Adiposity, Inflammation, and Physical Function in Overweight African American Adults with Osteoarthritis

BY

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THESIS
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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ADL	Activities of daily living
ADAPT	Arthritis Diet and Activity Promotion Trial
BLSA	Baltimore Longitudinal Study of Aging
BMI	Body mass index
CAROT	Influence of Weight Loss or Exercise on Cartilage Obese Knee OA Patients Trial
CRP	C-reactive protein
CT	Computed Tomography
DXA	Dual-energy x-ray absorptiometry
FAST	Fitness Arthritis and Seniors Trial
FFA	Free fatty acids
FNS!	Customary Fit & Strong!
FNS!+	Fit & Strong! Plus
IDEA	Intensive Diet and Exercise for the Elderly
IL-6	Interleukin-6
LIFE	Lifestyle Interventions and Independence for Elders
MRI	Magnetic Resonance Imaging
NHANES	National Health and Nutrition Examination Survey
OA	Osteoarthritis
PA	Physical activity
PASE	Physical Activity Scale for the Elderly
RCT	Randomized clinical trial
SAT	Subcutaneous adipose tissue
SE	Self-efficacy
TNF-α	Tumor-necrosis factor α

TUG	Timed up-and-go test
U.S.	United States
VAT	Visceral adipose tissue
WC	Waist circumference
WOMAC	Western Ontario and McMasters University Osteoarthritis Index

SUMMARY

Osteoarthritis (OA) affects over 30 million United States (U.S.) adults[1] and 80% of those with OA have some degree of mobility limitation[2]. Rising adiposity levels play a serious, detrimental role to the progression of OA and physical disability, particularly in older adults[3,4]. Furthermore, excess visceral body fat can promote the overproduction of inflammatory proteins, including C-reactive protein (CRP), that have been linked to the onset and worsening of OA, lean muscle tissue atrophy, and overall functional decline[3, 4]. Thus, reducing total and regional body fat mass may have an impact on both joint burden and systemic inflammation that translates to improved physical function within the older population and particularly in those with existing OA.

The positive effects of physical activity (PA) combined with dietary weight management are evident from multiple randomized controlled trials (RCT) in older, overweight and obese adults with OA leading to greater weight loss[5, 6, 7, 8, 9, 10] reductions in systemic, low-grade inflammation[11, 12] and improvements in subjective and objective measures of physical function. However, these studies are limited in that they were largely tightly controlled efficacy trials, were focused on primarily non-Hispanic white cohorts, and presented limited data regarding associations between changes in adiposity, body composition, inflammation, and physical function. Thus, the aim of this study was to assess the impact of an 8-week PA vs. an 8-week PA plus dietary weight management intervention on adiposity, body composition, inflammation, and objective physical function in older, overweight/obese African American adults with OA and to assess the associations between changes in adiposity, body composition, inflammation, and physical function.

SUMMARY (CONTINUED)

Results from this study confirm that a combined dietary and physical activity intervention effectiveness trial is superior to PA alone in reducing body weight, percent and total body fat, and visceral fat mass and improving physical function based on the six-minute walk test. However, the combined program was not superior for reducing systemic inflammation. Although, in a post-hoc analysis, a greater reduction in CRP was associated with fewer seconds to complete the timed-up and go physical function test suggesting that lowering systemic inflammation can have a positive impact on physical function. Given the modest effect of the interventions on the adiposity, inflammatory and physical function measures compared to existing trials, additional studies conducted on larger samples including a longer follow-up period may be needed to fully explore the effects of the interventions these outcomes and how changes in adiposity and physical function translate to improved physical function. In addition, a larger sample that includes a significant number of non-Hispanic whites would allow for exploration of possible racial/ethnic differences in response to the intervention.

I. Introduction

A. Background

Approximately 70% of older adults in the U.S. are overweight (body mass index (BMI) 25 – 29.9 kg/m^2) or obese (BMI $\geq$ 30.0 kg/m^2)[13]. This is concerning given that excess body weight is major risk factor for the onset of chronic conditions including osteoarthritis (OA)[14] and Type 2 diabetes[15] as well as the gradual emergence of physical disability[6]. Physical limitations – generally defined as self-reported difficulty walking one-quarter mile or climbing a flight of stairs - is often a precursor to mobility disability which is associated with greater hospitalizations, long-term care admissions, and disability related to activities of daily living (ADL) (e.g., dressing, bathing, climbing stairs)[16]. Thus, interventions aimed at reducing body weight may have a positive impact on chronic conditions including OA and physical function within the older adult population.

B. Obesity, Adiposity, and Osteoarthritis

Higher total body fat and greater centrally located visceral adipose tissue (VAT) play a significant role in the pathogenesis of OA and age-related functional decline[6]. The sheer force of excess body weight on large joints (e.g., knee and hip) can adversely affect mobility and physical functioning across all age groups, including the elderly. In the Baltimore Longitudinal Study of Aging (BLSA), older adults (ages 60 - 79 years old) with BMI between 30 and 40 kg/m^2 exhibited poorer walking outcomes evidenced by reduced endurance in a 400-meter walk[17]. In the same study, higher percent body fat, another marker of adiposity, was associated with greater functional limitation even in those with BMI in the non-obese range. An inverse relationship between percent body fat and functional limitation was also observed in a cross-sectional analysis of 1,655 older adults in which lower walking speed and self-reported functional limitations were linked to greater fat mass[18]. Furthermore, excess VAT can promote the overproduction of pro-inflammatory proteins including CRP that have been linked to the onset of OA, lean muscle tissue atrophy, and overall functional decline[19, 20]. Therefore, reducing total and regional body fat mass may have an impact on both joint burden and systemic inflammation that translates to improved physical function within the older population and particularly in those with OA.

C. Osteoarthritis: Race and Sex

While disability can certainly increase with age, epidemiologic and clinical evidence suggests that sex as well as race may play a role in physical decline and prevalence of OA. For example, women aged 85 years and older are 72% more likely to exhibit difficulty with ADLs compared to age-matched men[21]. Statistics also show that African American women aged 65 years and older have higher rates of mobility limitation compared with non-Hispanic white women[22]. Also, while the prevalence of hand OA is higher among non-Hispanic whites, African Americans are more likely to experience OA of multiple large joints such as the knee and hip which can be more detrimental to physical function[23]. A partial explanation for this may be due to the disproportionate rate of obesity in the African American population, particularly among African American women whose rate of obesity (57%) is 21% higher compared to non-Hispanic white women (38%)[22]. In fact, evidence from a cross-sectional analysis found higher BMI and large waist circumference (WC) are independently associated with greater OA severity and that among women with high BMI and large WC, non-Hispanic Blacks were at greatest risk for poor mobility outcomes (findings were less consistent for men)[24]. This evidence suggests that interventions targeting obesity among African American women may yield significant and favorable effects on OA outcomes.

D. **Effects of Physical Activity and Weight Management on Osteoarthritis**

There are many studies indicating that consistent PA can have a positive impact on physical function and OA symptoms[25, 26, 27]. However, to date, only a handful of trials have examined the independent and combined effects of dietary weight management to promote weight loss plus physical activity on total and regional body fat, systemic inflammation and physical function in older overweight and obese adults with and without OA[12, 28, 29, 26,30-32]. Findings from these trials do support the superior effect of dietary weight management combined with PA on body weight, body composition, physical function and systemic inflammation among older overweight adults with and without OA. However, the existing studies were largely tightly controlled efficacy trials and not implemented under "real world" conditions. Furthermore, the existing trials were tested in largely non-Hispanic white cohorts.

E. **Purpose of the Study**

Clearly, there is a dearth of research examining the impact of physical activity plus dietary weight management trialed under "real world" conditions on adiposity, body composition, systemic inflammation and physical function in older overweight African American adults with OA. Conducting an effectiveness trial would help to demonstrate the public health applicability of such interventions. Furthermore, an analysis of changes in adiposity, lean mass, and inflammation following such an intervention, may provide significant insight into the concomitant roles these factors play on physical function – knowledge that is particularly essential given the lack of evidence in the literature. Thus, the primary purpose of this study was to assess and compare the impact of Customary Fit & Strong! (FNS!) (PA lifestyle intervention) and Fit & Strong! Plus (FNS!+) (PA plus dietary weight management lifestyle intervention) implemented in the community by certified fitness instructors on adiposity, body composition, systemic inflammation and physical function in an urban cohort of older, overweight and obese African American adults with self-reported lower extremity OA. The specific aims for this study are as follows:

F. **<u>Primary Aim</u>**

To determine and compare the impact of an 8-week physical activity lifestyle intervention and an 8-week physical activity plus dietary weight management lifestyle intervention on body weight, adiposity (i.e., BMI, % body fat, visceral fat mass), lean muscle mass, systemic inflammation and objective physical performance measures in 148 older overweight and obese African American adults with self-reported lower extremity OA. ***Hypothesis:*** *Combining physical activity with dietary weight management will produce greater changes in body weight, adiposity measures, body composition, inflammation, and physical function compared to physical activity alone.*

G. **<u>Secondary Aim</u>**

To determine whether post-intervention changes in adiposity, lean muscle mass, and systemic inflammation significantly correlate with changes in the objective physical performance measures. ***Hypothesis:*** *Decreases in overall and visceral adiposity and systemic inflammation and increases in lean muscle mass will be significantly associated with increased physical performance based on objective measures of physical function.*

II. BACKGROUND

A. Overview

Older adults – persons aged 65 years or older – comprise 14.5% of the U.S. population[33]. The proportion of older adults in the U.S. is projected to grow to 21.7% by 2040[33]. Advancing age is often accompanied by physical deconditioning and disability. There are several factors associated with a decline in physical function including certain chronic health disorders (e.g., obesity, OA) and acute conditions (e.g., fractures and falls). Changes in total body weight and fat (i.e., greater overall adiposity), body fat distribution (i.e., greater central adiposity) along with a gradual decrease in muscle mass and an increase in systemic inflammation may contribute to the development of chronic health conditions including OA that contribute to age-related functional decline[34]. Thus, interventions designed to reduce body fat and systemic inflammation while reciprocally preserving lean muscle mass may have a positive effect on mobility and physical functioning and even more so in those with degenerative joint disorders like OA. In this background section, the relationships between body adiposity, body fat distribution, systemic inflammation, lean muscle mass, and OA and physical function is discussed. The existing intervention studies examining the effects of PA alone and PA plus dietary weight management for weight loss on adiposity, body composition, inflammation, and physical function of older, overweight adults with and without OA is reviewed.

B. Overweight and Obesity in Older Adults

1. Epidemiology

Overweight is defined by the World Health Organization as a BMI between 25 - 29.9 kg/m^2 while obesity is characterized as a BMI greater than or equal to 30 (kg/m^2)[35]. More than one-third (38.5%) of adults in the U.S. $\geq$ 60 years of age have BMI in the obese range[36]. Obesity in older adults has risen in recent decades - a trend expected to continue[36]. This rise in overweight and obesity in older adults is partly due to greater rates of sedentary behavior. For example, in a study of 2,630 adults aged 60 years and older, time spent engaged in moderate to vigorous PA declined among consecutive older age groups (60-69, 70-79, and ≥80 years of age)[37]. Further, a meta-analysis of studies assessing inactivity and related health outcomes in older adults consistently found greater sedentary behavior associated with greater prevalence of overweight and obesity among this age group[38].

2. Race/Ethnicity, Sex, and Obesity

Overweight and obesity trends differ across racial/ethnic groups and by sex. The prevalence of obesity is higher among African Americans. Nearly half (47.9%) of older African American adults (≥ 60 years) are obese based on BMI[39]. Furthermore, African American women 60 years and older have among the highest prevalence of overweight and obesity with approximately one in two African American women with BMI's exceeding 30.0 (kg/m^2)[13].

3. Obesity as a Public Health Concern

The rise in excess adiposity among older adults and particularly among older African Americans is a significant concern given that overweight and obesity are linked to the development of chronic conditions such as cardiovascular disease, Type 2 diabetes, and OA that contribute to greater healthcare costs, disability, functional impairments, and higher long-term care admissions[40]. Furthermore, excess adiposity is also associated with longer hospital stays and greater likelihood of falls and falls with injury among older adults[41]. Thus, interventions designed to reduce excess body weight/fat among older adults may be critical to addressing and potentially improving physical function and quality of life within this population

<u>Osteoarthritis</u>

1. Epidemiology

Osteoarthritis is the most common joint disease worldwide[21]. The global prevalence continues to rise due to an aging world population and current obesity trends[42]. Osteoarthritis is most often characterized by articular cartilage degradation, synovitis (i.e., inflammation of synovial membrane), and subchondral bone sclerosis[14]. Major symptoms include joint pain and stiffness along with swelling around the affected joints that together lead to impaired physical function[14]. Osteoarthritis affects over 30 million U.S. adults[21] and the lifetime risk of developing knee OA is approximately 46%[43] making it a leading cause of disability among the elderly[21]. In fact, 80% of the affected population have some degree of mobility limitation and 25% are unable to complete major ADL[21]. Mobility limitation is often observed in individuals with knee OA, given that the associated joint is critical in ambulation[42]. Further, OA contributes more than $10 billion annually to healthcare costs in the U.S.; with a large proportion associated with knee and hip replacements[42]. Thus, preventing or treating OA may significantly curb losses in physical function, improve quality of life, and have a positive effect on national healthcare spending.

2. Risk Factors for Osteoarthritis: Overweight and Obesity

Overweight and obesity, along with age, sex, and race, are major risk factors for OA[21]. Overweight and obesity specifically, are the only known modifiable risk factors for OA. There is accumulating evidence that exposure to a high BMI throughout adulthood is a significant risk factor for OA[42]. In fact, one in every five Americans will be diagnosed with OA in their lifetime, while one in three obese individuals will be diagnosed with OA[21]. Additionally, body weight may influence the severity of OA symptoms – obese individuals have significantly greater knee joint degeneration, and have higher rates of surgical knee and hip replacement compared to age-matched healthy weight controls[42]. There are currently two major causal theories explaining the association between overweight/obesity and OA. The *mechanical theory* focuses on the effects of loading and cartilage degradation –specifically, repetitive application of a higher load on the knee joint that leads to degeneration of articular cartilage and sclerosis of the subchondral bone[44]. The second theory, known as the *metabolic theory*, surmises that OA arises through an indirect action of elevated pro-inflammatory cytokines stemming from increased adipose tissue that leads to joint degradation or, along with the mechanical stress, exacerbates joint degeneration[44]. This theory may account for the elevated risk of hand OA among obese patients, an increased risk not explained by the mechanical joint theory.

3. Sex, Race/Ethnicity, and Osteoarthritis

In addition to excess adiposity, sex and race/ethnicity are also significantly associated with risk for OA. Knee OA is more prevalent among older women (13%) compared to men (10%)[4]. The observed higher risk is likely attributed to sex hormones, genetics, and higher obesity rates in women[4]. Studies also indicate that there is a higher prevalence of knee OA among African Americans[45]. According to an analysis of National Health and Nutrition Examination Survey (NHANES) III data, there is a higher incidence of knee OA among African Americans compared to non-Hispanic whites [OR = 1.65, 95% CI: 1.17–2.37], as well as more symptomatic knee OA among [OR = 1.52, 95% CI: 1.06–2.19][45]. Further, data from the Johnson County Osteoarthritis Project indicated a 6% higher prevalence of knee OA among African Americans (32.4%) than non-Hispanic whites (26.8%)[45]. These findings may be partially explained by different rates of overweight and obesity among African Americans.

C. Adipose Tissue, Inflammation, Physical Function, and Osteoarthritis

1. Obesity and Physical Function

Risk of impaired physical function rises with the severity of obesity among older adults[6]. This can significantly affect the quality of life and independence of older adults as functional mobility – the ability to move around in the environment in order to perform ADL – becomes impaired. Common ADL include standing up from a seated position, walking, climbing stairs, and bending[6]. Obesity also hinders the independent completion of such daily tasks, regardless of age[46]. In BLSA, older adults (ages 60 - 79 years old) with higher BMI, exhibited poorer physical function evidenced by reduced endurance in a 400 meter walk[17]. Higher BMI is also linked to greater knee joint pain, which may impair physical function[6]. Further, data from the Framingham Heart study indicated that a 5.1 kg decrease in weight over a ten-year period lowered the risk for development of symptomatic knee OA among women by 50% [47]. This effect of weight on OA symptoms has also been observed in men, where a 5% weight loss significantly slowed knee cartilage degeneration[48]. Thus, there is consistent evidence that higher BMI is associated with greater functional limitations (particularly among OA patients) and reductions in body weight are a significant therapeutic target for combating these limitations.

Beyond total body weight, greater percent body fat may also negatively affect an individual's functional ability. For example in BLSA, higher percent body fat was associated with greater functional limitation even in those with BMI in the non-obese range[17]. A positive relationship between percent body fat and functional limitation was also seen in a cross-sectional analysis of 1,655 older adults in which lower walking speed and self-reported functional limitation was linked to greater overall fat mass[18].

D. Objective Performance Based Measures to Assess Physical Function in Older Adults with Osteoarthritis

Objectively assessing physical function is essential for monitoring changes in a population over time as well as in response to an intervention. There are several objective methods commonly used to assess physical function that are described below and summarized in **Table I**.

1. Six-Minute Walk Test

The six-minute walk distance test, a measure of aerobic capacity and endurance, has been used extensively in research interventions, particularly in those monitoring changes in physical function in adults with OA[8,29]. The six-minute walk test involves testing the maximal distance walked at a regular pace in six minutes. In an obese population, the six-minute walk test has shown good reproducibility and validity[49,50].

2. Timed Up-And-Go (TUG) Test

The TUG test measures physical function with a specific focus on balance, gait, and gait speed. It has been used extensively in research to evaluate balance and gait in older adults with and without OA[51]. The TUG test involves having a participant stand from a chair (when prompted), walk to a line on the floor at a regular pace, turn, walk back to the chair at a normal pace and sit down again[52]. The purpose of this test is to determine how long (seconds) it would take an individual to complete the prescribed task. The TUG test has high test-retest reliability[53]. However, in a prospective cohort of 259 older adults (≥ 65 years) the TUG test was limited in predicting risk of future falls[54]

3. 30-Second Chair-Stands

Finally, the 30-second chair-stands is a common measure of assessing leg strength and endurance. The 30-second chair-stand is completed by having a seated participant place his/her hands on the opposite shoulder, crossed at the wrists with feet flat on the floor, and when prompted, participant would rise to a full standing position and sit back down again[55]. The purpose of this test is to determine how many chair-stands a person can complete in 30 seconds. Several studies have documented high reliability of the test in older adults and in adults with OA[56,57].

Table I. Objective Performance Based Measures of Physical Function

Performance Measure	Description of Performance Measure
Six-minute walk test	Measure of distance walked in six minutes at a self-selected pace on a hard, flat surface.
Timed up-and-go (TUG)	Measure of postural stability, gait, and sway. Participant is asked to stand up from chair, walk a specific distance at a normal pace, turn, walk back to chair, and sit down.
30-Second Chair-Stands	This is a measure of leg strength and endurance. Participants are asked to sit in the middle of a chair, place their hands on the opposite shoulder crossed at the wrists, keep feet flat on the floor and, when prompted, to rise to a full standing position and sit back down. This is repeated for thirty seconds.

E. Research Methods for Measuring Body Fat

a. Body Mass Index

One of the most common methods to measure body adiposity is BMI. Body mass index is a simple calculation of weight in kilograms divided by height in meters squared. It is a quick estimate of body fat and of a person's risk for diseases linked to greater adiposity such as, cardiovascular disease and Type 2 diabetes. A BMI of 25.0 - 29.9 kg/m^2 would classify a person as overweight and, a BMI of 30.0 kg/m^2 or above categorizes a person as obese[58].

Although relatively non-invasive, quick, and cost-effective, there are several limitations to using BMI to assess body adiposity. Body mass index is merely a surrogate measure of body fat; it is a measure of excess weight and not necessarily excess fat[58]. Further, several factors may influence how well BMI correlates with total body fat such as age, race/ethnicity, and sex[13]. For example, at the same BMI, older adults generally have more body fat than younger adults, and women tend to have greater amounts of body fat than men; highly-trained individuals may have a greater BMI that is due to increased muscle mass and not fat mass[58]. Moreover, the relationship between BMI and body fat may not be comparable across racial/ethnic groups. For example, when BMI and percent body fat [measured via dual-energy X-ray absorptiometry (DXA)] was obtained in a population of 555 healthy adult women (20-33 years of age), non-Hispanic white and Hispanic women had 2.9% greater body fat compared to African American women for a given BMI ($p=0.02$)[59]. These factors should be considered when using BMI as a measure of body fat clinically and in biomedical research.

b. Waist Circumference

Waist circumference is a measure of the size of a person's waist that is used as a proxy for centrally located fat or VAT[60]. The measurement is taken on bare skin, around the waist at the umbilicus or top of the ileac crest on exhalation while the subject is in a standing position[58].

A greater WC has been correlated with higher circulating pro-inflammatory proteins and risk for several chronic diseases. Specifically, a WC greater than 102 centimeters (40 inches) in men and 88 centimeters (35 inches) in women indicates higher risk for cardiovascular disease and insulin resistance[11].

Although WC is a widely accepted indicator for VAT and predictor of chronic disease risk, there are some difficulties and disadvantages with obtaining and interpreting this measure. First, it may be difficult to accurately palpate the tip of the ileac crest in more obese individuals. The inter-observer variability has also been shown to be high (higher than for BMI) which may potentially misclassify some individuals in terms of their adiposity and disease risk[61]. Lastly, WC cannot provide information regarding overall adiposity and it does not differentiate between subcutaneous adipose tissue (SAT) and VAT depots[62]. Nonetheless, in the context of lifestyle intervention research, monitoring changes in WC may be more informative compared to BMI as it can provide an estimate of abdominal fat even when there is no observable change in BMI[62].

c. Whole Body Dual Energy X-ray Absorptiometry Body Scan

The determination of body composition (i.e., measuring bone, fat, and non-bone lean tissue) is significant to clinicians and researchers in understanding health and disease[63]. Information regarding the relative amount of bone vs. fat vs. muscle in different body types provides profound insight into body composition changes that accompany growth, aging, malnutrition, and disease[63]. There are several methods used to measure body composition and among them, DXA has become one of the most commonly used.

Although DXA is used clinically to diagnose osteoporosis and assess risk for development of fractures, DXA can also provide information regarding total and regional body fat mass and distribution, as well as lean mass and bone mass estimates. Through emission of low-energy X-ray, DXA can distinguish between the different compositions of these tissues[63]. However, a drawback of DXA is the weight and scanning field limits although some scanners accommodate individuals up to 450 lbs. Depending on a person's body shape, an individual may not fit within the scanning field. In such cases, a half-body scan is completed and the total body composition estimated. This may compromise the accuracy of the results[63]. Further, metal implants affect DXA scan results by increasing reported bone mineral content and giving skewed reported total body mass[64]. Despite the limitations, DXA scans provide relatively accurate data regarding total and regional adiposity, bone, and lean mass at a relatively low cost compared to other methods for assessing body composition [e.g., computed tomography (CT) and magnetic resonance imaging (MRI)].

d. Computed Tomography and Magnetic Resonance Imaging

The current gold standard for quantitative assessment of body composition, specifically adiposity, is CT and MRI[65]. Computed tomography provides a high-resolution assessment of adipose tissue through radiography to create single or multiple slices of a body section that can then be exploited for the assessment of total fat and fat subtype using specialized software[65]. Specifically, CT scans can provide quantification of certain adipose tissue regions (including subcutaneous, visceral, and intermuscular) as well as whole body skeletal muscle[66].

Magnetic resonance imaging provides similar results to CT but with no radiation exposure[67]. With high resolution and ability to quantify major body components at the tissue-level[68], multiple-slice MRI and CT are the preferred options for body fat and skeletal muscle volume calculation[65] with excellent accuracy in measuring muscle and fat areas, especially VAT in comparison to DXA[69]. However, use of CT and MRI is limited by accessibility and cost. Thus, use in intervention and epidemiologic research is modest[65].

F. Adipose Tissue Distribution and Type Across Race and Sex

There are several studies indicating that racial/ethnic and sex differences in adipose tissue amount, distribution, and type exist. For example, women tend to have higher overall fat mass compared to men[70], with levels considerably higher among African American women[13]. According to data from NHANES III, African American women have greater mean WC compared to non-Hispanic white women[62]. Surprisingly, research exploring adipose tissue differences in race reveal African American women tend to display less VAT and higher SAT in their central region (results obtained from CT scans)[71,72]. Further, MRI and CT data show that compared to women, men have lower mean SAT volume but, exhibit higher VAT levels[60,71,73] particularly among Caucasian men when compared to African American men at higher BMI and WC levels[60,73,74].

G. Biological and Molecular Effects of Excess Adiposity

The notion that adipose tissue is simply a storage site for body energy has been replaced by evidence indicating that adipose tissue is a complex endocrine organ with far-reaching metabolic roles[75]. Under normal physiologic conditions, adipose tissue secretes chemical messengers called adipokines[76]. These hormones provide a communication route between adipose tissue and multiple other tissue and organ systems (i.e., muscle, bone, liver, immune system) to influence energy balance, metabolism, and immune function, further highlighting the importance of fat in whole body homeostasis[77].

However, when adipose tissue expands with obesity and older age, the tissue undergoes molecular changes that ultimately affect whole body metabolic and immune homeostasis[75]. When adipocytes enlarge, free fatty acid (FFA) and glycerol release from adipocytes increases[75]. Higher circulating FFAs are associated with detrimental metabolic changes such as reduced insulin sensitivity[78]. Moreover, elevated FFAs inhibit insulin's anti-lipolytic action further increasing the rate of FFA release from adipocytes further exacerbating metabolic perturbations in obesity[79]. Notably, recent studies have also demonstrated potential links between higher circulating FFAs and greater systemic inflammation in obesity. Studies have shown that elevated FFAs activate hepatic pro-inflammatory pathways that increase the expression of several pro-inflammatory cytokines including tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6)[79].

The FFA induced pro-inflammatory signaling is not the only source of pro-inflammatory cytokine release in obesity. Compared with lean individuals, adipose tissue in obese individuals, particularly adipose tissue in the visceral region, exhibits a higher expression of pro-inflammatory cytokines, such as TNF-α and IL-6[75]. The largest contributor towards this rise in inflammation however, may not be the adipose tissue itself but macrophages that infiltrate adipose tissue[75,80]. With adipocyte hyperplasia and hypertrophy that is characteristic in obesity, there is accompanying tissue-level consequences including fatty acid flux, hypoxia, and adipocyte cell death[80]. These tissue-level changes lead to macrophage recruitment to the area. Macrophages are immune system cells that engulf and destroy damaged or dead cells. When targeting hypertrophied adipocytes[81], these immune cells have been shown to exhibit significant pro-inflammatory features, increasing the local expression of pro-inflammatory cytokines, such as IL-6 and TNF-α[80] as well as increasing expression of IL-6 and acute phase proteins distally in the liver[81]. In obesity, macrophage recruitment and a steady rise in the release of pro-inflammatory factors by the adipose tissue and liver ultimately leads to a chronic systemic pro-inflammatory state – a state linked to increased risk for chronic diseases. In sum, increased pro-inflammatory cytokine release from adipose tissue and the liver resulting from excess adiposity, likely contributes to the development of multiple chronic conditions including insulin resistance, cardiovascular disease, and OA[81].

H. Assessing Systemic Inflammation

Elevated levels of pro-inflammatory biomarkers are often observed with both obesity and aging and are linked to the development of chronic conditions, including OA[11]. Thus, monitoring pro-inflammatory proteins in obese older adults may be critical for predicting the onset and progression of OA and other debilitating chronic diseases. Further, monitoring levels in the context of an intervention may also help to explain how inflammation correlates or predicts changes in OA symptoms and physical function. Commonly used pro-inflammatory biomarkers used to determine systemic inflammation in epidemiologic and lifestyle intervention research includes, CRP, IL-6 and TNF-α. Each marker is described below.

1. C-reactive Protein

C-reactive protein is an acute phase protein that is produced by the liver in response to tissue injury/inflammation that is also commonly elevated in both obesity[82] and OA[83]. C-reactive protein is a sensitive and accurate marker of systemic inflammation[84] that can be measured from capillary blood via finger-stick or venous blood with concentrations from either blood source accurately reflecting a person's inflammatory burden[85].

High-sensitivity-CRP (hs-CRP) is commonly used in research to assess inflammation given it is a more sensitive assay that is able to detect CRP even at low concentrations compared to the standard assay[5]. Levels above 3 mg/L are indicative of high risk for cardiovascular disease[86].

Several studies have reported that CRP levels may differ based on sex and race/ethnicity. For example, levels tend to range higher among women[87] and among African American men and women compared to non-Hispanic whites and Hispanics (adjusted for BMI)[88,89]. When assessing CRP's relationship to obesity and other chronic conditions, it is important to understand other factors that can influence circulating CRP concentrations. For example, smoking status, acute infection, cold/flu, and inflammatory bowel diseases are associated with elevated CRP[90] independent of BMI and OA. Thus, these potential confounders should be considered when evaluating associations between CRP, body adiposity, and chronic diseases.

2. Interleukin-6

Interleukin-6 is a pro-inflammatory cytokine that is elevated in most inflammatory conditions including obesity[91] and OA[92]. Interleukin-6 is secreted by T-cells and macrophages in response to infection and trauma[93]. It's a major pro-inflammatory mediator responsible for triggering the acute phase response[93], where IL-6 binds to the IL-6 receptor to initiate a signaling cascade that induces release of several acute phase proteins including CRP from the liver[94].

Interleukin-6 is commonly measured from venous blood, and is often tested when underlying inflammatory conditions are suspected[2]. Interleukin-6 is often elevated in cardiovascular disease[95] and OA[2]. Thus, serum IL-6 tests are non-specific and levels may increase in response to several conditions making it difficult to predict the specific cause of inflammation[2].

Similar to CRP, there are differences in the concentration of this pro-inflammatory marker by race/ethnicity. Concentrations of IL-6 measured in the Health ABC study found significantly higher levels in African Americans compared to non-Hispanic whites[96]. Further, the coefficients of variation associated with measurement of this biomarker may be a potential disadvantage and should be considered when using IL-6 to assess systemic inflammation[97]. It is also important to note that levels tend to increase with exercise[98] which must be considered when evaluating results in the context of a lifestyle intervention. Nevertheless, evaluating changes in IL-6 may prove useful in examining potential benefits of interventions targeting obesity, OA, and physical function.

3. Tumor Necrosis Factor–α

Tumor necrosis factor-α is a pro-inflammatory cytokine elevated in many inflammatory states including obesity[99] and OA[92]. Elevated TNF-α is also associated with low lean body mass and is an important marker of lean body status in older adults, and an independent predictor of strength and functional status in older adults[98]. Secreted by activated macrophages and other immune cells, TNF-α, like IL-6, is involved in a pro-inflammatory and acute phase response; release of this cytokine increases (such as during infection) CRP and other acute phase mediators from the liver, thus regulating the acute phase response in acute and chronic diseases[100].

TNF-α is commonly measured in venous blood[101]. There are mixed results concerning differences in serum concentration of this cytokine across race/ethnicity and sex. Two studies have found that concentrations tend to range higher among men than women[96,102] while one found no difference between the sexes[103]. Further, data regarding racial differences in TNF-α levels are mixed with some studies finding higher levels in Caucasians compared to African American adults[96,104], and others finding no differences by race/ethnicity[105].

Although TNF-α is an accurate but non-specific marker of whole-body inflammation and is also associated with lean body mass and functional status in older adults[98,99], there are several disadvantages of using this marker when monitoring inflammatory status. Tumor necrosis factor-α is higher among smokers[106] and with several chronic conditions such as inflammatory bowel disease[107] and cancer[108] and thus, should be considered as covariates when evaluating IL-6.

I. Adipose Tissue-Associated Inflammation: Differences by Sex and Race

As described previously, adipose tissue is metabolically active and is associated with the release of pro-inflammatory cytokines[80]. This is particular to centrally located adipose tissue surrounding the viscera[109]. Body fat level and distribution play a critical role in the potential development of low-grade chronic inflammation-a state that may increase the risk of multiple conditions such as type 2 diabetes and OA[14].

As indicated above, there is evidence of differences in total body fat, body fat distribution, and fat sub-type across sex and race/ethnicity. These differences may result in different metabolic effects and risk for disease. For example, the relationship between CRP and VAT and SAT is sex-specific. In a study of 208 healthy men (mean age 42.2 years) and 145 healthy women (mean age 36.8 years), higher CRP (mg/L) concentrations were seen in women compared to men with the same VAT and SAT (measured through CT scan) area (cm^2)[102]. There was also a steeper slope seen in the relation between CRP (mg/L) and VAT and SAT in women compared to men.

Differences in adiposity-associated inflammation also exist across race. Data from 10,492 subjects assessed by NHANES (1999-2004) showed that African American women had greater association between WC and CRP (mg/L) than non-Hispanic white women, suggesting a more profound association between central adiposity and low-grade systemic inflammation among African American women[110]. Further, in a cohort of 369 men and women (≥45 years of age) multiple regression analysis showed African American women had higher IL-6 (pg/ml) concentrations relative to VAT area (cm^2) (measured by CT) compared to Caucasian women[74].

There were no differences across race/ethnicity, adiposity/body fat distribution and inflammation among men in either study.

J. Inflammation, Obesity, and Osteoarthritis

As discussed above, the metabolic theory accounts for one plausible explanation of OA development among obese individuals. The theory is supported by evidence that obesity is associated with increased circulating levels of pro-inflammatory cytokines and that cartilage degradation is mediated by pro-inflammatory cytokines including IL-6[111]. A high level of pro-inflammatory cytokines can promote tissue destruction by disrupting the balance of the anabolic and catabolic activities of chondrocytes, the major cell type of cartilage tissue, which may ultimately contribute to reduced expression of extracellular matrix components (necessary for support and tensile strength of cartilage) and increased production of proteolytic enzymes[112]. In fact, higher circulating IL-6 is associated with an increased risk of knee OA[113]. In older obese adults, higher circulating CRP, IL-6, and TNF-α, is linked to the onset of OA, OA severity, and impaired physical function[11,28,30]. This suggests that reducing body fat may improve an individual's inflammatory profile[11] and subsequently improve physical function in older obese adults and particularly in those with OA.

K. Body Fat Distribution, Inflammation, and Osteoarthritis

Body fat distribution may also be an important factor linking body fat to OA. In a study of 217 older women central obesity was significantly associated with locomotive syndrome, a weakening of the locomotive system (i.e., bones, muscles, nerves, and joints), lending to a decline in autonomy[89]. There was also heightened knee and lower back pain and lower physical performance in this cohort. In a study assessing possible correlations between changes in body composition (body fat measured through DXA), physical function, and OA symptoms, found that greater body fat reductions (following a physical activity and dietary weight management intervention) were associated with greater walking distance, and reduced self-reported pain based on Western Ontario and McMaster's University Osteoarthritis Index (WOMAC) scores[114]. However, change in systemic inflammation was not assessed[29].

Excess VAT is associated with localized and systemic-inflammation (Balistreri 2010). If inflammation increases within joints, the synovial lining of the joints may swell, thicken and lead to decreased joint space over time negatively affecting physical function[115]. Chronic inflammation may also affect the soft tissues surrounding joints leading to deterioration of muscles, tendons, and ligaments[113]. In fact, higher circulating IL-6 is associated with an increased risk of knee OA[113]. Thus, adipose-derived systemic inflammation may be a major player in exacerbating OA as well as declines in physical function in older adults[112].

L. Adiposity, Inflammation, Physical Function, and Osteoarthritis: Evidence from Human Studies

Several studies have examined links between adiposity, inflammation, physical function, and OA. In one study conducted in overweight/obese middle aged and older adults (n=167), those with higher plasma IL-6 took significantly fewer steps per day and engaged in less light and moderate PA compared to those with lower circulating concentrations[32]. In a study of 3,392 adults aged 55 and older, higher body fat percentage coupled with elevated CRP was associated with lower handgrip strength (measured with a handheld dynamometer) compared to a high body fat percentage alone[116]. Elevated CRP was also associated with greater walking limitation (measured through maximal walking speed over a distance of 6.1 meters)[116]. Furthermore, following an 18-month dietary weight management and PA program, decreased inflammation (IL-6) was significantly associated with increased physical function (steps/day) in overweight and obese older adults[32]. This data provides evidence that both inflammation and excess body weight play a significant role in physical function among older adults and reductions in pro-inflammatory cytokines and adiposity may lead to favorable changes in physical function and particularly in those with OA.

1. Physical Function and Body Composition Across Race and Sex

Some studies have shown there may be greater mobility limitation among African American women that is linked to excess body weight and body fat distribution[117,118]. For example, when measuring gait speed and physical function (ability to walk a quarter mile or climb ten steps) older African American women were more likely to display mobility impairment that was attributed to higher BMI, VAT, and intramuscular adipose tissue[117]. Further, a study of 85 female and 49 male sedentary older adults found body fat was significantly related to gait in women but not men[118]. More research needs to be performed understanding how racial/ethnic and sex differences in overall body fat, body fat distribution and body fat type impact mobility in older adults and particularly in those with OA. Further, there is a lack of evidence describing the role of systemic inflammation in mediating the relationship between adiposity indicators and physical function by race/ethnicity and sex. These relationships need to be examined more closely in older populations with OA, particularly due to the higher level of functional limitation seen in OA subjects and among older African American women.

M. Lean Muscle Mass and Physical Function

1. Muscle Mass and Sedentary Behavior

Adequate muscle mass and muscle strength is essential to performing daily tasks independently among the older population. Unfortunately, levels of lean muscle mass decrease steadily with age[119]. In younger populations (20-30 years), lean muscle mass represents about

50% of total body weight whereas among older adults aged 75-80 years, lean muscle mass measures closer to 25% of total body weight[119]. Around 50 years of age, individuals lose about 1-2% lean muscle mass and 1.5-5% loss in muscle strength annually[120].

One of the likely causes of muscle mass and muscle strength decline is a steady rise in sedentary behavior. Data from the 2014 Behavioral Risk Factor Surveillance System found that approximately 27.5% of adults 50 years and older reported no physical activity outside of work[3]. Further, inactivity prevalence significantly increases with age - 25.4% among adults aged 50–64 years and 35.3% among those aged ≥75 years[22]. Importantly, a sedentary lifestyle is a major predictor of loss of muscle mass and strength, which can significantly affect physical function particularly among older adults. For example, in a cross-sectional study of 162 men and women aged 60 years and older, higher levels of sedentary behavior was related to reduced muscle mass and strength[121]. In the same study, each 1-hour increment in overall daily sitting time was associated with a 33% increased risk of sarcopenia (defined as low appendicular skeletal muscle mass along with reduced muscle strength or gait)[121]. Therefore, gradually increasing PA levels within this population may promote the maintenance or accretion of lean muscle mass[122] and subsequently improve physical function.

2. Adiposity, Muscle Mass, and Muscle Strength

A sedentary lifestyle is also connected to rising adiposity in older adults. For example, among older adults aged 50 years and older, the prevalence of inactivity increases from 23.1% to 35.8% with increasing BMI category and differences in inactivity prevalence remained after adjusting for sex, age, and race/ethnicity[22]. Further, in an analysis of 3,055 adults older than 65 years, frailty (defined by a frailty index measuring accumulated deficits with aging such as, functional impairments and poor or fair self-rated health), was associated with higher BMI and large WC (≥ 88 cm in women and ≥ 102 cm in men)[123].

This rise in overall and central adiposity coupled with inactivity in older adults, can have a significant biological effect on muscle mass and muscle strength. Specifically, higher circulating FFAs, released from excess adipose tissue, can promote muscle lipid infiltration and increased lipid storage within muscle[19]. Fat accrual within muscle tissue reduces the tissue's quality and ability to proliferate. The deteriorated muscle tissue also exhibits reduced tone and ability to contract, negatively affecting muscle strength and ultimately physical function[19]. Excess adipose tissue can also promote muscle loss. As mentioned, excess adiposity, specifically VAT, is associated with increased circulating pro-inflammatory cytokines. Higher circulating levels of pro-inflammatory proteins negatively affects muscle mass. Specifically, pro-inflammatory cytokines such as IL-6 may impair myoblast differentiation and proliferation resulting in muscle fiber shrinkage and muscle loss[19]. These effects combined may have a significant deleterious effect on muscle mass and function and, subsequently, physical function, offering a strong rationale for decreasing adiposity while protecting lean muscle with age.

3. Differences in Muscle Mass Across Race and Sex

Recent literature has indicated that there are differences in muscle mass across race and sex in older adults. Compared to age-matched males, older women tend to have lower levels of skeletal muscle mass, lower muscle strength, and lower muscle density[124]. Further, African American men and women tend to have greater skeletal muscle mass compared to non-Hispanic white men and women[125].

The rate at which muscle mass declines with age may also vary across sex and race. In a study of 468 males and 1,280 females skeletal muscle measured by DXA declined less with age among African American men than Hispanic men but declined more compared to non-Hispanic white men ($p<0.05$)[125]. Notably, muscle mass also decreased most with age among African American women compared to non-Hispanic white and Hispanic women[125]. This is significant in view of the crucial role muscle mass plays in physical function. This also may be partly why older African American women have greater physical mobility impairment compared to men and women from other racial/ethnic groups.

4. Physical Activity and Muscle Mass

Higher levels of PA may help to preserve muscle mass and muscle strength in older adults. Increased PA can result in metabolic adaptations in skeletal muscle tissue (i.e., quality of mitochondria, muscle strength, and function) that ultimately promotes muscle growth and strength that translates to improved physical function[126]. In fact, in a study of 42 older men and women randomized to a PA or control group, a 25-week PA intervention significantly curbed muscle mass loss when compared to control subjects ($p<0.05$)[127]. Further, in a cross-sectional analysis of 66,582 adults age 60 years and older, grip strength was positively associated with time spent engaged in moderate-to-vigorous PA[128].

Recent evidence also suggests that there may be a positive effect of long-term PA on systemic inflammation and muscle mass. In NHANES III, a significant inverse association was observed between CRP and level of PA[129]. Further, in a systematic review of exercise on muscle strength and inflammation in older adults, aerobic and resistance training was associated with lower inflammation in the long-term and increased muscle mass and muscle strength[130]. Thus, regular PA may lower systemic inflammation and provide beneficial effects on muscle mass and muscle strength among older adults that translates to improved physical function.

N. Review of Studies Examining Physical Activity and/or Dietary Weight Management on Physical Function in Adults with and without Osteoarthritis

Obesity is a major risk factor for the development of OA[26]. Along with increasing adiposity, sedentary behavior among older adults with OA has been associated with worse physical function[131]. Accordingly, regular PA and weight reduction may promote significant improvements in physical function and OA symptoms. There have been several studies examining the effects of PA alone and PA combined with dietary weight management on OA symptoms and physical function in older overweight and obese adults with and without OA (**Tables II and III**).

1. Studies Examining the Effects of Physical Activity on Adiposity, Body Composition, Systemic Inflammation, and Physical Function in Adults with Osteoarthritis

Several studies have examined the effects of PA on adiposity, body composition, systemic inflammation, and physical function in persons with OA. Details of the studies are presented in **Table II**.

The Fitness Arthritis and Seniors Trial (FAST) was an three-arm RCT that assessed the effects of two exercise interventions vs. a health education control program on self-reported pain, subjective physical function (i.e., physical disability questionnaire developed for the FAST trial), and objective physical function (e.g., six-minute walk test, stair climb test) in older adults with OA[132]. The 18-month study was conducted in 439 older adults (mean age 69±6 years, 70% female, 74% non-Hispanic white). Briefly, the three interventions were as follows: an aerobic walking exercise program that met in group sessions with an exercise instructor three time a week for one hour for the first three months and transitioned to a homed-based walking program for the rest of the intervention; a resistance training exercise program that met in groups with an exercise instructor three times a week for one hour for the first three months and transitioned to a home-based resistance exercise program thereafter; and a health education control that met weekly in group sessions with a nurse for 1.5 hours for the first three months and then telephone calls (to discuss general health) from the nurse for the remainder of the intervention. Months 1-3 were considered the active phase, months 4-6 were the transition phase, and months 7-18 were the maintenance phase. Both exercise programs demonstrated greater improvements in objective and subjective performance measures post-intervention (at 18 months) compared to the health education control arm. The aerobic exercise participants exhibited greater scores post-intervention (at 18 months) in the six-minute walk test compared to both resistance exercise and control participants and resistance exercise participants exhibited significantly higher scores in the stair climb test compared to the other two intervention arms. This suggests there may be different benefits associated with aerobic vs. resistance exercises on physical function in older OA patients[132]. Body composition, adiposity, and inflammation were not assessed.

In another trial, the effect of PA on subjective measures of pain and objective measures of physical function was tested in 109 older adults (≥ 55 years, 64% female, mean BMI 26.4 ±3.0 kg/m^2, race/ethnicity not reported) with hip OA[133]. In this study, participants were randomized to a control (no treatment) or PA group (8-weeks of strength training exercises supervised by a physical therapist). Intervention effects on BMI, subjective (Groningen Activity Restriction Scale) and objective (20-meter walk, TUG, and stair climb test) measures of physical function and OA-related pain was assessed. Post-intervention, there were no significant changes in BMI between the two groups. The exercise group performed better on the TUG test post-intervention ($p<0.04$) but no significant change in distance walked or number of stairs climbed between the groups post-intervention. However, there were significant improvements in self-reported pain in the PA group ($p<0.05$) although the between group difference was not significant. The researchers did not evaluate body composition or systemic inflammation within the context of this trial.

The FNS! intervention program was a two-arm RCT that assessed the effect of PA and OA management compared to a wait list control group on physical function and pain in older adults with OA[134]. The study randomized 215 older adults (mean age 73 ± 6, ~80% female, ~70% non-Hispanic white) with physician diagnosed OA to either a control (provided a copy of *The Arthritis Helpbook* and a list of exercise programs in the community) or a PA plus OA self-management group-based program that met for 90 minutes three days a week for eight weeks. Both arms were followed for 12 months. The PA and OA self-management program included both resistance training and aerobic exercises supervised by a physical therapist. Subjective physical function was assessed using the WOMAC and objectively through the six-minute walk and timed stand tests. Outcomes were assessed at baseline, 2, 6, and 12 months. Significant differences were seen favoring the treatment group in overall self-reported pain (WOMAC) at 6 months compared to control. However, there was no significant between group differences in the timed stand test or six-minute walk test at 2, 6, or 12 months. There was no data reported on adiposity, body composition, or systemic inflammation[134,135].

In a 4-week intervention, 54 older adults (≥ 62 years, mean BMI 30.4 kg/m^2, 85% women, 89% non-Hispanic white) with knee or hip OA were randomized to an PA plus activity strategy training (program taught by occupational therapists to improve OA symptoms and safely engage in PA) vs. an PA plus OA education program[117]. The PA program offered in both groups consisted of resistance exercises using ankle weights. Subjective physical function and pain was measured through the WOMAC and Community Healthy Activities Model Program for Seniors questionnaires and PA objectively through a wrist-worn accelerometer. At post-intervention, pain decreased modestly for both groups (WOMAC) with no significant between group difference observed. Physical activity participation based on accelerometry data, increased slightly in the PA plus activity strategy training group and decreased in the PA plus education group with significant between group differences[117]. Changes in body weight, adiposity, body composition and inflammation were not evaluated.

In another study, older adults (≥50 years, 96% female, 83% non-Hispanic white, mean BMI 33.3 kg/m^2) with knee OA were randomized to either a control (met briefly with a physical therapist at the end of the intervention for lower extremity exercise instruction and received written educational materials) or a 24-week group PA program (walking and lower extremity strength training) to examine intervention effects on objective and subjective physical function[136]. The physical therapist led PA program met weekly for one hour for six weeks. The group was then provided an exercise video and written exercise guidelines to follow at home (instructed to follow three days a week) and received biweekly telephone calls (to monitor adherence). Objective measures of physical function included a six-minute distance walk test and Short Physical Performance Battery – consists of a TUG test, 4-meter walk, and ten-second balance test of four different stances (e.g., standing on one leg), and subjective assessment of OA symptoms and pain via the WOMAC. At post-intervention, there were significant improvements in the six-minute walk test and WOMAC scores in the PA group compared to control group. There were also significant within-group increases for the physical function battery in the PA arm but no significant between group difference. No data was reported regarding post-intervention changes in body weight, adiposity, body composition or systemic inflammation.

The effects of lower extremity PA on physical function was tested in 106 older adults (≥65 years of age, 24% male, 46% Hispanic, 40% non-Hispanic white) with lower extremity OA[137]. Participants were randomized to a health education program (met twice a week for eight weeks with a healthcare provider to discuss general health and topics related to OA) or an 8-week lower-extremity chair-based PA program led by a yoga instructor (twice/week 45 minute group sessions of chair exercises intended to improve posture and pain). Intervention effects on self-reported physical function and pain were tested through the Patient Reported Outcome Measurement System survey measures, WOMAC, and objectively via gait speed. At post-intervention, the PA group reported less pain ($p=0.02$) and demonstrated an increase in gait speed ($p=0.02$) compared to the health education control group. Changes in body weight, adiposity, body composition, and inflammation was not assessed.

The effect of a 4-week exercise program on objective (TUG) and subjective (WOMAC) measures of physical function was examined in a single group, pre-post test design. Thirty-four older adults (≥60 years, 15% male, mean BMI 25.5±3.9 kg/m^2, race/ethnicity not reported) with knee OA were recruited. The group met once a week for one hour and completed a range of motion leg exercises, stretching exercises, and muscle strengthening exercises as well as reviewed information regarding OA symptom management. The program was delivered by a health care professional that was specialized in exercise instruction for older adults. Results showed significant improvements in total WOMAC scores and TUG test at post-intervention ($p=0.01$)[131]. Changes in body weight, adiposity, body composition and inflammation were assessed

In a pilot trial of the Lifestyle Interventions and Independence for Elders (LIFE) study[138], 424 older adults, OA status unknown (mean age 76.8 ± 4.2, 68% female, 76% non-Hispanic white, mean BMI 30 ± 5.7 kg/m^2) were recruited and the effects of a PA intervention vs. health education control on objective physical function was assessed. The PA trial consisted of three phases all focused on aerobic, balance, and strength exercises led by exercise physiologists. Phase 1 (adoption): 3 center based supervised exercise sessions per week (40-60 minutes) for first two months. Phase 2 (transition): twice a week center based exercises plus 3 times a week home-based exercise (next 4 months). Phase 3 (maintenance): 3 times a week home-based intervention plus optional 1-2 week center based sessions and monthly telephone contacts. Outcome measures were obtained at baseline, 6 and 12 months and included objective measures of physical function (400-meter walk, chair stands) and systemic inflammation. Adiposity and body composition changes were not assessed. Objective physical function improved significantly in the PA intervention compared to the control (measured through 400-meter walk and chair stand) at 6 and 12 months[139]. C-reactive protein was not significantly different between the groups at 12 months. However, IL-6 was significantly lower in the PA arm compared to the health education arm at 12 months post-intervention[140].

Finally, the LIFE study RCT examined the effects of a combined home and center-based PA program vs. health education on objective physical function measures in older, sedentary men and women (mean age 78.9 ±5.2 years, mean BMI 30.2 ± 6.0 kg/m^2, 70% female, 76% non-Hispanic white) - not all participants had OA[141] The study had up to 42 months of follow-up with an average of mean 2.7 years. The PA intervention was conducted in a center (supervised) and in the participant's home (unsupervised) Participants met twice a week at the center to complete 60 minutes of aerobic and strength training with an exercise physiologist. At the same time, they were encouraged to increase physical activity throughout the day and progressively work towards a weekly walking goal of 150 minutes. The health education program involved 60-90 minute group sessions with topics pertaining to nutrition and safety that were held weekly for the first 26 weeks and then was offered twice per month with required attendance at least once per month for the duration of the study. Over 2.7 years follow-up, the PA intervention significantly reduced major mobility disability compared to the health education intervention (measured through the 400-meter walk)[142]. Intervention effects on body weight, adiposity, body composition and systemic inflammation have yet to be reported.

To summarize given the existing evidence, the effects of PA on physical function in older adults with OA is mixed. However, most findings suggest improvements in physical function following engagement in a structured exercise program. Further, several of these studies have shown reductions in OA pain and reduction of OA symptoms. These findings thus point to significant benefits of physical activity on mobility within this population. However, the existing evidence indicate that the majority of these trials failed to report changes in body weight, adiposity, body composition and systemic inflammation post-intervention and the majority of trials were conducted in largely non-Hispanic white cohorts.

Table II. Review of Trials Examining the Effects of Physical Activity on Adiposity, Body Composition, Inflammation, and Physical Function in Older Adults with and without Osteoarthritis

Study	Design/Length of Intervention	Participant Characteristics	Intervention Description	Intervention Effects on Adiposity, Body Composition, Inflammation and Physical Function
Fitness Arthritis and Seniors Trial (FAST)[132]	Design: Three arm RCT Interventions: • Aerobic Exercise Training • Resistance Exercise Training • Control Intervention length: 18 months	N = 439 older adults with knee OA Mean age: 69 (±6) years Sex: 70% female Race/Ethnicity: 74% non-Hispanic white Baseline BMI: NDR	Aerobic Exercise Training: 3-month facility-based walking program, 1 hour, 3 times per week led by an exercise instructor. Followed by a 15-month home-based walking program. Resistance Exercise Training: 3-month facility based program meeting for 1 hour, three times a week with an exercise instructor. Followed by a 15-month home-based resistance training program. Control - Health Education: 3-months, group sessions for 1.5 hours once/week led by trained nurse. Months 4-6, nurse called biweekly to ask about general health. Months 7-18, participants were contacted similarly but on a monthly basis.	Adiposity: NDR Body composition: NDR Inflammation: NDR Objective physical function: Both exercise arms performed significantly better on the six-minute walk test and stair climb compared to the health education group at 18 months. Subjective physical function and pain: Participants in both exercise arms significantly reported less disability and pain post-intervention compared to health education group at 18 months.

Fit & Strong! [134,135]	<u>Design:</u> Two-arm RCT <u>Interventions:</u> • PA and OA management • Control <u>Intervention length:</u> 8-week active intervention with outcomes assessed at 2, 6, and 12 months.	N= 215 older adults with lower extremity OA Mean age: ~70 years Sex: ~80 % female Race/ethnicity: ~70% non-Hispanic white Baseline BMI: NDR	<u>PA and OA management</u>: 8-weeks, 3 times per week for 90 minutes. Included aerobic and strengthening exercises for 60 minutes followed by a 30-minute manual-based didactic group session both led by a physical therapist. During the maintenance phase, staff tracked the maintenance of activity at quarterly intervals for a period of 10 months, either by telephone or at scheduled in-person interviews. <u>Control:</u> Provided a copy of the Arthritis Handbook and a list of exercise programs in the community.	Adiposity: NDR Body composition: NDR Inflammation: NDR Objective physical function: There was no significant between group difference for the timed stand test or six-minute walk test at 2, 6, or 12 months although distance walked improved significantly from baseline in the PA arm. Subjective physical function: A significant reduction in pain score (WOMAC) was reported in the PA group compared to control at 6 months with no significant difference at 2 or 12 months.

Tak et al.[131]	Design: Two-arm RCT Intervention: • PA • Control Intervention length: 8 weeks	N = 109 older adults with hip OA Mean age: 67.4 (±7.6) years Sex: 68% female Race/ethnicity: NDR Baseline BMI: 26.4 (±3.0) kg/m^2	PA: 8-week group-based strength training PA program. Once a week for 1 hour supervised by a physical therapist. Control: No contact	Adiposity: No significant change in BMI post-intervention between or within groups Body composition: NDR Inflammation: NDR Objective physical function: Significantly lower TUG test time in exercise group compared to control group. No significant change in 20-meter walk or stair climb test between or within groups. Subjective physical function and pain: Significant improvement in pain from baseline in PA group but not significantly different between groups.
Murphy et al.[116]	Design: Two-arm RCT Interventions:	N = 54 older adults with knee or hip OA Mean age= 75 (±7.2) years	PA + Activity Strategy Training: 1.5-hour group sessions 2 times a week for 4 weeks. Included stretching and resistance exercises. Activity Strategy Training involved	Adiposity: NDR Body composition: NDR Inflammation: NDR

	• PA + Activity Strategy Training • PA + OA Education <u>Intervention length</u>: 4 weeks	Sex: 88% female Race/ethnicity: 91% non-Hispanic white Baseline BMI: 30.1 (±4.8) kg/m^2	practicing techniques to facilitate activity performance and pain symptom management. Taught by occupational therapists. <u>PA + OA Education:</u> 1.5 hours sessions 2 times a week for 4 weeks. Exercise same as above. Education materials were from the Arthritis Foundation and were used in group sessions. Taught by occupational therapists.	Objective physical function: Peak physical activity significantly increased in the exercise plus activity strategy training group and decreased in the exercise plus OA education group with no significant between group differences. Subjective physical function and pain: Pain decreased post-intervention for both groups (WOMAC) with no significant between group difference.
Schlenk et al.[134]	<u>Design:</u> Two-arm RCT <u>Interventions:</u> • PA • Control <u>Intervention length</u>: 24-weeks	N = 26 older adults with OA Mean age: 63.2 (±9.8) years Sex: 96% female Race/ethnicity: NDR Baseline BMI: 33.3 (± 6.0) kg/m^2	<u>PA</u>: 1 hour, once a week group sessions for first 6 weeks (walking program with a physical therapist). After 6 weeks, instructed to follow specific lower-extremity strengthening exercises at home, 3 days a week. Received 9 biweekly telephone counseling sessions with a registered nurse during home-based exercise phase. <u>Control:</u> Met with a physical therapist for evaluation at the end of the intervention. Otherwise, no contact.	Adiposity: NDR Body composition: NDR Inflammation: NDR Objective physical function: The intervention group demonstrated greater improvement in minutes walked per week and significant increases in distance in a timed 400-meter walk compared to control arm at post-intervention Subjective physical function and pain: No significant difference in WOMAC scores between groups post intervention.

Park et al.[135]	<u>Design</u>: Two-arm RCT <u>Interventions</u>: • PA • Control <u>Intervention length</u>: 8 weeks	N = 106 older adults with lower extremity OA Mean age: 75.3 (±7.5) years Sex: 76% female Race/ethnicity: 46% Hispanic 40% non-Hispanic white Baseline BMI: NDR	<u>PA</u>: chair exercises twice/week 45 minute group sessions intended to improve posture and pain. Led by a yoga instructor screenings) that also included 5-10 min of gentle upper extremity stretching. <u>Health Education:</u> Group sessions twice a week (45 minutes) with a healthcare provider to discuss general health and topics related to OA.	Adiposity: NDR Body composition: NDR Inflammation: NDR Objective physical function: Significantly improved physical function (timed gait speed test) in the PA vs. health education control group at post-intervention Subjective physical function and pain: There was a significant decrease in pain (WOMAC) in the PA group compared to the health education control arm.

Lee et al.[129]	Design: Single-arm, pre-post design Intervention: • PA Intervention length: 4 weeks	N = 34 older adults with knee OA Mean age: 75 (±7.3) years Sex: 85% female Race/ethnicity: NDR Baseline BMI: 25.5 (±3.9) kg/m^2	PA: Seven exercises incorporated in program (two knee range-of-motion, two stretching exercises, three muscle strengthening exercises). Met once a week for one hour and were encouraged to follow exercise program at home. Led by exercise physiologist.	Adiposity: NDR Body composition: NDR Inflammation: NDR Objective physical function: Significant improvement in TUG test following intervention. Subjective physical function and pain: Significant improvements in total WOMAC score post-intervention.
Lifestyle Interventions and Independence for Elders-Pilot Study (LIFE-P)[138-140]	Design: Two-arm RCT Interventions: • PA Control Intervention length: 2 month adoption phase, 4 month transition phase, 6	N=424 participants Mean age: 76.8 ±4.2 Sex: 68% female Race/Ethnicity:	PA: Consisted of three phases all focused on aerobic, balance, and strength exercises. Phase 1 (adoption): 3 center based supervised exercise sessions per week (40-60 minutes) for first two months. Phase 2 (transition): twice a week center based exercises plus 3 times a week home-based exercise (next 4 months). Phase 3 (maintenance): 3 times a	Adiposity: NDR Body Composition: NDR Inflammation: CRP concentration was not significantly different between the groups at 6 and 12 months. However, IL-6 was significantly lower in the PA arm compared to the

	month maintenance phase	76% non-Hispanic white Mean BMI 30 ± 5.7 kg/m^2	week home-based intervention plus optional 1-2 week center based sessions and monthly telephone contacts. Health Education control: Weekly 60-minute meetings for first 26 weeks and monthly thereafter. Discussed health topics relevant to older adults such as medications and preventive health care.	health education arm 12 months post-intervention. Objective Physical Function: Participants in the PA intervention improved significantly more than control at 6 and 12 months (measured through 400-meter walk and chair stand). Subjective physical function and pain: NDR
Lifestyle Interventions and Independence for Elders (LIFE) Study [136,138]	Design: Two-arm RCT at 8 centers across the U.S. between 2/2010 and 12/2013. Interventions: • PA • Control Intervention length: 52 week active intervention with minimum 52 week maintenance phase	N = 1,635 older adults Mean age: 78.9 (±5.2) years Sex: 70% female Race/ethnicity: 76% non-Hispanic white Baseline BMI: 30.2 (±6.0) kg/m^2	PA: The PA intervention was designed to be performed at a center and at home. Participants met twice a week at the center to complete 60 minutes of aerobic and strength training with an exercise physiologist. At the same time, they were encouraged to increase physical activity throughout the day and progressively worked towards a weekly walking goal of 150 minutes. Health Education control: 60-90 minute weekly group sessions with topics pertaining to nutrition and safety that were held weekly for the first 26 weeks and then was offered twice per month with required attendance at least once per month for the duration of the study.	Adiposity: NDR Body composition: NDR Inflammation: NDR Objective physical function: Over 2.7 years follow-up, the PA intervention significantly reduced major mobility disability compared to the health education intervention (measured through the 400-meter walk). Subjective physical function and pain: NDR

2. Review of Trials Examining the Effects of Physical Activity Alone and Combined with Dietary Weight Management on Adiposity, Body Composition, Inflammation and Physical Function in Overweight and Obese Older Adults with and without Osteoarthritis

Details of the existing trials examining the effects of PA alone or combined with dietary weight management on adiposity, body composition, systemic inflammation, and physical function in older overweight and obese adults with and without OA are described in **Table III**.

In an early two arm RCT, the effects of a dietary weight management and PA vs. PA alone on BMI, subjective physical function (using FAST Functional questionnaire), and objective physical function (stair climb and six-minute walk test) was tested[143]. Twenty-four overweight and obese older adults [mean age 68 ± 4.0, mean BMI 36.5 ± 5.5 kg/m^2, 59% female] with knee OA were randomized. The PA program met one-hour three days per week for 6 months with an emphasis placed on aerobic walking and strength training supervised by exercise instructors. The dietary weight management and PA intervention included the same PA program with the addition of a one-hour nutrition class once a week with instructions on how to reduce caloric intake and follow a well-balanced diet. The type of interventionist used for the diet program was not reported. Both groups lost significant weight post-intervention with the PA plus dietary weight management group exhibiting greater weight loss compared to the PA alone arm. Further, stair climb time and six-minute distance walked improved in both groups with significantly greater improvement in the dietary weight management plus PA group. Finally, there was no significant within or between group differences for the self-reported physical function measures. There was no data regarding changes in systemic inflammation or body composition.

In the Arthritis, Diet, and Activity Promotion Trial (ADAPT) an 18-month RCT testing the effects of PA alone, dietary weight management alone, dietary weight management plus PA and control on weight loss, physical function, and systemic inflammation in 316 overweight and obese older adults (> 60 years old, 68% female, 21% non-white, BMI of at least 28 kg/m^2) with symptomatic knee OA[8]. The active phase of the intervention was 6 months with a 12-month maintenance phase. The four interventions were: dietary weight loss alone [nutrition counseling once a week during the active intervention phase and biweekly phone calls during the maintenance phase (length of meetings not mentioned), PA alone (60 minute facility-based 3 days/week of aerobic and resistance training during the active phase and monthly telephone calls to encourage continued exercise adherence at home during the maintenance phase), combined dietary weight management and PA (combination of both interventions), versus a control group (monthly 1 hour meetings with a health educator discussing topics such as OA, obesity, and exercise). Outcomes including BMI/body weight objective physical function via six-minute walk test and stair climb test, and subjectively via the WOMAC and venous blood to measures CRP, IL-6, and TNF-α were examined at baseline and 6, and 18 months; body composition was not evaluated. At 18 months post-intervention, the PA plus dietary weight management arm had the greatest reduction in body weight and BMI followed by the diet alone and exercise alone groups compared to the control group (6 month outcomes were not reported). The combined group also had greatest improvement in stair climb time (p=0.02) and six-minute walk test (p=0.0003) compared to the control throughout the 18 month intervention[8]. There was a significant decrease in CRP and IL-6 throughout the duration of the study in the dietary weight management groups (with and without PA) but not in the PA only arm[12]. There was no evidence of an association between post-intervention change in inflammation and change in physical function.

The effects of weight loss plus PA on physical function and body composition was also tested in a 6-month RCT of 87 older obese adults with knee OA (≥ 60 years, 62% female, 86% non-Hispanic white, mean BMI 34.5 kg/m^2)[29]. Participants were randomized to either a control (general health education) or weight loss plus PA group that also included twice daily meal replacements (shakes and bars) and a third meal chosen from a weekly menu plan (recipes provided). The physical activity intervention included a 3-day per week PA program with aerobic and strength training exercises supervised by an exercise physiologist. Self-reported physical function and pain was assessed through WOMAC and objective physical function via the six-minute walk test. Body composition was measured through DXA. The dietary weight loss plus PA group had a mean 8.7 kg (± 0.8%) weight loss post-intervention while the control group lost no weight. Body fat was also significantly lower after the 6-month intervention in the dietary weight loss plus PA group compared to the control ($p < 0.01$). Greater reductions in pain and stiffness (WOMAC) in the dietary weight loss plus PA group ($p < 0.05$) and greater walking distance on the six-minute walk test ($p < 0.01$) compared to controls was also observed. Pearson correlations between changes in body composition and physical function showed greater weight loss was associated with greater walking distance and lower WOMAC scores. Change in systemic inflammation was not evaluated.

The Arthritis Impact Measurement Scales (AIMS) study was a 12-month RCT with a 24-week active intervention phase and a 6-month maintenance phase testing the effects of dietary weight management alone, pain coping alone, combined dietary weight management plus pain coping and control on body weight, physical function and self-reported pain[10]. A total of 232 obese older adults [mean age 58 ±10.4, 79% female, 38% non-white, mean BMI 34.0 kg/m^2] with knee OA were randomized. The pain coping skills class led by a clinical psychologist met weekly for 60 minutes for the 24-week active intervention. The dietary weight management intervention focused on promoting lifestyle, PA, and diet led by a clinical psychologist; this program met weekly for 180 minutes for the first 12 weeks and biweekly for 60 minutes for the last 12 weeks of the active phase. The combined program was a combination of both programs above; during the first 12 weeks, participants attended weekly 2-hour behavioral weight management sessions and three 90 minute supervised exercise sessions per week. During the last 12 weeks, the 2-hour group sessions were held every other week followed by the 90- minute PA protocol. The control group received no contact. All intervention arms (not including control) also received 20-minute monthly phone calls during the 6-month maintenance phase focused on reinforcing the skills learned during the active intervention. Outcomes included BMI as well as subjective and objective physical function measures (velocity measurements at normal and fast speeds, and self-reported physical function and pain via the WOMAC and Catastrophizing Scale of the Coping Strategies for pain) measured at baseline, 6 and 12 months. At 24 weeks and 12 months post-intervention, the combined program was superior for reduction in body weight, BMI, and self-reported pain coping compared to either intervention alone or the control group. The combined group also exhibited significantly greater reductions in self-reported physical disability (24 weeks and 12 months) based on the WOMAC but no significant change in walking velocity compared to control, dietary weight management only, or pain coping skills only. Body composition changes and inflammation were not evaluated.

The Intensive Diet and Exercise for Arthritis (IDEA) trial was an 18-month RCT that examined the effects of dietary weight management alone, PA alone, and a combined program on adiposity, physical function, body composition and systemic inflammation[144]. In total, 399 overweight and obese older adults (≥ 55 years, 72% female, 19% non-white) with knee OA were randomized to one of three interventions that included a 6-month active intervention and a 12-month maintenance phase. The dietary weight management group met 3 days a week for 6 months with a nutrition interventionist to discuss what food changes to make and the importance of these changes; this arm also included meal replacements and meal plans designed to provide energy intake deficit of about 800 kcal a day. The PA only group met 3 days a week for one hour and engaged in strength training and aerobic exercises (interventionist not mentioned). The combined group met 3 days a week for 18 months and received both interventions described above. Outcomes including weight, BMI, body composition, objective physical function (gait analysis and six-minute walk), and subjective physical function (WOMAC), and inflammation were assessed at baseline and 6 and 18 months[11,30,144]. Mean weight loss at 6 and 18 months was significantly greater in the combined dietary weight management plus PA group (-10.6 kg, $p < .001$) compared with weight loss in the diet (-8.9 kg) or PA alone arms (-1.8 kg). Data also showed significantly greater reductions in total fat mass (DXA) in the combined group and dietary weight management alone arms compared to PA alone at 18 months (no difference at 6 months). The combined group however, lost significantly more lean mass than the PA and diet alone groups at 18 months. The combined group also reported significantly less pain (WOMAC), improved self-reported physical function (WOMAC) and increased walking speed (six-minute walk test) compared with the dietary weight management and PA alone treatments[30] at both 6 and 18 months. Furthermore, greater reductions in the circulating pro-inflammatory cytokine IL-6 was observed among the combined and dietary weight management only arms compared to the PA arm at 6 and 18 months. Where lower BMI and percent body fat were significantly associated with lower CRP and IL-6 levels overall[11]. There was also a significant dose-response relationship seen with lower IL-6 concentrations and pain as well as physical function at 18 months[30].

In another RCT, 107 obese older adults (OA status unknown, 67% female, 81% non-Hispanic white, mean BMI 37 kg/m^2) were randomized to one of four interventions for 6 months: control (given general information during monthly visits with research staff), PA only (three exercise sessions/week for 90 minutes with a physical therapist), dietary weight management only (prescribed a balanced diet 500-750 kcal/day deficit from daily energy requirements and met weekly with a dietitian), and PA plus dietary weight management[31]. The effects of the interventions were tested on body weight, body composition (DXA and MRI), and subjective (Functional Status Questionnaire – asks questions about ability to perform daily tasks) and objective physical function (walking 50 feet, TUG test, and stair climb) post-intervention. The active intervention was 6 months plus a 6-month maintenance period -outcome measures were assessed at baseline, 6 and 12 months. At 6- and 12-months post-intervention, the dietary weight management plus PA group demonstrated the greatest body weight changes. Significant changes in fat mass (MRI, DXA) were observed with a decrease of 6.3±2.8 kg in combined arm, 7.1±3.9 kg in the dietary weight management only group, and 1.8±1.9 kg in the PA along group compared to control. There was an increase in lean body mass (1.3±1.6 kg) in the PA group and a significant decrease in the combined (-1.8±1.7 kg) and dietary weight management only (-3.2 ±2.0 kg) groups. Furthermore, the combined group demonstrated significantly greater improvements on the objective physical function tests (walking 50 feet, TUG, stair climb) compared with the dietary weight management or PA alone arms at 6 and 12 months post-intervention although all three groups improved significantly from baseline compared to the control group. The effects of the intervention on inflammatory markers was not tested.

Finally, the Influence of Weight Loss or Exercise on Cartilage in Obese Knee Osteoarthritis Patients Trial (CAROT) was a 68-week RCT enrolling 192 obese older adults (mean age 62.5 ±6.4 years, 81% female) testing the effects of dietary weight management only, PA only, and control group on BMI, body composition (DXA) and subjective pain and physical function (Knee injury and Osteoarthritis Outcome Score questionnaire) and objective measures of physical function (six-minute walk test)[26]. Outcomes were examined at baseline and 68 weeks. During the first 16 weeks of the program, all participants engaged in an intensive dietary weight loss intervention that included partial meal replacements and nutrition education led by a dietitian. Following this initial weight loss period, participants were randomized to continue the dietary weight management program (partial meal replacement and 1 hour weekly nutrition sessions), or were placed in a PA program [consisted of facility and home-based group sessions of circuit training and stretching 3 days a week for 60 minutes (interventionist was not reported)], or a no treatment control. Systemic inflammation was not assessed in the context of this trial. Following the intervention (at 68 weeks), the dietary weight management arm proved most effective at reducing body weight (-11.0 kg) compared to the exercise group (6.2 kg) and control group and there were significantly greater reductions in body fat (DXA) observed in the dietary weight management arm compared to the PA and control arms at post-intervention. Lean body mass did not change significantly from baseline to post-intervention nor did the self-reported or objective measures of pain and physical function across the three arms.

To summarize, most studies exploring the effects of PA vs. PA plus dietary weight management on adiposity, body composition, inflammation, and physical function found greater weight loss in the combined interventions compared to PA alone although dietary weight management alone appeared to also have a significant effect on body weight. Further, most studies found greater improvements in subjective and objective physical function measures in the combined group compared to PA alone, dietary weight management alone or control. Few studies explored the effects of the interventions on systemic inflammation. However, two studies found greater reductions in inflammatory markers in the combined and diet alone groups compared to PA alone or control[11,12]. One study also found a significant dose-response relationship with reduction in IL-6 and improved pain and physical function post-intervention[11]. Finally, only one study assessed correlations between change in body composition and physical function finding greater weight loss to be associated with greater walking distance and lower WOMAC scores[29]. Together, these findings indicate the benefits of PA combined with dietary weight management on adiposity, body composition, systemic inflammation and physical function in older, overweight and obese adults with and without OA. However, data regarding associations between changes in inflammation and physical function and change in body composition and physical function is quite limited and should be further explored. Also, the majority of the trials were conducted in largely non-Hispanic white cohorts under tightly controlled efficacy conditions.

Table III. Combined Effects of Physical Activity and Dietary Weight Management on Adiposity, Body Composition, Inflammation and Physical Function of Older Overweight and Obese Adults with and without Osteoarthritis				
Study	**Design/Length of Intervention**	**Participants**	**Intervention Description**	**Intervention Effects on Adiposity, Body Composition, Inflammation and Physical Function**
Messier et al.[143]	Design: Two-arm RCT Interventions: • PA • PA + Dietary weight management Intervention length: 6 months	N = 24 overweight and obese older adults with knee OA Mean age: 68 (±4) years Sex: 59% female Race/ethnicity: NDR Baseline BMI: 36.5 (±5.5) kg/m^2	PA: 1-hour group sessions three days a week for 6 months. Aerobic walking and strength training. Supervised by exercise instructors. PA + Dietary weight management: Included PA program above plus a 1-hour nutrition class once a week with instructions on how to reduce caloric intake and follow a well-balanced diet. Interventionist for the diet program not reported.	Adiposity: The PA plus dietary weight management group lost significantly more weight post-intervention than the exercise alone arm. Body composition: NDR Inflammation: NDR Objective physical function: Stair climb improved from baseline in both groups at post-intervention but was statistically superior in the PA plus dietary weight management group. Six-minute walk test also increased significantly from baseline in both groups at post-intervention but improved more in the PA plus dietary weight management group. Subjective physical function and pain: There were no significant difference between groups for self-reported physical function at post-intervention.

Arthritis, Diet, and Activity Promotion Trial (ADAPT)[8,12,28]	Design: Four-arm RCT Interventions: • PA • Dietary weight management only • PA + Dietary weight management • Health education (control) Intervention length: 18 months (6 month active phase and 12 month maintenance)	N = 316 overweight and obese older adults with knee OA Mean age: 69.1 ±0.1 years Sex: 68% female Race/ethnicity: 21% non-white Baseline BMI: 34 ± 6 kg/m^2	PA: three, 60-min group-based PA sessions/week consisting of aerobic and resistance training for 6 months. Weekly phone calls during maintenance phase. Dietary weight management only: weekly group social-cognitive sessions for 6 months active phase with goal of 5% weight loss in 18 months. Biweekly phone calls during maintenance phase. PA + Dietary weight management: combination of above Health education (control): Monthly group-based health education	Adiposity: At 18 months post-intervention, the PA plus dietary weight management arm had the greatest reduction in body weight and BMI followed by the diet alone and exercise alone groups compared to the control (6 month outcomes not reported). Body composition: NDR Inflammation: There was a significant decrease in CRP and IL-6 throughout the duration of the study in the dietary weight management groups (with and without PA) compared to the PA only and control group. There was no difference in TNF-α among the groups at the follow-up time-points. Objective physical function: The PA + dietary weight management group had greatest improvement in physical function measured through stair climb time ($p=0.03$) and six-minute walk test ($p=0.0003$) compared with all groups at post-intervention throughout the 18 month intervention.

			No data reported on who led the interventions.	Subjective physical function and pain: WOMAC scores improved significantly at each time point for the dietary weight management plus PA group compared to control with no significant differences between exercise-only or diet-only groups and control. The combined group had significantly improved WOMAC scores at 18 months compared to control but that was comparable to the other intervention arms.
Miller et al.[29]	Design: Two-arm RCT Interventions: • PA + dietary weight management • Health education (control) Intervention length: 6 months	N= 87 older overweight and obese adults with knee OA Mean age: 69.3 (± 0.9) years Sex: 62% female Race/ethnicity: 86% non-Hispanic white Baseline BMI: 34.5 (±4.3) kg/m^2	PA + Dietary weight management: Partial meal replacements and weekly nutrition education and lifestyle behavior modification sessions led by registered dietitian. Also, engaged in facility-based exercise program 3 days per week for 60min/session (aerobic and strength) with an exercise physiologist.	Adiposity: Weight loss in the PA + dietary weight management group was significantly greater than the health education group. Body composition: The PA + dietary weight management group had a significant 5.4 kg reduction in body fat and 1.8 kg reduction in fat-free mass post-intervention compared to the control arm. Inflammation: NDR Objective physical function: The PA + Dietary weight management group showed significantly greater walking

			Health education (control): bimonthly group sessions on general health.	distance (510.0 m ± 73 m change) post-treatment compared to control (459.0 m ± 10.5 m) Subjective physical function and pain: There was a statistically significant -1.7 point change in the total WOMAC score in the control compared to -11.2 in the PA + dietary weight management group.
Somers et al.[10]	Design: Three-arm RCT Interventions: • Pain coping skills training • Behavioral weight management program • Pain coping skills training + Behavioral weight management program Intervention length:	N= 232 obese adults with knee OA Mean age: 58 (±10.4) years Sex: 79% female Race/ethnicity: 62% non-Hispanic white Baseline BMI: 34.0 kg/m^2	Pain coping skills training: weekly 60-min group sessions for first 12 weeks (biweekly for last 12) consisting of training designed to increase use of adaptive coping strategies (relaxation and changing activity patterns). Followed by monthly phone calls for next 6 months to focus on reinforcing skills Led by a clinical psychologist with specialty in behavioral medicine	Adiposity: The combined group achieved significantly greater weight loss (lost an average of 5% of pre-treatment weight) compared to the other two groups. Body composition: NDR Inflammation: NDR Objective physical function: No significant change in walking speed at post-intervention in any of the groups Subjective physical function and pain: The combined group exhibited significantly lower post-treatment

	24 week active intervention with 6 months maintenance period		Behavioral weight management: three 90-min exercise sessions/week (aerobic cycling sessions) with 60 minutes of nutrition sessions for first 24 weeks; received monthly phone calls to reinforce skills learned for next 6 months. Lead by psychologist with specialty in behavioral medicine. Pain coping skills training + Behavioral weight management: received both treatments.	pain -with similar results reported for the WOMAC.
IDEA Trial[7,11,30,144]	Design: Three-arm RCT Interventions:	N = 399 overweight and obese older adults with knee OA Mean age: 66 (±6) years	Dietary weight management: Partial meal replacements (up to 2 shakes/day). For third meal, subjects used	Adiposity: Mean weight loss at 6 and 18 months was significantly greater in the combined dietary weight management plus PA group (-10.6 kg, p <.001) compared with weight

	• Dietary weight management • PA • Dietary weight management + PA <u>Intervention length</u>: 18 months (6 month active intervention and a 12 month maintenance phase)	Sex: 72% female Race/ethnicity: 81% non-Hispanic white Baseline BMI: 33.6 (±3.7) kg/m^2	recipes that were 500-750 kcal. Initial diet plan provided 800-1,000 kcal deficit; as trial progressed, subjects received fewer meal replacements. Also met weekly with nutrition interventionist for first 6 months to discuss healthy dietary changes. Received monthly telephone calls during maintenance phase to monitor progress. <u>PA</u>: 1 hour, 3 days/week of aerobic walking and strength training. First 6 months center-based. Then received monthly telephone calls to monitor home-based activity. <u>Dietary weight management + PA</u>:	loss in the diet (-8.9 kg) or exercise alone arms (-1.8 kg). Body composition: Significantly greater reduction in total fat mass in combined group (DXA) at 18 months (no significant difference seen at other time points). The combined group however, lost significantly more lean mass than the PA and dietary weight management alone groups. Inflammation: Significant reductions in IL-6 at 6 and 18 months was observed in the combined and dietary weight management only arms compared to the PA arm. There was a significant dose-response relationship observed with reduction of IL-6 and pain as well as physical function at 18 months Objective physical function: Greater walking speed (six-minute walk test) in combined group compared with the dietary weight management and PA alone treatments at 6 and 18 months. Subjective physical function and pain: Combined group and PA

			combination of above programs. All programs were led by nutrition interventionists trained in behavioral therapy.	alone group reported significantly less pain (WOMAC) and self-reported physical function (WOMAC) at 6 and 18 months compared to dietary weight management alone.
Villareal et al.[31,145]	Design: Three-arm RCT Interventions: • Dietary weight management • PA • Dietary weight management + PA • Health education (control) Intervention length: 12 months Active intervention: 6 months Maintenance period: 6 months (no mention of contact with	N = 107 overweight obese older adults (OA status unknown) Mean age: 69 (±4) years Sex: 67% female Race/ethnicity: 81% non-Hispanic white Baseline BMI: 37 kg/m^2	Dietary weight management: prescribed balanced diet with energy deficit of 500-700 kcal/day and weekly meetings with a registered dietitian (length of session not mentioned). PA: instructed on diet that would maintain current weight & received 3 group-based exercise sessions/week consisting of 90 minutes aerobic, resistance, and balance exercises. This was led by a physical therapist	Adiposity: Significant decrease in body weight in diet group (-9.7 ± 5.4 kg) and in combined group (-8.6 ± 3.8 kg) at 6 and 12 months compared to PA or control. Body composition: Significant increase in lean body mass (DXA) by 2% at 6 and 12 months in PA group, and a decrease in the combined and dietary weight management only group. Significant between group changes in fat mass (MRI, DXA) were observed with a decrease of 6.3±2.8 kg in combined arm, 7.1±3.9 kg in the dietary weight management only group, and 1.8±1.9 kg in the PA along group compared to control (at 6 and 12 months). Inflammation: NDR Objective physical function:

	participants during maintenance period)		Dietary weight management + PA: Combination of above programs Health education (control): monthly group sessions with research staff where provided general information on healthy diets	The combined group exhibited significantly greater improvement in a battery of physical function measures (walking 50 feet, TUG test, and climbing one flight of stairs) compared to PA only, dietary weight management only, and control groups at 6 and 12 months post-intervention. Subjective physical function and pain: Physical function scores improved significantly in the combined group compared to the dietary weight management or PA alone groups at 6 and 12 months

Influence of Weight Loss or Exercise on Cartilage in Obese Knee OA Patients Trial (CAROT)[9,26,146]	Design: Two-arm RCT Interventions: • Dietary weight management • PA • Control (no treatment) Intervention length: 68 weeks 16 weeks of a dietary weight loss regimen (partial meal replacements and nutrition education) For 52 weeks randomized to one of the three arms above.	N = 192 obese older adults with knee OA Mean age: 62.5 (±6.4) years Sex: 81% female Race/ethnicity: NDR Baseline BMI: 37.3 (±4.7) kg/m^2	All participants: 16-week intensive dietary weight loss intervention Dietary weight management: 1 group session per week for 1 hour for 52 weeks plus 1 shake or snack bar per day. Sessions led by a registered dietitian. PA: For first 12 weeks, group-based PA program was facility based 2 days/week and at home 1 day/week. In the second 12 weeks, participants exercised 1 day/week at the facility at home 1-2 days/week. For the rest of the intervention, participants exercised at home 3 days/week	Adiposity: At 68 weeks, the dietary weight management arm proved significantly more effective at reducing body weight compared to the PA and control groups. Although dietary weight management and PA arms both groups had significantly greater weight loss compared to the control arm. Body composition: There was greater body fat loss (DXA) in the dietary weight management group compared to PA-only and control at 68 weeks. Lean body mass (DXA) did not change significantly from baseline to post-intervention in any of the groups. Inflammation: NDR Objective physical function: No significant between or within change in objective physical function measures in any groups at post-intervention. Subjective physical function and pain:

			consisting of circuit-training and stretching and was led by an exercise physiologist. <u>Control:</u> No attention provided following the first 16 weeks.	No difference in pain reduction between groups at post-intervention but all groups experienced significant within group decrease in pain at 68 weeks.

H. Summary

Osteoarthritis affects over 30 million U.S. adults and is one of the leading causes of physical disability among older populations[21]. There are multiple risk factors that increase the likelihood of developing OA including, age, sex, race/ethnicity, and obesity[21]. Obesity is a major modifiable risk factor for OA and is currently a key target to reduce the health and economic burden of OA. These is also evidence linking systemic inflammation and body composition measures to physical function among older adults with OA. Based on multiple existing studies, dietary weight management for weight loss combined with PA may be more beneficial than exercise alone or dietary weight management alone in improving physical function in obese older adults with OA[28-30]. Further, in the context of several of these trials, decreasing body fat combined with increased physical activity provided relief of knee OA symptoms that was associated with reductions in joint load and decreases in systemic inflammation[11,28,30]. Finally, two existing trials found reductions in inflammation following a combined diet and exercise program[11,12] and one found correlations between improved mobility and reduced inflammation[144]. However, the existing trials were largely tested under efficacy conditions using highly trained staff and in non-racial/ethnic minorities.

Both knee OA and obesity are higher among African Americans, with particularly high rates among African American women. Despite this, there is limited evidence of the real-world effects of physical activity combined with dietary weight management on adiposity, inflammation and physical function in older African Americans with OA. Thus, to address this significant research gap, we examined the effects of a physical activity program and physical activity plus dietary weight management program on adiposity, body composition, systemic inflammation and physical function in older, overweight and obese African American with OA.

III. METHODS

An ancillary study (American Cancer Society, Grant # 261775) to the Fit & Strong! Plus (FNS!+) Comparative Effectiveness Trial (herein referred to as the *parent study*, R01AG039374; NCT03180008)[147] was conducted between 2013 and 2015 to test the impact of the Customary Fit & Strong! (FNS!) and FNS!+ (PA + dietary weight management) interventions on body weight, adiposity, body composition, and systemic inflammation in a subset of the African American participants from the *parent study*

The *parent study* was an RCT designed to examine the comparative effect of PA and OA self-management vs. physical activity/OA management plus dietary weight management on body weight, dietary quality, and OA symptomatology in overweight and obese older adults with self-reported lower extremity OA. The *parent study* was designed to enroll and randomize 400 participants. Participants were recruited from neighborhoods located in the southeast, west and northeast regions of Chicago. Recruitment strategies for the *parent study* included in-person recruitment by research staff and advertisement postings at Chicago Park Districts and nearby senior housing/centers. Individuals were screened over the phone for study eligibility.

Eligibility criteria for the *parent study* included: 1) self-reported lower extremity OA of the knee, hip, ankle, feet, or lower back; 2) age 60 years and older; 3) not currently engaged in a weight loss or PA program; and 4) BMI of 25 - 50 kg/. Individuals were excluded from participation if they reported: 1) severe cardiovascular disease; 2) active thrombophlebitis; 3) recent pulmonary embolus; 4) acute systemic illness; 5) poorly managed diabetes; 6) other health conditions that may impede exercise; 7) less than 60 years of age; 8) BMI < 25 or > 50 kg/m^2; 9) current involvement in a weight loss or PA program; 10) uncomplicated hip or knee surgery in the past six months or complicated hip or knee surgery in the past year; 11) steroid use (particularly injection into the lower extremities in the past three months); 12) diagnosis of rheumatoid arthritis; and 13) a score of three or more on the 9-item Mini Mental Status Questionnaire[148].

Participants eligible for the *parent study* and agreeing to enrollment were screened for the ancillary study. In addition to the *parent study* eligibility and exclusionary criteria, the ancillary study required the following: 1) self-described as African American; 2) agreeable to venous blood draw and whole body DXA scan at baseline and post-intervention; 3) willing to travel to the University of Illinois at Chicago (UIC) for two study visits; 4) self-reported body weight ≤ 450 pounds due to the weight limitations of the DXA scanner; 5) willing to fast for at least 8 hours prior to the blood draw; 6) willing to refrain from certain medications that could confound blood test results; and 7) cancer free within the past five years. A total of 210 individuals were approached to participate in the ancillary study and 155 were eligible and enrolled. Of those enrolled, 148 participants had available baseline body composition data and were included in this analysis.

Both the *parent* and ancillary study procedures were reviewed and approved by the UIC Institutional Review Board. All participants signed an informed consent document prior to participation in the *parent* and ancillary research studies.

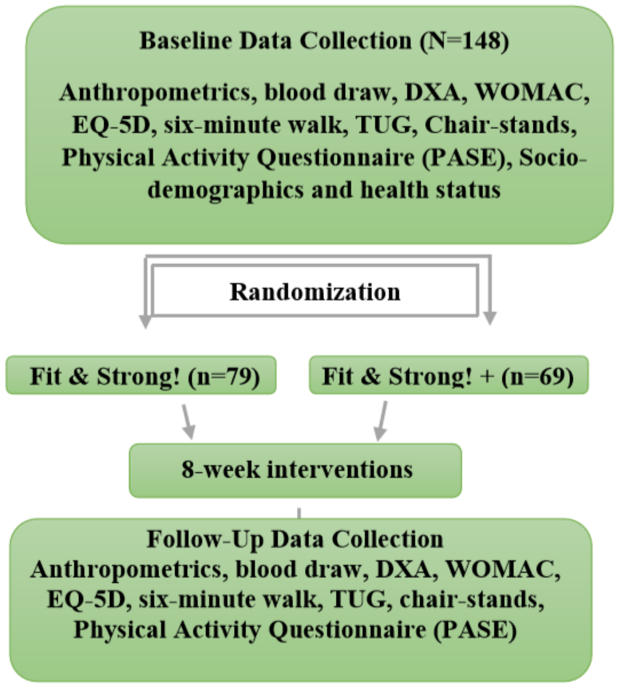
A. ***Parent Study*** **Interventions**

Following screening to determine eligibility and baseline assessments, subjects were randomized to one of the two interventions: FNS! or FNS!+. The two interventions were 8-weeks in length, community-facility and group-based programs, designed for older overweight and obese adults with lower extremity OA. The intervention sessions were led by certified exercise instructors. Each class accommodated approximately 17 enrollees. A comprehensive description of the *parent study* interventions has been published elsewhere (Smith-Ray et al, 2014). A brief description of the interventions follows:

Customary FNS! is an evidence-based PA/behavior change lifestyle program that is recommended by the Centers for Disease Control and Prevention and the National Council on Aging for older adults with OA. This intervention addresses symptoms experienced by older adults with OA by improving muscle strength and bone integrity. The program strengthens participants' self-efficacy (SE) for exercise and exercise adherence while subsequently diminishing OA related symptoms. *Customary* FNS! is a group-based program that meets for 90 minutes, 3 times per week, for 8 weeks (24 sessions in total). The first 60 minutes of the program focuses on multiple-component exercises including flexibility/balance (20 minutes), aerobics (20 minutes), and lower extremity strengthening using exercise bands and adjustable ankle weights (20 minutes). The remaining 30 minutes is dedicated to a manual-based curriculum predicated on group discussion/health education with a focus on OA symptom management. During week 6 of the intervention, subjects meet with exercise instructors to develop an individualized physical activity maintenance contract. The contract is intended to establish goals to maintain a minimum of 20 minutes of flexibility, aerobic, and strength training three or more times per week following completion of the 8-week program.

The FNS!+ intervention is a modified version of the *Customary* FNS! *program*, that includes the same 60 minutes of exercise, but with an added component that addresses SE for dietary weight management behaviors adapted from the Diabetes Prevention Program Group Lifestyle Balance curriculum[149]. The FNS!+ program condenses the OA-management focused curriculum of *Customary* F&S! and adds 16 topics that address dietary weight management behaviors to promote weight loss and weight loss maintenance. The program's goal is to improve dietary quality, lower overall body weight by at least 5% at 6 months, increase PA, decrease OA symptoms and promote maintenance of diet and PA changes over time. Participants that are less than 250 pounds at baseline were recommended to consume a 1200-1500 kilocalorie per day USDA MyPlate eating plan while those greater than 250 pounds were recommended to consume 1500-1800 kilocalories per day. Participants were encouraged to increase consumption of fruits, vegetables, whole grains, low fat dairy, and lean proteins while decreasing sugar sweetened beverages and saturated fats. To boost SE for dietary weight management-related behaviors, participants were asked to keep detailed food diaries. The food diaries along with weekly weigh-ins allowed participants and the interventionists to track progress. During week 6 of the intervention, participants meet with instructors to develop an individualized weight and exercise maintenance contract. The exercise goal follows the same guidelines as the *Customary FNS!* program while the weight management portion includes instruction on how to maintain positive lifestyle changes including referral to low-cost community programs that will help to bolster weight maintenance.

Figure I: Fit & Strong! Ancillary Study Design



DXA: Dual Energy X-ray Absorptiometry
WOMAC: Western Ontario and McMaster's University Osteoarthritis Index
EQ-5D: EuroQol-5D Health Questionnaire
TUG: Timed up-and-go

B. Ancillary Study Measures and Data Collection

Ancillary study participants attended data collection visits at the UIC Integrative Physiology Lab at baseline and within approximately ten days after completing the 8-week interventions. **Figure I** describes the design for the ancillary study. To prepare for the research visits, participants were instructed to refrain from: 1) foods or beverages, except water, for at least 8 hours; 2) vigorous exercise for 24 hours, 3) dietary supplements, and 4) certain medications including non-steroidal anti-inflammatory drugs, oral hypoglycemic agents and insulin; and to wear comfortable clothing free of excess metal for the DXA scan. Participants with a cold or flu or taking antibiotics in the past 7 days were scheduled at least one week after their course of antibiotics was completed or cold/flu resolved. At each data collection visit, participants completed surveys, physical assessments, a venous blood draw, and a whole body composition DXA scan. A description of the ancillary study measures follows.

1. Body Composition

Body composition was measured via DXA (GE Healthcare iLunar DXA, USA). If a participant was too large to fit within the regions of interest, a DXA half-body scan was completed, and whole-body parameters were estimated by the machine. DXA data used for this analysis includes total fat mass (g), total lean mass (g), trunk lean mass (g), visceral fat mass (g), visceral adipose tissue volume (cm^3), and percent body fat.

2. Systemic Inflammation

Venous blood was obtained from an antecubital vein, with subject fasting for at least 8 hours, at baseline and post-intervention by a phlebotomist. Samples were processed following standard procedures for serum and stored at -80º C until analysis. Measures of systemic inflammatory status included serum hs-CRP at Quest Diagnostics (Wood Dale, IL) via nephelometry and serum IL-6 and TNF-α via enzyme linked immunosorbent assay (R&D systems, Minneapolis, MN). Average coefficient of variation for hs-IL-6 was 9.18% and 13% for TNF-α.

C. *Parent Study* Measures and Data Collection

Several data points collected at baseline and 8-week follow-up for the *parent study* were also used for the ancillary study and included in this analysis. The *parent study* collected data on the same day as the ancillary measures at the UIC IPL or UIC Westside Research Office Building. The *parent study* measures are described below:

1. Anthropometrics

All research staff members were trained in adult anthropometric assessment using standard protocols and certified by a master trainer. Study participants were instructed to remove shoes, jewelry, eyeglasses, hats, hair ornaments, heavy clothing and to empty their pockets prior to anthropometric assessments. Height was measured to the nearest 0.5 cm in duplicate using a stadiometer (seca, Chino, CA). Weight was measured in duplicate to the nearest 0.1 kg using a digital scale (Tanita BWB 800, Arlington Heights, IL). Body mass index was calculated by dividing participant weight in kilograms by height in meters squared. Body mass index was classified using standard categories: 25.0-29.9 kg/m^2 (overweight), 30-34.9 kg/m^2 (grade I obesity), 35-39.9 kg/m^2 (grade II obesity), and ≥40 kg/m^2 (grade III obesity). Waist circumference was obtained to examine extent of abdominal obesity with the subject in an upright, standing position using an inelastic tape measure and obtained to the nearest 0.1 cm (Gullick II, Fitness Mart, Gay Mills, WI). The tape was placed at the narrowest part of the torso (if palpable, tip of ileac crest).

2. Self-reported Pain, Physical Function, and Physical Activity

Self-reported pain, stiffness, and physical function was assessed via the WOMAC[114]. This questionnaire was administered at baseline and post-intervention to examine change in self-reported pain (during walking, using stairs, and standing and stiffness and the degree to which physical functioning is affected by arthritis. The WOMAC includes five items for pain (score range 0-20), two for stiffness (score range 0-8), and 17 for functional limitation (score range 0-68)[114]. Higher scores indicate stronger OA symptoms. A total global score reported in this analysis.

The EQ-5D was administered at baseline and post-intervention to provide a profile of self-perceived health status across several domains[150] Questions pertain to self-perceived difficulty with engaging in everyday tasks (i.e., dressing, housework) as well as general pain/discomfort, and problems with ambulating[150]. This instrument has been used in several similar studies exploring adiposity and physical function outcomes in older adults[6,151].

Self-reported PA was measured using the Physical Activity Scale for the Elderly (PASE)[152]. This questionnaire is a reliable, measure of physical activity for older adults. Questions probe about the frequency and duration of specific activities in the past week, including leisure, sedentary, household, and activities that promote muscle strength. A higher total score indicates greater level of PA.

3. Objective Measures of Physical Function

Physical function was assessed objectively via the six-minute walk, chair stand, and TUG tests[108,153,154119]. Maximal walk distance during six minutes was measured using a Rolatape (Watseka, IL) and stopwatch. Participants were instructed to walk in a wide, well-lit hall while trained research staff walked behind the participant with the Rolatape measure. The test was performed on a flat surface, with a predetermined distance marked. Participants were instructed to walk at a comfortable, self-selected intensity and as far as possible in 6 minutes. Subjects were not given verbal feedback during the test. They were also told to minimize speaking unless necessary to avoid running out of breath and affecting their maximal walking speed[155]. Greater distance walked in 6 minutes reflects between physical function.

Lower extremity strength and endurance was also measured using the 30 second chair stand[154]. This test requires a chair with a straight back and no arm rests. Participants are instructed to fold their arms and sit in the middle of the chair with their back straight. When cued, the subjects would rise to a full standing position then sit back and down and repeating this for 30 seconds. This test has been performed in several studies assessing the physical function of older adults with OA[156,157].

The TUG test is a test of physical function and lower extremity strength[153]. Subjects are first asked to identify the line 3 meters away and, when instructed, stand from a chair, walk to the line on the floor at a comfortable pace, then turn, walk, and sit back down on the chair.

4. Socio-demographics and Health Status

At baseline, participants provided information regarding age, race/ethnicity, sex, household income, relationship status, level of education, and chronic conditions through administration of a demographic and health survey (GERI-AIMS)[158].

5. Data Management and Statistical Analysis

Data was collected via paper-based questionnaire and entered into a Research Electronic Data Capture (REDCap) database (Vanderbilt University, Nashville, TN) hosted by the University of Illinois Center for Clinical and Translational Sciences (grant #UL1TR002003).

Prior to statistical analysis, data entry errors and the distribution of variables was assessed. The top 5% of CRP values at baseline and post-intervention were coded as missing to avoid the influence of acute inflammation. Because of its non-normal distribution IL-6 and TNF-α were log transformed. Descriptive data is presented as means or geometric means and standard deviations (SD) or 95% confidence intervals (95% CI) for the continuous normally and non-normally distributed variables and frequencies for the categorical variables. Differences by treatment group at baseline were assessed via t-test, Chi-square or non-parametric equivalent. The correlations among the adiposity, body composition, inflammation, and objective measures of physical function at baseline were tested using Spearman rank correlations (unadjusted). Between and within group changes from baseline to post-intervention adjusted for baseline BMI, age, sex, and intervention site were assessed using generalized estimating equations (GEE) - a method that accounts for intra-individual correlation over time and allows for an intention to treat analysis approach vs. complete cases only. Spearman correlations were calculated to examine correlations among change values (Δ variable = post-intervention – baseline) for the adiposity, body composition, systemic inflammation, and objective measures of physical function. Lastly, a post-hoc analysis was performed within the F&S!+ group only to examine the intervention's effect on the adiposity, body composition, inflammatory, and objective measures of physical function stratified by baseline characteristics (e.g., BMI $\geq$ 30 kg/m^2, CRP $\geq$ 3.0) and post-intervention changes in BMI, body fat % and visceral fat mass (categories based on median split). All statistical analyses were conducted with SAS software (version 9.4, SAS Institute, Cary, NC).

IV. RESULTS

The baseline socio-demographic and health characteristics of the study participants are described in **Table IV**. Overall, 148 African American participants completed baseline assessments with mean age 66.8 ± 5.3 years. The majority of the participants were female (88%) and 17% reported that they currently smoked cigarettes. The majority of participants' self-reported hypertension (76%) at baseline had some college/technical school or a college degree (79%) and most reported they were divorced, widowed, or separated (60%). Finally, mean WOMAC total score was 27.2 (± 18.7) and average PASE score was 97.7 (± 64.0). At baseline, there were no statistically significant differences between the groups for any of the socio-demographic or health status indicators.

Table IV. Baseline Socio-demographic and Health Characteristics of Study Participants (N = 148)

Variable	Overall (N = 148)	Fit & Strong! (N = 79)	Fit & Strong! + Diet (N = 69)	P-value
Age, years, mean (SD)	66.8(±5.3)	67.2 (±5.7)	66.5 (±4.9)	0.42
Gender, n (%)				0.84
Female	130 (88%)	69 (87%)	61 (88%)	
Male	18 (12%)	10 (13%)	8 (12%)	
African American, n (%)	148 (100%)	79 (100%)	69 (100%)	---
Educational attainment, n (%)				0.77
< High school/GED	31 (21%)	18 (23%)	13 (19%)	
Some college/technical school	67 (45%)	36 (45%)	31 (45%)	
College degree	50 (34%)	25 (32%)	25 (36%)	
Current employment status, n (%)				0.42
Employed (full or part time)	22 (15%)	10 (13%)	12 (17%)	
Not employed	126 (85%)	69 (87%)	57 (83%)	
Household income, n (%)				0.95
< = $29.999	69 (47%)	37 (47%)	32 (46%)	
> = $30, 000	70 (53%)	42 (53%)	37 (54%)	
Relationship status, n (%)				0.89
Married/Living with significant other	28 (19%)	14 (18%)	14 (20%)	
Divorced/Widowed/Separated	88 (60%)	47 (59%)	41 (60%)	
Never married	32 (21%)	18 (23%)	14 (18%)	
Smoke, yes, n (%) (n = 147)	20 (17%)	13 (15%)	7 (10%)	0.25
Self-reported pre-existing chronic conditions, n (%)				
Hypertension, yes, n (%)	111 (76%)	62(78%)	49 (73%)	0.45
Type 2 diabetes, yes, n (%)	25 (20%)	16 (23%)	9 (16%)	0.28
OA severity (based on WOMAC, 0-96 total)[1]	27.2 (±18.7)	28.5(±19.3)	25.7 (±18.1)	0.36

The baseline anthropometric, adiposity, body composition, and pro-inflammatory markers are reported in **Table V**. There were no differences by treatment arm at baseline. All subjects were overweight or obese with a mean overall BMI of 34.9 kg/m^2 (± 5.9) with almost half of participants (48%) falling within the obese class II range (BMI ≥ 35.0 kg/m^2). Mean percent body fat was 44.9% (± 6.4) and mean CRP was 4.9 mg/L (± 3.5) with geometric means for IL-6 and TNF-α at 3.4 (95% CI: 3.1-3.7) and 4.4 (95% CI: 3.8 – 5.1), respectively.

Table V. Anthropometric, Body Composition, and Inflammatory Markers at Baseline (N = 148)				
Variable	**Overall (N = 148)**	**Fit & Strong! (N = 79)**	**Fit & Strong! + Diet (N = 69)**	**P-value**
Weight (kg), mean (SD)	93.7 (±17.4)	94.5 (±16.7)	92.7 (±18.2)	0.54
BMI (kg/m^2), mean (SD)	34.9 (±5.9)	35.0(±5.7)	34.7 (±6.2)	0.77
BMI category, n (%)				0.76*
Overweight (25 - 29.9 kg/m^2)	33 (22%)	18 (23%)	15 (22%)	
Obese Class I (30 - 34.9 kg/m^2)	45 (30%)	22 (28%)	23 (28%)	
Obese Class II (≥ 35 kg/m^2)	70 (48%)	39 (49%)	31 (50%)	
Waist circumference (cm), mean (SD)	113.4 (±14.0)	113.2 (±13.1)	113.6 (±15.1)	0.83
Waist circumference category, n (%)				0.19**
Women: ≤ 88 cm & Men: ≤ 102 cm	10 (7%)	3 (4%)	7 (10%)	
Women: > 88 cm Men: >102 cm	138 (93%)	76 (96%)	62 (90%)	
% Body fat, mean (SD)	44.9% (±6.4)	44.9% (±6.2)	45.0% (±6.7)	0.97
Total fat mass (g), mean (SD)	42,313.6 (±12,069.2)	42,555.2 (±11,574.6)	42,036.9 (±12,691.6)	0.80
Total lean mass (g), mean (SD)	47,990.0 (±7954.8)	47,433.0 (±8,208.4)	47,433.0 (±8,208.4)	0.43
Trunk fat mass (g), mean (SD)	22,771.3(±7,198.9)	22,641.7 (±6,880.6)	22,919.6 (±7,595.1)	0.82
Trunk lean mass (g), mean (SD)	22,213.2 (±3,784.4)	22,328.7 (±3,727.2)	22,080.9 (±3,872.0)	0.69
Visceral fat mass (g), mean (SD)	1573.8 (±748.3)	1573.2 (±770.4)	1574.5 (±727.7)	0.99
Visceral fat volume (cm^3), mean (SD)	1668.2 (±793.2)	1667.5 (±816.7)	1668.9 (±771.3)	0.99
hs-CRP (mg/L), mean (SD)† (N=127)	4.9 (±3.5)	4.2 (±3.2)	5.1 (±3.9)	0.15
IL-6 (pg/mL), geometric mean (95% CI) (N=147)	3.4 (3.1-3.7)	3.3 (2.9-3.7)	3.5 (3.1-3.9)	0.37
TNF-α (pg/mL), geometric mean (95% CI) (N=144)	4.4(3.8-5.1)	4.2 (3.2-5.1)	4.7 (3.8-5.6)	0.47

* Chi-square; **Fishers exact test
Abbreviations: BMI = body mass index; CI = confidence interval; cm = centimeters; hs-CRP = high sensitivity C-reactive protein; IL-6 = interleukin-6; SD = standard deviation; TNF-α = tumor necrosis factor-alpha.
† hs-CRP > 10 mg/L were omitted to rule out acute inflammation

Self-reported and objective physical performance were determined at baseline (**Table VI**). There were no significant differences between the treatment arms for self-reported or objective physical function measures at baseline. Overall, participants reported minimal difficulty with self-care or performing usual activities with approximately 50% reporting some difficulty walking. For the objective measures, participants were able to walk a mean of 1175 feet (± 304.1), complete approximately 8.3 (± 3.6) chair stands in 30 seconds, and complete the TUG test in 11.9 (± 4.3) seconds.

Table **VII**, reports the Spearman correlations between the adiposity, body composition, inflammation, and objective physical function measures at baseline. As expected, BMI was significantly positively correlated with the pro-inflammatory markers CRP and IL-6 but not with TNF-α. Waist circumference and percent body fat, total fat mass, and visceral fat mass were significantly positively correlated with CRP with greater fat mass and higher waist circumference correlated with higher CRP concentrations. Surprisingly, IL-6 and TNF-α were not significantly correlated with the body fat measures. Total lean mass was however positively associated with IL-6 and trunk lean mass with TNF-α but when controlled for BMI, the correlations were no longer significant. Body mass index was significantly inversely correlated with feet walked during the six-minute walk test and total fat mass measured via DXA was significantly inversely correlated with feet walked during the six-minute walk tests and number of chair stands completed in 30 seconds. However, no other adiposity, body composition or inflammatory measures were significantly correlated with the objective measures of physical function at baseline.

The attendance data for the two interventions is reported in **Table VIII**. There was no significant difference between the treatment arms for mean number of classes attended, or percentage of classes attended.

Table VI. Subjective and Objective Measures of Physical Function at Baseline (N = 148)

	Overall (N = 148)	Fit & Strong! (N = 79)	Fit & Strong! + Diet (N = 69)	P-value*
Subjective Measures of Physical Function**				
Self-care, n (%)				
I have no problems with self-care	134 (91%)	70 (89%)	64 (93%)	0.39
I have some problems with washing or dressing myself/I am unable to wash or dress myself	14 (9%)	9 (11%)	5 (7%)	
Performing usual activities, n (%)				
I have no problems with performing my usual activities	97 (66%)	51 (65%)	46 (67%)	0.79
I have some problems with performing my usual activities/I am unable to perform my usual activities	51 (34%)	28 (35%)	23 (35%)	
Walking, n (%)				
I have no problems in walking about	76 (51%)	42 (53%)	34 (49%)	0.64
I have some problems in walking about/I am confined to bed	72 (49%)	37 (47%)	35 (51%)	
Objective Measures of Physical Function				
Six-minute walk test (ft), mean (SD) (N=147)	1169.4 (±307.7)	1153.2 (±339.7)	1188.3 (±266.9)	0.49
Timed up and go (sec), mean (SD)	11.9 (±4.1)	12.2 (±5.0)	11.5 (±2.8)	0.33
Chair stands (# in 30 sec), mean (SD)	8.4 (±3.6)	8.4 (±3.8)	8.3 (±3.4)	0.92

*Chi-square; **EQ-5D questionnaire survey questions (https://euroqol.org/)

Abbreviations: ft = feet; SD = standard deviation; sec = seconds

Table VII. Spearman Unadjusted Correlation Coefficients between Anthropometric, Body Composition, Inflammation, and Objective Measures of Physical Function at Baseline (N = 148)						
Variables	hs-CRP (mg/L)	IL-6 (pg/mL)	TNF-α (pg/mL)	Six-min Walk Test (feet)	Timed Up and Go (seconds)	Chair stands (# of stands)
BMI (kg/m^2)	0.27[a]	0.16	0.04	-0.20[a]	0.11	-0.12
Waist circumference (cm)	0.31[a]	0.15	0.14	-0.17[a]	0.09	-0.16
% Body fat	0.26[a]	0.03	0.01	-0.15	0.11	-0.14
Total fat mass (g)	0.28[a]	0.11	0.09	-0.17[a]	0.10	-0.16[a]
Total lean mass (g)	0.13	0.26[a]	0.05	-0.05	0.04	-0.07
Visceral fat mass (g)	0.40[a]	0.22[b]	0.15	-0.02	0.10	-0.03
Trunk lean mass (g)	0.10	0.20[a]	0.16[a]	-0.10	0.05	-0.11
hs-CRP (mg/L)				-0.09	0.07	-0.05
IL-6 (pg/mL)				-0.19[a]	0.13	-0.06
TNF-α (pg/mL)				-0.03	0.007	0.05

N slightly lower for some variables (127 for hs-CRP, 147 for IL-6, 144 for TNF-α, 145 for Timed Up and Go, and 147 for Six-minute walk test).
[a] Significant at $p < .05$ (no correction for multiple testing because hypothesis driven analysis).
Abbreviations: BMI = body mass index; cm = centimeters; g = grams; hs-CRP = high sensitivity C-reactive protein; IL-6 = interleukin 6; mg/l = milligrams per liter; pg/ml = picograms per liter; TNF-α = tumor necrosis factor-alpha

Table VIII. Intervention Class Attendance (N = 147)*				
	Overall (N = 147)	**Fit & Strong (N = 79)**	**Fit & Strong + Diet (N = 68)**	**P-value**
Classes attended, mean (SD)	15.9 (±7.4)	15.3 (8.0)	16.6 (±6.6)	0.28
% of classes attended, mean (SD)	67.2 (±31.2)	65.0 (±33.9)	69.7 (±27.7)	0.36

* Class attendance data missing for 1 participant; 24 classes offered.

Intervention effects on adiposity, body composition, inflammation, and objective measures of physical function are presented in **Table IX**. The FNS!+ group experienced statistically significant reductions in body weight, WC, percent body fat, total fat mass, and trunk fat and estimated visceral fat mass compared to the FNS! group. The body weight, adiposity, and body composition measures remained largely unchanged in the FNS! arm at post-intervention. The FNS!+ arm also had statistically greater changes in distance walked on the six-minute walk test at post-intervention compared to the FNS! group. Although the between group difference was not significant, both groups experienced significant within group improvements from baseline for the TUG and chair-stands performance measures. The FNS! group experience significant within group decreases in TNF-α at follow-up. No other significant within or between group differences were observed for the inflammatory markers or lean muscle mass post-intervention.

Table IX. Intervention Effects on Body Weight, Adiposity, Body Composition, Inflammation, and Physical Function: Baseline to Post-Intervention (N = 148)

	Fit & Strong!			Fit & Strong! + Diet			P-value
	Baseline Least Sq. Mean (95% CI)	**Post-Intervention Least Sq. Mean (95% CI)**	**Change (95% CI)**	**Baseline Least Sq. Mean (95% CI)**	**Post-Intervention Least Sq. Mean (95% CI)**	**Change (95% CI)**	
Weight (kg)	97.0 (92.4, 101.6)	96.8 (92.4, 101.6)	-0.2 (-0.63, 0.24)	95.2 (89.8, 100.7)	93.5 (88.1, 98.9)	-1.7* (-2.4, -1.1)	<0.0001
BMI (kg/m^2)	33.9 (32.2, 35.5)	33.8 (32.1, 35.4)	-0.07 (-0.22, 0.09)	33.5 (31.7, 35.3)	32.9 (31.1, 34.6)	-0.7* (-0.9, -0.4)	<0.0001
Waist circumference (cm)	114.5 (112.6,116.5)	114.5 (112.6,116.4)	-0.04 (-1.3, 1.2)	115.4 (113.5, 117.4)	113.3 (111.4, 115.2)	-2.2* (-3.6, -0.78)	0.03
% Body fat	41.4 (40.6, 42.2)	41.2 (40.4 – 42.1)	-0.2 (-0.4, 0.1)	41. 5 (40.7, 42. 3)	40.6 (39.7, 41.5)	-0.9* (-1.2, -0.6)	0.0008
Total fat mass (g)	41,445 (40,289, 42,658)	41,194 (39,938, 42,450)	-280.0 (-562.4, 3.8)	41,377 (40,066, 42,687)	39,703 (38,303, 41,104)	-1673.0* (-2224.5, -1121.5)	<0.0001
Total lean mass (g)	54,420 (53,177, 55,663)	54,421 (53,185, 55,656)	-172.6 (-378.6, 379.4)	53,744 (52,193, 55,295)	53,572 (52,031, 55,113)	-172.2 (-508.0, 163.6)	0.49
Trunk fat mass (g)	22,854 (21,852, 23,856)	22,573 (21,572, 23,574)	-281.4 (-609.3, 46.8)	23,319 (22,226, 24,412)	21,920 (20,766, 23,074)	-1,399.2* (-1906.0, -892.3)	0.0003
Trunk lean mass (g)	24,620 (23,913, 25,328)	24,392 (23,708, 25,0475)	-228.8 (-532.4, 74.8)	24,534 (23,672, 25,395)	24,137 (23,288, 24,986)	-396.5* (-791.7, -1.2)	0.52
Visceral fat mass (g)	1,985.1 (1,1817.6, 2,152.5)	2,055.3 (1886.7, 2223.9)	70.3 (-4.8, 145.3)	1,997.2 (1,794.9, 2,199.5)	1,915.1 (1,683.4, 2,146.9)	--82.0* (-156.0, -8.1)	0.005
Visceral fat volume (cm^3)	2,104.1 (1,926.6, 2,281.6)	2,178.6 (1,999.9, 2357.3)	74.5 (-5.2, 154.1)	2,117.0 (1,902.6, 2,331.4)	2,030.0 (1,784.4, 2275.7)	-87.0 * (-165.3, -8.6)	0.005

hs-CRP (mg/L)	4.2 (3.2, 5.2)	4.7 (3.7, 5.7)	0.47 (-0.2, 1.1)	4.8 (3.8, 5.8)	4.9 (3.9, 6.0)	0.14 (-0.5, 0.8)	0.51
IL-6 (pg/mL)	3.2 (2.7, 3.7)	3.2 (2.8, 3.8)	0.05	3.6 (3.1, 4.3)	3.8 (3.2, 4.5)	0.2	0.78
TNF-α (pg/mL)	5.9 (3.6, 9.5)	3.8 (2.2, 6.4)	-2.0*	6.8 (4.3, 10.9)	5.2 (3.1, 8.6)	-1.6	0.59
Six-minute walk test (ft)	1174.7 (1087.5, 1262.0)	1218.4 (1131.8, 1305.0)	43.7 (-5.2, 92.6)	1187.9 (1094.2, 1281.7)	1327.9 (1226.7, 1429.1)	140.0* (94.9, 185.0)	0.005
Chair Stands (# of stands)	8.6 (7.7, 9.6)	9.8 (8.9, 10.8)	1.2* (0.7, 1.7)	8.4 (7.5, 9.3)	10.2 (9.2, 11.2)	1.8* (1.2, 2.5)	0.14
Timed Up and Go (sec)	12.1 (10.7, 13.6)	10.9 (9.7, 12.1)	-1.2* (-1.9, -0.6)	11.6 (10.6, 12.7)	9.9 (8.9, 10.9)	-1.7* (-2.3, -1.2)	0.25

From Generalized Estimating Equation (GEE) models adjusted for sex, baseline age, site, and baseline BMI (except when testing intervention effects on BMI). IL-6 and TNF-α were log transformed to improve normality and geometric means are presented. Ns are slightly different for each marker.

[a] Test for within-group difference from change in baseline to post-intervention visit: * < 0.05, ** < 0.01; *** < 0.001

[b] Test for difference between groups in change from baseline to post-intervention visit.

Abbreviations: BMI = body mass index; CI = confidence interval; cm = centimeters; ft = feet; g = grams; hs-CRP = high sensitivity C-reactive

Spearman correlation coefficients examining associations between change scores (post-intervention – baseline = Δ) for the adiposity, body composition, inflammation, and objective physical function measures are presented separately by treatment arm in **Tables X (FNS!) and XI (FNS!+)**.

In the FNS! arm, change in BMI was significantly inversely correlated with the change in number of steps walked on the six-minute walk test post-intervention (**Table X**). Also, in the FNS! group, changes in body fat, total fat mass and visceral fat mass were significantly positively correlated with CRP. Specifically, if change in body fat was negative or positive, change in CRP would change in the same direction. Further, change in lean muscle mass was significantly inversely associated with change CRP concentrations. Indicating that as lean muscle mass increased CRP decreased or if lean muscle mass decreased CRP increased. No other change variables were significantlycorrelated in the FNS! group.

In the FNS!+ arm (**Table XI**), the only change variables that were significantly correlated were visceral fat mass and the distance walked in the six-minute walk and TUG tests. Findings were somewhat contrary to our hypothesis that decreases in overall and visceral adiposity and systemic inflammation and increases in lean muscle mass would be significantly correlated with improved physical performance at post-intervention. However, a change in visceral fat mass was significantly inversely correlated with change in distance walked on the six-minute walk test such that if BMI decreased distance walked increased. Moreover, a change in visceral fat mass was positively associated with change in seconds required to complete the TUG test such that a decrease in visceral fat mass was associated with a decrease in seconds required to complete the TUG test.

Table X. Spearman Unadjusted Correlation Coefficients between Anthropometric, Body Composition, Inflammation, and Objective Measures of Physical Function Changes Post-Intervention Fit & Strong! (N=70)

Variables	hs-CRP (mg/L)	IL-6 (pg/mL)	TNF-α (pg/mL)	Six-minute Walk Test (feet)	Timed Up and Go (seconds)	Chair stands (# of stands)
BMI (kg/m^2)	-0.13	-0.06	-0.12	-0.25[a]	-0.0001	0.004
Waist circumference (cm)	0.04	0.06	-0.07	-0.12	-0.04	-0.21
% Body fat	0.34[a]	0.09	0.06	0.07	-0.06	0.09
Total fat mass (g)	0.28[a]	0.05	0.03	-0.06	-0.02	0.01
Total lean mass (g)	-0.27[a]	-0.03	-0.13	-0.19	-0.10	0.02
Visceral fat mass (g)	0.39[a]	0.02	0.02	0.01	0.007	0.05
Trunk lean mass (g)	-0.16	-0.10	-0.04	-0.17	0.07	-0.08
hs-CRP (mg/L)				0.04	-0.01	0.12
IL-6 (pg/mL)				0.07	-0.03	-0.008
TNF-α (pg/mL)				-0.05	0.09	0.02

N slightly lower for some variables (60 for hs-CRP, 69 for IL-6, 69 for TNF-α, 64 for chair stands, 69 for waist).

[a] Significant at $p < 0.05$ (no correction for multiple testing because hypothesis driven analysis).

Abbreviations: BMI = body mass index; cm = centimeters; g = grams; hs-CRP = high sensitivity C-reactive protein; IL-6 = interleukin 6; mg/l = milligrams per liter; pg/ml = picograms per liter; TNF-α = tumor necrosis factor-alpha

Table XI. Spearman Unadjusted Correlation Coefficients between Anthropometric, Body Composition, Inflammation, and Objective Measures of Physical Function Changes Post-Intervention Fit & Strong! + Diet (N=62)

Variables	hs-CRP (mg/L)	IL-6 (pg/ml)	TNF-α (pg/ml)	Six-min Walk Test (feet)	Timed Up and Go (seconds)	Chair stands (# of stands)
BMI (kg/m^2)	-0.04	0.11	-0.01	-0.02	-0.07	0.09
Waist circumference (cm)	0.13	0.17	0.14	0.03	-0.03	-0.22
% Body fat	0.07	0.17	0.13	-.12	0.09	0.008
Total fat mass (g)	0.06	0.17	0.15	-0.05	0.02	0.10
Total lean mass (g)	-0.10	-0.07	-0.008	0.03	-0.11	0.12
Visceral fat mass (g)	0.13	0.17	0.13	-0.26[a]	0.30[a]	-0.22
Trunk lean mass (g)	-0.13	-0.25	0.01	0.16	-0.17	0.20
hs-CRP (mg/l)				-0.12	0.04	-0.09
IL-6 (pg/ml)				-0.02	0.13	-0.05
TNF-α (pg/ml)				0.07	0.02	-0.13

N slightly lower for some variables (50 for hs-CRP, 69 for IL-6, 69 for TNF-α, 61 for Six-minute walk and Timed up and Go, 57 for chair stands, 61 for waist, 60 for DXA measures).

[a] Significant at $p < 0.05$ (no correction for multiple testing because hypothesis driven analysis).

Abbreviations: BMI = body mass index; cm = centimeters; g = grams; hs-CRP = high sensitivity C-reactive protein; IL-6 = interleukin 6; mg/l = milligrams per liter; pg/ml = picograms per liter; TNF-α = tumor necrosis factor-alpha

Table XII reports on the FNS! + intervention effects on objective measures of physical function stratified by baseline characteristics and post-intervention changes in BMI, % body fat, lean muscle mass, total body fat, visceral fat mass, and CRP. Post-intervention change in number of chair stands was significantly greater in participants with baseline % body fat < 43.6% compared to participants with greater % body fat. Further, those with baseline CRP < 3.0 mg/L had significantly greater post-intervention improvement in the TUG and chair stands tests compared to participants with higher CRP at baseline while controlling for age, sex, baseline BMI, and intervention site.

Subjects with greater change in visceral fat mass (loss of at least 93 g) at post-intervention took significantly fewer seconds to complete the TUG test and were able to perform significantly more chair stands in 30 seconds compared to participants that lost less visceral fat mass. Lastly, a greater post-intervention change in CRP was significantly associated with fewer seconds to complete the TUG test compared to those who experienced a lesser reduction in CRP post-intervention.

Table XII Intervention Effects on Objective Measures of Physical Function, Stratified by Baseline and Post-intervention Outcomes in the Fit & Strong! + arm (N=69)

	Δ Six-minute walk [feet (SE)]	**Δ Timed up and Go [seconds (SE)]**	**Δ Chair stands [# in 30 seconds, (SE)]**
Potential moderator			
Baseline BMI (kg/m^2)			
< 30 kg/m^2	137.5 (28.5)	-1.9 (0.4)	2.2 (0.5)
≥ 30 kg/m^2	140.2 (28.0)	-1.70 (0.4)	1.7 (0.4)
Baseline % body fat			
< 46.3 %	176.8 (32.9)	-1.9 (0.5)	**2.5 (0.5)***
≥ 46.3 %	107.0 (31.1)	-1.6 (0.3)	**1.1 (0.3)**
Baseline visceral fat mass (g)			
< 1,430 g	155.6 (33.1)	-1.7 (0.3)	2.2 (0.5)
≥ 1,430 g	123.5 (31.3)	-1.8 (0.5)	1.4 (0.5)
Baseline total lean mass (g)			
<46,217	134.0 (67.5)	-1.9 (0.4)	2.0 (0.4)
≥ 46,217	147.0 (33.3)	-1.6 (0.4)	1.6 (0.5)
Baseline hs-CRP (mg/L)			
< 3.0 mg/L	162.2 (37.9)	**-2.7 (0.5)***	**2.9 (0.5)***
≥ 3.0 mg/L	120.8 (66.3)	**-0.9 (0.3)**	**0.9 (0.4)**
Δ % BMI (kg/m^2)			
> - 0.71	120.3 (32.7)	-1.6 (0.4)	1.9 (0.5)
≤ - 0.71	160.5 (31.9)	-1.9 (0.4)	1.8 (0.5)
Δ body fat (%)			
> - 0.94	109.0 (25.5)	-1.7 (0.4)	1.8 (0.4)
≤- 0.94	168.8 (36.5)	-1.9 (0.4)	1.8 (0.5)
Δ visceral fat mass (g)			
> - 93.00	107.5 (33.2)	**-1.0 (0.3)***	**1.1 (0.4)***
≤ - 93.00	172.3 (31.3)	**-2.4 (0.5)**	**2.5 (0.5)**
Δ total lean mass (g)			
< - 86.5	132.8 (28.0)	-1.6 (0.4)	1.8 (0.5)
≥ - 86.5	145.2 (36.4)	-1.8 (0.4)	1.8 (0.4)
Δ hs-CRP (mg/L)			

> *0.25*	122.3 (27.2)	**-1.0 (0.3)***	1.6 (0.4)
≤ *0.25*	151.1 (33.7)	**-2.2 (0.4)**	1.9 (0.5)

From Generalized Estimating Equation (GEE) models adjusted for sex, baseline age, site, and baseline BMI (except when testing baseline BMI category). Ns are slightly different for each marker.
*Test for between-group difference < 0.05
Abbreviations: BMI = body mass index; g = grams; hs-CRP = high sensitivity C-reactive protein; mg/l = milligrams per liter; pg/ml = picograms per liter; SE = standard error.

V. DISCUSSION

This study examined the within and between groups effects of an 8-week PA plus OA self-management (FNS!) intervention and an 8-week PA/OA self-management plus dietary weight management (FNS!+) intervention on adiposity, body composition, systemic inflammation and physical function in older overweight and obese African American adults with self-reported lower extremity OA. To our knowledge, this ancillary study is the first to evaluate the effects of such interventions in a largely African American cohort. We found that after 8-weeks of the interventions, body weight, adiposity, and distance walked on the six-minute walk test was superior in the FNS!+ compared to the FNS! arm. However, we observed no significant differences between the intervention groups for the inflammatory markers although TNF-α decreased significantly from baseline in the FNS! group. In addition, we observed that decreases in visceral body fat were significantly associated with improved physical function at post-intervention based on the six-minute walk and TUG tests in the FNS!+ group.

The superior effects of a combined PA plus dietary weight management intervention compared to PA or dietary weight management alone on body weight and body composition in older overweight and obese adults with and without OA has been previously reported[7,10,26,28,29,31,143]. In these trials, as in our study, subjects in the combined intervention arm lost greater body weight compared to PA alone, dietary weight management alone, or control, which hints at the prominent role dietary change plays in weight loss and the added benefit of PA on creating an energy deficit. . The existing trials reported that participants lost 6% or more of their baseline body weight[10,26,28,29,31]. However, in the current study, participants in the FNS!+ arm lost only a modest amount of body weight at post-intervention (approximately 2% from baseline) far less than the existing trials. However, most of these studies had a 6-month active intervention phase that provided a greater opportunity for the adoption of positive health habits that are essential to observing a larger magnitude of weight loss over time. Studies suggest that it can take an individual up to 9 months to form and adopt a healthy lasting lifestyle behavior[159]. Thus, the short duration of our intervention may not have provided enough time for the healthy lifestyle behaviors to be adopted. In fact, the FNS!+ trial was designed to produce a 5% weight loss at 6-months[147]. Thus, it is possible that the subjects assessed will continue to lose weight through their 6-month follow-up. Another factor that could have influenced the difference in weight loss between our trial and the existing trials is the intensity of the dietary intervention. Several of the existing trials used meal replacements[26,29,144], which could translate to larger effects on body weight and adiposity vs. our strictly didactic, behavioral approach. Using meal replacements is not scalable in a public health setting although intensifying our dietary weight management intervention with a greater emphasis on self-monitoring may translate to greater weight loss. It is also possible that our results are more modest compared to the existing trials given the population studied. The previous trials accrued primarily non-Hispanic white participants. Studies that have compared the effects of dietary weight management lifestyle interventions among non-Hispanic white and African American adults have often found less success with weight loss among African American participants enrolled in the very same intervention[141].

We also observed significant decreases in body fat percentage, total body fat, and VAT in the FNS!+ compared to the FNS! arm. This is consistent with findings from four studies that also monitored body composition changes through DXA or MRI following a PA only or combined PA plus dietary weight management intervention for older adults with and without OA[26, 28, 30, 31,]. Three of these studies also found greater reductions in lean mass post-intervention in the combined PA and dietary weight management arm compared to PA alone arm[26, 30, 31]. The decrease in the lean muscle mass observed may be attributable to the intervention length and amount of weight lost. However, we found no significant between or within group changes in lean muscle mass at post-intervention. A concurrent reduction in both body fat and lean muscle mass may not be ideal for older adults due to the importance of lean muscle preservation for both physical and metabolic function. The longer term effects of FNS! and FNS!+ on both body fat and lean muscle mass needs to be evaluated in future trials.

In just 8 weeks, we observed significant improvements in the six-minute walk and chair-stands tests in the FNS!+ arm compared to the FNS! arm; both intervention groups had a significant change from baseline for the TUG test that was not significantly different between groups. Our findings are consistent with several of the existing trials that reported significantly greater distance walked on the six-minute walk test at post-intervention in the combined intervention group compared to PA alone, dietary weight management alone or control [29-31,143]. Although it was relatively modest, this may be a result of greater weight and body fat loss in the combined group. It was interesting to see, however, that a modest (about 2%) weight loss was associated with increased physical function, while most studies in the literature found this to be true with greater body weight and fat mass loss. As discussed in the background section, obesity may contribute to OA and functional decline in older adults through both mechanical and inflammatory effects[44] - effects that can be ameliorated with significant weight loss. The results from our trial are encouraging given they suggest that even a small amount of weight loss can have a positive impact on physical function in older overweight and obese adults with OA.

In the previous FNS! PA only trial[134,135], there was a significant difference in distance walked observed favoring the PA group compared to control. However, in the current trial comparing FNS! to FNS!+, we found at post-intervention the FNS!+ group walked significantly more steps post intervention compared to the FNS! arm with no significant change from baseline in the FNS! arm. We also observed significant within group changes for both groups from baseline for the TUG and chair stands tests indicating that both FNS! and FNS!+ are efficacious at improving stability and gait in just 8 weeks. This observed difference in effect for the FNS! arm may be due to the baseline weight status (overweight or obese) of the participants accrued. As suggested in previous studies, greater adiposity levels are consistently associated with worse physical function[29,89]. Further, the demographics of the participants accrued to the previous FNS! trials differed significantly from this investigation. In the previous trials, largely non-Hispanic white cohorts were recruited compared to a largely African American cohort in this comparative effectiveness trial. As discussed in the background section, African American older adults tend to be more physically deconditioned and with greater physical limitation compared to non-Hispanic white older adults[116, 117]. Given the weight and deconditioning status of our participants, it is possible that to observe similar effects to the previous FNS! trials, the FNS! intervention would have to be longer in duration and/or more intensive.

In our study, we found no effect of the interventions on circulating IL-6 or CRP. Interestingly, within the FNS! arm, TNF-α decreased significantly from baseline - a finding that was not observed in the FNS!+ group. The existing literature suggests that PA alone has minimal effects on circulating TNF-α concentrations in older adults so it's unclear why we observed this change[160]. The impact of PA alone and combined with dietary weight management on systemic inflammation in older overweight and obese adults with and without OA is somewhat mixed. For example, in the LIFE-pilot study[161], IL-6 decreased significantly in the PA intervention arm compared to the control arm at 12 months post-intervention although there was no significant between group differences reported for CRP. Studies suggest that IL-6 can decrease with long-term exercise training[162] whereas in the absence of weight loss, long-term PA has little effect on CRP levels[140]. In the IDEA trial[11,30] at 18 months, the dietary weight management and dietary weight management combined with PA arms had significantly lower circulating IL-6 and CRP concentrations compared to the PA arm. In a study conducted[12] in 316 older overweight and obese adults with OA, dietary weight management was associated with significant reductions in CRP and IL-6 at 18 months post-intervention compared to PA alone with no added benefit of PA on these circulating makers in the combined intervention group[12]. The two later findings suggest that weight loss is necessary for lowering both CRP and IL-6 concentrations in this population. In our study, body weight and regional fat losses in the PA plus dietary weight management arm were modest and far below the reductions reported in the existing literature. As mentioned above, this is likely a result of the short duration of our active interventions. Although we conducted *a priori* a sample size and power analysis for the inflammatory markers that suggested a sample size of 71 in each treatment arm would be sufficient to achieve 80% power to detect moderate effect sizes (0.46-0.48) for the inflammatory markers at post-intervention this was not the case. The estimations were however based on the existing efficacy trials that produced more significant weight loss so it is possible that a small sample size as well as differential use of anti-inflammatory medications between the two treatment arms affected our ability to detect significant time*intervention effects for the inflammatory biomarkers.

The relationships between body fat, body fat distribution, systemic low-grade inflammation and physical function in older adults with and without OA has been cited quite often in the literature[11,89,163] with reports suggesting that excess body weight, central adiposity, and systemic inflammation negatively impact physical function. However, few studies have analyzed the relationship between changes in these parameters following an intervention and changes in physical function in older adults with OA. We found that greater reduction in visceral fat mass was inversely correlated with steps walked on the six-minute walk test and positively correlated with number of chair-stands completed in 30 seconds in the FNS!+ group only. Our findings suggest that a reduction in visceral fat mass is significantly associated with improved physical function. The association between reduction in visceral fat mass and pain/mobility was not assessed in any of the existing trials examined, however, the IDEA trial[30] found total abdominal fat was significantly associated with mobility (although not a change correlation) and that greater overall total fat loss was associated with greater walking distance at 18 months. It's likely that a reduction in VAT, a fat depot largely associated with increased systemic inflammation, translates to lower systemic inflammation lending to a beneficial effect on physical function for older overweight and obese adults with OA.

A reduction in total body fat and percent body fat was not associated with changes in physical function at post-intervention. This was somewhat surprising given that greater total body weight loss following a 6-month RCT of dietary weight management plus PA was associated with greater walking distance in older, overweight and obese adults with OA compared to a control[29]. Also surprising was that changes in total and regional adiposity were significantly correlated with reductions in CRP in the FNS! group but not in the FNS!+ arm. In the IDEA trial[11], body weight reduction and regional fat loss were significantly associated with decreases in CRP at 18 months post-intervention, while IL-6 reductions were significantly associated with reduced VAT mass. Further, in the same trial there was a significant dose-response relationship with lower IL-6 levels and pain as well as function at 18 months[30]. However, in our post-hoc analysis of the FNS!+ group, we did observe that persons with greater post-intervention change in CRP were able to complete the TUG test in fewer seconds compared to those with lesser post-intervention changes in CRP suggesting that lowering systemic inflammation can have a positive impact on physical function.

The effects of FNS!+ on the objective physical outcomes measures were greater in participants with lower percent body fat and CRP levels at baseline. However, it is important to acknowledge that this was a post-hoc analysis and these comparisons were not *a priori* nor were we powered to detect such stratum-specific differences[27, 84]. Nonetheless, researchers from the HEALTH ABC study suggested that greater baseline adiposity could dampen the effects of lifestyle interventions on physical function[16, 46, 6]. Thus, the degree of body adiposity and systemic inflammation at baseline may blunt the positive impact of FNS!+ on mobility although this would need to be tested in a larger trial can that could appropriately test stratum specific effects.

Our study offers multiple strengths including recruitment of an urban African American older adult sample given they are largely understudied despite their disproportionate risk for both obesity and OA. Our study used a randomized comparative effectiveness design trialed in a “real world” community based setting. Also the investigative and data analytic teams were not involved in the assessing the physical function measures at baseline or post-intervention which may have helped to reduce bias. Finally, we used DXA to examine body composition, and used more than one marker of systemic inflammation. However, this study is not without limitations. First, the short duration of the intervention may have inhibited our ability to observe significant changes in the adiposity, body composition and the inflammatory markers. If resources permitted and given the *parent study* design to achieve 5% weight loss at 6-months in the FNS!+ arm, repeating these assessments at the 6 month time-point may translate to more significant adiposity, body composition, inflammation, and physical function changes. It is also possible that differences in the habitual diet of the study subjects hindered our ability to clearly examine the intervention effects on body weight, body composition, and systemic inflammation given that diet can independently influence these outcomes. Although dietary intake data was obtained at baseline and post-intervention, it was not available for in the current analysis. A comprehensive assessment of medication use was not examined. As mentioned above, differential use in anti-inflammatory medications and dietary supplements could have confounded our results. Lastly, our small sample size may have been a limiting factor in detecting statistically significant differences between the two treatment arms for the inflammatory parameters.

VI. FUTURE DIRECTIONS

Although the current ancillary study offers many strengths and presents analyses currently limited in the literature, there are several limitations to the study and this presents avenues towards improvement in future interventions. First, a longer intervention may be implemented in order to provide more profound insight into the effects of weight loss and body composition changes on inflammation following a physical activity and dietary weight management intervention in older, overweight and obese adults with OA. The intensity of the intervention could also be addressed. As mentioned, the trials currently in the literature implemented different dietary weight loss interventions. Our study, through a didactic format, focused on encouraging the adoption of healthier habits and healthier food choices. However, it would be insightful to observe the possible effect of a more intense dietary intervention compared to the intervention implemented here; for example, the same information regarding healthier food habits may be provided along with an additional session teaching individuals methods of behavioral change. Also, a maintenance phase should be included following the active intervention to assess the effects of the interventions on long term adherence, weight maintenance, inflammatory levels, and physical function. Further, dietary quality should be included in the analysis. As previously mentioned, diet may have significant metabolic effects and could play a role in inflammatory changes and body composition and thus evaluating changes in dietary quality could provide profound insight into its potential mediating role in body composition, inflammation, and physical function. Finally, studies have suggested that racial/ethnic and sex differences exist in body composition, systemic inflammation, and mobility outcomes among older adults with OA[71,110,118]; Thus having a cohort matching African American, Hispanic, and Caucasian participants along with a larger percentage of male participants to observe potential statistical differences in post-intervention outcomes would provide greater understanding of these racial/ethnic and sex differences.

VII. CONCLUSION

Osteoarthritis affects over 30 million U.S. adults[21] and 80% of those with OA have some degree of mobility limitation[21]. Rising adiposity levels are significantly linked to the progression of OA and physical disability in older adults[19,20] which is particularly concerning within an African American population given the greater prevalence of obesity[21]. The force exerted from excess body weight on large joints (e.g., knee and hip) can adversely affect mobility and physical functioning across all age groups, including the elderly[11]. Furthermore, excess visceral fat can promote the overproduction of inflammatory proteins, including CRP, that have been linked to the onset of OA, lean muscle tissue atrophy, and overall functional decline[19, 20]. Although PA is beneficial for reducing OA-related pain and improving mobility, reducing total and regional body fat mass along with PA may have an even more profound impact on physical function given its supposed impact on joint burden and systemic inflammation.

In fact, PA plus dietary weight management compared to either approach alone, has been shown to be superior for reducing total and regional body fat mass and physical function in older overweight and obese adults OA – with several studies showing an equal effect of dietary weight management with and without PA on systemic inflammation[11,12,30]. However, existing trials have tested the intervention effects in largely non-Hispanic white cohorts and not in African Americans despite the unequal burden of both obesity and OA in this population. In our study, we tested the comparative effectiveness of PA vs. PA plus dietary weight management on adiposity, body composition, systemic inflammation and physical function in a sample of 148 older overweight and obese African American adults with lower extremity OA. We found superior effects of the FNS!+ intervention (PA + dietary weight management) compared the FNS! intervention on body weight, WC, percent body fat, total fat mass, trunk fat and estimated

VAT compared to the FNS! group with no adverse effect on lean muscle mass. We also observed that the FNS!+ arm had statistically greater changes in distance walked on the six-minute walk test at post-intervention compared to the FNS! group with both groups showing significant improvement from baseline for the TUG and chair stands tests. However, we did not see an effect of the interventions on circulating CRP or IL-6 concentrations. Although, in our post-hoc analysis, a greater reduction in CRP was associated with fewer seconds to complete the TUG test in the FNS!+ arm suggesting that lowering systemic inflammation can have a positive impact on physical function. Additional studies conducted on a larger sample including a longer follow-up period are needed to fully explore the effects of FNS!+ compared to FNS! on the adiposity, body composition, and inflammatory outcomes and how changes in these parameters translate to improved physical function. In addition, a larger sample that included a significant number of non-Hispanic whites would allow for exploration of possible racial/ethnic differences in response to the interventions.

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