th quartile mean weight loss was 5.9 (3.0) kg and the mean change in CRP was 1.0 (2.8) mg/L[35]. Although it seems that 6-months of exercise training at 4, 8, or 12 kcal/kg/week did not improve CRP in previously sedentary, overweight and obese, postmenopausal women, participants that experienced reduced weight had a decreased CRP level (0.15 mg/L; $p<0.001$)[35]. In conclusion, aerobic training exercise in postmenopausal sedentary women was associated with decreased CRP levels if there was a reduction in weight[35].

Supporting that CRP could potentially change with weight loss due to exercise training is the Inflammation and Exercise (INFLAME) study conducted by Church et al[36]. The purpose of the study was to examine whether aerobic exercise without dietary intervention can reduce CRP in individuals with elevated CRP[36]. The study randomized sedentary men and women (N=162) with elevated CRP (≥ 2.0 mg/L) into a non-exercise group or an exercise group that trained for 4

months at moderate- to vigorous activity (60-80% VO_2max)[36]. Results indicated there was no differences in median change in CRP between the control and exercise groups (0.0[-0.5, 0.9] verses [-0.8, 0.7] mg/L, p=0.4)[36]. However, similar to Stewart et al.[35] change in weight was correlated with change in CRP[36]. For both weight loss and body fat loss, the exercise group tertile with the largest reduction in these variables had significant reductions in CRP compared to all groups with less weight and body fat loss ($P < 0.05$)[36]. Church et al.[36] concluded that exercise without weight loss is not associated with a reduction in CRP. When these results were further analyzed, the changes in the weight and fat in the exercise group were associated with the changes in CRP, proposing that exercise-induced reductions in CRP are primarily due to reductions in weight and body fat[36].

Furthermore, studies prescribing a higher exercise intensity show greater effects than a low or moderate exercise intensity[33,34]. Goldhammer et al.[33] found that aerobic training may lower the risk for coronary artery disease (CAD) by modifying inflammation levels. Throughout a 12-week aerobic exercise training program at 70-80% of individual maximum heart rate, 28 male and female patients ages 64 and older underwent 45 minute sessions of continuous aerobic exercise for 3 days a week[33]. Plasma CRP levels were examined in response to the exercise training, and indicated a reduction in CRP levels by 48% from 7.5±4.2 to 3.9±3.5 mg/L ($p<0.001$) independent of changes in body weight or BMI[33]. The relationship of physical activity with lower levels of inflammation and CRP may provide another cardioprotective mechanism[33].

Similarly, Akbarpour et al.[34] conducted a study to investigate the effect of 12 weeks of aerobic training on inflammatory markers of CVD in obese men. Subjects (n=16) were non-athlete, obese men assigned to an experimental group or a control group[34]. The experimental group underwent 3 aerobic training sessions per week at 75-85% of the maximum heart rate for

12 weeks, while the control group did not participate in aerobic training[34]. The investigators discovered that aerobic training significantly decreased CRP levels (p=0.002) in the experimental group [34]. The conclusion was drawn that regular aerobic training does decrease the risk of CVD by reducing the levels of CRP[34].

Contrary to the studies above, Huffman et al.[37] sought to determine if modulating fitness with exercise training produced changes in CRP in a population at risk for cardiovascular disease. Huffman et al.[37] enrolled 193 overweight men and women to a 6-month intervention of low amount-moderate intensity, low amount-high intensity, or high amount-high intensity aerobic training or no physical activity. Although the intervention showed significant improvements in fitness, visceral adiposity, and subcutaneous adiposity, and insulin sensitivity, the 6 months of aerobic training did not significantly affect CRP (p> .20)[37].

As previously stated, there are conflicting results regarding the interaction between exercise training and CRP. Through further examination of these studies, decreased CRP is associated with exercise greater than low intensity. Therefore, it can be concluded that moderate to high intensity aerobic training decreases CRP levels and thus systemic inflammation[33,34]. While previous research emphasizes that various intensities of aerobic training do improve CRP concentration levels, however, there is a gap of knowledge supporting the effect of specific exercise intensity on CRP concentrations. Research has shown that low cardiorespiratory fitness is associated with high CRP levels[17,24], and high intensity exercise is more effective at improving cardiorespiratory fitness. Therefore, it is plausible that high intensity exercise could be more beneficial at improving CRP levels[33,34].

Summary

Racial health disparities have been shown in CVD with African Americans having a

substantially greater risk compared to Caucasian Americans. One potential factor explaining racial differences in CVD may be increased levels of systemic inflammation in African Americans compared to Caucasians. Epidemiological studies have shown that CRP (a marker of systemic inflammation) is an independent risk factor for cardiovascular mortality[6,7], which is higher in African Americans compared to Caucasians. Additionally, African Americans have increased levels of obesity and lower cardiorespiratory fitness, and elevated CRP levels compared to Caucasians. Although results have been inconsistent in studies related to exercise interventions to improve CRP levels, many studies have had primarily Caucasian participants and/or have used different intensities of aerobic training. Studies evaluating moderate intensity exercise generally find either no change in CRP with exercise training or improvement in participants that lose weight with exercise. Further, studies which have utilized high intensity aerobic exercise have seen consistent reductions in CRP. This may be due to greater mobilization of fat (particularly visceral fat) in high intensity exercise compared to moderate. However, little data exist directly comparing moderate to high intensity exercise training on CRP levels in obese adults; furthermore, no studies, to our knowledge, have evaluated the effect of different exercise intensity in African Americans and CRP levels. A study comparing exercise training intensity on CRP levels in obese African Americans may find a decrease in CRP levels due to decreased fat loss from aerobic exercise training. Thus, aerobic exercise training may represent a potential intervention to improve CRP levels in obese African Americans.

Chapter III: Methods

The purpose of the present study was to determine the effects of moderate and high intensity aerobic exercise training on CRP in obese African-American men and women. Data for the present study was obtained from the High Intensity exercise to Promote Accelerated improvements in Cardiorespiratory fitness (HI-PACE) study database (37). Overall, the HI-PACE study was primarily looking at the change in CRF following the exercise intervention. The HI-PACE methodology has been approved by the East Carolina Institutional Review Board. Each participant signed a written informed consent prior to study enrollment.

Participants

Participants were recruited using flyers, website advertisement, and e-mail distributions. A sample size of 60 will be recruited for this study. Inclusion criteria includes: African American race, 35-65 years of age, classified as obese (30.0-45.0 kg/m^2) and sedentary (not exercising ≥ 20 minutes on ≥ 3 days/week for the last 3 months). Exclusion criteria included: a diagnosis of type 2 diabetes (blood glucose value >125 mg/dL), any known cardiovascular diseases, unsafe high resting blood pressure (systolic >180 mmHg; diastolic > 100 mmHg), significant medical conditions/diseases, life threatening conditions, pregnancy or planning to be pregnant, current engagement in dietary or weight loss interventions, and non-adherence to study protocols.

Participant Screening

Study staff screened participants based on the HI-PACE inclusion/exclusion criteria via telephone interview. Next, if the participant is eligible, then an orientation session was scheduled with the research coordinator to further discuss study design, procedures, and associated risks

and benefits. During the screening visit, participant medical/medication history and screening measurements (i.e. resting blood pressure measurements, BMI, and waist circumference) were performed for inclusion/exclusion purposes. Additionally, a fasted blood draw was performed and sent to a clinical laboratory for lipid, glucose, and insulin analyses, and a comprehensive metabolic panel. Physical activity levels were measured using a Fitbit Flex (Fitbit Inc., San Francisco, CA) for 7 days.

Participant Assessment: Baseline and Follow Up

The participants were provided with a written informed consent prior to testing. After enrollment, baseline measurements including cardiorespiratory fitness (CRF), BMI, DEXA, and waist circumference were assessed prior to beginning the exercise intervention. At the 12-week, mid-intervention point, CRF, body weight, and other anthropometric measures were assessed. Following the 24-week intervention, these measures were repeated. To determine body mass index (BMI, in kg/m2), a Digi Tol calibrated scale (Mettler Toledo, Columbus, OH) was utilized. The height was measured with the utilization of a stadiometer. Body composition was measured with the utilization of dual energy x-ray absorptiometry (DEXA). Participants laid motionless on the DEXA machine until scan is complete. Waist circumference was measured at the natural waist (inferior border of the rib cage, superior aspect of the iliac crest) via a Gulick tape measure.

Blood Draw: Pre and Post Intervention

Participants completed a 12-hour fasted blood draw at the East Carolina Heart Institute. A venous blood sample of a total of 21 mL of blood was drawn by the study nurse pre and post exercise intervention. Blood samples were sent to a clinical laboratory (LabCorp Inc.,

Burlington, NC) for a complete analysis of metabolic, lipid, insulin level measures, CRP, and blood chemistries. The serum separator tube was sent to LabCorp for measurement of C-reactive protein.

Exercise Intervention

Participants were randomized to the moderate intensity (MOD-INT; n = 20), high intensity (HIGH-INT; n = 20), or non-exercise control group (n = 20) for a 24-week intervention. The moderate intensity group participated in aerobic exercise at 50% of their VO_2 max, and the high intensity group participated in aerobic exercise at 75% of their VO_2 max. Participants underwent supervised exercise for 3-4 days/week on a treadmill to sustain effective control of energy expenditure. Both groups obtained 600 MET-minutes/week, which met the current PA guidelines (500-1,000 MET-minutes/week). Due to the participants being sedentary, both groups exercised at 200-300 MET-minutes during week 1. Each week, the volume of exercise increased by 50 MET-minutes until the 600 MET-minute level was achieved by week 7. MET-minutes were calculated utilizing the ACSM equations based on treadmill speed and grade, and participant weight.

Participant heart rate were recorded every five minutes by research staff with the use of a Zephyr Bioharness 3 Monitors (Annapolis, MD) to invigilate prescribed exercise intensities for each group. The Zephyr Bioharness 3 Monitor recorded heart rate every second the participant is wearing the monitor. To collect the mean heart rate for each session, research staff analyzed the heart rate data during exercise time via a sub-session annotation on the Omnisense software[38]. The sub-session of exercise time created is specific to the time and will exclude non-exercise heart rate data (e.g. warmup, cool down) from the calculation[38]. Through this process, exercise

intensities were more accurately calculated due to the continuous second-by-second heart rate monitoring as opposed to using five minute intervals[38].

Statistical Analysis

For the present study, we tabulated a means and standard deviations for continuous variables. A one-way ANOVA was conducted to compare continuous variables, and a Spearman correlation conducted to compare baseline categorical variables. To measure the change in CRP across the intervention groups, an ANOVA was performed with an adjustment for baseline values. We used an alpha level of <0.05 for all statistical analyses. A Spearman correlation was used to analyze the correlation between baseline variables with CRP. Change scores were computed to measure change in CRP across baseline variables (ex: body composition, VO_2 ml/kg/min, total cholesterol, etc.). An independent samples T-Test was used for the analyzation of CRP in responders vs. non-responders with equal variances assumed. Responders were accounted for CRP levels <0 mg/dL, while non-responders were accounted for CRP levels >0 mg/dL.

Chapter IV: Results

Baseline characteristics for each treatment group are shown in Table 1. There were 11 participants in the control group, 10 participants in the moderate intensity exercise group, and 13 in the high intensity exercise group. There were no significant differences between the randomization groups for age, gender, weight, BMI, waist circumference, body fat percentage, glucose, insulin, and CRP ($p > 0.05$). Baseline CRP was significantly associated with weight ($r=0.458$, $p=0.006$), BMI ($r=0.537$, $p=0.001$), fat-mass ($r=0.454$, $p = 0.010$), WC ($r=0.436$, $p= 0.010$), estimated METS ($r=0.392$, $p=0.032$), and triglycerides ($r=0.369$, $p=0.032$). The correlation between baselineVO_2 max (ml•kg•min) and CRP approached significance ($r=-0.299$, $p=0.086$).

We did not observe significant change in CRP levels among study groups in the MOD or the HIT group compared to the CON in obese African-American adults ($p=1.00$). Further, the association between exercisers and change in CRP and fat-mass approached a significant change ($r=-0.379$, $p=0.07$). The HIGH-INT group had a larger increase in VO_2 max (ml•kg•min; L/min) ($p<0.05$) compared to the CON group. Also, there was a significant relationship between the CON group and MOD intensity group in estimated METS ($p<0.01$). Data for changes in clinical risk factors between participants based on change in CRP are shown in Table 2. There were no significant changes found in CRP for any clinical risk factors between non-responders and responders ($p>0.05$).

Chapter V: Discussion

The primary finding of the present study is moderate nor high intensity training reduced C-reactive protein in obese African Americans. Further, we did not find significant changes in weight or WC in 6-months of exercise alone, which is in contrast to previous studies in the literature[35,36]. It is important to emphasize that aerobic exercise training has other health benefits such as improvements in cardiorespiratory fitness[17–19,32]. Therefore, other intervention strategies along with exercise may be needed to reduce systemic inflammation in obese African Americans (e.g. weight loss, nutritional interventions, pharmacological). This is the first study to our knowledge which has evaluated the effect of exercise training (or exercise intensity) on CRP levels, specifically in obese African Americans who are at increased risk for cardiovascular disease and diabetes.

Baseline mean CRP values for the HI-PACE participants reported to be 5.5 mg/L, which places this population at high risk for CVD according to the AHA[24]. The results of this study suggest that 6 months of aerobic exercise at moderate or HIGH-INT exercise does not reduce CRP levels in obese African Americans. These results are consistent with the overall results of several large randomized-controlled trials. In the STRRIDE study, Huffman et al.[37] observed that 9-months of low amount-moderate intensity (19.3 km/wk at 40-55% peak VO_2), low amount-high intensity (19.3 km/wk at 65-80% peak VO_2) or high amount-high intensity group (32.2 km/wk at 65-80% peak VO_2)[37] did not alter CRP in response to exercise training[37]. Similarly the INFLAME[36] study observed no significant reduction in CRP with aerobic exercise group at moderate-to vigorous-intensity (60-80% VO_2 max) compared to a control group for a 4 month intervention period[36]. In line with these studies, Stewart et al.[35] found no significant changes in CRP in response to 6 month of moderate intensity exercise training at 4, 8, or 12 kcal/kg/week (KKW). Based on the data from

the above studies and the current study, exercise intensity does not appear to be a major modifier for systemic inflammation in obese African Americans at risk for CVD.

Another theme of the literature is that exercise-related reductions in weight or fat mass may be necessary to lower CRP in overweight and obese adults. In the present study, we did not observe an association between the change in CRP in exercisers ($p>0.05$). Risk factors for high levels of CRP such as body weight, fat mass, and waist circumference did not significantly change in the study, therefore this could account for seeing no change in CRP. For example, we observed a 0.64 kg change in weight for the MOD-INT group and -0.38 kg change for the HIGH-INT group, respectively, and a mean overall change in weight of 0.06 kg in all exercisers. Furthermore, studies with evidence showing that weight is associated with change in CRP observed a weight change in the exercise groups of about 1-3 kg, which is larger than the present study[36,39]. Church et al.[36] concluded that exercise training without weight loss is not associated with a change in CRP, however, the tertile with largest weight reduction (<-1.3 kg) had significant reductions in CRP compared to all groups[36]. Similarly, Stewart et al.[35] found that those who lost <-2.6 kg had a significantly lowered CRP after the exercise intervention compared to the lowest tertile. Previous literature has reported that Caucasians may lose more weight in response to exercise training compared to African Americans[40]. Also, it has been observed that African American women have a significantly lower resting metabolic rate compared to Caucasian women, which may contribute to a lower magnitude of weight loss in African American[41]. The INFLAME (15% African American) and DREW (90.4% African American) studies included a mix of races, but a subgroup analysis for weight loss across race was not performed[35,36]. Thus, it is plausible that since we had only African American participants that this may account for the low amount weight loss (and in turn lack of response in CRP) in exercisers in the present study.

The present study had several strengths. The exercises intervention was supervised between controlling the differences in intensities and high adherence in both intensity groups. In addition, total exercise volume was equivalent in both the MOD-INT and HIGH-INT groups. A weakness of the study would be that the present study is an efficacy-based trial and therefore, this does not represent a true real-life exercise in a community-based setting such as an exercise training at YMCA or local gym. Another limitation of the sample was the preponderance of females. Additionally, we did not control for changes in diet, which may affect inflammatory markers as well as fat and weight changes. Also, the results of this study will not be generalizable to African Americans with type II diabetes or CVD, where systemic inflammation may be higher at baseline.

In conclusion, we observed that neither moderate or high intensity aerobic decreased systemic inflammation levels in obese African Americans. Secondly, CRP was not improved with a change in fat-mass in exercisers. Future research could allow for the enrollment of Caucasian and African Americans, allowing for a more direct comparison between the two races for the intervention variables measured. Also, it could entail an interval training aerobic group, as well as a resistance training exercise group to bring forth further comparisons in intervention variables. Lastly, future studies may want to combine dietary and exercise to potentially lower CRP to a greater extent than exercise alone.

Tables and Figures

Table 1: Baseline Participant Characteristics

Variable	Control (n=11)	Mod Int. (n=10)	High Int. (n=13)
Age (yrs.)	4965±6.6	50.7±6.8	48.4±9.3
Female (%), n	72.7, 8	80.0, 8	76.9, 10
Weight (kg)	89.7±18.8	99.0±13.0	100.1±18.3
BMI (kg/m2)	32.2±6.2	35.5±4.6	35.5±5.9
WC (cm)	94.3±13.4	97.7±9.3	102.6±13.1
Fat Mass (kg)	39.2±8.9	42.9±7.2	42.2±6.4
VO2 (L/min)	1.9±0.5	1.9±0.5	1.9±0.6
VO2 (ml/kg/min)	20.9±5.7	19.2±5.0	18.8±4.2
Est METs (kcal/kg/hr)	8.0±1.6	7.1±1.7	7.5±1.5
Glucose (mg/dL)	90.7±8.1	93.4±8.0	92.0±9.9
Insulin (uIU/mL)	11.5±7.2	14.2±6.3	16.3±8.2
Total Cholesterol (mg/dL)	184.8±30.0	188.4±45.7	165.8±32.0
HDL (mg/dL)	55.5±11.0	57.1±15.0	50.5±16.1
LDL (mg/dL)	109.8±25.5	115.1±46.8	94.7±23.5
Triglycerides (mg/dL)	97.6±53.1	81.2±21.4	102.7±43.0
CRP (mg/L)	4.1±3.4	4.7±3.2	6.9±8.6

Table 2. Change in Intervention Statistics; Mean (CI)

Variable	Control (n=11)	Mod Int. (n=10)	High Int. (n=13)
Δ Weight (kg)	1.55 (-0.93 to 4.02)	0.64 (-1.96 to 3.25)	-.38 (-2.39 to 1.62)
Δ BMI (kg/m2)	0.60 (-0.30 to 1.50)	0.25 (-0.65 to 1.16)	-0.08 (-0.85 to 0.69)
Δ WC (cm)	-0.13 (-2.90 to 2.65)	1.67 (-2.68 to 6.02)	-1.17 (-2.98 to 0.64)
Δ Fat Mass (kg)	-0.35 (-1.16 to 0.47)	-0.01 (-1.63 to 1.61)	-0.72 (-2.00 to 0.57)
Δ VO2 (L/min)	-0.02 (-0.19 to 0.15)	0.15 (.02 to 0.29)	0.23 (0.10 to 0.35)
Δ VO2 (ml/kg/min)	-0.45 (-2.62 to 1.73)	1.41 (-0.47 to 3.28)	2.65 (1.15 to 4.15)
Δ Est METs (kcal/kg/hr)	-0.28 (-0.91 to 0.35)	1.65 (0.44 to 2.87)	1.02 (0.36 to 1.70)
Δ Glucose (mg/dL)	1.36 (-2.83 to 5.56)	-1.70 (-5.94 to 2.54)	-1.85 (-6.83 to 3.14)
Δ Insulin (uIU/mL)	-1.45 (-3.66 to 0.78)	-5.11 (-9.53 to -0.69)	-2.63 (-6.62 to 1.36)
Δ Total Cholesterol (mg/dL)	-9.36 (-23.36 to 4.63)	2.00 (-11.87 to 15.87)	1.08 (-13.48 to 15.63)
Δ HDL (mg/dL)	-4.45 (-8.53 to -0.38)	-0.30 (-3.90 to 3.30)	1.54 (-2.41 to 5.48)
ΔLDL (mg/dL)	-7.12 (-16.70 to 2.48)	1.08 (-9.75 to 11.91)	3.37 (-8.14 to 14.88)
Δ Triglycerides (mg/dL)	-2.82 (-18.31 to 12.67)	5.90 (-9.37 to 21.17)	-13.77 (-27.01 to -0.53)

Table 3. Changes in Intervention Characteristics: Non-Responders and Responders

Variable	Non-Responder (n=14)	Responder (n=20)
Δ Weight (kg)	-0.09	0.99
Δ BMI (kg/m2)	0.01	0.40
Δ WC (cm)	-0.79	0.56
Δ Fat Mass (kg)	-1.55	0.43
Δ VO_2 (L/min)	0.17	0.09
Δ VO_2 (ml/kg/min)	1.96	0.80
Δ Est METs (kcal/kg/hr)	0.95	0.67
Δ Glucose (mg/dL)	-0.07	-1.25
Δ Insulin (uIU/mL)	-3.76	-2.43
Δ Total Cholesterol (mg/dL)	3.36	-6.00
Δ HDL (mg/dL)	1.36	-2.55
Δ LDL (mg/dL)	1.13	-1.97
Δ Triglycerides (mg/dL)	-0.21	-7.4
Δ CRP (mg/L)	3.66	-2.27

Fig 1. Change in CRP Across Intervention Groups

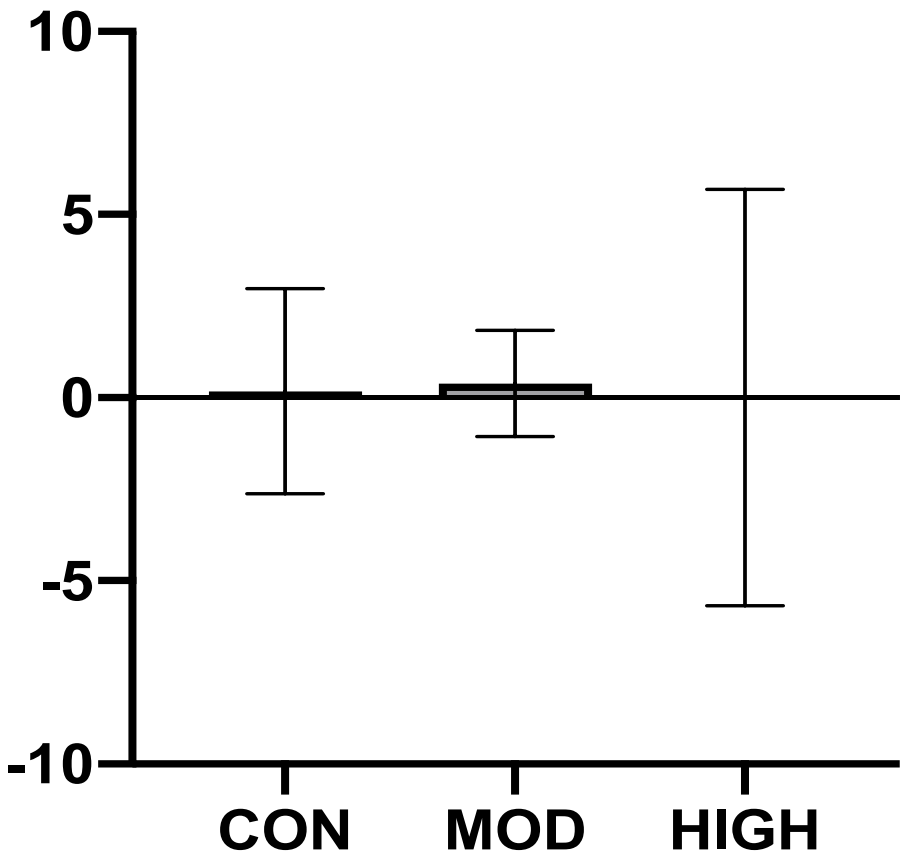

Fig 2. Change in CRP vs. Change in Weight

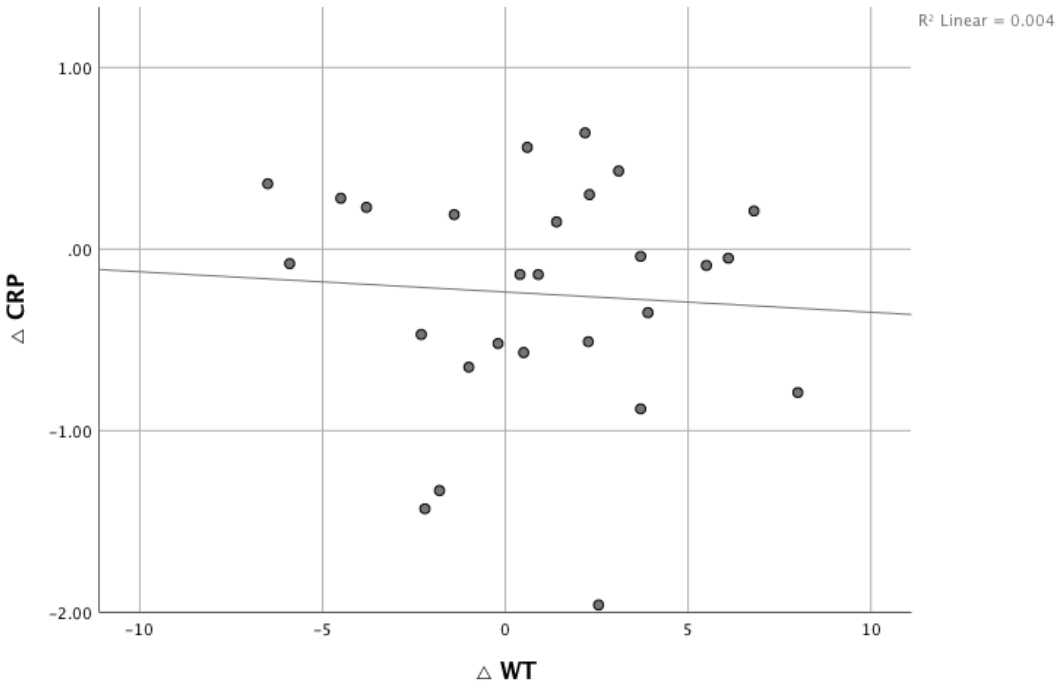

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Fig 3. Change in CRP vs. Change in Fat-Mass

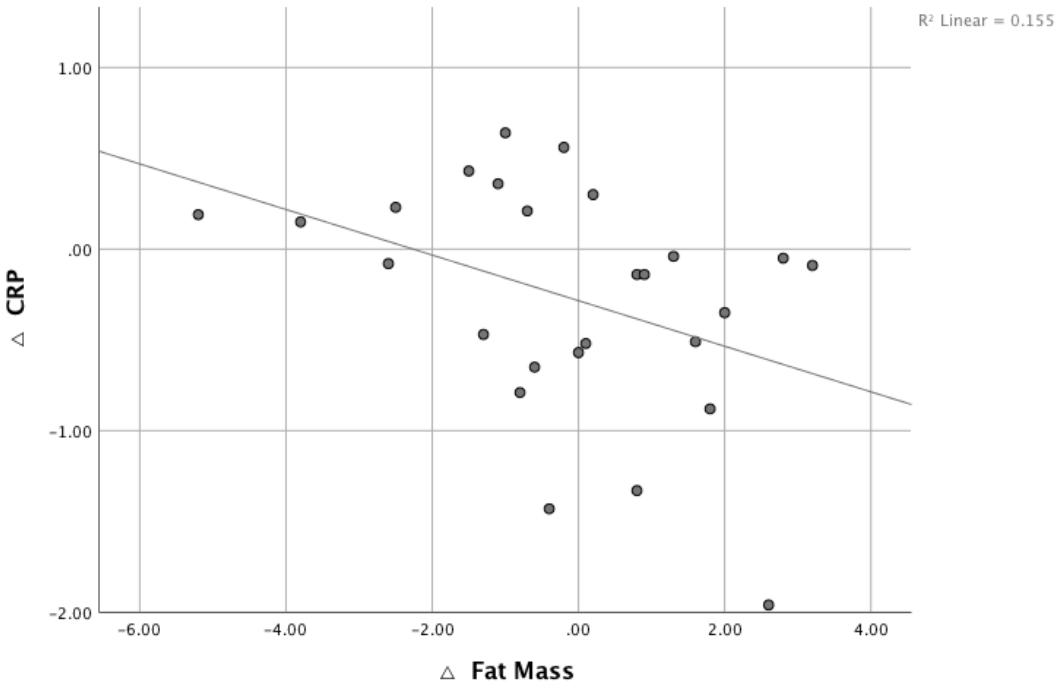


Fig 4. Change in CRP vs. Change in Insulin

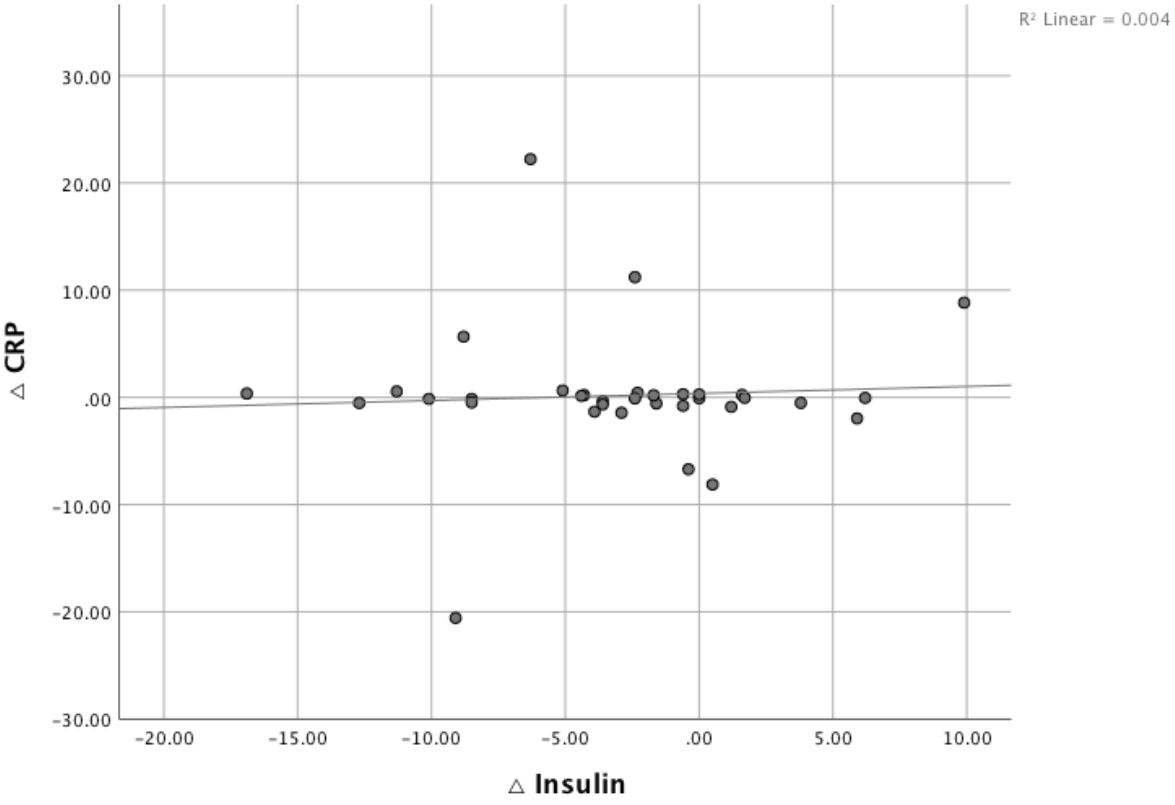
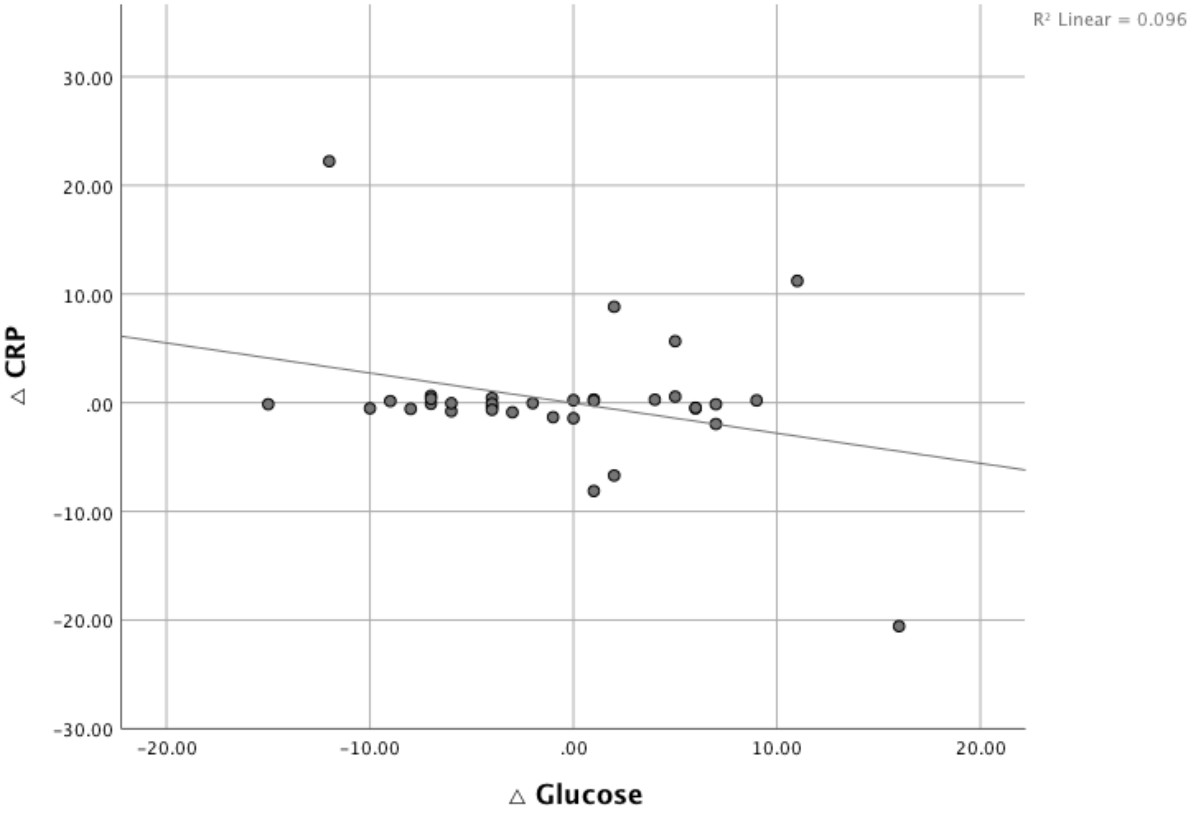


Fig 5. Change in CRP vs. Change in Glucose



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APPENDIX: IRB APPROVAL

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

From: Biomedical IRB
To: Damon Swift
CC:

Patricia Brophy
Date: 12/12/2019
Re: CR00008209
UMCIRB 14-001737
Effects of Exercise Training Intensity on Fitness and Insulin Sensitivity in African Americans (HI-PACE)

I am pleased to inform you that at the convened meeting on 12/11/2019 12:15 PM of the Biomedical IRB, this research study underwent a continuing review and the committee voted to approve the study. Approval of the study and the consent form(s) is for the period of 12/11/2019 to 12/10/2020.

The Biomedical IRB deemed this study Greater than Minimal Risk.

Changes to this approved research may not be initiated without UMCIRB review except when necessary to eliminate an apparent immediate hazard to the participant. All unanticipated problems involving risks to participants and others must be promptly reported to the UMCIRB. The investigator must submit a continuing review/closure application to the UMCIRB prior to the date of study expiration. The investigator must adhere to all reporting requirements for this study.

Approved consent documents with the IRB approval date stamped on the document should be used to consent participants (consent documents with the IRB approval date stamp are found under the Documents tab in the study workspace).