THE INFLUENCE OF METABOLIC GENOTYPES ON DIET AND EXERCISE INDUCED WEIGHT LOSS IN WOMEN

A Dissertation

by

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ABSTRACT

The purpose of this study was to retrospectively determine the influence of genetic profiling on diet type and exercise for weight loss, body composition, and biomarkers of metabolic health in previously sedentary women. SNPs in obesity candidate genes ADRB2-79, ADRB2-46, PPARγ2, FABP2, and ADRB3 were evaluated to predict health outcomes. Eighty-six women (age 37.5±13.4 yrs; ht 163.7±6.9 cm; wt 82.0±16.8 kg; 40.8±5.1% body fat) were randomized to the control (CTRL), American Heart Association (AHA), Curves Complete-I (CC-I), or Curves Complete-II (CC-II) program for 24-wks (N=86). Participants in the diet groups followed a 1,400 kcal/d diet for 1 wk; 1,500 kcal/d diet for 23 wks (AHA 55%:15% CHO:PRO, CC-I 25%:45% CHO:PRO, CC-II 15%:45% CHO:PRO), while participating in supervised resistance circuit (3x/wk) and Zumba exercise (1x/wk). Remaining subjects in the CTRL had no diet or exercise intervention. Body composition, anthropometrics, resting energy expenditure (REE), physical activity, and psychosocial assessments were measured at 0, 4, 8, 12, 16, 20 and 24 weeks. VO_2max capacity, upper and lower body isotonic strength and endurance, and lipid biomarkers were assessed at 0, 12, and 24 weeks. Data were analyzed using multivariate analysis of variance for repeated measures. MANOVA of body composition data revealed time x diet interaction (Wilks' Lambda $p=0.05$) with no difference observed among diet groups ($p=0.86$), as all diet groups significantly improved these variables and CTRL had no deviation from baseline after 24 wks. MANOVA of body composition (body weight, fat mass, lean mass, fat-free mass, and body fat %) revealed an overall time effect (Wilks' Lambda $p<0.001$), but no time x match interaction ($p=0.99$) when analyzed as a genetically True (T) or False (F) match to diet. Both

T and F participants matched to diet revealed similar weight loss (F -4.25±0.93; T -4.63±0.85 kg, p=0.61). Results indicate that women following a controlled diet and exercise program experience similarly favorable changes in body composition, cardiovascular fitness, and biomarkers of health. However, diets designed for weight loss based on SNP profiles elicits further research, as no time x genetic match interactions in body weight or composition were observed in T and F matches to diets.

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CHAPTER I

INTRODUCTION AND RATIONALE

Background

The prevalence of obesity among adults in the United States in 2011-2012 was an estimated 34.9%, with no significant statistical change since 2003-2004 [1]. Despite the efforts of healthcare professionals, this epidemic is ongoing, as the causative factors of obesity are continuously shown to be as metabolically diverse and interactive. The most obvious external and environmental contributor to weight gain is excessive caloric intake concurrent with limited physical activity (PA), resulting in a state of positive energy balance. Chronic exposure to this homeostatic disruption eventually alters nutrient sensitivity and decreases phenotype flexibility. Physiological and molecular mechanisms that regulate metabolic activity become impaired, and the consequential cascade alters the normative responsiveness to glucose, triglyceride, and protein consumption [2]. Well established, identifiable risk factors that indicate metabolic functional dysregulation and subsequent morbidity include dyslipidemia, elevated low density lipoprotein (LDL), hypertension, and insulin resistance [2, 3]. Not surprisingly, this decline in cellular regulation extends to a decline in mechanical function, and further incites weight gain.

While much attention has been given to dietary strategies for optimizing weight loss results, these efforts have not been consistently successful as long-term solutions [4-7, 9, 10]. An array of well-designed clinical trials have been exhaustively examined - ranging from very low energy diets (VLED <800 kcal/day) [11-14], ketogenic diets [15-18, 24], low fat [18-24], and very high protein diets (>2g/kg) [25-27]. Research has shown that caloric

restrictive interventions elicit weight loss and improve body composition acutely, although most follow up measures after one year or more indicate weight regain with only a diminutive decrease from the initial baseline. The addition of physical activity (PA) tends to improve long term weight loss maintenance in several meta-analyses [4-7], yet sustained PA with an emphasis on an exercise training (ET) regimen may be necessary to maintain health outcomes, regardless of initial weight loss [8]. Even still, weight maintenance remains a challenge despite the method or intensity of the initial treatment. Recent data from the National Institute of Health (NIH) demonstrated that contestants participating in a popular weight loss television show experienced an initial significant decrease in resting energy expenditure (REE) and dramatic slowing of metabolism which may have biologically in part, contributed to most contestant's weight regain 6-years post-intervention. Weight loss at the end of the competition was (mean±SD) 58.3±24.9 kg ($p< 0.001$), and REE decreased by 610±483 kcal/day ($p= 0.004$). After 6 years, 41.0±31.3 kg of the lost weight was regained ($p< 0.001$), while REE was 704±427 kcal/day below baseline ($p< 0.001$) and metabolic adaptation was -499±207 kcal/day ($p< 0.001$) [28]. Additional clinical trial results reveal as few as ~10% maintain significant continuation of weight loss from baseline after 3 to 5 years [9,10]. Considering the relatively low success rate of these investigations and the high variability of individual responsiveness, a body of growing research is directing attention to genetic factors and their potential interaction with hypocaloric intake, specific macronutrients, and/or exercise activity.

For example, Bouchard et al. investigated the variability between pairs of identical twins, as well as the correlation within the pairs in response to a controlled exercise

intervention [29]. Seven pairs of adult, sedentary males completed the 93-day trial, in which subjects expended ~4.2MJ (1,000 kcal) during exercise 2x/day on a cycle ergometer every 9 out of 10 days. Although all participants experienced significant reductions in body composition measurements and biochemical markers of lipid oxidation (body weight, body mass index ([BMI], fat mass [FM], visceral adipose tissue [VAT]), fasting triglycerides [TAG], and cholesterol [CHL]), significant variability existed between groups (i.e.: set of twins) denoted by the F-Ratio on each of these measurements ($p \leq 0.05$). Intraclass coefficients (ICC) were also significant within group response on each parameter ($p \leq 0.05$). All subjects underwent the same relative exercise and dietary composition protocol for three months in a clinically controlled environment. These results attribute to the contention that individuals may oxidize preferentially more lipids relative to carbohydrates, and that the high or low lipid oxidization phenotypes are influenced by, as of yet, undefined genes.

Hainer et al. [30] later conducted an experiment with a similar examination of metabolic response in twin pairs; however, her aim was to investigate metabolic response to diet induced weight loss versus exercise induced. 14 pairs of obese female identical twins (age = 39±1.7 years) underwent a 40-day inpatient protocol of a very low caloric deficit (VLCD) of 1.6 MJ/day for 4 weeks. Body composition measurements were obtained via hydrodensitometry and metabolic rate via indirect calorimetry, verbatim to Bouchard's [29] previous method of data acquisition on exercise response in twin pairs. Hainer obtained similar results in significant losses in body composition parameters ($p \leq 0.001$), but not resting metabolic rate (RMR). Additionally, all body composition ICC were significant within groups ($p \leq 0.002$), yet high variability existed between pairs. For example, body weight loss ranged from 5.9 kg and 12.4 kg (ICC=0.85; F=12.8, [$p \leq 0.001$]). Fat mass reduction range

was between 3.1 kg and 12.4 kg (ICC=0.88; F=17.0 [$p \leq 0.001$]). The high correlation between twin pair members ($r=0.778$, $p<0.001$) in response to therapeutic weight loss suggests a strong genetic contribution to metabolic efficiency denoted by the residual of the measured energy deficit regressed on the estimated energy deficit.

In addition to the non-inherited environmental factors such as caloric overconsumption and lack of physical activity, the aforementioned studies conducted by Bouchard et al. and Hainer et al. reveal inherited DNA genotypes and epigenetic factors can determine a phenotypical adaptation to a particular stimulus. As such, when assessing obesity-related etiology, consideration has to be given to the variations of metabolic candidate or "susceptibility" genes as plausible mediators involving lipid oxidation, glucose metabolism, thermogenic effects of food, and oxidative status [31]. To date, over 547 candidate genes have been linked to obesity-related phenotypes [32].

Nutrigenetics

This relatively new approach targeting gene-diet interaction is known as nutrigenetics. Specifically, nutrigenetics investigates the modifying effects of qualitative (single nucleotide polymorphisms [SNPs], small deletions, duplications, or insertions) or quantitative (large duplications or deletions) gene variants in response to a dietary protocol. Qualitative variants can alter the regulatory region of a gene (i.e., the promoter region) or coding/noncoding sequences; whereas quantitative changes directly affect the level of expression [33]. SNPs are the most common sequence variations in the human genome, with over 10 million identified to date from genome wide association studies (GWAS) [34]. SNPs are base pair substitutions that alter the allele pattern as homozygous or heterozygous at specific chromosome loci. When a nucleotide of a gene is modified (e.g. adenine to thymine

[AA to AT], guanine to cytosine [GG to GC] or any variation thereof) at a coding or promoter region, an amino acid substitution takes place altering the protein's binding affinity and possible functionality. Depending on the number SNPs of in the gene, and whether any of them have known functional effects, analyses can be conducted using individual SNPs or combinations of SNPs, such as haplotypes [35]. These polymorphisms may contribute to individual nutrient sensitivity; thereby presenting a valid and novel approach to personalized nutrition for weight loss, maintenance, and optimal health.

The implication of metabolic effects of SNPs arose from studies examining the effects of components found in coffee on cardiovascular disease (CVD), with contraindicative results on plausible risk factors [36-41]. Weggemans et al. [42] was the first to report that a polymorphism in the apolipoprotein E (*APOE*) gene resulted in elevated LDL cholesterol in response to cafestol, a dipertene molecule present in primarily unfiltered coffee. In a follow up study, individuals with the *ApoA1* 83 CC genotype had greater elevations in LDL cholesterol in response to cafestol compared to those with the *ApoA1* 83 CT genotype [43]. The identification of SNPs in candidate genes to examine the association between coffee and coronary heart disease (CHD) has been beneficial in the association of CHD and causal risk factor components in coffee. This was further demonstrated by Cornelis et al. [44], who was the first to incorporate a genetic modifier of caffeine metabolism in the analysis of coffee and risk of myocardial infarction. Cytochrome P450 (CYP)1A2 accounts for over 95% of caffeine clearance from the plasma. With typical amounts of caffeine consumption from dietary sources, the large variability in the enzyme activity of cytochrome P450 (CYP)1A2– mediated metabolism has been targeted for the inter-individual variability in caffeine metabolism [45-47]. The -163C>A polymorphism in the *CYP1A2* gene has been

associated with reduced caffeine metabolism as a result of decreased enzyme inducibility [44, 48]. These findings suggest an increased risk of myocardial infarction associated with coffee consumption, but only among individuals who were carriers of the -163C allele, corresponding to the genotype associated with a slower rate of caffeine metabolism.

With the novel identification of SNPs in candidate genes now known to be associated with metabolism of dietary components and CHD, scientists have been optimistic in identifying additional SNPs responsible for phenotypical differences in obesity, body composition, and health risk factor components. Indeed, a plethora of cohort investigations such as the ongoing Quebec Family Study conducted between 1979 – 2002 have identified significant familial aggregation and several genetic influences associated with BMI, adiposity, leptin, fat free mass (FFM), subcutaneous, abdominal and visceral fat distributions, physical activity levels, metabolic rates and additional behavioral characteristics [49-54]. These large scale associative cohort studies have led to the development of investigating candidate genes within the scope of a dietary and/or exercise intervention. Though intervention trials are relatively scarce in the developmental stages, nutrigenetics has already become a sought out implication as a marketable solution for weight loss based on metabolic genotypes. However, the findings within the literature of controlled trials examining the influence of metabolic candidate gene SNPs have yet to be elucidated.

Although a standardized weight loss intervention is immediately effective for most individuals, high variability still exists in regards to response and maintenance of controlled behavioral change. In addition to behavioral modifications, it is probable that SNPs in candidate metabolic genes modulate intracellular processes at selected sequence coding regions. Previous research [55, 56] has determined that allele variants in adrenergic receptors

(ADRB2-79, ADRB2-46, ADRB3), peroxisome proliferator activated receptor (PPARγ2), and fatty acid binding protein (FABP2), may influence responsiveness to dietary macronutrient distribution. However, these findings have yet to be followed up with a concurrent exercise protocol. Examining the efficacy of exercise with dietary intervention based on metabolic genotype will help develop predictable models for optimal weight loss strategies.

Statement of the Problem

Does a metabolic genetic profile influence results in individuals participating in a fitness and weight loss program when assigned to a specified diet?

Purpose

The purpose of this study was to:

1. Retrospectively determine the influence of genetic profiling by diet type and exercise for weight loss, body composition, and biomarkers of metabolic health
2. Assess whether a high CHO (55% kcal) or high PRO (45% kcal) macronutrient distribution may have more favorable results for weight loss, body composition, fitness measurements, and biomarkers of metabolic health in previously sedentary women during a six-month weight loss trial

General Study Overview

This study was a 24-week weight loss intervention trial in women aged 18-60 years. To ensure homogeneity among groups, participants were randomized based on age, BMI, and baseline body fat percentage, and assigned to one of four groups: CC-I (30% CHO kcal, 45% PRO kcal, 25% FAT kcal), CC-II (20% CHO, 45% PRO, 35% FAT), AHA (55% CHO kcal, 15% PRO, 30% FAT), or control (CTRL). Except the CTRL group, all participants in a

treatment group (CC-I, CC-II, AHA) adhered to a diet consisting of 1500 total kcal/day, and exercise was performed on a hydraulic resistance circuit for 30 min/day, 4x/week. Additionally, participants in the treatment groups were instructed to walk 10,000 steps on non-resistance exercise days. Buccal cheek swabs were obtained at baseline to determine individual SNPs in the candidate genes FABP2 (rs1799883), PPARγ2 (rs1801282), ADRB3 (rs4994), ADRB2, (rs1042713) and (rs1042714). Body composition (fat mass [FM], Fat-free mass [FFM], percent body fat) by DEXA scan, anthropometric measurements (body weight, waist circumference, hip circumference), resting energy expenditure (REE) via indirect calorimetry, complete blood counts, dietary intake and weekly physical activity, and psychosocial quality of life were assessed at 0, 4, 8, 12, 16, 20, and 24 weeks. Maximal cardiopulmonary exercise capacity (VO_2max) and upper and lower body single repetition max isotonic strength (1 RM), fasting glucose, lipid panels, insulin concentrations, were assessed at 0, 12, and 24 weeks.

Hypotheses

H1: Significant differences in body composition, measures of fitness, and biochemical markers of health will be observed in participants assigned to the treatment groups (AHA, CC-I, and CC-II) in comparison to the CTRL group.

H2: Participants matched to a True (T) diet that favors their metabolic genetic profile will experience significantly greater weight loss and improvements in body composition than the False (F) unmatched participants.

H3: Participants matched to a True (T) diet that favors their metabolic genetic profile will experience significant improvement in biochemical markers of health than the False (F) unmatched participants.

Limitations

The study was conducted within the following parameters:

1. 86 sedentary overweight, female participants (BMI > 25) between the ages of 18-50 years were recruited to participate in the study.
2. Participants were recruited with flyers posted on campus, electronic communication via the Texas A&M University general information system, and advertisements in the local newspaper.
3. Participants were recruited from the Texas A&M University and the Bryan/College Station community from those who respond to advertisements for the study. Thus, the selection process was not truly random. This may have affected the conclusions that can be applied to the general population.
4. Familiarization and testing sessions were conducted in the Exercise and Sport Nutrition Laboratory (ESNL) at Texas A&M University.
5. Participants were matched for age and BMI and randomly assigned to one of three treatment groups or a control group.
6. Participants had not consumed any nutritional supplements that may affect muscle mass or metabolism for at least three months prior to the start of the study.
7. Participants had not participated in an aerobic and/or anaerobic training program for three months prior to the start of the study.
8. Participants had no known disease or health contraindication to exercise, or otherwise obtained physician clearance prior to the start of the study.
9. Participants were not pregnant or lactating prior to and throughout the duration of the study.

10. Participants in the CC-I, CC-II, and AHA groups were required to adhere to the fitness program consisting of 3 regular circuit workouts and one Zumba workout each week throughout the trial.
11. Participants in the CC-I and CC-II groups were required to participate in one weekly nutritional coaching session throughout the investigation.
12. Participants in the CTRL group were requested not to make lifestyle modifications throughout the investigation.
13. Participants in the treatment groups were required to follow the CC-I, CC-II, or AHA diet within a free-living environment.
14. Treatment participants were assigned absolute caloric intakes without consideration of relative body mass and composition.
15. There were innate limitations of the laboratory equipment that were used for data collection and analysis.
16. There were innate limitations in the sensitivity of the technologies and protocols utilized to identify quantifiable changes in the criterion variables.
17. Participant daily schedules and inherent circadian rhythms that exist for all humans due to slightly different testing times, stresses, etc., may have affected results.

Assumptions

1. Participants accurately answered the entrance criteria screening questions and the health and activity history forms.
2. Participants followed the CC-I, CC-II, or the AHA diet protocol as specified according to dietary recall records.
3. Participants were direct in completing questionnaires.

4. Participants were direct in completing food recalls and activity logs.
5. Participants in the CC-I and CC-II groups adhered to the nutritional coaching sessions.
6. Participants in the CC-I, CC-II, and AHA groups followed intensity guidelines for all workouts.
7. Participants maximally exerted themselves to voluntary exhaustion during strength and maximal cardiopulmonary testing.
8. Participants adhered to verbal and written instructions and refrained from exercise for 48 hours prior to testing.
9. Participants fasted for at least 10 hours prior to lab collection.
10. Participants reported any adverse events to the study coordinator.
11. All laboratory equipment was calibrated and functioning properly for all testing sessions.
12. The population from which the sample was drawn from was normally distributed.
13. The inter-individual variance between the groups were approximately equal.

CHAPTER II

REVIEW OF THE LITERATURE

Strategies for Weight Loss

Non-pharmaceutical techniques have long been evaluated to measure the efficacy of weight loss response to a particular stimuli, or response to a combination of interventional approaches. To evaluate the efficacy of diet induced protocols, extensive research has been conducted examining the acute [57-59] and long-term responses to the macronutrient distribution of fats, carbohydrates (CHO) and dietary protein intake [60-66]. To evaluate exercise induced physiological adaptations, intervention methods have been implemented to measure markers of metabolism (i.e., REE, lipid profile, insulin), fitness and cardiovascular functioning (i.e., max strength, VO2max) and body composition (i.e., fat mass, fat-free mass, BMD) [67-71].

Macronutrient Composition

The ongoing investigation for optimal macronutrient partitioning of fat, carbohydrate, and protein intake remains controversial within the extensive body of literature. Determinant responses to energy intake may include mechanistic factors such as levels of insulin resistance, thermogenesis [72], and rates of fat oxidation, which are just a few examples of how substrate utilization may vary extensively among individuals. For example, Volek et al. [65] concluded that a carbohydrate restricted ketogenic diet was superior to a low fat diet in terms of weight loss and fat mass reduction in overweight men (n=15) and women (n=13). Alternatively, Nordmann MD et al. [73] conducted a meta-analysis of 447 weight loss subjects from 6 studies and found that although carbohydrate restricted diets are as effective

as low fat diets in terms of weight loss, potential favorable changes in triglyceride and HDL cholesterol values from a low-fat diet should be considered against potential unfavorable changes in LDL cholesterol values from a carbohydrate restricted diet.

High protein percentage diets have also gained notable interest as a strategy for maintenance of fat free mass, while concurrently reducing body weight and fat mass [74-76]. Halton et al. [72] conducted a systematic review of randomized studies that intervened weight loss with a high protein diet strategy. Indeed, satiety and thermogenesis increased and overall energy intake decreased as a result when compared to a lower protein content. However, Halton additionally notes that some evidence suggests that diets higher in protein result in an increased weight loss and fat mass reduction when compared to diets lower in protein, but findings have been inconsistent.

Dansinger et al. randomly assigned 160 participants to either Atkins (carbohydrate restriction, n=40), Zone (macronutrient balance, n=40), Weight Watchers (calorie restriction, n=40), or Ornish (fat restriction, n=40) diet groups for 18 months. Participants self-reported diet adherence after 2 months [77]. Subjects had known hypertension, dyslipidemia, or fasting hyperglycemia and were considered overweight or obese (mean BMI=35). Higher compliance was associated with greater weight reduction and lowering cardiac risk factors among all diet groups ($r = 0.60$; $p<0.001$). Weight loss was not correlated with diet type ($r = 0.07$; $p=0.40$). For each diet, decreasing levels of HDL cholesterol, C-reactive protein, and insulin were significantly associated with weight loss (mean r=0.36, 0.37, and 0.39, respectively) with no significant difference between diet groups ($p=0.48$, $p=0.57$, $p=0.31$, respectively).

Despite the conflicting results from these data, we must consider each nutrient does contribute a vital role in metabolic efficiency. Additionally, limitations such as participant compliance [77], study design, and external behavioral influences (i.e.: physical activity) must be regarded when interpreting results.

Diet and Exercise Intervention

The contribution of exercise is increasingly revealing its potential as a vital component of not only weight loss, but metabolic markers of health in the reduction of disease risks such as Type 2 Diabetes and cardiovascular disease. Research from our laboratory has extensively exhibited that exercise is a necessary augment to dietary intervention for weight loss [64, 78-86]. Although the debate regarding the optimal ratio of CHO, fat, and PRO in the diet is ongoing, data from our laboratory suggest that low to moderate kcal/day diets partitioned for CHO and PRO preference is equally effective when combined with a structured exercise program for reducing the prevalence of metabolic syndrome (MetS) in overweight and/or obese women (N=661) [79]. Lockard et al. retrospectively examined eight weight loss studies conducted in the Exercise and Sport Nutrition Lab over an 11-year period. All studies examined were 10-week weight loss intervention trials consisting of exercise sessions that included resistance and aerobic training for 30 minutes, 3-4x/week. In addition to exercise, 370 participants were assigned to a high protein (HP) (N=370) or high carbohydrate (HC) (N=291) diet for the duration of the 10-week study. Results concluded that no significant differences were observed between a HC or HP intake in regards to serum glucose (-0.07 ± 0.03 vs -0.08 ± 0.04 mM, P=0.87), serum triglycerides (-0.16 ± 0.04 vs -0.09 ± 0.04 mM, P=0.20), HDL (-0.21 ± 0.03 vs -

0.19 ± 0.04 mM, P=0.68). Additionally, reductions in MetS z-score were significantly different in both HP and HC groups (49% to 42%, 42% to 36%, P<0.01) respectively.

However, previous reports from our laboratory contrast Lockard et al.'s recent observations. Kreider et al. concluded that obese women assigned to a HP diet experienced greater weight loss (-4.4 ± 3.6 kg vs -2.6 ± 2.9 kg), fat loss (-3.4 ± 2.7 kg vs -1.7 ± 2.0 kg), decreased serum glucose (-3% vs -2%), and decreases in serum leptin levels (–30.8% vs –10.8%) when compared to a HC diet with equivalent kcal/day intake after the 10-week weight loss trial [78]. 221 subjects were prescribed low-fat (30%) hypocaloric diets that consisted of 1200 kcals/day for 1 week (phase 1) and 1600 kcals/day for 9 weeks (phase 2) with HP or HC. The exercise intervention was analogous to the method used in the studies analyzed by Lockard et al. Participants exercised 3x/week in a circuit-style resistance training interspersed with aerobic conditioning for 30 minutes.

Despite the differences in these observations, exercise remained a key constant contribution to improvements in overall health and fitness among all stratified intervention groups within the scope of the 10 week studies. The trial methods as reported by Lockard et al. and Kreider et al. were consistent with diet and exercise protocols, and were conducted and monitored in the Exercise and Sport Nutrition Lab. It is plausible to suggest the results from Lockard et al. observations carry a higher statistical power due to the larger N-size and the number of studies included in the analysis. However, the opposing efficacy of a HP or HC diet in these two findings suggest alterative influences on weight loss, body composition, and metabolism. Although diet and exercise have shown to be effective among all weight loss intervention groups, differences observed between HP/HC results may be due to genetic influences yet to be elucidated.

Genetic Influence on Metabolism

PPARγ2

The transcriptional factor Peroxisome Proliferator-Activated Receptor gamma 2 (PPARγ2 [rs1801282]) is a nuclear hormone receptor involved in the expression of adipocyte differentiation [87], the storage of lipids in adipocytes, insulin sensitivity [88], decreasing inflammation and initiating reverse cholesterol transport [89]. PPARγ2 is expressed primarily in adipose tissue, and has an established affinity for polyunsaturated fatty acids (PUFAs). Activated PPARγ2 induces LPL and fatty acid transporters (CD36) and enhances adipocyte differentiation [88], in addition to inhibiting cytokine and *COX2* expression, perhaps by modulating NF-κB function. A genetic variant of PPARγ2 results in a substitution of alanine for proline at amino acid 12 (Pro12Ala). As a result of increased PPARγ2 transcription initiation, carriers of homozygous Pro12 have been considered to possess the 'thrifty gene' as a protective mechanism in the storage of lipids and induction of adipogenesis [88]. Interestingly, the allele variant Ala12 has also been correlated to a higher BMI in obese populations and appears to have no effect in non-obese individuals [90], although the Ala12 variant has a lower frequency than Pro12 carriers.

An early intervention study conducted by Lindi et al. investigated glucose tolerance and the incidence of type 2 diabetes (T2D) in 522 Finnish subjects [91]. Although the Ala12 allele carriers had a higher risk for development of T2D (95% CI, 1.20, 3.72) at 3-years post intervention, the Ala12Ala genotypes lost more weight than those with Pro12Pro or Pro12Ala genotypes ($p=0.043$). Additionally, none of the subjects with the Ala12Ala genotype developed T2D in the intervention group versus control. These results thus suggest that Ala12 carriers may be predisposed to T2D development in obese populations; however,

improvements in dietary intake and physical activity may oppose the diabetic predisposed impact due to increased insulin sensitivity.

Three independent case control studies conducted by Ghoussaini et al. in 2005 involving 2126 cases and 1124 controls yielded similar results in the French Caucasian population [92], in which the Pro12Ala SNP (Pro/Pro) contributed to insulin resistance when the type 2 diabetic (T2D) cohort was stratified by obesity classification ($p=0.03$, $OR=1.81$). The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) revealed an association with the Pro12 allele in glucose tolerant obese adults ($p=0.01$) and fasting insulin levels, and a trend ($p=0.06$) in normal adults. In normal glucose tolerant children however, there was no significant associations with the Pro12Ala polymorphism.

Similarly, Regieli et al. conducted a cohort investigating Pro12Ala variances in male CAD patients [93] with similar results of the 12Ala carriers for decreased risk of cardiovascular morbidity and mortality; therefore, suggesting a protective mechanistic role in inherited risk factors and determination of vascular health. As several studies have exhibited the protective measurable mechanisms of variant carriers of the PPARγ2, it has become a highly regarded target of investigation in the context of dietary and exercise intervention research. Table 2.1 highlights weight loss intervention studies on PPARγ2 SNPs.

FABP2

Fatty acid binding protein (FABP2) is abundantly distributed in small intestinal epithelial cells and has be identified as one of the genes that regulates intracellular metabolism [94]. FABP2 is responsible for absorption and intracellular transport of dietary long chain fatty acids (LCFA) [95]. A SNP occurs as a result of guanine at codon 54 of FABP2 gene is transformed into adenine, alanine encoding allele and-threonine coding allele

(Ala54Thr). Agren, J et al. showed that carriers of the Thr54 allele have a 2x higher affinity for LCFA than those homozygous for the Ala54 allele [96]. In vitro, allele substitutions that increase FABP2 affinity for LCFA (such as Ala54 → Thr54) is associated with an increase in triglyceride transport in human intestinal cells [97, 98]. Furthermore, the Thr54 substitution has been shown to be associated with insulin resistance, increased fatty acid binding, and increased fat oxidation. [99]. Baier et al. reported that among the Pima Indian population of non-diabetics, Ala54 homozygotes (40M/28F), heterozygotes (28M/29F) and Thr54 homozygotes (7M/5F), those who were homozygous or heterozygous for the threonine-encoding allele were found to have a higher mean fasting plasma insulin concentration ($p<0.04$), a lower mean insulin-stimulated glucose uptake rate ($p<0.04$), a higher mean insulin response to oral glucose and a mixed meal, and a higher mean fat oxidation rate ($p<0.002$) compared with Pimas who were homozygous for the alanine-encoding allele.

Inconsistent with these findings however; Martinez-Lopez [100] showed within an 8 week very low calorie diet (VLCD) intervention, Thr54 allele carriers experienced more favorable responses to a moderate fat diet among Hispanic (n=109) overweight participants. These contradicting results may indicate that genotype does not necessarily differentiate changes in weight loss, fitness, or biochemical markers of health when introduced to a dietary intervention such as caloric restriction. Table 2.2 highlights weight loss intervention studies on FABP2 SNPs.

ADRB2 and ADRB3

The ADRB2 and ADRB3 genes code for ß2 and ß3 adrenergic receptors, respectively. These receptors are part of the adrenergic system, which stimulates lipid mobilization in adipose tissue [101] through the thermogenic effect of catecholamines,

specifically epinephrine and norepinephrine [102]. Thus ADRB2 and ADRB3 play a role in lipolytic energy expenditure, responsible for activating lipid mobilization from triglyceride breakdown to free fatty acid (FFA) and glycerol molecules [88, 103].

Adrenergic-receptor beta3 (ADRB3) is primarily located on the surface of visceral and brown adipose cells, and promotes lipolysis and thermogenesis by releasing norepinephrine from the sympathetic nerves when stimulated by the consumption of food or exposure to cold temperature [104, 105]. The Trp64Arg variant of ADRB3 has been associated with lower resting metabolic rate [106], weight gain [107], visceral obesity [108, 109], and difficulty losing weight [110]. Adipose cells with ADRB3 of Trp64/Arg64 or Arg64/Arg64 showed 0.66 lowered ability to produce intracellular lipolytic glycerol [111] and cyclic AMP (cAMP) [112] compared with those with Trp64/Trp64.

Although ADRB2 and ADRB3 are integral to lipid metabolism, and single nucleotide polymorphisms of these genes have been correlated with differences in BMI, body composition [113], and energy expenditure [88] in cross-sectional analyses [88,113]; others have displayed inconsistency, particularly when lifestyle behavioral modifications have been implemented into a research study design [114,115]. For example, Saliba et al. did not find any effect of the ADRB2 and ADRB3 polymorphisms in response to a weight loss intervention. Tables 2.3 and 2.4 highlight intervention studies investigating ADRB2 and ADRB3 variants at selected SNPs.

Table 2.1 PPARγ2 Literature Review of SNP (rs1801282 [Pro12Ala])										
Author/ Journal/ Year	**Variables**		**Title**	**Population**				**Measured Outcomes**	**Results**	**Conclusion**
	Gene	**SNP**		**BMI**	**Age**	**No./Gender/ Health/Ethnic**	**Diet/ Duration**			
Rosado et al., Ann Nutr Metab, 2010 [89]	PPARγ2	rs1801282 (Pro12Pro Pro12Ala Ala12Ala)	Interactions of the PPAR gamma 2 polymorphism with fat intake affecting energy metabolism and nutritional outcomes in obese women	37.66	34.59 (20-49)	60 F (50 Pro12Pro + 10 Pro12Ala/ Ala12Ala); Obese; Spanish	~30% TEE; 10weeks (70days)	BW, REE and PPEE (indirect calorimetry and nitrogen excretion), FM, FFM (bio impedance), diet assessment, RMR, WHR, leptin, food records	At baseline, MUFA intake inversely correlated with fat oxidation and BMI in Ala allele carriers, while a lower PUFA intake (%) in the long-term trial was associated with an increase in RQ only in Ala carriers but not in the Pro12Pro genotype.	Fat oxidation and energy expenditure may be lower in Pro12Pro carriers compared to Pro12Ala/Ala12Ala genotypes, while in obese women with Ala polymorphisms, fat oxidation was negatively correlated with the MUFA and PUFA (%) intake.
Regieli JJ, Diabetes Care, 2009 [93]	PPARγ2	rs1801282 (Pro/Ala)	PPARγ Variant Influences Angiographic Outcome and 10-Year Cardiovascular Risk in Male Symptomatic Coronary Artery Disease Patients	25.9 ± 0.11 (C/C), 26.3 ± 0.26 (C/G), 25.8 ± 0.60 (G/G)	55.7 ± 0.34 (C/C), 55.7 ± 0.74 (C/G), 57.0 ± 1.7 (G/G)	679; (540 Pro12Pro, 126 Pro/Ala, 13 Ala/Ala)	10 yr cohort, N/A	Ejection fraction, NYHA FC, Hypertension history, Prior MI, glucose, HDL, LDL, TG, CRP	The 12Ala allele was associated with less extensive focal (P = 0.001) and diffuse (P = 0.002) atherosclerosis and lower 10-year cardiovascular risk. Hazard ratios were 0.10 (95% CI 0.01–0.70, P = 0.02) for ischemic heart disease and 0.24 (0.08–0.74, P = 0.013) for vascular death, per each added copy of 12Ala, respectively.	Carriers of the 12Ala allele have less widespread CAD and are considerably protected against 10-yr cardiovascular morbidity and mortality. These long-term findings in patients with manifest CAD support an important role of PPARγ in determining vascular risk.

Table 2.1 PPARγ2 Literature Review of SNP (rs1801282 [Pro12Ala]) (*cont)*										
Author/ Journal/ Year	**Variables**		**Title**	**Population**				**Measured Outcomes**	**Results**	**Conclusion**
	Gene	**SNP**		**BMI**	**Age**	**No./Gender/ Health/Ethnic**	**Diet/ Duration**			
Lindi et al., Diabetes, 2002 [91]	PPARγ2	Pro12Ala	Association of the Pro12Ala Polymorphism in PPARγ2 with 3-Year Incidence of T2DM and Body Weight Change in the Finnish Diabetes Prevention Study	31.1 ± 4.6	40-68	490 (161 M, 329 F), pre-diabetic; Finnish	7x/yr dietary consult w RD, and 3-mo FU appts. Diet Rx: <30% FAT, <10% SatF, 15g fiber/1k kcal. 30 min/d EX suggested daily for 36 months	BW, BMI, WC, HC, glucose, insulin, 4-day food recall logs	Ala/Ala control group > risk for T2DM vs wild-type (P<0.05). After 36 months, Ala/Ala genotypes sig reduced BW vs wild type (P<0.043). Pro/Ala also sig reduced BW vs wild type @ 36 mo (P<0.05)	Ala allele in codon 12 of the PPAR-γ2 gene was associated with the development of T2DM in the high-risk IGT pop. In contrast, Ala12Ala subjects who followed an intensive diet and EX protocol lost sig more BW vs subjects with the Pro12Pro genotype, and none of subjects with the Ala12Ala genotype developed T2DM.
Nicklas et al., Diabetes, 2009 [90]	PPARγ2	Pro12Ala	Genetic variation in the peroxisome proliferator-activated receptor-G2 gene (Pro12Ala) affects metabolic responses to weight loss and subsequent weight regain	31.8 (25-40)	61 wild type; 57 Ala12 allele carriers	70 F, post-menopausal (Pro/Pro, n=56) (Pro/Ala and Ala/Ala, n=14); Caucasian	LCD < 250-350 kcal/day; 24weeks	BF%, FM, FFM (DXA), SWAT and VWAT (single slice tomography b/w L-4 and L-5), VO2max, RMR, glucose, insulin	Pro/Pro -8.4 kg, Pro/Ala -7.6 kg; BMI, BF%, visceral and subcutaneous FM, RMR, VO2max, substrate oxidation, glucose and insulin responses. No diff b/w genotypes. Weight regain after 12mo sig greater in Ala allele carriers	Pro12Ala show Ala allele, as a result of a lower binding affinity and reduced ability to transactivate promotors, is assoc. w/ reduced capacity to activate transcription and mediate adipogenesis. It is possible that WL may have resulted in less efficient stimulation of PPARγ2 target genes w/ Ala causing less adipogenesis and thus greater insulin sensitivity.

Table 2.1 PPARγ2 Literature Review of SNP (rs1801282 [Pro12Ala]) (*cont)*										
Author/ Journal/ Year	**Variables**		**Title**	**Population**				**Measured Outcomes**	**Results**	**Conclusion**
	Gene	**SNP**		**BMI**	**Age**	**No./Gender/ Health/Ethnic**	**Diet/ Duration**			
Curti et al, MetS and Rel Dis-orders, 2013 [116]	FTO PPARγ2 ApoA1	FTO: T/A, PPARγ2: Pro12Ala, ApoA1: -75G/A	FTO T/A and Peroxisome Proliferator-Activated Receptor-G Pro12Ala Polymorphisms but Not ApoA1 -75 Are Associated with Better Response to Lifestyle Intervention in Brazilians at High Cardiometabolic Risk	30.4 ± 0.48	56.6 ± 0.99	138, CMD risk, 90.6% MetS; Brazilian	Group 1: 850mg metformin 2x/d + lifestyle mod. Group 2: 16 sessions on diet, EX, and behavior mod. Meeting 8x FU. All treatment groups <500-1000 kcal TEE per AHA rec for WL 36 weeks	BW, BMI, WC, BP, CRP, adipocytokines, 3-day food recall records	Anthropometric measurements, 2-hr plasma glucose, insulin, HDL-C, and ApoB improved significantly for all subjects, regardless of genotype.	In Brazilian individuals, the FTO T/A polymorphism induces a favorable impact on inflammatory status and glucose metabolism. The Pro12Pro PPARγ2 genotypes correlate with a more favorable lipid profile, while the Ala allele carriers exhibited decreased BP (P<0.001).
Goyenechea et al., Br J Nutr, 2006 [117]	PPARγ2 IL-6	PPARγ2: Pro12Ala IL-6: -174G>C	Weight regain after slimming induced by an energy-restricted diet depends on interleukin-6 and peroxisome-proliferator-activated-receptor-gamma2 gene polymorphisms	35.8	34.7	67 (45 W, 22 M); Obese BMI = 35.8±4.8; Caucasian	~500kcal < TEE; AHA diet for WL (55% CHO, 15% PRO, 30% FAT) for 70d; 1yr (62wk) FU	BW, BMI, FM, FFM, Blood sample (IL-6, PPARγ2), 3-day food records	The C allele of the -174G>C IL-6 gene was more frequently observed (P<0.032) in subjects with successful WM (<10% weight regain). The C allele partially protected against weight regain (OR 0.24; P<0.049), while the conjoint presence of both gene variants (C+ in IL-6 and Ala+ in PPARγ2) further augmented WM (OR 0.19; P<0.043).	The C allele of the -174G/C SNP gives protection against weight regain. The presence of the Ala allele of the PPARγ2 together with the C allele strengthens this protection. These findings support a role for these polymorphisms on weight regulation and suggest a synergetic effect of both IL-6 and PPARγ2 variants on WM after following WL diet.

Table 2.1 PPARγ2 Literature Review of SNP (rs1801282 [Pro12Ala]) (*cont)*

AHA: American Heart Association, CHO: Carbohydrate, PRO: Protein, RD: Registered Dietitian, CAD: Coronary Artery Disease, CMD: Cardiovascular Metabolic Disease, NYHA-FC: New York Heart Association Functional Class, HDL-C: High Density Lipoprotein Cholesterol, LDL: Low Density Lipoprotein, TG: Triglyceride, MI: Myocardial Infarction, TEE: Total Energy Expenditure, REE: Resting Energy Expenditure, RMR: Resting Metabolic Rate, WHR: Waist Hip Ratio, BW: Body Weight, BMI: Body Mass Index, BF%: Body Fat Percentage, BP: Blood Pressure, SWAT: Subcutaneous White Adipose Tissue, VWAT: Visceral White Adipose Tissue, LCD: Low Calorie Diet, EX: Exercise, MetS: Metabolic Syndrome, T2DM: Type 2 Diabetes Mellitus, CRP: C-Reactive Protein, MUFA: Monounsaturated Fatty Acid, PUFA: Polyunsaturated Fatty Acid, FM: Fat mass, FFM: Fat-free mass, WC: Waist Circumference, HC: Hip Circumference, WM:Weight Management, WL: Weight Loss, FU: Follow Up, OR: Odds Ratio, M: Male, F: Female

Table 2.2 FABP2 Literature Review of SNP (rs1799883 [Ala54Thr])

Author/ Journal/ Year	Variables		Title	Population				Measured Outcomes	Results	Conclusion
	Gene	SNP		BMI	Age	No./Gender/ Health/Ethnic	Diet/ Duration			
Martinez -Lopez, Nutrition, 2013 [100]	FABP2	Ala54Thr	Effect of Ala54Thr polymorphism of FABP2 on anthropometric and biochemical variables in response to a moderate-fat diet	32.7 ± 6.1	38.6+/- 11.3	109 (20 M+89 F); Hispanic	8 weeks: -500kcal/d, 30% FAT, (<7% SatF, 10–15%MUF, 10%PUF), 15%PRO, 55% CHO	BW, BF%, WC, HC, RMR, BP, glucose, insulin, lipid profile, CRP. 24-hr recall dietary records	Thr54 allele carriers showed sig decrease in WL, BMI, WC, WHR, and CRP ($P < 0.05$). After RMR was adjusted, the decreases in WC, WHR, and CRP remained sig bw the 2 genotypes.	Thr54 allele carriers experienced more favorable overall responses to a moderate-fat diet.
de Luis et al., Diabetes Res Clin Pract, 2008 [118]	FABP2	Ala54Thr	Influence of Ala54thr polymorphism of FABP2 on weight loss and insulin levels secondary to two hypocaloric diets: a randomized clinical trial	34.3	46.5	204(50M+154 F); Non-diabetic outpatient; n/a	Diet1: LF (1500kcal/d; 52%CHO/ 20%PRO/ 27%FAT) Diet2:LC (1507kcal/d; 38%CHO/ 26%PRO/ 36%FAT) + Aerobic EX 60min/3x/wk for 12wks	BW, BP, glucose, Lipoprotein, CRP, Insulin, lipid profiles; Leptin, Adiponectin, Resistin, TNF-a, IL-6	Diet1+WT: ↓ BMI, FM, WC, WHR, SBP, DBP, Glucose, TC, TG, Insulin; Diet2+WT: ↓ BMI, WT, FM, WC, SBP, DBP; Both+WT: ↓Leptin	Similar WL is associated with different changes, depending on the FABP2 genotype with both diets; WL is associated with a greater decrease in serum leptin concentration with LF diet

Table 2.2 FABP2 Literature Review of SNP (rs1799883 [Ala54Thr]) *(cont)*										
Author/ Journal/ Year	**Variables**		**Title**	**Population**				**Measured Outcomes**	**Results**	**Conclusion**
	Gene	**SNP**		**BMI**	**Age**	**No./Gender/ Health/Ethnic**	**Diet/ Duration**			
de Luis, Ann Nutr Metab, 2006 [119]	FABP2	Ala54Thr	Influence of ALA54THR Polymorphism of Fatty Acid Binding Protein 2 on Lifestyle Modification Response in Obese Subjects	34.1 ± 5.1	45.5+/-16.7	69 (14 M, 55 F), obese BMI>30, non-diabetic; Spanish	12 weeks: Mediterranean Hypocaloric diet (1,520 kcal; 52% CHO, 25% FAT, and 23% PRO). EX consisted of aerobic exercise at least 60min/3x/wk	REE, tetrapolar BIA, BP, BW, glucose, lipoprotein(a), CRP, insulin, HOMA-IR, lipid profiles adipocytokines (leptin, adiponectin, resistin, TNF-a, IL-6), 3 day food log	WL of -3.17+/-3.5 kg (3.5%). The % of WL responders was similar in both groups (89.2 vs. 90.6%). Carriers of the Thr54 allele had a diff response in that they had a sig ↓ in systolic BP and glucose levels, whereas the Ala54Ala carriers had a sig ↓ in FM, LDLc, and leptin	WL, BC, and biomarkers of metabolic health are associated with different correlations, depending on FABP2 genotype.
Takakura, Diab Res Clin Practice, 2005 [120]	FABP2	Ala54Thr	Thr54 allele of the FABP2 gene affects resting metabolic rate and visceral obesity	32.9 ± 5.8	58.4 ± 9.6	80 F treatment group (obese); 146F control group (healthy); Japanese	28 weeks: 1200 kcal/day (60% CHO, 20% fat)	BW, BMI, RMR, VWAT, SWAT (via CT scan), WHR, insulin, HOMA-IR, HbA1C, 7 day food records	Thr54 carriers, adjusted RMR was sig lower than the Ala54 wild type. Thr54 carriers showed sig inc WC post diet and EX therapy vs subjects with Ala/Ala genotype. Thr54 carriers demonstrated greater BW at 20 y/o vs Ala/Ala genotypes	Thr54 allele carriers are associated with lower adjusted RMR, resistance in reducing VWAT and early onset of obesity in Japanese obese women
Weiss EP et al., Am JClin Nutr; 2007 [121]	FABP2	Ala54Thr	FABP2 Ala54Thr genotype is associated with glucoregulatory function and lipid oxidation after a high-fat meal in sedentary nondiabetic men and women	29.2 ± 4.1	58 ± 6.2	50 M sedentary non-smoking; 72F post-menopausal; n/a	LF diet, RD class 2x/wk 6wks pre-trial	BW, FM, FFM (DXA), BMI, VO2max, OGTT, insulin, lipid profiles, TEE, 7 day food records	Thr54 carriers < glucose tolerance (P=0.05), ISI (P=0.02), and higher fasting glucose (P=0.03) and OGTT insulin AUC (P=0.03) vs Ala/Ala. Thr54 carriers have inc postprandial lipid OX rates (P=0.01)	Sedentary nondiabetics on a LF diet, Thr54 carriers have lower glucose tolerance and insulin action, and higher lipid oxidation rates than Ala54 homozygotes. This may suggest glucoregulatory dysfunction in Thr54 allele carriers.

Han, J Exerc Nutr Biochem 2013 [122]	FABP2	Ala54Thr	Effects Ala54Thr polymorphism of FABP2 on obesity index and biochemical variable in response to a aerobic exercise training	25.6 ± 5.7 (AA), 26.4 ± 10.6 (AT/TT)	45.9 ± 7.4 (AA), 47.3 ± 7.8 (AT/TT)	243W, abdominally obese, Korean	12 wk Aerobic EX (2x/wk 20 min stretch, 60 min walking + dance) gradual inc intensity	BW, BMI, WHR, VWAT and SWAT (area), LM, OGTT, HOMA-IR, NEFA, HDL, LDL, LPL, VO2max, REE, 24hr food recall	Ala54Ala and 54Thr carriers sig decreased BW (P<0.001), BMI (P<0.001), %BF (P<0.001), WC (P<0.001), WHR (P<0.001), LM (AA p<0.022; AT/TT P<0.001), RHR (P<0.001), VWAT (AA p<0.005; AT/TT p<0.001), SWAT (P<0.001), insulin (AA p<0.005; AT/TT p<0.001) and sig increased VO2max (P<0.001). AA sig decreased NEFA (P<0.05), fasting glucose (P<0.05), OGTT (P<0.05) and sig increased HDL (P<0.005). AT/TT sig decreased SBP (P<0.001), DBP (P<0.01), LPL (P<0.05), LDL (P<0.001), HOMA-IR (P<0.01)	Aerobic EX in middle-aged Korean women with visceral obesity improves BC, cardiorespiratory fitness, blood lipids, fasting glucose and HOMA-IR regardless of the FABP2 Ala54Thr SNPs

TEE: Total Energy Expenditure, REE: Resting Energy Expenditure, DBP: Diastolic Blood Pressure, SBP: Systolic Blood Pressure, TG: Triglyceride, TC: Total Cholesterol, LF: Low Fat, WT: Wild Type, BC: Body Composition, BW: Body Weight, BMI: Body Mass Index, %BF: Body Fat Percentage, WC: Waist Circumference, HC: Hip Circumference, CRP: C-Reactive Protein, OX: Oxidation, EX: Exercise, MUFA: Monounsaturated Fatty Acid, PUFA: Polyunsaturated Fatty Acid, FM: Fat mass, FFM: Fat-free mass, OGTT: Oral Glucose Tolerance Test, SWAT: Subcutaneous White Adipose Tissue, VWAT: Visceral White Adipose Tissue, LM: Lean Mass, WHR: Waist Hip Ratio, HOMA-IR: Homeostatic Model Assessment of Insulin Resistance, NEFA: Non Esterified Fatty Acid, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, LPL: Lipoprotein Lipase, RHR: Resting Heart Rate, SNP: Single Nucleotide Polymorphism, M: Male, F: Female

Table 2.3 ADRB3 Literature Review of SNP (rs4994 [Trp64Arg])

Author/ Journal/ Year	Variables		Title	Population				Measured Outcomes	Results	Conclusion
	Gene	SNP		BMI	Age	No./Gender/ Health/Ethnic	Diet/ Duration			
Shiwaku et al., Int J Obes Relat Metab Disord, 2003 [123]	ADRB3	Trp64Arg	Difficulty in losing weight by behavioral intervention for women with Trp64Arg polymorphism of the beta3-adrenergic receptor gene	24.8	54.3 ± 7.9	76 F; Healthy; Japanese	↓ 10% dietary intake + 7000 steps / day for ~90days	BW, BMI, WC, HC, REE, HDL, LDL, TG, insulin, glucose, leptin, HOMA-IR	At baseline BMI, BW, BF, WC, HC, Arm skin fold, REE, lipid and glucose profile no sig diff by genotype; ↓BW 69% (Trp/Trp) and 48% (Trp64Arg); Sig diff HDL and LDL in both genotypes	Trp64Arg mutation of ADRB3 > difficulty in WL through behavioral intervention although it is not related to obesity-related phenotypes and REE prior to intervention

Table 2.3 ADRB3 Literature Review of SNP (rs4994 [Trp64Arg]) *(cont)*										
Author/ Journal/ Year	**Variables**		**Title**	**Population**				**Measured Outcomes**	**Results**	**Conclusion**
	Gene	**SNP**		**BMI**	**Age**	**No./Gender/ Health/Ethnic**	**Diet/ Duration**			
de Luis et al., Ann Nutr Metab, 2009 [124]	ADRB3	Trp64Arg	Influence of Trp64Arg polymorphism of beta 3-adrenoreceptor gene on insulin resistance, adipocytokines and weight loss secondary to two hypocaloric diets	34.7	45.8	193 (48 M+145 F), (172 Trp/Trp, 21 Arg64 carriers); (96 Diet I, 97 Diet II), Obese, Non-diabetic; n/a	Diet1: LF (1500kcal/d; 52%CHO/20%PRO/27%FAT) Diet2:LC (1507kcal/d; 38%CHO/26%PRO/36%FAT) + Aerobic EX 60mins/3x/wk for 12wks	BW, BP, FM, FFM, WC, WHR, RMR, VO2, glucose, Lipoprotein (a), CRP, Insulin, HOMA, LDL, HDL, TG; Leptin, Adiponectin, Resistin, TNF-a, IL-6	In Trp/Trp carriers BMI, WL, FM, WC, SBP, glucose, TG, insulin, HOMA and leptin sig decreased regardless of the diet type. In Arg64 carriers, this was the case for BMI, WL, WC, FM and leptin. Only leptin had a sig ↓in the wild-type group (diet I 13.7%, diet II 26.3% ($P<0.05$ for both). In Arg64 carriers, leptin decreased as well (diet I 22.5%, diet II 30.1%, $p<0.05$ for both).	The metabolic effect of mild WL by 2 hypocaloric diets is greatest in Trp/Trp wild type subjects. Improvement in glucose, insulin, and HOMA-IR is better in Arg64 allele carriers.
Nakamura et al., Nutr Res, 2000 [125]	ADRB3	Trp64Arg	Association between ADRB3 polymorphism and a lower reduction in the ratio of visceral fat to subcutaneous fat area during weight loss in Japanese obese women	28.7	48.1	90 F (50 premenopausal, 40 post); obese; Japanese	12 weeks: LCD 1400kcal/day; 1.5g/BW (kg) PRO, 30g FAT, 20g fiber. Ex: walking 60 min, 3-7x/week @ 50% VO2max	VWAT, SWAT (MRI), TC, HDL, LDL, FM, FFM, TG, glucose, insulin	Obese premenopausal Arg64 carriers ↓ VWAT/SWAT ratio, but not Trp64 homozygotes ($p=0.009$). Absolute changes in VWAT in 5 Arg64 homozygotes was sig less than those in 50 obese Trp64 homozygotes	An AA Arg substitution at residue 64 of ADBR3 may play an important role in regulation of VWAT and SWAT distribution in Japanese obese women.
Tahara et al, Obesity Research & Clin Practice, 2011 [126]	ADBR3	Trp64Arg	Influence of ADRB3 Trp64Arg polymorphism on the improvement of MetS by exercise in Japanese middle-aged males	26.7 (T/T), 25.6 (T/A)	48 (T/T), 50 (T/A)	23 (T/T), 13 (T/A); MetS; Japanese	3mos, 10k step pedometer	WC, TG, HDL, SBP/DBP, BW, TC, LDL, fasting insulin	MetS improvement 21.7% (T/T) and 53.8% (T/A)	After adjustment for age, calorie limitation, and 10K+ and 12K+ steps/day during trial, the OR of Trp/Arg for improvement of MetS relative to Trp/Trp SNP were 5.1 ($p = 0.043$), 4.9 ($p = 0.051$), 3.7 ($p = 0.074$), and 5.0 ($p = 0.045$), respectively.

Table 2.3 ADRB3 Literature Review of SNP (rs4994 [Trp64Arg]) *(cont)*										
Author/ Journal/ Year	**Variables**		**Title**	**Population**				**Measured Outcomes**	**Results**	**Conclusion**
	Gene	**SNP**		**BMI**	**Age**	**No./Gender/ Health/Ethnic**	**Diet/ Duration**			
Rawson et al., Metabo-lism, 2002 [127]	ADRB3	Trp64Arg	No effect of the Trp64Arg beta(3)-adrenoceptor gene variant on weight loss, body composition, or energy expenditure in obese, Caucasian postmenopausal women	35.6 ± 6.3 (>27)	57.8 ± 6.6	34 F (19 carriers, 15 non Trp64Arg carriers), obese, postmenopausal, clinically healthy	~13.5±2.6 mos: 1200 kcal/d 55%CHO<30%FAT, <7%SatF, ~15%PRO; <200mg/d CHL)	BW, FM, FFM, REE, TEE, TEF, PAEE	All subjects ↓BW, BMI, BF%, FFM and FM (P<0.05) post-intervention. No sig diff detected between genotypes	Changes in body composition and energy expenditures were similar between carriers and non-carriers of the gene variant following WL. This suggests the presence of the Trp64Arg variant should not hinder weight reduction.
Kim OY et al., Int Jour Obesity, 2004 [128]	ADRB3 UCP3	ADRB3: Trp64Arg UCP3: -55C→T	Additive effect of the mutations in the b3-adrenoceptor gene and UCP3 gene promoter on body fat distribution and glycemic control after weight reduction in overweight subjects with CAD or metabolic syndrome	25.8 ± 0.26	53.6 ± 1.28	224 (163 TT, 61 Arg64 carriers) overweight/ obese, Korean	12 wk, -300 kcal/d TEE (60%CHO, 20%FAT, 20%PRO)	BW, BMI, BC (CT scan), HDL, LDL, VLDL, Insulin, TG, OGTT	All subjects lost ~ 5% in BW. Highest decreases in abdominal adipose tissue at L1 and L4 levels were observed in the 'wild-type' (TT-CC) group (P<0.001) and the second highest in 'only UPC3 promoter variant' (TT-CT) group (P<0.001). Both variant-carriers had the smallest reduction only in visceral fat area at L4. All subjects except both variant-carriers (TA-CT) had sig reductions in fasting glucose and FFA. The response areas of glucose (P<0.01) and insulin (P<0.05) were reduced largest in the 'wild-type' group (TT-CC) and second largest in the 'UCP3 promoter variant' (TT-CT) group	All subjects showed similar weight reduction after -300 kcal/d deficit for 12 wks. However, the beneficial effects on BF distribution and glycemic control (OGTT) were greatest in the 'wild-type' (TT-CC) group and smallest in 'both variants' (AA-TT) group. These effects were reduced in carriers with ADRB3 Arg64 allele carriers (TA/AA) than with UCP3 gene promoter variant (TT-CT).

Table 2.3 ADRB3 Literature Review of SNP (rs4994 [Trp64Arg]) *(cont)*

BC: Body Composition, BMI: Body Mass Index, BW: Body Weight, FM: Fat Mass, FFM: Fat Free Mass, BF%: Body Fat Percentage, WC: Waist circumference, HC: Hip circumference, HDL: High density lipoprotein, LDL: Low density lipoprotein, VLDL: Very Low Density Lipoprotein, TC: Total Cholesterol, TG: Triglycerides, HOMA: Homeostatic Model Assessment of Insulin Resistance, LCD: Low Calorie Diet, BP: Blood pressure, SBP: Systolic BP, DBP: Diastolic BP, MetS: Metabolic Syndrome, RMR: Resting metabolic rate, CRP: C-reactive protein, FFA: Free Fatty Acid, CAD: Coronary Artery Disease, WL: Weight Loss, VWAT: Visceral white adipose tissue, SWAT: Subcutaneous white adipose tissue, PAEE: Physical activity energy expenditure, OGTT: Oral Glucose Tolerance Test, TEE: Total Energy Expenditure, TEF: Thermic Effect of Feeding, CHO: Carbohydrate, PRO: Protein, CHL: Cholesterol, SatF: Saturated Fat, M: Male, F: Female

Table 2.4 ADRB2 Literature Review of SNPs (rs1042713 [Arg16Gly]) and (rs1042714 [Gln27Glu])

Author/ Journal/ Year	Variables		Title	Population				Measured Outcomes	Results	Conclusion
	Gene	SNP		BMI	Age	No./Gender/ Health/Ethnic	Diet/ Duration			
Ruiz et al., Obesity, 2011 [129]	ADBR2	rs1042714 (Gln/Glu) rs1042713 (Arg/Gly)	Role of beta(2)-adrenergic receptor polymorphisms on body weight and body composition response to energy restriction in obese women: preliminary results	34	36.7	78 F, Obese; Spanish	600kcal <RMR (55% CHO / 30% FAT / 15% PRO), RD consult 1x/wk for 12weeks	BW, BMI, FM, FFM, LM (DXA), RMR, 3-day food records	ADRB2 Glu27 allele carriers ↓ BW (P=0.002) and LM (P=0.001) but no sig diff in FM, WC, RMR in Glu27 allele carriers vs Gln/Gln wild type subjects.	The Gln27Glu polymorphism has a modulating effect on diet-induced changes on BW and BC, and should be considered in future treatments of obesity.
Saliba LF et al., Genetics and Molecul Biology, 2014 [130]	ADRB2 ADRB3 GHRL	ADRB2: rs1042714 rs1042713 ADRB3: rs4994 GHRL: rs69621 (Leu/Met)	Obesity-related gene ADRB2, and the response to a weight loss diet intervention in adult women	>30	20-50 (45% 30-39)	109 F, Obese, Brazilian, premenopausal, clinically healthy	7 weeks; <600kcal TEE	BW, BMI, SES	The WL intervention resulted in decreased BMI over the 7-week period ($P < 0.001$), for high and low SES ($p < 0.05$) and mainly for participants with 30-49 y	The intervention did not result in a GHRL statistically sig diff in WL bw WT or mutant carriers and although, the ADRB3 and polymorphisms did not moderate WL, the ADRB2 Glu27 allele carriers demonstrated a ↓BMI vs WT in the low SES (P=0.018) and the 30-39 y (P =0.036) groups, suggesting a role for this polymorphism related to BMI control.

Table 2.4 ADRB2 Literature Review of SNPs (rs1042713 [Arg16Gly]) and (rs1042714 [Gln27Glu]) *(cont)*										
Author/ Journal/ Year	**Variables**		**Title**	**Population**				**Measured Outcomes**	**Results**	**Conclusion**
	Gene	**SNP**		**BMI**	**Age**	**No./Gender/ Health/Ethnic**	**Diet/ Duration**			
Rauhio A., Maturitas, 2013 [131]	ADRB2 FTO	ADBR2: rs1042714 (Gln>Glu) FTO: rs9939609 (T>A)	Association of the FTO and ADRB2 genes with body composition and fat distribution in obese women	>30	~39	75 F; Clinically healthy, Obese, premenopausal	3mo:wt reduction+ 9mo: wt maintain; VLED	BW, BMI, WHR, BC (DXA)	Gln/Gln carriers of the ADRB2 gene had smaller gynoid fat-% compared with both the Gln/Glu and Glu/Glu carriers ($p = 0.050$ and $p = 0.009$, respectively). The Gln homozygotes had smaller total BF% and higher total LBM% than Glu homozygotes ($p = 0.018$ and $p = 0.019$, respectively).	ADRB2 genotype was associated with android/gynoid fat distribution. However, all women in the study group lost weight similarly independently of genotype. Neither the FTO nor ADRB2 genotype had statistically significant effect on weight reduction or weight maintenance.
Verhoef S., Physiology & Behavior , 2014 [132]	ADRB2 PPARγ2 FTO MC4R PPARD PPARγC1A	ADRB2: rs1042713 (Arg/Gly) PPARγ2: rs1801282	Genetic predisposition, dietary restraint and disinhibition in relation to short and long-term weight loss	32.0 ± 3.1	20-50	150 (39M + 111F), BMI 27-38, clinically healthy	8 wk VLED (50g CHO, 52g PRO, 7g FAT/day) 3 mo WM	BW, WC, HC, BC (Bod Pod)	All subjects reduced BW, BMI, FM, WC, HC after 5 mo ($p<0.001$) No significant differences in BW for ADRB2 rs1042713 and PPARD	During long-term WL, genetic effects are primarily regulated by changes in eating behavior.
Bea J.,Behav . Genet., 2010 [133]	ADRB2 ADRB3 ADRA2B	ADRB2: rs1042714 (Gln/Glu) ADRB3: rs4994 (Trp/Arg)	Lifestyle modifies the relationship between BC and adrenergic receptor genetic polymorphisms, ADRB2, ADRB3 and ADRA2B: A secondary analysis of a RCT of PA among postmenopausal women	25.3 ± 3.8	55.5 ± 4.8	148 normal, overweight, and obese, clinically healthy postmenopausal women 320 sedentary randomized in EX or CTRL group for secondary analysis	12 mo high intensity RE + mod impact weight bearing EX (75min/3x/ wk)	BW, BC (DXA)	No main effect of individual genes on change in BC, although interactions were observed for ADRB2 Glu allele carriers w increase in lean soft tissue (LST) in EX vs CTRL ($p=0.02$). No changes observed in Gln/Gln w EX. ADRB3: All participants increase in LST ($p<0.05$) w no sig diff between genotypes	Strong positive effect of EX on BC across all genotypes. Susceptibility to adverse BC changes in sedentary postmenopausal women suggest that changes with inactivity may be more profound in certain genetic backgrounds. Thus, EX may play a protective role against adverse genetic influences on obesity.

BW: Body weight, BMI: Body mass index, FM: Fat mass, FFM: Fat-free mass, LM: Lean mass, BF%: Body Fat Percentage, LBM%: Lean Body Mass Percentage, PA: Physical Activity, RD: Registered Dietitian, RE: Resistance Exercise, RMR: Resting metabolic rate, GHRL: Ghrelin, SES: Socioeconomic status, WC: Waist circumference, HC: Hip circumference, WHR: Waist Hip Ratio, BC: Body composition, VLED: Very low energy diet, CHO: Carbohydrate, PRO: Protein, WL: Weight loss, EX: Exercise, CTRL: Control, WT: Wild Type, M: Male, F: Female

Rationale for the Study

Gardner et al. [55] conducted a large scale, 12-month controlled randomized weight loss study for women: The A to Z Weight Loss Trial. Briefly, they compared four popular weight loss diets: Zone (40% kcal CHO, 30% kcal fat, 30% kcal protein), Atkins (<20 g/d CHO x 2-3 months, then ≤50 g/d CHO), LEARN (55-60% kcal CHO, <10% kcal saturated fat) and Ornish (≤10% kcal fat).

Based on the growing body of literature of the SNPs outlined in Tables 1-4, and specifically Gardner's study, Dopler-Nelson et al. [56] conducted a retrospective analysis of the A to Z trial data based on allele patterns for these candidate obesity genes and dietary group assignment. 101 out of 311 Caucasian participants from the A to Z trial gave consent to participate. 31 had been assigned to the Atkins diet, 32 to the Zone diet, 26 in the Ornish group, and 34 in the LEARN diet group. The four candidate genes selected for analysis were fatty acid binding protein 2 (FABP2 [Ala54Thr]), peroxisome-proliferator activated- receptor gamma 2 (PPARγ2 [Pro12Ala]), beta-2 adrenergic receptor (ADRB2 [Arg16Gly] and [Gln27Glu]), and beta-3 adrenergic receptor (ADRB3 [Arg64Trp]). Metabolic genotyping based on SNP allele variants was determined from buccal cheek swab DNA samples, and categorized participants as a "true" match or a "false" match from their A to Z trial diet. Participants in the appropriate dietary group (True Match) for their genotype allele pattern resulted in 2-3x greater BW reduction over 12 months compared to those in inappropriate dietary groups (False Match) for their metabolic profile (p=0.02). Women assigned to a genotype appropriate diet lost 5.3% of their initial body weight compared with 2.3% among those not matched to genotype. Additional findings were similar for reduced waist circumference (p=0.01), decreased triglycerides (p=0.007), and increased HDL (p= 0.01)

[56]. These findings indicate plausible cause for further investigation of potentially influential SNPs in candidate obesity-related genes (i.e. metabolic profiling) as a reliable model to predict the efficacy of an individual's response to a specific diet composition. As a result, greater improvements in body composition and biomarkers of health may be based on diet type and individual genotypes.

As a follow-up to replicate the findings of Dopler-Nelson's investigation of the A to Z trial, this study examined the genetic influence of SNP allele patterns in women assigned to a specified hypocaloric diet (AHA, CC-I, CC-II) for 24 weeks. Additionally, a structured exercise program was included in our study design, whereas an exercise protocol was not considered in the A to Z trial investigation.

CHAPTER III

METHODS

Study Design

Experimental Approach

This study was conducted as a randomized comparative effectiveness trial from November 2013 to May 2015, with retrospective analysis of genetic influence on weight loss. The weight loss intervention included a 6-month diet and exercise program. Participants were randomized to a control group, or one of three weight loss treatment groups. The treatment groups were assigned to a hypocaloric diet consisting of varying nutrient compositions as defined in Table 3.1. All weight loss treatment groups were assigned to the same exercise protocol for the duration of the study.

Table 3.1 Summary of Dietary Assignments

Diet	Kcals	Macronutrients	% Diet Content	g/d	Kcals/d	g/kg/d (90kg)
American Heart Association - High Carbohydrate / Low Fat Diet (AHA)						
1 Week	1,400 kcals/d	CHO PRO FAT	55 15 30	193 53 47	770 210 420	2.14 0.58 0.52
23 Weeks	1,500 kcals/d	CHO PRO FAT	55 15 30	206 56 50	825 225 450	2.28 0.62 0.56
Curves Complete I - Moderate Carbohydrate / High Protein / Low Fat Diet (CC-I)						
1 Week	1,400 kcals/d	CHO PRO FAT	30 45 25	105 158 39	420 630 350	1.17 1.75 0.43

Table 3.1 Summary of Dietary Assignments *(cont)*						
Diet	**Kcals**	**Macronutrients**	**% Diet Content**	**g/d**	**Kcals/d**	**g/kg/d (90kg)**
23 Weeks	1,500 kcals/d	CHO PRO FAT	30 45 25	113 169 42	450 675 375	1.25 1.88 0.47
Curves Complete II - Carbohydrate Restricted / High Protein / Moderate Fat Diet (CC-II)						
1 Week	1,400 kcals/d	CHO PRO FAT	20 45 35	70 158 54	280 630 490	0.78 1.75 0.60
23 Weeks	1,500 kcals/d	CHO PRO FAT	20 45 35	75 169 58	300 675 525	0.83 1.88 0.65

American Heart Association (AHA) Diet

Participants in the American Heart Association (AHA) program followed the AHA dietary guidelines for weight loss. In concurrence with this plan, subjects followed the phase 1 hypocaloric kcal intake diet (1,400 kcals/day) for one week, and the phase 2 higher kcal intake diet (1,500 kcals/day) for the following 23 weeks. The AHA macronutrient content for both phase 1 and 2 diets was 15% protein, 55% carbohydrate, 30% fat. Subjects assigned to the AHA group followed a booklet based nutrition plan designed using the Diabetic Exchange List (The Exchange Diet) developed by the American Dietetic Association [134].

Curves Complete I (CC-I) Diet

Participants in the CC-I group followed the Curves Complete diet administered online. CC-I subjects were provided with login and username instructions for the online nutrition management program. In concurrence with this plan, subjects followed the phase 1 hypocaloric kcal intake diet (1,400 kcals/day) for one week, and the phase 2 higher kcal

intake diet (1,500 kcals/day) for the following 23 weeks. The CC-I macronutrient composition for phase one (1400 kcal/day for 1 week) and phase two (1500 kcal/day for 23 weeks) of the diet was 45% PRO, 25% CHO, 20% FAT. A registered dietitian reviewed the higher protein diet and exercise plan with subjects at baseline. Additionally, CC-I participants received nutritional coaching sessions with the study coordinator or RD 1x/week for approximately 15 minutes to discuss any dietary challenges or concerns.

Curves Complete II (CC-II) Diet

Participants in the CC-II group followed the Curves Complete diet administered via a booklet based exchange diet similar to AHA, but with different food options to meet respective macronutrient requirements. In concurrence with this plan, subjects followed the phase 1 hypocaloric kcal intake diet (1,400 kcals/day) for one week, and the phase 2 higher kcal intake diet (1,500 kcals/day) for the following 23 weeks. The CC-II macronutrient composition for phase one (1400 kcal/day for 1 week) and phase two (1500 kcal/day for 23 weeks) of the diet was 45% PRO, 15% CHO, 30% FAT. A registered dietitian reviewed the higher protein diet and exercise plan with subjects at baseline. Additionally, CC-II participants received nutritional coaching sessions with the study coordinator or RD 1x/week for approximately 15 minutes.

Exercise Protocol

For all treatment groups (AHA, CC-I, and CC-II) the physical training protocol included three regular resistance circuit workouts and one circuit combined with Zumba workouts each week for 24 weeks, while maintaining a greater than 75% compliance record (72 out of 96 workouts). Attendance was recorded at each workout session in order to monitor compliance. The circuit equipment was located in the Exercise and Sports Nutrition

Laboratory (ESNL) at Texas A&M University. The circuit utilized the computerized CurvesSmart system (Curves International, Waco, TX, USA) equipped with software designed by MYTRAK (version 4.2.0.0, copyright 2004-2010, MYTRAK Health System, Mississauga, Ontario, Canada). The circuit consisted of 13 bi-directional hydraulic resistance exercise machines that worked all major muscle groups (i.e., elbow flexion/extension, knee flexion/extension, shoulder press/latissimus pull, hip abductor/adductor, chest press/seated row, horizontal leg press, squat, abdominal crunch/back extension, chest flies, oblique, shoulder shrug/dip, hip extension, and side bends). During the circuit workouts, subjects were instructed to complete as many repetitions as possible during a 30 second interval on each resistance machine. Between machines, subjects performed floor-based aerobic exercises or stepping exercise designed to maintain an elevated heart rate. Subjects performed the entire circuit twice during the 26-minute regular circuit workout. During the circuit combined with Zumba workout, subjects performed 1 minute of Zumba dance moves in between 1 minute of resistance exercise on each machine. All Zumba classes were taught by a certified Zumba instructor. Subjects were assisted with self-monitoring of heart rate in order to maintain an aerobic capacity between 60-80% of target heart rate by calculating age-predicted maximal heart rate (220-age). All subjects were provided with Polar FT heart rate monitors for the duration of the workout. Subjects were also advised to perform 5 minutes of whole body stretching after all circuit workouts. In addition to circuit training, subjects were instructed to walk for 10,000 steps/day on non-resistance circuit workout days (3x/week). All subjects in the treatment groups were provided with a pedometer to monitor and record steps on their physical activity log. In the event participants required travel outside the Bryan/College Station area,

they were provided with a travel pass valid for 30 days at any Curves franchise location. Workouts completed outside the ESNL facility were recorded upon return from travel.

Independent and Dependent Variables

The independent variables within the weight loss program were the 1) assigned dietary protocol – American Heart Association (AHA), Curves Complete-I (CC-I), or Curves Complete-II (CC-II) and 2) genetic match to diet based on metabolic profiles defined as *a*) Fat Trimmer, *b*) Carbohydrate Reducer, or *c*) Better Balancer. If a participant met the Fat Trimmer genotype profile, the diet is designed to contain ~50-60% CHO, ~30% FAT, and 15-20% PRO. This would optimally fit the assignment of the AHA diet, and thus a participant would be considered a True (T) genetic match to the AHA diet, and a False (F) match to the CC-I or CC-II diet. The Carbohydrate Reducer diet profile is designed to contain <30% CHO, ~30-35% FAT, and >40% PRO. This profile optimally fits the assigned CC-II diet, and thus a participant would be considered a True genetic match to CC-II and a False match to AHA or CC-I diet. The Better Balancer profile's diet is designed to contain ~30-40% CHO, ~30% FAT, and ~30% PRO. This nutrient makeup is similar to the "Zone diet" and as such, a Better Balancer was determined a True (T) match to the AHA and CC-I diets or a False match to the very low CHO CC-II diet.

Dependent variables included: body weight, hip and waist anthropometric measurements, resting energy expenditure (REE), body composition (DEXA), fasting clinical blood profiles (cholesterol [HDL and LDL], glucose, triglycerides, insulin), maximal cardiopulmonary exercise capacity (VO_2max), maximum upper and lower extremity strength capacity (1RM) and maximum isotonic strength endurance capacity (80% 1RM), standardized quality of life (SF-36), levels of physical activity (METs –

min/wk), and estimated dietary energy intake (kcal/day).

Testing Schedule

The study included a baseline testing session followed by 6 monthly testing sessions. Immediately following the baseline testing session, participants were allocated into American Heart Association (AHA), Curves Complete-I (CC-I), Curves Complete-II (CC-II), or the control (CTRL) group. Participants were randomized into one of the four groups: 3 weight management treatment groups (AHA, CC-I, CC-II) or CTRL based on age, body fat percentage, and body mass index (BMI: calculated as kg/m^2). Dietary intake and weekly physical activity (IPAQ), anthropometric measurements, resting energy expenditure (REE), body composition, serum clinical chemistry panels, whole blood counts and hormone concentrations, and quality of life were assessed at 0, 4, 8, 12, 16, 20 and 24 weeks to determine differences in weight reduction program effects. Maximal cardiopulmonary exercise capacity (Peak VO_2) and upper and lower body isotonic strength and endurance were assessed at 0, 12 and 24 weeks to ascertain chronic program effects on measures of fitness. Table 3.2 displays the general research design and time course for the testing session assessments.

Table 3.2 Overview of Research Design and Testing Schedule

Familiarization	*Baseline (T1)*	*4 Weeks (T2)*	*8 Weeks (T3)*	*12 Weeks (T4)*	*16 Weeks (T5)*	*20 Weeks (T6)*	*24 Weeks (T7)*
Familiarization Session Complete Paperwork Review Medical history Physical Exam Fasting Blood Determination of Qualifications to Participate Group Assignment: -Control (CTRL) -AHA -CC-I -CC-II Phase I – 1, kcals/d for 1 week Phase II – 1, kcals/d for weeks	Diet Record Review Body Weight Hip and Waist Measurements Resting Energy Expenditure DEXA[a] Scan Fasting Blood DNA Genotyping Maximal Cardiopulmonary Exercise Test 1RM[b] and 80% 1RM Isotonic Leg Press and Bench Press Measures Survey Completion[c] IPAQ[d]	Diet Record Review Body Weight Hip and Waist Measurements Resting Energy Expenditure DEXA[a] Scan Fasting Blood Survey Completion[c] IPAQ[d]	Diet Record Review Body Weight Hip and Waist Measurements Resting Energy Expenditure DEXA[a] Scan Fasting Blood Survey Completion[c] IPAQ[d]	Diet Record Review Body Weight Hip and Waist Measurements Resting Energy Expenditure DEXA[a] Scan Fasting Blood Maximal Cardiopulmonary Exercise Test 1RM[b] and 80% 1RM Isotonic Leg Press and Bench Press Measures Survey Completion[c] IPAQ[d]	Diet Record Review Body Weight Hip and Waist Measurements Resting Energy Expenditure DEXA[a] Scan Fasting Blood Survey Completion[c] IPAQ[d]	Diet Record Review Body Weight Hip and Waist Measurements Resting Energy Expenditure DEXA[a] Scan Fasting Blood Survey Completion[c] IPAQ[d]	Diet Record Review Body Weight Hip and Waist Measurements Resting Energy Expenditure DEXA[a] Scan Fasting Blood Maximal Cardiopulmonary Exercise Test 1RM[b] and 80% 1RM Isotonic Leg Press and Bench Press Measures Survey Completion[c] IPAQ[d]

[a]Dual Energy X-ray Absorptiometry; [b]Repetition Maximum; [c]Body Image questionnaires: Standardized quality of life (SF-36), Rosenberg Self Esteem Scale (RSES), Social Psychological Anxiety Scale (SPAS); [d]International Physical Assessment Questionnaire
AHA – American Heart Association Recommended Diet (Phase I 1,400 kcals/d, Phase II 1,500 kcals/d at 55% C, 15% P, 30% F) and Exercise Program
CC-I – Curves Complete I (Phase I 1,400 kcals/d, Phase II 1,500 kcals/d at 30% C, 45% P, 25% F) and Exercise Program
CC-II – Curves Complete II (Phase I 1,400 kcals/d, Phase II 1,500 kcals/d 20% C, 45% P, 35% F) and Exercise Program

Participant Eligibility

This research protocol was reviewed and approved by the University Institutional Review Board before initiation. Participants were recruited through advertisements in local newspapers, campus-wide electronic communication, and ESNL webpage advertisement. Interested participants were asked to contact the laboratory for an initial telephone prescreening interview. General entrance criteria included being an apparently healthy woman between ages of 18 and 60 years with a BMI greater than 22.5 and no recent participation in a diet or exercise program. Participants were not allowed to participate in the study if the subjects reported the following at baseline: a recent weight change of (±3.2 kg or ±7 lb) within 3 months; any uncontrolled metabolic or cardiovascular disorder, including known electrolyte abnormalities, heart disease, arrhythmias, diabetes, or thyroid disease, or a history of hypertension, hepatorenal, musculoskeletal, autoimmune, or neurological disease; taking any weight loss supplements and/or ergogenic levels of nutritional supplements that affect muscle mass, anaerobic exercise capacity (i.e. creatine, ergogenic levels of caffeine, HMB, etc.), anabolic/catabolic hormone levels (i.e. androstenedione, DHEA), or weight loss (i.e. ephedra, thermogenics) within 3 months; a history of pregnancy or lactation within the past 12 months or intention to become pregnant during the next 12 months; participation in a regular exercise program within the past 3 months; and any condition that is classified as high risk for cardiovascular disease according to American College of Sports Medicine criteria [135].

Familiarization Session

Individuals who met initial entrance criteria were invited to attend a familiarization session in which the details of the study were explained. During this session, participants

received written and verbal explanation of the study protocol, design, equipment, and testing procedures that would be required throughout the study. A registered dietitian (RD) provided instruction on accurate dietary record completion and estimation of food portion sizes. Subjects meeting eligibility criteria were informed of the study requirements and signed an informed consent statement in compliance with the Human Subjects Guidelines of the Texas A&M University. Potential study participant's height, weight, heart rate (HR), and blood pressure (BP) were attained and recorded on the general screening form upon completion of signing the informed consent.

Medical Monitoring

Potentially eligible participants filled out personal and medical history information at the familiarization session. Based on review of this information recorded on the general screening form, the study coordinator and on-site registered nurse (RN) determined whether the participant had met entry criteria to participate in the study. Information obtained during the familiarization session was reviewed by the research coordinator to determine if all requirements were met to participate in the study. Participants with a controlled medical condition were required to have their general practitioner approve and sign the physician's consent form prior to participation in the study.

Participant Selection

Figure 3.1 outlines the stratification of study participants. A total of 267 individuals responded to the study recruitment advertisements. Of these, 241 met the entrance criteria and were requested to attend familiarization sessions. During these sessions, 44 eligible participants did not consent to participate. 197 women were cleared to participate in the study, completed baseline testing and were randomized to one of four groups as further

explained in the study design below. Eighty-six women completed the 24-week study. The primary reasons participants dropped out of the study were due to time constraints, job and school related conflicts, transportation difficulties, and relocation.

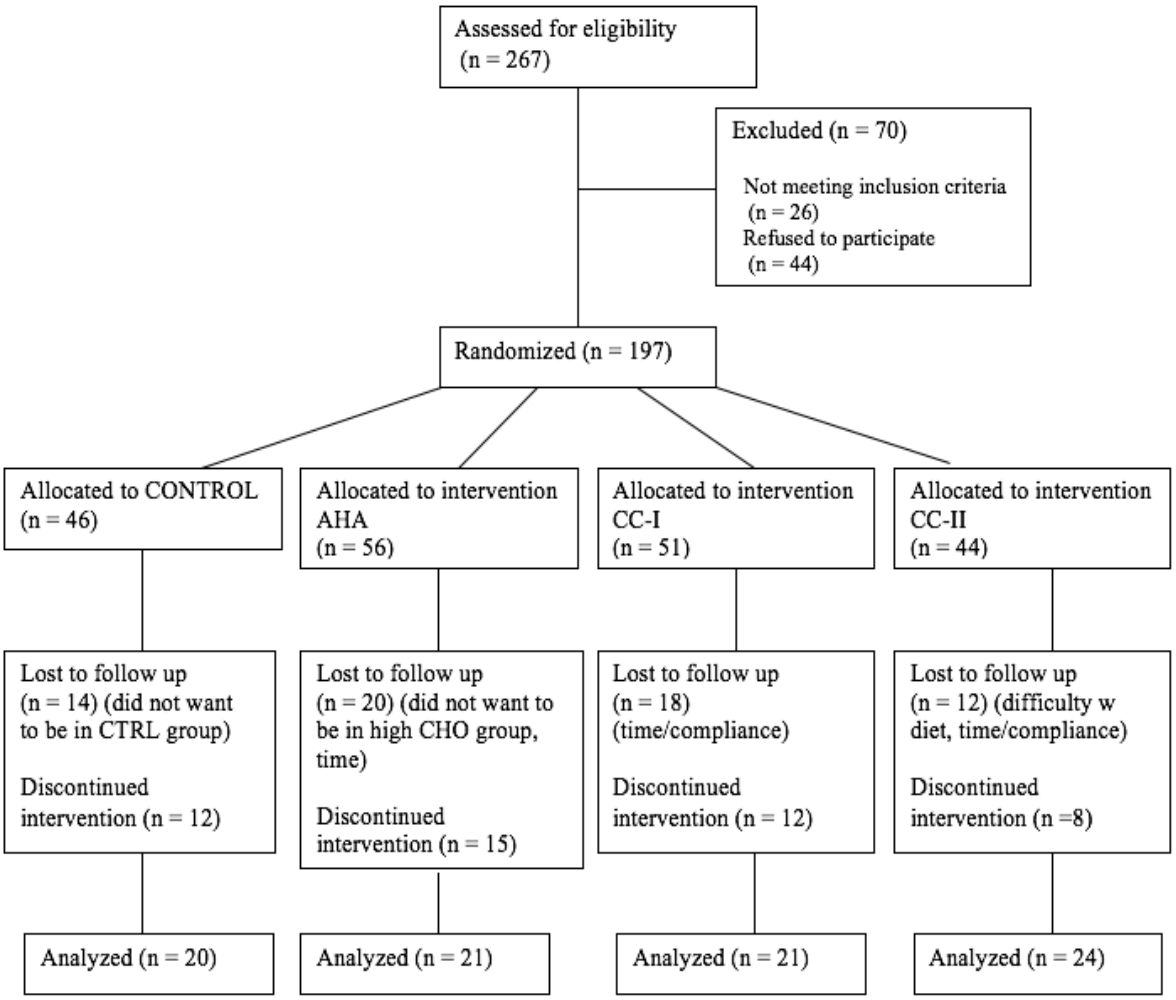

Figure 3.1 Participant Consort Diagram

Testing Session Requirements

Participants were instructed to refrain from exercise for 48 hours and fast for at least 12 hours prior to reporting to the ESNL for testing sessions. The baseline testing session, 12

week, and 24 week testing sessions were identical and consisted of dietary inventory review, weekly physical activity assessment [International Physical Activity Questionnaire (IPAQ)], anthropometric assessments (body mass, waist and hip circumference), resting energy expenditure, resting heart rate and systolic and diastolic blood pressure (BP), body composition analysis (DEXA), blood collection (metabolic panels, blood lipids, white and red blood cells), cardiorespiratory and muscular fitness assessments, psychosocial assessments [standardized quality of life (SF-36), Rosenberg Self Esteem Scale (RSES) and Social Physique Anxiety Scale (SPAS)]. Additional testing sessions occurred during the fourth, eighth, sixteenth, and twentieth weeks, and included all baseline measurements, excluding cardiorespiratory and muscular fitness assessments.

Testing Session Protocols

Metabolic Genotyping

Subject's buccal cheek swab samples were obtained in the ESNL at baseline (T1) to determine SNPs in obesity candidate genes FABP2 (rs1799883), PPARγ2 (rs1801282), ADRB3 (rs4994), ADRB2, (rs1042713) and (rs1042714), and sent to Interleukin Genetics (Waltham, MA) for metabolic profile analysis. Based on the SNPs of these genes, participants were matched according to their allelic profile to one of three metabolism efficiency categories: Fat Trimmer, Carb Reducer, or Better balancer according to Interleukin Genetics profiling algorithm.

Dietary Inventories

A registered dietitian instructed all subjects on precise documentation of food intake and accurate estimation of food portion size. Participants recorded all food and fluids consumed over a four-day period (including one weekend day) prior to each testing session.

Dietary inventories were reviewed with participants at each testing session to ensure accuracy, completeness, and legibility. Dietary information was then analyzed to determine the average caloric intake and macronutrient content using Food Processor 11.1.620 database Nutrition Analysis Software Version 11.1.0 (ESHA Nutrition Research, Salem, OR, USA). A registered dietitian review all analyzed dietary information.

Weekly Physical Activity Assessment

Physical activity patterns were quantified by assessing responses to the 7-day version of the International Physical Activity Questionnaire (IPAQ) [136-138]. This assessment tool evaluated the frequency and intensity of job-related physical activity; transportation physical activity; housework, house maintenance, and caring for family related physical activity; and recreation, sports, and leisure-time physical activity based on established metabolic equivalent (MET) levels for common activities. The IPAQ defined light physical activity as walking level intensities (3.3 METs), moderate physical activity as activities at a 4.0 MET level, and vigorous physical activity as activities at an 8.0 MET level. The IPAQ has been identified as a valid indicator of general changes in physical activity patterns [136-139].

Psychometric Assessments

Psychological self-assessments were administered with Body Image Questionnaires comprised of three sections. Participants completed the SF-36 Health-Related Quality of life (QOL) inventory [140], Rosenburg Self-Esteem (RSE) [141], and the Social Physique Anxiety Scale (SPAS) [142]. The SF-36 quality of life questionnaire has been validated for the measurement of psychosocial dimensions that may be influenced by general improvement in health and/or weight loss [143, 144]. The SF 36 assessed a number of

physical and mental components including physical functioning (i.e. the ability to perform most vigorous physical activities without limitation to health), role physical (i.e., ability to work and perform daily activities), bodily pain (i.e., limitations due to pain), general health (i.e., assessment of personal health), vitality (i.e., feeling of having energy), social functioning (i.e., ability to perform normal social activities), role emotion (i.e., problems with work or other daily activities), and mental health (state of feelings of peacefulness, happiness, and calm). The RSE measures self-esteem using a four-point Likert scale that ranges from one (strongly agree) to four (strongly disagree). Total scores range from 10 to 40; the higher the score, the greater the correlation with higher self-esteem. The Social Physique Anxiety Scale (SPAS) consists of 12 questions that use a five-point Likert scale that ranges from one (not at all true) to five (extremely true). Totals range from 12 to 60, with an increase in social physique anxiety correlating with an increase in score. This portion of the questionnaire is used to evaluate the level of self- anxiety as a result of the degree to which she perceives that others are devaluing her body. Several studies have shown the internal consistency (r=0.90), predictive validity, and the construct validity [142, 145-146].

Anthropometrics and Body Composition

Height and total body weight were determined according to standard procedures using a Healthometer (Bridgeview, IL, USA) self-calibrating digital scale with a precision of ± 0.02 kg. Hip and waist circumference were measured using a Gulick tension standardized measuring tape per guidelines established by the American College of Sports Medicine [135].

Body Composition

Bone mineral density (BMD) and body composition including fat mass and fat free mass, (excluding cranium) were measured using a Hologic Discovery W QDR series Dual Energy X-ray Absorptiometry (DEXA) system (Hologic Inc, Waltham, MA, USA) equipped with APEX software (APEX Corporation Software, Pittsburgh, PA, USA). Dual-Energy X-Ray Absorptiometry has been validated as an accurate method for body composition assessment [147-150]. Participants were informed of any inherent risks that could present from radiation exposure and completed a radiation exposure questionnaire prior to all scans. Quality control (QC) calibration procedures were performed on a spine phantom (Discovery W-CALIBER Model DPA/QDR-1 anthropometric spine phantom) prior to each testing session. During the DEXA scan, participants lay supine with as minimal movement possible. A low dose of radiation scanned their entire body for approximately six minutes. The DEXA regions of the body (right arm, left arm, trunk, right leg, and left leg) were differentiated by density for determination of fat mass (FM), fat-free mass (FFM), lean mass (LM), and bone mineral density (BMD). Radiation exposure from DEXA for the whole body scan is approximately 1.5 mR per scan. Mean test-retest reliability studies performed with this Hologic system have yielded mean coefficients of variation for total bone mineral content and total fat free/soft tissue mass of 0.31% to 0.45% with a mean intra-class correlation of 0.985 [151].

Resting Energy Expenditure

Resting energy expenditure assessments were conducted according to standard protocols using the Parvo Medics TrueMax 2400 Metabolic Measurement System (ParvoMedics, Inc, Sandy, UT, USA). This test was conducted in a fasted state with the

participants lying supine on an exam table. A clear metabolic canopy was placed over the subject's head and neck, so that resting inspired oxygen (O_2) and carbon dioxide (CO_2) expired could be determined to predict resting energy expenditure via indirect calorimetry. The participants remained motionless yet awake for approximately 20 minutes. Metabolic measurements were recorded after the first 15 minutes during a five-minute period in which principle variables, such that VO_2 mL/min, respiratory quotient (RQ), and kcal/D changed less than 5% [152]. Mean test-retest reliability studies on 14 participants from a previous study revealed test-retest correlations (r) of collected oxygen uptake range from 0.315 to 0.901 (mean=0.638) and coefficient of variation range from 8.2% to 12.0% (mean=9.9%) with a mean intraclass coefficient of 0.942; $p<0.001$ [153].

Blood Collection and Analysis Procedures

At least 10-hour fasted and whole blood and serum samples were collected using standard phlebotomy techniques. Approximately 20-24 mL venous blood were obtained prior to each testing session in BD Vacutainer EDTA and SST tubes for analysis (BD Franklin Lakes, NJ, USA). Whole blood samples were analyzed for complete blood counts with platelet differentials utilizing an Abbott Cell Dyn 3500 automated hematology analyzer (Abbott Laboratories, Abbott Park, IL, USA). Serum samples were obtained by centrifugation at 3500 rpm for 10 minutes in a Megafuge 40R (Unity Lab Services Thermo Fisher Scientific, Asheville, NC, USA). Samples were then aliquoted under a Class II A2 Biological Safety Cabinet (Labconco, Kansas City, MO, USA) and stored at -80C in an Innova U725 Ultra-Low Temperature Freezer (USA Scientific, Ocala, FL, USA). Serum samples were analyzed for a metabolic panel of fasted triglyceride concentrations, CHL (total cholesterol, LDL, and HDL), and glucose concentrations using the COBAS® c-111

analyzer (Roche Diagnostics, Basel, Switzerland). Fasting insulin was assayed in duplicate via a commercially available Enzyme Linked Immunosorbent assay (ELISA) kit (No. 80-INSHU-E10, ALPCO, Salem, NH) using a BioTek ELX-808 Ultramicroplate reader (BioTek Instruments Inc, Winooski, Vermont) at an optical density of 450 nm against a known standard curve using standard procedures with BioTek Gen5 Analysis software (BioTek Instruments Inc, Winooski, VT). The intra-assay coefficient of variation has been shown to range from 2.9% to 6.2%, with an inter-assay coefficient of variation range of 5.4% to 8.6% (ALPCO, Salem, NH). The homeostasis Model Assessment for insulin resistance (HOMA-IR) was calculated as the product of fasting insulin times fasting glucose expressed in standard units divided by 405 [154].

Cardiopulmonary Efficiency

Resting heart rate was determined by palpitation of the radial artery and resting blood pressure was assessed in the supine position utilizing a mercurial sphygmomanometer (American Diagnostic Corporation, model #AD-720, Hauppuage, NY, USA) using standard procedures [135].

Maximal Cardiopulmonary Exercise Test

Cardiopulmonary exercise tests were performed at baseline, 12 weeks, and 24 weeks by ESNL graduate research assistants in accordance to Graded Exercise Test (GXT) standard procedures adherent the American College of Sports Medicine (ACSM) *Guidelines for Exercise Testing and Prescription* [135]. Maximal Cardiopulmonary exercise tests (peak VO_2) were performed utilizing the Bruce treadmill protocol [155]. Standard test termination criteria were utilized to assess maximal volitional fatigue [135]. The Nasiff Cardio Card electrocardiograph (Nasiff Associates, Inc, Central Square, NY, USA) was used to assess

cardiac rhythm and function using a standard 12-lead arrangement [135]. Electrode sites were cleansed with a sterile alcohol pad in a circular motion. Once the site was dry, electrodes were placed on the 4th intercostal space at the right sternal border (V1), the 4th intercostal space at the left sternal border (V2), equidistant between V2 and V4 (V3), the 5th intercostal space at the mid- clavicular line (V4), the 5th intercostal space at the anterior axillary line (V5), the 5th intercostal space at the midaxillary line (V6), the right subclavicular fossa (RA), the left subclavicular fossa (LA), the right abdomen (RL) and left abdomen (LL) line. While the subject was in a supine position, resting blood pressure, heart rate, and the 12-lead ECG were obtained. The 12-lead ECG was reviewed to ensure that no contraindications for exercise testing were present based on the ACSM guidelines [135]. The participant was then asked to stand and step onto the treadmill. Standing blood pressure, heart rate, and a 12-lead ECG was obtained and reviewed for accuracy and assessment of potential abnormalities. A sterile mouthpiece, attached to a head harness, was then secured on the participant and a nose clip placed on their nose. Expired gases were collected using a ParvoMedics 2400 TrueMax Metabolic Measurement System (ParvoMedics Inc, Sandy, UT, USA). Gas and flow sensors were calibrated before testing and were found to be within 3% of previous calibration points. Once the participant was ready to begin the GXT protocol, the participant was instructed to straddle the treadmill with both legs while the treadmill was turned on to a speed of 2.0 mph and at a 0% grade. The participant then stepped onto the tread belt while holding the handrails with both hands. Once comfortable walking on the treadmill, the participant was instructed to let go of the handrail and begin walking freely.

Table 3.3 Treadmill Bruce Protocol

Stage	*Speed (MPH)*	*Grade (%)*	*Duration (minutes)*	*METS*
Warm-up	2.0	0	2	3.3
1	1.7	10	3	4.5
2	2.5	12	3	6.5
3	3.4	14	3	9.7
4	4.2	16	3	13.5
5	5.0	18	3	17
6	5.5	20	3	20.5

Participants performed the Bruce treadmill protocol [155] following the speeds and grades delineated in Table 3.3. Heart rate (HR), ECG tracings, and expired gases were monitored continuously throughout the GXT. Blood pressure (BP) and ratings of perceived exertion (RPE) were obtained toward the end of each 3-minute stage. Subjects were encouraged to exercise to their maximum aerobic capacity unless they experienced clinical signs that required test termination as stated by the ACSM *Guidelines for Exercise Testing and Prescription* [135]. Symptoms may include a decline in systolic blood pressure > 10 mmHg from baseline, angina, ataxia, dizziness, syncope, cyanosis, nausea, dangerous dysrhythmias (ventricular tachycardia, supraventricular tachycardia, new atrial fibrillation, or A-V block, increasing or multi-form premature ventricular contractions), an excessive rise in systolic blood pressure over 250 mmHg or diastolic over 115 mmHg, chronotropic impairment, technical difficulties of the ECG or metabolic monitoring systems, or other signs or symptoms requiring termination of the test. Voluntary maximal exertion was indicated by re-grabbing the treadmill handrails. The test was then immediately terminated and the participant continued an active recovery period for three minutes followed by a three-minute seated recovery period. Heart rate, blood pressure, and ECG were obtained during both recovery stages. Table 3.3 describes the Bruce Protocol for stress test methods.

Isotonic Strength Tests

Absolute strength measured by 1RM was determined using an isotonic Olympic bench press (Nebula Fitness, Versailles, OH, USA) and a standard hip sled/leg press (Nebula Fitness, Versailles, OH, USA) in accordance with the guidelines provided by the National Strength and Conditioning Association (NSCA). Hand positioning on the bench press and foot and seat position on the hip sled/leg press were standardized between trials. Muscular endurance was determined by performing repetitions to failure at 80% of 1RM load on the bench press and leg press using standard lifting techniques and testing criteria [156]. All exercise testing sessions were conducted using standardized ACSM guidelines and NSCA procedures, and were supervised by certified laboratory assistants experienced in strength exercise testing.

To test for upper body strength and endurance, participants performed a one repetition maximum (1 RM) test on the isotonic bench press and the Nebula Fitness (Versailles, OH, USA) Olympic Power Station (#1005). Participants performed a warm-up (2 sets of 10 repetitions at approximately 50% of anticipated 1RM) followed by progressive lifts starting at an estimated 70% of the anticipated 1RM. A 2-minute rest interval was required between each set. Load was increased by 5-10 lbs until the 1RM was reached. Once the 1RM was attained, subjects performed as many repetitions as possible with 80% of their 1 RM effort. Following the upper body strength testing, lower body strength testing was performed. Participants rested for 5 minutes, then performed a warm up of 10 repetitions at approximately 50% of anticipated maximum on the Nebula 45° Leg press. Participants then performed 5 successive lifts on the leg press at their estimated 70% of 1RM and increased by

25-45 lbs. until 1RM was attained. Once the 1RM was achieved, subjects performed continuous repetitions to failure 80% of their 1 RM effort. Test-retest reliability of performing these strength tests on resistance-trained subjects in the ESNL have yielded low mean coefficients of variation and high reliability for the bench press (1.9%, intraclass r=0.94) and leg press/hip sled (0.7%, intraclass r=0.91) [157].

Statistical Methods

Only subjects who completed the 24-week trial were included in the T x D (Time x Diet) analyses. Subjects who completed T2 but did finish the study were included in the T x M (Time x Match) weight loss analysis to ascertain whether N-size may influence results. Missing data were replaced using the last observed value method or by replacing missing values with the series mean method. Baseline demographic data were analyzed by one-way Analysis of Variance (ANOVA). Data were normally distributed. Study data were analyzed by Multivariate Analysis of Variance (MANOVA) with repeated measures (IBM SPSS Statistics version 22.0.0.0, SPSS Inc, Chicago, IL.). Overall MANOVA effects were examined using Wilks' Lambda time and group x time p-levels as well as MANOVA univariate group effects. Greenhouse-Geisser univariate tests of within of within-subjects time and group x time effects and between-subjects univariate group effects were reported for each variable analyzed within the MANOVA model. In some instances, repeated measures ANOVA was run on variables not included in a MANOVA design with univariate group, time, and group x time interaction effect reported. Variables with baseline differences determined by ANOVA were analyzed using analysis of covariance (ANCOVA). Delta values or percent difference were calculated and analyzed on select variables by ANOVA for repeated measures to assess changes from baseline values. Delta values were calculated by

subtracting the first testing session (T1) from later testing sessions (T7-T1). Percent differences were calculated by subtracting T1 from the later testing session, then performing division by T1 followed by multiplication by 100 [(T7-T1)/T1•100]. Confidence Intervals (CI) were reported for significant differences in group mean deltas. The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated by ($\frac{\boldsymbol{Glucose\ x\ Insulin}}{\mathbf{405}}$) when glucose is expressed in mass units (mg/dL) and insulin is expressed in μIU/ml.

Data were considered statistically significant when the probability of type I error was 0.05 or less and statistical trends were considered when the probability error ranged between >0.05 to <0.10. If a significant group, treatment and/or interaction alpha level was observed, Tukey's Least Significant Difference (LSD) post hoc analyses were performed to determine where significance was obtained. Power analysis of previous studies using similar designs and subject populations indicated that a sample size of 30 subjects per group yielded high power (>0.8) for delta values of 0.75 to 1.25 for weight and fat loss. Data are presented as means ± standard deviation (SD), and group means ± standard error of the mean (SEM).

CHAPTER IV

RESULTS

Results

Eighty-six apparently healthy but sedentary women (age 37.5±13.4 years; height 163.7±6.9 cm; weight 82.0±16.8 kg; BMI 30.5±5.9 kg/m^2; body fat 31.4±9.7 kg) completed the 24-week study (CTRL n=20, AHA n=21, CC-I n=21, CC-II n=24) with greater than 75% compliance. No significant differences were observed among diet groups in baseline age, height, weight, BMI, or fat mass as determined by ANOVA in Table 4.1.

Table 4.1 Baseline Demographics for Control (CTRL), AHA, CC-I, and CC-II

	Diet Group (n=86)	*CTRL (n=20)*	*AHA (n=21)*	*CC-I (n=21)*	*CC-II (n=24)*	*p-value*
Age (years)	37.5±13.4	37.3±14.1	38.7±12.9	38.1±13.2	36.3±14.1	0.94
Height (cm)	163.7±6.9	165.5±7.6	162.6±6.3	162.9±5.4	163.9±7.9	0.52
Weight (kg)	82.0±16.8	78.9±17.4	81.2±17.2	82.9±17.5	84.4±15.7	0.75
BMI[a] (kg/m²)	30.5±5.9	28.7±5.5	30.6±5.9	31.2±6.3	31.1±6.1	0.51
DXA[b] FM[c]	31.4±9.7	28.0±9.9	32.0.1±9.8	32.1±10.1	33.2±9.7	0.34

All data is presented as means ± SD at baseline. Significance level was set at 0.05. [a]Body mass Index, [b]Dual Energy X-ray Absorptiometry, [c]Fat Mass

In the AHA group, 7 were true matches to this diet as fat trimmers or better balancers, and 12 were false matches as carb reducers. In the CC-I group, 7 were true matches to this diet as fat trimmers or better balancers, and 12 were false matches as carb reducers. In the CC-II group, 13 were true matches as carb reducers and better balancers, and 8 were false matches as fat trimmers. No significant differences were observed between genetic matches in baseline age, height, weight, BMI, or fat mass as determined by ANOVA in Table 4.2.

Table 4.2 Baseline Demographics for True and False Genetic Matched Participants								
	Matched	**AHA (n=19)**		**CC-I (n=19)**		**CC-II (n=21)**		**p-value**
	(n=59)	***True (n=7)***	***False (n=12)***	***True (n=12)***	***False (n=7)***	***True (n=13)***	***False (n=8)***	
Age (years)	38.2±13.3	39.0±13.6	40.5±12.9	36.6±11.4	39.3±18.0	37.6±15.2	36.4±12.5	0.79
Height (cm)	163.3±6.8	161.5±4.9	162.9±7.0	162.1±6.7	164.6±2.4	165.2±6.6	162.8±10.9	0.69
Weight (kg)	83.6±16.8	82.2±14.8	82.1±19.9	87.9±20.9	75.1±9.8	88.9±15.0	79.5±14.3	0.83
BMI[a] (kg/m²)	31.2±6.2	31.4±4.3	30.9±7.1	33.3±7.2	27.7±3.3	31.7±5.6	30.5±7.5	0.99
DXA[b] FM[c]	32.8±9.8	32.9±8.0	32.3±11.5	34.6±11.9	28.0±6.5	35.1±9.0	31.1±9.7	0.88

All data is presented as means ± SD at baseline. Significance level was set at 0.05. [a]Body mass Index, [b]Dual Energy X-ray Absorptiometry, [c]Fat Mass

Dietary Intake

Table 4.3 presents percent changes in nutritional intake at 0, 4, 8, 12, 16, 20, and 24 weeks of program participation. Complete food records were measured by a self-reported, four-day diet log on all participants completing the study. MANOVA were run on absolute energy intake (kcals/d), and macronutrient intake expressed as a percentage of total calories consumed per day. MANOVA results of dietary intake data revealed an overall Wilks' Lambda time effect ($p<0.001$), time by diet ($p=0.001$) and diet group (D) differences among diet groups ($p<0.001$). MANOVA univariate analysis revealed significant time effects for protein and carbohydrate intake and total kilocalories/day consumed ($p<0.001$), but a time effect did not occur in fat intake ($p=0.43$). Time by diet (T x D) interaction was significant for protein and carbohydrate consumption ($p<0.001$), and T x D did not have an effect on fat intake ($p=0.21$) or total kilocalories/day consumed ($p=0.22$). However, post hoc tests showed total kilocalories/day were significantly higher in the CTRL diet compared to AHA (371.8 kcal/d; 95% CI, 199.0, 544.6), CC-I (436.3 kcal/d; 95% CI, 263.4, 609.1), and CC-II (345.8 kcal/d; 95% CI, 178.7, 512.9). There was a greater increase in protein intake as a percentage of macronutrient distribution measured at 0 and 24 weeks in the CC-I (+6.22±1.58%, $p<0.001$)

Table 4.3 Absolute % of Nutritional Intake at 0, 4, 8, 12, 16, 20, and 24 weeks

		Week								
Variable	**Diet**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**Group (SEM)**	**GG p-value**
PRO (%)	CTRL	16.6±5.2	17.3±3.9	17.8±4.2	20.5±6.2*	18.5±3.6	19.3±3.4†	18.9±3.7	18.43±1.1	T < 0.001
	AHA	17.7±4.5	17.22±2.7	18.9±5.3	17.9±3.1	18.9±3.6	19.2±3.9	19.0±4.0	18.40±1.1	D <0.001
	CC-I	20.7±6.4[ad]	26.63±6.9*[ab]	26.8±6.6*[abd]	28.5±7.6*[abd]	26.8±6.3*[abd]	27.1±6.9*[abd]	26.9±8.2*[ab]	26.20±1.1[ab]	TxD < 0.001
	CC-II	17.2±4.0	29.74±11.1*[ab]	31.4±9.9*[abc]	33.8±9.3*[abc]	30.9±9.5*[abc]	31.5±7.8*[abc]	30.8±8.3*[ab]	29.33±1.0[ab]	
	Mean	**18.0±5.2**	**23.0±9.0***	**24.0±8.9***	**25.5±9.5***	**24.1±8.3***	**24.5±7.9***	**24.2±8.3***		
CHO (%)	CTRL	42.5±10.1	43.3±8.4[bcd]	44.4±9.4[cd]	42.5±9.3[bcd]	42.4±9.4[bcd]	43.2±9.2[bcd]	43.0±11.0[d]	43.05±1.6[bcd]	T < 0.001
	AHA	46.6±9.5	51.4±7.2*[acd]	48.3±8.5[cd]	50.4±7.5[acd]	50.8±8.5[acd]	50.3±9.0[acd]	51.1±9.0†[acd]	49.83±1.6[acd]	D < 0.001
	CC-I	43.9±10.7	35.8±12.8*	36.3±10.5*	36.0±6.6*	36.5±8.4*	36.1±8.9*	38.2±8.4*	37.5±1.6	TxD < 0.001
	CC-II	46.0±6.5	34.8±10.5*	34.4±10.9*	31.0±11.7*	31.5±9.4*	31.2±8.6*	32.4±10.4*	34.48±1.5	
	Mean	**44.8±9.2**	**41.1±11.9***	**40.61±11.3***	**39.7±11.6***	**40.0±11.4***	**39.9±11.4***	**40.8±11.9***		
FAT (%)	CTRL	39.9±7.7	38.9±6.1	36.5±7.3	36.9±7.4	37.2±9.2	36.7±8.6	37.5±10.8	37.65±1.3	T = 0.43
	AHA	34.7±7.6	31.1±6.4	32.7±5.5	31.3±7.9	30.3±7.8	30.7±9.0	30.2±10.0	31.58±1.3[acd]	D = 0.013
	CC-I	34.5±8.8	35.4±8.5	35.4±8.3	34.6±8.1	36.4±8.5	36.4±8.9	34.5±7.3	35.32±1.3	TxD = 0.22
	CC-II	36.6±7.4	35.3±8.1	33.5±7.4	35.1±7.6	37.5±7.0	37.3±7.3	39.1±11.2	36.33±1.3	
	Mean	**36.4±8.0**	**35.2±7.7**	**34.5±7.2**	**34.5±7.9**	**35.4±8.5**	**35.4±8.7**	**35.5±10.4**		
Energy Intake (kcal/d)	CTRL	2075±558	1988±491	1773±521	1911±623	1755±414	1784±515	1630±387	1845±61[bcd]	T < 0.001
	AHA	1743±571	1431±254	1400±283	1496±584	1386±213	1430±274	1428±368	1474±61	D < 0.001
	CC-I	1480±531	1480±349	1361±213	1324±295	1347±274	1420±278	1450±390	1409±61	TxD = 0.22
	CC-II	1721±485	1410±339	1343±317	1489±334	1466±329	1525±400	1544±518	1500±57	
	Mean	**1754±566**	**1571±432***	**14645±387***	**1553±515***	**1488±349***	**1539±401***	**1514±424***		

Table 4.3 Absolute % of Nutritional Intake at 0, 4, 8, 12, 16, 20, and 24 weeks *(cont)*

Values are represented as means ± standard deviation (SD) except group means are ±standard error mean (SEM). N=86; CTRL (n=20), AHA (n=21), CC-I (n=21), CC-II (n=23). GG= Greenhouse-Geisser. T= Time effect. D= Diet effect. T x D= Time x Diet effect. *= significant time effect from baseline p<0.05 (post hoc LSD). †= a trend from baseline p > 0.05 and p < 0.1 (post hoc LSD). All letter superscripts represent significance from post hoc LSD. a= significantly different than CTRL (p < 0.05). b= significantly different than AHA (p < 0.05). c= significantly different than CC-I (p < 0.05). d= significantly different than CC-II (p < 0.05).

Table 4.4 Relative Nutritional Intake (g/kg) at 0, 4, 8, 12, 16, 20, and 24 weeks

		Week								
Variable	**Diet**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**Group (SEM)**	**GG p-value**
PRO (g/kg/d)	CTRL	1.11±0.42^{d}	1.11±0.36	1.0±0.35	1.22±0.4	1.03±0.28	1.09±0.33	0.99±0.3	1.1±0.1	T < 0.001
	AHA	0.97±0.41	0.8±0.23†^{acd}	0.86±0.27	0.86±0.29^{acd}	0.87±0.22	0.92±0.26	0.9±0.29	0.9±0.1^{cd}	D < 0.001
	CC-I	0.93±0.32	1.27±0.43*	1.17±0.29*^{b}	1.22±0.4*	1.18±0.33*^{bd}	1.26±0.37*^{bd}	1.27±0.45*^{b}	1.2±0.1	TxD < 0.001
	CC-II	0.86±0.27	1.3±0.61*	1.31±0.56*^{ab}	1.58±0.58*^{abc}	1.43±0.54*^{abc}	1.52±0.6*^{abc}	1.5±0.66*^{ab}	1.4±0.1^{ab}	
	Mean	**0.96±0.36**	**1.12±0.47***	**1.09±0.43***	**1.23±0.5***	**1.14±0.42***	**1.21±0.47***	**1.18±0.51***		
CHO (g/kg/d)	CTRL	2.89±1.07^{c}	2.78±0.81^{cd}	2.53±0.97*^{cd}	2.75±1.44^{cd}	2.42±0.9*^{cd}	2.51±0.99^{cd}	2.34±1.09*^{cd}	2.6±0.2^{cd}	T < 0.001
	AHA	2.55±1.02	2.38±0.61^{cd}	2.24±0.76^{cd}	2.42±0.74^{cd}	2.39±0.8^{cd}	2.46±0.83^{cd}	2.52±1.01^{cd}	2.4±0.2^{cd}	D < 0.001
	CC-I	2.05±0.87	1.75±0.98^{†ab}	1.64±0.64*^{ab}	1.58±0.51*^{ab}	1.65±0.58*^{ab}	1.7±0.5^{†ab}	1.81±0.55^{ab}	1.7±0.2	TxD = 0.025
	CC-II	2.37±0.81	1.48±0.57*^{ab}	1.43±0.67*^{ab}	1.45±0.62*^{ab}	1.44±0.51*^{ab}	1.49±0.57*^{ab}	1.53±0.6*^{ab}	1.6±0.1	
	Mean	**2.46±0.97**	**2.08±0.9***	**1.94±0.88***	**2.03±1.04***	**1.96±0.83***	**2.02±0.86***	**2.03±0.92***		
FAT (g/kg/d)	CTRL	1.23±0.52^{bcd}	1.14±0.42^{bcd}	0.93±0.37*^{bcd}	1.05±0.48†^{bcd}	0.94±0.32*^{bc}	0.93±0.29*^{b}	0.86±0.26*	1.0±0.1^{bcd}	T = 0.001
	AHA	0.87±0.36	0.65±0.23*	0.69±0.27*	0.7±0.34†	0.63±0.22*	0.69±0.33†	0.68±0.32†	0.7±0.1	D < 0.001
	CC-I	0.74±0.38	0.76±0.27	0.71±0.25	0.67±0.24	0.72±0.22	0.78±0.31	0.75±0.26	0.7±0.1	TxD = 0.015
	CC-II	0.86±0.43	0.68±0.25*	0.63±0.25*	0.73±0.25	0.79±0.27	0.81±0.33	0.85±0.37	0.8±0.1	
	Mean	**0.92±0.46**	**0.8±0.35***	**0.74±0.31***	**0.78±0.36***	**0.77±0.28***	**0.8±0.32***	**0.79±0.31***		

Table 4.4 Relative Nutritional Intake (g/kg) at 0, 4, 8, 12, 16, 20, and 24 weeks *(cont)*

		Week								
Variable	**Diet**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**Group (SEM)**	**GG p-value**
Energy Intake (kcal/kg/d)	CTRL	27.5±9.2^{bcd}	26.0±7.2^{bcd}	22.9±7.5*^{bcd}	25.3±10.3^{bcd}	22.7±6.0*^{bcd}	23.0±6.5*^{cd}	21.2±5.6*	24.1±1.1 ^{bcd}	T = 0.001
	AHA	22.1±7.6	18.7±4.7*	18.6±5.8*	19.5±6.1	18.7±5.0*	19.7±6.1	19.8±6.9	19.6±1.1	D = 0.001
	CC-I	18.8±6.8	19.3±6.0	17.9±4.5	17.5±4.7	17.8±4.1	19.0±4.6	19.2±4.9	18.5±1.1	TxD = 0.05
	CC-II	20.7±7.2	17.3±4.7*	16.7±4.9*	18.7±4.5	18.6±4.8	19.3±5.8	19.6±6.4	18.7±1.0	
	Mean	**22.2±8.2**	**20.2±6.6***	**18.9±6.1***	**20.2±7.3***	**19.4±5.3***	**20.2±5.9***	**19.9±5.9***		

Values are represented as means ± standard deviation (SD) except group means are ±standard error mean (SEM). N=86; CTRL (n=20), AHA (n=21), CC-I (n=21), CC-II (n=23). GG= Greenhouse-Geisser. T= Time effect. D= Diet effect. T x D= Time x Diet effect.). # = significant diet effect p<0.05 (univariate). *= significant time effect from baseline p<0.05 (post hoc LSD). †= a trend from baseline p > 0.05 and p < 0.1 (post hoc LSD). All letter superscripts represent significance from post hoc LSD. a= significantly different than CTRL (p < 0.05). b= significantly different than AHA (p < 0.05). c= significantly different than CC-I (p < 0.05). d= significantly different than CC-II (p < 0.05).

and CC-II diet groups (+13.6±1.47%, p<0.001). Percentage of protein and carbohydrate intake from 0 to 24 weeks did not change among the CTRL and AHA group participants. Carbohydrate intake did decrease in CC-I (-5.72±2.65%, p=0.03) and CC-II (-13.6±2.47%, p<0.001) as a percentage of total caloric consumption from 0 to 24 weeks. Table 4.4 presents relative changes in nutritional intake expressed in grams per kilogram of body weight. As consistent with the findings from the percentage distribution MANOVA, an overall time, time x diet, and diet group effects were observed (Wilks' Lambda, p<0.001). Post hoc tests reveal an overall increased protein intake in CC-I (0.30 g/kg/d; 95% CI, 0.10, 0.50) and CC-II (0.47 g/kg/d; 95% CI, 0.28, 0.67) compared to AHA. Concomitantly, an overall decreased carbohydrate intake was observed in CC-I vs CTRL (-0.86 g/kg/d; 95% CI, -1.27, -0.45) and AHA (-0.68 g/kg/d; 95% CI, -1.09, -0.27). The overall decrease in carbohydrate intake was significant in CC-II compared to CTRL (-1.01 g/kg/d; 95% CI, -1.4, -0.61) and AHA (-0.82 g/kg/d; 95% CI, -1.22, -0.43).

Physical Activity Level

Physical activity was assessed at 0, 4, 8, 12, 16, 20, and 24 weeks by the International Physical Activity Questionnaire (IPAQ), and validated for consistency with a seven-day exercise log report. MANOVA revealed an overall significance for time (Wilks' Lambda p<0.001) and time x diet (Wilks' Lambda p=0.007) effect for physical activity. An overall effect was observed for differences among diet groups (p<0.001). As detailed in Table 4.5 below, analyses of low level PA (MET=3.3) revealed the CTRL group had no significant difference in low PA from baseline (p=0.38) after 24-weeks, whereas all diet groups increased PA (AHA 1208±201; CC-I 1203±201; CC-II 899±188 MET-min/wk, p<0.001 respectively). Analyses of moderate PA (MET=4) revealed no significant difference from

baseline for CTRL (p=0.84), and significant increases for the diet groups after 24-weeks (AHA 728±136; CC-I 703±136; CC-II 480±128 MET-min/wk, p<0.001 respectively). Analyses of vigorous activity (MET=8) from 0 to 24 weeks revealed similar results in terms of significant changes from baseline for the diet groups (AHA 2173±212; CC-I 1467±212; CC-II 1667±199 MET-min/wk; p<0.001 respectively). CTRL had no deviation from baseline (p=0.81). AHA was significantly higher than CC-I (783±276 MET-min/wk; p=0.006) and CC-II (548±267 MET-min/wk; p=0.043) at 24 weeks. Figure 4.1 demonstrates the delta changes for total METs 24 weeks. CTRL had no change from baseline (p=0.74), and all diet groups significantly increased overall physical activity (AHA 4109±292; CC-I 3373±292; CC-II; 3046±273 MET-min/wk, p<0.001 respectively). Additionally, AHA was significantly higher than CTRL (p<0.001), and higher than CC-I (1046±447 MET-min/wk; 95% CI 156.9, 1935.7) and CC-II (1095±433 MET-min/wk; 95% CI 233.9, 1956.3). No differences were observed in PA due to job-related activity. An overall trend was observed among all groups for increased PA as a form of transportation, i.e. walking or bicycling (p=0.07). An increase in PA was observed in the CTRL group compared to AHA (p=0.012), CC-I (p=0.007), and CC-II (p=0.001) at week 12 due to household based activities; however, no TxD interaction was observed, as household PA significantly increased for all groups after 24 weeks (p=0.02). From 0 through 24-weeks, the diet groups significantly increased recreational activity (AHA 928±120, CC-I 931±120, CC-II 1070±112 MET-min/wk; p<0.001 respectively). All groups were significantly higher than CTRL after 24 weeks (AHA 524±174 MET-min/wk; 95% CI 178.3, 869.8; CC-I 496±174; 95% CI 150.4, 841.9; CC-II 624±168; 95% CI 288.5, 958.6). Time spent sitting (MET=1) during vehicle transport, at work, or at home was decreased among all four groups (p<0.001). Although an overall diet

group difference was observed (p=0.001), no significant interaction occurred, as the CTRL had consistently higher mean mins/wk spent seated in comparison to the diet treatment groups (AHA, CC-I and CC-II).

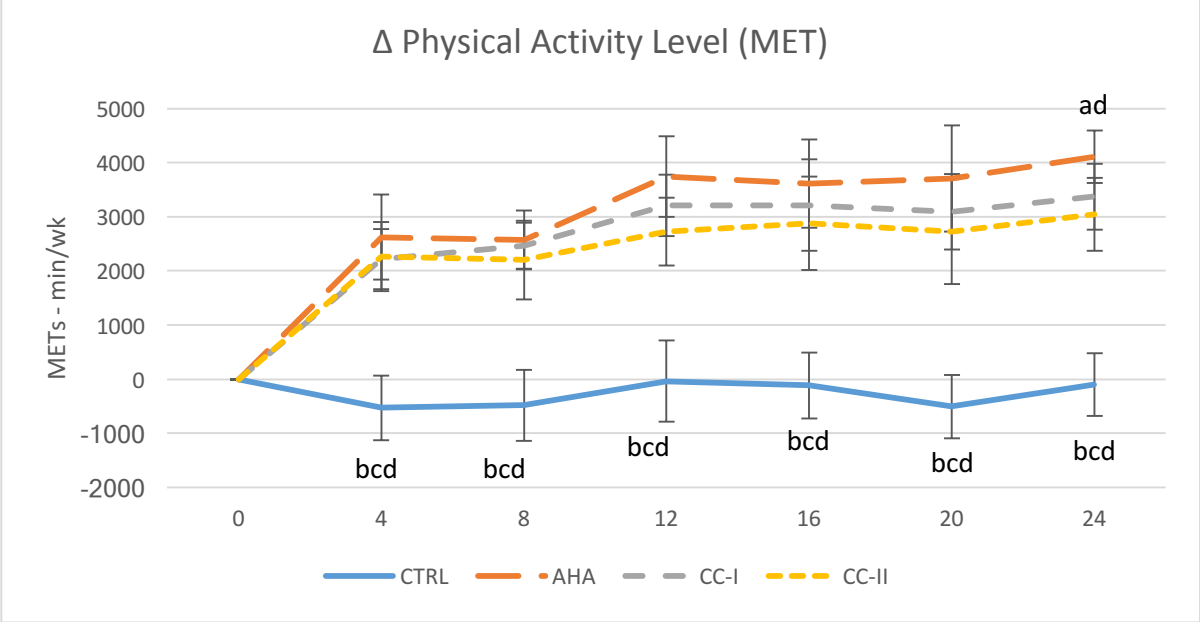

Figure 4.1 Diet Δ Physical Activity Level (MET). Data present mean (95% CI) from baseline for total self-assessed physical activity levels over 24 weeks. Control (CTRL), American Heart Association (AHA), Curves Complete-I (CC-I), and Curves Complete-II (CC-II); N=86. LSD post hoc symbols p<0.05: a= significant difference from CTRL, b= significant difference from AHA, c= significant difference from CC-I, d= significant difference from CC-II. CI: Confidence Interval. MET: Metabolic Equivalent of Task.

Table 4.5 Diet Changes in Physical Activity at 0, 4, 8, 12, 16, 20, and 24 weeks

		Week								
Variable	**Diet**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**Group (SEM)**	**GG p-value**
Low PA (MET-min/wk)	CTRL	1029±1140[c]	798±941[bcd]	732±697[bcd]	867±1097[bcd]	986±1016[bd]	785±980[bcd]	848±1001[bcd]	864±130[bcd]	T < 0.001
	AHA	830±707	1944±1027*[ac]	1799±739*[a]	2252±1142*[ac]	1925±876*[a]	1910±1123*[a]	2038±891*[a]	1814±127[ac]	D < 0.001
	CC-I	524±597[a]	1399±737*[ab]	1674±826*[a]	1611±700*[ab]	1506±739*	1476±750*[a]	1727±652*[a]	1417±127[ab]	TxD<0.001
	CC-II	654±359	1779±728*[a]	1665±860*[a]	1776±793*[a]	1702±834*[a]	1622±898*[a]	1553±817*[a]	1536±119[a]	
	Mean	**753±750**	**1498±952***	**1483±879***	**1641±1049***	**1542±919***	**1462±1013***	**1550±935***		
Mod PA (MET-min/wk)	CTRL	884±706	532±713	725±658	1001±1289	851±1407	680±842	913±1097	798±130	T < 0.001
	AHA	349±333	574±651	777±871	872±639	1043±867	736±551	1077±650	775±126	D = 0.89
	CC-I	423±371	744±728	713±654	991±533	1232±955	885±394	1126±730	873±126	TxD = 0.12
	CC-II	534±1136	541±394	669±502	829±438	813±365	805±462	1015±634	744±118	
	Mean	**543±748**	**596±623**	**719±668**	**919±769***	**980±948***	**779±574***	**1033±780***		
High PA (MET-min/wk)	CTRL	365±983	423±538[bcd]	342±469[bcd]	375±476[bcd]	327±621[bcd]	310±709[bcd]	418±683[bcd]	365±124[bcd]	T < 0.001
	AHA	144±191	1432±956*[a]	1321±866*[a]	1945±1041*[ad]	1964±1012*[a]	2381±1586*[ad]	2317±917*[acd]	1643±121[acd]	D < 0.001
	CC-I	67±162	1088±709*[a]	1097±527*[a]	1625±784*[a]	1490±968*[a]	1745±1281*[a]	1533±897*[ab]	1235±121*[ab]	TxD<0.001
	CC-II	103±203	1233±690*[a]	1160±697*[a]	1413±728*[ab]	1653±1105*[a]	1589±1254*[ab]	1769±1015*[ab]	1274±113[ab]	
	Mean	**165±505**	**1058±816***	**993±748***	**1353±962***	**1381±1117***	**1523±1434***	**1531±1109***		
Total PA (MET-min/wk)	CTRL	2279±1962[bcd]	1752±1442[bcd]	1798±1121[bcd]	2243±2227[bcd]	2164±1983[bcd]	1775±1414[bcd]	2178±1748[bcd]	2027±242[bcd]	T < 0.001
	AHA	1323±835[a]	3949±1571*[a]	3897±1442*[a]	5069±1580*[ad]	4932±1599*[a]	5027±2239*[a]	5432±1254*[acd]	4233±236[acd]	D < 0.001
	CC-I	1013±685[a]	3231±1309*[a]	3484±1002*[a]	4227±1326*[a]	4228±1689*[a]	4106±1684*[a]	4386±1488*[ab]	3525±236[ab]	TxD<0.001
	CC-II	1291±1297[a]	3553±850*[a]	3494±1167*[a]	4019±935*[ab]	4169±1448*[a]	4016±1740*[a]	4337±1291*[ab]	3554±221[ab]	
	Mean	**1461±1345**	**3152±1520***	**3196±1415***	**3913±1833***	**3903±1934***	**3764±2118***	**4114±1835***		

Table 4.5 Diet Changes in Physical Activity at 0, 4, 8, 12, 16, 20, and 24 weeks *(cont)*

		Week								
Variable	**Diet**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**Group (SEM)**	**GG p-value**
Job PA (MET-min/wk)	CTRL	794±1396	540±746	492±717	589±1104	791±1264	478±825	578±1009	609±204	T = 0.56
	AHA	686±1419	504±1010	669±1202	609±972	593±946	695±1079	633±1231	627±199	D = 0.99
	CC-I	574±694	633±1120	500±648	530±798	528±950	522±741	454±634	534±199	TxD = 0.84
	CC-II	692±1394	562±1200	581±1025	737±1072	501±828	523±927	601±1022	599±187	
	Mean	**685±1247**	**560±1026**	**562±918**	**621±981**	**597±989**	**554±891**	**567±983**		
Transport PA (MET-min/wk)	CTRL	413±564	247±485	246±260	317±368	433±583	261±327	337±448	322±72	T = 0.068
	AHA	354±352	241±364	305±363	319±399	456±448	312±275	430±456	345±71	D = 0.94
	CC-I	252±340	371±425	306±392	269±435	330±374	245±317	384±486	308±71	TxD = 0.67
	CC-II	232±349	252±421	312±484	221±404	317±412	310±491	350±441	285±66	
	Mean	**309±407**	**277±421**	**294±383**	**279±398**	**381±454**	**283±363**	**375±451**		
House PA (MET-min/wk)	CTRL	987±1214	971±760	659±548	1410±1809	1278±1629	713±713	817±867	976±91[bcd]	T = 0.02 ‡
	AHA	687±378	662±317	450±317	665±351	714±362	646±251	612±294	634±89	D = 0.014 #
	CC-I	578±381	586±344	502±367	610±379	819±436	659±339	632±327	627±89	TxD = 0.16
	CC-II	657±393	636±312	617±322	481±312	729±398	635±297	635±348	627±83	
	Mean	**722±680**	**708±478**	**558±397***	**774±975**	**875±874***	**662±425**	**671±503**		
Rec PA (MET-min/wk)	CTRL	219±276	446±486[bcd]	451±438[bcd]	720±581*[bcd]	413±486 [bcd]	570±712* [bcd]	573±516*[bcd]	485±50[bcd]	T < 0.001
	AHA	168±84	1232±557*	1188±607*	1207±519*	1215±592*	1378±681*	1097±648*	1069±49[a]	D < 0.001
	CC-I	138±95	1198±504*	1196±529*	1198±661*	1126±683*	1159±505*	1069±565*	1012±49[a]	TxD = 0.015
	CC-II	127±87	1358±596*	1124±540*	1228±575*	1267±595*	1171±603*	1196±490*	1067±46	
	Mean	**161±155**	**1076±638***	**1001±606***	**1098±612***	**1021±676***	**1079±684***	**996±597***		

Table 4.5 Diet Changes in Physical Activity at 0, 4, 8, 12, 16, 20, and 24 weeks *(cont)*

		Week								
Variable	**Diet**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**Group (SEM)**	**GG p-value**
Seated min/wk: (MET-min/wk)	CTRL	3469±1126	3425±1071	3136±650	3249±842	3214±773	3093±995	3433±1152	3288±76	T < 0.001
	AHA	3236±506	2670±583	2819±514	2863±558	2851±568	2857±526	2872±480	2881±74	D = 0.001
	CC-I	3308±406	2925±552	2661±510	3051±594	2815±546	2999±425	3030±536	2970±74	TxD=0.16
	CC-II	3453±314	2984±572	2723±576	2679±497	3101±574	3018±504	2684±568	2949±69	
	Mean	**3368±647**	**2995±753***	**2827±583***	**2947±654***	**2996±630***	**2991±636***	**2989±763***		

Values are represented as means ± standard deviation (SD) except group means are ±standard error mean (SEM). N=86; CTRL (n=20), AHA (n=21), CC-I (n=21), CC-II (n=23). GG= Greenhouse-Geisser. T= Time effect. D= Diet effect. T x D= Time x Diet effect. *= significant time effect from baseline p<0.05 (post hoc LSD). †= a trend from baseline p > 0.05 and p < 0.1 (post hoc LSD). All letter superscripts represent significance from post hoc LSD. a= significantly different than CTRL (p < 0.05). b= significantly different than AHA (p < 0.05). c= significantly different than CC-I (p < 0.05). d= significantly different than CC-II (p < 0.05). PA: Physical Activity. MET: Metabolic Equivalent of Task.

Table 4.6 Diet Changes in Body Composition, Anthropometric Measurements, and REE at 0, 4, 8, 12, 16, 20, and 24 weeks

		Week								
Variable	**Diet**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**Group (SEM)**	**GG p-value**
Total Mass (kg)	CTRL	78.9±17.4	79.2±17.2	79.7±17.8	79.5±18.0	79.7±18.0	79.7±18.2	79.8 ± 18.0	79.5±3.7	T < 0.001
	AHA	81.2±17.2	79.6±16.9*	78.8±16.7*	78.1±16.9*	77.8±16.8*	77.1±16.9*	76.6 ± 17.2*	78.5±3.6	D = 0.94
	CC-I	82.9±17.5	81.3±16.9*	80.4±16.6*	79.5±16.0*	78.9±15.9*	78.4±15.5*	78.3 ± 15.6*	79.9±3.6	TxD < 0.001
	CC-II	84.4±15.8	82.7±15.4*	81.8±15.5*	80.8±15.6*	80.5±16.6*	80.4±15.9*	80.1 ± 16.1*	81.5±3.4	
	Mean	**82.0±16.7**	**80.8±16.3***	**80.3±16.3***	**79.5±16.3***	**79.3±16.6***	**78.9±16.4***	**78.73 ± 16.5***		
Fat mass (kg)	CTRL	28.1±9.9	28.2±9.4	28.1±9.8	28.8±10.1	28.5±10.4	28.6±10.3	28.6±10.2	28.4±2.2	T < 0.001
	AHA	32.0±9.8	30.6±9.5*	29.7±9.3*	29.1±9.7*	28.7±9.9*	28.2±10.2*	27.8±9.9*	29.5±2.1	D = 0.928
	CC-I	32.1±10.1	31.0±9.4*	30.2±9.8*	29.4±9.4*	28.7±9.6*	28.2±9.6*	27.9±9.7*	29.6±2.1	TxD < 0.001
	CC-II	33.2±9.2	31.9±9.2*	30.7±9.1*	29.7±9.4*	29.1±9.6*	29.2±10.1*	28.7±9.8*	30.4±1.9	
	Mean	**31.4±9.8**	**30.5±9.3***	**29.8±9.4***	**29.2±9.5***	**28.8±9.7***	**28.56±9.9***	**28.3±9.7***		

Table 4.6 Diet Changes in Body Composition, Anthropometric Measurements, and REE at 0, 4, 8, 12, 16, 20, and 24 weeks *(cont)*

		Week								
Variable	**Diet**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**Group (SEM)**	**GG p-value**
Fat free mass (kg)	CTRL	44.8±8.1	44.8±8.5	45.2±8.6	44.9±8.4	44.9±8.3	44.9±8.6	44.7±8.6	44.9±1.6	T = 0.61
	AHA	43.0±7.3	43.0±7.4	42.9±7.4	42.8±7.3	43.0±6.9	42.9±6.9	42.9±7.1	42.9±1.6	D = 0.771
	CC-I	44.4±7.6	44.1±7.9	44.6±7.7	44.3±7.7	43.8±7.1	44.0±6.7	44.3±6.7	44.2±1.6	TxD = 0.89
	CC-II	44.9±7.0	44.8±6.3	45.1±6.6	45.2±6.4	44.9±6.4	45.0±6.2	45.3±6.3	45.0±1.5	
	Mean	**44.3±7.4**	**44.2±7.4**	**44.5±7.5**	**44.3±7.4**	**44.2±7.1**	**44.2±7.0**	**44.3±7.1**		
BF %	CTRL	37.8±6.0[bd]	37.9±5.8[bc]	37.8±6.0	37.7±6.4	38.1±6.4	38.0±6.2	38.1±6.7	37.9±1.2	T < 0.001
	AHA	42.2±4.3[a]	41.2±4.3*[a]	40.5±4.1*	39.8±4.6*	39.2±5.3*	38.9±5.6*	38.7±5.2*	40.1±1.2	D = 0.57
	CC-I	40.7±5.1	40.3±5.2	38.8±5.5*	38.3±5.9*	37.6±5.9*	37.1±6.4*	36.6±6.2*	38.5±1.2	TxD < 0.001
	CC-II	42.0±4.0[a]	40.9±4.6*[a]	39.8±4.5*	38.7±5.3*	38.2±5.5*	38.1±6.2*	37.6±5.9*	39.3±1.1	
	Mean	**40.8±5.1**	**40.1±5.1***	**39.3±5.1***	**38.6±5.5***	**38.3±5.7***	**38.0±6.0***	**37.7±5.9***		
Waist (cm)	CTRL	85.9±12.3	85.7±11.2	85.7±12.3	87.0±11.1	87.0±11.6	85.7±12.3	85.9±12.3	86.1±2.8	T < 0.001
	AHA	88.7±16.2	87.2±14.9†	87.1±16.0 †	86.2±14.0*	85.2±15.1*	86.3±15.4*	84.3±14.7*	86.4±2.7	D = 0.91
	CC-I	91.4±14.0	89.0±13.9*	88.4±12.3*	88.4±11.7*	88.2±10.1*	86.9±11.8*	87.3±12.1*	88.5±2.7	TxD = 0.006
	CC-II	88.7±11.7	87.3±11.0†	86.2±10.9*	85.5±11.0*	84.7±11.2*	85.3±11.9*	85.1±12.1*	86.1±2.5	
	Mean	**88.7±13.5**	**87.3±12.6***	**86.9±12.7***	**86.7±11.8***	**86.2±12.0***	**86.0±12.7***	**85.7±12.6***		
Hip (cm)	CTRL	109.6±12.3	110.1±11.5	110.7±12.0	110.9±11.5	110.7±12.1	110.2±12.2	110.8±12.4	110.4±2.5	T < 0.001
	AHA	112.4±13.9	110.7±12.5*	110.1±13.6*	110.3±12.5*	109.2±11.8*	109.5±13.3*	108.1±13.2*	110.0±2.5	D = 0.92
	CC-I	114.1±10.6	112.1±10.7*	110.5±11.1*	109.1±10.6*	110.1±10.4*	109.7±10.3*	109.2±10.8*	110.7±2.5	TxD < 0.001
	CC-II	115.3±10.0	113.5±10.4*	111.2±11.3*	111.5±9.7*	111.2±10.4*	111.2±10.8*	111.3±11.5*	112.2±2.3	
	Mean	**113.0±11.7**	**111.7±11.1***	**110.7±11.8***	**110.5±10.9***	**110.3±11.0***	**110.2±11.5***	**109.9±11.8***		

Table 4.6 Diet Changes in Body Composition, Anthropometric Measurements, and REE at 0, 4, 8, 12, 16, 20, and 24 weeks *(cont)*

		Week								
Variable	**Diet**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**Group (SEM)**	**GG p-value**
REE (kcal/d)	CTRL	1375±243	1369±266	1411±253	1423±273	1438±259	1361±311	1388±272	1395±55	T = 0.43
	AHA	1394±321	1410±260	1323±294†	1351±285	1338±254	1398±258	1329±323	1364±53	D = 0.90
	CC-I	1418±286	1371±227	1417±269	1407±302	1378±288	1315±325	1361±323	1381±53	TxD = 0.16
	CC-II	1476±219	1445±259	1426±238	1383±282	1399±288	1387±316	1406±224	1418±50	
	Mean	**1419±267**	**1401±251**	**1395±263**	**1390±282**	**1388±271**	**1366±300**	**1372±283**		

Values are represented as means ± standard deviation (SD) except group means are ±standard error mean (SEM). N=86; CTRL (n=20), AHA (n=21), CC-I (n=21), CC-II (n=23). GG= Greenhouse-Geisser. T= Time effect. D= Diet effect. T x D= Time x Diet effect. *= significant time effect from baseline $p<0.05$ (post hoc LSD). †= a trend from baseline $p > 0.05$ and $p < 0.1$ (post hoc LSD). All letter superscripts represent significance from post hoc LSD. a= significantly different than CTRL ($p < 0.05$). b= significantly different than AHA ($p < 0.05$). c= significantly different than CC-I ($p < 0.05$). d= significantly different than CC-II ($p < 0.05$).BF%= Body Fat Percentage, REE= Resting Energy Expenditure.

Body Composition, Anthropometry and Resting Energy Expenditure

Table 4.6 presents changes in body composition, anthropometry, and resting energy expenditure data observed at 0, 4, 8, 12, 16, 20, and 24 weeks of program participation. MANOVA of body composition data revealed overall time (Wilks' Lambda $p<0.001$) and time by diet interaction ($p=0.05$) with no differences observed among groups ($p=0.86$). Univariate analysis revealed a significant time by diet interaction for differences in total body weight (CTRL 0.77±00.98, AHA -4.60±0.96, CC-I -4.59±0.96, CC-II -4.34±0.89 kg; $p<0.001$) fat mass (CTRL 0.53±0.79, AHA -4.23±0.78, CC-I -4.16±0.78, CC-II -4.51 ±0.73 kg; $p<0.001$), and body fat percentage (CTRL 0.33±0.78, AHA -3.55±0.76, CC-I -4.15 ±0.76, CC-II -4.44±0.72; $p<0.001$), as all diet treatment groups experienced a decrease in these variables, while the control group had no deviation from baseline. Post hoc comparisons of weight loss from 0 to 24 weeks show the diet treatment groups AHA, CC-I, and CC-II demonstrated a significant decrease from CTRL. At 24 weeks, total differences in weight loss compared to the control group was AHA (-5.38kg; 95% CI, -8.10, -2.65), CC-I (-5.37kg; 95% CI, -8.09, -2.65), and CC-II (-5.11kg; 95% CI, -7.75, -2.47). No differences in weight loss among the diet treatment groups were observed at any time point as demonstrated in Figure 4.2.

Time by diet changes in fat mass are parallel with total weight loss results as shown in Figure 4.3. At 24 weeks, fat mass decreased in the diets AHA (-4.76kg; 95% CI, -2.54, -6.97), CC-I (-4.69kg; 95% CI, -2.47, -6.9), and CC-II (-5.04kg; 95% CI, -2.89, -7.12) as compared to participants assigned to CTRL. Figure 4.4 demonstrates no significant differences in fat-free mass were observed within or among diet groups.

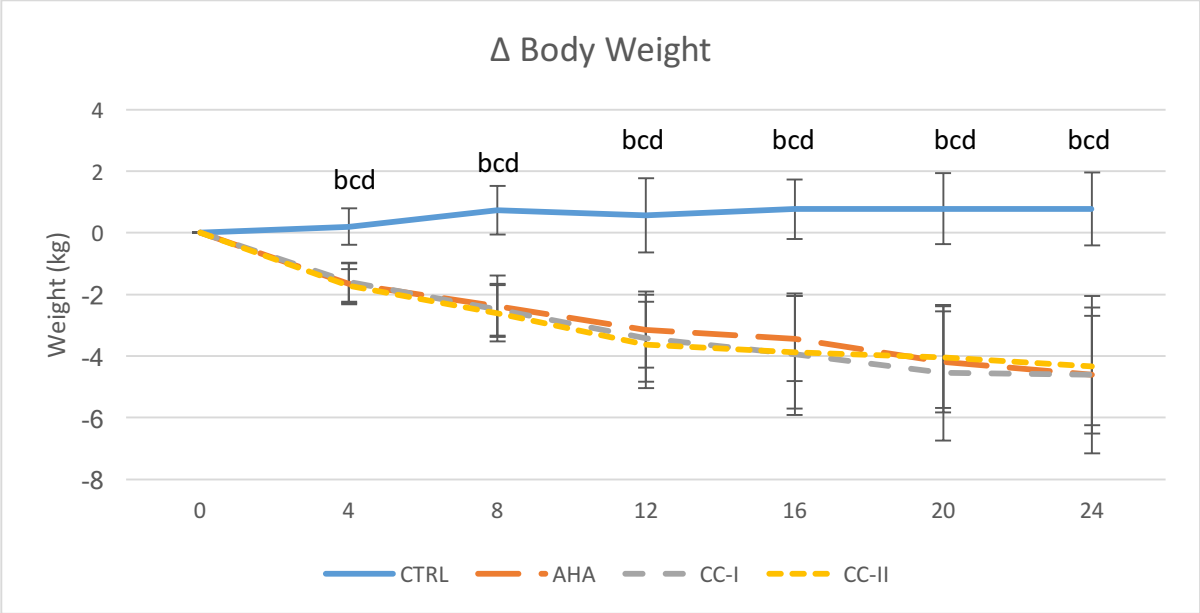

Figure 4.2 Diet Δ Body Weight. Data present mean (95% CI) from baseline for total body weight over 24 weeks. Control (CTRL), American Heart Association (AHA), Curves Complete-I (CC-I), and Curves Complete-II (CC-II); N=86. CI: Confidence Interval. LSD post hoc symbols p<0.05: b= significant difference from AHA, c= significant difference from CC-I, d= significant difference from CC-II.

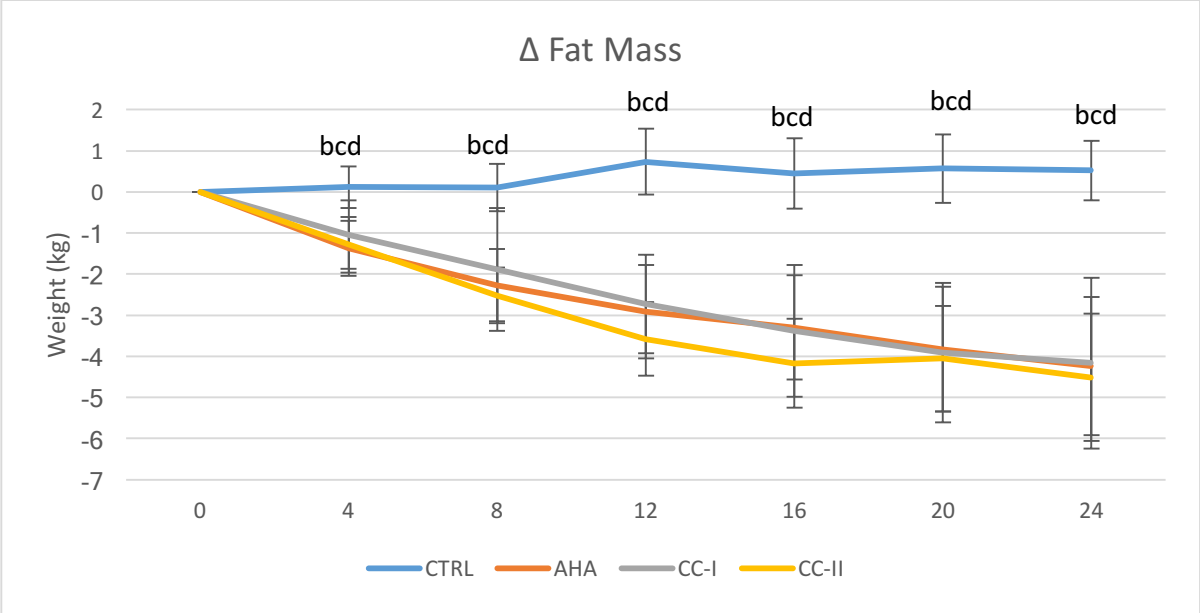

Figure 4.3 Diet Δ Fat Mass. Data present mean (95% CI) from baseline for fat mass over 24 weeks. Control (CTRL), American Heart Association (AHA), Curves Complete-I (CC-I), and Curves Complete-II (CC-II); N=86. CI: Confidence Interval. LSD post hoc symbols p<0.05: b= significant difference from AHA, c= significant difference from CC-I, d= significant difference from CC-II.

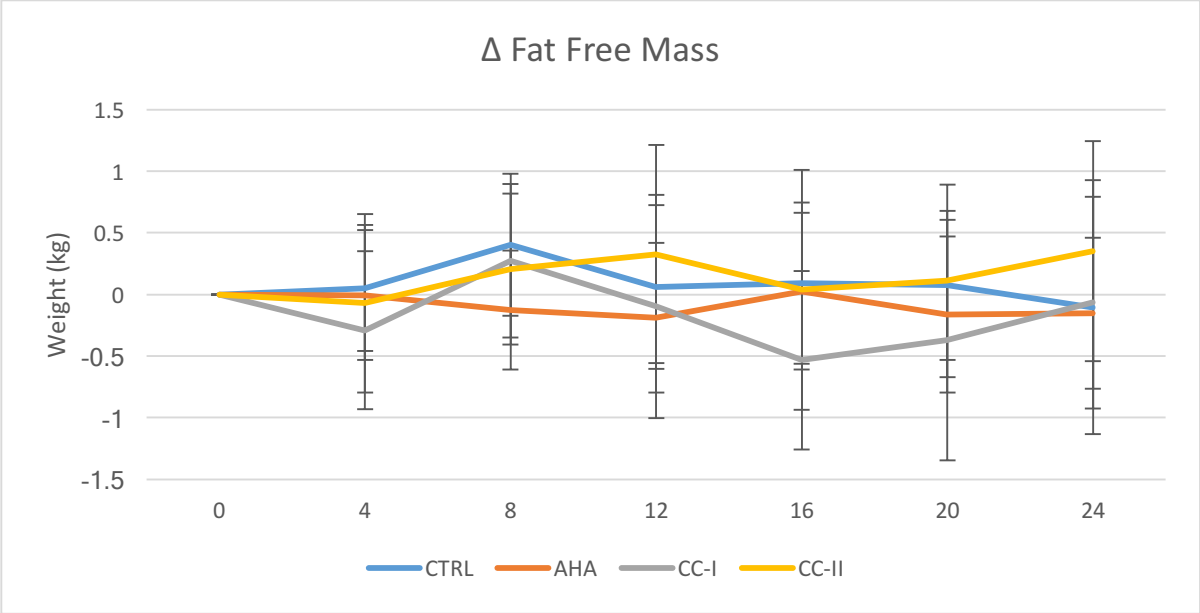

Figure 4.4 Diet Δ Fat Free Mass. Data present mean (95% CI) from baseline for fat-free mass over 24 weeks. Control (CTRL), American Heart Association (AHA), Curves Complete-I (CC-I), and Curves Complete-II (CC-II); N=86. CI: Confidence Interval.

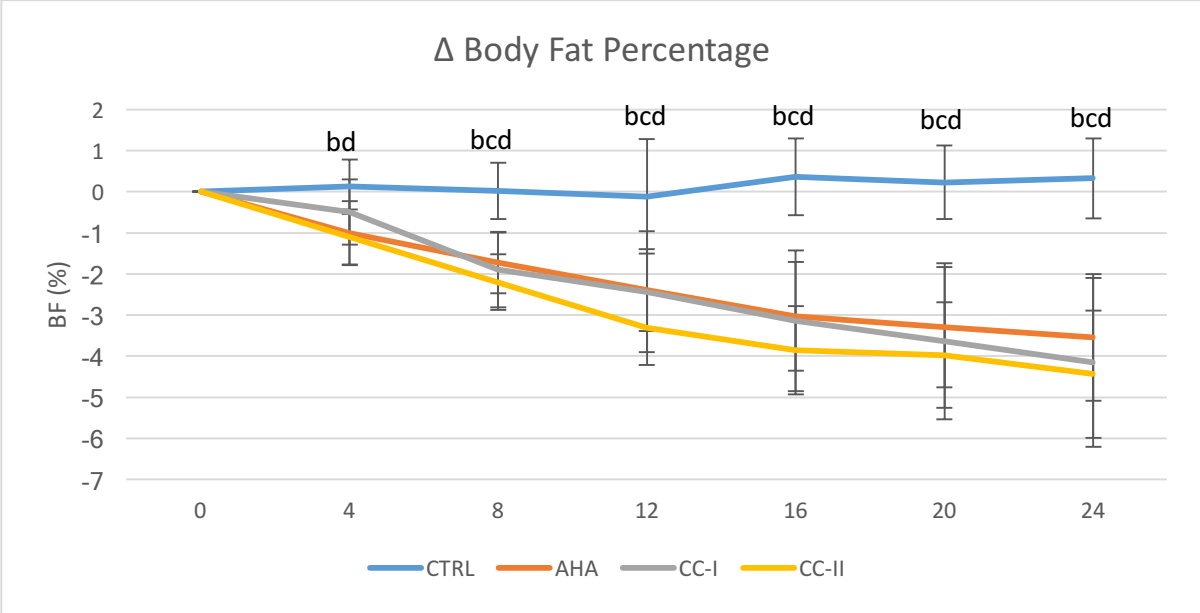

Figure 4.5 Diet Δ Body Fat Percentage. Data present mean (95% CI) from baseline for body fat percentage over 24 weeks. Control (CTRL), American Heart Association (AHA), Curves Complete-I (CC-I), and Curves Complete-II (CC-II); N=86. CI: Confidence Interval. LSD post hoc symbols p<0.05: b= significant difference from AHA, c= significant difference from CC-I, d= significant difference from CC-II.

At 24 weeks, total differences in body fat percentage compared to the control group was AHA (-4. 5%; 95% CI, -7.5, -1.4), CC-I (-5.37; 95% CI, -2.65, -8.09), and CC-II (-5.11; 95% CI, -2.47, -7.75) ($p<0.001$) as seen in Figure 4.5.

MANOVA of anthropometric data revealed overall time (Wilks' Lambda $p<0.001$) and time by diet effects (Wilks' Lambda $p=0.01$). Univariate analysis revealed significant time x diet group effects for waist and hip measurements. After 24 weeks, all diet treatment groups had decreased waist circumference (CTRL 0.00±0.43; AHA -1.72±0.42, CC-I -1.58±0.42, CC-II -1.43±0.39 cm; $p=0.006$) and hip circumference (CTRL 0.50±0.40; AHA -1.69±0.39, CC-I -1.94±0.39, CC-II -1.58±0.36 cm; $p<0.001$), whereas the CTRL experienced no change from baseline. No differences were observed among diet groups for waist ($p=0.908$) and hip ($p=0.922$) measurements. Although all diet groups reduced both waist and hip circumference, the waist-hip ratio (WHR) remained consistent among all four diet groups as seen in Figure 4.6.

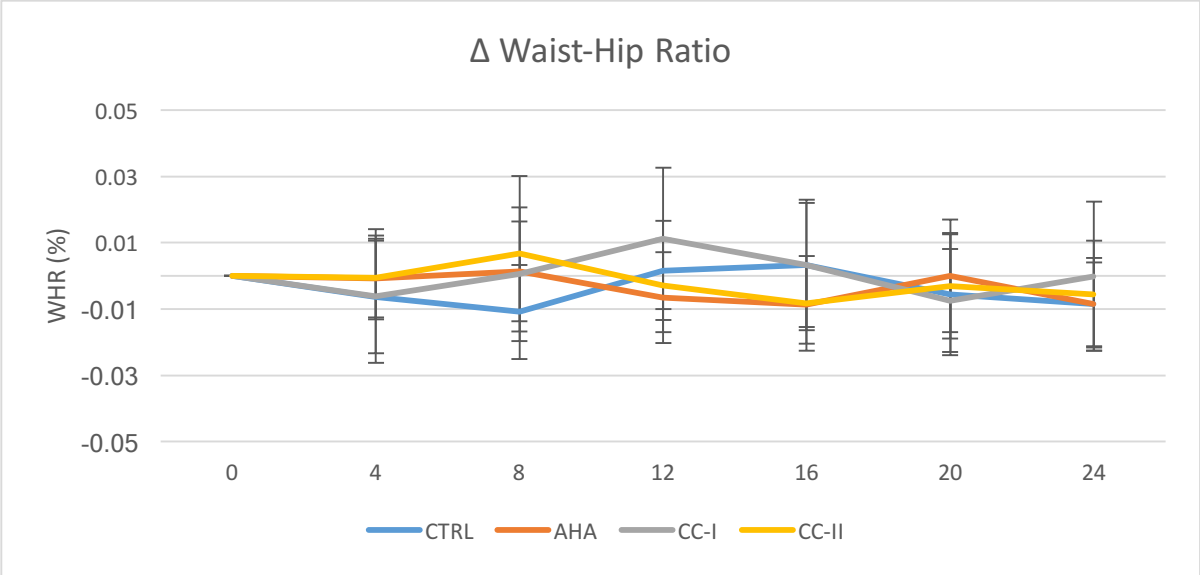

Figure 4.6 Diet Δ Waist-Hip Ratio. Data present mean (95% CI) from baseline for waist-hip ratio over 24 weeks. Control (CTRL), American Heart Association (AHA), Curves Complete-I (CC-I), and Curves Complete-II (CC-II); N=86. CI: Confidence Interval.

Table 4.7 Diet Changes in Fitness Measurements at 0, 12, and 24 weeks

Variable	Diet	Week 0	Week 12	Week 24	Group (SEM)	GG p-value
GXT Time (secs)	CTRL	547.2±111.5	545.6±98.1	555±93.5	549.3±21.3	T < 0.001
	AHA	521.5±90.7	554.7±88.6*	569.3±97.2*	548.5±20.8	D = 0.96
	CC-I	514.6±106.3	547.0±124.2*	574.2±114.9*	545.3±20.8	TxD = 0.02
	CC-II	524.4±85.9	573.5±79.1*	580.1±104.5*	559.3±19.4	
	Mean	**526.6±97.5**	**555.9±97.2***	**570.2±101.7***		
VO_2max (ml/kg)	CTRL	26.0±6.1	25.4±5.9	25.92±6.1	25.8±1.3	T < 0.001
	AHA	23.6±4.3	27.2±5.0*	27.7±4.9*	26.2±1.2	D = 0.996
	CC-I	24.1±6.0	26.4±7.1*	27.6±7.7*	26.0±1.2	TxD < 0.001
	CC-II	23.5±4.7	26.4±5.9*	27.9±5.7*	25.9±1.1	
	Mean	**24.3±5.3**	**26.4±6.0***	**27.3±6.1***		
Bench Press 1RM (kg)	CTRL	32.3±9	34.3±9.9	33.8±10	33.4±1.9	T < 0.001
	AHA	33.1±7.9	34.7±8.8	35.7±7.9	34.5±1.9	D = 0.86
	CC-I	32.1±10.7	35.4±11.2	36.8±10.4	34.8±1.9	TxD = 0.24
	CC-II	33.2±7.8	35.7±8.1	38.2±7.7	35.7±1.8	
	Mean	**32.7±8.7**	**35.1±9.4***	**36.2±9***		
Bench Press Reps*kg (80%)	CTRL	210.2±101.1	184.1±73.4	203.8±77.8	199.4±17.0	T =0.078
	AHA	211.3±83.6	221.1±92.6	249.2±110.5	227.2±16.6	D = 0.42
	CC-I	222.5±90.1	229.7±98.2	248.3±125.5	233.5±16.6	TxD = 0.36
	CC-II	196.4±98.6	253.4±127.6	252.5±111.6	234.1±15.5	
	Mean	**209.6±92.5**	**223.6±102.6**	**237.2±110.6***		
Leg Press 1RM (kg)	CTRL	188.0±61.4	212.3±68.6	225.3±79.2	208.5±14.9	T < 0.001
	AHA	201.9±7	218.1±71.9	227.3±75.1	215.7±14.6	D = 0.32
	CC-I	187.6±62.7	207.3±72.2	224.2±73.5	206.3±14.6	TxD = 0.96
	CC-II	221±68.0	239.5±68.5	258.0±78.9	239.5±13.6	
	Mean	**200.5±67.1**	**220.1±70.2***	**234.6±76.8***		
Leg Press Reps*kg (80%)	CTRL	2237.4±1072.3	2520.7±1211.0	2279.6±905.3	2345.9±277.8	T =0.011
	AHA	2309.2±1361.7	2893.5±1972.5	2888.1±2220.4	2696.9±271.1	D = 0.156
	CC-I	1970.8±1239.5	2155.8±1015.7	2561.2±1736.0	2229.3±271.1	TxD = 0.58
	CC-II	2720.9±1315.8	2909.8±1702.7	3383.1±1535.3	3004.6±253.6	
	Mean	**2324.8±1265.1**	**2631.2±1538.9***	**2804.9±1692.9***		

Values are represented as means ± standard deviation (SD) except group means are ±standard error mean (SEM). N=86; CTRL (n=20), AHA (n=21), CC-I (n=21), CC-II (n=23). GG= Greenhouse-Geisser. T= Time effect. D= Diet effect. T x D= Time x Diet effect. # = significant diet effect $p<0.05$ (univariate). *= significant time effect from baseline $p<0.05$ (post hoc LSD). †= a trend from baseline $p > 0.05$ and $p < 0.1$ (post hoc LSD). GXT: Graded Exercise Test. Series mean was used to replace 0.9% missing values (n=5) for 516 data points.

Repeated Measures ANOVA revealed no significant time (Wilks' Lambda p=0.43) or time x diet group interaction (p=0.16) in resting energy expenditure (REE), and no differences were observed among diet groups (p=0.90).

Cardiorespiratory Fitness, Muscular Strength and Endurance

Table 4.7 presents changes in fitness variables data observed at 0, 12, and 24 weeks of program participation. MANOVA of cardiovascular fitness reveals an overall time effect and time x diet interaction (Wilks' Lambda p<0.001) with no difference among diet groups (p=0.78). Univariate analysis showed a significant time x diet interaction for peak oxygen uptake (VO_2max) in ml/kg/min (CTRL -0.035±0.77; AHA 4.17±0.72; CC-I 3.48±0.72; CC-II 4.40±0.67, p<0.001) and maximal time to exhaustion in seconds (CTRL 7.80±12.99; AHA 47.86±12.67; CC-I 59.59±12.68; CC-II 55.69±11.86, p=0.02), as all diet treatment groups experienced a significant increase in VO_2max and treadmill time to voluntary exhaustion in comparison to the control group.

MANOVA of isotonic maximal strength and endurance measurements reveal an overall time effect but no time x diet interaction (Wilks' Lambda p<0.001 and p=0.54, respectively). No differences among diet groups were observed (p=0.56). Although all treatment diet groups (AHA, CC-I, CC-II) significantly improved bench press 1RM at 24 weeks and the CTRL did not, a lack of time x diet interaction (p=0.24) was observed as the CTRL demonstrated a slight increase in strength from baseline for a significant time effect (CTRL 3.25±2.77; AHA 5.71±2.70; CC-I 10.24±2.70; CC-II 10.83±2.52 kg, p<0.001). A similar pattern was observed in leg press 1RM. All diet treatment and control subjects significantly improved strength from baseline (CTRL 82.25±21.45; AHA 55.81±20.94; CC-I 80.71±20.94; CC-II 81.25±19.59 kg, p<0.001) without a time x diet interaction (p=0.96).

Table 4.8 Diet Changes in Fasting Blood Lipids at 0, 12, and 24 weeks

Variable	Diet	Week 0	Week 12	Week 24	Group (SEM)	GG p-value
Total CHL (mg/dl)	CTRL	200±53.5	193.5±40.1	202.4±47.1	198.6±8.3	T < 0.001
	AHA	203.4±39.9	181.5±41.1*	198.7±38.8	194.5±8.1	D = 0.55
	CC-I	202.9±50.4	190.0±48.0†	179.2±34.2*	190.7±8.1	TxD = 0.08
	CC-II	195.2±41.6	174.7±32.7*	178.9±36.4*	182.9±7.6	
	Mean	**200.2±45.8**	**184.5±40.6***	**189.3±40.0***		
LDL-c (mg/dl)	CTRL	125.1±51.1	115.2±41.5	129.1±43.9	123.1±10.7	T < 0.001
	AHA	136.14±43.7	142.34±51.3	129.3±41.1	135.94±10.4	D = 0.034
	CC-I	185.2±71.7^{ab}	190.1±72.9^{abd}	124.9±59.1*	166.8±10.4^{ab}	TxD < 0.001
	CC-II	159.32±67.6	142.44±59.4*	120.5±41.8*	140.76±9.8	
	Mean	**152.0±63.2**	**147.7±62.6**	**125.7±46.2***		
HDL-c (mg/dl)	CTRL	56.4±19.9	52.0±15.8	58.2±17.8	55.5±3.6	T =0.001
	AHA	63.42±18.9	54.16±16.9	61.0±17.6	59.5±3.5	D = 0.87
	CC-I	61.43±19.4	56.75±18.9	57.7±16.6	58.6±3.5	TxD = 0.45
	CC-II	58.02±18.5	55.46±14.8	60.8±18.5	58.11±3.3	
	Mean	**59.78±19.0**	**54.65±16.4***	**59.52±17.4**		
Triglycerides (mg/dl)	CTRL	123.9±64.4	129.6±64.9	117.5±56.9	123.7±11.6	T = 0.001
	AHA	107.8±52.3	96.1±45.9	98.8±47.4	100.9±11.3	D = 0.21
	CC-I	151.1±75.2	138.1±62.7†	107.8±50.6*	132.3±11.3	TxD = 0.023
	CC-II	119.9±59.2	103.6±48.7*	107.3±52.1	110.3±10.6	
	Mean	**125.5±64.0**	**116.2±57.5***	**107.7±51.3***		

Values are represented as means ± standard deviation (SD) except group means are ±standard error mean (SEM). N=86; CTRL (n=20), AHA (n=21), CC-I (n=21), CC-II (n=23). CHL= Cholesterol. LDL-c= Low density lipoprotein cholesterol. HDL-c= High density lipoprotein cholesterol. GG= Greenhouse-Geisser. T= Time effect. D= Diet effect. T x D= Time x Diet effect. # = significant diet effect p<0.05 (univariate). *= significant time effect from baseline p<0.05 (post hoc LSD). †= a trend from baseline p > 0.05 and p < 0.1 (post hoc LSD). All letter superscripts represent significance from post hoc LSD. a= significantly different than CTRL (p < 0.05). b= significantly different than AHA (p < 0.05). c= significantly different than CC-I (p < 0.05). d= significantly different than CC-II (p < 0.05). To convert mg/dL cholesterol to mmol/L, multiply mg/dL by 0.026. To convert mmol/L cholesterol to mg/dL, multiply mmol/L by 38.6. Cholesterol of 194 mg/dl=5.04 mmol/L. To convert mg/dL triglyceride to mmol/L, multiply mg/dL by 0.0113. To convert mmol/L triglyceride to mg/dL, multiply mmol/L by 88.6. Triglyceride of 137 mg/dl=1.55 mmol/L.

Biochemical Markers of Health by Diet

Table 4.8 presents changes in blood lipid biomarkers of health observed at 0, 12, and 24 weeks. MANOVA of these measurements reveal an overall time effect (Wilks' Lambda $p<0.001$) and time x diet interaction (Wilks' Lambda $p<0.001$). Univariate analysis showed a significant interaction for low density lipoproteins (CTRL 3.92±12.21; AHA -6.80±11.92; CC-I -60.25±11.92; CC-II -38.80±11.15 mg/dL, $p<0.001$), as all diet treatment groups lowered LDL concentration, while the control group experienced a slight increase. A significant time x diet interaction was observed in triglyceride concentration (CTRL -6.41±10.58; AHA -8.99±10.32; CC-I -43.26±10.32; CC-II -12.64±9.66 mg/dL, $p=0.023$). All diet treatment groups experienced a greater decrease in serum triglycerides versus the CTRL. A time x diet trend was observed in total cholesterol (CTRL 2.37±7.28; AHA -4.63±7.11; CC-I -23.85±7.11; CC-II -16.18±6.65 mg/dL, $p=0.081$), as all diet treatment groups experienced a decrease in total cholesterol concentration in comparison to the CTRL.

Table 4.9 presents changes in fasting glucose concentration observed at 0,12, and 24 weeks, and insulin and HOMA-IR at 0 and 24 weeks of program participation. No overall Wilks' Lambda significant time effects were observed for glucose ($p=0.70$); however, time by diet analysis revealed significant differences ($p=0.001$) as only CC-I reduced glucose concentration ($p=0.001$), and the CTRL saw an increase in glucose ($p=0.041$) from baseline to 24 weeks (CTRL 8.78±4.24; AHA 5.53±4.14; CC-I -14.85±4.14; CC-II -3.58±3.87 mg/dL, $p<0.001$). A time effect was observed for insulin concentrations in µIU/ml at 24 weeks ($p<0.001$) without a significant time x diet interaction ($p=0.224$). Although all diet groups (including CTRL) reduced insulin levels from baseline to 24 weeks (CTRL -0.87±0.79; AHA -2.09±0.77; CC-I -1.11±0.77; CC-II -

2.84±0.72 p<0.001), only AHA and CC-II observed a significant decrease (p=0.008 and p<0.001, respectively) so no time x diet interaction occurred. A significant overall Wilks' Lambda time effect was observed (p=0.037), with no time x diet effect (p=0.18) nor differences among groups (p=0.58). Although all diet treatment groups reduced HOMA-IR, only CC-II had a significant decrease from baseline (-0.78±0.31, p=0.02). These observations partially accept Hypothesis 1.

Table 4.9 Diet Changes in Fasting Glucose, Insulin and HOMA-IR at 0, 12, and 24 weeks

		Week				
Variable	**Diet**	**0**	**12**	**24**	**Group (SEM)**	**GG p-value**
Fasted Glucose (mg/dl)	CTRL	95.4±17.9	100.1±34.3[b]	104.2±44.5*[c]	99.9±3.8	T =0.70
	AHA	87.7±9.8[cd]	86.2±12.2	93.2±9.1	89.0±3.7	D = 0.24
	CC-I	102.0±15.4	98.4±17.6 †	87.2±7.6*	95.3±3.7	TxD < 0.001
	CC-II	96.6±8.0	93.38±9.3	93.0±12.7	94.3±3.5	
	Mean	**95.5±13.9**	**94.4±20.5**	**94.2±23.6**		
Fasted Insulin (µIU/ml)	CTRL	11.7±7.3	-	10.9±6.9	11.3±1.4	T < 0.001
	AHA	10.6±5.8	-	8.5±6.8	9.5±1.4	D = 0.85
	CC-I	10.8±8.1	-	9.7±7.2	10.3±1.4	TxD = 0.22
	CC-II	11.6±5.9	-	8.7±4.7	10.2±1.3	
	Mean	**11.2±6.7**	**-**	**9.4±6.4***		
HOMA - IR	CTRL	2.9±2.5	-	3.2±4.5	3.1±0.5	T = 0.037
	AHA	2.4±1.5	-	2.02±1.8	2.2±0.5	D = 0.58
	CC-I	2.6±2.1	-	2.1±1.5	2.4±0.5	TxD = 0.18
	CC-II	2.8±1.4	-	2.01±1.1	2.4±0.4	
	Mean	**2.7±1.9**	**-**	**2.3±2.6***		

Values are represented as means ± standard deviation (SD) except group means are ±standard error mean (SEM). N=86; CTRL (n=20), AHA (n=21), CC-I (n=21), CC-II (n=23). GG= Greenhouse-Geisser. T= Time effect. D= Diet effect. T x D= Time x Diet effect. *= significant time effect from baseline p<0.05 (post hoc LSD). †= a trend from baseline p > 0.05 and p < 0.1 (post hoc LSD). All letter superscripts represent significance from post hoc LSD. a= significantly different than CTRL (p < 0.05). b= significantly different than AHA (p < 0.05). c= significantly different than CC-I (p < 0.05). d= significantly different than CC-II (p < 0.05). To convert mg/dL glucose to mmol/L, multiply mg/dL by 0.0555. To convert mmol/L to mg/dL, multiply mmol/L by 18.0. Glucose of 99 mg/dl=5.5 mmol/L To convert µIU/ml insulin to pmol/L, multiply µIU/ml by 6.945. To convert pmol/L to µIU/ml, multiply pmol/L by 0.144. Insulin of 13.8 µIU/ml=95.8 pmol/L. Homeostatic Model Assessment of Insulin Resistance. T=time alpha level. D=diet group alpha level. T x D=time by diet group interaction alpha level.

Table 4.10 Changes in Psychological Self-assessments at 0, 4, 8, 12, 16, 20, and 24 weeks

		Week								
Variable	**Diet**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**Group (SEM)**	**GG p-value**
Quality of Life (SF36)	CTRL	125.6±13.2	130.5±13.4	133.1±1.8	134.4±11.2	132.9±13.6	133.2±13.9	134.7±13.1	132.1±2.1	T < 0.001
	AHA	125.9±12.4	132.9±9.6	135.9±8.4	136.1±7.9	136.8±8.8	137.05±10.3	136.4±13.5	134.4±2.0	D = 0.17
	CC-I	129.5±11.0	138.2±7.8	136.0±14.3	139.1±9.0	139.3±8.1	141.5±6.8	141.5±7.3	137.9±2.0	TxD = 0.79
	CC-II	131.0±16.1	136.4±9.9	139.1±7.4	135.4±23.6	140.2±9.0	138.6±10.9	139.8±11.8	137.2±1.9	
	Mean	**128.1±13.4**	**134.6±10.6***	**136.2±11.2***	**136.3±14.7***	**137.5±10.2***	**137.7±10.9***	**138.2±11.8***		
Social Anxiety	CTRL	33.5±8.6	34.9±7.4	36.0±8.0	36.5±8.5	34.2±9.2	36.6±9.9	36.0±8.8	35.4±1.9	T < 0.001
	AHA	30.3±8.1	32.3±8.5	34.4±8.5	34.0±9.3	34.8±9.6	34.9±8.6	35.1±9.0	33.7±1.9	D = 0.86
	CC-I	31.4±8.7	32.7±9.1	35.7±7.6	35.4±7.6	37.7±8.4	37.3±8.7	37.7±8.2	35.4±1.9	TxD = 0.20
	CC-II	33.0±9.5	34.3±10.1	35.3±10.9	36.3±11.7	36.7±10.9	36.9±11.3	37.8±12.4	35.8±1.8	
	Mean	**32.1±8.7**	**33.6±8.8***	**35.4±8.8***	**35.6±9.4***	**35.9±9.5***	**36.4±9.6***	**36.7±9.8***		
Self-esteem (Rosenberg)	CTRL	30.9±3.5	31.1±3.8	31.3±3.5	30.9±4.1	32.2±4.4	31.6±4.4	32.1±4.2	31.4±0.7	T =0.003
	AHA	29.6±3.6	29.8±2.8	29.7±3.2	31.0±3.5	30.2±3.8	31.1±3.5	31.1±3.0	30.4±0.7^{cd}	D = 0.031
	CC-I	32.8±3.5	32.7±2.9	33.1±3.2	32.8±3.7	33.2±3.5	33.4±3.4	33.9±3.4	33.1±0.7	TxD = 0.41
	CC-II	31.8±4.1	32.8±3.4	32.5±3.6	32.2±3.8	31.7±5.5	33.6±3.4	32.8±3.9	32.5±0.7	
	Mean	**31.3±3.8**	**31.6±3.4**	**31.7±3.6**	**31.7±3.8**	**31.8±4.5**	**32.5±3.8***	**32.4±3.9***		

Values are represented as means ± standard deviation (SD) except group means are ±standard error mean (SEM). N=86; CTRL (n=20), AHA (n=21), CC-I (n=21), CC-II (n=23). GG= Greenhouse-Geisser. T= Time effect. D= Diet effect. T x D= Time x Diet effect. †= a trend from baseline $p > 0.05$ and $p < 0.1$ (post hoc LSD). All letter superscripts represent significance from post hoc LSD. a= significantly different than CTRL ($p < 0.05$). b= significantly different than AHA ($p < 0.05$). c= significantly different than CC-I ($p < 0.05$). d= significantly different than CC-II ($p < 0.05$).

Psychosocial

Table 4.10 presents changes in psychosocial assessments observed at 0, 4, 8, 12, 16, 20, and 24 weeks of program participation as determined by the SF36 Quality of Life (QOL), Social Physique Anxiety Scale (SPAS), and Rosenberg Self-Esteem Scale (RSES) Questionnaire inventories. MANOVA of SF36 QOL indices revealed an overall time effect (Wilks' Lambda, $p<0.001$), and no significant time x diet interaction ($p=0.34$). All diet groups, including CTRL, reported an improvement in QOL (CTRL 9.1±2.69; AHA 10.57±2.63; CC-I 12.03±2.63; CC-II 8.75±2.46, $p=0.798$). Univariate ANOVA of physique dependent social anxiety, measured by the Social Physique Anxiety Scale (SPAS), demonstrated that all four diet groups improved feelings of self-confidence and reduced social anxiety, although no time by diet interaction was observed (CTRL 2.5±1.36; AHA 4.81±1.33; CC-I6.24±1.33; CC-II 4.75±1.24, $p=0.20$). No time by diet interaction were observed in measures of self-esteem as reported by the Rosenberg Self-Esteem Scale (RSES) (CTRL 1.12 ±0.72; AHA 1.42±0.70; CC-I 1.05±0.70; CC-II 1.08±0.66, $p=0.41$). However, all diet groups, including CTRL, improved perceptions of self-esteem as an overall time effect was observed ($p<0.001$).

Genetic Match Results

Body Composition

Table 4.11 demonstrates changes in body composition variables as dependent on genetically matched to diet (M) only in the treatment groups (N=59), excluding CTRL. Participants were retrospectively analyzed as a true or false match to their assigned diet group based on their metabolic profile variants of FABP2 (Ala54Thr), ADRB-2 (Gln27Glu and Arg16Gly), ADRB-3 (Trp64Arg), and PPARγ2 (Pro12Ala). MANOVA of body composition variables measured by DEXA (body weight, fat mass, fat-free mass, and

body fat percentage) revealed an overall time effect (Wilks' Lambda $p<0.001$), but not a time x match interaction ($p=0.99$). Figure 4.7 shows that both false and true matches reduced a significant amount of body weight (kg) over 24 weeks, with no time by match interaction (F -4.25±0.93; T -4.63±0.85 kg, $p=0.61$). A trend was observed in true and false match differences in absolute values (kg) of body weight ($p=0.099$) and fat-free mass ($p=0.07$), as the true matches tended to be consistently higher than false matches. However, the relative percentage of body fat remained unchanged ($p=0.97$) between both groups. Figure 4.8 shows that both false and true matches lost a significant amount of fat mass (F -4.26±0.78; T -4.18±0.72 kg, $p<0.001$). Neither false or true genetic matches experienced a change from baseline in fat free mass ($p=0.79$) at 24-weeks. However, Figure 4.9 demonstrates a significant difference in delta values ($p=0.032$) between matches at 16 weeks. The falsely matched participants slightly gained FFM (0.28 kg; 95% CI, -0.35, 0.91) whereas the true matched participants lost FFM (-0.62 kg; 95% CI, -1.19, -0.06). Figure 4.10 illustrates the decrease in body fat percentage (F -4.45±0.75; T -4.24±0.69%, $p<0.001$) with no time x match interactions ($p=0.86$ and $p=0.79$, respectively).

Table 4.11 Genetic Changes in Body Composition and Anthropometric Measurements at 0, 4, 8, 12, 16, 20, and 24 weeks

		Week								
Variable	**Genetic Match**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**Group (SEM)**	**GG p-value**
Total Mass (kg)	FALSE	79.5±15.9	77.9±15.7	77.5±15.4	76.6±15.2	76.3±15.1	75.6±15.1	75.3±15.2	77.0±3.1	T < 0.001
	TRUE	87.1±17.1	85.4±16.5	84.2±16.8	83.3±16.9	83.2±17.3	82.7±16.8	82.4±17.0	84.0±2.8	M = 0.099
	Mean	**83.6±16.8**	**82.0±16.4***	**81.2±16.4***	**80.3±16.3***	**80.0±16.6***	**79.4±16.3***	**79.2±16.5***		TxM = 0.61
Fat mass (kg)	FALSE	30.8±9.7	29.6±9.4	28.7±8.9	27.9±9.2	27.3±9.2	27.0±9.6	26.5±8.8	28.3±1.8	T < 0.001
	TRUE	34.4±9.8	33.2±9.4	31.9±9.6	31.3±9.9	30.8±10.3	30.6±10.4	30.3±10.7	31.8±1.7	M = 0.16
	Mean	**32.8±9.9**	**31.6±9.5***	**30.4±9.4***	**29.8±9.6***	**29.2±9.9***	**28.9±10.1***	**28.6±9.9***		TxM = 0.86
Fat free mass (kg)	FALSE	42.5±6.3	42.5±6.5	42.8±6.8	42.79±6.4	42.8±6.3	42.63±6.02	42.8±6.5	41.1±1.3	T = 0.79
	TRUE	46.2±7.5	46.0±7.5	46.1±7.4	45.97±7.6	45.62±7.1*	45.8±6.85	46.0±6.7	44.3±1.2	M = 0.072
	Mean	**44.5±7.2**	**44.41±7.2**	**44.58±7.3**	**44.52±7.2**	**44.33±6.83**	**44.35±6.62**	**44.5±6.7**		TxM = 0.43
BF %	FALSE	41.6±4.1	40.5±4.2	39.3±4.6	38.9±5.4	38.0±5.4	37.5±6.1	37.1±6.1	39.0±0.9	T < 0.001
	TRUE	41.4±4.5	40.6±5.0	39.6±4.7	38.5±5.3	37.9±5.5	37.6±5.8	37.2±5.5	39.0±0.9	M = 0.97
	Mean	**41.5±4.3**	**40.6±4.6***	**39.5±4.6***	**38.7±5.3***	**37.9±5.4***	**37.6±5.9***	**37.1±5.7***		TxM = 0.79
Waist (cm)	FALSE	86.3±14.1	84.8±13.6	84.7±13.9	84.2±12.5	84.1±13.3	84.1±13.8	83.1±13.0	84.5±2.4	T < 0.001
	TRUE	93.0±12.9	91.1±12.3	89.7±12.4	89.6±11.4	88.3±10.8	88.7±11.7	88.3±12.5	89.8±2.2	M = 0.106
	Mean	**89.9±13.8**	**88.2±13.2***	**87.4±13.2***	**87.1±12.1***	**86.4±12.1***	**86.6±12.8***	**86.0±12.9***		TxM =0.22
Hip (cm)	FALSE	112.6±12.3	110.5±12.3	109.9±12.9	109.1±11.8	109.3±11.5	108.9±12.3	108.2±12.5	109.8±2.2	T < 0.001
	TRUE	115.9±11.2	113.9±10.8	112.4±11.1	112.0±10.9	111.8±10.7	111.9±11.4	111.4±12.1	112.8±2.0	M = 0.33
	Mean	**114.4±11.8**	**112.4±11.5***	**111.3±11.9***	**110.7±11.3***	**110.7±11.1***	**110.5±11.8***	**109.9±12.3***		TxM = 0.91
REE (kcal/D)	FALSE	1362±260	1395±263	1336±252	1324±273	1333±237	1321±286	1303±316	1339±47	T = 0.41
	TRUE	1503±290	1435±233	1463±274	1461±292	1422±297	1434±323	1426±283	1449±43	M = 0.09
	Mean	**1439±283**	**1416±246**	**1405±269**	**1398±289**	**1382±273**	**1382±309**	**1370±302**		TxM = 0.54

Values are represented as means ± standard deviation (SD) except group means are ±standard error mean (SEM). N=59; FALSE (n=27), TRUE (n=32). GG= Greenhouse-Geisser. T= Time effect. M= Match effect. T x M= Time x Match effect. # = significant match effect $p<0.05$ (univariate). *= significant time effect from baseline $p<0.05$ (post hoc LSD). †= a trend from baseline $p > 0.05$ and $p < 0.1$ (post hoc LSD).

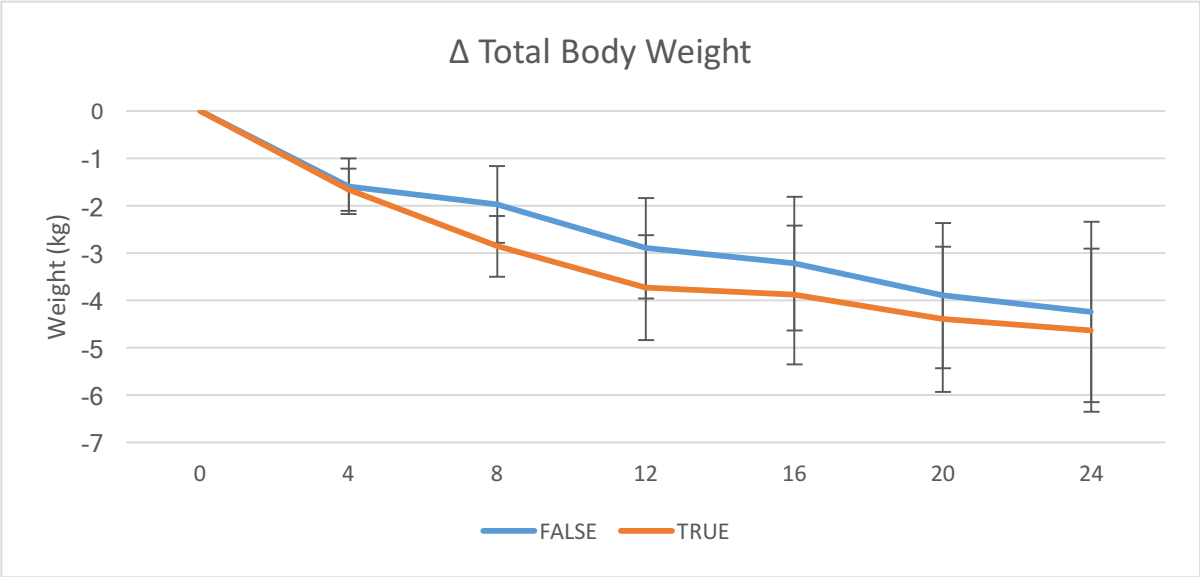

Figure 4.7 Genetic Δ Total Body Weight. Data present mean change (95% CI) from baseline for total body weight in False and True genetic matches over 24 weeks; N=59. CI: Confidence Interval.

Figure 4.8 Genetic Δ Fat Mass. Data present mean change (95% CI) from baseline for body fat mass in False and True genetic matches over 24 weeks; N=59. CI: Confidence Interval.

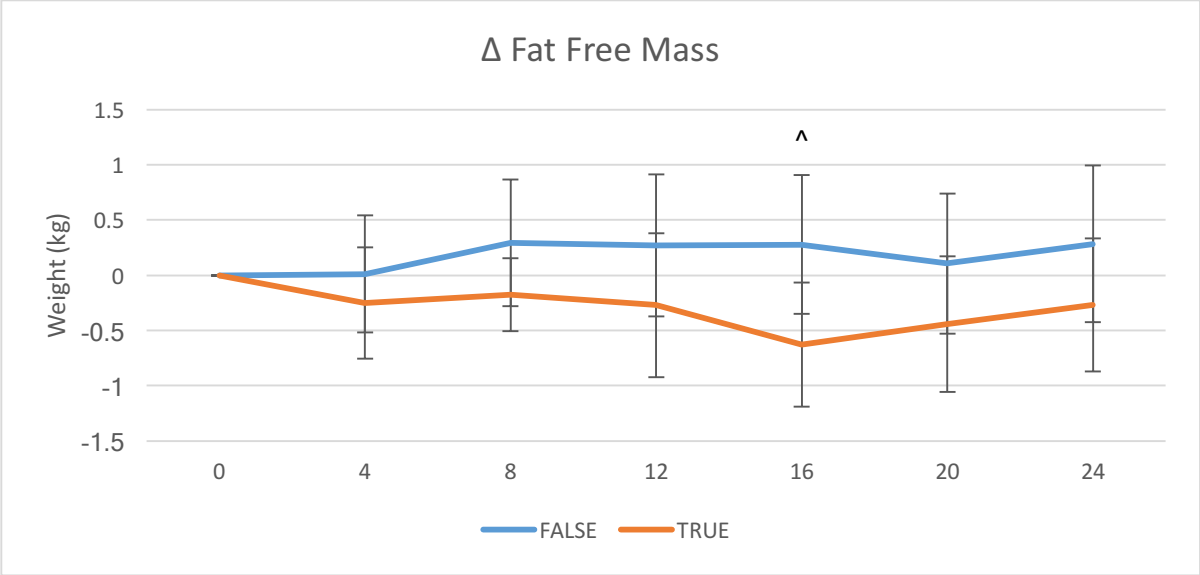

Figure 4.9 Genetic Δ Fat Free Mass. Data present mean change (95% CI) from baseline for fat free mass in False and True genetic matches over 24 weeks; N=59. LSD post hoc analysis is indicated by the following superscripts: ^ represents p < 0.05 difference between matches (groups). CI: Confidence Interval.

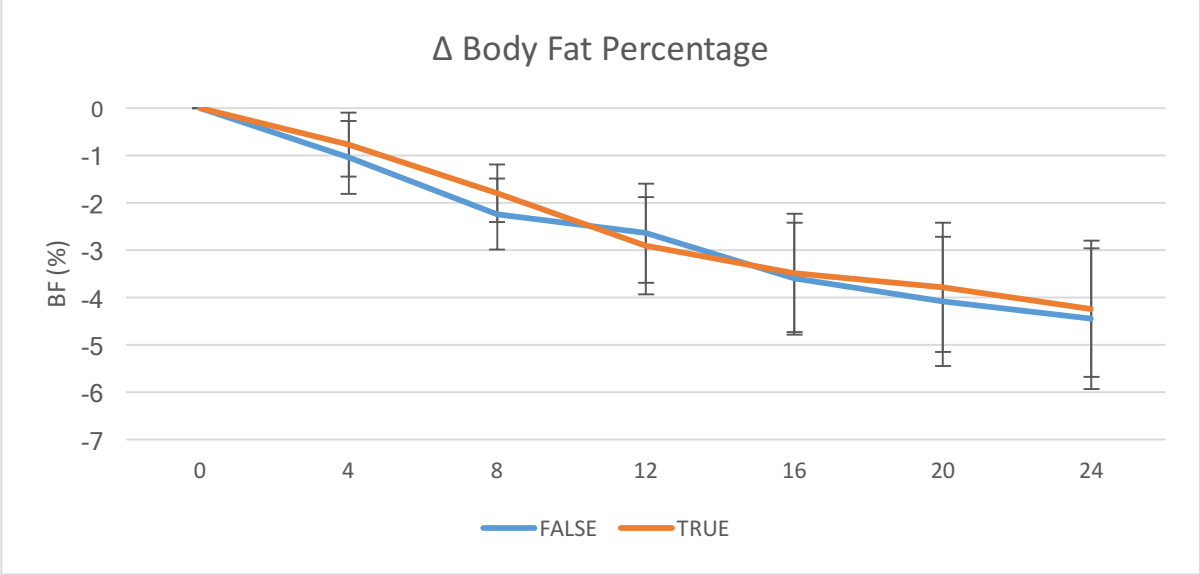

Figure 4.10 Genetic Δ Body Fat Percentage. Data present mean change (95% CI) from baseline for body fat percentage in False and True genetic matches over 24 weeks; N=59. CI: Confidence Interval.

MANOVA of anthropometric measurements revealed an overall time effect (Wilks' Lambda $p<0.001$) but no time x match interaction ($p=0.20$). Univariate analysis of waist measurement reveals a significant reduction in waist circumference for both false and true matches (F -3.16±1.02; T -4.64±0.93 cm, $p<0.001$) with no time by match interaction ($p=0.23$). Univariate analysis of hip measurement reveals a significant reduction in hip circumference for both false and true matches (F -4.45±0.93; T -4.54±0.86 cm, $p<0.001$) with no time by match interaction ($p=0.91$). No significant differences between or within genetically matched participants were observed in terms of waist-hip ratio as demonstrated in Figure 4.11.

Repeated Measures ANOVA revealed no significant time (Wilks' Lambda $p=0.41$) or time x diet group interaction ($p=0.54$) in resting energy expenditure (REE), although a trend was observed between T and F matches ($p=0.09$), as true matches tended to intake higher kcals/day at each time point. These observations reject Hypothesis 2.

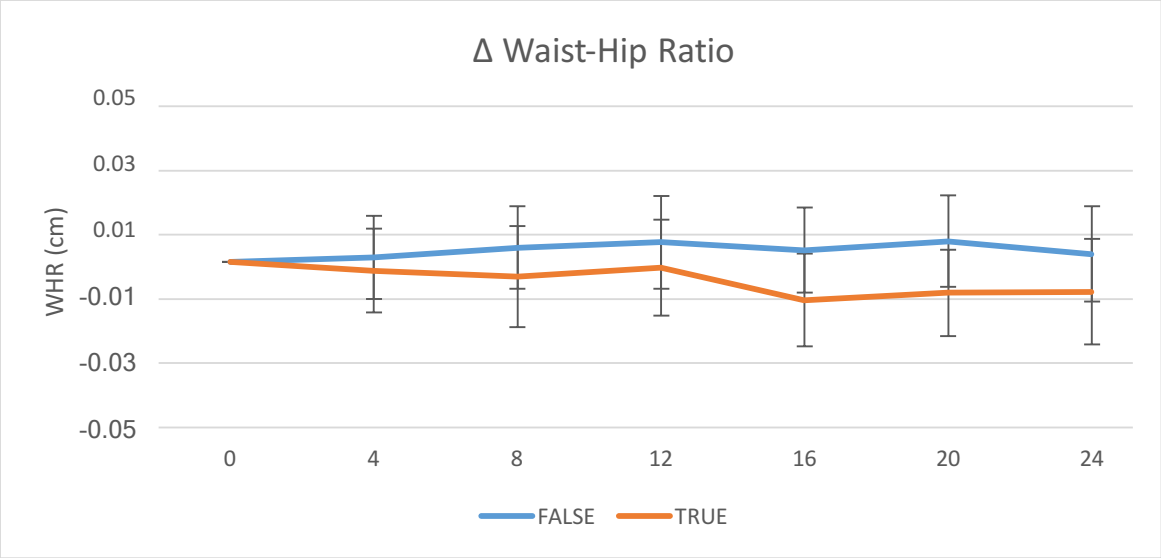

Figure 4.11 Genetic Δ Waist-Hip Ratio. Data present mean change (95% CI) from baseline for Waist-Hip Ratio in False and True genetic matches over 24 weeks; N=59. CI: Confidence Interval.

Table 4.12 Relative Changes in Body Composition at 0, 4, 8, 12, 16, 20, and 24 weeks

		Week (N-size)						
Variable	**Diet Match**	**0**	**4 (N=83)**	**8 (N=73)**	**12 (N=64)**	**16 (N=66)**	**20 (N=62)**	**24 (N=59)**
Body Weight (kg)	FALSE	0±0	-1.78±1.5	-2.18±2.2	-3.35±3	-3.71±3.7	-4.29±4	-4.25±4.8
	TRUE	0±0	-1.35±1.7	-2.44±2.5	-3.61±3.2	-3.64±4.2	-4.48±4.2	-4.63±4.8
	Mean	**0±0**	**-1.52±1.6**	**-2.33±2.4**	**-3.48±3.1**	**-3.67±4**	**-4.39±4.1**	**-4.46±4.8**
TxM			*p=0.24*	*p=0.65*	*p=0.74*	*p=0.95*	*p=0.86*	*p-0.86*
Fat mass (kg)	FALSE	0±0	-1.31±1.7	-2.03±1.8	-3.04±2.5	-3.69±3	-3.95±3.3	-4.26±4
	TRUE	0±0	-1.12±1.7	-2.38±2	-3.07±2.6	-3.52±3.1	-4.01±3.6	-4.17±4.1
	Mean	**0±0**	**-1.2±1.7**	**-2.23±1.9**	**-3.06±2.5**	**-3.6±3**	**-3.98±3.4**	**-4.21±4**
TxM			*p=0.63*	*p=0.44*	*p=0.97*	*p=0.82*	*p=0.95*	*p=0.93*
Fat free mass (kg)	FALSE	0±0	-0.05±1.5	0.17±1.5	0.07±1.7	0.07±1.7	-0.06±1.7	0.28±1.8
	TRUE	0±0	-0.17±1.6	-0.09±1.3	-0.18±1.8	-0.42±1.8	-0.38±1.7	-0.27±1.7
	Mean	**0±0**	**-0.12±1.5**	**0.02±1.4**	**-0.06±1.7**	**-0.19±1.7**	**-0.23±1.7**	**-0.02±1.7**
TxM			*p=0.72*	*p=0.43*	*p=0.57*	*p=0.26*	*p=0.46*	*p=0.23*
BF %	FALSE	0±0	-0.97±1.9	-2.04±1.9	-2.59±2.6	-3.54±2.8	-3.99±3.3	-4.45±3.8
	TRUE	0±0	-0.77±1.8	-1.72±1.6	-2.84±2.8	-3.44±3.4	-3.85±3.7	-4.24±4
	Mean	**0±0**	**-0.85±1.8**	**-1.85±1.7**	**-2.73±2.7**	**-3.49±3.1**	**-3.92±3.5**	**-4.33±3.8**
TxM			*p=0.63*	*p=0.45*	*p=0.72*	*p=0.89*	*p=0.87*	*p=0.84*

Delta values are represented as means ± standard deviation (SD) difference from baseline (0 week) through 24 weeks. T x M= Time x Match Interaction effect as determined by one-way ANOVA. P-levels represent TxM interaction of participants who completed the study up to that testing session. BF%: Body fat percentage.

To determine if N-size may have influenced overall genetic match results, delta changes from baseline in body composition (body weight, fat mass, and body fat percentage) were analyzed that included dropped participants who did not complete the study as shown in Table 4.12. Although N-size was larger between weeks 0-20, no differences in relative measures of body composition were observed between T and F matches to diet by genetic profile.

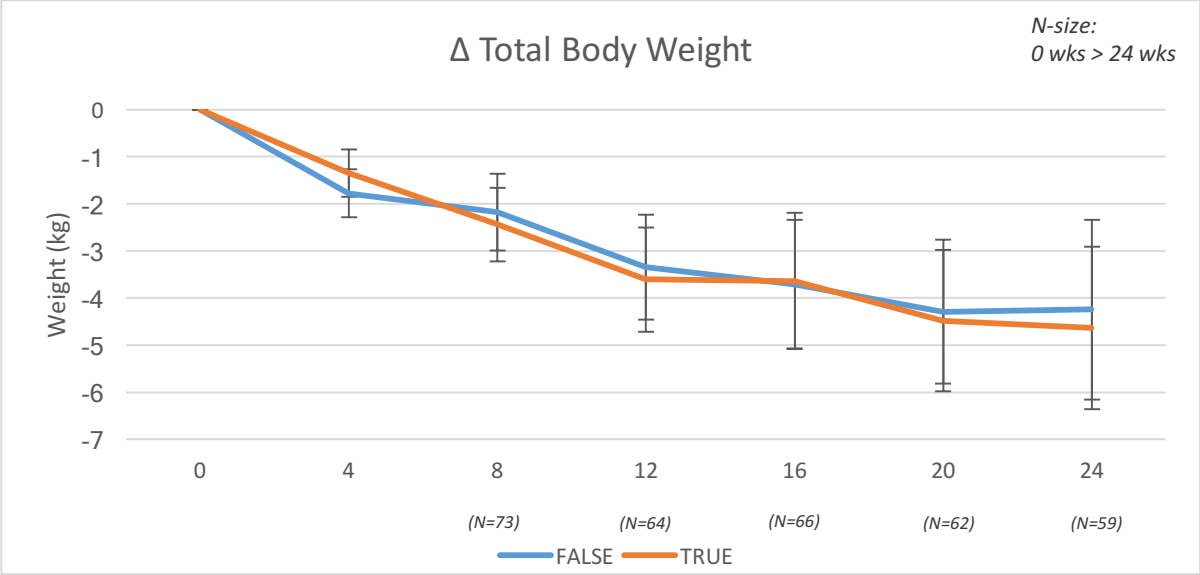

Figure 4.12 Genetic Δ Total Body Weight [N=83 →59]. Data present mean change (95% CI) from baseline for total body weight in False and True genetic matches over 24 weeks, including dropped participants. 0 weeks N=83, 4 weeks N=83, 8 weeks N=73, 12 weeks N=66, 16 weeks N=64, 20 weeks N=62, 24 weeks N=59. CI: Confidence Interval.

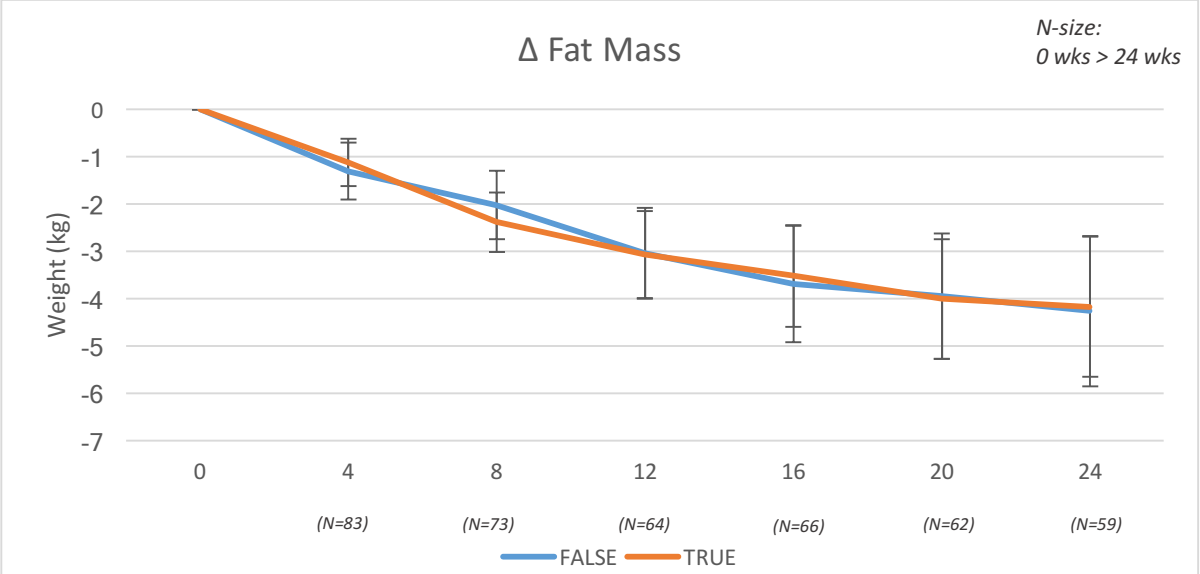

Figure 4.13 Genetic Δ Fat Mass [N=83 →59]. Data present mean change (95% CI) from baseline for fat mass in False and True genetic matches over 24 weeks, including dropped participants. 0 weeks N=83, 4 weeks N=83, 8 weeks N=73, 12 weeks N=66, 16 weeks N=64, 20 weeks N=62, 24 weeks N=59. CI: Confidence Interval.

Biochemical Markers of Health by Genetics

Table 4.13 demonstrates the changes in blood lipid variables as dependent on metabolic match to diet type in the treatment groups. MANOVA of blood lipids revealed an overall time effect (Wilks' Lambda $p<0.001$) but not a time x genetic match interaction (Wilks' Lambda $p=0.30$). Univariate analysis of total cholesterol concentration revealed both false and true matches reduced CHL (F -14.11±6.88; T -15.20±6.32 mg/dL, $p<0.001$) without a significant time x match interaction ($p=0.16$). However, a match interaction was observed ($p=0.01$), as false matches had higher values relative to the true matches throughout the 24-week trial. Univariate analysis of LDL concentrations revealed an overall time effect ($p<0.001$) as both false and true matches had significantly reduced LDL levels measured at 24 weeks. A time x genetic interaction was observed, as the true diet matches experienced a significantly greater loss in LDL concentration from baseline (F –31.29±12.94; T -44.41±11.89 mg/dL, $p=0.04$). Univariate analysis of HDL concentrations showed an overall time effect ($p=0.003$), although the only difference from baseline was observed in the false matched group at 12 weeks. A match group difference was observed as the false matches had significantly higher mean HDL levels (F 64.36±2.84; T 54.72±2.61, $p=0.015$) than the true matched group. No significant time x match interaction was observed ($p=0.16$). Figures 4.14-4.17 demonstrate relative changes in the blood lipid concentrations for True and False genetic matches at 0, 12, and 24 weeks.

Table 4.13 Genetic Changes in Fasting Blood Lipids at 0, 12, and 24 weeks

Variable	Genetic Match	Week 0	Week 12	Week 24	Group (SEM)	GG p-value
[a]Total CHL (mg/dl)	FALSE	214.98±42.92	186.15±46.9	200.86±37.56	200.66±6.2 #	T < 0.001
	TRUE	188.73±37.42	175.14±31.37	173.53±33.02	179.13±5.7	M = 0.013
	Mean	**200.74±41.81**	**180.18±39.28***	**186.04±37.47***		TxM = 0.16
[b]LDL-c (mg/dl)	FALSE	159.53±57.94 #	153.32±57.36 #	128.24±41.02*	147.03±9.9	T < 0.001
	TRUE	168.02±72.27	167.78±73.88	123.62±55.03*	153.14±9.1	M = 0.65
	Mean	**164.13±65.68**	**161.17±66.67**	**125.73±48.76***		TxM = 0.04
[c]HDL-c (mg/dl)	FALSE	68.94±19.44	58.48±16.74	65.68±18.5	64.36±2.8 #	T = 0.003
	TRUE	55.56±16.42	52.67±16.26	55.94±15.56	54.72±2.6	M = 0.015
	Mean	**61.68±18.94**	**55.33±16.6***	**60.4±17.52**		TxM = 0.16
[d]TAG (mg/dl)	FALSE	122.16±61.63	110.95±57.07	104.58±50.18	112.57±9.9	T = 0.001
	TRUE	131.12±63.37	114.76±55.27	107.7±52.03	117.86±9.2	M = 0.698
	Mean	**127.02±62.2**	**113.02±55.65†**	**106.27±50.77***		TxM = 0.81

Values are represented as means ± standard deviation (SD) except group means are ±standard error mean (SEM). N=59; FALSE (n=27), TRUE (n=32). GG= Greenhouse-Geisser. T= Time effect. M= Match effect. T x M= Time x Match effect. # = significant match effect p<0.05 (univariate). *= significant time effect from baseline p<0.05 (post hoc LSD). †= a trend from baseline p > 0.05 and p < 0.1 (post hoc LSD). [a]CHL: Cholesterol, [b]LDL-c: Low Density Lipoprotein concentration, [c]HDL-c: High Density Lipoprotein concentration, [d]TAG: Tri(acyl)glycerides. To convert mg/dL cholesterol to mmol/L, multiply mg/dL by 0.026. To convert mmol/L cholesterol to mg/dL, multiply mmol/L by 38.6. Cholesterol of 194 mg/dl=5.04 mmol/L [b]To convert mg/dL triglyceride to mmol/L, multiply mg/dL by 0.0113. To convert mmol/L triglyceride to mg/dL, multiply mmol/L by 88.6. Triglyceride of 137 mg/dl=1.55 mmol/L.

Figure 4.14 Genetic Δ Total Cholesterol. Data present mean change (95% CI) from baseline for total cholesterol concentration in False and True genetic matches over 24 weeks; N=59. LSD post hoc analysis is indicated by the following superscripts: ^ represents p < 0.05 difference between matches (groups). CI: Confidence Interval.

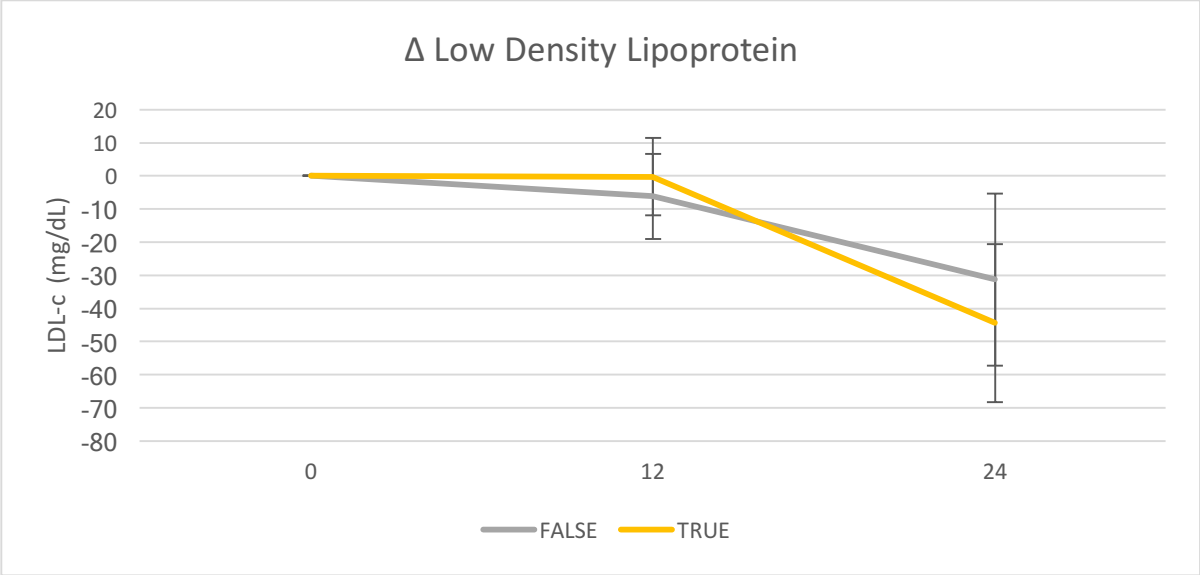

Figure 4.15 Genetic Δ Low Density Lipoprotein. Data present mean change (95% CI) from baseline for low density lipoprotein concentration in False and True genetic matches over 24 weeks; N=59. CI: Confidence Interval.

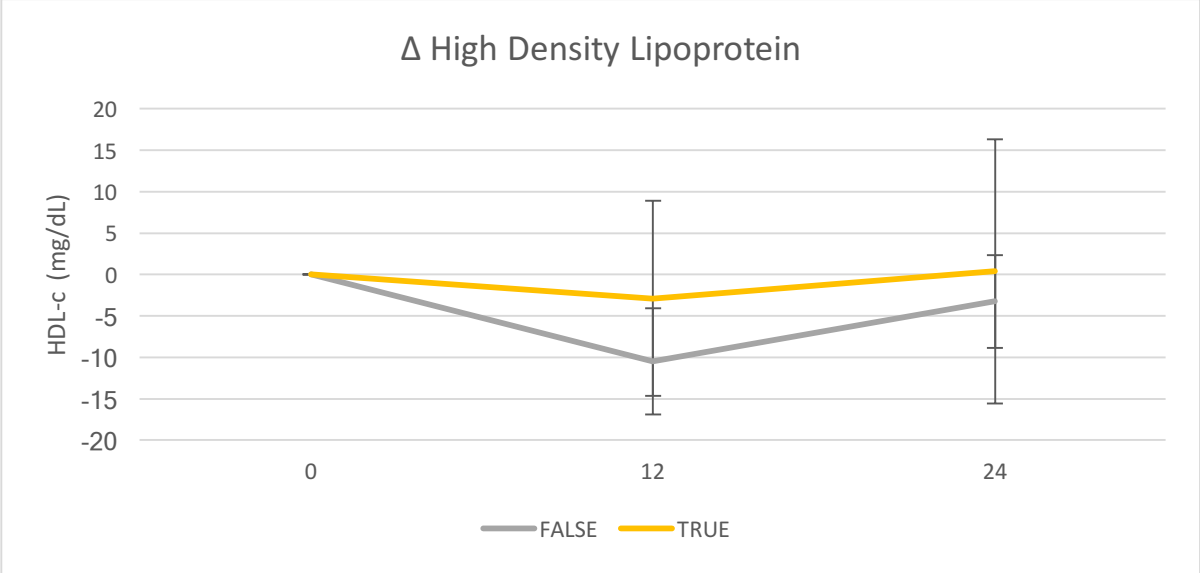

Figure 4.16 Genetic Δ High Density Lipoprotein. Data present mean change (95% CI) from baseline for high density lipoprotein concentration in False and True genetic matches over 24 weeks; N=59. CI: Confidence Interval.

Figure 4.17 Genetic Δ Triglycerides. Data present mean change (95% CI) from baseline for triglyceride concentration in False and True genetic matches over 24 weeks; N=59. CI: Confidence Interval.

Table 4.14 demonstrates the changes in fasting glucose and insulin concentrations at baseline through 24 weeks. MANOVA of glucose concentrations at 0, 12, and 24 weeks revealed an overall time effect (Wilks' Lambda p=0.05) but not time x match interaction (Wilks' Lambda p=0.32). Falsely matched participants had a significant decrease in glucose levels at 12 weeks from baseline (-4.59±2.12 mg/dL, p=0.034); however, the levels increased back to a non-significant change from baseline at 24 weeks (-1.57±3.03 mg/dL, p=0.61). True matched participants demonstrated a trend in decreased glucose levels at 24 weeks (-5.44±2.79 mg/dL, p=0.056). MANOVA of insulin concentrations at baseline and 24 weeks revealed an overall time effect (Wilks' Lambda p<0.001) but no time x match interaction (p=0.64). Both false and true matches decreased insulin levels in at 24 weeks (F -1.71±0.70; T -2.16±0.65 μIU/ml, p<0.001). An overall match trend demonstrated that true matches tended to have higher concentrations at 0 and 24 weeks

compared to false matched participants (p=0.098). An overall Wilks' Lambda time effect was observed for HOMA-IR (p<0.001), as both false and true matches reduced measures of insulin resistance from 0 to 24 weeks (F -0.48±0.20; T -0.59±0.19, p<0.001). No significant time x match interaction was observed (p=0.68) and there was no significant difference between T or F matches (p=0.23). These observations reject Hypothesis 3.

Table 4.14 Genetic Changes in Fasting Glucose and Insulin at 0, 12, and 24 weeks

		Week				
Variable	**Genetic Match**	**0**	**12**	**24**	**Group (SEM)**	**GG p-value**
[a]Fasted glucose (mg/dl)	FALSE	95.1±14.5	90.5±16.7*	93.5±10.1	93.0±1.8	T = 0.037
	TRUE	95.2±10.9	93.1±10.9	89.7±10.6 †	92.7±1.6	M = 0.87
	Mean	**95.1±12.6**	**91.9±13.8***	**91.5±10.5** †		TxM = 0.024
[b]Fasted Insulin (µIU/ml)	FALSE	9.5±6.7	-	7.8±6.4	8.7±1.2	T < 0.001
	TRUE	12.4±6.4	-	10.2±5.7	11.3±1.1	M = 0.098
	Mean	**11.1±6.6**	**-**	**9.1±6.1***		TxM = 0.64
HOMA - IR	FALSE	2.3±1.8	-	1.9±1.7	2.1±0.3	T < 0.001
	TRUE	2.9±1.5	-	2.3±1.3	2.6±0.3	M = 0.23
	Mean	**2.6±1.7**	**-**	**2.1±1.5***		TxM = 0.68

Values are represented as means ± standard deviation (SD) except group means are ±standard error mean (SEM). N=59; FALSE (n=27), TRUE (n=32). GG= Greenhouse-Geisser. T= Time effect. M= Match effect. T x M= Time x Match effect. # = significant match effect p<0.05 (univariate). *= significant time effect from baseline p<0.05 (post hoc LSD). †= a trend from baseline p > 0.05 and p < 0.1 (post hoc LSD). [a]To convert mg/dL glucose to mmol/L, multiply mg/dL by 0.0555. To convert mmol/L glucose to mg/dL, multiply mmol/L by 18.0. Glucose of 99 mg/dl=5.5 mmol/L. [b]To convert µIU/ml insulin to pmol/L, multiply µIU/ml by 6.945. To convert pmol/L to µIU/ml, multiply pmol/L by 0.144. Insulin of 13.8 µIU/ml=95.8pmol/L. Homeostatic Model Assessment of Insulin Resistance.

CHAPTER V

SUMMARY AND CONCLUSIONS

Summary

Obesity and its subsequent consequences of developing concerning medical conditions has been a focal point of health practitioners and researchers, as this condition has not appeared to subside despite the increased awareness of diet and exercise benefits. Although interventions such as increased physical activity and a reduction in caloric intake renders weight loss for most, variability in response to an identical stimulus still exists among individuals. Inherited genetic variability attributes to these differences, and may influence metabolic responses depending on SNPs of candidate genes responsible for nutrient absorption, tissue delivery, and the efficient utilization of stored energy. As such, it may be possible to predict outcomes such as weight loss, body composition, lipid biomarkers, and markers of insulin resistance when intervened with a specific diet and exercise protocol. This study first examined the efficacy of a standardized exercise protocol with participants assigned dietary protocols, and then examined the genetic influence of the results.

Reported inventories of dietary intake demonstrated participants in the dietary intervention groups were adherent to the total 1500 kcal/day requirements throughout weeks 4-24 as reported by group means (AHA 1474±61, CC-I 1409±61, CC-II 1500±57 kcal/day); however, CC-I and CC-II assigned to 45% PRO intake/day came short of this requirement as reported by the group means (CC-I 26.2±1.1, CC-II 29.3±1.0% PRO). Participants in AHA were better able to meet their assigned nutrient distribution requirements (15% PRO, 55% CHO, 30% FAT) as reported by group means (18.4±1.1%

PRO, 49.8±1.6% CHO, 31.6±1.3% FAT). Although the percentage of PRO distribution fell short in CC-I and CC-II, the relative intake (g/kg/day) had a considerable increase from baseline (CC-I 0.30 g/kg/d; 95% CI, 0.10, 0.50) and (CC-II 0.47 g/kg/d; 95% CI, 0.28, 0.67) when compared to the AHA diet group.

Self-reported levels of physical activity demonstrated the significant increase in METs-min/week in all diet intervention groups. Low levels of physical activity (PA) were calculated from the amount of walking related activity when at work, in transit, or during leisure time. As described in the methods, all participants in the diet treatment groups were recommended to walk 10k steps/day on non-resistance circuit exercise days, and participants were provided a pedometer to record and monitor their progress. The time, time by diet, and diet group effects were significant ($p<0.001$), as the interaction is clearly due to the significant increase in low PA among all the diet treatment groups (AHA, CC-I, CC-II) relative to the control group. This increase is likely due to the increase in walking during recreational activity. As expected, recreational activity had the most prominent increase in regards to METs-min/wk from baseline to week 24 in the intervention groups (AHA 928±120, CC-I 931±120, CC-II 1070±112 MET-min/wk; $p<0.001$) which may be attributed the exercise protocol of 30 min/day, 4x/week of resistance and Zumba exercise, in addition to the recommended steps/day.

All participants in this study included in the diet and exercise treatment groups (AHA, CC-I, CC-II) had significant reductions in body weight ($p<0.001$), fat mass ($p<0.001$), body fat percent ($p<0.001$), waist ($p=0.006$) and hip circumference ($p<0.001$), while maintaining fat-free mass ($p=0.90$) after 24 weeks. Additionally, all participants in the diet treatment groups experienced a significant increase in relative VO_2max ($p<0.001$) and GXT time (secs) to exhaustion ($p=0.02$) as measured by the Bruce Protocol

cardiopulmonary stress test. These initial findings suggest adherence to a hypocaloric structured diet that includes supervised resistance training interspersed with low-impact callisthenic exercise is effective in promoting positive body composition changes, cardiovascular capacity and muscular strength. Additionally, the results from this study support recent findings from our laboratory that indicate diet induced weight loss, when combined with a structured exercise program, reduces symptoms of metabolic syndrome (MetS) despite differences in PRO:CHO distribution [158].

A central hypothesis of this study was to determine the efficacy of a six-month diet and exercise weight loss intervention based on the influence of single nucleotide polymorphisms (SNPs) in metabolic regulatory genes ADRB2, ADRB3, FABP2, and PPARγ2 in previously sedentary women. The allele patterns comprised of different genotypes potentially attribute to biological functions responsible in nutrient and energy metabolism, and can be classified into three different categories of pre-determined metabolic efficiencies loosely referred to as "carb reducer," "fat trimmer," or "better balancer" defined by Interleukin Genetics®. The subsets of pre-determined metabolic efficiency were categorized by a low CHO diet responsive genotype (carb reducer), a low-fat diet responsive genotype (fat trimmer), and a balanced diet responsive genotype (better balancer). These categorical stratifications were used to retrospectively predict participants' response to their randomized dietary protocol by assigning them as a true match (T) or false match (F) to AHA, CC-I or CC-II.

Although all diets in our study were hypocaloric in daily intake (1500 kcal/day), the macronutrient composition varied in PRO:CHO:FAT as discussed previously. In contrast, the diets analyzed by Dopler-Nelson [54] from genetic samples in the 12-month, cohort A to Z trial [55] included the Atkins (CHO restricted) [159], Zone (low CHO)

[160], LEARN (Lifestyle, Exercise, Attitudes, Relationships, and Nutrition; low FAT, high CHO) [161], and Ornish diet (very high CHO) [162]. In Gardner's A to Z trial, the primary objective was to examine the degrees of CHO intake on weight loss and related metabolic variables in overweight, premenopausal women. In contrast, our study examined two high PRO diets (CC-I and CC-II) in comparison to one low PRO, high CHO American Heart Association (AHA) diet. High PRO was not a primary consideration in Gardner's initial study prior to Dopler-Nelson's retrospective analysis. Dopler-Nelson sought to examine the obesity candidate SNPs in ADRB2-79, ADRB2-46, ADRB3, FABP2, and PPAR γ2. The analysis [56] suggested a genetically influenced response to diet type in terms of weight loss and waist circumference reduction; however, few studies have replicated the design with the addition of exercise. Our study was designed to replicate the findings of Dopler-Nelson by categorically distributing SNP allele patterns and diet type; however, our results did not show the same statistical significance. Specifically, Dopler-Nelson reported that 101 overweight women in a dietary intervention study (A to Z trial) who were on a diet appropriate to their genotype (T) lost a mean of 5.2 kg body weight, whereas those who were not on a genotype appropriate diet (F) lost only 1.65 kg (p=0.013). In contrast, our study demonstrated that all participants in a diet and exercise intervention had similar weight reduction outcomes (F -4.25±0.93; T -4.63±0.85 kg, p=0.61) regardless of genetic match to diet. Additionally, women who were matched to a genotype appropriate diet in Dopler-Nelson's analysis reduced waist circumference by 6.6 cm, and those who did not match their genotype to diet reduced waist circumference by 3.0 cm (p=0.01). In our study, all participants reduced waist circumference without a significant difference between T or F genetic match to diet (F -3.16±1.02; T -4.64±0.93 cm, p=0.23). Additional data from Dopler-Nelson included differences in decreased

triglycerides (p=0.007) and increased HDL-c (p=0.01) in T matches compared to F matches to diet; however, the exact values were not reported.

According to Stanford's Dopler-Nelson report [56], identifying candidate genes influencing metabolism were shown to affect outcomes based on macronutrient distribution; however, these results have not been easily replicated in further investigations, especially with required exercise training as an additional component. Exercise was only a suggestion in the A to Z trial analyses [55], and can be determined as irrelevant to Dopler-Nelson's diet x genetic influence on weight loss and related metabolic factors. Because each of these obesity-related gene SNPs have differentiating effects on nutrient and exercising metabolism, this flux adds to the convolution of possible individual results.

In our study, overall changes in body weight, fat-mass, fat free mass, body fat percentage, waist and hip circumference were not dependent on participants' genetic false or true match to their specified diet. MANOVA of body composition variables (body weight, fat mass, lean mass, fat-free mass, and body fat percentage) revealed an overall time effect (Wilks' Lambda $p<0.001$), but not a time x match interaction ($p=0.99$), as all participants significantly reduced body weight in kg ($p=0.61$) independent of false or true genetic match to diet type. Both false and true matched participants lost a significant amount of fat mass ($p<0.001$) and body fat percentage ($p<0.001$) with no time x match interactions ($p=0.86$ and $p=0.79$, respectively). Neither false or true matches to diet experienced a change in fat free mass ($p=0.79$) from 0 to 24 weeks. However, a significant difference in FFM was observed at week 16, in which the false matches had maintained FFM, and the true matches slightly decreased FFM ($p=0.03$). This may be possibly due to the higher relative body composition of FFM in the true matches. As such, a slight loss of

FFM was parallel with overall weight loss. Consistent with this observation, a trend in T/F group differences in absolute values of body weight ($p=0.099$), fat-free mass ($p=0.07$), and notably fat mass ($p=0.16$) was present throughout the duration of the study, as the true matches tended to be higher than false matches. However, the relative percentage of body fat remained unchanged ($p=0.97$) between both groups. Anthropometric measurements revealed an overall time effect ($p<0.001$) but as with the measures of body composition, no time x match interaction was observed ($p=0.20$). As with body composition, true matches tended to have larger waist and hip measurements than false measurements for an overall Match trend; however, the reduction in anthropometrics were relative throughout the duration of the study. Both false and true matches significantly reduced waist circumference ($p<0.001$) with no time and a significant reduction in hip circumference was also observed for both false and true matches ($p<0.001$) with no time by match interaction ($p=0.91$).

In regards to lipid biomarkers and markers of insulin resistance, analysis of total cholesterol concentrations revealed both false and true matches reduced values ($p<0.001$) without a significant time x match interaction ($p=0.16$). However, a group effect was observed ($p=0.01$), as false matches had higher values relative to the true matches throughout the 24-week trial. This may be attributed to the higher HDL-c in F matches relative to the T matches. The analysis of HDL concentrations showed an overall time effect ($p=0.003$), although the only difference from baseline was observed in the false matched group at 12 weeks. A group difference was observed ($p=0.015$) as the false matches had significantly higher mean HDL concentrations than the true matched group. No significant time x match interaction was observed ($p=0.16$). Analysis of LDL concentrations revealed an overall time effect ($p<0.001$) as both false and true matches

had significantly reduced LDL levels by the end of the trial. A time x match interaction was observed, as the true diet matches experienced a significantly greater loss in LDL from baseline ($p=0.04$). The attribution to this interaction is due to differences at baseline (F 159.5±57.9; T 168.0±72.3 mg/dL, $p=0.05$) as true matches were higher in LDL-c; however, at week 24 both groups were significantly lower in absolute LDL-c (F -31.29±12.94; T -44.41±11.89 mg/dL, $p=0.04$) without a mean group difference ($p=0.65$). Falsely matched participants had a significant decrease in glucose levels at 12 weeks from baseline (-4.59±2.12 mg/dL, $p=0.034$); however, the levels increased back to a non-significant change from baseline at 24 weeks ($p=0.61$). True matched participants demonstrated a trend in decreased glucose levels at 24 weeks ($p=0.056$), and the overall time effect reveals false and true matches decreased insulin levels in at 24 weeks ($p<0.001$). Both false and true groups reduced measures of insulin resistance from 0 to 24 weeks, as an overall time effect was observed in HOMA-IR ($p<0.001$).

Discussion

This investigation clearly demonstrates the efficacy of a controlled diet and exercise induced weight loss protocol among all diet and exercise intervention groups (AHA, CC-I, CC-II) when compared to CTRL. However, the lack of differentiation between true and false genetic matches to diet type on most outcomes may be attributed to the substantial increase in physical activity among all intervention participants. The same five genetic variants (SNPs) in Dopler-Nelson's analysis [56] were matched to determine individual metabolic profiles as predictors of response to diet type. However, each SNP has been shown to differ in its potential contribution in response to exercise.

For example, several studies have investigated the role of ADRB 2 and 3 polymorphisms on the risk of developing obesity and assessed the effect of physical

activity on this risk. In a case-control study it was observed that the effect of the ADRB3 variant on obesity changes depending on the recreational physical activity levels. According to a study conducted on 313 Spanish subjects [163], carriers of Arg64 alleles in the ADRB3 gene could reduce the risk of developing obesity if their physical activity level was ≥ 20 MET hours/week. Additionally, in the HERITAGE Family Study, it was observed that carriers of Arg16 and Arg64 alleles, respectively, for ß2- and ß3- adrenergic receptors showed a greater decrease in fat mass in response to endurance training (METs > 6) than subjects with other allelic combinations [164]. Alternatively, results of other studies found no differences in weight loss in participants with various polymorphisms of the ADRB3 gene [127, 165-166]. However, these discordances could be due to a lack of homogeneity of the study groups (obese versus non-obese subjects, diabetics versus non-diabetics) or to ethnic differences.

SNPs in FABP2 have been shown to result in greater binding of the fatty acids released in the intestine from dietary fat, which in turn results in higher absorption of fat [99, 167]. The Ala54Thr polymorphism has been linked with obesity in multiple clinical research studies that indicate individuals with the Thr54 form of the protein demonstrate increased absorption and/or processing of dietary fatty acids by the intestine. The Thr54 variant has also been associated with elevated BMI and body fat [168], increased abdominal fat [169] and obesity and higher plasma leptin levels [170]. Multiple dietary intervention clinical research studies show that the Ala54Thr polymorphism affects the response to changes in dietary fat in test meals. It has been reported that individuals with 54Thr/Thr homozygous variant show increased levels of postprandial triglycerides [171, 172] and increased levels of 14-18-carbon fatty acids [96, 173] compared with the 54Ala/Ala form of the protein. A group of obese, non-diabetic patients analyzed before

and three months after a lifestyle modification program, consisting of hypocaloric diet (1,520 kcal/day) and aerobic exercise three times per week [119], showed that carriers of the Thr54 allele failed to have a significant reduction in fat mass, plasma LDL-c, and leptin levels when compared to the wild-type 54Ala/Ala homozygotes. Similarly, although the evidence of gene-diet interaction is strong involving the Pro12Ala polymorphism of PPARγ [174-177], few studies have examined the level of influence on exercising metabolism. As such, including PPARγ genotype as a predictor of response to diet and exercise has yet to be elucidated.

Limitations

Understanding how genetic polymorphisms contribute to metabolic processes can be valuable in evaluating human response to dietary intake, absorption, and the efficacy of energy expenditure. However, metabolic adaptions to exercise and diet can influence, and may override hereditary genetic dispositions (such as SNPs) in identified obesity related genes. A primary consideration is the specific metabolic function of each SNP. For example, FABP2 plays a significant role in nutrient absorption, whereas the adrenergic receptors (ADRB2 and ADRB3) have regulatory roles in exercising metabolism. As in Dopler-Nelson's study [56], analyzing ADRB2 and ARDB3 SNPs to match a true or false diet may be inaccurate without previously considering the effects of physical activity. The addition of exercise to a weight loss intervention requires a more analytical and replicable investigation of each SNPs influence on nutrient absorption and utilization before determining a metabolic profile to a diet designed to optimize results. Furthermore, the exercise intensity and frequency among participants in the treatment groups may interact with the polymorphisms (SNPs) of the genes analyzed (ADRB2, ADRB3, FABP2, and PPARγ) to influence DNA expression, and as such result in homogeneous means among

all treatment groups. Finally, Dopler-Nelson's analysis based genetically assigned match to diet on carbohydrate metabolism; whereas in our study, genetic matches were determined on very high protein diets without primary consideration of carbohydrate distribution. Interleukin Genetics did not match participants in AHA; therefore, these participants were matched based on previously similar categorical data with high carbohydrate distributions.

Conclusion

Future research should continue to evaluate the influence of exercise on metabolic regulatory genes when assigned a specified diet protocol. In addition to assessing SNPs, examining the expression of proposed candidate genes has potential to augment the understanding of physical activity induced changes in metabolic mechanisms, and subsequent weight loss results. Secondarily, monitoring the success of weight maintenance following a structured program may be beneficial in correlating SNPs to hereditary disposition to either regain weight, or successfully uphold the results from the initial weight loss intervention. Although this study did not provide evidence of genetic influence based on diet intervention, it does maintain that women adhering to a hypocaloric diet plan, regardless of macronutrient distribution, while participating in a supervised resistance-exercise based program, is effective in successful weight loss, body composition changes, cardiovascular capacity, muscular strength and endurance, and improvements of biochemical markers of health.

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APPENDIX A

TEXAS A&M UNIVERSITY HUMAN SUBJECTS PROTECTION PROGRAM CONSENT FORM

Project Title: Effects of a Carbohydrate Restricted, High Protein, High Fat Diet on Weight Loss and Health Outcomes in Women Participating in the Curves Fitness & Weight Loss Program

You are invited to take part in a research study being conducted by Dr. Richard Kreider, a researcher from Texas A&M University and funded by Curves International. The information in this form is provided to help you decide whether or not to take part. If you decide to take part in the study, you will be asked to sign this consent form. If you decide you do not want to participate, there will be no penalty to you, and you will not lose any benefits you normally would have.

Why Is This Study Being Done?
The purpose of this study is to determine if a carbohydrate restricted, high protein, high fat diet (20% carbohydrate, 45% protein, 35% fat; CC-II) promotes more favorable changes in weight loss and health outcomes compared to a traditional high carbohydrate, low protein, low fat diet (55% carbohydrate, 15% protein, 30% fat; AHA) and the Curves moderate carbohydrate restricted, high protein, and low fat diet (30% carbohydrate, 45% protein, 25% fat; CC-I).

Why Am I Being Asked To Be In This Study?
You are being asked to be in this study because you are a female between the ages of 18 and 60 years of age with a Body Mass Index (BMI) > 22 and a body fat percentage > 30%. You will not be allowed to participate in this study if you report a recent weight change of plus or minus 7 lbs. within the past 3 months. In addition you will not be allowed to participate in this study if you report any uncontrolled metabolic or cardiovascular disorder; including known electrolyte abnormalities, heart disease, arrhythmias, diabetes, thyroid disease, or a history of hypertension, hepatorenal, musculoskeletal, autoimmune, or neurological disease; if you are taking any weight loss supplements and/or ergogenic levels of nutritional supplements within the last 3 months that may affect body composition and/or anabolic/catabolic hormone levels; a history of pregnancy or lactation within the past 12 months or intentions to become pregnant during the next 12 months; participation in a regular exercise program within the past 3 months; or, the presence of any absolute or relative contraindications for exercise testing or prescription as outlined by the American College of Sports Medicine unless your personal physician feels the condition is controlled, would not be a limitation for you to participate in the study, and clears you for participation. If you do not qualify for this study we will keep your contact information (phone number and/or e-mail) and contact

you at a later date for potential entry into a similar study.

How Many People Will Be Asked To Be In This Study?
Approximately 400 people will be invited to participate in this study locally.

What Are the Alternatives to being in this study?
The alternative to being in the study is not to participate.

What Will I Be Asked To Do In This Study?
You will be asked to not exercise for 48 hours nor eat or drink calorie containing drinks for 12 hours before each testing session/visit. You will also be asked to record all food and drinks you eat and drink on food record forms for four days (including one weekend day) prior to all of the testing sessions/visits. Your participation in this study will last up to approximately six months and include eight visits (visit 1 ~ 1 hour/visit 2,5 and 8 ~ 3 hours/visit 3,4,6 and 7 ~ 1.5 hours). These visits are detailed below and in Table 1.

Visit 1 (week one) - Familiarization
This visit will last about one hour. During this visit the details of the study will be explained, human subject consent forms will be signed, personal and medical history information will be completed, and you will have a general physical that will include measurement of fasting blood to determine if you can participate in the study. You will donate approximately 5 ml (about 1 teaspoon) of fasting blood from a vein in your arm according to standard procedures. You will also be weighed and have your height measured.

Visit 2, 5 and 8 (week 0, 12 and 24) – (T1,T4 and T7)
These visits will last about three hours. During these visits you will first be asked to complete a physical activity questionnaire, a quality of life inventory, a social physique anxiety scale, a self-esteem scale, a body image questionnaire and an eating satisfaction inventory. These items will take about 30 minutes to complete. Two cheek swabs will then be taken from the inner cheek during visit 2 (baseline, T1) only. Interleukin Genetics will only be evaluating DNA to assess which diet may be more effective from a metabolism viewpoint. The samples will be destroyed after analysis. You will then have your resting energy expenditure determined. This will take about 30 minutes. You will then donate approximately 20 milliliters (4 teaspoons) of blood from a vein in your arm. Blood samples will be obtained by standard/sterile procedures using a needle inserted into a vein in your arm. This will take about 15 minutes. You will then have your total body composition measured, total body water determined, hip/waist measurements determined, resting blood pressure determined and heart rate measured. Collectively these tests will take about 30 minutes. You will then be prepared to perform a maximal treadmill test. This test will take about 30 minutes to complete. You will then perform a one repetition maximum and 80% of 1 repetition maximum endurance repetition test on the bench press and hip/leg sled using standard procedures. These tests will take about 30 minutes to complete. In the event of an emergency during an exercise test proper emergency response protocols (calling 9-911 for serious injury or a medical emergency,

calling Biosafety/EHS for cleanup assistance or spill team response, calling UPD for incidents in public areas, retrieving AED located in the lab, performing CPR or other First Aid techniques, etc.) will be followed by the Exercise & Sport Nutrition Laboratory (ESNL) staff depending on the severity of the emergency.

Visit 3,4,6 and 7 (week 4,8,16 and 20) – (T2, T3, T5 and T6)
These visits will last about one and a half hours. The same tests will be performed at visits 3, 4, 6 and 7 minus the exercise tests (maximal treadmill test, bench press test and hip/leg press test).
After baseline testing you will be matched according to BMI, age and body fat percentage and randomly assigned to one of four groups including: 1.) a no exercise, no diet intervention control group (C); 2.) an American Heart Association recommended high carbohydrate, low protein, and low fat diet (55% carbohydrate, 15% protein and 30% fat) group (AHA); 3.) the Curves Complete moderate carbohydrate, high protein, low fat diet (30% carbohydrate, 45% protein and 25% fat) group (CC-I); or, 4.) the Curves Complete carbohydrate restricted, high protein, high fat diet (20% carbohydrate, 45% protein, 35% fat) group (CC-II). If you are in groups 2, 3 or 4 you will consume 1,400 kcals/day for 1 week and 1,500 kcals/day at the prescribed macronutrient intakes for 23 weeks. Meal plans on the Curves Complete diets will be provided with limited food options for the first two weeks.
Thereafter, more variety in food choices will be provided to meet macronutrient goals. Additionally, the Curves Complete diets will be designed by a dietitian with a goal of providing foods with low amounts of saturated fat. In addition, if you are in groups 2, 3 or 4 you will be expected to exercise four days per week using the Curves 30 minute circuit training program. Each circuit style workout consists of 14 resistance exercises that work all major muscle groups. These are set up with floor-based calisthenics exercises (e.g., running/skipping in place, arm circles, Zumba dance, etc.) designed to maintain an elevated heart rate. You may also be asked to wear a heart rate monitor. All exercise sessions will be held in the Exercise and Sport Nutrition Laboratory. Research Assistants will monitor your exercise sessions and record your attendance. You will also be encouraged to walk for 30 minutes at a brisk pace and/or accumulate 10,000 steps per day on non-circuit training days. The International Physical Activity Questionnaire (IPAQ), daily physical activity logs and daily steps recorded from a pedometer will be used to assess physical activity patterns.

You may be removed from the study by the investigator for these reasons:

- You do not show up for your scheduled testing sessions/visits and the investigators are unable to contact you to reschedule.
- You do not follow your assigned diet protocol.
- You do not follow your assigned exercise protocol.

Are There Any Risks To Me?
The things that you will be doing are greater than risks that you would come across in everyday life. Although the researchers have tried to avoid risks, you may feel that some questions/procedures that are asked of you will be stressful or upsetting. You do not

have to answer anything you do not want to. You will be exposed to a low level of radiation during the body composition test, which is similar to the amount of natural background radiation you would receive in one month while living in College Station Texas. In addition, a very low level of electrical current will be passed through your body during the body water test. This analyzer is commercially available and has been used in the health care/fitness industry as a means to assess body composition and body water for over 20 years. The use of these analyzers have been shown to be a safe method of measuring body composition and total body water and are approved by the FDA. You will donate approximately 4 teaspoons (20 milliliters) of blood during the initial familiarization/screening visit and then again at each of the seven testing sessions throughout the study using standard procedures. These procedures may cause a small amount of pain when the needle is inserted into the vein as well as some bleeding and bruising. You may also experience some dizziness and/or faint if you are unaccustomed to having blood drawn. The exercise tests that will be performed may cause symptoms of fatigue, shortness of breath, and/or muscular fatigue/discomfort. The exercise tests may also cause short-term muscle soreness and moderate fatigue for several days following the tests. You may also experience muscle strains/pulls during the exercise testing and/or training program. However, exercise sessions will be conducted by trained personnel and monitored to ensure you follow appropriate exercise guidelines. You will follow a prescribed dietary regimen involving consuming 1,400 or 1,500 calories per day during various phases of the program. In addition, one group will eat a high percentage of calories in the form of protein. Although the total amount of total protein is not excessive (169 grams/day) it may be higher than you are accustomed to eating and may exceed recommended protein intake for active individuals. As a result, you may experience weight loss or gain, feelings of hunger or fullness, and/or changes in appetite and/or mood during various phases of the dietary intervention. In addition your risk to participation in this study may be greater if you have medical clearance to participate with a controlled medical condition. The likelihood of any of these occurring is slim.

Are There Any Benefits To Me?
The direct benefit to you being in this study is to know more about your health and fitness status from the tests to be performed. However, even if no individual benefit is obtained, you will be paid for your participation.

Will There Be Any Costs To Me?
Other than your time, there are no costs for taking part in the study.

Will I Have To Pay Anything If I Get Hurt In This Study?
If you suffer any injury as a result of taking part in this research study, please understand that nothing has been arranged to provide free treatment of the injury or any other type of payment. However, all needed facilities, emergency treatment and professional services will be available to you, just as they are to the community in general. You should report any injury to Dr. Richard Kreider at 979-845-1333. You will not give up any of your legal rights by signing this consent form.

Side effects (injury) can happen in any research study. These effects may not be your fault or the fault of the researcher involved. Known side effects have been described in the "Are there any risks to me?" section of this consent form. However, side effects that are not currently known may happen and require care. You do not give up any of your legal rights by signing this form.

Will I Be Paid To Be In This Study?
You will receive a total of $300 ($20 for the Familiarization and $40 for each additional testing session T1 – T7) in one check at the end of the study. Payment will occur after finishing all eight sessions and after all study materials (food records, etc.) have been turned in to the study staff. You will be paid on a prorated basis if you are unable to complete the entire study.

Will Information From This Study Be Kept Private?
The records of this study will be kept private. No identifiers linking you to this study will be included in any sort of report that might be published. Research records will be stored securely and only Exercise & Sport Nutrition Laboratory staff will have access to the records.

Information about you will be stored in locked file cabinets in a locked file room in an ID card swipe access controlled laboratory. Computer files will be protected with a password. This consent form will be filed securely in an official area.

People who have access to your information include the Principal Investigator and research study personnel. Representatives of regulatory agencies such as the Office of Human Research Protections (OHRP) and entities such as the Texas A&M University Human Subjects Protection Program (HSPP) may access your records to make sure the study is being run correctly and that information is collected properly.

The agency that is funding this study (Curves International) and the institutions(s) where study procedures are being performed (Texas A&M University) may also see your information. However, any information that is sent to them will be coded with a number so that they cannot tell who you are. Representatives from these entities can see information that has your name on it if they come to the study site to view records. If there are any reports about this study, your name will not be in them.

Information about and related to this study will be kept confidential to the extent permitted or required by law.

Who may I Contact for More Information?
You may contact the Principal Investigator, Richard Kreider, PhD, to tell him about a concern or complaint about this research at 979-845-1333 or rkreider@hlkn.tamu.edu. You may also contact the Co- Investigator/Laboratory Research Associate, Chris Rasmussen, at 979-458-1741 or crasmussen@hlkn.tamu.edu.

For questions about your rights as a research participant; or if you have questions, complaints, or concerns about the research, you may call the Texas A&M University Human Subjects Protection Program office at (979) 458-4067 or irb@tamu.edu.

What if I Change My Mind About Participating?
This research is voluntary and you have the choice whether or not to be in this research study. You may decide to not begin or to stop participating at any time. If you choose not to be in this study or stop being in the study, there will be no effect on your student status, medical care, employment, evaluation, relationship with Texas A&M University, etc. Any new information discovered about the research will be provided to you. This information could affect your willingness to continue your participation.

STATEMENT OF CONSENT
I agree to be in this study and know that I am not giving up any legal rights by signing this form. The procedures, risks, and benefits have been explained to me, and my questions have been answered. I know that new information about this research study will be provided to me as it becomes available and that the researcher will tell me if I must be removed from the study. I can ask more questions if I want. A copy of this entire consent form will be given to me.

Participant's Signature	Date
Printed Name	Date

INVESTIGATOR'S AFFIDAVIT:
Either I have or my agent has carefully explained to the participant the nature of the above project. I hereby certify that to the best of my knowledge the person who signed this consent form was informed of the nature, demands, benefits, and risks involved in his/her participation.

Signature of Presenter	Date
Printed Name	Date

APPENDIX B

Title Page Pg 1 of 6

General Screening Form

Study: Curves #2 **IRB:** IRB2013-0495F

Texas A&M, College Station, TX

Screening# ☐

Subject Initials ☐

Consent Date ☐☐ mm ☐☐ dd ☐☐☐☐ yyyy

Screening Date ☐☐ mm ☐☐ dd ☐☐☐☐ yyyy

Subject ID ☐

Personal Data

Visit: SCREENING **Screening #:** ☐☐☐

Name: _____

Address: _____

Phone #: _____

E-mail: _____

Local PCP: _____ ☐ None

_____

Demographics

Visit: SCREENING **Screening #:** ☐☐☐

Sex: ☐ M ☐ F

DOB: ☐☐ mm ☐☐ dd ☐☐☐☐ yyyy Age at enrollment: _____y

Race:
(Mark all which apply)

- ☐ White
- ☐ Black or African American
- ☐ Native Hawaiian or Other Pacific Islander
- ☐ Asian
- ☐ American Indian/Alaska Native
- ☐ Unknown

Ethnicity:
(Mark only 1)

- ☐ Hispanic or Latino
- ☐ Not Hispanic or Latino
- ☐ Unknown

General Health & Physical Exam

Visit: SCREENING **Screening #:** ___

PMHx: _____

Surgical Hx: _____

Allergies and drug reactions: _____

Medications:

SHx: Lives with: _____ Where: _____

Occupation Hx: _____

Smoking: Duration: _____ PPD x _____ Yrs EtOH: _____
Former smoker: when stopped: _____ Duration: _____ PPD x _____ Yrs

Vital signs:

HR: ____ m

BP: ____ / ____ mmHg

Anthropometry:
Height: ____ . ____ cm Weight: ____ . ____ kg BMI: ____ . ____ kg/m2

____ . ____ in ____ . ____ lb

General Health & Physical Exam

Visit: SCREENING **Screening #:**

ROS:	fever chills sweats wtΔ fatigue appetite sleep
Skin:	itching rash sores susp. moles/lesions- healing recentΔ
Head:	dizzy fainting HA/LOC trauma
Eyes:	correction Δvision-double tearing itching/redness
Ears:	Δhearing ringing earache vertigo/tinnitus
Nose:	epistaxis rhinorrhea allergies
Mouth/Throat:	bleeding gums sore mouth/throat swollen neck
CV:	angina palpitations DOE orthopnea/PND edema Pulm:
	SOB wheeze cough hemoptysis TB
Hematologic:	bruise /bleed easily transfusion hx
GI:	dysphagia N / V abd pain GERD hematochezia jaundice
GU:	freq urgency hesitancy dys- hematuria incont UTI's stones
Genital:	testicular masses hernias
Endocrine:	polyuria polydipsia skin/hair ? thyroid hx
Vascular:	claudication DVT hx
MSK:	jt pain stiffness arthritis gout
Neuro:	numbness weakness/atrophy seizure/tremor
Psych:	depression anxiety recent memoryΔ
Female:	regular dysmenorrhea pregnancies menopause
Breast:	skinΔ lumps pain discharge

PE:	Gen: Well
Skin:	cap refill: no rash lesions:
Head:	no trauma no bruising no masses
Eyes:	PERRLA EOMI no ptosis sclera clear
Ears:	good acuity TM: nl reflex/intact
Nose:	nl
Mouth/Throat:	nl/pink, moist mucous membranes no lesions
Neurological:	Alert & oriented×3, nl MS via conversation
Cranial Nerves:	II - XII intact/nl
Motor:	5/5 UE/LE's bil
Sensation:	intact LT UE/LE's
DTRs:	symmetric/nl biceps knee ankle
Gait/Station:	nl
Neck:	no LAD no masses no bruits no JVD supple stiff
Chest:	CTA bil equal expansion
Extremities:	no C/C/E Major jts: no swelling full ROM
Heart:	Reg no M/R/G
Pulses Bil:	PT / DP: 2+
Abdomen:	soft, NT/ND BS + no masses / organomegaly

Assessment: _____

_____

_____

_____

Blood Draw: ☐ Y ☐ N _____

Blood draw performed by: _____

Lab Results Reviewed: ☐ Y ☐ N

Eligible based on General Health and Physical Exam: ☐ Y ☐ N

_____ Date: ☐☐ ☐☐☐☐☐☐☐☐

Signature of staff member performing exam mm dd yyyy

_____ Date: ☐☐ ☐☐☐☐☐☐☐☐

Signature of Principal Investigator (page 2-13) mm dd yyyy

APPENDIX C

Texas A&M
UNIVERSITY

Dear Provider: One of your patient's would like to participate in a study titled "Effects of a Carbohydrate Restricted, High Protein, High Fat Diet on Weight Loss and Health Outcomes in Women Participating in the Curves Fitness & Weight Loss Program" that is being conducted by the Exercise & Sport Nutrition Laboratory (ESNL) at Texas A&M University. In order to do so, she must meet the selection criteria described below and/or have approval from her personal physician to participate in the study. The study will involve having sedentary and overweight female participants participate in the Curves exercise and weight loss program or a control program for 24 weeks. The assessments to be performed are listed below. Please check the test/tests you **do not** feel comfortable having your patient complete (if any). In addition please staple a copy of your letterhead to this form to verify that it has been reviewed.

_____Fasting blood

_____Bench press assessments

_____Leg press assessments

_____Diet intervention (see table attached)

_____Fasting resting energy expenditure (REE)

_____Bioelectrical Impedance Analysis (BIA)

_____Bone densitometry (DEXA)

Maximal cardiopulmonary stress test (Bruce Protocol)

Details about these specific tests are included below and in the attached participant consent form. If you feel she meets the entrance criteria and/or any existing medical condition that she may have is under control and **would not** be a limitation for her to participate in the study, please sign the medical clearance below.

Selection Criteria

Approximately 100 sedentary and overweight female participants (BMI > 22 and/or body fat percentage > 30%) between the ages of 18 and 60 will participate in this study. I understand that in order to participate in this study, a trained individual will examine me to determine whether I qualify to participate.

Participants **will not** be allowed to participate in this study if they:

1. have recent history of weight change (±7 lb within 3 months);
2. have any metabolic disorders including known electrolyte abnormalities; heart disease, arrhythmias, diabetes, thyroid disease, or hypogonadism; a history of hypertension, hepatorenal, musculoskeletal, autoimmune, or neurological disease; if they are taking thyroid, hyperlipidemic, hypoglycemic, anti-hypertensive, or androgenic medications;
3. have been pregnant or lactating within the past 12 months or are planning to become pregnant during the next 12 months;
4. have participated in a planned exercise program or have exercised regularly (> 30 min/d 3 days/wk) within the past three months;
5. have taken any weight loss medications and/or dietary supplements that may affect muscle mass or body weight during the three month time period prior to beginning the study;
6. have any absolute or relative contraindications for exercise testing or prescription as outlined by the American College of Sports Medicine;

The only exception to these selection criteria will be if the prospective participant has a medical condition or history that the participant's personal physician feels is controlled and therefore would not be a limitation for them to participate in the study.

Medical Clearance

I medically clear_____to participate as a participant in this study.

Name _____ Date _____

Signature _____

IRB NUMBER: IRB2013-0495F
IRB APPROVAL DATE: 08/21/2013
IRB EXPIRATION DATE: 08/15/2014

Diet Breakdown.

Diet	Kcals	Macronutrients	Diet Content (%)	g/d	Kcals/d	g/kg/d (90 kg)
AHA Recommended High Carbohydrate / Low Fat Diet (AHA)						
1 Week	1,400 kcals/d	CHO PRO FAT	55 15 30	193 53 47	770 210 420	**2.14** **0.58** **0.52**
23 Weeks	1,500 kcals/d	CHO PRO FAT	55 15 30	206 56 50	825 225 450	**2.28** **0.62** **0.56**
Curves Complete I –Moderate Carbohydrate / High Protein / Low Fat Diet (CC-I)						
1 Week	1,400 kcals/d	CHO PRO FAT	30 45 25	105 158 39	420 630 350	**1.17** **1.75** **0.43**
23 Weeks	1,500 kcals/d	CHO PRO FAT	30 45 25	113 169 42	450 675 375	**1.25** **1.88** **0.47**
Curves Complete II –Carbohydrate Restricted / High Protein / High Fat Diet (CC-II)						
1 Week	1,400 kcals/d	CHO PRO FAT	20 45 35	70 158 54	280 630 490	**0.78** **1.75** **0.60**
23 Weeks	**1,500 kcals/d**	**CHO** **PRO** **FAT**	**20** **45** **35**	**75** **169** **58**	**300** **675** **525**	**0.83** **1.88** **0.65**

Blood Samples. Participants will fast overnight for twelve (12) hours and then donate approximately 4 teaspoons of fasting venous blood (20 milliliters) 8 total times throughout the duration of the 24 week study. Blood samples will be obtained using standard phlebotomy procedures using standard sterile venipuncture of an antecubital vein by laboratory technician's trained in phlebotomy in compliance with guidelines established by the Texas Department of Health and Human Services. The phlebotomists and lab technicians will wear personal protective clothing (gloves, lab coats, etc.) when handling blood samples. Participants will be seated in a phlebotomy chair. Their arm will be cleaned with a sterile alcohol wipe and sterile gauze. A standard rubber tourniquet will then be placed on the brachium. An antecubital vein will be palpated and then a 23 gauge sterile needle attached to a plastic vacutainer holder will be inserted into the vein using standard procedures. Two serum separation vacutainer tubes (red tops) and one EDTA vacutainer tube (purple top) will be inserted into the vacutainer holder for blood collection in succession using multiple sample phlebotomy techniques. Once samples are obtained, the vacutainer

holder and needle will be removed. The needle will be discarded as hazardous waste in a plastic sharps container. The site of the blood draw will then be cleaned with a sterile alcohol wipe and gauze and a sterile Band-Aid will be placed on the site. The blood collection tubes will be labeled and placed in a test tube rack for later analysis.

Resting Energy Expenditure Assessment. Resting energy expenditure assessments will be made according to standard protocols using the Parvo Medics TrueOne 2400 Metabolic Measurement System. This will involve the participants lying down on an exam table, having a light blanket placed over them to keep warm and inserting ear plugs in their ears to reduce distractions. A see through metabolic canopy will then be placed over their neck and head so that metabolic measurements can be obtained. The participant will lie motionless without going to sleep for 15-minutes. Metabolic measurements will then be obtained to determine resting oxygen uptake and energy expenditure.

Body Composition Assessments (BIA & DEXA). Participants will undergo body composition tests in the ESNL. Prior to each assessment, height will be measured using standard anthropometry and total body weight will be measured using a calibrated electronic scale with a precision of +/-0.02 kg. Total body water will then be estimated using a Xitron 4200 Bioelectrical Impedance Analyzer (*San Diego, CA*) which measures bio-resistance of water and body tissues based on a minute low energy, high frequency current (500 micro-amps at a frequency of 50 kHz) transmitted through the body. This analyzer is commercially available and has been used in the health care/fitness industry as a means to assess body composition and body water for over 20 years. The use of this device has been approved by the Food and Drug Administration (FDA) to assess total body water and the current to be used has been deemed safe. This is measured through four electrodes placed on the body: one electrode will be placed on the posterior surface of the right wrist, in between the radial and ulna styloid processes (wrist bones), another electrode will be placed on the posterior surface of the right hand at the distal base of the second metacarpal; the third electrode will be placed on the anterior surface of the right foot at the distal end of the first metatarsal. Participants will lie on a table in the supine position and electrodes will be connected to the analyzer. After they are connected, age, gender, weight, height, and activity level are entered into the unit by the technician. After the unit has measured the resistance, which takes approximately 30 seconds, the unit then calculates total body water and body water percent.

Body composition/bone density will then be determined using a calibrated Hologic Discovery W dual-energy x-ray absorptiometry (DEXA) by qualified personnel with limited x-ray technology training under the supervision of Richard B. Kreider, PhD, MX. The DEXA body composition test will involve having the participant lie down on their back in a standardized position in a pair of shorts/t-shirt or a gown. A low dose of radiation will then scan their entire body for approximately six (6) minutes. The DEXA segments regions of the body (right arm, left arm, trunk, right leg, and left leg) into three compartments for determination of fat, soft tissue (muscle), and bone mass. Radiation exposure from DEXA for the whole body scan is approximately 1.5mR per scan. This is similar to the amount of natural background radiation a person would receive in one month while living in College Station, TX. The maximal permissible x-ray dose for non-occupational exposure is 500 mR per year. Total radiation dose will be less than 5mR for the entire study. Since women of child bearing age may serve as subjects in this study, each subject will complete a questionnaire related to their menstrual cycle timing, sexual activity, use of birth control pills, and desire to become pregnant (see attached). DEXA tests will be performed within 14-days of the onset of their period in menstruating women of child bearing age who do not use oral contraceptives according to NCRP and ARP radiology standards in order to reduce the possibility of exposure of an unknown fetus to radiation.

Strength Tests. All strength/exercise tests will be supervised by certified lab assistants experienced in conducting strength tests using standard procedures. Strength testing will involve the participants performing one repetition maximum (1 RM) on the isotonic bench press and the Nebula Fitness Olympic Power Station. Participants will warm-up (2 sets of 8 – 10 repetitions at approximately 50% of anticipated maximum) on the bench press. Participants will then perform successive 1 RM lifts starting at about 70% of anticipated 1RM and increasing by 5 – 10 lbs until they reaches their 1RM. Participants will then rest for 10 minutes and warm-up on the Nebula 45° Leg press (2 sets of 8 – 10 repetitions at approximately 50% of anticipated maximum). They will then perform successive 1RM lifts on the leg press starting at about 70% of anticipated 1RM and increasing by 10 – 25 lbs until reaching the subject's 1RM

Cardiopulmonary Exercise Tests. Cardiopulmonary exercise tests will be performed by trained exercise physiologists in accordance to standard procedures described by the American College of Sports Medicine's (ACSM) *Guidelines for Exercise*

Testing and Prescription. This will involve preparing the participant's skin s for placement of 10 ECG electrodes. Electrode sites will be cleansed with a sterile alcohol gauze using a circular motion. The site will be allowed to air dry or will be dried with a gauze pad. Electrodes will then be placed on the right subclavicular fossa (RA), left subclavicular fossa (LA), right abdomen (RL), left abdomen (LL), 4th intercostals space at the right sternal border (V1), 4th intercostals space at the left sternal border (V2), equidistant between V2 and V4 (V3), 5th intercostal space at the midclavicular line (V4), 5th intercostal space at the anterior axillary line (V5), and 5th intercostals space at the axillary line (V6) of the chest. The participant will then be attached to an ECG. Resting blood pressure, heart rate, and a 12-lead ECG will be obtained. The exercise specialist will then review the 12-lead ECG to ensure that no contraindications for exercise testing are apparent based on the ACSM guidelines. Participants will then be seated on a treadmill. A sterile mouthpiece attached to a head harness will be secured on them. The participant will then have a nose clip placed on their nose. Resting expired gases will be collected using the Parvo Medic 2400 TrueOne Metabolic Measurement System. Once the participant is ready to begin the test protocol, they will be instructed to straddle the treadmill with both legs while the treadmill is turned on at a speed of 1.7 mph and at a 0% grade. The participant will then use one foot to repeatedly swipe the belt in order to gauge the speed of the motion. Once they are familiar with this speed, they will step onto the belt while still gripping the handrail with both hands. Once the participant becomes comfortable walking on the treadmill, he/she will let go of the handrail and begin walking freely. The participant will then perform a standard symptom-limited Bruce treadmill maximal exercise test using the following speeds and grades:

Stage	Speed	Grade(%)	Duration(min.)
1	1.7	10	3
2	2.5	12	3
3	3.3	14	3
4	4.2	16	3
5	5.0	18	3
6	5.5	20	3
7	6.0	22	3

The participant will be encouraged to exercise to their maximum unless they experiences clinical signs to terminate the exercise test as stated by the ACSM's *Guidelines for Exercise Testing and Prescription* (i.e., angina, dyspnea, dizziness, a decline in systolic blood pressure, dangerous dysrhythmias [increasing or multi-form premature ventricular contractions, ventricular tachycardia, supraventricular tachycardia, new atrial fibrillation, or A-V block], lightheadedness, confusion, ataxia, cyanosis, nausea, excessive rise in systolic blood pressure over 250 mmHg or diastolic over 120 mmHg, chronotropic impairment, failure of the monitoring system, or other signs or symptoms for terminating the test). The test may also be terminated at the request of the participant. Once the exercise test is complete, the participant will observe a 3-6 minute active recovery period followed by a 3-6 minute seated recovery period. The normal exercise time to maximum of the Bruce treadmill protocol for untrained women is typically about 9 minutes (near the completion of stage III or just entering stage IV). Heart rate (HR), ECG tracings, and expired gases will be monitored continuously throughout the exercise test. Blood pressure (BP) and ratings of perceived exertion (RPE) will be obtained toward the end of each stage. Participants will be asked to report any unusual signs or symptoms to the exercise specialists during the exercise test. These tests will determine maximal aerobic capacity and anaerobic threshold to determine the effects of the exercise training on fitness and exercise capacity.

APPENDIX D

Texas A&M University: Exercise & Sport Nutrition Laboratory
Trial: Effects of a Carbohydrate Restricted, High Protein, High Fat Diet on Weight Loss and Health Outcomes in Women Participating in the Curves Fitness & Weight Loss Program

Radiation Exposure Questionnaire for Women of Child Bearing Age

Radiation exposure may affect fetal development. Although the DEXA test will only expose you to a small amount of radiation (1.5Mr per scan), you should be aware that there is a possibility that if you become pregnant during the course of the study that the x-ray exposure may be harmful to the fetus. Therefore, it is important to conduct x-ray tests within 10-14 days of the start of a female's menstrual cycle if the she is of child bearing age, sexually active, and/or is not taking birth control pills. The following questionnaire must be completed so that we know when it is an appropriate time to conduct the DEXA body composition tests. Please be assured that this information will be kept confidential within the limits permitted by law.

Current Age? _____
Age of first period? _____
Date of last period? _____
Normal length of menstrual cycle? _____
Do you use birth control pills? _____
Are you pregnant or have a desire for pregnancy? _____

Note: If you happen to get pregnant during the course of this study, you must notify research assistants so that appropriate precautions can be made.

I confirm that I have completed this questionnaire honestly and agree to notify researchers within the ESNL of any change in the length of my menstrual cycle and/or pregnancy status.

_____ _____
Name Date

_____ _____
Staff Signature Date

IRB NUMBER: IRB2013-0495F
IRB APPROVAL DATE: 08/21/2013
IRB EXPIRATION DATE: 08/15/2014

APPENDIX E

Texas A&M University: Exercise & Sport Nutrition Laboratory
Trial: Effects of a Carbohydrate Restricted, High Protein, High Fat Diet on Weight Loss and Health Outcomes in Women Participating in the Curves Fitness & Weight Loss Program.

Demographics ESNL Staff Initials: _____

Name:_____ Testing Session: _____ Group:_____
Date: _____ D.O.B.: _____ Age: _____

Resting Measures ESNL Staff Initials: _____

Psychological Questionnaires/Informed Consent:

HLKN Informed consent: _____ Body Image: _____
Radiation consent: _____ MOS SF-36: _____
Activity Log: _____ Self-Esteem:_____
Food Log: _____ Eating Satisfaction: _____
IPAQ: _____ Social Physique Anxiety Scale: _____

Physiological Parameters: ESNL Staff Initials: _____

Height: _____in.
Weight: _____lb.
REE: _____#1 or #2
Time: _____am
Last Meal: _____am/pm
Hrs Fasted: _____hr.
Last Wkout: _____hr.
Lab (EBNL): _____(2) SST Tubes/ (1) EDTA Tube
Time: _____am
ECG (Rest): _____#1 or #2
Max Test: _____#1 or #2
Notes: _____
Yr. /Menopause _____

Waist: _____in.
Hip: _____in.
Resting H.R.: _____bpm.
Resting B.P.: _____/_____mmHg
BIA: _____
FFM (kg) _____ _____
FM (kg) _____ _____
TBW (L) _____ _____
ICW (L) _____ _____
ECW (L) _____ _____
Handheld BIA: _____#1 or #2
DEXA: _____

Exercise Measures: Strength Testing: ESNL Staff Initials: _____

Leg Press: Foot Position: _____ Sled Position: _____
Preceding Weights/Reps:

_____x_____:_____x_____:_____x_____:_____x_____:_____x_____:_____x_____:_____x_____:_____x_____

1 RM: _____
80% 1RM:_____80% 1RM repetitions: _____

Bench Press: Hand Position: _____
Preceding Weights/Reps:
_____x_____:_____x_____:_____x_____:_____x_____:_____x_____:_____x_____:_____x_____:_____x_____

1 RM: _____
80% 1RM:_____80% 1RM repetitions: _____

IRB NUMBER: IRB2013-0495F
IRB APPROVAL DATE: 07/11/2014
IRB EXPIRATION DATE: 07/01/2015