THE EFFECT OF WEIGHT LOSS AND EXERCISE ON CARDIOVASCULAR STRUCTURE AND FUNCTION IN CLASS II AND III OBESE WOMEN

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Introduction: Obesity is a public health concern in its association with various comorbidities, especially cardiovascular disease. Negative structural and functional changes of the left ventricle are associated with obesity and research is conflicting as to the effect of diet-induced and diet plus exercise-induced weight loss in Class II and III obese adults. **Purpose:** The purpose of this study was to examine effect of diet-induced or diet plus exercise-induced weight loss on cardiac structure and function in Class II and III obese women. **Methods:** 24 healthy, sedentary, obese women (BMI: 35.0 to <45 $kg/m^{2;}$ Age: 45.4 $\pm$ 6.9yrs.) underwent a 12-week diet and exercise intervention: caloric restriction alone (DIET), caloric restriction plus aerobic training (DIET+AT), and caloric restriction plus resistance training (DIET+RT). Subjects reported to UPMC Presbyterian Hospital to undergo Cardiac MRI to measure left ventricular mass (LVM), myocardial fibrosis (Ve), end diastolic volume (EDV), end systolic volume (ESV), and ejection fraction (EF). **Results:** 18 out of 24 subjects completed the intervention. 16 out of 24 completed 12 week Cardiac MRI at UPMC Presbyterian. Body weight significantly decreased across all treatment groups (~4.5kg lost, p=0.001). Subjects in the DIET group had significantly greater reduction in LVM (-7.2 ± 3.9g) than the DIET+AT (2.3 ± 4.7g) and DIET+RT (-0.2 ± 3.5g) groups (p=0.007). Subjects in the DIET+RT group had a significantly higher Ve score at 12 weeks (27.9 ± 1.5%) than subjects in the DIET+AT (26.5 ± 1.4%) and DIET (24.0 ± 0.8%) groups (p=0.010). There were no significant changes in EDV, ESV, or EF at 12 weeks between groups (p>0.159). **Conclusions:** In conclusion, only LVM in the DIET group and Ve in the

DIET+RT showed statistical changes from baseline. Further investigations into the effect of weight loss and exercise on cardiac structure and function in Class II and III obese adults are warranted to expand upon the results of this investigation.

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1.0 INTRODUCTION

1.1 OBESITY PREVALENCE

Obesity is a growing public health concern in association with increased risk for cardiovascular disease[1], diabetes[2,3], certain cancers[4,5,6] and other metabolic disorders[7]. While the rate of overweight and obesity appears to have slowed slightly over the past decade, both are still prevalent in the United States[8]. Greater than 65% of American adults are classified as overweight (BMI $\geq$ 25 kg/m^2) and more than 32% of American adults are classified as obese (BMI $\geq$ 30 kg/m^2)[8]. Additionally, more than 14% of American adults are classified as Class II Obese (BMI 34.9 – 39.9kg/m^2) and approximately 6% are classified as Class III Obese (BMI $\geq$ 40kg/m^2)[8]. Unfortunately, overweight and obesity are prevalent outside of the United States as well. In 2003, the World Health Organization estimated that there are more than one billion overweight adults and 300 million obese adults globally[9]. Growing evidence linking the association between obesity and the risk for development of multiple metabolic diseases, particularly cardiovascular disease (CVD), suggests the need for weight reduction in American adults.

1.2 CARDIOVASCULAR DISEASE PREVALENCE

Cardiovascular disease claims more lives per year than cancer[10] and the estimated cost to treat CVD per year is over $500 billion[10]. Obesity is an independent risk factor for cardiovascular disease[11] in its association with dyslipidemia, hypertension, glucose intolerance, inflammatory markers, and increased total blood volume[11]. Weight gain in adulthood, and even adolescence, has a severe impact on CVD risk factors, even in individuals who are normal weight by BMI classification[12]. Moreover, a ten-year follow up of the Nurses' Health Study and the Health Professionals Follow-up Study showed that cardiovascular disease risk increased as both men and women gained weight through adulthood compared to normal weight age-matched controls[13].

The risk for chronic diseases increases in a curvilinear fashion as BMI increases[14]. Mortality rates also increase in a curvilinear fashion as a BMI of 35kg/m^2 represents approximately three years of life lost, while a BMI of 40kg/m^2 represents approximately six years of life lost[14]. Research has shown that as much as a 20-year reduction in life is associated with morbid obesity[15].

Additionally, the location of adipose tissue can have a varying impact on cardiovascular disease risk. A stronger correlation to cardiovascular disease is apparent when adipose tissue is deposited in the abdomen as opposed to general total body obesity[16]. It is believed that this is due to an increase in visceral fat associated with abdominal adiposity compared to general obesity[16].

Aside from the increased risk in comorbidities associated with obesity, research also shows a strong correlation between obesity and structural changes. Specifically, left ventricular hypertrophy has been shown to have a strong association with cardiovascular mortality[17]. Left ventricular hypertrophy falls into a disease classification referred to as subclinical cardiovascular

disease. This term refers to subclinical conditions, or conditions that do not manifest signs and symptoms of cardiovascular disease. The Framingham Heart Study showed that 63% of women who died suddenly of cardiovascular disease had no previous signs or symptoms of the disease[18], exemplifying the need to better detect these abnormalities. While left ventricular hypertrophy appears to be rare among normotensive normal weight adults[19], it is prevalent in normotensive and hypertensive obese adults. Increased adipose tissue results in an increase in total blood volume, which in turn creates a greater workload placed on the heart to circulate the added volume. As more blood flows through the heart, the walls and musculature of the left ventricle adapt by increasing in size. This increase in left ventricle size eventually leads to dysfunction in the chamber and subsequent cardiac mortality if adipose tissue continues to accumulate on the body. However, a reduction in weight may reverse these negative effects and reduce cardiovascular disease risk[20].

1.3 EFFECT OF WEIGHT LOSS ON CARDIOVASCULAR DISEASE RISK

A weight loss of 5-10% from initial body weight has been shown to decrease health risk[21]. Moreover, the National Institutes of Health recommends a weight loss of 10% initial body weight in adults with a BMI of $\geq$ 25kg/m^2 [22]. Four year results from the Look AHEAD Trial showed that with an intensive lifestyle intervention, sustained weight loss and subsequent improvements in fitness, glycemic control, and cardiovascular risk factors are seen in individuals with type 2 diabetes[23]. Weight loss had also been shown to decrease arterial pressure[24]. As little as an 8kg weight loss is substantial to produce significant reductions in both systolic and diastolic blood pressures in hypertensive individuals[24]. Additionally, weight loss appears to

decrease left ventricular mass via a decrease in chronic volume overload[25]. This subsequent decrease in ventricular mass and volume decreases cardiovascular mortality risk. Studies that utilize aerobic and resistance training in the reduction of left ventricular hypertrophy in obese adults are rare, however training shows an increase in left ventricle mass in normal weight athletes[26]. While training in addition to caloric restriction may result in no change in left ventricular mass in obese adults, the quality of the myocardium may improve, therefore decreasing cardiovascular disease risk.

1.4 EFFECT OF PHYSICAL ACTIVITY AND WEIGHT LOSS ON CARDIOVASCULAR DISEASE RISK

Physical activity has an additive effect to diet on weight loss and therefore has a greater impact on cardiovascular disease risk. Physical activity has been shown to further reduce weight by 1 to 2 kg when added to caloric restricition[21]. Physical activity also has an effect on cardiovascular disease risk independent of body weight and weight loss. Physical activity has been shown to reduce resting systolic and diastolic blood pressures as well as insulin resistance and glucose tolerance[3]. Additionally, physical activity has been shown to reduce cardiovascular disease risk by approximately 20% in men and women when compared to age-matched sedentary controls. This reduction in risk increases to approximately 30% with high-intensity physical activity[27].

Unfortunately, physical inactivity is widespread and has become a prominent cause of death in the United States[7]. Physical inactivity has been shown to worsen chronic diseases, as well as increase risk for cardiovascular disease, stroke, type 2 diabetes, and obesity[7] in apparently healthy adults. While adults are recommended to accumulate 150 minutes of

moderate-intensity or 75 minutes of vigorous-intensity physical activity each week to promote health[21], over one third of the population reported not accumulating the required time[28]. The aforementioned statistics exemplify the need for effective strategies to increase physical activity and subsequently decrease body weight to reduce chronic disease risk. Figure 1 helps represent the need for such strategies by depicting the two outcomes of overweight and obesity.

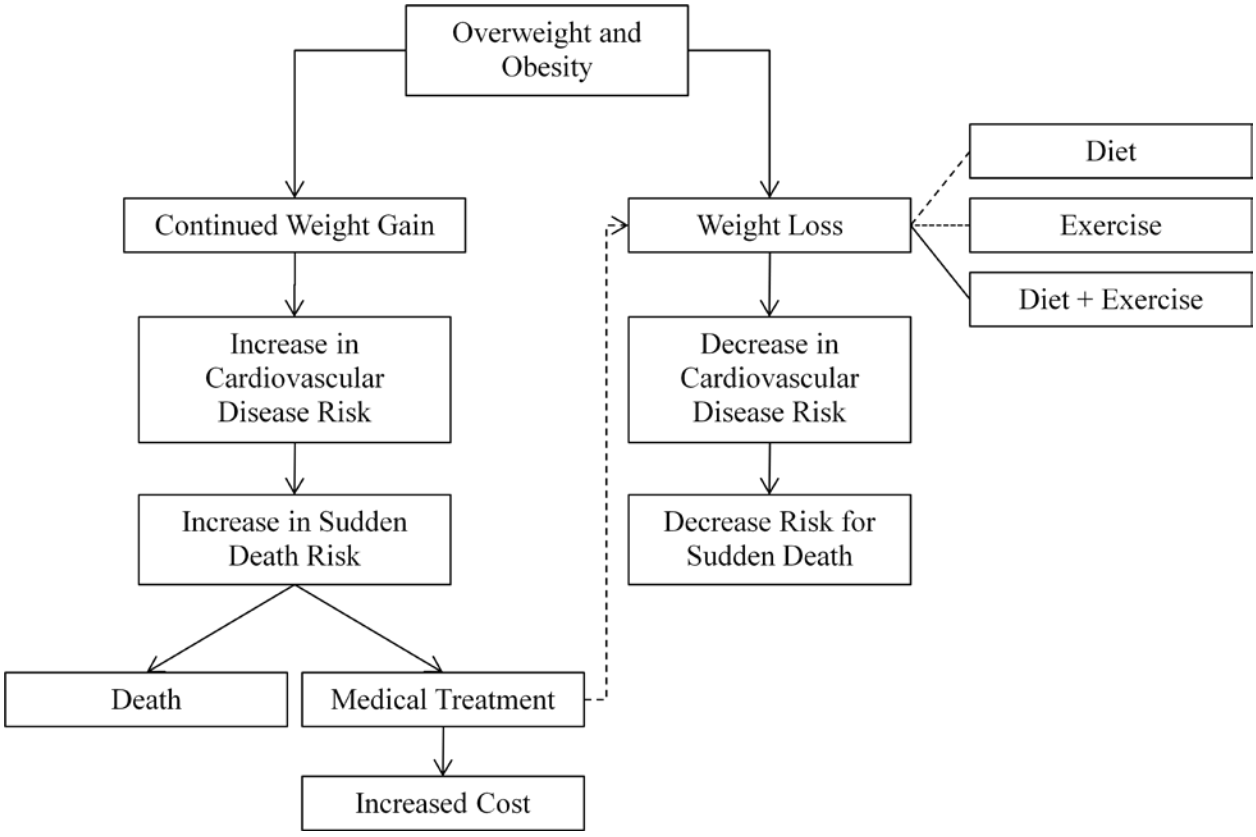


Figure 1: Potential Overweight and Obesity Pathways

1.5 TRAINING METHODS TO IMPROVE WEIGHT LOSS

Behavioral weight loss interventions are designed to modify an individuals' eating and physical activity habits, specifically by reducing calorie intake and increasing calorie expenditure. These

changes, theoretically, should create an energy deficit and subsequent weight loss, therefore reducing chronic disease risk. Most notably, aerobic-type activities are prescribed for greatest weight loss. Recently, greater attention has been paid to the importance of resistance training in maintaining lean body mass and improving cardiovascular disease risk while dieting[29-30]. Additionally, resistance training offers a segue into an aerobic exercise regimen as many obese individuals may find it difficult to perform the aerobic activities for the required amount of time. Beginning with resistance training allows the individual to increase strength which is crucial for performing aerobic exercises.

While research is contradictory as to the effect of resistance training on subclinical cardiovascular disease, aerobic training appears to have a beneficial effect. Weight loss, independent of training status, also appears to have similar benefits. However, few studies have examined the role of training and weight loss in obese individuals with respect to subclinical cardiovascular disease. It is important to determine if weight loss itself is the primary factor for improvements in subclinical cardiovascular disease in obese adults, or if the mode by which weight loss occurred, i.e. caloric restriction alone, caloric restriction plus aerobic training, or caloric restriction plus resistance training, is more critical.

1.6 DETECTION OF SUBCLINICAL CARDIOVASCULAR DISEASE

When a patient enters a physician's office for cardiovascular risk screening, the most common testing that occurs is a family history questionnaire, physical examination, and serum blood chemistry analysis. Based on these results, the patient is given a Framingham Risk Score[31], which expresses the 10-year risk of the patient for cardiac events. Current practice guidelines

mandate that only moderate or high risk patients receive further testing and treatment[32]. However, from this test, nearly 85% of individuals will be put into a low risk category[32]. Many of these low risk patients have a varying degree of subclinical cardiovascular disease, meaning that most likely their first symptom of cardiovascular disease will be an adverse event. This presents the need to better understand, detect, and categorize varying levels of subclinical cardiovascular disease before it leads to cardiac death.

Historically, left ventricular mass has been analyzed using echocardiography. However, this method has a low sensitivity (7%) and unreliable accuracy for the detection of left ventricular hypertrophy[32-34]. Additionally, because echocardiography is only a two-dimensional measurement, it must use algorithms to estimate total volume and mass of the heart. These algorithms are only validated against a normal heart shape, therefore making them unreliable in the estimation of the size of an abnormal heart (i.e. hypertrophy due to chronic volume overload).

Cardiac magnetic resonance imaging (CMRI) is widely becoming the most reliable measure of heart mass and volume. This technique measures the heart by taking individual "slices" of the heart and stacking them on each other, creating a three-dimensional image. Additionally, it is widely used in longitudinal studies due to its excellent interstudy reproducibility[35].

Therefore, the scope of this study will be to examine the effect of weight loss and either aerobic or resistance exercise on subclinical cardiovascular disease in obese adults.

1.7 SPECIFIC AIMS

The specific aims of this study are:

1.) To compare the changes in body weight between three intervention groups: diet only (DIET), diet plus aerobic training (DIET+AT), and diet plus resistance training (DIET+RT) during a 12-week training study in Class II and III obese women.

2.) To compare changes in left ventricle mass between three intervention groups: DIET, DIET+AT, and DIET+RT during a 12-week training study in Class II and III obese women.

3.) To compare changes in cardiovascular function (end diastolic volume, end systolic volume, ejection fraction, and fibrosis) between the three intervention groups: DIET, DIET+AT, and DIET+RT during a 12-week training study in Class II and III obese women.

4.) To compare changes in cardiorespiratory fitness between three intervention groups: DIET, DIET+AT, DIET+RT during a 12-week training study in Class II and III obese women.

5.) To compare changes in muscular strength as determined by 1-Repition Maximum between three intervention groups: DIET, DIET+AT, and DIET+RT during a 12-week training study in Class II and III obese women.

6.) To compare changes in body composition between three intervention groups: DIET, DIET+AT, and DIET+RT during a 12-week training study in Class II and III obese women.

7.) To determine the association between changes in weight, aerobic and muscular fitness, and body composition, and left ventricular mass and function between three intervention

groups: DIET, DIET+AT, and DIET+RT during a 12-week training study in Class II and III obese women.

1.8 HYPOTHESES

The specific hypotheses of this study include:

1.) The DIET+AT group will lose more body weight than the DIET+RT group and the DIET+RT group will lose more body weight than the DIET only group.

2.) The DIET+AT group will have a greater decrease in left ventricular mass than the DIET+RT group and the DIET+RT group will have a greater decrease in left ventricle mass than the DIET group.

3.) The DIET+AT group will show a greater improvement in cardiovascular function than the DIET+RT group and the DIET+RT group will show a greater improvement in cardiovascular function than the DIET group.

4.) The DIET+AT group will have a greater increase in cardiorespiratory fitness than the DIET+RT group and the DIET+RT group will have a greater increase in cardiorespiratory fitness than the DIET group.

5.) The DIET+RT group will have a greater increase in 1RM than the DIET+AT and the DIET+AT group will have a greater increase in 1RM than the DIET group.

6.) The DIET+AT group will have a greater improvement in body composition than the DIET+RT group and the DIET+RT group will have a greater improvement in body composition than the DIET group.

2.0 REVIEW OF LITERATURE

2.1 INTRODUCTION

Obesity is a complex chronic disease that encompasses genetic, cultural, physiological, and metabolic factors[22]. Obesity has reached epidemic proportions in men and women and poses a significant public health challenge in its association with other chronic diseases. Excess body weight is a major contributor to preventable death in the United States and needs to be reduced to decrease the prevalence of weight-related comorbidities.

Behavioral interventions can be implemented for obese individuals to reduce caloric intake and increase caloric expenditure, therefore reducing body weight. Adults with the greatest amount of excess body weight appear to have the most to gain from these interventions, yet this group appears to be targeted the least[36]. Thus, appropriate and effective interventions that focus on adults with the greatest levels of obesity need to be employed to reduce weight and improve health.

2.2 OBESITY PREVALENCE

The classification of overweight and obesity is often based on body mass index (BMI), calculated as weight in kilograms divided by the square height in meters. A BMI of 25.0 to

29.9kg/m^2 is classified as overweight while a BMI of greater than 30.0kg/m^2 is classified as obese. More specifically, a BMI of 30.0 to 34.9kg/m^2 is classified as Class I Obese, BMI of 35.0 to 39.9kg/m^2 is classified as Class II Obese, and a BMI of greater than 40.0kg/m^2 is classified as Class III Obese. Based upon estimates from the National Health and Nutrition Examination Survey (NHANES), the rate of overweight and obesity has been increasing over the past several decades for children, adolescents, and adults of all racial and ethnic groups[10]. Approximately 68% and 33% of American adults, 20 years of age or older, are classified as either overweight or obese, respectively. Moreover, nearly 15% of American adults are classified as Obese Class II and 6% are classified as Obese Class III. The rate of increase in morbid obesity is high, in that between the five year span from 2000 to 2005, prevalence rates increased by 50%[37]. While a greater percentage of men are categorized in the overweight and Obese Class I categories, women make up a greater percentage of those classified as Obese Class II and III for any age group[10].

The rising prevalence of obesity reflects the shift in eating and physical activity behaviors of the American population. Low-fat, complex carbohydrate meals have been replaced by high-fat, high-sugar diets, and a decrease in physically demanding work has led way to less active lifestyles. This chronic energy imbalance, i.e. greater calories consumed than burned, has led to a marked increase in overweight and obesity.

Obesity has been shown to be associated with musculoskeletal difficulties[13], sleep apnea[38], as well as diabetes[39], hyperlipidemia[40], hypercholesterolemia[41], cancer of the breast[42] and colon[43], cardiovascular disease[44], and increased mortality[45]. Increased mortality due to obesity has been linked to the strong association of excess body weight to cardiovascular disease risk[46].

2.3 CARDIOVASCULAR DISEASE PREVALENCE

The American Heart Association estimates that more than 81 million American adults have one or more types of cardiovascular disease[10]. Cardiovascular disease encompasses stroke, congenital heart disease, coronary artery disease, hypertension, and heart failure. Nearly 35% of all deaths in 2006 were attributed to at least one form of cardiovascular disease[10].

The most recent statistics suggest that cardiovascular disease is one of the leading causes of preventable death in the United States. Nearly one third of these deaths occurred before the person was 75 years of age, which is well below the expected average life span for American adults. It is estimated that if all forms of cardiovascular disease would be eliminated, average life expectancy would increase by 7 years[10].

2.3.1 The Effect of Obesity on Cardiovascular Disease

Obesity has been shown to be an independent risk factor for cardiovascular disease and contributes to cardiovascular disease risk factors, including: hypertension, dyslipidemia, and diabetes[1,13,15,24,47]. Two-year follow-up data from the Multi-Ethnic Study of Atherosclerosis (MESA) shows in 6814 adults free of clinical cardiovascular disease, cardiovascular disease risk was increased in all racial/ethnic and sex groups with high body mass index values[48]. A higher body mass index was associated with a 6-20mmHg higher systolic blood pressure, a 4-14mg/dL reduction in HDL cholesterol, and 18-55 mg/dL higher triglyceride levels compared to normal weight adults. Furthermore, Wannamethee showed in a 12-year follow-up of 6,916 men, a significant weight gain (>10%) from initial body mass index resulted in a significant risk of developing type 2 diabetes[49], an independent risk factor for cardiovascular disease.

Obesity has also been linked to cardiac mortality. In a 14-year follow-up of 5,881 Framingham Heart Study participants, the risk for heart failure increased by 5% in men and 7% in women with every 1 kg/m^2 increase in BMI[50]. This evidence is supported by Alpert et al, who showed a significant probability of developing heart failure as duration of morbid obesity increased[51].

Increased cardiovascular morbidity and mortality may also be attributed to factors such as coronary artery calcification, increased left ventricular mass, and increased carotid intima-media thickness. These have been observed in obese men and women in higher prevalence than their normal-weight age-matched counterparts[48].

2.3.2 Subclinical Cardiovascular Disease

Subclinical cardiovascular disease is an umbrella term for conditions of the cardiovascular system that do not manifest signs or symptoms. Generally, the first sign or symptom of subclinical cardiovascular disease is either a sudden cardiac event or sudden cardiac death. Subclinical cardiovascular disease is measured using the following techniques: carotid intima-media thickness, arterial pulse wave velocity, fibrosis, and left ventricular hypertrophy.

The National Institutes of Health determined subclinical cardiovascular disease to be of significant public health concern for two reasons: 1.) there can be a gradual progression of subclinical disease to clinical presentation with symptoms if not treated and 2.) subclinical disease is an earlier, more medically treatable state than manifested clinical disease[32].

2.3.3 The Effect of Obesity on Left Ventricular Hypertrophy

Left ventricular hypertrophy is an independent risk factor for cardiovascular morbidity and mortality[26]. This condition occurs in response to a chronic volume overload associated with obesity. Adipose tissue is a highly metabolic tissue and the body must respond by increasing total blood volume and cardiac output. These circulatory changes cause left ventricular morphology in the form of cavity dilation, which is then believed to elicit a hypertrophic response from the myocardium[52]. Chronic hypertrophy is dangerous because it increases the risk for the development of heart failure and sudden death[53]. This is evident in further examination of the Framingham Heart Study. Men in that study that had left ventricular hypertrophy as detected by electrocardiograph had an 8.1% higher risk of sudden death compared to only a 1.9% risk of sudden death in men who did not have left ventricular hypertrophy. Likewise, women with left ventricular hypertrophy had a 0.9% risk, compared to a 0.4% risk of sudden death in those who did not have left ventricular hypertrophy[48].

2.4 WEIGHT LOSS AND HEALTH RISK

The literature suggesting the association between obesity and diseases such as cardiovascular disease, diabetes, and dyslipidemia is vast. However, there is evidence that suggests weight loss may improve the outcomes of, or even eliminate, these diseases[54]. Even a modest weight loss of 10% initial body weight has been shown to be sufficient to improve health[21].

In some cases, the reduction of body weight has minor consequences. Weight loss has been shown to be linked to a greater risk of gallstone formation, loss of lean body mass, mild

liver dysfunction, and other less serious conditions[55]. However, the benefits of weight loss far outweigh the risks, and the adverse effects are not convincing enough to contraindicate weight loss[55].

2.4.1 The Effect of Weight Loss on Cardiovascular Disease Risk

Cardiovascular death rates have been linked to higher body mass index in both men and women. The risk of death from cardiovascular disease in severely obese adults (BMI $\geq$ 35kg/m^2) is nearly 3 times greater compared to normal weight (BMI 18.5 – 24.9kg/m^2)[56]. In general, weight reduction reduces blood volume, stroke volume, and cardiac output, along with filling pressures in all chambers of the heart[11]. These factors, in addition to reduction in other cardiovascular disease risk factors, contribute to the improvement in cardiovascular morbidity and mortality seen with weight loss.

Modest weight loss of approximately 5-10% initial body weight has been shown to improve diabetes outcomes in individuals with diagnosed type 2 diabetes, as well as prevent the development of diabetes in high-risk overweight and obese adults[57]. Insulin resistance associated with diabetes has been linked to increased inflammatory markers, especially C-reactive protein, which is a predictor of atherosclerosis and cardiac morbidity[57]. Kelley et al found that after 16 weeks, obese adults had substantial weight loss (12.7 $\pm$ 2 kg) following a very intensive weight loss regimen. Insulin sensitivity improved rapidly and continued to improve with sustained weight loss[58].

In a longer prospective study, Sjostrom et al examined 10-year follow-up rates of diabetes and diabetes related factors in 4,047 obese subjects who underwent gastric bypass surgery. Weight loss after 10 years decreased by 16.1% in the subjects who underwent gastric

bypass surgery compared to a 1.6% increase in the non-treatment control group. Ten-year recovery and incidence rates were markedly lower in the surgery treatment group compared to controls, suggesting a decrease in diabetes risk with long term weight loss[59].

Abnormally high levels of blood lipids classify another risk factor to cardiovascular disease. Weight loss has been shown to reduce LDL-C and triglyceride blood levels, and HDL-C concentrations are typically increased when weight loss is sustained[57]. Wadden et al conducted a prospective evaluation of 25 obese women over a 100-week period. At 100 weeks follow-up those women who lost >10% initial body weight had significantly greater reductions in total LDL-C and triglyceride levels compared to women who had only lost 5-10% of initial body weight. Furthermore, subjects who regained weight during the final 50 weeks of observation experienced significant increases in LDL-C levels ($p=0.05$)[60]. This suggests that at least 5% weight loss is necessary for beneficial reductions in total blood lipids, and these values can revert to baseline with weight regain.

An additional contributor to cardiovascular disease is hypertension. Weight loss is shown to reduce blood pressure, and does so in a dose-response manner[55]. Some studies suggest that clinically meaningful reductions in both systolic and diastolic blood pressure can occur before an overweight or obese person reaches ideal body weight[61,62]. Much like with diabetes, weight loss can prevent the onset of hypertension in overweight and obese men and women. A prospective study by Huang et al demonstrated that long-term weight loss after 18 years of age was related to a significantly lower risk for hypertension. Furthermore, weight regain significantly increased the risk for the development of hypertension. Relative risk for 5.0-9.9kg lost was 0.85 and 0.74 for a loss of greater than 10kg compared to less than 2kg weight loss. Conversely, for a gain of

5.0-9.9kg, relative risk was 1.74 and significantly higher (5.21) for a weight gain of greater than 25.0kg[63].

2.4.2 The Effect of Weight Loss on Left Ventricular Hypertrophy

Hypertrophy and remodeling of the left ventricle due to chronic obesity are associated with increased risk for morbidity and mortality[17]. Thus, it is important to implement successful weight-loss strategies to reduce left ventricular hypertrophy and improve cardiovascular disease risk.

In a 6-month study of 82 overweight and obese adults, Hinderliter et al found that participants in diet only and diet plus physical activity groups lost significant weight from baseline (7.4 and 2.3kg, respectively). Concomitant with these decreases in weight were reductions in left ventricular relative wall thickness ($p=0.003$), posterior wall thickness ($p=0.05$), and septal thickness ($p=0.004$), with a trend in reduction of left ventricular mass ($p=0.08$) compared to the control group[64].

These results are confirmed by more recent studies of Rider[65] and de las Fuentas[66], who showed that significant weight loss over a 1 or 2 year period results in beneficial changes in left ventricular mass and function in obese men and women.

2.5 PHYSICAL ACTIVITY AND WEIGHT LOSS

Physical activity is shown to be beneficial in reducing body weight, as well as preventing weight gain and weight regain[67]. Regular physical activity is recommended by all public health agencies

as a critical component of weight loss. Moderate intensity physical activity between 150 – 250 minutes per week is effective in preventing weight gain. However, this amount of physical activity will only produce modest weight loss without sufficient caloric restriction. Greater amounts of physical activity, at least 250 minutes per week, are needed to produce significantly meaningful weight loss. Moreover, long term weight loss may require up to at least 300 minutes per week of moderate intensity physical activity[68].

2.5.1 The Effect of Aerobic Training on Weight Loss

Studies that examine sedentary overweight and obese adults with physical activity as the only intervention generally result in 3 – 5% reduction from baseline weight. As aforementioned, significantly greater weight loss may require higher levels of physical activity. Unfortunately, most individuals may find this amount of physical activity off-putting or difficult to attain. Nonetheless, studies that examine a dose of physical activity no greater than 150 minutes per week show no significant reduction in baseline body weight.

Gwinup et al found that obese women who walked for no more than 30 minutes per day did not see any significant reduction in baseline weight. Additionally, it was not until the women approached or exceeded 30 minutes per day that weight loss was significant. Weight loss generally paralleled time spent walking when the amount exceeded 30 minutes per day[69].

A more recent study by Jeffery et al showed that obese men and women who walked for $\geq$ 75 minutes per day had significantly greater weight loss at 12 months (8.5 $\pm$ 7.9kg) and 18 months (6.7 $\pm$ 8.1kg) than did those in a standard obesity treatment group (6.1 $\pm$ 8.8, 4.1 $\pm$ 7.3kg, respectively)[70].

Even more recent, Christiansen et al examined the effect of exercise and diet-induced weight loss on 79 obese adults over a 12-week intervention. Subjects in the exercise only group participated in three 60 – 75 minute training sessions per week. Subjects in this group reported an average of 3.5 kg weight loss at the end of the 12-week intervention.

2.5.2 The Effect of Resistance Training on Weight Loss

Resistance training is becoming an integral component of exercise prescriptions that target weight reduction. Resistance training is recognized by the American College of Sports Medicine as critical in maintaining health, and it is recommended to perform resistance exercises at least twice weekly[68].

Current research has shown that resistance training reduces fat mass and increases lean body mass. This relationship, however, results in little to no weight loss[71-74]. The premise behind performing resistance training is that regular (2 to 3 times per week) resistance training is associated with at least a 1 to 2 kg increase in lean body mass. This increase in lean body mass will, in turn, increase resting metabolic rate and increase daily energy expenditure over time[71].

To further examine the effect of resistance training on weight loss, Kraemer et al[75] found that after a 12 week intervention involving diet only, diet plus aerobic training, or diet plus aerobic and resistance training, there was no significant difference in weight loss between the three groups. Participants in the group that received resistance training had a higher percentage of their total body weight loss represented by fat mass.

Similarly, Rice et al[76] found that during a 16-week intervention including obese men, reductions in weight and adipose tissue where not significantly different between those who

received a hypocaloric diet or hypocaloric diet with either resistance or aerobic training. Lean body mass was only preserved with resistance training at the end of the 16 week period.

Given the association of visceral fat depots to cardiovascular disease, of potentially greater importance is the effect of resistance training on visceral adipose tissue. Sixteen weeks of resistance training alone showed significant reductions in visceral fat[74]. In addition, Ross et al demonstrated significant reduction in visceral fat between obese men randomized into diet alone, diet plus aerobic training, or diet plus resistance training. However, there was no significant difference between the groups, but visceral fat mass was decreased greater than total body subcutaneous fat mass in the training groups[77].

These findings suggest that the effect of resistance training on weight loss may not be any greater than the effect of aerobic training. However, resistance training appears to preserve lean body mass in the presence of calorie restriction, therefore improving the metabolic profile of the individual[30].

2.6 PHYSICAL ACTIVITY AND CARDIOVASCULAR DISEASE

Both aerobic and resistance training have been shown to be beneficial when added to caloric restriction on reducing body weight. Regular physical activity is recommended by the American College of Sports Medicine[68] to improve health outcomes as well, independent of weight change. All healthy adults ages 18-65 years are recommended to attain at least 30 minutes of moderate-intensity physical activity at least 5 days per week or vigorous-intensity physical activity at least 20 minutes 3 days per week. Additionally, 8 – 10 muscle strengthening activities should be performed at least 2 days per week to maintain good health and physical independence[78].

Furthermore, activity exceeding the recommended amount will result in greater improvements in health.

Counterproductive to an increase in physical activity is an increase in sedentary behaviors. Physical inactivity has become widespread in the United States and contributes to cardiovascular disease, congestive heart failure, stroke, type 2 diabetes, and other chronic diseases[7]. Men who spend more than 10 hours per week in a car or more than 23 hours per week in other combined sedentary behaviors are at least 80% more likely to die from cardiovascular disease than those who spend less than 4-10 hours, respectively[7]. Thus, public health promotion efforts need to target sedentary behaviors and emphasize the benefits of increased physical activity for cardiovascular disease risk.

2.6.1 The Independent Effect of Aerobic Training on Cardiovascular Disease

There is a growing body of literature that supports a reduced risk of cardiovascular disease with increased levels of physical activity and cardiorespiratory fitness. Regular physical activity is especially important in individuals with insulin-resistant conditions such as type 2 diabetes and obesity[79]. Regular physical activity also reduces stress and anxiety, which are possible correlates to future cardiovascular events[80]. Additionally, there is a dose-response relationship to the amount of physical activity performed and risk for cardiovascular disease[27].

Haapanen et al examined 1,072 men ages 35-63 years. Men who accumulated moderate intensity physical activity showed a significant reduction in cardiovascular disease risk compared to those who only did light activity. Even as little as one or more hour per week of gardening was associated with a reduction in cardiovascular disease mortality[81].

Further examination of 6,131 men and women in the Alameda County Study[82] showed that physical activity was inversely related to cardiovascular disease risk in both men and women. Long walks and swimming were associated with at least a 50% reduction in cardiovascular disease mortality compared to those who did not participate in long walks or swimming.

One of the largest prospective studies to examine women, the Nurses Health Study, followed 72,488 women ages 40 to 65 years. Brisk walking of 3 hours or more per week resulted in a relative risk of cardiovascular disease mortality of 0.65 compared to not walking. The association was similar in those women who participated in vigorous walking 3 hours or more per week compared to women who did not walk[83].

2.6.2 The Independent Effect of Resistance Training on Cardiovascular Disease

A reduction in skeletal muscle mass secondary to aging or reduced physical activity contributes to an increase in cardiovascular disease risk factors[30]. The role of resistance training on cardiovascular disease risk factors in obese adults is vague; however, the cardiovascular adaptations to resistance training in normal weight athletes and leisurely-active adults have been well-documented[18,29,84,85].

In adults free of underlying cardiovascular disease, the greatest improvements in health from resistance training tend to be a result of an improved metabolic profile from an increase in skeletal muscle mass[30]. Additionally, these improvements have been shown without an increase in cardiovascular fitness or body fat percentage[86].

The effects of resistance training on blood pressure are not as well documented as with aerobic training, but the current literature suggests that it is beneficial. Cornelissen and

Fagard conducted a meta-analysis[87] of 9 randomized controlled trials where resistance training was the only form of treatment. Their results show that resistance training can reduce systolic blood pressure by 3.2mmHg and diastolic blood pressure by 3.5mmHg. These results suggest that moderate intensity resistance training is not contraindicated for adults with high-normal blood pressure.

These results seem modest, but a reduction of only 3mmHg in systolic blood pressure has been shown to reduce cardiac morbidity by nearly 10%, stroke by nearly 15%, and all cause mortality by nearly 5%[88].

Even when the outcome is not weight loss, aerobic and resistance training have beneficial effects on the cardiovascular system. While many adults participate in behavioral interventions to reduce body weight, an increase in physical activity achieved through these programs has beneficial effects on health. These programs should focus on the weight-loss effects of physical activity, as well as the cardiovascular benefit achieved independent of weight loss.

2.7 IMAGING TECHNIQUES TO DETECT CARDIOVASCULAR DISEASE

The detection of subclinical cardiovascular disease has previously been through use of two-dimensional echocardiography. However, given that hypertrophy is an abnormal state of the heart, echocardiography produces widely variable and inaccurate measurement of the left ventricle[32-34]. This error is the result of a general formula used to estimate a three-dimensional shape of the heart from the two-dimensional image. This technique is accurate when measuring a

normal heart; however the increased myocardium of the left ventricle is not accounted for in the formula.

A more accurate measure, cardiac magnetic resonance imaging (CMRI), has been adopted as the primary measuring tool in large epidemiological studies[32]. CMRI obtains multiple images of the heart measured at 1-cm intervals from the mitral valve plane to the heart apex[32]. These images are able to depict the inner and outer border of the myocardial wall, thus providing an accurate measure of ventricular volume. Volume is then multiplied by myocardial density ($1.05 g/cm^3$) to obtain mass. This method allows for any abnormalities in left ventricular shape to be accounted for in the images. CMRI has a much smaller error rate (5%) than electrocardiography (20%)[32] and has been determined to be the most accurate and reliable measure of left ventricular mass and volume[35].

2.8 SUMMARY

Obesity has reached epidemic proportions and is a serious public health concern. Obesity is directly related to cardiovascular disease risk. Reducing body weight through diet and exercise can improve cardiovascular-related outcomes associated with obesity. Regular aerobic and resistance training has beneficial independent effects on cardiovascular health, as well.

Class II and III obese adults are at greater risk for cardiovascular disease and other comorbidities, yet this population has not been studied in great detail[39]. While these individuals would benefit greatly from a clinical weight loss and behavioral modification intervention, this literature is currently lacking outside of the realm of bariatric surgery[36]. Training studies including aerobic training are even more rare, with resistance training in this population being

completely absent from the literature. This suggests a need to explore the effect of weight loss and different training modalities on cardiovascular morphology in Class II and III obese adults.

3.0 METHODOLOGY

3.1 SUBJECTS

A total of 33 women between the ages 30 – 55 years were recruited to participate in this study. Subjects were required to be apparently healthy, yet sedentary and obese according to BMI stratification ($\geq$ 35.0 kg/m^2 - $\leq$ 45.0 kg/m^2). While morbid obesity has been shown to be associated with a greater number of comorbidities[22], little research has been conducted to determine the association between the effect of weight loss and exercise training on cardiac structure and function in Class II and Class III obese adults. Individuals at low or moderate risk according to ACSM guidelines were recruited while those individuals at high risk were excluded from this study. Individuals with conditions that have negative influences on weight loss were also excluded. Additionally, individuals meeting the following conditions were excluded:

1. Currently pregnant, pregnant in the past 6 months, or planning on becoming pregnant in the next 6 months. Women who are currently pregnant have different nutritional needs and potentially have limitations to physical activity than non-pregnant women. Moreover, vigorous exercise is not recommended for women who are pregnant, which would limit the ability of these women to participate in the graded exercise test in this study. Pregnancy is also a contraindication for performing a DXA analysis of body composition. Women who have been pregnant within the past 6 months or who are breast feeding may

not be weight stable, which would potentially confound the influence of the proposed interventions on changes in body weight and body composition in this study.

2. Regularly exercising for greater than 60 minutes per week. An important component of the design of this study is to examine the effect of either aerobic or resistance exercise to an energy restricted diet. Therefore, to minimize the potential of a confounding effect, it is important to include only sedentary individuals in this study, which will also allow for maximal effects of the prescribed exercise on outcome measures.
3. Taking prescription or over-the-counter medications that affect body weight, metabolism, blood pressure, or heart rate. This study will examine the effect of a behavioral lifestyle intervention on weight loss, with the intervention including changes in physical activity and/or dietary behaviors. Therefore, medications that affect body weight could confound the results of this study, and are excluded.
4. Having physical limitations that hinder or prevent exercise. The ability to perform physical activity is imperative in the two intervention arms including aerobic or resistance exercise. Physical limitations could prevent exercise, thus not fully measuring the added effect of exercise to diet in weight loss.
5. Currently being treated for coronary heart disease, diabetes mellitus, hypertension, or cancer. Individuals with these conditions may require additional medical clearance and supervision that is outside the proposed scope of this study, or may require alterations in the intervention that would limit their ability to comply to the standardized intervention that is proposed.
6. Having a resting systolic blood pressure of $\geq$ 150mmHg of diastolic blood pressure of $\geq$ 100mmHg or currently taking any medications that affect blood pressure or heart rate

(i.e. beta blockers). Hypertension at these levels may contraindicate participation in the exercise prescribed as part of the interventions in this study. Moreover, cardiorespiratory fitness in this study is being assessed using a submaximal exercise test to 85% of age-predicted maximal heart rate that is not supervised by a physician. Therefore, blood pressure at these levels may pose a safety concern in this study. Additionally, if taking medications that affect the heart rate response to exercise, the termination heart rate during the graded exercise test will not be able to be determined.

7. Currently enrolled in an exercise or weight control study or participating in an exercise or weight control study in the past 6 months. Enrollment in an outside weight loss study, or recent participation in a weight loss study may confound the weight loss interventions proposed for this study.
8. Have lost and not regained > 5% body weight in the past 6 months. This may confound the effects of the intervention on weight loss, body composition, and other outcomes measured in this study. Moreover, based on our experience, the intervention may shift to a focus on prevention of weight regain rather than continued weight loss in these individuals.
9. Currently being treated for any psychological problems or taking any psychotropic medications. Receiving an intervention for psychological issues may confound the effect or may affect compliance to the intervention proposed for this study. Moreover, many psychotropic medications can affect body weight, and therefore should be excluded form this study.

3.2 RECRUITMENT AND SCREENING

Subjects were recruited through several media outlets in the Greater Pittsburgh Area that included: television and Craigslist advertisements as well as local flier postings. Additionally, letters were mailed to individuals registered in the Obesity and Nutrition Research Center (ONRC) database. The University of Pittsburgh Institutional Review Board (IRB) approved all recruitment methods and materials. Interested individuals were provided with the telephone number of the University of Pittsburgh Physical Activity and Weight Management Research Center. Upon calling, individuals talked to trained staff and masters and doctoral level graduate students to receive further information of the methodology of the study. This initial screening included a brief description of the study and upon further interest by the individual, questions regarding demographic background, physical health, and medical history determined eligibility.

Upon successful completion of the phone screening, eligible participants were invited to attend an orientation session where complete details of the study were given by the Principal Investigators (PIs) and Director of the Physical Activity and Weight Management Research Center. Individuals attending the orientation were encouraged to engage in a "question-and-answer" session following the overview. Additional orientation sessions were scheduled to accommodate the needs of all eligible participants. Committed participants completed informed consent documents to participate and were asked to complete a Physical Activity Readiness Questionnaire (PAR-Q)[89] to detect those at high risk for participating in regular exercise. Finally, individuals were required to obtain physician's written consent to ensure safety during this weight loss and exercise intervention.

Eligible participants with signed informed consent, physician clearance, and who were determined to be low risk for exercise underwent baseline assessments. Assessments included

measurements of: height, weight, body composition, cardiorespiratory fitness, muscular strength, cardiac structure and function, physical activity, and dietary intake. Assessment procedures are described in Section 3.3 below. Participants who completed baseline assessments were randomized to one of three intervention groups (see Figure 2 below). The University of Pittsburgh Institutional Review Board approved all study procedures.

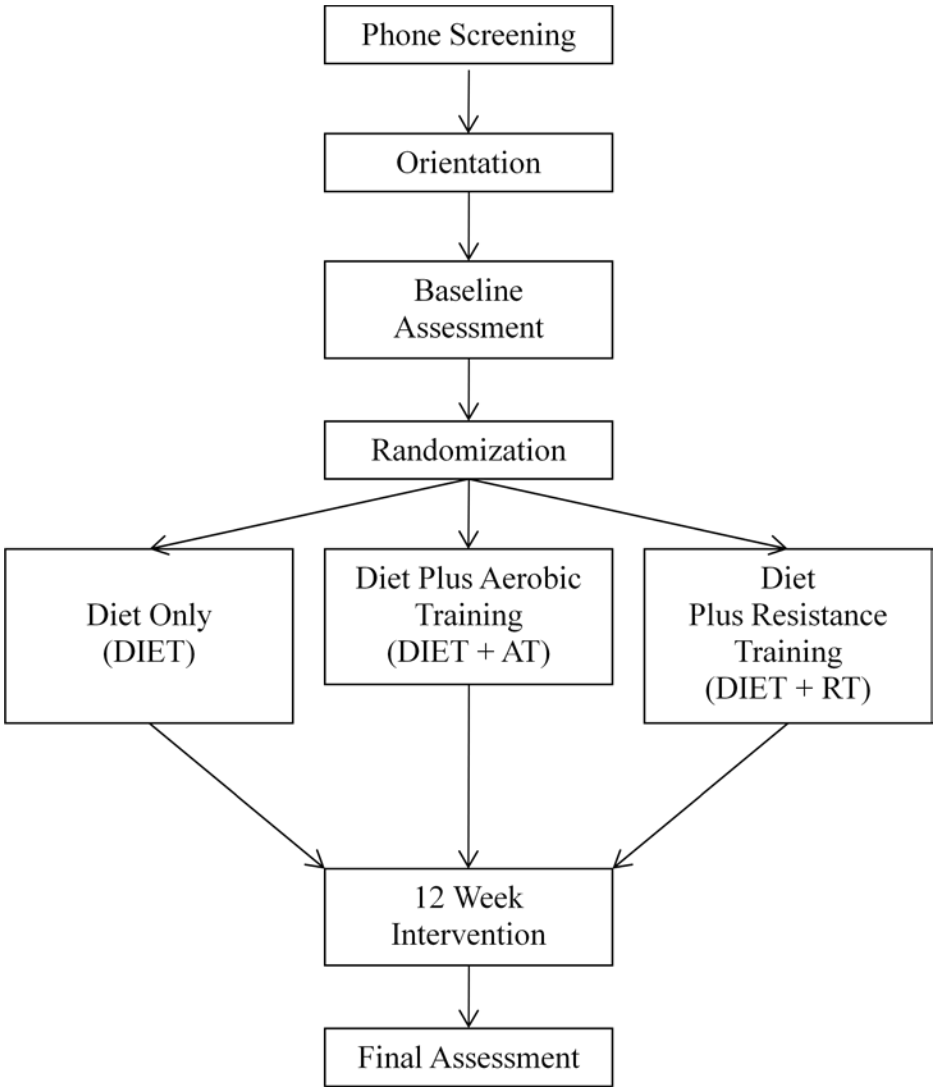


Figure 2: Study Progression

3.3 ASSESSMENT PROCEDURES

Assessments occurred at 0 (baseline) and 12 (final) weeks at the University of Pittsburgh Physical Activity and Weight Management Research Center. Assessments were conducted between 7:30 and 10:30am Monday through Friday and required approximately 90 to 120 minutes to complete. The assessments included measurements of: height, weight, body mass index, anthropometric measurements, body composition, cardiorespiratory fitness, muscular strength, cardiac structure and function, physical activity, and dietary intake. Subjects were required to report to the University of Pittsburgh Medical Center Presbyterian Hospital at an additional appointment time for cardiac magnetic resonance imaging to measure cardiac structure and function.

3.3.1 Height, Body Weight, and Body Mass Index

Height was measured to the nearest 0.01cm at the baseline assessment only using a wall-mounted stadiometer (Perspective Enterprises; Portage, MI). Participants had height measured with shoes removed. Body weight was measured to the nearest 0.1kg on a Tanita WB-110A digital scale (Tanita Corporation; Arlington Heights, Il) at 0 and 12 weeks with shoes removed and in a lightweight hospital gown. Body mass index was calculated as body weight in kilograms divided by square height in meters (kg/m^2).

3.3.2 Body Composition

Body composition was assessed using a GE Lunar Prodigy dual-energy x-ray absorptiometer (DXA) (GE Healthcare; Madison, WI). Calibration and scanning speed was performed prior to testing per manufacturer guidelines. Subjects were asked to remove any jewelry or metal items and be robed in the lightweight hospital gown. Subjects were required to undergo a pregnancy test prior to having the DXA scan completed. The low level radiation that is present with the scan can potentially harm the fetus. Participants were asked to lay motionless on the DXA bed for 10-15 minutes while the machine scanned total body mass. Measurements that were attained included: percent body fat, total fat mass, total lean mass, and bone mineral density. An individual-specific printout was attained for each subject and included in that subjects' assessment data folder. A trained professional conducted each DXA scan.

3.3.3 Anthropometric Measurements

Elevated adipose tissue, especially in the abdominal region, has been linked to increased risk for cardiovascular disease[90]. Abdominal adiposity was measured by waist circumference and waist-to-hip ratio. Measurements were taken at 0 and 12 weeks with subjects dressed in the lightweight hospital gown. Waist and hip circumferences were measured to the nearest 0.1cm using a Gulick tape measure. Waist circumference was measured horizontally at the iliac crest. Hip circumference was taken at the largest circumference horizontally at the buttocks. Two measurements were taken at each site, and a third was taken if the first two measurements differed by more than 2.0cm. The mean of the two closest measurements was recorded for data collection.

Resting heart rate was measured at the radial artery for 30 seconds following a five-minute resting period during which the participant sat quietly in the upright position with feet flat on the floor. Resting blood pressure was taken immediately after the resting heart rate measurement and was performed using a standard vertical mercury sphygmomanometer with the stethoscope placed on the antecubital space on the left arm of the participant. Two blood pressure measures were taken with a one-minute waiting period between each measurement. A third blood pressure was taken if the difference between the systolic blood pressure was $\geq$ 10mmHg or if diastolic blood pressure was $\geq$ 6mmHg. If the resting systolic blood pressure was $\geq$ 150mmHg or diastolic blood pressure was $\geq$ 100mmHg the subject was excluded.

3.3.4 Cardiorespiratory Fitness

Cardiorespiratory fitness was assessed via a submaximal graded exercise test utilizing a modified Balke protocol at 0 and 12 weeks. All graded exercise tests were performed at the Physical Activity and Weight Management Research Center and were conducted by a certified Exercise Specialist as recognized by the American College of Sports Medicine. The metabolic cart (SensorMedics Vmax Metabolic Measuring Cart; SensorMedics; Yorba Linda, CA) was calibrated for air volume and gas analysis prior to each test.

The following protocol was administered for each graded exercise test: Subjects entered the testing room and were given a brief overview of the test. The subject was then familiarized with the Borg 15-point Rating of Perceived Exertion (RPE) Scale[91]. The subject was prepared by cleaning each site with rubbing alcohol where the 12-lead electrocardiograph (EKG) leads were to be placed. The subject was then fully hooked up to the EKG and be fitted to the airflow mouthpiece and head support system. The speed of the treadmill was set at 80.4 m/min (3.0mph)

and remained constant throughout the test. The grade of the treadmill started at 0% and increased by 2.5% every 3 minutes. Heart rate and 12-lead EKG were monitored continuously throughout the test. Blood pressure and ratings of perceived exertion were obtained at the end of each stage and at test termination. Expired gas volumes and concentrations were measured continuously throughout the duration of the test using the metabolic cart. Termination of the test occured at 85% of the subjects' age-predicted maximal heart rate as determined by the equation 220-age. Criteria for termination included subject report of any of the signs or symptoms that are indicative of test termination as described by the American College of Sports Medicine. Upon attaining 85% maximal heart rate, subjects performed a three minute active recovery period at 0% grade and a speed between 2.0 – 2.5 mph with the gas analyzing mouthpiece and headgear removed. A recovery blood pressure was taken and the subject sat on the hospital bed for three minutes to allow heart rate and blood pressure responses to return toward resting values. All EKG printouts were sent to a board certified cardiologist to ensure no contraindications to participating in exercise. All testing staff and personnel were certified in cardiopulmonary resuscitation (CPR) and use of the Automated External Defibrillator (AED), with safety equipment readily accessible in the testing room.

3.3.5 Muscular Strength

Muscular strength was assessed at baseline and 12 weeks utilizing the chest press, seated row, and leg press. These muscle groups were tested as they represented the largest muscle groups that were exercised throughout the course of the intervention. Additionally, these measures allowed for the assessment of strength gains in both upper and lower body musculature. All

resistance training assessments were conducted on plate-loaded machines to ensure proper safety of the participant while performing each exercise.

The chest press and seated row were conducted to assess one of two separate upper body strength gains. The subject started by sitting on the Precor™ vertical chest press machine. The seat was adjusted for participant height so that the handles of the machine were at mid-chest level and the feet flat on the floor. The hands were placed on the machine handles at either a prone or neutral grip, dependant upon participant preference. The subject warmed up with a set of 5 repetitions with 25 pounds loaded on the weight stack. Once the warm-up phase was completed, a rating of perceived exertion (RPE) was attained using the 10-point OMNI RPE scale. If the RPE was less than 5, the weight increased by 10 pounds. No further warm-up was performed if the RPE was greater than 7. The assessment trial began after a 30 second rest period. At that point, single-repetition effort was performed with the resistance progressively increased by 1-20 lbs until the subject could no longer complete the selected repetitions. The goal was to determine 1-Repetition Maximum within 4-6 trials, with rest periods of 60 seconds minute between trials. All repetitions of the assessment were performed at the same speed and range of motion remained consistent throughout the trial. The final weight successfully lifted was recorded as the absolute 1-Repetition Maximum). This same protocol was then repeated for the seated row to attain a second measure of upper body strength. For this assessment, the subject sat on the Precor™ seated row machine with the seat positioned so that feet were flat on the floor and hands at a neutral grip. The final weight successfully lifted was recorded as the absolute 1-Repetition Maximum for this exercise.

The leg press was the final measure of muscular strength gains as it represented lower body strength. The participant sat on the Precor™ leg extension apparatus with knees resting in a

flexed position over the leg pad. Assessment staff assisted the subject in placing the seat of the apparatus at a setting that allowed the knee to maintain a 90-degree angle of flexion. The subject warmed up and 1-Repetition Maximum was determined following protocol aforementioned for upper body strength measurements.

The final weight obtained through 1-Repetition Maximum testing during baseline assessments was used to develop a strength training protocol for each participant ensuring that each person was trained to her individual ability.

3.3.6 Cardiac Structure and Function

Subjects underwent an imaging technique to assess changes in left ventricular mass, fibrosis, end diastolic volume, end systolic volume, and ejection fraction at 0 and 12 weeks. Scans were conducted and read by a cardiologist blinded to treatment group assignment. Left ventricular mass and end diastolic volume were determined by steady state free precession cine pulse sequences, which yield high temporal resolution (30 frames per cardiac cycle) and high spatial resolution (typical acquisition parameters: 1.6 x 2.3 mm in plane spatial resolution, 6 mm thick slices, 4 mm gap, flip angle 50 degrees, 1100 Hz/pixel; TR 3.0 msec; TE 1.2 msec FOV 40x 36 cm; matrix 256 x160; GRAPPA acceleration factor 2; retrospective ECG gating to capture the entire cardiac cycle). To compute left ventricular mass, the volume of myocardium enclosed by tracing all of the endocardial and epicardial borders at end diastole were multiplied by the thickness of the slice plus the interslice gap and myocardial density (1.04 g/mL). The blood pool volume enclosed by endocardial borders yielded left ventricular end diastolic volume. Papillary muscle mass was included in the left ventricular volumetric measure and excluded from left ventricular mass measures. Measurements were assisted by semi-automated algorithms on

workstations (2 Siemens Leonardo workstations with Argus software; 1 Vital Images workstation and 4 PCs with Medis QFLOW and QMASS software).

Prior to the scan, the participant registered and was directed to the Cardiovascular Institute. The participant then changed into a hospital gown with only clothing above the waist removed. Any metallic objects (e.g. watch, glasses, jewelry, ear rings, etc.) were removed and placed in a secure locker. The participant then received an IV line for the contrast dye and blood sampling. The participant then lied in the supine position on the scanner table with four ECG electrodes attached. She was given head phones with disposable ear covers to allow communication with the technologist. A squeeze ball alarm was placed in the participant's hand to alert the technologist immediately of an emergency. Anterior cardiac chest coils were then placed on the participant's chest. These are the antennae that permit signal capture to generate the required images. The table and participant were moved to the center of the short/wide bore magnet (Siemens Espree model) and scanning commenced for pre-contrast sequences. The technologist then entered the suite to hand inject the gadolinium contrast (Prohance 0.1-0.2 mmol/kg contrast dose) and observed for any adverse reactions. The participant was then removed in the same fashion as the beginning of the scan (but in reverse order) after images were successfully acquired.

3.3.7 Physical Activity

Physical activity was assessed at baseline and 12 weeks using the Paffenbarger Physical Activity Questionnaire[92]. This particular questionnaire estimates the average number of flights of stairs and city blocks walked each day for the sole purpose of exercise. Additional information regarding any sport, recreation, or fitness activities that the subject participated in over the

previous week was documented. If any illness, family circumstance, or vacation made the previous week out of the ordinary, the subject recalled the last normal week. Results were converted to kilocalories per week. A trained staff member or graduate student from the Physical Activity and Weight Management Research Center administered this questionnaire.

3.3.8 Dietary Intake and Eating Behaviors

Dietary intake was assessed using the Block Food Frequency Questionnaire (FFQ) (Block, 2005.1). This questionnaire measures how often in the past year a person consumes a certain food, ranging from "Never" to "Every Day". Additionally, portion sizes are also determined, ranging from "1/4 cup" to "2 cups". This questionnaire has been previously validated in estimating daily caloric intake[93]. Dietary intake was measured at 0 and 12 weeks.

Eating behaviors were assessed using the Eating Behavior Inventory (EBI)[94]. This questionnaire includes a 26-point checklist regarding eating and shopping habits. Responses can range from "Never of Hardly Ever" to "Always or Almost Always". This questionnaire has been previously validated[94].

3.4 EXPERIMENTAL DESIGN

This study was a 12-week randomized controlled trial (RCT) to examine the effect of weight loss with and without either aerobic or resistance training on cardiac structure and function in Class II and III obese adults. This intervention was conducted at the University of Pittsburgh Physical Activity and Weight Management Research Center. Upon successful completion of baseline

assessments and physician clearance, subjects were randomly assigned into one of three groups: 1.) standard behavioral weight loss: diet only (DIET), 2.) diet plus aerobic training (DIET+AT), and 3.) diet plus resistance training (DIET+RT). Each group and its corresponding intervention will be provided in further detail below. The study timeline is illustrated in Figure 3.

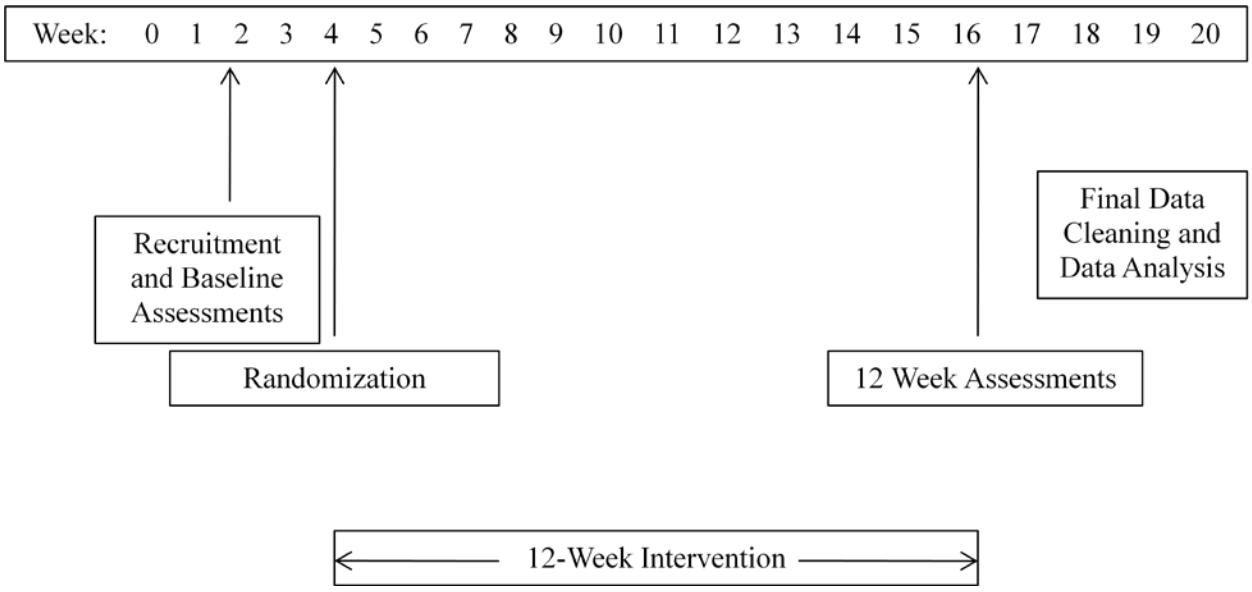


Figure 3: Study Timeline

3.5 STANDARD BEHAVIORAL WEIGHT LOSS INTERVENTION: DIET ONLY

The diet only intervention arm (DIET) was conducted at the University of Pittsburgh Physical Activity and Weight Management Research Center. This intervention included a 12-week behavioral education program in which participants attended weekly group sessions. Group sessions lasted approximately 30 – 45 minutes and were conducted by graduate students educated in nutrition, exercise physiology, and behavior modification. Group sessions focused on approaches that change eating behaviors based on the Social Cognitive[95] and Problem Solving[96] Theories.

Subjects were weighed prior to each group session. These weekly values allowed the interventionists, as well as subjects, to monitor weight changes over the course of the intervention. If a participant missed a group session, that participant was required to make-up that session with one of the interventionists before the next meeting. In the case of vacation or extended absence, appropriate materials were provided for the participant. The timeline for group sessions is outlined in Table 1.

Table 1: Session Type by Intervention Week

Session	Intervention Week											
	1	2	3	4	5	6	7	8	9	10	11	12
Group Session (Individual Sessions as Necessary)	×	×	×	×	×	×	×	×	×	×	×	×

3.5.1 Dietary Component

Participants were given a calorie and fat gram goal at the beginning of the intervention according to their initial body weight (Table 2). Calorie and fat gram goals were adjusted throughout the course of the intervention as the participant fell into lower weight categories. The fat gram goals were set in accordance with USDA Dietary Guidelines that set a fat gram range of 20 - 25% of total calories[97].

Table 2: Calorie and Fat Gram Goals by Baseline Body Weight

Starting Weight (lbs)	Calorie Goal	Fat Gram Goal
≤175	1200	27g
175-219	1500	33g
220-249	1800	40g
250+	2100	47g

Participants were also given a copy of The Calorie King Calorie, Fat, and Carbohydrate Counter, along with sample meal plans and recipes aimed at helping them in making healthy food choices. Food log diaries were provided throughout the 12-week period to track daily calorie and fat gram consumption over the course of a single week. These diaries were turned in every week to be reviewed and commented on by the interventionists. Suggestions were made in regards to: healthier food choices, portion control, etc. If a participant did not turn in a diary, or returned a semi-completed diary, an interventionist spoke to the participant either in person or over the phone to determine the cause of the problem or to offer modifications in completing the diary.

3.6 DIET PLUS AEROBIC TRAINING

Participants in the diet intervention who also receive aerobic training (DIET+AT) also received all of the educational components as described above for the DIET group. This group participated in supervised progressive aerobic training three days per week as shown in Table 3. Participants were required to attend three sessions per week at the University of Pittsburgh

Physical Activity and Weight Management Research Center. These supervised exercise sessions progressed from 60 to 180 minutes per week of moderate-intensity aerobic exercise (e.g., treadmill walking, recumbent cycling, adaptive motion trainer, elliptical trainer). Moderate-intensity aerobic exercise was classified as 3 – 6 metabolic equivalents (METs), or three to six times the amount of work compared to a resting state. The American College of Sports Medicine and the American Heart Association recommend the equivalent of 450 – 750 MET minutes per week, or greater than 150 minutes per week [68]. The intensity was set to increase at the rate prescribed to take full advantage of the relative brevity of this study.

Participants were encouraged to not miss any training sessions throughout the course of the study. Attempts were made during the remainder of the week or following week to have the participant make up a missed session. These exercise sessions were conducted and supervised by trained graduate students at the University of Pittsburgh who were instructed not to provide any additional information relative to weight loss or dietary change to the participants during these sessions.

Table 3: Aerobic Training Protocol for DIET+AT Group

	Supervised Exercise			
Intervention Week	Days per Week	Minutes per Day	Total Minutes per Week	Exercise Intensity (% of age-predicted maximal heart rate)
1	3	20	60	60-65
2	3	30	90	60-65
3	3	40	120	60-65
4	3	50	150	65-70
5-12	3	60	180	65-70

3.7 DIET PLUS RESISTANCE TRAINING

Participants in the diet plus resistance training group (DIET+RT) also received all of the educational components of the DIET group. This group was prescribed a supervised resistance training protocol for a frequency of three days per week. The protocol started the participants at a low volume of exercise at an intensity of 60-65% of 1-repetition maximum with low sets and repetitions and alternated volume and intensity throughout the intervention with a general trend toward increasing intensity, as outlined in the ACSM Position Stand: Progression Models in Resistance Training for Healthy Adults[98]. Percent of 1-Repetition maximum was decreased before the participant increased sets and repetitions to allow the participant's musculature to prepare for the added stress.

Table 4 illustrates the resistance training protocol. The first week of training was devoted to familiarizing the participants with the resistance training equipment and ensuring proper safety protocol was followed when performing the exercises. The resistance exercises used icluded the following: Leg Press; Seated Row; Chest Press; Pulldown; Shoulder Press; Bicep Curl; Tricep Extension; Leg Extension; and Seated Leg Curl. Table 5 illustrates the timeline for various exercises in the resistance training intervention arm.

In the event that a participant was uncomfortable with a particular exercise, that exercise was avoided or substituted for exercises that utilized resistance bands and tubing. Participants were encouraged to not miss any training sessions throughout the course of the study. Attempts were made during the remainder of the week or following week to have the participant make up

a missed session. The training sessions were conducted and supervised by graduate students of the University of Pittsburgh trained in the use of the equipment and qualified to respond to adverse events.

Table 4: Resistance Training Protocol for DIET+RT Group

	Supervised Exercise			
Intervention Week	Days per Week	Minutes per Day	Total Minutes per Week	Exercise Intensity (% of age-predicted maximal heart rate)
1	3	20	60	60-65
2	3	30	90	60-65
3	3	40	120	60-65
4	3	50	150	65-70
5-12	3	60	180	65-70

Table 5: Timeline for Introduction of Various Exercises for DIET+RT Group

Exercise	Intervention Week											
	1	2	3	4	5	6	7	8	9	10	11	12
Lower Body Exercises												
Leg Press	X	X	X	X	X	X	X	X	X	X	X	X
Leg Extension				X	X	X	X	X	X	X	X	X
Leg Curl				X	X	X	X	X	X	X	X	X
Back Exercises												
Seated Row	X	X	X				X	X			X	X
Pulldown				X	X	X			X	X		
Chest Press	X	X	X	X	X	X	X	X	X	X	X	X
Shoulder Exercises												
Shoulder Press							X	X	X			X
Upright Row (Dumbbell)				X	X	X					X	
Lateral Raise (Tubing)	X	X	X							X		
Bicep Exercises												
Machine Curl				X	X	X						
Dumbbell Curl										X	X	X
Tubing Curl							X	X	X			
Tricep Extension												
Machine				X	X	X				X		X
Dumbbell							X	X	X		X	

3.8 STATISTICAL ANALYSES

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software, version 17.0. Statistical significance was set at $p < 0.05$. Analyses were conducted

using individuals completing the assessment protocol at 0 and 12 weeks, and with intent-to-treat analysis carrying the baseline data forward. The following analyses were performed:

1. Descriptive analysis to examine the mean baseline characteristics (age, weight, BMI), body composition, daily physical activity, and dietary intake.
2. Descriptive analysis to examine process measures, including: session attendance; dietary logging; self-reported caloric intake; and self-weighing frequency. One-way analysis of variance (ANOVA) will be used to examine any differences in the process measures among groups
3. 3 x2 repeated measures ANOVA will be performed on left ventricle morphology as a function of group and time to determine differences between the variables. The main effect of time will be examined between 0 and 12 weeks; the main effect of group will examine any differences among randomized groups. The group x time interaction will be examined to determine patterns of difference among groups for weight loss between 0 and 12 weeks. Post hoc pairwise comparisons will be used, if needed, to determine differences in weight loss between the randomized groups.
4. 3 x 2 repeated measures ANOVA will be performed on weight loss as a function of group and time to determine differences between the variables. The main effect of time will be examined between 0 and 12 weeks; the main effect of group will examine any differences among randomized groups. The group x time interaction will be examined to determine patterns of difference among groups for weight loss between 0 and 12 weeks. Post hoc pairwise comparisons will be used, if needed, to determine differences in weight loss between the randomized groups.

5. 3 x 2 repeated measures ANOVA will be performed on dietary intake by group to determine if there are differences between the variables. The main effect of time will determine any differences between 0 and 12 weeks. The main effect of group will determine any differences between randomized group. Group x time interaction will be examined to determine patterns of difference between the groups for dietary intake between 0 and 12 weeks. Post hoc pairwise comparisons will be used, if needed, to determine differences in weight loss between the randomized groups
6. 3 x 2 repeated measures ANOVA will be performed on body composition by group to determine if there are differences between the variables. The main effect of time will determine any differences between 0 and 12 weeks. The main effect of group will determine any differences between randomized groups. Group x time interaction will be examined to determine patterns of difference between the groups for body composition between 0 and 12 weeks. Post hoc pairwise comparisons will be used, if needed, to determine differences in weight loss between the randomized groups

3.9 POWER ANALYSIS

The primary aims of this study are to examine the effect of the interventions (DIET, DIET+AT, DIET+RT) on left ventricular changes that have been shown to be associated with increase risk of CVD. The results from this study are intended to fulfill the dissertation requirement of the investigator and to provide important pilot data that can be used to support an appropriately powered larger study. The pilot data of importance that will be obtained from this study will include the following: 1) effect sizes of differences between the intervention conditions for the

proposed left ventricular measures, 2) measures of compliance to the proposed doses of exercise in the DIET+AT and DIET+RT groups, 3) measures of compliance and feasibility for attendance at supervised exercise sessions, 4) data on recruitment of subjects to participate in a study of this nature. Therefore, it is proposed that 30 subjects be recruited and complete the intervention, with 10 subjects completing the study in each condition, and 5 subjects per study condition reporting for CMRI scans. Given the cost of each scan, performing more CMRI scans than proposed would be cost-prohibitive and would hinder the feasibility of this study.

4.0 RESULTS

The purpose of this study was to examine the effect of weight loss induced by diet alone or in combination with either aerobic or resistance exercise on cardiovascular structure and function in Class II and III Obese women during a 12-week intervention. This was a pretest-posttest randomized controlled weight loss trial with assessments conducted at 0 and 12 weeks. The results of this study are presented below:

4.1 SUBJECT CHARACTERISTICS

A total of 24 Class II and III Obese women between the ages of 30 – 55 years with a body mass index (BMI) of 35.0 – 44.9 kg/m^2 were randomized to this investigation. Assessment measures and intervention protocol were conducted at the University of Pittsburgh Physical Activity and Weight Management Research Center (PAWMRC) and University of Pittsburgh Medical Center Cardiovascular Magnetic Resonance Center (CMRC). Subjects had a mean age of 45.4 ± 6.9 years and mean BMI of 39.0 ± 2.7 kg/m^2 at the start of the intervention. A series of one-way analyses of variance (ANOVA) revealed no significant difference between treatment groups at baseline ($p>0.061$) for baseline demographics, body composition, dietary intake, physical activity, cardiorespiratory fitness, muscular strength or cardiovascular outcome measures. These data are presented in Table 6.

Table 6: Differences in Baseline Characteristics by Treatment Group

Characteristics	Total (N=24) (Mean±S.D.)	DIET (N=8) (Mean±S.D.)	DIET+AT (N=8) (Mean±S.D.)	DIET+RT (N=8) (Mean±S.D.)	p-value
Age (years)	45.4 ± 6.9	46.6 ± 8.8	43.9 ± 5.9	45.5 ± 6.1	0.741
Weight (kg)	104.2 ± 10.6	104.2 ± 11.3	107.2 ± 13.3	101.3 ± 6.8	0.757
Body Mass Index (kg/m^2)	39.0 ± 2.7	39.7 ± 2.2	39.0 ± 3.2	38.4 ± 2.7	0.622
Waist Circumference (cm)	111.9 ± 7.2	115.3 ± 8.5	109.9 ± 7.1	110.6 ± 5.2	0.284
Hip Circumference (cm)	128.6 ± 8.9	126.3 ± 3.9	132.6 ± 12.4	127.0 ± 7.9	0.316
Waist-to-hip ratio	0.87 ± 0.07	0.91 ± 0.06	0.83 ± 0.07	0.87 ± 0.05	0.061
Body Composition Regional %Fat (%) Tissue %Fat (%)	 48.9 ± 3.6 50.2 ± 3.5	 48.2 ± 3.8 49.5 ± 3.8	 49.8 ± 4.4 51.1 ± 4.4	 48.6 ± 3.7 49.9 ± 3.8	 0.715 0.708
Race %African American %Caucasian %Other	 20.8 (N=5) 75.0 (N=18) 4.2 (N=1)	 0.0 (N=0) 100.0 (N=8) 0.0 (N=0)	 25.0 (N=2) 75.0 (N=6) 0.0 (N=0)	 37.5 (N=3) 50.0 (N=4) 12.5 (N=1)	0.508
Dietary Intake (kcal/day) %Fat %Protein %Carbohydrate	2056.0±644.2 38.1±5.5 15.2±3.3 64.7±8.6	2024.6±264.4 37.2±2.2 13.5±0.9 49.3±3.5	2088.3±276.4 35.8±1.7 15.4±0.8 49.3±2.7	2055.3±154.4 41.3±1.5 16.6±1.6 41.5±2.2	0.982 0.107 0.175 0.108
Eating Behavior Inventory	69.2 ± 9.7	67.6 ± 13.1	69.6 ± 8.9	70.6 ± 6.6	0.844
Self Reported Physical Activity (kcal/week)	473.7 ± 445.6	322.1 ± 300.8	570.9 ± 516.7	528.1 ± 504.4	0.511
VO_2 at 85% APMHR* (ml/kg/min)	20.4 ± 3.6	21.8 ± 4.3	20.1 ± 3.7	19.2 ± 2.6	0.372
Time to Reach 85% APMHR* HR (min)	5.8 ± 2.7	7.0 ± 2.7	4.9 ± 3.4	5.3 ± 1.7	0.286
Left Ventricle Mass (g)	87.9 ± 16.3	94.5 ± 25.5	85.9 ± 14.3	83.9 ± 3.4	0.593
Myocardial Fibrosis (%)	25.6 ± 2.0	24.2 ± 1.8	25.9 ± 1.8	26.8 ± 1.9	0.242
End Systolic Volume (mL)	55.4 ± 15.9	51.9 ± 24.9	56.1 ± 12.9	57.9 ± 10.2	0.863
End Diastolic Volume (mL)	141.5 ± 30.4	136.9 ± 48.2	141.4 ± 22.4	146.1 ± 21.4	0.790
Ejection Fraction (%)	61.4 ± 5.2	63.3 ± 7.9	60.6 ± 3.9	60.4 ± 3.5	0.711

*APMHR = Age Predicted Maximal Heart Rate (220-age)

4.2 RETENTION

Figure 4 illustrates overall retention of the cohort. One subject in the DIET group was lost due to relocation while the other was lost for unknown reasons. Neither of the subjects lost in the DIET+AT group gave reasons for their discontinuation in the study, while both subjects in the

DIET+RT group were lost due to injuries sustained outside of the intervention. Overall, retention rates for each of the three groups were identical (N=6, 75%).

The 18 subjects who completed baseline and final assessments at PAWMRC and 16 who completed final scans at CMRC will be referred to as “completers”. Subjects who did not complete final assessments at PAWMRC (N=6) will be referred to as “non-completers”. Data for two subjects who did not complete their 12-week scans at CMRC were not available and therefore will not be included in the results. One subject was unable to reschedule her appointment after difficulty placing the intravenous (IV) line during her first scheduled appointment at week 12. The other participant encountered claustrophobia during the baslien scan and was uncomfortable with another scan at week 12. Baseline characteristics between completers and non-completers are presented in Table 7. There was a trend toward a significance difference observed for waist circumference (completers: 113.6 ± 7.2cm, non-completers: 107.2 ± 4.6cm; $p=0.056$), however no significant differences were observed for the other baseline characteristics ($p>0.56$).

When examined by treatment group, non-completers in the DIET group (24.5 ± 1.3ml/kg/min) had significantly higher VO_2 at 85% age-predicted maximal heart rate (APMHR) than the completers (20.9 ± 4.6ml/kg/min; $p<0.05$). Inversely, completers in the DIET+AT group (21.1 ± 3.8ml/kg/min) had significantly higher VO_2 at 85% APMHR than the non-completers (17.2 ± 0.4ml/kg/min; $p<0.05$). Non-completers in the DIET and DIET+RT groups had significantly longer time to reach 85% APMHR (8.8 ± 0.7min and 4.7 ± 0.0min, respectively) compared to completers in the DIET (6.4 ± 2.9min) and DIET+RT (5.0 ± 1.9min) groups ($p<0.05$). Inversely, completers in the DIET+AT group had significantly longer time to reach

85% of APMHR compared to the non-completers (5.3 ± 4.0min and 3.7 ± 0.5min, respectively; $p<0.05$). These data are presented in Table 8.

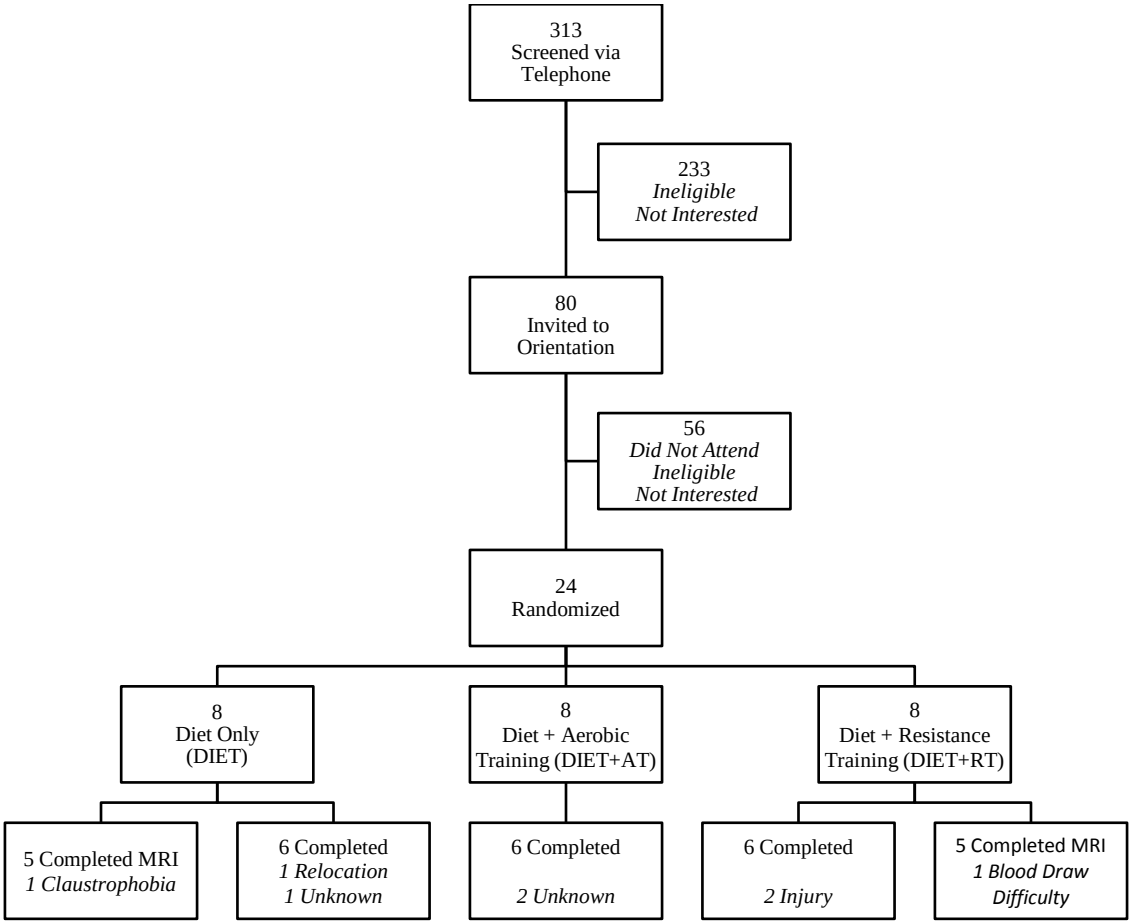


Figure 4: Study Retention and Enrollment Across Groups

Table 7: Differences in Baseline Characteristics by Completers and Non-Completers

Characteristics	Total (N=24) (Mean±S.D.)	Completers (N=18) (Mean±S.D.)	Non-Completers (N=6) (Mean±S.D.)	p-value
Age (years)	45.4 ± 6.9	44.9 ± 6.6	46.7 ± 7.9	0.598
Weight (kg)	104.2 ± 10.6	105.0 ± 10.9	101.9 ± 10.1	0.550
Body Mass Index (kg/m^2)	39.0 ± 2.7	39.3 ± 2.6	38.1 ± 2.9	0.352
Waist Circumference (cm)	111.9 ± 7.2	113.6 ± 7.2	107.2 ± 4.6	0.056
Hip Circumference (cm)	128.6 ± 8.9	129.3 ± 9.5	126.7 ± 7.1	0.551
Waist-to-hip ratio	0.87 ± 0.07	0.88 ± 0.07	0.85 ± 0.04	0.280
Body Composition %Fat - Regional %Fat - Tissue	 48.9 ± 3.6 50.2 ± 3.5	 48.9 ± 4.0 50.2 ± 4.0	 48.7 ± 3.5 50.0 ± 3.5	 0.937 0.924
Race %African American %Caucasian %Other	 20.8 (N=5) 75.0 (N=18) 4.2 (N=1)	 27.8 (N=5) 72.2 (N=13) 0.0 (N=0)	 0.0 (N=0) 83.3 (N=5) 16.7 (N=1)	0.339
Dietary Intake (kcal/day) %Fat %Protein %Carbohydrate	2056.0±644.2 38.1±5.5 15.2±3.3 64.7±8.6	2201.9±157.3 38.6±1.4 15.8±0.8 45.9±2.1	1618.5±120.9 36.4±1.9 13.3±1.1 49.3±3.1	0.052 0.407 0.103 0.418
Eating Behavior Inventory	69.2 ± 9.7	68.5 ± 9.8	71.2 ± 9.7	0.577
Self Reported Physical Activity (kcal/week)	473.7 ± 445.6	466.4 ± 428.9	495.5 ± 535.8	0.894
VO_2 at 85% APMHR* (ml/kg/min)	20.4 ± 3.6	20.2 ± 3.8	20.9 ± 3.4	0.701
Time to Reach 85% APMHR* (min)	5.8 ± 2.7	5.8 ± 2.9	6.3 ± 2.3	0.597
Left Ventricle Mass (g)[¥]	88.1 ± 15.6	87.9 ± 16.3	89.6 ± 12.2	0.895
Myocardial Fibrosis (%)[¥]	25.5 ± 2.1	25.6 ± 2.0	24.4 ± 2.8	0.462
End Systolic Volume (mL) [¥]	55.1 ± 15.0	55.4 ± 15.9	53.3 ± 0.6	0.858
End Diastolic Volume (mL) [¥]	143.1 ± 28.9	141.5 ± 30.4	155.9 ± 7.1	0.524
Ejection Fraction (%)[¥]	61.9 ± 5.1	61.4 ± 5.2	65.8 ± 1.9	0.260

*APMHR = Age Predicted Maximal Heart Rate (220-age)

[¥]Data for only 18 subjects is available for CMRI (16 completers, 2 non-completers)

Table 8: Baseline Characteristics by Treatment Group and Completion

Characteristics	DIET		DIET+AT		DIET+RT	
	Completers (N=6) (Mean±S.D.)	Non-Completers (N=2) (Mean±S.D)	Completers (N=6) (Mean±S.D.)	Non-Completers (N=2) (Mean±S.D)	Completers (N=6) (Mean±S.D.)	Non-Completers (N=2) (Mean±S.D)
Age (years)	48.7±7.8	40.3±11.4	41.9±5.2	49.8±4.9	44.1±5.8	50.0±6.4
Weight (kg)	105.8±12.7	99.2±5.1	108.9±12.0	101.9±21.1	100.2±7.6	104.6±2.2
Body Mass Index (kg/m^2)	40.3±2.1	38.0±2.0	39.0±3.1	39.3±5.0	38.8±2.7	37.2±2.9
Waist Circumference (cm)	118.3±7.1	106.2±5.8	110.2±7.9	109.3±6.3	112.2±4.7	106.1±4.6
Hip Circumference (cm)	127.6±3.6	122.4±2.0	133.6±13.2	129.4±13.4	126.6±9.2	128.3±3.3
Waist-to-hip ratio	0.93±0.05	0.87±0.06	0.83±0.09	0.85±0.04	0.89±0.05	0.83±0.01
Body Composition %Fat - Regional %Fat - Tissue	 49.2±3.1 50.5±3.1	 45.3±4.3 46.5±4.3	 49.8±5.2 51.1±5.2	 49.6±1.3 50.8±1.4	 47.7±3.9 49.0±4.0	 51.4±1.0 52.7±1.0
Race %African American %Caucasian %Other	 0.0 (N=0) 100.0 (N=6) 0.0 (N=0)	 0.0 (N=0) 100.0 (N=2) 0.0 (N=0)	 16.7 (N=1) 83.3 (N=5) 0.0 (N=0)	 50.0 (N=1) 50.0 (N=1) 0.0 (N=0)	 50.0 (N=3) 50.0 (N=3) 0.0 (N=0)	 0.0 (N=0) 50.0 (N=1) 50.0 (N=1)
Dietary Intake (kcal/day)	2216.2±774.7	1449.9±184.1	2183.5±899.9	1802.7±107.3	2206.0±323.1	1603.1±517.7
Eating Behavior Inventory	67.8±14.7	67.0±11.3	67.5±7.0	76.0±14.1	70.6±7.0	70.5±7.8
Self Reported Physical Activity (kcal/week)	350.2±349.5	238.0±59.4	471.0±358.4	870.5±993.5	578.2±586.1	378.0±59.4
VO_2 at 85% APMHR*(ml/kg/min)	20.9±4.6	24.5±1.3[a]	21.1±3.8	17.2±0.4[a]	18.6±2.7	21.0±1.1
Time to Reach 85% APMHR* (min)	6.39±2.87	8.8±0.7[a]	5.3±3.9	3.7±0.5[a]	5.0±1.9	6.3±0.0[a]
Left Ventricle Mass (g)[Ω]	94.5±25.5	----	85.9±14.3	----	83.9±3.4	----
Myocardial Fibrosis (%)[Ω]	24.2±1.8	----	25.9±1.8	----	26.8±1.9	----
End Systolic Volume (mL)[Ω]	51.9±24.9	----	56.1±12.9	----	57.9±10.2	----
End Diastolic Volume (mL)[Ω]	136.9±48.2	----	141.4±22.4	----	146.1±21.4	----
Ejection Fraction (%)[Ω]	63.3±7.9	----	60.6±3.9	----	60.4±3.4	----

[a]mean difference significant at $p < 0.05$

*APMHR = Age Predicted Maximal Heart Rate (220-age)

[Ω]Only 5 subjects from DIET and DIET+RT completed CMRI at Week 12

NOTE: Only data for the 18 study completers are available for CMRI data (1 non-completer in DIET and DIET+RT each)

4.3 CHANGES IN BODY WEIGHT AND BODY MASS INDEX (BMI)

A 3×2 repeated measures ANOVA was performed on body weight and body mass index as a function of time and treatment. Completers analysis revealed significant weight loss from 0 to 12 weeks in the DIET (-3.2 ± 2.4kg), DIET+AT (-5.9 ± 3.1kg) and DIET+RT (-4.9 ± 4.1kg) ($p<0.001$) groups, however the differences between groups ($p=0.400$) and group by time interaction ($p=0.376$) were not significant (Figure 5). Similarly, analyses for BMI revealed a significant reduction in BMI for the DIET (-1.2 ± 0.9kg/m^2), DIET+AT (-2.1 ± 1.1kg/m^2) and DIET+RT (-1.9 ± 1.7kg/m^2) groups from 0 to 12 weeks ($p<0.001$) but no significant group ($p=0.387$) or group by time interaction ($p=0.468$). These data are presented in Table 9. Moreover, percent total weight loss across all groups was -4.7 ± 3.9% with no differences between treatment groups (DIET: -3.0 ± 2.1%, DIET+AT: -5.4 ± 2.8%, DIET+RT: -4.7 ± 3.9%; $p=0.380$). These data are represented in Figure 6.

Intent-to-treat analyses were also conducted for all outcome data (Table 10). This analysis included the baseline value being carried forward for the six non-completers to assume no change. A 3×2 repeated measures ANOVA revealed a significant time effect of weight between the DIET (-2.4 ± 2.5kg), DIET+AT (-4.4 ± 3.8kg) and DIET+RT (-3.7 ± 4.2kg) ($p<0.001$) treatment groups but no significant group effect ($p=0.582$) or group by time interaction ($p=0.521$) (Figure 5). Likewise, BMI analysis revealed a significant reduction in BMI for the DIET (-0.9 ± 0.9kg/m^2), DIET+AT (-1.6 ± 1.3kg/m^2) and DIET+RT (-1.4 ± 1.7kg/m^2) ($p<0.001$) treatment groups, but no group effect ($p=0.478$) or group by time interaction ($p=0.593$). Percent total weight loss across all groups was -3.5 ± 3.3% with no differences between treatment groups (DIET: -3.0 ± 2.8%, DIET+AT: -4.1 ± 3.5%, DIET+RT: -3.5 ± 3.9%; $p=0.839$) (Figure 6).

Table 9: 12 Week Outcome Differences Between Treatment Group - Completers

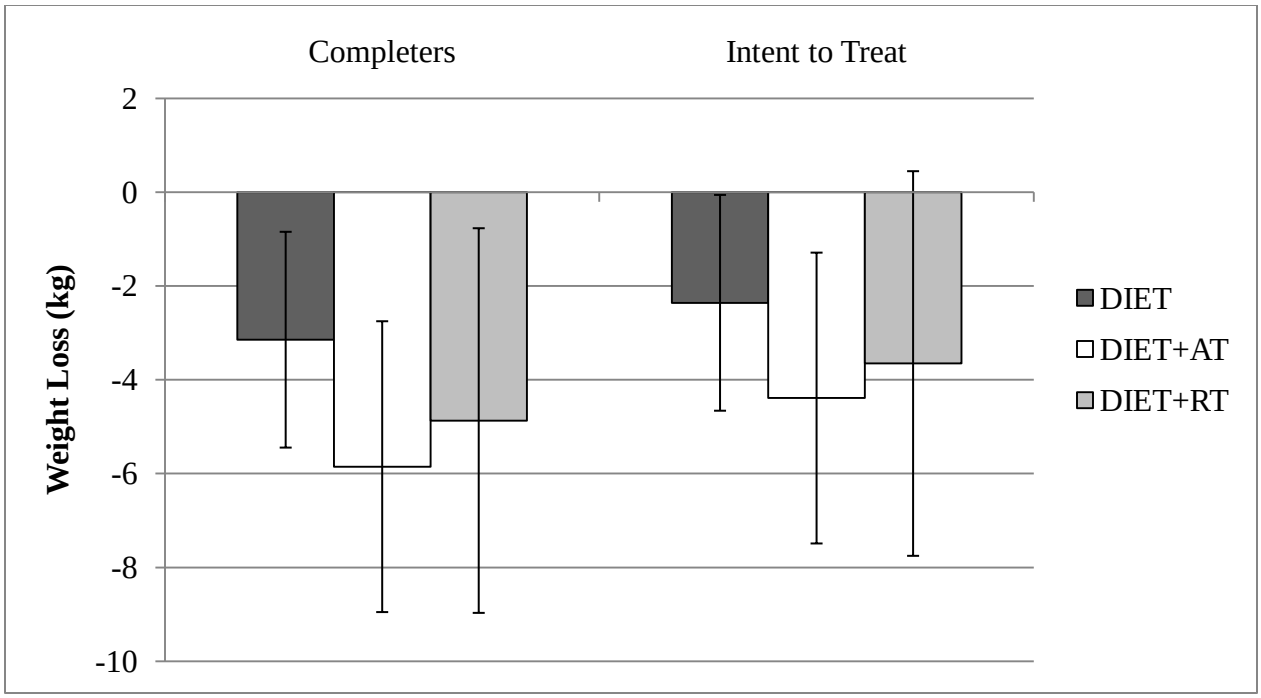
Outcome Variable	DIET (N=6) (Mean±S.D.)	DIET+AT (N=6) (Mean±S.D)	DIET+RT (N=6) (Mean±S.D.)	Group Effect	Time Effect	Group x Time Effect
Weight (kg)						
0 Weeks	105.8±12.7	108.9±12.0	100.2±7.6	0.400	<0.001	0.376
12 Weeks	102.7±12.5	103.1±12.2	95.4±6.1			
Body Mass Index (kg/m^2)						
0 Weeks	40.3±2.1	39.0±3.1	38.8±2.7	0.387	<0.001	0.468
12 Weeks	39.1±2.2	36.9±3.6	36.9±1.8			
Dietary Intake (kcal/day)				0.985	0.001	0.905
0 Weeks	2216.2±774.7	2183.5±899.9	2206.0±323.1			
12 Weeks	1490.6±593.2	1630.1±634.8	1565.9±336.7			
Eating Behavior Inventory						
0 Weeks	67.8±14.7	67.5±7.0	70.5±6.3	0.133	<0.001	0.291
12 Weeks	88.7±7.7	82.8±7.5	96.5±7.0			
Self Reported Physical Activity (kcal/week)						
0 Weeks	350.2±349.5	471.0±358.4	578.2±586.1	0.506	.057	0.730
12 Weeks	522.3±849.7	925.8±780.3	1084.0±1009.6			
VO_2 at 85% APMHR* (ml/kg/min)						
0 Weeks	20.9±4.6	21.1±3.8	18.6±2.7	0.454	0.128	0.883
12 Weeks	21.3±4.6	22.2±3.9	19.6±2.1			
Time to Reach 85% APMHR* (min)						
0 Weeks	6.4±2.9	5.3±4.0	5.0±1.9	0.690	<0.001	0.094
12 Weeks	7.3±2.8	7.9±3.5	6.1±1.1			
Muscular Strength by 1-RM (kg)						
Leg Press						
0 Weeks	50.0±26.4	78.8±43.5	71.2±46.0	0.364	0.098	0.060
12 Weeks	52.6±20.8	75.8±44.0	94.3±52.9			
Chest Press						
0 Weeks	31.0±11.6	46.2±15.5	42.0±10.1	0.189	<0.001	0.179
12 Weeks	38.6±13.5	49.2±15.5	50.8±10.2			
Seated Row						
0 Weeks	32.2±10.5	43.2±20.5	41.7±15.0	0.431	<0.001	0.204
12 Weeks	40.1±11.8	46.6±17.0	51.9±13.0			

*APMHR = Age Predicted Maximal Heart Rate (220-age)

Table 10: 12 Week Outcome Differences Between Treatment Group - Intent-to-Treat

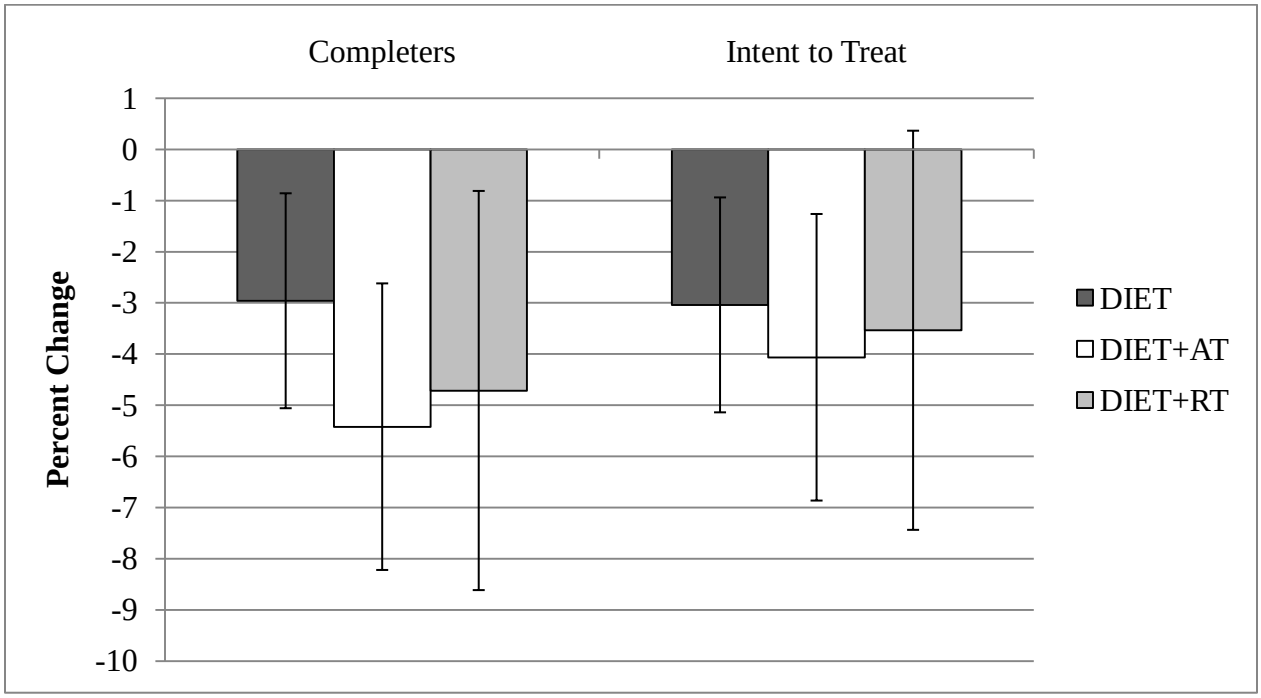
Outcome Variable	DIET (N=8) (Mean±S.D.)	DIET+AT (N=8) (Mean±S.D)	DIET+RT (N=8) (Mean±S.D.)	Group Effect	Time Effect	Group x Time Effect
Weight (kg)						
0 Weeks	104.2±11.3	107.2±13.3	101.3±6.8	0.582	<0.001	0.521
12 Weeks	101.8±10.9	102.8±13.0	97.7±6.7			
Body Mass Index (kg/m^2)						
0 Weeks	39.7±2.2	39.0±3.2	38.4±2.7	0.478	<0.001	0.593
12 Weeks	38.8±2.1	37.5±3.7	36.9±1.9			
Dietary Intake (kcal/day)						
0 Weeks	2024.6±747.9	2088.3±781.8	2055.3±436.8	0.969	<0.001	0.994
12 Weeks	1118.0±852.9	1222.5±925.9	1171.6±817.8			
Eating Behavior Inventory						
0 Weeks	67.6±13.1	69.6±8.9	70.5±6.1	0.437	<0.001	0.515
12 Weeks	83.3±12.7	81.1±8.9	90.0±13.7			
Self Reported Physical Activity (kcal/week)						
0 Weeks	322.1±300.8	570.9±516.7	528.1±504.4	0.379	0.055	0.735
12 Weeks	451.3±730.4	912.0±759.3	907.5±914.0			
VO_2 at 85% APMHR* (ml/kg/min)						
0 Weeks	21.8±4.3	20.1±3.7	19.2±2.6	0.397	0.122	0.882
12 Weeks	22.1±4.2	20.9±4.1	19.9±1.9			
Time to Reach 85% APMHR* (min)						
0 Weeks	7.0±2.7	4.9±3.4	5.3±1.7	0.395	0.001	0.161
12 Weeks	7.7±2.5	6.8±3.6	6.1±1.0			
Muscular Strength by 1-RM (kg)						
Leg Press						
0 Weeks	55.4±35.8	71.6±40.4	71.3±40.3	0.485	0.109	0.067
12 Weeks	57.4±32.7	69.3±40.2	88.6±47.1			
Chest Press						
0 Weeks	33.8±15.1	44.0±13.7	41.2±10.6	0.384	<0.001	0.282
12 Weeks	39.5±15.5	46.3±14.2	47.7±12.0			
Seated Row						
0 Weeks	33.5±11.4	39.8±18.6	41.8±14.3	0.458	0.001	0.296
12 Weeks	39.5±12.1	42.3±16.6	49.5±13.6			

*APMHR = Age Predicted Maximal Heart Rate (220-age)



NOTE: Significant time effect (p<0.001)
NOTE: Between group comparisons were not statistically significant

Figure 5: Weight Loss Across Treatment Groups - Completers and Intent-to-Treat



NOTE: **S**ignificant time effect (p<0.001)
NOTE: Between group comparisons were not statistically significant

Figure 6: Percent Weight Loss Across Treatment Groups - Completers and Intent-to-Treat

4.4 CHANGES IN DIETARY INTAKE AND EATING BEHAVIORS

A 3×2 repeated measures ANOVA showed a significant reduction in dietary intake for completers from 0 to 12 weeks in all treatment groups ($p=0.001$). Weight loss eating behaviors, as measured by the Eating Behavior Inventory, significantly improved in all treatment groups from 0 to 12 weeks ($p<0.001$). No differences were observed between groups ($p=0.133$). See Table 9. Not shown are changes in macronutrient composition among treatment groups. Completers analysis revealed a significant reduction in calorie intake and percent of calories from fat and a significant increase in percent of calories from carbohydrates ($p<0.024$) across all groups. There was no significant change in protein intake over 12 weeks ($p=0.571$).

Intent-to-treat analysis showed significant reductions in 12 week dietary intake from baseline in all groups ($p=0.001$). Similarly, weight loss eating behaviors improved over 12 weeks ($p<0.001$), although there were no group differences ($p=0.478$). See Table 9. Macronutrient composition was consistent with completers analysis when examined intent-to-treat.

4.5 CHANGES IN PHYSICAL ACTIVITY

Weekly self-reported energy expenditure (kcal/week) in leisure-time physical activity was assessed using the Paffenbarger Physical Activity Questionnaire. Results from a 3×2 repeated measures ANOVA showed completers self-reported greater weekly caloric expenditure at 12 weeks then at baseline ($p=0.057$). Although there were no significant group differences ($p=0.506$), subjects in the exercise conditions reported expending nearly 400-500 kilocalories

more per week than the diet only group (See Table 9). Intent-to-treat analysis revealed similar findings for time (p=0.055) and group (p=0.379) effects.

4.6 CHANGES IN CARDIORESPIRATORY FITNESS

Cardiorespiratory fitness was measured during a submaximal graded exercise test and expressed as: oxygen consumption at 85% APMHR (VO_2) and time to reach 85% APMHR expressed as minutes. A repeated measures 3×2 ANOVA revealed no significant differences in the change of VO_2 at 85% APMHR from 0 to 12 weeks for the DIET (0.48 ± 2.6ml/kg/min), DIET+AT (1.0 ± 2.2ml/kg/min) and DIET+RT (0.9 ± 1.8ml/kg/min) (p=0.883) treatment groups with no significant group effect (p=0.454) or group by time effect (p=0.883). While there was also no significant group or group by time effect for time to reach 85% APMHR (p=0.690 and 0.094, respectively), there was a significant time effect (p<0.001) for the DIET (0.9 ± 0.7min), DIET+AT (2.6 ± 2.0min) and DIET+RT (1.1 ± 0.9min) intervention groups (Table 9). Furthermore, cardiorespiratory fitness was not significantly different between groups at week 12 (p=0.214) when examined in absolute terms (mL/min). Interestingly, subjects in the DIET and DIET+AT groups reduced absolute VO_2 (-20.9 ± 255.8mL/min and -10.2 ± 243.2mL/min, respectively) at week 12.

Intent-to-treat analysis revealed no significant change from 0 to 12 weeks in oxygen consumption in the DIET (0.4 ± 2.2ml/kg/min), DIET+AT (0.8 ± 1.9ml/kg/min) and DIET+RT (0.7 ± 1.6ml/kg/min) (p=0.122) treatment groups. Moreover, there were no significant group differences (p=0.397) or group by time interaction (p=0.882). Further analyses showed a significant increase in time to reach 85% of maximal heart rate in the DIET (0.7 ± 0.7min),

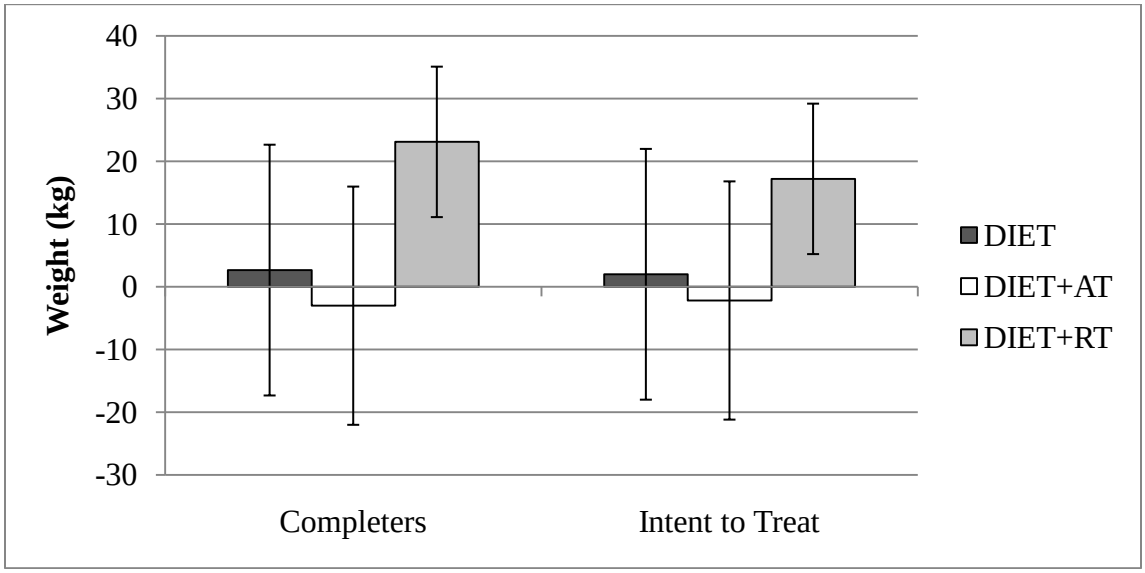
DIET+AT (1.9 ± 2.1min) and DIET+RT (0.8 ± 0.9min) ($p<0.001$) intervention groups but no significant group effect ($p=0.395$) or group by time interaction ($p=0.161$) as shown in Table 10.

4.7 CHANGES IN MUSCULAR STRENGTH

Muscular strength was assessed utilizing three different exercises: leg press, chest press, and seated row. The maximal weight lifted one time was recorded as the one-repetition maximum. A 3×2 repeated measures ANOVA showed that change in weight lifted on the leg press for completers in the DIET, DIET+AT, and DIET+RT ($p=0.098$) was 2.6 ± 21.5kg, -3.0 ± 20.4kg, and 23.1 ± 9.7kg, respectively ($p=0.098$). Completers did have a significant increase in weight lifted on the chest press (DIET: 7.6 ± 5.3kg; DIET+AT: 3.0 ± 6.2kg; DIET+RT: 8.7 ± 4.2kg) and seated row (DIET: 8.0 ± 5.7kg; DIET+AT: 3.4 ± 8.2kg; DIET+RT: 10.2 ± 4.7kg) ($p<0.001$) from baseline. Moreover, while the changes in strength are not statistically significant between groups, subjects in the resistance training group showed greater improvements in all strength measures. Data are shown in Table 9. Changes in maximal strength can be seen in Figures 7 - 9.

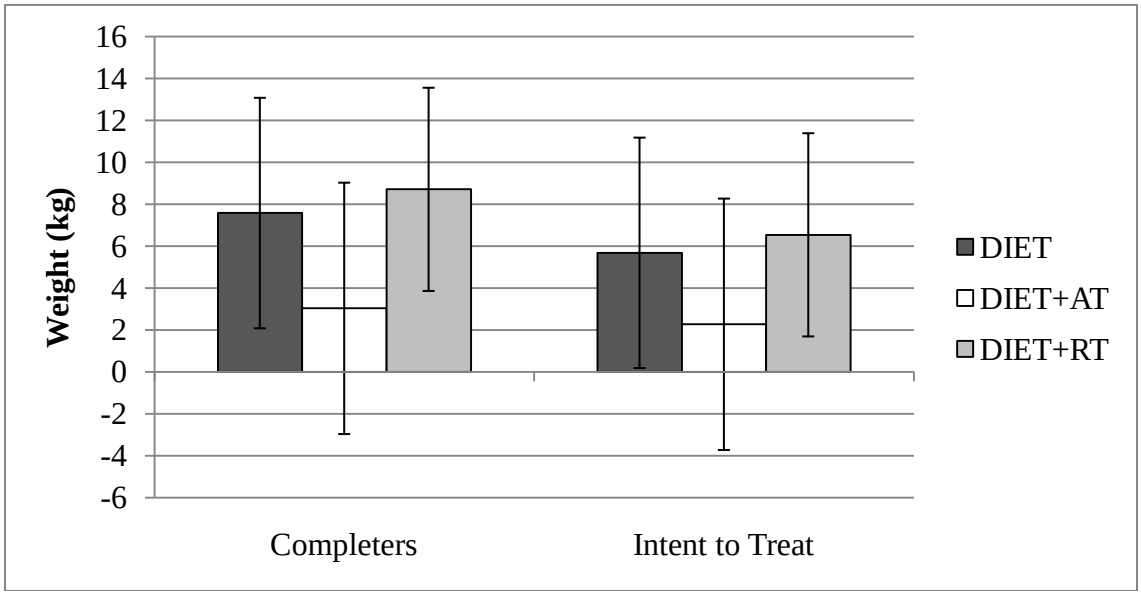
Similar results are shown for intent-to-treat analysis of the strength measures (Table 10). No significant change was observed from 0 to 12 weeks for the weight lifted on the leg press ($p=0.109$) for the DIET (2.0 ± 18.1kg), DIET+AT (-2.3 ± 17.3kg) or DIET+RT (17.3 ± 14.2kg) treatment groups. Maximal weight lifted on the chest press at 12 weeks increased significantly ($p<0.001$) for the DIET (5.7 ± 5.7kg), DIET+AT (2.3 ± 5.4kg) and DIET+RT (6.5 ± 5.4kg) treatment groups. Likewise, maximal weight lifted on the seated row significantly increased ($p=0.001$) at 12 weeks for the DIET (6.0 ± 6.0kg), DIET+AT (2.5 ± 7.1kg) and DIET+RT (7.7 ± 6.2kg) treatment groups compared to baseline. There were no between group differences

(p>0.384) or group by time interactions (p>0.067) for the leg press, chest press, or seated row (See Figure 7 - 9).



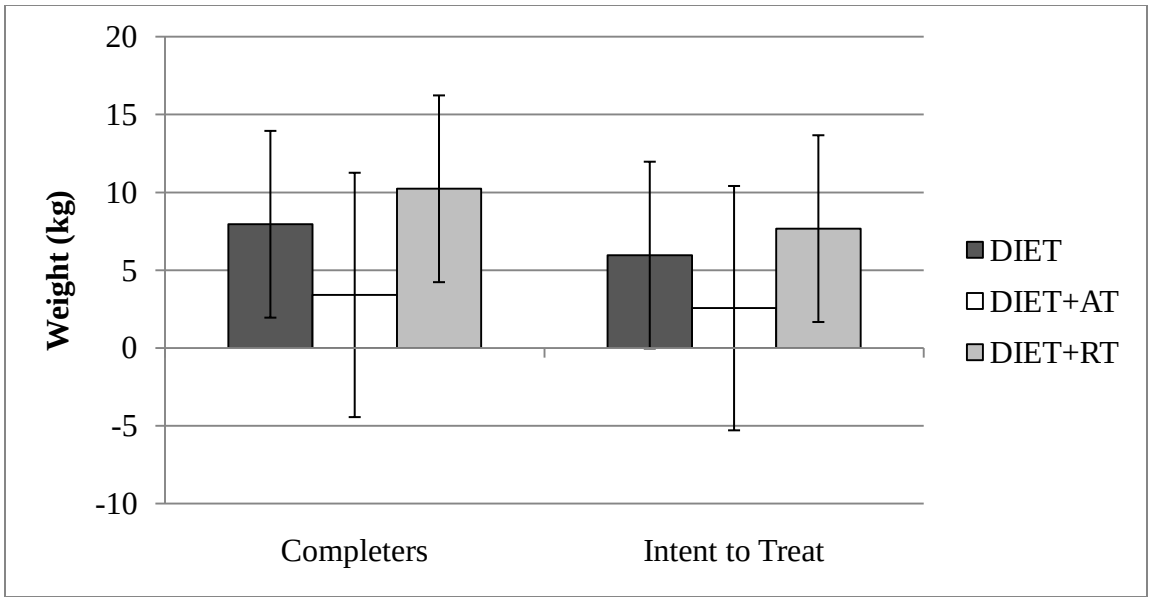
NOTE: Time effect not statistically significant
NOTE: Between group comparisons were not statistically significant

Figure 7: Leg Press Strength Change - Completers and Intent-to-Treat



NOTE: Time effect statistically significant (p<0.001)
NOTE: Between group comparisons not statistically significant.

Figure 8: Chest Press Strength Change - Completers and Intent-to-Treat



NOTE: Time effect statistically significant ($p<0.001$)
NOTE: Between group comparisons not statistically significant

Figure 9: Seated Row Strength Change - Completers and Intent-to-Treat

4.8 CHANGES IN ANTHROPOMETRIC MEASUREMENTS AND BODY COMPOSITION

Anthropometric measurements included a circumference measure at the waist and another at the hip. Body composition was determined using the iDXA with body fat percentage, fat and lean mass, bone mineral content, and bone mineral density extracted. A 3×2 mixed ANOVA for completers revealed a significant decrease from 0 to 12 weeks in waist (DIET: -4.4 ± 6.1cm; DIET+AT: -4.9 ± 4.2cm; DIET+RT: -7.8 ± 4.0cm) and hip (DIET: -4.0 ± 2.7cm; DIET+AT: -5.4 ± 4.8cm; DIET+RT: -7.8 ± 3.9cm) circumferences ($p<0.001$). Waist circumference was significantly different between treatment groups ($p=0.047$) as shown in Table 11. Post hoc analysis showed the DIET+RT group had significantly lower waist circumferences than the

DIET+AT group (p=0.005) and the DIET+AT group had significantly lower waist circumferences than the DIET group (p=0.037) at 12 weeks. There were no significant changes in bone mineral content or bone mineral density from baseline (p>0.064) or between groups (p>0.789) at 12 weeks. Body fat percentage significantly decreased in the DIET (-0.6 + 1.2%), DIET+AT (-1.5 ± 1.6%) and DIET+RT (-1.6 ± 0.15%) treatment groups over time (p=0.003). There was no group (p=0.625) or interaction (p=0.437) effect at 12 weeks for body fat percentage. Fat mass significantly decreased from 0 to 12 weeks in all treatment groups (DIET: -2.2 ± 2.3kg; DIET+AT: -3.6 ± 2.4kg; DIET+RT: -3.8 ± 3.4kg) (p<0.001) and lean mass showed a trend (p=0.053) towards reduction (DIET: -0.9 ± 0.9kg; DIET+AT: -0.6 ± 2.4kg, DIET+RT: -0.9 ± 1.2kg). Neither fat nor lean mass was different between groups at 12 weeks (p=0.330 and 0.822, respectively). See Table 11.

Intent-to-treat analysis revealed similar results for decreases in waist (p<0.001) and hip (0<0.001) circumference at 12 weeks for the DIET (waist:-3.3 ± 5.5cm; hip:-3.0 ± 2.9cm), DIET+AT (waist: -3.6 ± 4.2cm; hip:-4.1 ± 4.8cm) and DIET+RT (waist: -5.9 ± 4.9cm; hip: -4.7 ± 4.1cm) treatment groups. As shown in Table 12, body fat percentage (p=0.003), fat mass (p<0.001) and lean mass (p=0.05) was significantly lower at week 12 for all treatment groups. No other treatment or interaction effects were seen.

Table 11: 12 Week Body Composition Defferences Between treatment Group - Completers

Outcome Variable	DIET (N=6) (Mean±S.D.)	DIET+AT (N=6) (Mean±S.D)	DIET+RT (N=6) (Mean±S.D.)	Group Effect	Time Effect	Group x Time Effect
Waist Circumference (cm)						
0 Weeks	118.3±7.1	110.2±7.9	112.2±4.7	0.047	<0.001	0.440
12 Weeks	113.9±3.4	105.4±7.6	104.4±6.1			
Hip Circumference (cm)						
0 Weeks	127.6±3.6	133.6±13.2	126.6±9.2	0.352	<0.001	0.583
12 Weeks	123.6±3.7	128.2±12.9	120.3±6.6			
Waist-to-hip ratio						
0 Weeks	0.93±0.05	0.83±0.09	0.89±0.05	0.040	0.197	0.628
12 Weeks	0.92±0.03	0.83±0.07	0.87±0.06			
Bone Mineral Content (kg)						
0 Weeks	2.7±0.5	2.8±0.4	2.7±0.4	0.789	0.064	0.601
12 Weeks	2.7±0.5	2.8±0.4	2.7±0.4			
Bone Mineral Density (g/cm^3)						
0 Weeks	1.32±0.14	1.32±0.14	1.33±0.13	0.978	0.753	0.533
12 Weeks	1.32±0.13	1.32±0.14	1.32±0.12			
Body Fat – Regional (%)*						
0 Weeks	49.2±3.1	49.8±5.2	47.7±3.9	0.617	0.002	0.441
12 Weeks	48.6±3.4	48.3±6.0	46.1±3.0			
Body Fat – Tissue (%)°						
0 Weeks	50.5±3.1	51.2±5.2	49.0±4.0	0.625	0.003	0.437
12 Weeks	49.9±3.3	49.6±6.0	47.4±3.1			
Fat Mass (kg)						
0 Weeks	51.3±6.3	54.2±10.2	51.0±7.8	0.330	<0.001	0.560
12 Weeks	49.2±6.1	50.6±11.8	43.7±4.5			
Lean Mass (kg)						
0 Weeks	50.6±7.4	51.2±5.7	49.2±4.6	0.822	0.053	0.921
12 Weeks	49.6±7.3	50.6±6.9	48.3±3.9			

*****body fat percentage with bone mineral content included

°body fat percentage without bone mineral content included

Table 12: 12 Week Body Composition Differences Between Treatment Group - Intent-to-Treat

Outcome Variable	DIET (N=8) (Mean±S.D.)	DIET+AT (N=8) (Mean±S.D)	DIET+RT (N=8) (Mean±S.D.)	Group Effect	Time Effect	Group x Time Effect
Waist Circumference (cm)						
0 Weeks	115.3±8.5	110.0±7.1	110.6±5.2	0.119	<0.001	0.542
12 Weeks	111.9±5.1	106.3±7.1	104.8±5.5			
Hip Circumference (cm)						
0 Weeks	126.3±3.9	132.6±12.4	127.0±7.9	0.289	<0.001	0.697
12 Weeks	123.3±3.3	128.5±12.1	122.3±6.8			
Waist-to-hip ratio						
0 Weeks	0.91±0.06	0.83±0.07	0.87±0.05	0.041	0.155	0.775
12 Weeks	0.91±0.04	0.83±0.06	0.86±0.05			
Bone Mineral Density (g/cm^3)						
0 Weeks	1.32±0.12	1.31±0.15	1.32±0.11	0.966	0.840	0.424
12 Weeks	1.32±0.11	1.31±0.15	1.32±0.11			
Bone Mineral Content (kg)						
0 Weeks	2.7±0.4	2.7±0.5	2.7±0.3	0.953	0.062	0.608
12 Weeks	2.7±0.4	2.7±0.5	2.7±0.3			
Body Fat – Regional (%)*						
0 Weeks	48.2±3.6	49.8±4.4	48.6±3.7	0.786	0.003	0.501
12 Weeks	47.7±3.6	48.6±5.1	47.4±3.6			
Body Fat - Tissue (%)°						
0 Weeks	49.5+3.5	51.2+4.4	50.0±3.8	0.786	0.003	0.483
12 Weeks	49.0+3.6	50.0+5.1	48.8±3.6			
Fat Mass (kg)						
0 Weeks	49.7±6.6	53.2±9.9	48.9±5.9	0.518	<0.001	0.648
12 Weeks	48.1±6.1	50.5±10.9	46.1±5.9			
Lean Mass (kg)						
0 Weeks	50.7±6.3	50.5±6.0	48.8±4.0	0.748	0.050[a]	0.923
12 Weeks	50.0±6.2	50.1±6.8	48.2±3.3			

*****body fat percentage with bone mineral content included

°body fat percentage without bone mineral content included

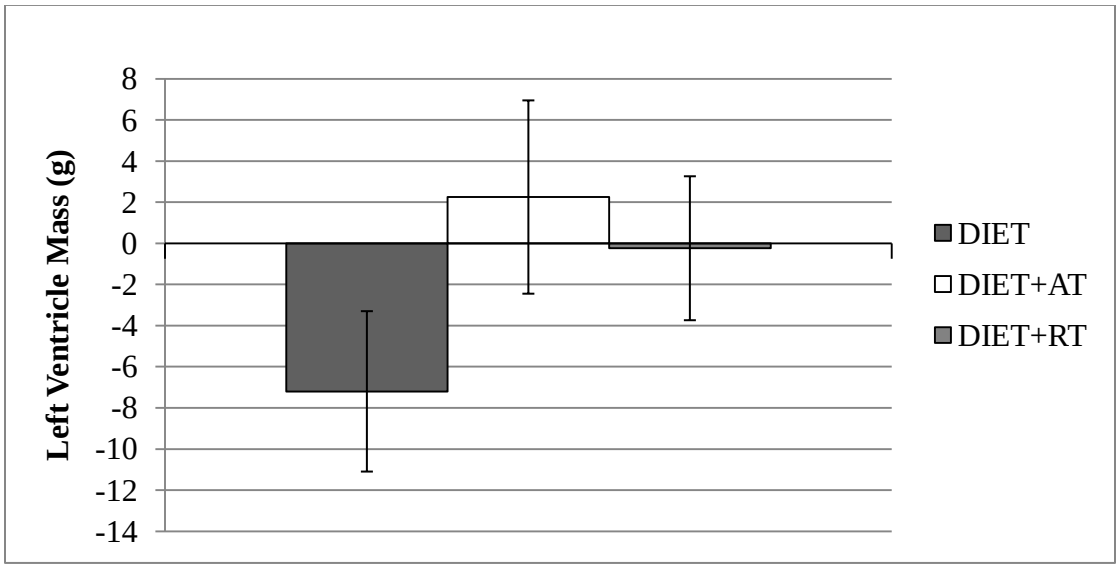
4.9 CHANGES IN CARDIAC STRUCTURE AND FUNCTION

Sixteen subjects completed baseline and 12 week scans at CMRC (DIET=5, DIET+AT=6, DIET+RT=5). The subject in the DIET group was lost due to claustrophobia while the subject in

the DIET+RT group was lost for unknown reasons. Data are presented for completers only and are seen in Table 13.

4.9.1 Left Ventricular Mass

The pattern of change in left ventricular mass (LVM) between treatment groups was significantly different at week 12 from baseline (p=0.007) (See Figure 10). Subjects in the DIET (-7.2 ± 3.9g) group had a trend toward statistically significant greater reductions from baseline compared to the DIET+RT group (-0.2 ± 3.5g) (p=0.059) and statistically significant greater reduction than the DIET+AT group (2.3 ± 4.7g) (p=0.008). Change scores for the DIET+AT and DIET+RT groups were not statistically significant (p=0.616). At week 12, LVM was not significantly different between groups (p=0.784).

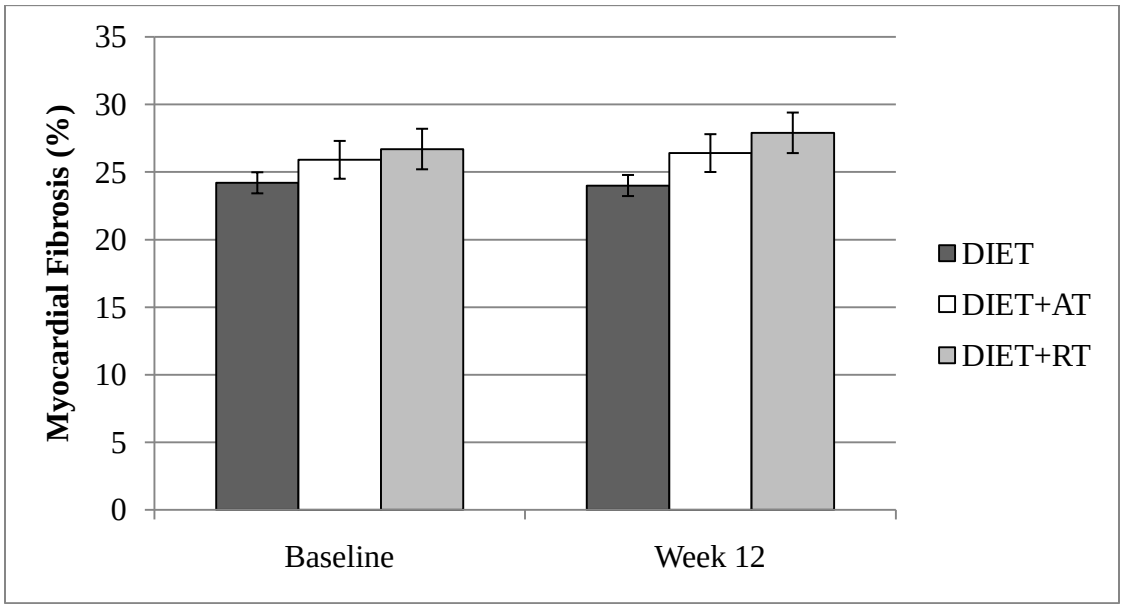


NOTE: LVM change score statistically significant (DIET>DIET+AT and DIET+RT, p=0.007)
NOTE: Between group comparison not statistically significant

Figure 10: Left Ventricular Mass Change Scores - Completers

4.9.2 Myocardial Fibrosis

There was a significant treatment effect (p=0.010) for myocardial extravascular extracellular volume fraction (Ve), i.e. myocardial fibrosis. Subjects in the DIET+RT group had a significantly higher percentage of Ve at 12 weeks (27.9±1.5%) than the DIET and DIET+AT treatment groups. While not statistically significant, there was a reduction in Ve in the DIET group (-0.2 ± 1.8%) and an increase in both the DIET+AT (0.6 ± 1.1%) and DIET+RT (1.2 ± 1.3%) treatment groups from 0 to 12 weeks (p=0.433). See Figure 11.



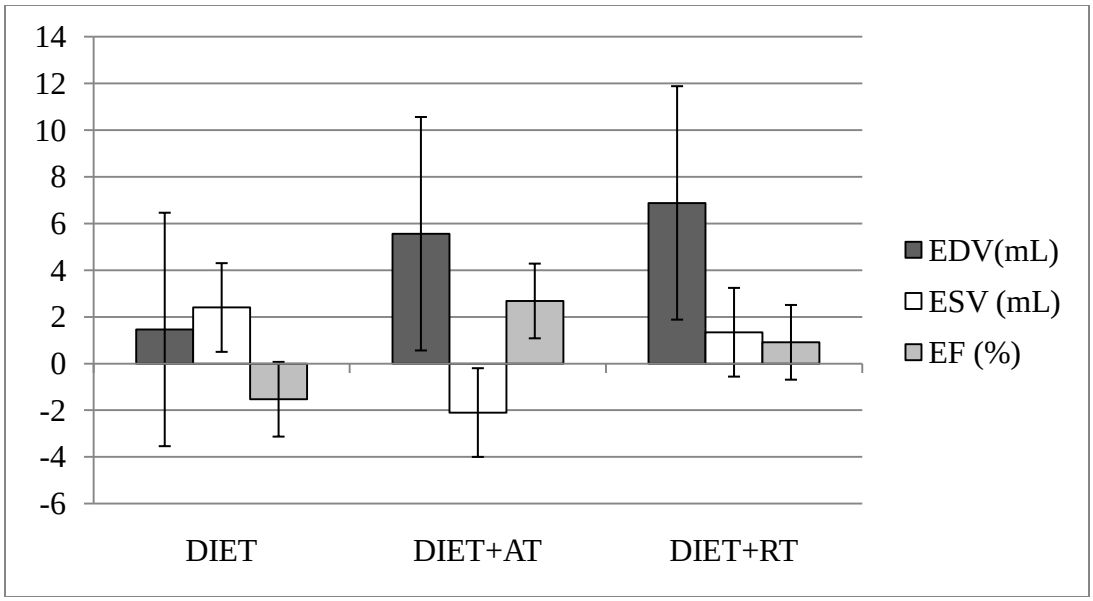
NOTE: Between group comparison statistically significant (DIET+RT>DIET+AT, p<0.05)
NOTE: Time effect not statistically significant

Figure 11: Myocardial Fibrosis Change Scores - Completers

4.9.3 Volumetric Measurements

There were no significant between group differences in end diastolic volume (EDV), end systolic volume (ESV), or ejection fraction (EF) at week 12 (p>0.159). While the pattern of change was

not significantly different, Figure 12 shows that there are quantifiable differences in the change scores. Subjects in the exercise groups appear to have a greater increase in end diastolic volume. Additionally, end systolic volume decreased in the DIET+AT group and increased in the DIET and DIET+RT groups. Ejection fraction increased in the exercise conditions and decreased in the diet only group.



NOTE: Between group comparisons not statistically significant
NOTE: Time effect not statistically significant

Figure 12: Volumetric Measurement Change Scores – Completers

Table 13: Cardiac MRI Differences Between Treatment Group at 12 Weeks

Outcome Variable	DIET (N=5) (Mean±S.D.)	DIET+AT (N=6) (Mean±S.D)	DIET+RT (N=5) (Mean±S.D.)	Group Effect	Time Effect	Group x Time Effect
Left Ventricle Mass (g)						
0 Weeks	94.5±25.5	85.9±14.3	83.9±3.4	0.784	0.119	0.007
12 Weeks	87.3±23.3	88.1±12.3	83.7±6.1			
Myocardial Fibrosis (%)						
0 Weeks	24.2±1.8	25.9±1.8	26.8±1.9	0.010	0.153	0.348
12 Weeks	24.0±0.8	26.5±1.4	27.9±1.5			
End Systolic Volume (mL)						
0 Weeks	51.9±24.9	56.1±12.9	57.9±10.2	0.866	0.607	0.202
12 Weeks	54.3±24.7	54.0±10.5	59.3±10.8			
End Diastolic Volume (mL)						
0 Weeks	136.9±48.2	141.4±22.4	146.1±21.4	0.836	0.150	0.763
12 Weeks	138.4±43.9	147.0±22.3	152.9±24.5			
Ejection Fraction (%)						
0 Weeks	63.3±7.9	60.6±3.9	60.4±3.4	0.839	0.433	0.159
12 Weeks	61.8±6.7	63.3±3.6	61.3±2.4			

Table 14: Correlations Between Cardiac MRI Outcomes and baseline Body Weight

Variable (Baseline Value)	LVM (g)	Fibrosis (%)	EDV (mL)	ESV (mL)	EF (%)
Body weight (kg)	0.509*	-0.125	0.713**	0.674*	-0.276
Body Mass Index (kg/m2)	-0.063	-0.414	0.154	0.251	-0.133
Waist Circumference (cm)	0.350	-0.015	0.323	0.373	-0.133
Fat Mass (kg)	0.191	-0.352	0.577*	0.600**	-0.356
Lean Mass (kg)	0.785**	0.026	0.573*	0.585*	-0.253
Body Fat (%)	-0.424	-0.484*	0.090	0.129	-0.110

*Significant correlation at $p<0.05$

*Significant correlation at $p<0.001$

Correlational analyses were performed to determine an association between baseline measures of body weight and body composition and baseline cardiac MRI outcome variables. Baseline body weight and lean mass were correlated to statistically significant higher left ventricular mass ($p<0.031$), end diastolic volume ($p<0.013$), and end systolic volume ($p<0.011$). Fat mass was correlated to statistically significant greater end diastolic ($p=0.012$) and end systolic ($p=0.009$) volume. Finally, Body fat percentage was correlated to a statistically significant lower percentage of myocardial fibrosis ($p=0.042$). See Table 14.

Correlational analyses were also performed to determine an association between the change in cardiovascular structure and function and body weight, body mass index, waist circumference, fat mass, percent body fat, cardiorespiratory fitness, and muscular strength. Correlations are presented in Table 15. Only overall time to reach 85% APMHR was significantly correlated to end systolic volume and ejection fraction. No other significant correlations were observed.

Table 15: Correlations Between Cardiac Structure and Function and Primary Outcome Variables

Variable (Change Score)	LVM (g)	Fibrosis (%)	EDV (mL)	ESV (mL)	EF (%)
Body weight (kg)	-0.358	0.082	0.043	0.233	-0.093
Body Mass Index (kg/m^2)	-0.436	0.053	0.029	0.171	-0.029
Waist Circumference (cm)	-0.200	0.206	0.091	-0.133	0.297
Fat Mass (kg)	0.028	0.003	0.209	0.037	0.103
Lean Mass (kg)	0.019	0.441	-0.041	-0.006	0.082
Body Fat (%)	-0.050	-0.229	0.185	0.052	0.079
GXT Time at 85% APMHR (min)	0.254	-0.053	-0.027	-0.510*	0.565*
VO_2 at 85% APMHR (ml/kg/min)	0.156	-0.091	-0.068	0.029	-0.076
Leg Press (kg)	-0.003	0.196	-0.289	-0.082	-0.178
Chest Press (kg)	-0.107	-0.046	-0.161	0.103	-0.368
Seated Row (kg)	-0.440	-0.205	-0.096	0.083	-0.111

*Significant correlation at $p<0.05$

4.10 PROCESS MEASURES

Descriptive analyses were conducted to examine: behavioral intervention session attendance, exercise session attendance, use of the food diary as represented by reported caloric intake days, self-reported calorie intake, and self-reported weight. These data are shown in Table 16.

4.10.1 Attendance

Completers analysis revealed subjects attended nearly 90% (89.3 ± 9.8%) of all behavioral intervention sessions. These sessions included individual make-up sessions in addition to the regular weekly group meetings. These data were not normally distributed; therefore the Kruskal-Wallis nonparametric test was used. Attendance was not significantly different between groups (DIET: 88.9 ± 4.3%; DIET+AT: 91.7 ± 12.9%; DIET+RT: 87.5 ± 11.5%) (p=0.144).

4.10.2 Exercise Adherence

Subjects in the exercise groups attended approximately 85% (84.6 ± 14.2%) of all available sessions. Subjects in the DIET+AT (85.7 ± 13.9%) and DIET+RT (83.5 ± 15.8%) groups did not significantly differ in total exercise session attendance (p=0.806) at 12 weeks.

4.10.3 Dietary Self-Monitoring

Subjects self-reported an average dietary intake of 1344.1 ± 241.0 kilocalories per day in their food diary. A one-way ANOVA revealed no significant difference (p=0.542) between the DIET (1436.3 ± 313.3kcal), DIET+AT (1306.3 ± 260.9kcal), and DIET+RT (1289.1 ± 125.4kcal) groups. The nonparametric Kruskal-Wallis test was performed on the data for the documentation of daily caloric intake and self-reported daily weight. There was no significant difference in the percentage of days that subjects documented caloric intake (p=0.358) or the number of self-reported weight days per week (p=0.341).

Table 16: 12-Week Process Measure Differences Between Treatment Group

Outcome Variable	Total (N=6) (Mean±S.D.)	DIET (N=6) (Mean±S.D.)	DIET+AT (N=6) (Mean±S.D)	DIET+RT (N=6) (Mean±S.D.)
Behavioral Intervention Session Attendance (%)	89.3 ± 9.8	88.9 ± 4.3	91.7 ± 12.9	87.5 ± 11.5
Exercise Session Attendance (%)	84.6 ± 14.2	----	85.7 ± 13.9	83.5 ± 15.8
Days Diet was Self-Reported (%)	78.7 ± 23.2	87.3 ± 10.2	81.0 ± 15.3	67.9 ± 35.4
Self-Reported Calorie Intake Per Day	1344.1 ± 241.0	1436.3 ± 313.3	1306.8 ± 260.9	1289.1 ± 125.4
Self-Reported Weight Days Per Week	1.1 ± 2.1	0.5 ± 1.0	0.7 ± 0.8	2.2 ± 3.0

5.0 DISCUSSION

This investigation sought to examine the effect of weight loss induced by diet alone or in combination with exercise on body weight, cardiovascular structure and function, muscular strength, cardiorespiratory fitness, and body composition in Class II and III Obese women. Subjects were randomly assigned to one of three treatment groups: diet only (DIET), diet in combination with aerobic exercise (DIET+AT), or diet in combination with resistance exercise (DIET+RT). A total of 8 subjects were randomized into each of the three treatment groups. It was hypothesized that the DIET+AT group would have the greatest reduction in body weight and body composition in addition to the greatest improvement in cardiovascular structure and function and cardiorespiratory fitness, whereas the DIET+RT group would have the greatest increase in muscular strength. The summary of these findings are outlined below:

5.1 BODY WEIGHT

The findings of the current investigation do not support the hypothesis that the DIET+AT group would lose significantly more body weight than the DIET+RT group and the DIET+RT group would lose more weight than the DIET group. Rather, weight loss at 12 weeks was not significantly different between groups (See Table 9). These data are less than those found by Ross et al who revealed no significant difference in body weight lost at 12-weeks for males in

the diet-induced (-7.8kg) and diet plus exercise-induced (-7.8kg) weight loss groups[16]. In a slightly longer study (16 weeks), Idoate et al showed weight loss for the diet-induced weight loss group of -6.4kg and weight loss in the diet plus resistance exercise induced group of -7.7kg[99].

Subjects across all treatment groups lost on average 4.6kg (-4.4%) of baseline body weight ($p<0.001$). The findings support those of Polzien et al who showed a 4.5kg weight loss during a 12-week behavioral weight loss intervention in overweight adults who were prescribed a reduced calorie diet and exercised 20-40 minutes per day five days per week[100]. The overall weight loss seen across treatment groups is of clinical importance. A reduction of as little as 5-10% of baseline body weight has been shown to reduce cardiovascular disease risk[21] and was nearly attained in the current investigation. This finding suggests that subjects in this intervention may have decreased the risk for type 2 diabetes, hypertension, and hyperlipidemia in as little as 12 weeks. While there was no significant difference between the intervention groups for weight loss at 12 weeks ($p=0.400$), completers in the exercise groups lost approximately 2.5kg more body weight than subjects in the diet only group at 12 weeks. While these findings do not support the initial hypothesis, a pattern toward greater weight loss is present. Goodpaster et al revealed similar findings in six month weight loss of Class II and III obese adults, with an added weight loss of 2 – 3kg in exercisers versus non-exercisers[39]. The additional weight loss observed in those assigned to exercise conditions (DIET+AT and DIET+RT) compared to dietary restriction alone (DIET) in the current investigation may reflect additional differences in the intervention across treatment arms. For example, subjects in DIET+AT and DIET+RT engaged in three supervised exercise sessions per week, and this resulted in up to an additional 36 hours of contact with the intervention staff (48 hours total) compared to the 12 hours of intervention contact time received by DIET. Perri et al has suggested that added behavioral contact time may

be important for increasing weight loss[101]. It is possible that subjects in DIET+AT and DIET+RT received additional information about weight loss or diet behaviors even though instructors for the exercise sessions were told to not participate in such discussions. Thus, future studies should confirm the differences in weight loss observed in this study with the addition of exercise in a design that equates for contact time between participants and intervention staff.

Furthermore, the results from the current investigation are consistent with the American College of Sports Medicine's statement that physical activity in bouts of ≥150 minutes per week will result in a 2 – 3kg weight loss[68]. Thus, while not statistically significant, the weight loss results from the current study are consistent with weight loss data in the current literature.

Across all treatment groups, dietary intake was significantly lower (-639kcal) at week 12 from baseline (<0.001). In addition, eating behaviors significantly improved (+20.7 on EBI scale) from baseline to week 12. Furthermore, total dietary intake from percent fat was significantly less at week 12 from baseline (-6.7%) across all groups. These results are slightly higher than findings by Jakicic et al who showed a reduction of -498kcal in daily caloric intake and percent calories from fat (4.5 %)[102]. Furthermore, in a six month behavioral weight loss intervention, Pellegrini et al found that all subjects increased their eating behavior score by ~14.3 on the EBI scale[103], slightly less than the increase of 20.7 in the current investigation.

5.2 BODY COMPOSITION AND ANTHROPOMETRIC MEASUREMENTS

The hypothesis that the DIET+AT group would have a greater improvement in body composition than the DIET+RT group and the DIET+RT group would have a greater improvement in body composition than the DIET group was not supported by the current findings. Waist and hip

circumferences were significantly reduced across all treatment groups from 0 to 12 weeks ($p<0.001$). Subjects in the DIET+RT group had a significantly lower waist circumference (-7.8 ± 4.0cm) compared to the DIET+AT (-4.9 ± 4.2cm) and DIET (-4.4 ± 6.1cm) groups at 12 weeks. Previous research has shown that both aerobic and resistance training are successful in decreasing waist circumference[104]. The results of this investigation are similar to the findings by Ross et al that show a significantly greater decrease in waist circumference in the diet and resistance training group (-10.0 ± 5.7cm) compared to the diet and aerobic training group (-8.6 ± 2.8cm) over a 16-week period[77]. Fat and lean mass were not significantly different between the treatment groups but were significantly reduced over 12 weeks in all treatment groups (See Table 11). These findings add to those of Geliebter et al that showed a significant decrease in fat mass after 8 weeks in the diet (-6.8 ± 2.6kg), diet plus aerobic exercise (-7.2 ± 3.0kg), and diet plus resistance exercise (-6.7 ± 2.8kg) groups. Perhaps more importantly, fat free mass was significantly reduced at 8 weeks in all treatment groups with subjects in the diet plus resistance training group preserving significantly more muscle mass (-1.1 ± 2.3kg lost)[105] compared to the diet plus aerobic training group (-2.3 ± 2.4kg) and diet only (-2.7 ± 2.1) groups. These results are similar to the lean mass lost for the DIET+RT group (-0.9kg) in the current investigation, but not the DIET (-1.0kg) or DIET+AT (-0.6kg) groups. The ability of resistance exercise to decrease the reduction of lean body mass may not occur in interventions in shorter than 12 weeks in duration.

5.3 CARDIOVASCULAR STRUCTURE AND FUNCTION

Severe obesity is associated with abnormalities in cardiac structure and function[57]. Weight loss, especially in individuals with severe obesity, has been shown to significantly improve cardiac structure and function[106]. This investigation was aimed at determining the effect of the addition of these two exercise modalities to caloric restriction on changes in left ventricular mass, myocardial extravascular extracellular volume fraction (fibrosis score), and volumetric changes characterized by end diastolic volume, end systolic volume, and ejection fraction.

The hypotheses that the DIET+AT group would show a greater improvement in both cardiovascular structure and function than the DIET+RT and DIET groups were not supported by the findings of this investigation. Subjects in the DIET group had a significantly greater reduction in left ventricular mass (-7.2g, p=0.007) than both the DIET+AT (+2.3g) and DIET+RT (-0.2g) groups. These findings are similar to other data that suggest a reduction in LVM with diet-induced weight loss. Rider et al showed a reduction of LVM of 10g in subjects who underwent a low glycemic index diet[65]. However, these results need to be interpreted with caution as weight loss in the cohort was as much as 20kg over a one-year period of time. Interestingly, the DIET+AT group showed an increase in LVM in response to aerobic training, although not significantly different from baseline. This finding is not consistent with a review examining fit adults by Kokkinos et al who suggest that moderate-intensity exercise can improve hemodynamics and reduces the amount of work required by the left ventricle, ultimately reducing left ventricular mass[107]. However, a study by Reid et al revealed a non-significant increase in left ventricular mass in overweight adults after a 12 week diet (3.0g) and diet plus aerobic exercise (3.0g) program at 70% maximal work 90 minutes per week[108]. It is possible that left ventricular mass remained unchanged or elevated due to the intensity of the prescribed

exercise in the Reid study and the current investigation. Studies that have shown a successful reduction in left ventricular mass with exercise have been at higher intensity and frequency[64]. Highly trained athletes have been shown to have increased LVM, although it is unlikely in this population and duration of training that subjects in the DIET+AT group would adapt by increasing LVM[109].

While there may not have been a statistically significant change in LVM with exercise, there is speculation that the quality of the myocardium may improve with body weight and fat mass loss. The measurement of myocardial fibrosis in the context of a weight loss intervention is an unexplored area of research. Myocardial fibrosis is the hallmark measure of pathologic cardiac remodeling and is characterized by an accumulation of interstitial collagen[110]. The increased collagen interferes with normal electrical signaling and mechanical function of the heart. It was hypothesized that a reduction in body weight, specifically fat mass, would result in a significant decrease in myocardial fibrosis. The current investigation did not support this hypothesis as significant differences were observed between treatment groups at 12 weeks for myocardial fibrosis (See Table 13). The measure and analysis of myocardial fibrosis in the context of this weight loss intervention were exploratory and inconclusive; however a paradox may exist with exercise training, weight loss, and the measurement of fibrosis in this population. Subjects in both exercise groups increased myocardial fibrosis percentage from baseline to 12 weeks (Figure 9) even though both had significant reductions in body weight and fat mass at 12 weeks from baseline (Figure 5). One possible explanation for this finding may be that the measurement of fibrosis in the current investigation did not adjust for capillary beds in the myocardium. The contrast dye used in this study is unable to detect these capillaries and measurements assume a constant value. While the increase in extracellular space may be due to

an increase in collagen fibers, it may be possible that the increase detected by our measurement was due to an increase in vascularization with exercise[111]. If, in the current investigation, vascularization within the myocardium increased with exercise, the result would be appropriate given the increase in left ventricular mass of the DIET+AT and DIET+RT groups, resulting in improvement of the composition of the myocardium as a result of exercise training. Przyklenk and Groom showed that after four weeks of voluntary exercise two hours per day six days per week, albino rats demonstrated an increase in myocardial revascularization following an infarction[112]. These findings may lend promise to the possibility that the DIET+AT and DIET+RT in the current investigation increased fibrosis score at 12 weeks due to an increase in capillary density. However, Tharp and Wagner revealed no change in myocardial capillary multiplication in albino rats that underwent a training regimen varying from 90 to 300 minutes per week, suggesting that improvements in myocardial blood flow due to exercise may be a result of an increase in the size of the coronary arteries or improved collateral circulation[113]. Thus, the effect of weight loss and exercise on myocardial fibrosis needs to be explored further and future investigations should incorporate the appropriate intravenous dye to measure capillary density change within the left ventricle in response to diet, exercise, and weight loss.

The volumetric data also does not support the hypothesis that the DIET+AT group would have a significantly greater improvement in cardiovascular function compared to the DIET+RT and DIET groups. End diastolic volumes increased for all treatment groups from baseline to 12 weeks, however the findings were not statistically significant ($p=0.150$). End systolic volumes increased for the DIET and DIET+RT groups, whereas it decreased in the DIET+AT group. Karnassis et al reveal opposite findings in volumetric data in relation to decreased body weight. Long term follow-up of bariatric surgery patients revealed significantly lower end diastolic

volume in patients that maintained a BMI of less than 32kg/m^2 (87.0±12.2mL) compared to those with a BMI greater than 42kg/m2 (113.0±23.8)[114]. However, Dehmer et al show an acute increase in end diastolic volume during supine exercise of approximately 25mL[115]. Furthermore, four weeks of exercise training has been shown to increase left ventricular diastolic diameter from 4.98 to 5.11cm[116]. An increase in end diastolic volume associated with exercise training seen in the current investigation may suggest that exercise training was sufficient to maintain left ventricular end diastolic volume that has been shown to decrease with weight loss.

5.4 CARDIORESPIRATORY FITNESS

There was no significant time or group effect for change in VO_2 at 85% of APMHR. However, when examining the change scores the DIET+AT group increased their treadmill time by 1.9 minutes, whereas the DIET+RT and DIET groups increased their time each by 0.8 minutes. These findings partially support the hypothesis that the DIET+AT group would have a significantly greater improvement in cardiorespiratory fitness than the DIET+RT and DIET groups, though not statistically significant. The lack of statistically significant findings is supported by Mendonca et al who suggest over 12 weeks the addition of resistance training two days per week to an aerobic training regimen is not sufficient to significantly improve submaximal VO_2 compared to aerobic exercise alone[117].

Further examination of the data reveal that the DIET and DIET+AT groups showed a slight decrease in absolute VO_2 at 12 weeks. These results are not consistent with the current literature by Church et al that shows an improvement in VO_2 Peak over six months in all three different aerobic exercise training groups[118]. Thus, these findings in combination with a greater

increase in time to reach 85% APMHR across groups may suggest an alternative adaptation to aerobic training seen in this population. One possible explanation may be that subjects in all groups lost significant weight from baseline. Reduction in body weight, specifically adipose tissue, would require a lesser metabolic cost of activity at a given intensity. Subjects may have been able to achieve a greater treadmill time from baseline simply because they became more mechanically efficient as they increased work without a subsequent increase in VO_2 during submaximal exercise. Finally, there may be central and/or peripheral responses to exercise that occur short-term that allowed the subjects to increase treadmill time from baseline. As little as 16 weeks of submaximal aerobic training has been shown to improve ateriovenous oxygen difference in healthy, young adults[119], resulting in greater improvements in maximal oxygen uptake. The current investigation did not measure central or peripheral adaptations to exercise and only 85% APMHR VO_2 was obtained. The possible explanations given for an increase in treadmill time are speculative and future research should focus on determining a treatment effect of exercise training on submaximal oxygen consumption in this population.

An increase from baseline to 12 weeks in self-reported physical activity was observed for completers (377.6 ± 744.7kcal) and in the intent-to-treat analysis (283.2 ± 661.7kcal), possibly adding to the finding of non-significant group differences at 12 weeks. While it was expected that the DIET+AT and DIET+RT groups would see a significantly higher increase in kilocalorie expenditure per week, these groups were not significantly different from the DIET group at week 12 ($p=0.506$). A closer examination of mean kilocalorie expenditure does show that the DIET+AT group (approximately 454kcal) and the DIET+RT group (approximately 506kcal) had greater caloric expenditure than the DIET group (approximately 172kcal) per week. These changes are less than Jeffery observed at six months for dieters (+551kcal/week) and high

volume exercisers (+1121kcal/week)[70]. The mean caloric expenditure may not be significantly different between groups due to an increase in physical activity by the DIET group outside of the intervention. At the beginning of the study, subjects in each group were asked to not engage in a structured exercise plan for the duration of the intervention. However, they were told that they should maintain their normal activities of daily living yet they increased their caloric expenditure (+172kcal/wk). Future studies should focus on controlling physical activity outside of supervised exercise sessions to better determine the effect of exercise on the outcome variables.

5.5 MUSCULAR STRENGTH

Subjects in all three treatment groups showed significant improvements in upper body strength measures from baseline to 12 weeks ($p<0.001$). There was a trend toward increase in lower body strength ($p=0.098$) measured by the leg press but no significant differences in any maximal strength measure between groups ($p>0.189$). These findings do not support the hypothesis that the DIET+RT group would have a greater increase in muscular strength compared to the DIET+AT and DIET groups. However, while not significant, the DIET+RT group did have a greater change score for all three strength measures compared to the other two groups (See Table 9 and Figure 7). These trends in maximal strength change scores are similar to those found by Donges et al who show a greater increase in lower and upper body strength in resistance trained subjects (+45kg and +17kg, respectively) compared to aerobic trained (+19kg and +2.8kg, respectively) subjects and controls (+2.7kg and +0.6kg, respectively) during a 10-week training protocol[120]. The short duration of this intervention, in addition to the gradual increase of stimulus

(Tables 4 and 5), may have caused a non-significant difference between treatment groups for maximal weight lifted.

5.6 LIMITATIONS AND FUTURE DIRECTIONS

This investigation examined the effects of diet alone or in combination with exercise on changes in cardiovascular structure and function in Class II and III obese adults and thus served as a pilot investigation. There are several factors that may have impacted the main outcomes and the results should be interpreted accordingly. Future studies should consider the following:

1. This investigation included a small sample size that was likely not large enough to elicit between group differences in body weight, cardiovascular measures, body composition, physical activity and dietary intake. However, the current study provides effect size to adequately power a future study. Future studies should employ a similar intervention to a larger sample of subjects.
2. This investigation was 12 weeks in duration which may not have been enough time to provide sufficient stimulus to detect significant differences between the treatment groups. Future studies should examine the main outcome variables over a longer period of time.
3. This investigation included females only; therefore the findings cannot be generalized to men as well. Therefore, future studies should include males to determine gender differences in the outcome variables.
4. The stimulus provided by the aerobic training protocol may not have been aggressive enough to elicit an expected response from the outcomes. For example, there was a five week period over which intensity increased to the prescribed 180 minutes per week,

which may not have been enough time at the prescribed dose of aerobic exercise. Future studies should consider a greater volume of aerobic exercise for the given time period to detect greater differences in the outcome variables.

5. Subjects in the DIET+RT group may not have been exposed to a sufficient resistance stimulus to result in significant differences in strength measures between treatment groups. Future studies should consider a more aggressive resistance exercise protocol, such as the protocol used by Donnelly[121], to provide sufficient stimulus to maximize strength gains. The exercises involving Thera-bands and resistance tubing may not have elicited a large enough stimulus to result in a significantly greater improvement in strength in the DIET+RT group.
6. Weight loss in the DIET+AT and DIET+RT treatment groups were greater than in the DIET group, although not statistically significant. The exercising groups were required to attend three supervised exercise sessions per week in addition to the weekly group meeting. It is possible that the additional contact may have positively influenced weight loss behaviors in the DIET+AT and DIET+RT groups. Future investigations may need an additional contact (in person or telephone) per week to the DIET group to increase contact and standardize with the exercise groups.
7. This investigation did not include the measure of traditional cardiovascular disease risk factors such as total cholesterol and blood lipids. Future investigations should include these markers to determine cardiovascular disease risk pre and post weight loss induced by diet or diet in addition to aerobic or resistance exercise in Class II and III obese adults.
8. This investigation employed a submaximal exercise test to determine cardiorespiratory fitness. It is possible that the statistically significant changes not seen in VO_2 at 85%

APMHR between the treatment groups may be observed at maximal effort. Future investigations should utilize a maximal treadmill test to examine differences in maximal oxygen uptake between treatment groups.

9. Visceral adiposity has been shown to be associated with increased risk for cardiovascular disease[8]. However, this measurement was not attained for the current investigation. Future studies should include CT scan or MRI to appropriately determine this measure of adiposity and examine its association with weight loss and exercise training in this population.
10. The outcome variables obtained from the cardiac MRI (left ventricular mass, fibrosis, end diastolic volume, end systolic volume, and ejection fraction) were taken at rest and therefore may not reflect responses to exercise. Future investigations should incorporate techniques to measure these variables, especially end diastolic volume, end systolic volume, and ejection fraction after an acute bout of exercise (physical stressor) to examine exercise-induced changes in these variables.
11. The subjects in this investigation had a mean age of 45.4 years and ranged from 32 to 55 years. These results can not be generalized to individuals of younger or older age demographic. Therefore, future investigations should seek to understand the effect of weight loss and exercise on left ventricular mass, fibrosis, end diastolic volume, end systolic volume, and ejection fraction on populations such as adolescents and the elderly.
12. Subjects were prescreened for use of medications that influence blood pressure and heart rate response. However, no further screening of medication use was conducted. Therefore, future investigations should perform more detailed screening into medication use to examine their possible effect on these cardiovascular outcome variables.

5.7 CONCLUSION

In conclusion, the current investigation was successful in producing weight loss, increasing muscular strength, and improving body composition and dietary habits. Several important conclusions can be drawn from this study even though cardiovascular structure and function outcomes showed little significant difference between treatment groups.

First, an intervention including behavioral, diet, and exercise therapy can be successfully implemented in Class II and III obese women. Second, quantifiable changes were seen in cardiovascular structure and function outcomes. Left ventricular hypertrophy is associated with poor health outcomes. In this investigation, exercise appeared to counteract the effect of weight loss on LVM reduction. However, it appears that cardiac structure and function can improve in Class II and III obese women in response to exercise training and modest weight loss. The elevated end diastolic volumes in the DIET+AT and DIET+RT groups may reflect an acute effect of exercise on this measure and not chronic adaptations seen with exercise training. Lastly, this study showed that cardiac MRI is a feasible technique to measure and detect positive changes in left ventricular structural and functional changes in Class II and III obese women.

The findings are promising and may require longer duration and an increased sample size to find clinical significance. This investigation served as a pilot study and thus, additional studies should be conducted to replicate and improve upon the findings of this study. Future studies should include a longer duration and increased sample size to be better able to detect between group differences. In addition, future studies should incorporate a more aggressive training protocol for both aerobic and resistance exercise to better determine the effect of exercise on changes in cardiovascular structure and function in this population.

APPENDIX A

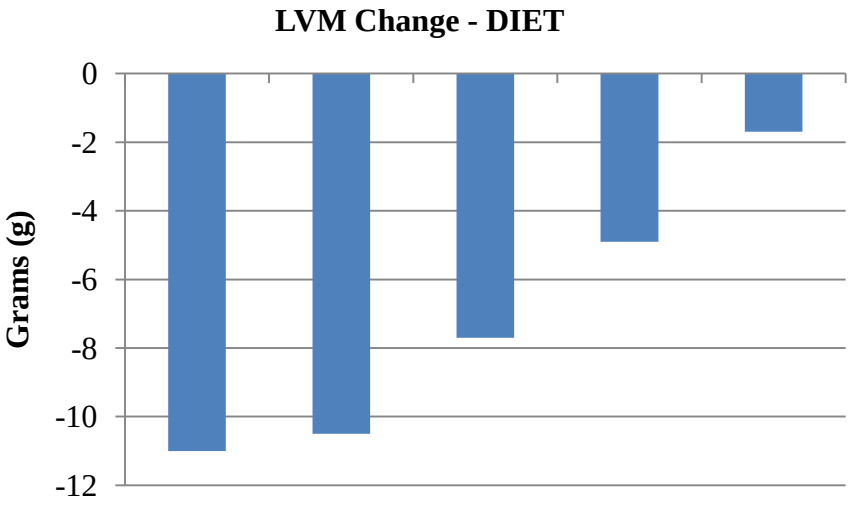
CARDIAC MRI OUTCOME VARIABLES – ABSOLUTE VALUES

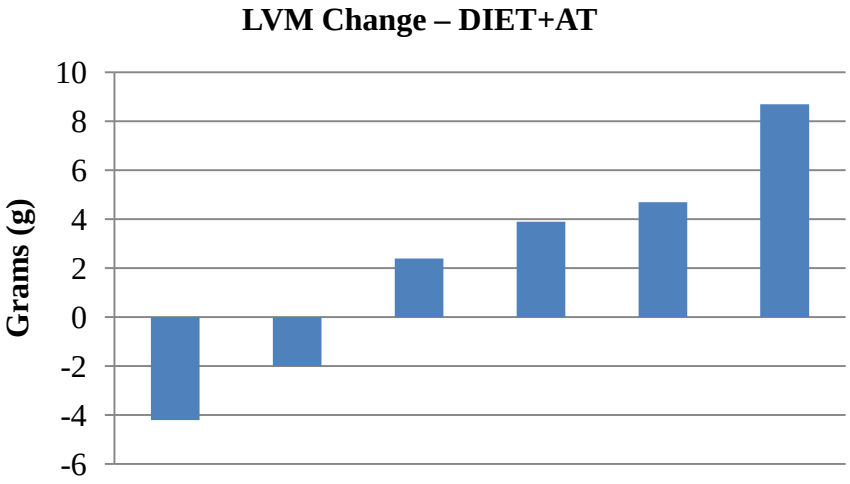
	Outcome Variable									
	Left Ventricular Mass (g)		Myocardial Fibrosis (%)		End Diastolic Volume (mL)		End Systolic Volume (mL)		Ejection Fraction (%)	
Subject	Baseline	Week 12	Baseline	Week 12	Baseline	Week 12	Baseline	Week 12	Baseline	Week 12
1	93.3	89.1	28.3	28.4	165.8	178.4	70.0	69.4	57.7	61.1
3	84.2	86.6	24.8	26.7	161.4	178.9	72.0	74.4	55.4	58.4
4	82.6	77.1	28.1	29.7	172.7	169.1	62.8	65.0	63.6	61.5
5	123.6	112.6	22.9	23.5	170	185.2	84.8	90.6	50.1	51.0
6	113.5	108.6	25.9	25.1	197.5	178	66.7	67.1	66.2	62.3
7	87.8	91.0	24.8	27.5	138	159.9	50.8	56.1	63.1	64.9
8	86.0	86.0	29.0	29.3	118.1	118.1	45.9	45.9	61.1	61.1
9	65.8	69.7	24.2	26.4	106.6	123.3	41.2	44.2	61.3	64.1
10	103.7	101.7	23.4	24.6	151	147.2	66.1	57.1	56.2	61.2
11	77.2	85.9	26.6	27.4	160.8	167.5	66.6	61.4	58.5	63.3
14	61.9	60.2	24.3	23.1	84.3	85.5	25.7	33.2	69.5	61.1
15	96.8	101.5	26.0	25.3	126.9	140.4	42.5	42.1	66.5	70.0
17	78.4	80.8	26.6	26.5	137.5	125.2	50.4	50.0	63.3	60.1
21	96.6	86.1	25.8	23.9	137.6	138.7	52.3	47.7	61.9	65.6
24	76.7	69.0	21.7	24.2	95.1	104.4	29.8	32.7	68.6	68.6
25	78.9	77.6	26.8	26.2	140.1	138.7	58.2	55.0	58.4	60.3

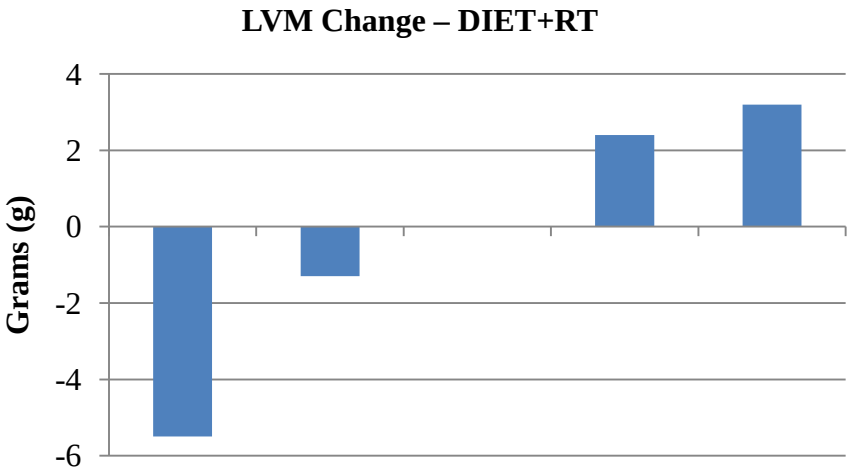
*Subjects 18 and 23 did not complete 12 Week Cardiac MRI. Baseline data not shown.

APPENDIX B

INDIVIDUAL LEFT VENTRICULAR MASS CHANGE SCORES

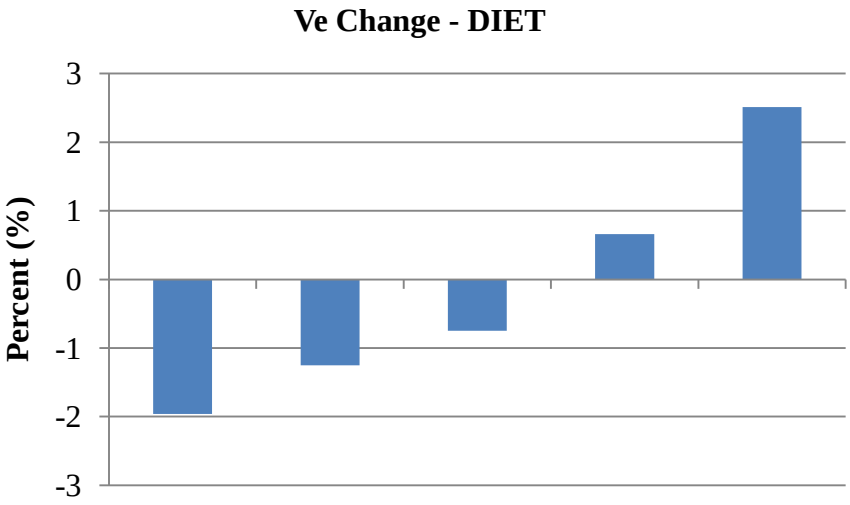

LVM Change - DIET
Grams (g)
0
-2
-4
-6
-8
-10
-12

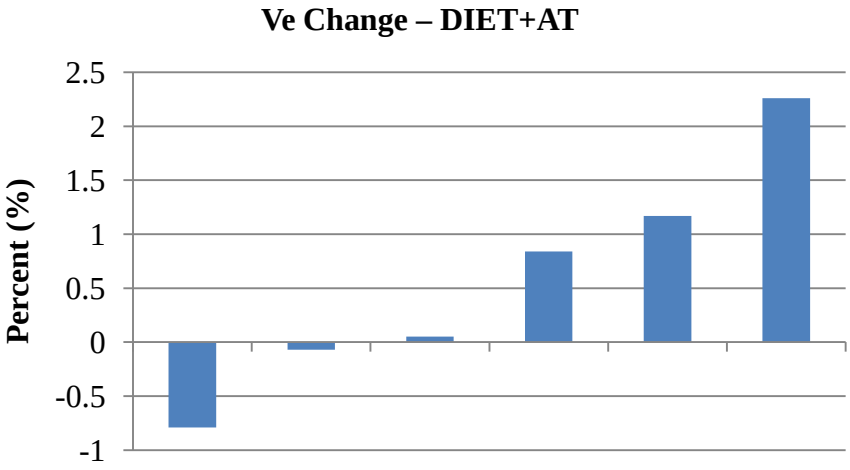

LVM Change – DIET+AT
Grams (g)
10
8
6
4
2
0
-2
-4
-6

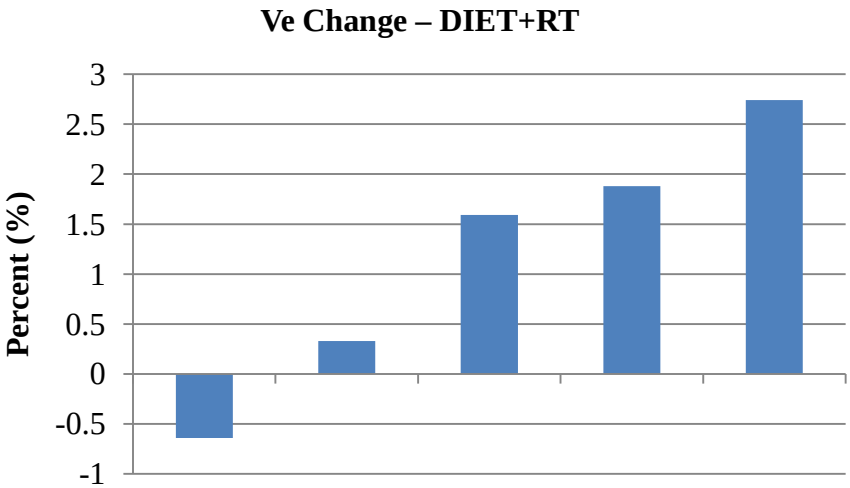

LVM Change – DIET+RT
Grams (g)
4
2
0
-2
-4
-6

APPENDIX C

INDIVIDUAL MYOCARDIAL FIBROSIS (Ve) CHANGE SCORES

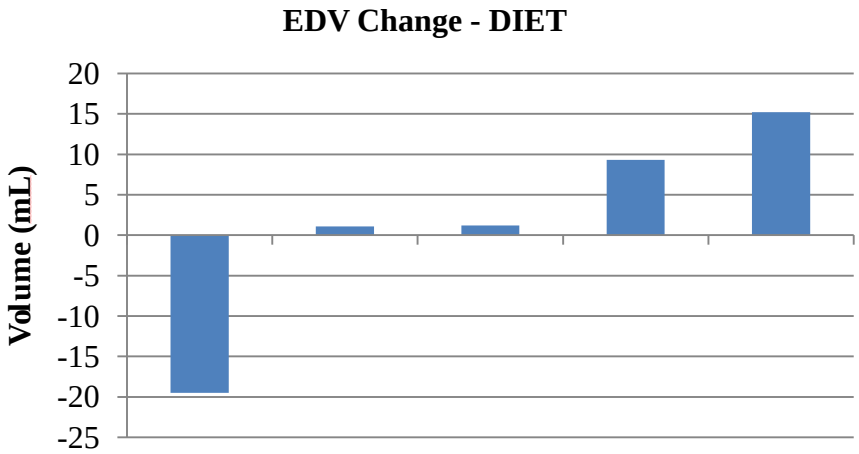

Ve Change - DIET
Percent (%)
3
2
1
0
-1
-2
-3

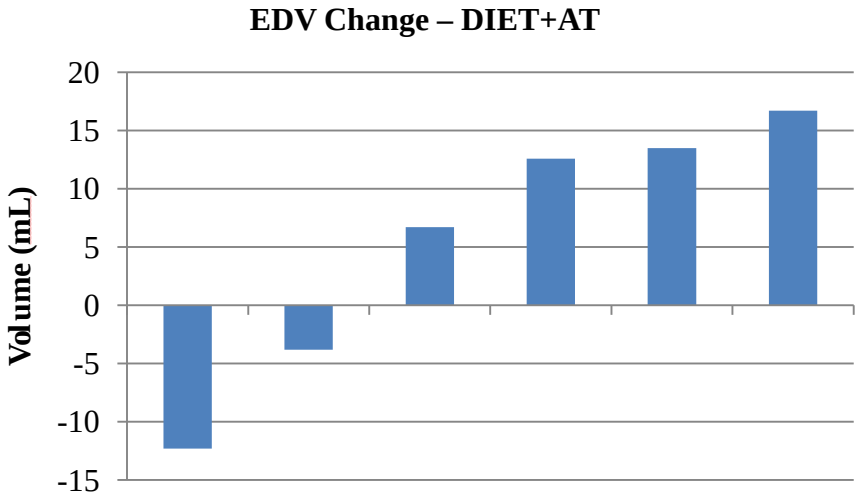

Ve Change – DIET+AT
Percent (%)
2.5
2
1.5
1
0.5
0
-0.5
-1

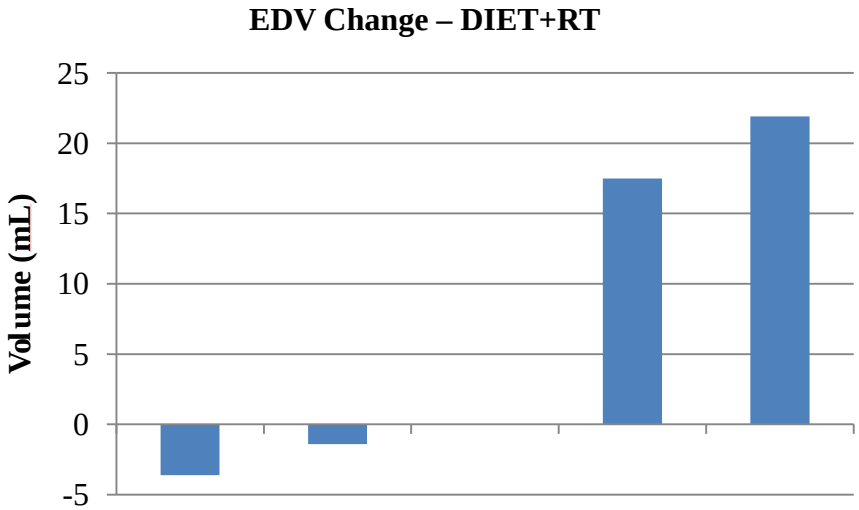

Ve Change – DIET+RT
Percent (%)
3
2.5
2
1.5
1
0.5
0
-0.5
-1

APPENDIX D

INDIVIDUAL END DIASTOLIC VOLUME CHANGE SCORES

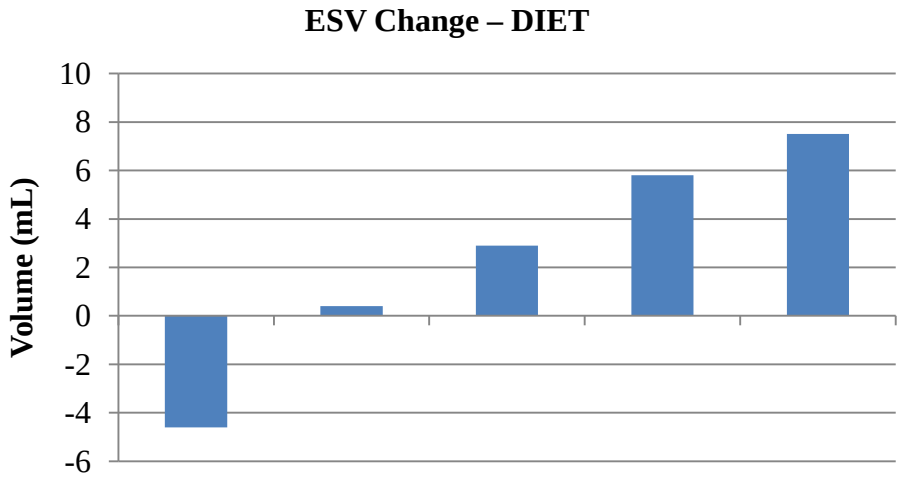

EDV Change - DIET
Volume (mL)
20
15
10
5
0
-5
-10
-15
-20
-25

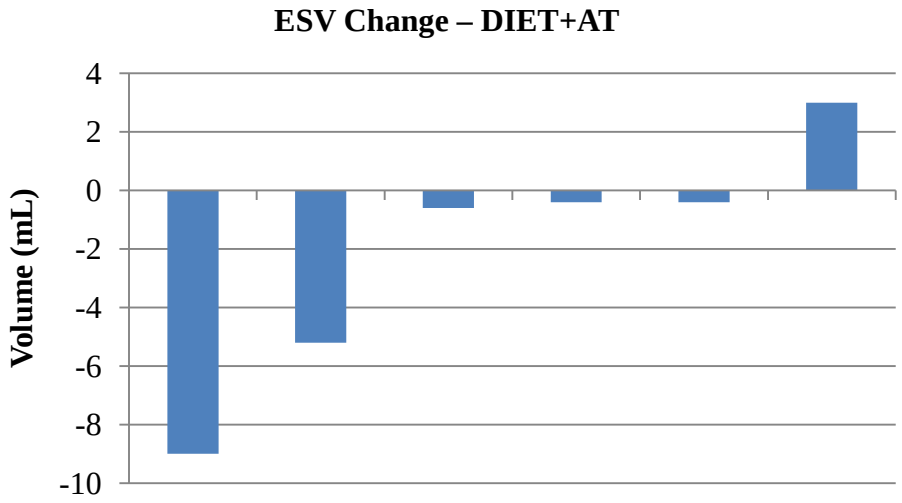

EDV Change – DIET+AT
Volume (mL)
20
15
10
5
0
-5
-10
-15

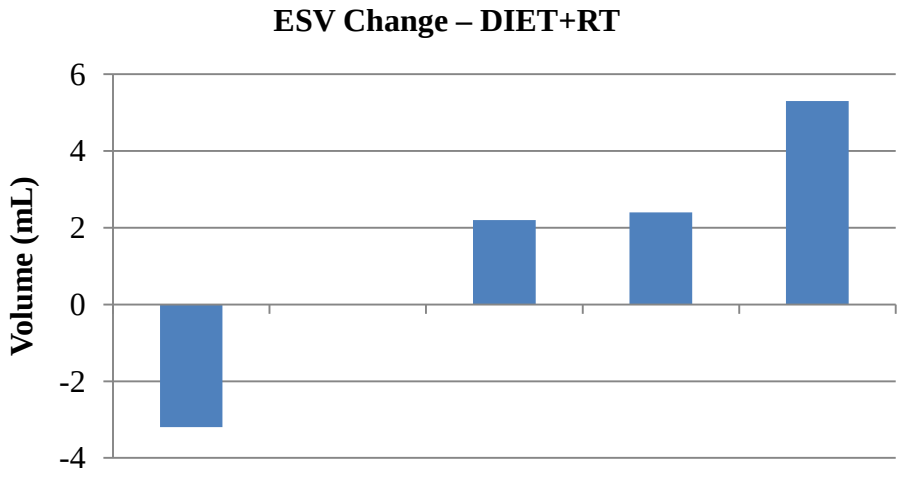

EDV Change – DIET+RT
Volume (mL)
25
20
15
10
5
0
-5

APPENDIX E

INDIVIDUAL END SYSTOLIC VOLUME CHANGE SCORES

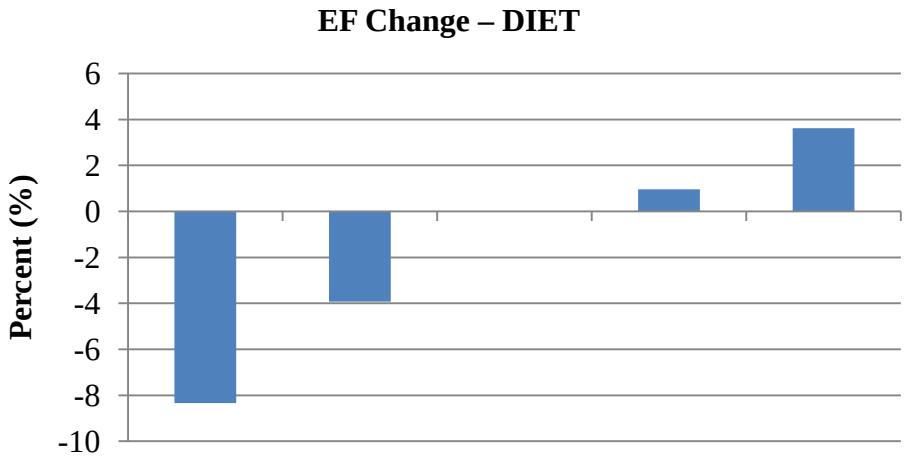

ESV Change – DIET
Volume (mL)
10
8
6
4
2
0
-2
-4
-6

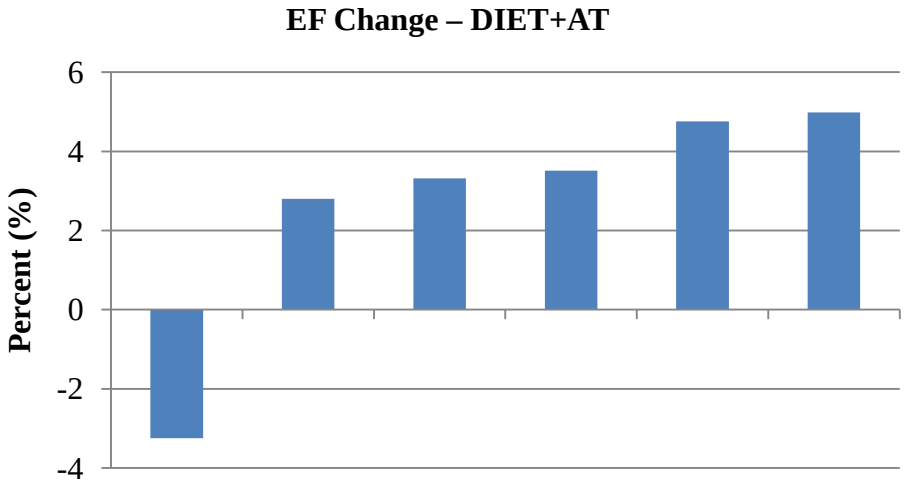

ESV Change – DIET+AT
Volume (mL)
4
2
0
-2
-4
-6
-8
-10

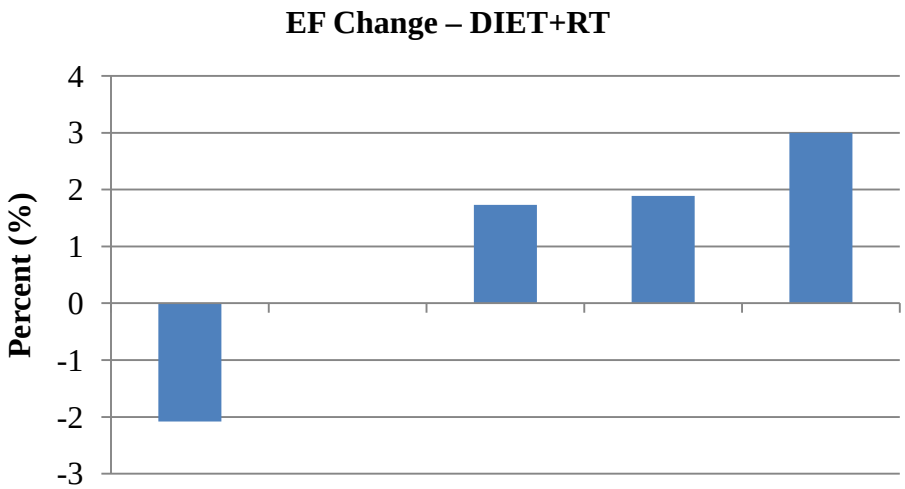

ESV Change – DIET+RT
Volume (mL)
6
4
2
0
-2
-4

APPENDIX F

INDIVIDUAL EJECTION FRACTION CHANGE SCORES


EF Change – DIET
Percent (%)
6
4
2
0
-2
-4
-6
-8
-10


EF Change – DIET+AT
Percent (%)
6
4
2
0
-2
-4


EF Change – DIET+RT
Percent (%)
4
3
2
1
0
-1
-2
-3

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