# EFFECTS OF A DIETARY RESTRICTION PLUS EXERCISE PROGRAM ON CENTRAL ADIPOSITY IN OBESE OLDER WOMEN

By

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For my parents.

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| | |
|---|---|
| BMI | Body Mass Index |
| DR+E | Dietary Restriction plus Exercise |
| SAT | Subcutaneous adipose tissue |
| SPPB | Short Physical Performance Battery |
| VAT | Visceral adipose tissue |

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Aging is associated with an increase in central adiposity and an accelerated loss of muscle mass. These body composition changes can increase risk of functional decline and ultimately disability in older adults. The current study tested whether a weight loss intervention in which dietary restriciton was combined with a multi-component exercise program could reduce central fat depots (i.e., visceral and subcutaneous adipose tissue) in obese older women. Twenty-five obese older women (age range = 55-79 years) with mild to moderate physical impairments were randomly assigned to a dietary restriction plus exercise (DR+E) intervention group or successful aging educational control for 24 weeks. Participants in the DR+E group attended weekly weight management sessions, as well as three structured exercise sessions each week. Participants in the successful aging educational control attended monthly health education lectures. Visceral and subcutaneous adipose tissues within the abdominal region were measured by magnetic resonance imaging, and analyses of covariance were conducted to examine changes in volume from baseline to post-treatment. Relationships between changes in central adiposity, body weight, and physical function were also examined. Participants in the DR+E group had a

significantly greater reduction in visceral adipose tissue compared to participants in the successful aging group (-1057.4 ± 347.0 $cm^3$ vs. 199.9 ± 378.2 $cm^3$; $p < .05$), and significantly greater reduction in subcutaneous adipose tissue compared to participants in the successful aging group (-2970.6 ± 1345.1 $cm^3$ vs. 1096.6 ± 1406.9 $cm^3$, $p = .05$). There was a strong, positive correlation between changes in body weight and subcutaneous adipose tissue ($r = .57$, $p < .01$); however, there were no other significant associations between changes in body weight, adiposity, or physical function. Our findings indicate that a lifestyle intervention involving moderate reductions in dietary intake combined with a multi-component physical activity program can produce significant reductions in central fat depots in obese older women.

CHAPTER 1
INTRODUCTION

## The Obesity Epidemic

By the year 2050, the number of older adults living in the United States is expected to double from 40.2 million to 88.5 million (1). This trend, taken together with the increasing prevalence of obesity, is alarming as approximately two-thirds of older adults (age 60 years and older) are overweight and one-third of older adults are obese (2). Thus, the current shift in the age distribution of the American population may increase the number of obese older adults even without an increase in obesity prevalence (1).

A person's body weight is the result of multiple convergent factors that influence behaviors associated with physical health. Genetics, metabolic regulation, environmental factors, culture, and socioeconomic status all impact body weight throughout the lifespan (3). Obesity is caused by an imbalance in energy intake and expenditure, resulting in a state of prolonged positive energy balance (4). Behavioral and environmental factors (ex., food intake and sedentary lifestyle) have largely contributed to the increasing prevalence of obesity. Recently, an analysis of four nationally representative surveys of food intake in the U.S. population consisting of 36,846 adults (aged ≥ 19 years), identified that average daily energy intake has increased from 1,765 kcal/day in 1977-78 to 2,164 kcal/day in 2003-06 (5). Concurrently, data from the National Health Interview Survey indicates that approximately 40% of adults do not participation in any physical activity behaviors (6).

Excess body weight reaching obesity, classified based on the measurement of body mass index (BMI) greater than 30 $kg/m^2$, is associated with increased risk of total mortality (7). More than 400,000 deaths per year are attributed to obesity (8). Many older adults are obese and this is associated with increased morbidity and reduced quality of life. Obesity has been clearly established as a risk factor for many chronic health conditions in older adults such as diabetes mellitus, hypertension, cardiovascular disease, osteoarthristis, and certain cancers (9). Excess weight also accelerates the development of osteoarthritis (10). In addition, it can be accompanied by pain and suffering, reduced quality of life, and medical costs for treatment (11-13).

**Demographic Variations in Obesity Prevalence**

Considerable subgroup variation exists in the prevalence of obesity according to age, sex, and race/ethnicity. According to NHANES 2009-2010 data, obesity prevalence do not differ between men and women (14). Examination of ethnic/racial subgroups reveals trends that indicate there are higher rates of obesity among some subgroups, which may be the result of factors such as genetics, education, environment, or cultural practices (15). Across the lifespan, nearly half of African American females are obese and significantly different from African American males and Caucasian females (16). Moreover, the highest rates of overweight, as defined by a BMI greater than 25-29.9 $kg/m^2$, are observed among non-Hispanic, African American females between the ages of 40 to 59 years of age (81.5%) and 60 years of age and older (81.7%), and the highest rates of obesity are observed among non-Hispanic, African American females between the ages of 40 to 59 years of age (53.2%) (16). Thus, obese older African-American women represent a particularly high-risk population.

**Obesity in Older Adults.** The prevalence of obesity is increasing in older adults (17). As in younger adults, obesity in older adults is associated with increased risk of morbidity (18). Some evidence suggest that high body weight may not be an important adverse factor for mortality in older adults and an ideal BMI appears to be higher in older than in younger adults (19). Based on NHANES (1999 to 2002) data, however, an estimated 25% of excess deaths in individuals over 70 years old are attributed to obesity (20). Notably, the relationship between mortality and BMI in older adults may be misleading since variations in body composition (i.e., lean mass vs. fat mass) are not captured by BMI. With aging, there is an increase in fat mass and a decrease in lean body mass (21). These body composition changes can lead to older adults having more body fat compared to younger adults who have the same BMI.

**Age-Related Changes in Body Composition**

Body composition changes in older age as fat-free mass decreases while fat mass increases and gets redistributed in the abdominal area (22-24). These changes in body composition (i.e., muscle loss and fat gain) can occur independently from changes in body weight and BMI (25), and are accelerated after middle age, especially during menopause (21). Controlling for BMI, women and older adults have a higher percent body fat than men and younger individuals (26). Therefore, central adiposity may be more important in assessing risk than total body fatness, especially in older adults.

**Sarcopenia.** Normal aging is associated with physiological changes that result in functional decline. After the age of 50 years, the rate of lean tissue mass loss is estimated to be approximately 1% to 2% annually (23). This reduction of muscle mass, strength, and quality with aging, can lead to sarcopenia, defined as *poverty of flesh* describing age-related loss of muscle mass (27), and the decline of physical function. Some estimates indicate that approximately one-quarter to one-half of adults aged 65 and older are sarcopenic (28), though the true prevalence is difficult to ascertain given the lack of a universally accepted definition of sarcopenia. While loss of muscle mass explains a significant component of weakness, several other mechanisms may underlie and contribute to the accelerated rate of muscle loss and strength observed in older adults. Some potential mechanisms contributing to functional decline (or sarcopenia) likely include hormonal changes (29), low levels of physical activity (30-31), and fat accumulation within the muscle (32). In addition, obesity has been identified as important contributor to the progression of sarcopenia (33-34), due to the accumulation of adipose tissue and subsequent increases in both cortisol and pro-inflammatory cytokines (35). These physiological changes can promote abdominal fat accumulation, the development of insulin resistance, and skeletal muscle atrophy (36-37).

Increased adiposity combined with lower skeletal muscle influences the development of functional decline (38). A key determinant of functional abilities is the relative relationship of muscle strength to body mass (39-41). Evidence suggests that obese older adults typically possess a reduced strength to body mass ratio compared with non-obese older adults. Relative muscle mass has recently been reported to decrease by 0.02 kg/year for every standard deviation increase in fat mass (i.e., SD = 7.1 kg for males and SD = 9.1 kg for females) (42). In a cross-sectional study of postmenopausal women, participants who were overweight or obese showed that a 10 kg increase in fat mass was significantly associated with lower physical performance, lower physical activity, and higher frequency of impairments in activities of daily living (43). Thus, obesity contributes to reducing muscle mass beyond the progressive physiological changes associated with normal aging and may accelerate the rate of functional decline.

**Central Adiposity.** Central obesity is determined by the accumulation of both subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) in the abdominal region. Visceral adipose tissue is metabolically active (34), making the excess accumulation of VAT particularly hazardous in the pathogenesis of metabolic abnormalities (44) and cardiovascular disease (45). Visceral adipose tissue, located in the body cavity beneath the abdominal muscles, secrets adipokines (e.g., TNF-α and IL-6) and other protein molecules, and promotes a pro-inflammatory state which interferes with metabolic regulation (22, 46-47). This interference can lead to insulin resistance (48-50), hyperinsulinemia and hyperglycemia (48, 51), high blood pressure (52), metabolic syndrome (53), and non-alcoholic fatty liver disease (54). In fact, visceral adipose tissue is a stronger predictor of metabolic alterations than total body fat percentage (49). In contrast to VAT, there is little evidence that SAT is associated with risk of pathology and may even have a protective effect on metabolic parameters (55). Inflammation may contribute to the development of diseases such as atherosclerosis (56), autoimmune disease (57), and certain cancers (58).

Central adiposity is a stronger risk factor for morbidity and mortality than BMI, total body fat, or other sites of fat predominance (49, 59-60). The relative risk of death imposed by central adiposity for vascular diseases reaches a risk equivalent to that reported for hypercholesterolemia, hypertension, and smoking (49). In obese postmenopausal women, atherogenic levels of lipids and lipoproteins were independently related to central adiposity (61).

Consistent with the subgroup variations in the prevalence of obesity, difference in body fat distribution can be seen by age, sex, and race/ethnicity independent of BMI.

Studies indicate that older males have more adipose tissue within the abdominal cavity and less SAT compared to middle-aged males (62) and age is positively correlation with VAT in females (63). African American women have higher rates of central adiposity compared to African-American men and Caucasians (64-66).

Among older adults, the relationship between inflammation and increased risk of disability has been established (67-68). As pro-inflammatory cytokines promote systemic inflammation and progressive destruction of tissue, these protein molecules have a direct effect on physical function by accelerating body composition changes (67, 69) and impact cognitive function by accelerating brain atrophy typical of the aging process (70-71).

**Functional Decline in Obese Older Adults**

As the population ages, the risk of physical and/or cognitive impairments secondary to obesity and related lifestyle behaviors threatens the health, safety, and quality of life in older adults.  If current obesity trends continue, there will also be an increase in chronic illness in an otherwise already vulnerable population. Physical function, a marker of performance in domains such as activities of daily living and mobility tasks, is a strong determinant of independent living and health (Guralnik & Simonsick, 1993). As such, the definition of disability was expanded in the International Classification System of Functioning, Disability, and Health (ICF) to include functional impairments (e.g., deficits in strength or cardiorespiratory fitness) along with a range of behaviors including either discrete tasks/actions (i.e., walking tests, stair climbing, and balance tests) or participation in life situations (73). Physical impairments and disabilities in older adults can lead to a loss of independence (74), increased use of support services (75), hospitalization (76-77), and mortality (78-79). Compared to adults with a normal body weight, obese older adults experience impairments in basic activities of daily living approximately five years earlier and are twice as likely to develop functional impairments and/or activities of daily living disabilities (80). In addition, cognitive decline has been linked to disability onset in older adults (81). Several cross-sectional studies suggest a negative relationship between obesity and cognitive function in older adults (82-84). Thus, obesity places older adults at high risk for the development of disability (80).

**Physical Function.** The relationship between obesity and physical function has been widely examined (38, 85-88), and data show that high body weight and high BMI are associated with increased risk for functional impairment and disability. Furthermore, the relationship between body composition and physical function indicates that fat mass, but not fat-free mass, is more predictive of functional limitations (42, 89). Several studies suggest that central adiposity, measured by waist circumference, may adversely impact mobility (90-91); however, the results of these studies are limited by their use of an anthropomorphic index measure of body fat distribution and subjective measures of physical function (i.e., self-report assessment tools). Therefore, the relationship between central adiposity and physical function is not well understood and should be examined using objective functional assessment tools and site-specific quantification of visceral and subcutaneous adipose tissue.

**Cardiac Function.** Impairments in cardiac function in obese patients is attributed to excess body weight and duration of obesity (92), and there is evidence that visceral fat accumulation is a specific risk factor for metabolic abnormalities (93-96) that can lead to cardiovascular and metabolic disease (97-100). Cardiovascular disease, cerebrovascular disease, and diabetes mellitus are among the top ten leading causes of death in older adults living in the U.S. (101). Notably, as survival rates are increasing (102), individuals are living wide range of disabilities including motor disorders, memory loss, sensory problems, and depression (103).

## Guidelines for the Treatment of Obesity

### Weight Loss for Obese Older Adults

According to the National Institute of Health (2000) clinical guidelines for the treatment of overweight and obesity in adults, weight loss is recommended for individuals with a BMI equal to or greater than 30 $kg/m^2$ and for individuals with a BMI between 25 and 29.9 $kg/m^2$ with two or more risk factors including hypertension, cigarette smoking, high low-density lipoprotein cholesterol, impaired fasting glucose, family history of early cardiovascular disease, and age (male ≥ 45 years, females ≥ 55 years) (4). The recommendation for weight loss in older adults has been controversial. Several longitudinal observational studies show that weight loss in older adults is associated with increased mortality (104-106); however, most observational studies often fail to distinguish intentional weight loss (e.g., to promote health) and unintentional weight loss (e.g., as a precursor to illness). Additionally, some critics argue that weight loss in this population can accelerate the loss of lean body mass that occurs with aging (107). Despite these claims, The American Society of Nutrition and the North American Association for the Study of Obesity (4,17) both recommend intentional weight loss for older adults only in the case of obesity combined with weight-related comorbidities or functional limitations. Evidence supports that a reduction in body weight, even if modest (e.g., 5-10%), produces beneficial effects on metabolic, cardiac, and physical function in obese older adults (108-111).

### Lifestyle Treatment Approach

Lifestyle interventions represent the first line of intervention in the behavioral treatment of obesity (4). Lifestyle interventions consist of calorie restriction, physical activity, and behavioral modification with the goal of creating a negative energy balance for weight loss. Caloric restriction of 500 to 1000 kcals below baseline intake is recommended for a weight loss of approximately 0.4-0.9 kg per week. Elements of physical activity include aerobic training, resistance training, and flexibility exercises. The 2008 Physical Activity Guidelines for Americans recommends at least 150 minutes of moderate-intensity aerobic activity every week plus muscle-strengthening activities on two or more days per week for older adults (6). Behavioral modification includes self-monitoring, goal setting, social support, stimulus control, and relapse prevention. Benefits of lifestyle interventions often extend beyond weight loss to include improvements in hypertension, glucose intolerance, hyperlipidemia, physical functioning, and quality of life (112-116). Studies to date indicate lifestyle interventions which combine dietary restriction and physical activity have favorable effects in obese older adults on changes in body weight, body composition, and measures of physical function.

**Body Weight.** The ability of lifestyle interventions to produce clinically meaningful reductions in body weight in older adults has now been well established (17,108,113-115,117). Research indicates that lifestyle modification programs combining a moderate energy-deficit diet, increased physical activity, and behavior modification typically yield weight loss results of approximately 5 to 8.5 kg (5 to 10%)

reduction of body weight after six months (118). Weight loss of this magnitude has consistently been associated with clinically significant reductions in risk factors for cardiovascular disease, diabetes, and other health conditions (119-121).

**Body Composition.** Lifestyle interventions can produce significant reductions in VAT and SAT in older obese adults (117,122-123). The combination of moderate energy-deficit diet and increased aerobic exercise training yielding a 4-9% body weight loss can directly reduce VAT (124) and even greater reductions can be seen when mean weight loss exceeds 10% reduction in body weight (125).

Two randomized control trials demonstrate the benefit of a comprehensive lifestyle approach to reducing central adiposity. Santanasto and colleagues (2011) randomized obese older adults to a six month physical activity program, with or without a weight loss intervention (123). Participants in the weight loss intervention lost significantly more body weight than participants in the physical activity alone group. The weight loss group also lost significant amounts of total abdominal fat, visceral adipose tissue, and subcutaneous adipose tissue after six months, compared to no change in the physical activity alone group. Similarly, the Diet, Exercise, and Metabolism for Older Women study (117), compared the effects of caloric restriction alone versus caloric restriction plus aerobic exercise at a moderate- or vigorous-intensity in sedentary, obese postmenopausal women. After 20 weeks, there was no significant difference in weight loss between groups; however, both abdominal visceral fat volume and subcutaneous fat volume decreased significantly among all groups. Decreases in abdominal visceral fat were directly related to the amount of weight lost.

Both calorie restriction and exercise-induced weight loss can decrease VAT volumes in obese older adults (126-128). In a study in which obese older adults followed dietary restriction for six months without physical activity, results showed significant weight loss and a decrease in fat mass (129). Irwin and colleagues (2003) studied overweight and obese postmenopausal women randomized to an exercise (i.e., walking) or no exercise (i.e., stretching) control group (130). After 12 months, women in the exercise group showed significantly larger reductions in total body fat, VAT, and SAT, compared to women in the control group. Women who exercise for approximately 200 minutes per week reduced their body weight and percent of VAT without reducing their energy intake. This outcome illustrates a significant dose response for greater body fat loss with increasing duration of exercise. Thus, examination of the literature on groups following dietary restriction with or without exercise shows similar weight loss, loss of body fat, and reductions in VAT (131).

Given the concern for the loss of lean mass in older adults, adding exercise training to a dietary restriction program helps preserve lean mass during weight loss (132-133). Beyond that, the benefits of regular physical activity can also impact cardiometabolic health by reducing triglyceride levels, increasing high density lipoprotein levels, reducing resting blood pressure, increasing glucose tolerance, and reducing insulin resistance (134)

**Physical Function.** Several studies indicate that physical function in obese older adults is improved following lifestyle intervention (108,113,115,135). Santanasto and colleagues (2011) examined physical function outcomes following six months of a physical activity program, with or without a weight loss intervention, in obese older adults (123). Significant improvements in physical function as measured by the Short Physical Performance Battery were achieved by the weight loss plus physical activity group only. The relationship between physical function and body composition was strongly inversely correlated with mean change in visceral adipose tissue and subcutaneous adipose tissue.

## Rationale for Current Study

Age-related changes in body composition play an important role in functional decline and risk for disability. Obesity can accelerate the progression of sarcopenia and physical disability in older adults (34,136-137). While some degree of sarcopenia is inevitable in older adults, contributing factors such as poor diet and sedentary lifestyle are modifiable and should be the focus of treatment for reducing obesity and functional decline. As such, dietary modifications and increased physical activity play an important role in maintaining lean muscle mass. However, the recommendation for weight loss in overweight and obese older adults has been controversial. This controversy is due to concerns that weight loss can accelerate the loss of lean tissue that occurs with aging. Thus, the potential risks and benefits of weight loss in obese older adults should be tested in the context of a lifestyle-based treatment program that can help reduce body fat mass while retaining lean mass. To date, there is some empirical support for the efficacy of lifestyle interventions on adaptive changes in physical function in obese older adults.

Few studies have explored the relationship between body fat distribution and physical function in obese older adults. In most studies, surrogate measures of fat mass distribution (i.e., waist circumference) were used rather than direct measures of body fat distribution (i.e., duel-energy x-rays, magnetic resonance imaging, or computed tomography) to assess the association between body fat distribution and physical function (138-139). Efforts have been made to generate predictive values of simple anthropometric measurements on regional body fat distribution. Differences between predicted and observed values of SAT were small; however, differences between predicted and observed values of VAT were large (140). There is limited information on the effect of lifestyle interventions on body composition, specifically the impact of treatment on reducing central fat depots (i.e. visceral and subcutaneous adipose tissue) in obese older adults. As body composition changes with aging, it is important to design interventions that can effectively reduce central adiposity, the fat depots that have been most associated with increased levels of pro-inflammatory cytokines and also contribute to muscle atrophy in obese older adults.

Although sex differences are not evident in the prevalence of obesity among older adults, it is important to consider that sex differences in body fat distribution have been noted independent of BMI. Even with equal BMI, women typically have a higher body fat percentage than men (141). In women, there is a shift in body composition around the time of menopause. A simultaneous acceleration in muscle loss paired with redistribution of fat to the central region places women at a particularly high risk for developing obesity related co-morbidities. Thus, obese older women represent a particularly important population for examining the effects of lifestyle interventions on weight loss, body composition, and physical functioning.

It remains critical to determine the best therapeutic approach for losing body fat, retaining muscle and bone mass, and prolonging functional mobility to extend quality of life throughout the lifespan in obese older women. Therefore, more research is needed to examine the relationship between weight loss and regional body fat distribution, the effect of lifestyle treatments on central adiposity, and the role of central adiposity in maintaining physical function and delaying functional decline.

## Specific Aims and Hypotheses

This study has two specific aims. The first aim was to evaluate changes in central adiposity in obese older women following a six-month lifestyle-based weight loss intervention consisting of dietary restriction and a multi-component exercise program. We hypothesized that as compared to the educational control group, the Dietary Restriction plus Exercise group would produce greater reductions in both abdominal visceral adipose tissue volume and abdominal subcutaneous tissue volume.

The second aim was to examine the association between changes in body weight, regional fat distribution, and physical function. We hypothesized that among individuals randomized to the Dietary Restriction plus Exercise group, greater reductions in body weight would be associated with greater reductions in visceral adipose tissue volume and subcutaneous adipose tissue volume. Furthermore, we hypothesized that among individuals randomized to the Dietary Restriction plus Exercise group, greater reductions in visceral adipose tissue volume and subcutaneous adipose tissue volume would be associated with improvements in physical performance.

# CHAPTER 2
# MATERIALS AND METHODS

## Research Methods and Procedures

The current study was a secondary analysis of data from a pilot, randomized controlled trial (142). The parent study was designed to demonstrate the feasibility, acceptability, and efficacy of a weight loss program combined with moderate exercise in improving physical function in sedentary obese, older adult women with mild to moderate physical impairments. The effects of a 24-week lifestyle-based weight loss plus comprehensive exercise intervention on body weight, physical function, and muscle strength were assessed and racial differences between Caucasian and African American women were examined.

### Participants

Thirty-four sedentary women between the ages of 55 to 79 years old, with BMI > $28kg/m^2$, who had mild to moderate physical impairment, were enrolled in the parent study.  A sedentary lifestyle was defined as engaging in less than 20 minutes per week of aerobic exercise over prior two months. Physical limitation was defined based on performance on the Short Physical Performance Battery (SPPB), with scores in the range of 4 to 10 indicating mild to moderate physical impairment.

Participants were excluded for any of the following: body weight over 300lbs; weight loss of 10lbs within the past six months; history of surgery for weight loss; hospitalization within the past six months; significant underlying disease likely to limit lifespan and/or increase risk of interventions (cancer or any condition with a life expectancy < 5 years with the exception of non-melanoma skin cancer; serious infectious diseases; myocardial infarction, cerebrovascular accident, or unstable angina within the past six months; NYHA Class 3 or 4 congestive heart failure; aortic stenosis; chronic hepatitis; cirrhosis; kidney disease; solid organ transplantation; chronic gastrointestinal disorders; fibromyalgia; chronic fatigue syndrome; major psychiatric disorder); metabolic exclusions (i.e., resting blood pressure > 160/90 mmHg, fasting blood glucose > 160 mg/dl, fasting triglycerides > 400 mg/dl; patients on medication for hypertension, diabetes, or hyperlipidemia will not be excluded unless their values suggest “poor control”); medication exclusions (i.e., antipsychotic agents; monoamine oxidase inhibitors; systemic corticosteroids; antibiotics for HIV or TB; chemotherapeutic drugs; or current use of prescription weight-loss drugs); physical limitations likely to prevent exercise participation (i.e., use of walker; breathing problems that limit physical activity); conditions or behaviors likely to affect the conduct of the trial (e.g., unwilling or unable to give informed consent; unwilling to accept random assignment; likely to move out of area within next two years; unable to attend weekly meetings; unwilling to complete paperwork; participation in another randomized research project; unwilling or unable to comply with study requirements or schedule); contraindications to MRI (MR-incompatible implants or severe claustrophobia); contraindications to muscle biopsy (i.e., lidocaine allergy).

**Recruitment.** A total of 412 women responded to the study recruitment announcements. Three hundred and fifty-eight women were excluded at the telephone screening phase, and 17 individuals were excluded after completing the in-person medical screening assessment. A total of 37 participants were eligible to participate in the study. Of these, 34 participants were randomized to the DR+E intervention or educational control.  The sample size included in the current study was 25 obese older women from the parent study. In total, nine participants were not included due to lack of post-intervention follow-up or inability to provide body composition measurements. Participants were recruited by the Aging and Rehabilitation Research Center, in conjunction with the Weight Management Lab, at the University of Florida from September 2006 to December 2008. Recruitment methods included direct mailings, solicitations at community-based facilities, and the use of a Participant Registry maintained by the Institute on Aging at the University of Florida. All participants provided written informed consent and all protocols were approved by the Institutional Review Board (IRB-01) at the University of Florida.

### Procedure

This study was a single-blinded, 24-week randomized clinical trial in which participants were randomly assigned to a comprehensive lifestyle intervention or to a successful aging education group. All groups meetings were held in a community-based center (i.e., church facility).

**Dietary Restriction plus Exercise (DR+E) Group.** The intervention was designed to produce a modest weight loss of 7-10% of initial body weight. Participants met weekly for 60-minute group-based weight management sessions and discussed topics related to behavior modification for weight loss, such as goal setting and self-monitoring. At each weight management session, participants were provided with treatment plans including specific objectives for each meeting, particular methods to accomplish the objectives, and illustrative handouts. Groups were co-led by a registered dietician and a behavioral specialist. Adherence was monitored by weekly review of food diaries, physical activity logs, and weigh-ins. Participants were provided with dietary restriction guidelines, calculated according to their self-reported energy intake at baseline on food diaries, to facilitate weight loss. Guidelines for restriction ranged from 500-1000 kcals per day and followed the American Heart Association recommendations for macronutrient intake (i.e., 55% of energy coming from carbohydrates, 30% from fats, and 15% from protein) (143).

In addition to dietary restriction, participants engaged in a multi-component exercise program that incorporated both structured and home-based physical activity. For the aerobic exercise component, participants were instructed to walk for 150 minutes per week. The exercise regimen was based on the protocols designed for the ADAPT Study (113) and LIFE Trial (144), which demonstrated the safety and efficacy of walking plus light resistance training as the exercise modality for use in older adults with mild to moderate impairments in mobility.  Participants attended three community-based, supervised exercise sessions per week. Safety during exercise was monitored by trained interventionists, certified in CPR, and potential adverse experiences and symptoms were observed and recorded. For example, blood pressure and heart rate were monitored before and after each supervised exercise session. Participants were supervised by exercise physiologists and certified personal trainers. Sessions included aerobic activity (i.e., walking), lower body resistance strength training, and flexibility exercises. During each session, participants completed two 15-minute bouts of walking, separated by lower body resistance-training exercises (i.e., wide leg squat, standing leg curl, seated knee extension, side hip raise, and toe stand). Participants aimed for two sets of 10 repetitions of each exercise with 60 second rest between sets. Resistance-baring exercises were monitored and resistance was gradually increased using adjustable ankle weights as participants improved their fitness.  Upon completion of these exercises, participants performed a series of flexibility exercises. To help participants estimate the intensity level at which they were exercising, the Borg Perceived Exertion scale, a 15-point self-assessment tool ranging from “easy” to “very hard,” was used and participants were asked to walk at an intensity level equivalent to “somewhat hard.” A total of 90 minutes of aerobic activity was conducted at these supervised sessions, and the remaining 60 minutes were to be done at home.

**Successful Aging Educational Group.** The successful aging educational control group met monthly for group-based health education lectures on topics relevant to aging, but did not include lectures on weight loss, diet, or physical activity. Participants were to maintain their usual eating and physical activity patterns, and were asked not to engage in any intentional weight loss for six months. As an incentive for participation in the control group, the full 24-week DR+E intervention was offered at the end of their six month assessment.

**Measurements**

**Body weight.** Body weight was measured in a fasting state following a morning void. Height and body weight were measured using a stadiometer, and body mass index (BMI) was calculated by dividing the participant’s weight in kilograms by the square of her height in meters.

**Central Adiposity.** Visceral and subcutaneous adipose tissue within the abdominal region was measured volumetrically over five contiguous axial slices (10-mm thickness) at the L4-L5 vertebral space by a T1-weighted 3D-Magnetic Resonance Imaging (MRI) scanner (Philips Medical Systems, Bothell, WA). The 3D data were collected using a fast gradient-echo sequence, with TR=100ms, TE=10ms, flip angle of 30˚ and a chemically-selective fat suppression was utilized.  The fat suppression enhanced muscle as high signal intensity pixels and adipose tissue as low signal intensity pixels to allow for segmentation. Images were analyzed using a freely-available software program called MIPAV (version 1.3; Medical Image Processing, Analysis and Visualization). Currently, multi-slice volume MRI is empirically supported as the gold standard reference for measuring regional adipose tissue volumes (125,145).

**Physical Function.** Two objective performance-based tests were used to assess physical performance: The Short Physical Performance Battery and 400-m walk test.

The Short Physical Performance Battery (SPPB) is related to mobility disability and activities of daily living disability (146) and is highly predictive of subsequent disability among non-disabled older adults living in the community (147-148). Performance on the SPPB has been found to predict four year incident mobility disability (148). It is designed to assess lower-extremity function by measuring three timed subtests: five timed repetitive chair stands, standing balance (i.e., hold tandem and semi-tandem foot position for 10 seconds), and gait speed during a 4-m walk at one's usual pace. Each subtest is scored from 0 to 4, with 0 indicating inability to complete test and 4 indicating maximal performance. A summary score from 0 to 12 is calculated for the SPPB, where higher scores indicate better physical function. The results of these three subtests are moderately correlated (Spearman correlation coefficients range from 0.39 to 0.48) based on over 5,000 participants in the Established Populations for Epidemiologic Studies of the Elderly (147). Interclass correlation coefficient values ranging from .88 and .92 have been reported for this measure (149). Regarding change in SPPB scores, based on data from the LIFE-P trial, a minimally significant change is 0.3 to 0.8 points and a substantial change is 0.4 to 1.5 points (150).

The 400-m walk test measures completion time (in seconds) on a standard walking course based on a participant's walking speed at their usual pace. In older adults between the ages of 70 to 79 years old, the 400-m walk test has been shown to predict five-year incident mobility disability (151). Participants were required to complete the 400-m course in 15 minutes, but were permitted to stop during the walk if necessary. Previous studies have demonstrated the high test-retest reliability of the 400-m walk test (152). Regarding change in 400-m walk time, based on data from the LIFE-P trial, a minimally significant change is 20 to 30 seconds, and a substantial change is 50 to 60 seconds (150).

**Statistical Analyses**

Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) for Windows, version 20.0 (IBM). Descriptive statistics were used to identify sample characteristics and provide summary indices of selected measures. One-way analysis of co-variance (ANCOVA) was used to determine any differences between the two groups' baseline characteristics and change outcomes. The main outcomes of interest were change from baseline to six months for abdominal visceral adipose tissue and abdominal subcutaneous adipose tissue. Changes in MRI measures of central adiposity were compared using ANCOVA, using age, race, and baseline measurements of VAT and SAT as the covariates, to evaluate differences between DR+E and successful aging groups. Values of VAT and SAT that are negative denote a decrease from baseline to six-month follow-up and values that are positive denote an increase from baseline. Correlation coefficients were used to quantify the relationships between changes in body composition, body weight, and physical performance outcomes with Person product-moment correlation coefficients.

# CHAPTER 3
# RESULTS

## Sample Characteristics

At baseline, participants (N = 25) had a mean age of 64.0 ± 6.2 years, weighed, on average, 94.8 ± 15.7 kg and had a mean BMI of 36.1 ± 5.1 kg/m$^2$, classifying them as obese (Class II). At baseline, there were no statistically significant differences between the DR+E group and successful aging control group on demographic, anthropometric, and physical function measures (see Table 1). Participants were evenly divided by race (African-American and Caucasian) across both groups; however due to the relatively small sample size of each group, racial difference in body fat distribution were not analyzed.

## Weight Loss and Physical Function

The primary outcome of the parent study (i.e., walking speed) was found to increase significant among participants in the DR+E group compared to participants in the successful aging control group. Scores on the short physical performance battery also improved significantly among participants in the DR+E group and successful aging control group, and participants in the DR+E group lost significantly more weight than participants in the control group.

In accordance with the parent study, participants in the DR+E group had clinically meaningful improvements in walking speed and performed significantly better than participants in the control group (mean speed change ± SE in DR+E group = 0.17 ± 0.04 m/s, $p < .01$; mean completion time change ± SE in control group = 0.03 ± 0.04 m/s, $p = 0.66$; mean difference = 0.15 m/s, $p < .05$). Scores on the SPPB improved in both the DR+E and control groups (mean score change in the DR+E group ± SE = 1.8 ±

0.4, $p < .01$; mean score change in the control group ± SE = 1.0 ± 0.4, $p = 0.13$).  In addition, participants in the DR+E group lost significantly more weight than participants in the control group (- 7.02 ± 1.1 kg vs. 0.16 ± 1.1 kg, $p < .001$). The average body weight loss for participants in the DR+E group was 7.3% of their initial body weight.

**Central Adiposity**

Both markers of abdominal adiposity (i.e., visceral and subcutaneous adipose tissue) decreased significantly from baseline to six-months among participants in the DR+E group. Visceral adipose tissue decreased significantly within the DR+E group compared to no significant change within the successful aging control group (mean VAT change in the DR+E group ± SE = -1057.4 ± 347.0 $cm^3$, $p < .01$; mean VAT change in the control group ± SE = 199.9 ± 378.2 $cm^3$, $p = .87$). As illustrated in Figure 1, the DR+E group had a significantly greater reduction in visceral adipose tissue after six months compared to the control group (mean VAT difference = 1257.4 ± 521.2 $cm^3$, $p < .05$). Subcutaneous adipose tissue also decreased significantly within the treatment group after six months compared to no significant change within the control group (mean SAT change in the DR+E group ± SE = -2970.6 ± 1345.1 $cm^3$, $p < .05$; mean SAT change in the control group ± SE = 1096.6 ± 1406.9 $cm^3$, $p = .66$) As illustrated in Figure 2, participants in the DR+E group had a significantly greater reduction in SAT after six months compared to participants in the control group (mean SAT difference = 4067.1 ± 1979.8 $cm^3$, $p = .05$).

**Changes in Body Weight and Central Adiposity**

There was a large, positive correlation between changes in body weight and change in SAT ($r = .57$, $p < .01$). There was no significant correlation between change in body weight and changes in VAT ($r = .30$, $p = .15$). Notable, changes in VAT and SAT had a large, positive correlation ($r = .725$, $p < .001$).

## Changes in Central Adiposity and Physical Function

Relationships between body composition changes and physical function were found to be non-significant. There was no correlation between total SPPB change scores and changes in VAT ($r = .04$, $p = .84$) or changes in SAT ($r = -.09$, $p = .69$). In addition, there was no correlation between changes in 400m walking speed (m/s) and changes in VAT ($r = -.29$, $p = .17$) or changes in SAT ($r = .02$, $p = .93$).

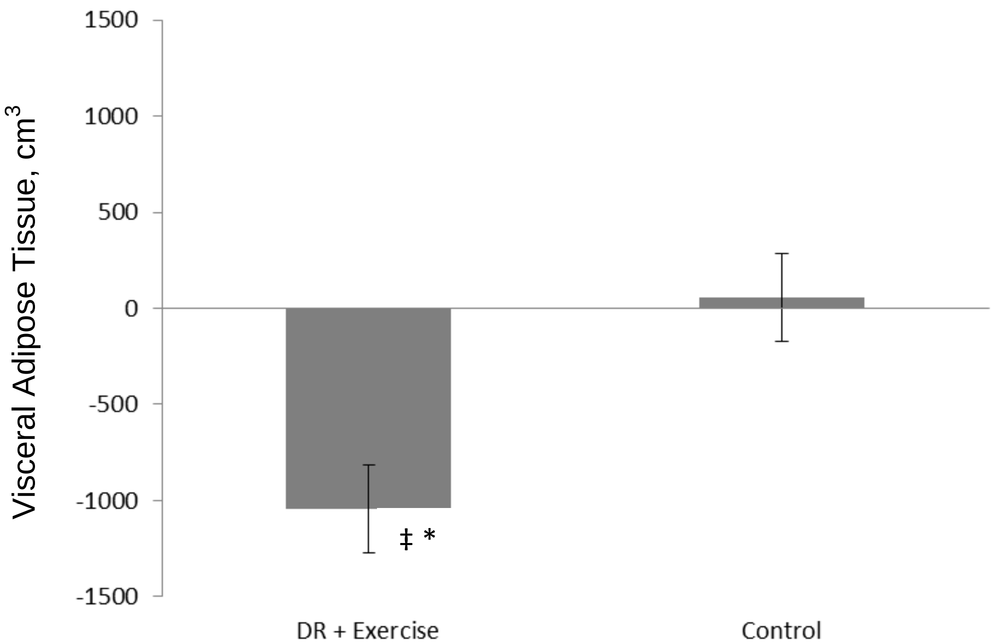
## Changes in Body Weight and Physical Function

There was no correlation between change in body weight and changes in 400-m walking speed ($r = -.30$, $p = .16$) or total SPPB change scores ($r = -.32$, $p = .11$).

Table 3-1. Participant Demographics and Baseline Characteristics

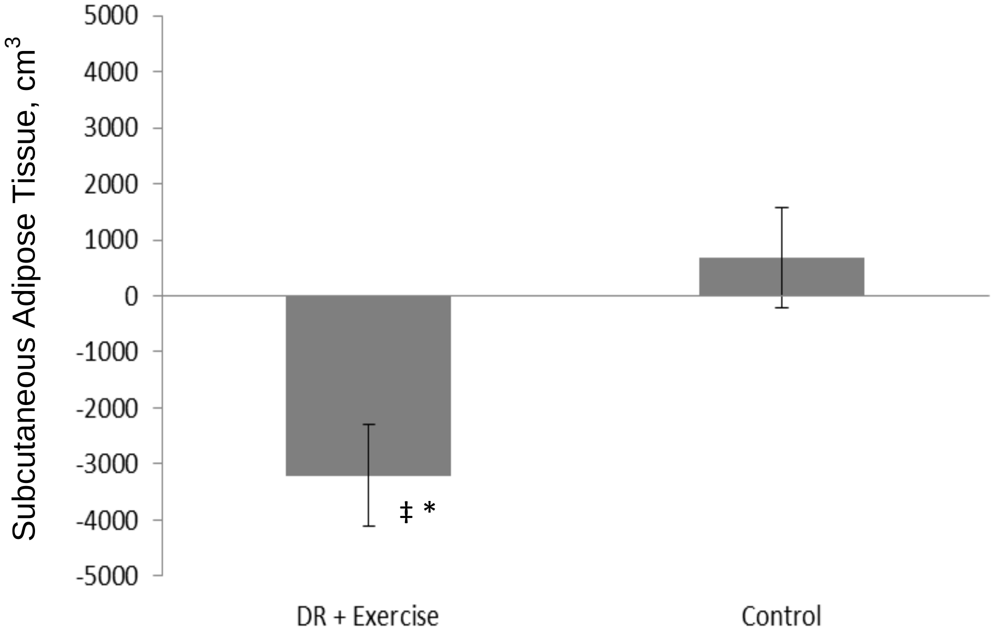
| | DR+E<br>Mean (S.D.) | Control<br>Mean (S.D.) |
|---|---|---|
| Age (years) | 63.9 (4.8) | 64.2 (7.6) |
| Education (years) | 14.2 (2.2) | 15.1 (2.7) |
| Race: | | |
| Caucasian | 7 | 6 |
| African American | 6 | 6 |
| Weight (kg) | 97.4 (12.9) | 92.1 (18.5) |
| BMI ($kg/m^2$) | 36.9 (3.6) | 35.1 (6.4) |
| VAT ($cm^3$) | 4532.6 (2028.5) | 3920.6 (1982.1) |
| SAT ($cm^3$) | 15431.9 (4537.6) | 14316.6 (5903.9) |
| SPPB (score) | 9.2 (0.8) | 9.3 (1.1) |
| W400 (seconds) | 434.9 (78.9) | 388.9 (64.8) |

No significant group differences




‡Significant decrease from BL to W24 ($p < .01$)
*Significant between group differences ($p < .05$)

Figure 3-1. Mean changes in VAT volume between groups after 24 weeks of intervention.




‡Significant decrease from BL to W24 ($p < .05$)
*Significant between group differences ($p = .05$)

Figure 3-2. Mean changes in SAT volume between groups after 24 weeks of intervention.

# CHAPTER 4
# DISCUSSION

## Summary and Future Directions

The purpose of the current study was to examine the impact of a six-month, lifestyle-based weight loss intervention on changes in central body fat distribution in obese older women, a population that is at particularly high risk for obesity-related comorbidities and subsequent disabilities. The major finding of this study was that a lifestyle-based intervention produced significant changes in regional body fat distribution. Specifically, participants in the DR+E intervention group lost significant levels of visceral and subcutaneous adipose tissue located in the central region of the body. Moreover, participants in the DR+E intervention group had significant changes in body fat distribution after six months compared to the participants in the successful aging educational control group.

The parent study (142) demonstrated the feasibility, acceptability, and efficacy of this DR+E program in improving physical function in sedentary, obese older adult women with mild to moderate physical impairments. To determine the relationship between central adiposity and physical function, we examined changes in body weight, regional body fat distribution, and physical function outcomes. Our hypotheses were that greater reductions in body weight would be associated with greater reductions in VAT and SAT, and greater reductions in VAT and SAT would be associated with improvements in physical performance. In partial support of these hypotheses, reductions in body weight were found to be strongly and directly related to reductions in SAT. No relationship was found between changes in body weight and changes in VAT. Additionally, no significant relationships were noted between changes in body weight or central adiposity with changes in physical function measures. Notably, there was a positive correlation between changes in VAT and SAT.

To date, only a few studies have investigated the effects of lifestyle interventions which combine dietary restriction and exercise on regional body fat distribution using technologies that can measure levels of internal visceral and subcutaneous adipose tissue. Although most studies show a positive effect of weight loss on central adiposity, these results are limited by the use of anthropomorphic measures (i.e., waist-to-hip ration and waist circumference). While these measures are widely used as measures of adiposity and can be useful tools in monitoring health status they are unable to assess body fat distribution directly. This makes them inaccurate for assessing health risks associated with central adiposity (153); therefore a strength of the present study compared to many previous studies was that central body fat depots (i.e., visceral and subcutaneous adipose tissue) were measured directly using magnetic resonance imaging technology.

The findings of this study are promising regarding the potential of lifestyle-based interventions to reduce chronic systemic inflammation by cytokines released in VAT and to decrease the risk for cardiometabolic diseases. Even small differences in VAT volume can significantly improve plasma insulin and lipid metabolism, and alter the risk profile for cardiovascular disease (51, 154-155). Similar results were reported by Santanasto and colleagues (2011) who found that physical activity plus weight loss significantly reduced total abdominal fat, VAT, and SAT compared to no change in the successful aging control group (123). Moreover, mean changes in VAT were significantly different between intervention groups. Notably, although SAT is not thought to be as harmful as VAT, there is evidence of a critical VAT threshold effect (51). At the point where metabolic syndrome has begun to develop, SAT may become more like metabolically-active VAT. More evidence is needed to support this theory; however, our findings show that lifestyle-based interventions can significantly reduce SAT, thereby minimizing potential deleterious effects of high levels of SAT.

This study was designed to more closely examine the relationship between changes in body weight, body fat distribution, and physical function. In a previous study, decreases in abdominal visceral fat were directly related to change in body weight (117). We found a significant relationship between changes in body weight and in SAT, but this was not observed for changes in VAT. It has been previously shown that changes in regional body fat distribution can occur independently from changes in body weight and BMI (25). Therefore, changes in VAT may occur independently of weight loss and appear to be more strongly impacted by other components of the lifestyle-based intervention (i.e., exercise training). While some studies have shown that VAT reductions can occur in the absence of significant weight loss among middle-aged adults (156-158), this association has yet to be made in older adults.

In contrast to hypotheses, no significant relationships were observed between changes in central adiposity and changes in physical function measures. Previous studies have demonstrated that intentional weight loss in obese older adults is associated with improvements in walking speed (135). Furthermore, data compiled from three randomized clinical trials combined showed that every 1 kg loss of fat mass predicts a 0.01 m/s increase in walking speed in obese older adults (135). Decreased flexibility, limited range of motion, and fatigue associated with both aging and central obesity likely contribute to functional decline in obese older adults. In addition, a sedentary lifestyle may also contribute to a decline in functional status in this population. Changes in body fat distribution, particularly the accumulation of VAT, are particularly hazardous in the pathogenesis of metabolic abnormalities (i.e., pro-inflammatory state) that can contribute to both cognitive and functional decline. Thus, there are multiple contributors that can impact physical function and more research is needed to evaluate the relative effect of these factors.

Findings from our study also showed no associations between changes in body weight and physical function. This finding is in contrast to findings from the literature, which suggest that there is a strong inverse relationship between weight change and physical function (108,113). In a recent study, the magnitude of weight loss was associated with improvements in walking speed, but not overall SPPB score (135). Still, it has also been suggested that the relationship between leg strength and gait speed is non-linear in older adults (159). Additional research to assess the nature of this relationship will help to provide more information on the independent effects of weight loss and exercise.

## Strengths and Limitations

The current study is significant and innovative as it is among the first randomized controlled trials to directly examine changes in body fat distribution in obese older women. We examined the response of abdominal adipose tissue to the recommended comprehensive lifestyle intervention for weight loss in obese older adults which was designed to minimize muscle and bone loss. Specifically, we measured visceral and subcutaneous adipose tissue within the abdominal region directly by magnetic resonance imaging. The design of our lifestyle-based intervention was a comprehensive and safe approach for the treatment of obesity in older adults.  Our ethnically/racially diverse sample of postmenopausal women is an important aspect of this study because obese older African-American women represent an important underserved population for examining the effects of lifestyle approaches on central adiposity and physical functioning. The results of this study support the need for continued investigation on the key pathways linking central adiposity, inflammation, and functional decline commonly observed in obese older adults.  This study also has clinical importance as it highlights the importance of evaluating changes in abdominal fat distribution when working with obese older adults to monitor risk of cardiometabolic diseases, cognitive decline, and functional impairments.

There are a few limitations to consider when interpreting the results of this study. First, the sample size was small as some women dropped out before the six-month follow-up visit and some image scans were unavailable or not interpretable. The small sample size did not allow for racial differences to be examined within groups. Second, the duration of the study was only six months and therefore the study duration may not have been sufficient to detect potential changes in body fat distribution, which may occur over longer time periods.  Studies with larger study samples followed over longer time periods are needed to further evaluate the effects of a comprehensive lifestyle intervention on central adiposity. Third, this experimental design did not allow for an understanding of whether dietary restriction alone, exercise alone, or the combined effects of dietary restriction plus exercise were responsible for the observed reductions in VAT and SAT.

## Conclusions

There is an urgent need for intervention studies testing lifestyle strategies for improving or maintaining functional status in obese older adults. The rising prevalence of obesity and its related co-morbidities contribute to the increasing prevalence of disability among older populations, particularly obese older African-American women. As such, identification of older adults at high risk for disease and/or disability from increased central fat depots will be an important focus of clinical practice and future research.

The results of this study indicate that a comprehensive six-month, lifestyle intervention consisting of dietary restriction plus a multi-component exercise program can produce reductions in abdominal body fat in obese older women with mild to moderate functional impairments. Specifically, dietary restriction plus exercise is an effective treatment approach for producing significant reductions in visceral and subcutaneous adipose tissues in the high risk population of obese older African American and Caucasian women.

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# BIOGRAPHICAL SKETCH

Christy Karabetian obtained a Bachelor of Arts from Concordia University in Montreal, Quebec, with a double major in psychology and sociology. She was involved in research at the Center for Research in Human Development at Concordia University, and in community service work with underserved populations in Montreal. She completed a Master of Arts in mental health and behavioral medicine from Boston University School of Medicine in Boston, Massachusetts. During her graduate studies, Ms. Karabetian received training in research and clinical skills at the Boston University Medical Center. Following her studies, Ms. Karabetian accepted a position with a large, multi-center NIA funded study, *Comprehensive Assessment of Long-term Effects of Reducing Energy Intake (CALERIE)*, and gained direct experience in clinical trial operations, behavioral counseling, and collect data for outcome measures. Ms. Karabetian participated in workshops for continuing education on such topics as sports nutrition, biofeedback, and motivational interviewing. In August 2011, she began her current position as a graduate research assistant in the Department of Clinical and Health Psychology at the University of Florida, under the mentorship of Dr. Stephen Anton. Ms. Karabetian's research interests are in the role that lifestyle factors have in influencing obesity, metabolic disease conditions, and physical function.