Enhanced Protein Intake During Obesity Reduction in Older Male Veterans:

Differences in Physical Function and Muscle Quality Responses by Race

Funding Agency: United States (U.S.) Department of Veterans Affairs Rehabilitation R&D (Rehab RD) Service

Principal Investigator: Connie W. Bales, PhD, RD

11/30/2023

In addition to Dr. Bales, the study team includes two physicians (Kim M. Huffman, PhD, MD and Shelley McDonald, PhD, DO) who will review data for safety concerns, reviewing adverse events and new study findings, and making required decisions to protect the health of the subject.

Parent Research Protocol: ***Enhanced Protein Intake During Obesity Reduction in Older Male Veterans: Differences in Physical Function and Muscle Quality Responses by Race***

Principal Investigator: Connie W. Bales, Ph.D., R.D.

Purpose

The purpose of this research is to restore physiological function in obese black and white older Veterans using an innovative weight loss diet that is higher in protein and enhanced by cultural tailoring, safe, low impact exercise, and intensive adherence support. Recognizing the increasing prevalence of type 2 diabetes with age and its links with poor muscle quality, we will study men with pre-diabetes, assessing changes in insulin sensitivity, as well as physical function. Our objectives are (1) to determine the impact of a muscle-preserving obesity treatment on physical function and an array of critical secondary outcomes in obese older male Veterans with pre-diabetes, and (2) to examine racial (black versus white) differences in treatment responses. Equal numbers of obese, older white and black male Veterans with pre-diabetes are randomized to an enhanced protein group or control weight loss group consuming RDA-level protein. The intervention stands to benefit large numbers of Veterans by improving their functional status; it will also reduce the VHA burden of care for their diabetes. It will advance the RR&D mission by "improving musculoskeletal composition and maximizing physical function" in obese older Veterans with pre-diabetes, yielding novel results on the interactions of insulin sensitivity with muscle quality and exploring racial differences in treatment responses.

Background and Significance:

The impact of late life obesity on physical limitations and reduced independence in older adults is under-studied. Yet, most of the ≥40% of older Veterans who are obese have reduced physical function due to the combination of excess body fat and age-related decline in muscle mass/strength (sarcopenic obesity). Close to one in four Veterans receiving health care from the VA has diabetes and there is a high prevalence of obesity in this group; moreover, the majority of these Veterans are 65 years and older [1,2]. Of special interest as we attempt to sort out the benefit/risk of obesity reduction is its impact on older African Americans, who have higher rates of obesity and are more likely to develop obesity-related functional decline and chronic health conditions like type 2 diabetes than their white counterparts. These Veterans are in critical need of interventions to restore their physiological function and ability to resume normal activities of living and achieve social autonomy. The primary focus of the proposed research is on the detrimental influences of obesity on physical function in older individuals who are at very high risk for frailty. Unless effective obesity interventions can be found, the functionally disabled, obese older adult may become the "most commonly encountered phenotype of frailty" in the near future [3].

Both obesity and the aging process lead to compromised muscle function. With age, lean muscle mass declines from about 50% of total body weight in young adults to about 25% at 75–80 yrs [4]. The progressive deterioration of muscle quantity and quality leads to slower movement, a decline in strength and power, and increased risk for falls [5]. Obesity also causes deterioration of muscle quality and loss of physical function. Thus, the combination of sarcopenia and obesity markedly accelerates functional decline. Greater adiposity favors the accumulation of lipid between and within muscles (reduced muscle quality). Moreover, in most obese individuals, there is persistent low grade inflammation resulting from chronic activation of the innate immune system that leads to muscle depletion by enhancing protein breakdown and impairing myogenesis in parallel [6,7]. Progressive muscle atrophy due to disuse contributes further to functional decline. Aging and obesity also precipitate impaired physical function through their association with increased insulin resistance and its progression to type 2 diabetes. Thus, insulin resistance is the third component of the "triple threat" to physical function in obese older adults. Increasingly, higher BMI, age, and comorbidity are being identified as significant co-risk factors for functional decline [8].

Obesity is the single most important risk factor for developing type 2 diabetes [9] and obesity reduction markedly slows the progression to prediabetes. However, weight reduction is difficult to achieve in adults of all ages [10,11] and it is especially challenging to treat in older adults, who have lower basal metabolic rates, calorie requirements, and rates of physical activity [12-14]. Moreover, efforts to reduce body weight in obese older adults raise concerns about the concomitant loss of lean body mass [15]. Lowering of muscle mass is a concern not only for future functional status but it is also linked with impaired glucose uptake and tolerance, even in those without diabetes [16].

A higher protein intake during obesity reduction could help circumvent loss of muscle mass and strength. Protein intakes exceeding the RDA level (≥0.8 g/kg) are linked with better preservation of lean mass [17,18] and new findings from the Framingham study have confirmed the benefits of high quality (animal) protein for protection of appendicular lean mass [19], preservation of grip strength [20] and decreased risk of function decline in the long-term [21]. While muscle becomes more resistant to anabolic stimulation with age, there is encouraging evidence that generous and balanced intakes of high quality (complete) protein can help off-set age-related anabolic resistance in the aging muscle [22-24]. Short-term studies have shown that the essential amino acids, especially leucine, initiate the mTOR signaling pathway and stimulate muscle protein synthesis [25-27]. A generous and balanced intake of protein at each meal (~30 grams) may be essential for optimal protein synthesis in the aging muscle [28,29]. Higher protein during obesity reduction may thus reduce the risk of physical frailty by increasing muscle anabolism; improvements in muscle quality may also result [17,29-32]. Our recent studies have confirmed the feasibility and efficacy of balanced higher protein weight loss diets for weight reduction and for improving physical function [33] and we seek to test this in vulnerable older Veterans with prediabetes.

Our study is particularly unique because the impact of higher protein intake on glucose handling is not well understood. The results of a recent trial suggested that a higher protein intake might blunt insulin sensitivity benefits accrued from weight loss [34]. However, at least two independent randomized controlled trials have demonstrated a beneficial effect of higher protein intakes on insulin sensitivity [35,36] and a recent systematic review found no detrimental effect of a higher protein diet in those with type 2 diabetes or those at risk of developing it [37]. Given the potential benefit of higher protein intake for function, we seek to better understand its impact on the high-risk populations groups who stand to benefit most, including those who are at elevated risk for developing type 2 diabetes.

Late-life obesity is one of the greatest health care challenges facing VHA as large numbers of Veterans approach old age. Obesity's impact on physical function is under-studied in many of those at highest risk for frailty, including obese older men with prediabetes. Thus, the proposed research addresses an important gap in the evidence needed to guide obesity treatment and diabetes prevention in older Veterans. It is based on evidence that balanced protein feeding benefits muscle function and the hypothesis that, in concert with moderate calorie restriction, it will provide an effective obesity treatment that preserves muscle while reducing body fat and improving glucose handling. The research also includes careful documentation of study participation and intervention adherence in order to analyze differential responses due to race, socio-economic status, and other factors unique to older Veterans. This will be the first randomized controlled trial to examine balanced feeding of a higher protein diet during a period of metabolic challenge (caloric restriction) in those with prediabetes and the first study to look at racial differences in response of obese older men to this regimen. There are very few studies of racial differences in response to obesity interventions.

Thus, the importance of our exploratory aim for understanding the unique challenges facing obese black men in later life and the potential benefit of new obesity treatments for them is underscored.

Specific Aims

Aim 1: ***To compare a balanced, higher-protein weight loss diet to a control weight loss diet with regards to the primary outcome of physical function.***

Introduction. This proposal focuses on interventions to improve physical function in obese older white and black men who have prediabetes, a common condition strongly associated with obesity; 5 to 10 % of those with prediabetes progress to type 2 diabetes within one year [38]. To date, the majority of weight loss study populations are predominantly female, despite substantial increases in rates of obesity in men [39-41]. Our study focuses on obese older men because of the scarcity of well-controlled studies of effective obesity interventions for men and because older male Veterans have a higher prevalence of diabetes (33% for 65-74 yr olds and 31.5% for 75 and older) than older female Veterans (26.9% for 65-74 yr olds and 25.7% for 75 and older) [42]. Older Veterans who are obese are in critical need of interventions to restore their physiological function and ability to resume normal activities of living and achieve social autonomy. We know that obesity treatment can improve function and potentially restore muscle quality but it can also threaten loss of lean mass (25% or more of weight lost) [15] unless the intervention is designed to protect the muscle.
The *objective of this aim* is to confirm the efficacy of a balanced higher protein weight loss diet for weight reduction and for improving physical function [33] in a population of vulnerable older male Veterans with prediabetes. The *rationale* for this aim is founded upon evidence that balanced protein feeding benefits muscle function and the hypothesis that, in concert with moderate calorie restriction, it will provide an effective obesity treatment that preserves muscle while reducing body fat. Upon completion of Aim 1, it is our expectation that the findings will show that a higher-protein weight reduction diet will result in improved functional performance (by Short Physical Performance Battery) relative to the control diet.

Specific Aim 2: ***To compare a balanced, higher-protein weight loss diet to a control weight loss diet with regards to impact on muscle quality, insulin sensitivity, lean body mass, rates of physical activity, recent falls/fear of falling, instrumental activities of daily living, and quality of life.***

Introduction. Obesity is the single most important risk factor for developing type 2 diabetes [9] and obesity reduction markedly slows the progression to prediabetes. However, weight reduction is difficult to achieve in adults of all ages [10,11] and it is especially challenging to treat in older adults, who have lower basal metabolic rates, calorie requirements, and rates of physical activity [12-14]. Lowering of muscle mass is a concern not only for future functional status but it is also linked with impaired glucose uptake and tolerance, even in those without diabetes [16]. The objective of this aim is to assess the broad metabolic and physiological effects of a higher-protein weight loss regimen, including its impact on muscle quality, insulin sensitivity, lean body mass, rates of physical activity, recent falls/fear of falling, instrumental activities of daily living, and quality of life relative to a control weight loss treatment. We will test the working hypothesis that an effective weight loss intervention will benefit insulin sensitivity and reduce the deleterious effects of obesity on muscle function, muscle quality, and the ability to be physically active and that these benefits will be greater in the higher-protein group than in the control weight loss group. We hypothesize that, compared to the control diet, the higher-protein regimen will lead to superior muscle quality and equal or superior improvements in insulin sensitivity, proportion of body lean and fat mass, physical activity by accelerometer, instrumental activities of daily living (IADLs), recent falls/fear of falling, and quality of life.

Aim 3 (Exploratory): ***To assess racial differences in responses to the two diet treatments with regards to weight loss, function, muscle quality, insulin sensitivity, body composition, physical activity, recent falls/fear of falling, IADLs, and quality of life****.*

Introduction. Racial differences in pre-diabetes and type 2 diabetes are well recognized; blacks have higher rates of obesity and are twice as likely to develop type 2 diabetes as non-Hispanic whites [43]. Yet, there are very few studies of racial differences in response to obesity interventions. Even studies focusing on African Americans include low percentages (30% or less) of men [44] and there is evidence that traditional weight loss interventions are less effective for black individuals [45,46], under-scoring the need for further study. As captured in this exploratory aim, this trial was designed to assess the differential impact of race on responses of insulin resistance during a hypo-caloric diet providing higher, balanced amounts of protein. We hypothesize that there will be a race differential in the responses of several outcomes to the diet treatments. It is our expectation that there will be less weight loss in blacks than whites and smaller improvements in function, muscle quality, and insulin sensitivity. This is based on literature findings on racial differences and our published findings in black women, as well as the tendency for more type 2 diabetes in the black population. Based on indirect evidence, we also speculate blacks will have lesser improvements in lean mass preservation, physical activity, recent falls/fear of falling, IADLs, and quality of life. Additionally, we expect to identify determinants of study participation and intervention adherence that indicate racial differences and that these results can be used for cultural adaptation in future intervention trials.

Design

This is a randomized controlled study. The subject numbers and group allocations are based on the primary outcome of functional status, as well as our previous experience with protein enhanced nutrition interventions. Our experiment is a repeated measures design, with the purpose of assessing change over time for the WL-Protein arm relative to the WL-Control arm. With this design, we will be able to derive effects sizes (effectiveness), and to assess differences between the two arms.

Setting: Screening, baseline, outcome testing and intervention meetings will be conducted at the Sarah W. Stedman Center for Nutritional Studies on the Center for Living Research and Wellness campus at Duke University. Diet and exercise classes will be offered virtually via WebEx or in person at the Center for Living campus. Anthropometrics, functions tests, and blood collection will take place in the Clinical Research Unit there or may be conducted virtually if needed. The Isokinetic knee extension peak torque testing and BodPod body composition measurements will be done in the Sports Sciences Institute, which is adjacent to the Stedman Building. The thigh CT scans will be conducted in Radiology at the Veterans Affairs Medical Center in Durham.

We will enroll participants until we reach a total of 112 study completers. We anticipate enrolling approximately 160, allowing for a 30% dropout rate.

Study Arms:

- ***Arm 1:*** **WL-Control (*n=56* completers)**
  10%* WL diet with 0.8 g protein/kg body wt/day
- ***Arm 2:*** **WL-Pro (*n*=56 completers)**
  10%* WL diet 1.4 g protein/kg body wt/day; ≥30g high quality protein per meal

Participants enrolled after 10/1/2023 will participate in a shortened study period of 3 months, with only 0 and 3 month assessments for most measures, as noted in the added footnotes below. Their weight loss prescription will be targeted to an expectation of at least 5-10% loss of body weight.

Measurements:

After the participant has been consented and HIPAA Authorization forms have been signed, screening and baseline assessments will be conducted:

Screening process:

Screening Visit : Consent; confirm BMI ≥30 kg/m^2, confirmed SPPB score of 4-11, confirmed fasting plasma glucose ≥95 and <126 mg/Dl or A1c between 5.7-6.4 (will be confirmed with LapCorp results), and confirmed Mini-Cog score ≥3 (if less than 3, confirm participant can conduct all ADLs).

Upon the completion of all baseline assessments (see below), the study biostatistician will then use permuted-block randomization to assign participants to WL-Control or WL-Protein groups. The following variables will be blocked in this order: 1) Race (white versus non-white, 2) Couple/Single status. An equal number of participants will be randomized across the two arms to end up with N=84 (42 black and 42 white) in each arm.

Measures and Data Collection Points

Primary outcome: Physical function (SPPB)

Secondary outcomes: muscle quality (the ratio of knee extensor peak torque to thigh muscle area (cm^2) assessed by using compute tomography (CT) (in Nm/cm^2); insulin sensitivity,Air Displacement Plethysmograph (BodPod) to measure body weight, lean mass, and body fat; waist circumference, function tests (handgrip, 8-ft up and go, 30-sec chair stand, 6-min walk); physical activity (Actigraph); recent falls and fear of falling, diet adherence and nutritional adequacy; activities of daily living and independent activities of daily living; and quality of life and mood indicators (SF-36 Health Status questionnaire, Profile of Mood States questionnaire, and Pittsburgh Sleep Quality Index).

Measurement/Procedure	Time Points[1]	Method
Diet/Intervention		
Body weight	Weekly	Same scale, light clothing and no shoes, measured to nearest 0.1 kg
3-day diet record; Daily food journal (Adherence)	0, 3, 6 months	3-day diet record by multiple pass; analyzed Food Processor (Version 10.13, 2013; ESHA Research); Daily food journal assessed by RD
Protein checklist	Monthly	RedCap analysis
Actigraph, Axis accelerometer (activity counts, step counts, physical activity intensity)	0, 3, 6 months; 7	Actigraph WGT3X-BT activity counts at 1-s epoch from three orthogonal axes at 30 Hz sampling frequency. We

[1] Participants who are consented after 10/1/2023 will participate in a shortened version of the study. Data will be collected at month 0 and month 3 as outlined in this table. Body weights will still be collected weekly and the Nutrition and Exit questionnaires will be conducted at 3 months.

	days each time point	have been using Actigraphs in previous studies and therefore have not included in the budget.
Nutrition Questionnaires	0 months	Food Security Questionnaire
Nutrition Questionnaires	0, 6 months	Nutrition Literacy Questionnaire
Intervention Evaluation	6 months	Exit Questionnaire
Tissue, metabolic analyses		
Routine chemistries, blood	0, 3, 6 months	Metabolic Panel (LabCorp)
Function, body composition		
SPPB (6, 64, 66)	0, 3, 6 months	Balance (side-by-side, semi-tandem, tandem), gait speed (4-meter timed walk), strength (chair stands).
6-minute walk test (aerobic endurance)	0, 3, 6 months	As many walking laps as possible in six minutes between cones placed 40 meters apart
8-ft Up and Go: (agility/dynamic balance)	0, 3, 6 months	Begins seated. On word 'go' stands, walks around a cone 8 feet away, returns to seated.
30 second chair stands: (lower body strength)	0, 3, 6 months	With arms across chest, stand up completely, returns to seated as many times as possible in 30 seconds.
Isokinetic knee extension peak torque (muscle strength)	0, 3, 6 months	Knee extensor at 60°/s with a dynamometer (HUMAC NORM Isokinetic Extremity System). Average peak torque for three trials will be recorded.
Computerized axial tomography (CT) scan	0, 3, 6 months	Cross sectional area of the thigh without contrast to determine muscle mass.
Isometric hand grip (upper body strength)	0, 3, 6 months	Jamar Hand Dynamometer (Sammons Preston Rolyan). Highest of two trials/hand.
Minimal waist circumference	0, 3, 6 months	At smallest horizontal circumference above umbilicus and below xiphoid process.
Body Composition: BodPod	0, 3, 6 months	Air displacement plethysmography method (Life Measurement, Inc., Concord, CA). The BodPod is has excellent sensitivity and test-to-test reliability, ease of use, and non-invasive nature, which is important for full participation from this population.
Recent falls, fear of falling	0, 3, 6 months	Fall Information Questionnaire
Questionnaires		
Mini-Cog (64)	Baseline	Screens for cognitive impairment with minimal language content, reduces cultural and educational bias. A 3-item recall component plus a Clock Drawing Test. Score ≥3 for participant to be study eligibleif less than 3, confirm participant can conduct all ADLs).
Quality of Life; Mood; Depression; Stress; Sleep; Life Satisfaction	0, 3, 6 months	SF-36; POMS; CES-D; Perceived stress; Pittsburgh sleep; Frustration Discomfort; SWL
Cognitive Testing Questionnaires	0, 3, 6, months	Symbol Digit Modalities; Grooved Pegboard; Hopkins Verbal Learning Test; Trail Making Test
Cantab	0, 3, 6 months	A battery of computerized tests, including: reaction time, paired associates learning, spatial working

		memory, pattern recognition memory, delayed matching to sample, and rapid visual information processing will be administered using the CANTAB

Selection of Subjects

Subjects will be obese (BMI ≥30 kg/m^2) male Veterans aged 55 yrs and older, with mild to moderate functional impairment (Short Physical Performance Battery aggregate score of 4 to 11 units). Although the lower age limit is 55 years, there is no upper age limit and we expect the mean age of enrollees to be in the range of at least 65-70 years. We will enroll an equal number of black and white men in the study population. At the point of screening, race and ethnicity of potential participants will be ascertained using the categories specified in the OMB (Office of Management and Budget) Standards for the Classification of Federal Data on Race and Ethnicity. At screening, Veterans will be asked to self-identify as to ethnicity of Spanish/Hispanic/Latino (yes or no), and race of either Asian, American Indian/Alaska Native, Black or African American, White, or Native Hawaiian or Other Pacific Islander.

Inclusion Criteria

- Male Veterans
- African American or White
- Obese (BMI ≥ 30 kg/m^2)
- Age ≥ 55 years
- Pre-diabetes (fasting plasma glucose ≥95 and <126 mg/dL or HbA_{1c} 5.7-6.4%)
    - Will allow inclusion of HbA_{1c} up to 6.9 if fasting plasma glucose is within pre-diabetes range
    - Will allow inclusion of fasting plasma glucose up to 140 if HbA_{1c} is within pre-diabetes range
- Age-normal renal function
- English speaking
- Able to record dietary intake or has a proxy who can record dietary intake
- Willing and able to be randomized to either intervention group
- Light smoking (Less than 10 cigarettes/day)

Exclusion Criteria

- Presence of unstable or symptomatic life-threatening illness. Glomerular filtration rates (GFR) less than 45 mL/min. A GFR of 45-59 requires bi-monthly testing per our established algorithm [50]. Those with a GFR <45 mL/min are excluded.
- Mini-Cog score of <3 and inability to conduct ADL's.
- Neurological conditions causing functional impairments, including Parkinson's disease, multiple sclerosis, and permanent disability due to stroke.
- Inability to complete physical function assessment.
- History of significant weight instability or fluctuations.
- Currently taking non-oral medications to control blood sugar and A1c (i.e. insulin). Oral glucose lowering medications will be allowed if stable dose and frequency over the last 3 months
- Unwillingness to adhere to the diet structure of the study or following a diet that interferes with the diet structure of the study. Contraindicated medications, including narcotic mail-outs and active substance abuse.

- Any psychiatric condition that would prevent the subject from participating in a group intervention setting, including diagnosed personality disorders.
- Primary care provider disapproves participation.

To protect vulnerable populations or those subjects who may be susceptible to coercion or undue influence against, any Veteran who is approached by staff will be told that their participation is voluntary, and they may choose not to answer any questions that they find too sensitive. Also, Veterans will be told that their participation will not affect their care at the VA. The study staff member will explain the study in detail. No study procedures will begin until formal, written informed consent has been obtained.

Study Interventions

Caloric Prescription, Diet Monitoring and Exercise Intervention for Both Arms:
All subjects will receive the same attention and support, meeting individually with an interventionist weekly for weeks 1-2. Individualized calorie prescriptions for a weight loss of ~1-2 pounds per week, calculated by a dietitian, are derived from estimated total energy expenditure (TEE) [51]:

--*TEE for OB men:* 864 – (9.72 x Age [y]) + PA x (14.2 x Weight [kg] + 503 x Height [m].

The calorie level for a weight loss of ~1-2 pounds (average of 0.6 kg) per week will be calculated, generally a reduction of 500 to 1000 kcal/day. The intervention diet will be culturally tailored to meet the individual preferences of the target population and adapted to make sure low-income participants are able to afford the healthy foods in their diet plan. After 2 individual sessions, participants will continue to be submit their weights each week and attend weekly group sessions that provide a curriculum designed to enhance diet compliance [50]; this includes group support, goal setting, self-monitoring, stress management, problem solving, and relapse prevention, daily diet journaling, email/phone reminders, and tutorials for on-line tools during the entire 6-month intervention. (It should be noted that for participants enrolled after 10/1/2023, the study period will be 3 months instead of 6.) To insure a supportive weekly group size, we will wait to begin the intervention until the first cohort has at least 5 participants in each arm.

Nutritional adequacy will not be compromised; protein intakes are adequate in both arms and the diet pattern will be rich in essential vitamins and minerals [52]. Additionally, daily low dose multivitamin/mineral supplement, and calcium/vitamin D supplement will be provided, based on menu nutrient content and to achieve consistency (no other supplements permitted unless prescribed by physician).

Physical activity and falls-prevention components of the intervention: Participants in both groups will attend a weekly session of safe, low intensity exercises to encourage safe progression to a more functional lifestyle, including individualized exercise prescriptions for those with military-acquired or other limitations. Instructions will be provided for safe repetition of the exercises at home on at least 2 more days per week. Additionally, weekly support group sessions will include training on falls reduction and safe ways to become more physically active.

WL-Control Diet: 0.8 g protein per kg body weight. Participants will receive careful guidance for consuming only 15% of total calories from protein per day. Expressed another way, control participants will consume about ~0.8 g protein per kg body weight. Each week, participants will be provided 7 servings of whey protein

powder (15 g/serving) to support diet affordability and provided recipes for low calorie smoothies. The whey protein will be portioned by our research staff and delivered to the participants weekly on Duke's campus.

WL-Protein Diet: 1.4 g protein/kg body weight/day, ≥30 g of high-quality protein per meal. Subjects will receive careful guidance for evenly distributing ≥90 g high-quality protein between 3 meals plus snacks per day. Each meal includes ≥30 g high quality protein, provided directly to WL-Protein for two of three meals daily plus 1 snack, as lean red meats, whey protein, a high-protein milk-based, lactose-free beverage, and chicken. Twenty-one servings of high quality (30 g/serving) protein (lean red meats, whey protein, a high-protein milk-based, lactose-free beverage, and chicken) will be provided to participants each week to increase compliance and enhance affordability. Weighed, individual servings will be chilled or frozen, and delivered to the participants at weekly group meetings in thermal bags. For those unable to transport the bags or using public transportation, delivery to the home will be arranged. The 30 g high quality protein for the third meal of the day will be per participant's choice.

Food record data analyses from previous studies indicates the WL-Control group will be consuming a typical American quantity/ distribution of protein (mean of 22 g per meal with range of 11-30 g), while the WL-Protein group will be consuming the target intake of ≥30 g per meal.

Supplemental Project Research Protocol: Feasibility and Acceptability of a Remote Obesity Intervention for Prediabetes: Improving Function on Older Veterans at high Risk During COVID-19 Isolation

Background and Project Summary:
Social isolation was recognized as a major threat to the health of older adults long before the Covid-19 pandemic, with as many as one third reporting being isolated and feeling lonely.[54,54] As the pandemic is predicted to persist throughout 2020, there is growing concern that long periods of COVID-19 related isolation will foster negative physical and mental health outcomes and speed the progression of physical frailty.[55] Building upon our preliminary findings (described below) and evidence from a large body of established literature on social isolation, we characterized (Table 1) some of the most important risks being faced by our older Veterans and explored opportunities to use remote interventions to reduce obesity and restore their physical function despite their need to isolate.[56] The proposed research takes the next step by exploring the feasibility, acceptability, and effectiveness of our remote intervention in Veterans who are at especially high risk of further functional decline due to isolation. In our preliminary surveys, we identified "high risk characteristics" that may lead to greater social isolation. Using the same target population in the parent trial, we will specifically recruit and enroll Veterans meeting these age and COVID-19 related social isolation risk factors in addition to the parent trial inclusion criteria. As explained in the Aims section, the feasibility and acceptability of the intervention for this cohort will be determined, as will the successful attributes and time demands of the specialized attention they will require from interventionists. Pilot data on the effectiveness of the Protein treatment relative to the Control for restoring physical function in this population will also be acquired.

Table 1. Risks Imposed by Age- and COVID-19-Related Social Isolation[1]

Loss or Lack of:	Aging-related Isolation	Pandemic-related Isolation
Social Interaction	✓	✓
Financial resources, income	✓	✓
Access to medical care	✓	✓
Access to food, cooked meals	+/-	✓
Opportunity to exercise safely	✓	✓
Fulfilling relationships	✓	+/-

[1]The +/- symbol indicates that this may or may not be true, depending on circumstances/resources.

Specific aims:

Aim 1: *To evaluate the feasibility (recruitment and retention) and acceptability (participant satisfaction) of a virtual diet and exercise obesity intervention in Veterans at higher risk for* negative physical and mental health outcomes *during COVID-19 isolation.*

Aim 2: *To determine the effect size for subsequent studies of virtual interventions for high risk obese older Veterans with physical function as the outcome of primary interest (virtual SPPB).* Outcomes will also be collected for the secondary measures of weight loss, physical function, insulin resistance (Glycated Hemoglobin; Hb A1c), cognitive function, and quality of life.

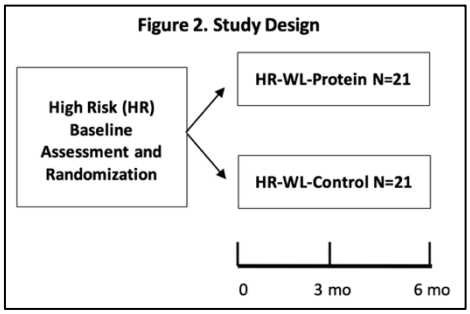
Table 2. High-Risk Criteria Due to COVID-related Isolation (≥2)

Criteria	Definition
Isolated living environment	Lives alone or eats all meals alone
Risk of sarcopenia	Score of ≥ 4 on SARC-F screener
Poor access to medical care	≤10% Service connection
Sensory impairment	Hearing and/or visual impairments that impacts IADLs and/or ADLs
Caregiver burden	Caregiver for grandchildren, children, and/or spouse
Chronic pain	Moderate, severe, or very severe response to SF-36 pain question

Exploratory Aim 3 (given restoration of full in-person clinical research testing visits):
To determine the effect size for subsequent studies of virtual interventions for high risk obese older Veterans with regards to the primary outcome of (in-person) SPPB and the in-person secondary outcomes of insulin sensitivity and muscle quality (thigh CT scan, knee extensor peak torque).
Achievement of this Aim would allow comparison of the high-risk participants to the participants that do not have 2 or more age and/or COVID-19 related social isolation risk factors (Table 2).

Significance with regard to COVID-19 impact on Veterans:
The COVID-19 pandemic and resulting social isolation is worsening health conditions in all older adults, including Veterans. Obesity is promoted by overeating due to increased stress and/or reduced access to healthy food options. In our recent recruitments for obesity trials, many of our participants are reporting experiencing a marked weight gain since the pandemic came to our community. Deterioration of physical fitness and function are also being documented.[57] In addition to exacerbating chronic conditions like type 2 diabetes and hypertension, obesity increases the risk of serious complications and death if a COVID-19 infection occurs. There is a critical and time-dependent need to develop strategies to reverse the trend towards obesity-related physical frailty in our vulnerable older Veterans. The proposed research can be initiated quickly because effective remote interventions have already been developed in the parent trial and are ready for use in this study. Another significant point is that the trial also enrolls a substantial proportion of African American Veterans, an important advantage because minority older adults are known to be more vulnerable to COVID-19 complications.[58]

Study Design: High risk, obese, male Veterans with prediabetes and SPPB score of 4-11 (out of 12), aged ≥55 yrs will be randomized to a higher protein, calorie-restricted diet OR a calorie-restricted diet with RDA level protein in a 6-month trial (**Fig. 2**).



Selection of Subjects:
From the parent study, 42 participants will have 2 or more age and/or COVID-19 related social isolation risk factors (Table 2). These individuals will be randomized into the Parent study's WL-Protein arm (n=21) or the WL-Control arm (n=21)

Randomization: The following variables will be blocked in this order: 1) Race (white versus black, 2) chronic health conditions (≥3 versus <3), and 3) physical function, SPPB score (≥8 versus <8). An equal number of participants will be randomized across the two arms to end up with N=42.

Arm 1: **High Risk Weight Loss Protein (HR-WL-Protein; n = 21 completers)** 10% WL diet with 1.4g protein/kg body wt/day; ≥30g high quality protein per meal

Arm 2: **High Risk Weight Loss Control (HR-WL-Control; n = 21 completers)** 10% WL diet with 0.8g protein/kg body wt/day

Screening (*Two-step process*):
Screening Visit Level 1: Confirm 2 or more high risk criteria (see Table 2), confirm BMI ≥30 kg/m^2, confirm SPPB score of 4-11, confirm fasting plasma glucose ≥95 and <126 mg/dL, confirm Mini-Cog ≥3 (or ability to complete all ADL's).
Screening Visit Level 2: Routine blood and urine chemistries and confirm age-normal renal status.

Aim 1:
Feasibility: Recruitment, retention, and intervention resources (defined in detail below)
Acceptability (6 months): participant satisfaction of intervention (defined in detail below)
Aim 2:
Physical Performance (0, 3, 6 months): Short Physical Performance Battery (SPPB) including three domains Balance (side-by-side, semi-tandem, tandem), gait speed (4-meter timed walk), and lower extremity strength (chair stands)
Anthropometrics: Body weights and body composition using Bod-pod.
Insulin Resistance: Glycated Hemoglobin (HbA1c), assessed in whole blood.
Cognition Testing: (all virtual) CANTAB battery of tests--reaction time, paired associates learning, spatial working memory, pattern recognition memory, delayed matching to sample, and rapid visual information. Other tests are the Symbol Digit Modalities Test of global cognitive ability, the Hopkins Verbal Learning Test of verbal learning, recall, and recognition and the Trail Making Test (TMT) of psychomotor speed and executive function in which participants connect dots according to either number (part A) or alternating number/letter (part B) will be administered virtually as a timed, 2-part, test.
Aim 3:
Muscle Quality (0,3,6 months): the ratio of knee extensor peak torque (Nm) assessed using isokinetic dynamometer to thigh muscle area (cm^2) assessed by using computed tomography

Measurement/Procedure	Time Points[2]	Method
Diet/Intervention		
Body weight	Weekly	Same scale, light clothing and no shoes, measured to nearest 0.1 kg

[2] Participants enrolled after 10/1/2023 will complete a shortened study period of 3 months. Their data will be collected at month 0 and month 3, as outlined in this table. Body weights will still be collected weekly and the Nutrition and Exit questionnaires will be conducted at 3 months.

3-day diet record; Daily food journal (Adherence)	0, 3, 6, months	3-day diet record by multiple pass; analyzed Food Processor (Version 10.13, 2013; ESHA Research); Daily food journal assessed by RD
Protein checklist	Monthly	RedCap analysis
Actigraph, Axis accelerometer (activity counts, step counts, physical activity intensity)	0, 3, 6 months; 7 days each time point	Actigraph WGT3X-BT activity counts at 1-s epoch from three orthogonal axes at 30 Hz sampling frequency. We have been using Actigraphs in previous studies and therefore have not included in the budget.
Nutrition Questionnaires	0,	Food Security Questionnaire
Nutrition Questionnaires	0, 6 months	Nutrition Literacy Questionnaire
Intervention Evaluation	6 months	Exit Questionnaire
Tissue, metabolic analyses		
Routine chemistries, blood	0, 3, 6 months	Metabolic Panel (LabCorp)
Function, body composition		
SPPB (6, 64, 66)	0, 3, 6 months	Balance (side-by-side, semi-tandem, tandem), gait speed (4-meter timed walk), strength (chair stands).
Virtual SPPB	0, 3, 6 months	Balance (side-by-side, semi-tandem, tandem), gait speed (4-meter timed walk), strength (chair stands). All assessments administered virtually.
6-minute walk test (aerobic endurance)	0, 3, 6 months	As many walking laps as possible in six minutes between cones placed 40 meters apart
8-ft Up and Go: (agility/dynamic balance)	0, 3, 6 months	Begins seated. On word 'go' stands, walks around a cone 8 feet away, returns to seated.
30 second chair stands: (lower body strength)	0, 3, 6 months	With arms across chest, stand up completely, returns to seated as many times as possible in 30 seconds.
Isokinetic knee extension peak torque (muscle strength)	0, 3, 6 months	Knee extensor at 60°/s with a dynamometer (HUMAC NORM Isokinetic Extremity System). Average peak torque for three trials will be recorded.
Computerized axial tomography (CT) scan	0, 3, 6 months	Cross sectional area of the thigh without contrast to determine muscle mass.
Isometric hand grip (upper body strength)	0, 3, 6 months	Jamar Hand Dynamometer (Sammons Preston Rolyan). Highest of two trials/hand.
Minimal waist circumference	0, 3, 6 months	At smallest horizontal circumference above umbilicus and below xiphoid process.
Body Composition: BodPod	0, 3, 6 months	Air displacement plethysmography method (Life Measurement, Inc., Concord, CA). The BodPod is has excellent sensitivity and test-to-test reliability, ease of use, and non-invasive nature, which is important for full participation from this population.
Recent falls, fear of falling	0, 3, 6 months	Fall Information Questionnaire
Questionnaires		
Mini-Cog (64)	Baseline	Screens for cognitive impairment with minimal language content, reduces cultural and educational bias. A 3-item recall component plus a Clock Drawing Test. Score ≥3 for

		participant to be study eligible (if less than 3, confirm participant can conduct all ADLs).
Quality of Life; Mood; Depression; Stress; Sleep; Life Satisfaction	0, 3, 6 months	SF-36; POMS; CES-D; Perceived stress; Pittsburgh sleep; Frustration Discomfort; SWL
Cognitive Testing Questionnaires	0, 3, 6 months	Symbol Digit Modalities; Grooved Pegboard; Hopkins Verbal Learning Test; Trail Making Test
Cantab	0, 3, 6 months	A battery of computerized tests, including: reaction time, paired associates learning, spatial working memory, pattern recognition memory, delayed matching to sample, and rapid visual information processing will be administered using the CANTAB

Intervention for High Risk Veterans:
A weight loss of 10% [3]is targeted for both groups; all will participate in nutrition and exercise group sessions delivered remotely by registered dietitian interventionists. To combat the impact of age and COVID-19 isolation and the requirement of the intervention to be delivered remotely due to COVID-19, tools and strategies will be implemented to reduce barriers of participating in the obesity reduction intervention. Table 3 outlines example interventions that will be incorporated and documented for usefulness and time demands. These components will complement intervention tools already in the parent study and will be utilized when needed to assist all participants (both high risk and non-high risk) in adherence to the weight loss intervention.

Table 3. Example Intervention Tools to Combat COVID-19 Isolation

Challenges/Barriers	Intervention Tools
Lack of device to participate in remote intervention	All participants will be provided a tablet to ensure they can participate in the remote intervention
Sensory impairment	-Additional 1:1 time with interventionist to ensure needs are met -Utilization of text-to-speech functionality on devices to accommodate participants who experience vision impairment -Provision of speakers that can be adjusted by the participant to meet their hearing needs
Difficulties with using technology	Real time tech support will be provided by a member of research team to assist participants having difficulties with the virtual intervention
Increased caregiver burden	Connect Veteran with VA and community resources (Durham Community Resource Connections) for caregiver respite
Lives alone or eats alone	Pair Veteran with another participant or interventionist to share in virtual meals

Subject Recruitment
This study will utilize a Request for HIPAA waiver of Authorization and waiver or alteration of informed consent process to identify potential participants for this research study. Each year of the study we will use the VA Informatics and Computing Infrastructure (VINCI) to conduct a query to identify Veterans seen at the Durham VAMC in the past year who were age $\geq$ 55 yrs, were obese (BMI ≥30 kg/m^2), and had prediabetes identified by either a HbA_{1c} between 5.7 and 6.4 % or a fasting blood glucose of ≥95 to <126 mg/dl. We will also work with the MOVE program coordinator, Katherine Catolico, and the Diabetes Management Clinic at the VA, to recruit patients who fit the above description. Finally, we will conduct face to face recruitment at VA organizations within the community and local libraries. We will also provide flyers to various VA clinics for providers and clinic staff to share with veterans. Potential clinics include primary care and specialty clinics at the Durham VA, Hillandale, Raleigh and Wake County, and Clayton clinics.

[3] Participants enrolled after 10/1/2023 will have a goal of 5-10% reduction in body weight due to the shortened study period.

We will contact Veterans who meet inclusion criteria by mail via a recruitment letter signed by the PI that describes the study and emphasizes eligibility based on the fact that their prediabetes increases their risk for developing type 2 diabetes. In the letter, potential participants will call our office number and will be given an opportunity to "opt-out" and decline participation and/or further contact regarding participation. Five business days after the mailing, Veterans who have not called the study number to decline participation will be called by a study staff member to request their participation in the research study (see telephone screen script). Following a script, the recruiter will describe the study, query about potential exclusions and assess overall interest in participation. Interested and eligible subjects will then be scheduled for their first screening visit.

Additional recruitment methods include the advertisement of the study via third parties, including Facebook or Instagram, Craigslist, DukeList and Google ads. Advertisements will direct interested participants to contact the study team for more information about the study.

Consent Process

On the day of the consent meeting, potential participants will be presented a full description of the study measurements, the interventions, and the randomization process. The participant will be told that their participation is voluntary, and they may choose not to answer any questions that they find too sensitive. Also, Veterans will be told that their participation will not affect their care at the VA. The study staff member will explain the study in detail. The participant will be given as long as they need to read through the consent form and HIPAA Authorization. Study staff will answer all questions and concerns. No study procedures will begin until formal, written informed consent has been obtained. This visit will determine if a participant is eligible to participate in the study. If a participant does not qualify, they will be given a letter indicating the reason of disqualification, and other resources/ programs for which they may qualify based on their condition. This visit will take place at the Duke Center for Living and will last approximately 90 minutes.

Adverse Events

All adverse events will be reported per Durham VAMC requirements. Given that the study population is older, somewhat functionally impaired and with metabolic risk factors, and based on our prior experience with a similar (non-Veteran) population, we anticipate that we will have adverse events, including one or more serious adverse events during the study period but that these adverse events will not be associated with the intervention, which is low risk. The most likely adverse event relating to the intervention would be a minor musculoskeletal injury during the exercise class. We will work to prevent this with close supervision by a trained exercise instructor and providing safety guidelines for when exercising at home. All Serious, Unanticipated and Related adverse events will be reported to the IRB within 5 business days of hearing of the event. All other adverse events will be reported at continuing review.

Costs and/or Payments to Subjects

Study participants in both arms may receive up to $325 for full participation in the study. Payment information is provided in the informed consent document. The study involves three time points; compensation will be $75 for completing Baseline Visits, $100 for Midpoint Visits and $125 for Endpoint Visits). Participants enrolling after 10/1/2023 may receive up to $200 for participation due to the shortened study period. Participants may receive compensation for travel, or food support if determined by the PI. Participants who do not qualify at screening will still receive $25 for participating. Payment will be issued to participants via a direct deposit or check.

Risk/Benefit Assessment

The risk to human subjects for participation in this study is minimal compared to the potential health benefits they will receive from participating in the interventions and receiving detailed health, diet and body composition evaluations. The study is carefully designed for safety. Our study staff is carefully trained and has experience in implementing nutrition intervention in older, frail populations. They also have the expertise to safely conduct physical function measures. Furthermore, the study physician, Dr. Shelley McDonald, will always be "on page"; she and another physician co-investigator will be available as needed for consultation regarding medical concerns related to study participation. The low intensity chair exercises are carefully guided to improve strength, flexibility and balance, and the weight reduction diet is mildly restrictive, leading to a very safe, gradual rate of weight loss. Workbooks provided at the beginning of the study will include a listing of warning signs with instructions should injury or other health problems occur. Participants will be provided contact information for Dr. Bales and all study team members and encouraged to communicate with them about any concerns regarding the nutrition supplement or any other aspects of the study. All reported events will be recorded in the adverse event log (including the subject's name, date, and event description) and the PI, mentor team, and data safety monitoring board will be notified. All health occurrences will be recorded and regularly reviewed by the study staff and reported to VA IRB according to IRB guidelines. The expected average weight loss will be 1-2 pounds per week. In addition, weight loss will be carefully monitored in each subject by a licensed, board certified Registered Dietitian clinician. The increased protein in the protein supplementation arm will not exceed safe limits for total intake and has been studied extensively in older adults with no adverse effects. Additionally, we will use screening blood testing to exclude from enrollment subjects with GFR <45. Phlebotomy carries minimal risk of infection and temporary pain. The CT-scan is the method of choice for the muscle quality measure because of the very low radiation dose (less than 10 mSv per scan) and the ease of undergoing the measurement.

A number of potential health benefits that may accrue to participants and important scientific knowledge will likely result from this work. Subjects will receive a weight loss intervention that is very likely to produce a modest but metabolically beneficial amount of weight loss and an exercise intervention that will help them be more physically active. Furthermore, we expect that participants will achieve substantial life-style modifications that could be sustained as a part of their personal health regimen in the setting of their community environment. Information collected from this study will benefit others through a greater understanding of how to best maintain muscle function and improve insulin sensitivity while reducing obesity in the older population.

Data and Safety Monitoring

The individuals responsible for data safety and monitoring will be the PI, the Registered Dietitian, the project coordinator, and the study Co-Investigators (Drs. Starr, McDonald, Huffman, and Pieper). Further data safety and monitoring will be provided by the PI. There will be several ongoing mechanisms for monitoring and reporting of adverse events: 1) ongoing participant contact via study personnel, 2) study telephone number provided to participants to report concerns related to study participation; and 3) weekly meetings between the PI and study personnel.

In addition, an internal data safety advisory group will be established to monitor the study and assure that subject safety and confidentiality is being protected. This group will receive annual reports on subject enrollment and regular reports of any adverse events that occur. They will meet with Drs. Bales, Starr, McDonald, Huffman, and Pieper on an annual basis for review of study progress and results. The advisory

group will review clinical events to identify any excess event rate in the study population over that expected based upon historical experience. Based on our extensive previous experience, we have already established safety limits for an interim measure of renal function (GFR drops below 45) that could result in temporary or permanent discontinuation of individual subjects in the unlikely event that these limits are exceeded.

The PI will meet at least weekly with study personnel to discuss participants' reactions to outcome measures and assessments, weekly telephone calls, and any adverse events or unanticipated problems. Monthly meetings between the investigators and the project coordinator will allow for ongoing progress reports, including the number of participants currently involved in the study and scheduled data collection from participants, as well as notification and review of any AEs. Safety monitoring for adverse events (AEs) will be conducted in real time by the PI and/or project coordinator. The following information about adverse events will be collected: 1) the onset and resolution of the AE, 2) an assessment of the severity or intensity (use existing grading scales whenever possible), 3) an assessment of the relationship of the event to the study (definitely, probably, possibly or not related), and 4) action taken (e.g., none, referral to physician, start or increase concomitant medication). The PI will determine the severity of the event, will assign attribution to the event, and will monitor the event until its resolution. All adverse events will be reported per Durham VAMC requirements. All Serious, Unanticipated and Related adverse events will be reported to IRB within 5 business days of hearing of the event. All other adverse events will be reported at continuing review.

Withdrawal of Participants

If a participant decides to withdraw from the study, they will be instructed to contact the PI and discuss the reason for withdrawal. This information will be documented to help better understand the reasons that the participant was unable to complete the study.

Data Analysis and Statistical Considerations

Data management and quality control: We will employ REDCap (Research Electronic Data Capture) hosted within VIREC for data entry. Key components of this activity include data entry screen programming and database testing and validation. The database will include study default parameters and ranges for database, protocols, users, and access rights. Access and data entry to the database will be controlled by login permissions, and the database will be backed up daily, with full backups occurring weekly, and quarterly backups retained for perpetuity. The database will be routinely checked for data integrity and quality. In addition, since some data will require direct download from computerized databases (e.g. VA patient information, lab findings) a final relational database will be built to be used for analysis in SAS, combining data from all data sources. This process will include quality control, developing an appropriate query, validation, and justification procedures, auditing, developing a manual of procedures and documentation, interim reporting of data flow, and maintaining security and patient confidentiality of the data base. The analysis database derived from this source data will be de-identified. Identifying information will be viewed and managed only by the data manager and appropriately consented data collection staff.

Quality control procedures will be established for each component of the study. At each level of data management, and for each subject contact, strict adherence to VHA policy will be observed regarding HIPAA, IRB and other VHA patient quality controls. These procedures include not identifying any patient or provider on any of the reports generated from this study. All computer files will be password protected. Files containing names and addresses will have a separate password, will be accessible only to personnel who need to contact the subjects, and will be stored separately. Ultimately, a de-identified file appropriate for analysis will be

produced for report generation and analysis. All analysis and data management personnel are current with all VA mandated security training.

Analysis Plan for the parent protocol (Aims 1 and 2):

This design is a two-armed clinical trial, with replicate measures at three time points: baseline, three, and six months. Since subjects are randomized to either WL-Control or WL-Protein arm, and the groups are presumed equal at baseline, the analysis is straightforward. Following the Good Clinical Practice Guidelines for the analysis of a clinical trial, we will employ mixed models, analyze under an Intent to Treat (ITT) criteria, and control for baseline and assess the impact of Time, Treatment Group and the interaction of these variables on the outcomes. Relative to the usual repeated measures designs, mixed models have several advantages: 1) missing values present no particular difficulties in estimation and the estimates are unbiased as long as the set of variables leading to MAR are estimated, 2) the usual assumption of conditional independence (compound symmetry) used in standard repeated measures need not be made, and 3) the actual times of measurement need not be equivalent across subjects. Controlling for the individual baseline values for the particular outcomes, the trajectories over time and differences in those trajectories will be assessed. Following the statistical principles section from the International Conference on Harmonization, we will select covariates (e.g., age, race, number of comorbidities) for the primary models a priori, but we also will conduct auxiliary sensitivity analyses that evaluate whether potential group imbalances bias the treatment effect estimate. These analyses will be performed using conventional testing for confounding. We note that we have listed numerous measures to be analyzed as outcomes, but have listed only 1 primary outcome (physical function, Aim 1).

For any particular outcome, the general form of the model will be:

$Y_{it} = \beta 0 + \beta\ 1(\text{group}) + \beta\ 2(\text{time}_t) + \beta\ 3(\text{group}*\text{time}_t) + \beta\ 4(\text{covariates}) + \varepsilon_{it}$

Where i is an indicator of person, and time is defined as t=1, 2 (measuring month 3, and 6), and the β's are regression coefficients connecting the predictors to the outcome. For brevity, we list β4 as a vector of K regression coefficients linking the K covariates to the outcome. As defined, the overall test of the intervention effect will be the joint effect of group and group*time on 2 df (β1 and β2) assessing an overall effect of group, and if this group effect is constant over time. If significant, follow-up tests will assess where group differences lie. In particular, we note that if the time by group interaction is rejected, we will test if the groups differ at the end of 6 months (a test of effect at the completion of the intervention). We will carefully examine model assumptions, including the distribution of model residuals, additively, linearity, and influential observations, and will, if necessary, re-parameterize the models or transform the outcomes accordingly.

In addition to the impact of the intervention on the secondary outcomes, we will assess mediation of the group effect on the primary outcome by demographic, comorbid and adherence variables. Subjects may differ in their process of change depending on baseline demographic and functional status values. Second, we will assess the functional form of the change over time, by looking at non-linear functions of change. For example, change in function and performance is likely to be non-linear, initially changing quickly and leveling at points distal from baseline. It would be important to note if this change differed by group. Finally, we will assess whether the trajectories of change, irrespective of group assignment, are similar for individuals. In this application, we have listed several variables, which we expect to change as result of the intervention. We further hypothesize that all these variables will change in the same pattern. To test this hypothesis, across the range of outcome measures, we can look at overall change through the use of multivariate tests (Boc[59] or Anderson[60]) for the singly measured functional items, and by assessment of correlated trajectories for those outcomes measured repeatedly. With appropriate weighting for number of observations per individuals, the correlation between individual trajectories can be assessed. A positive correlation between the trajectories for any two outcomes will indicate that the subjects changed similarly for the 2 outcomes, and will provide

additional support for the notion that the intervention had a generalized effect across the outcomes. Significant correlations would perhaps indicate mechanistic/causal linkage between variables over time, or, from a reliability standpoint, may indicate that the subsequent trial may want to employ summary measures aggregating across outcome measures, or, alternatively, employ multivariate tests across several outcomes to assess the group differences, reducing the chance of Type-I error inherent in the testing of multiple variables. We will not adjust for Type-I error rate for these secondary outcomes.

Analysis Plan (Aim 3):
Primary outcome data collected during the trial will be analyzed for differences due to race. Using the same analytic strategy listed in the analysis of Aims 1 and 2, race (B/W) will be included into the analytic structure for the physical function (SPPB) outcome, first as a main effect (mediating), and secondly, as an interaction (moderating) with group. If the physical function change outcome is normally distributed, we will employ, 2-way ANCOVA, with race and group serving as factors, and controlling for baseline physical function. While our working hypotheses are directional, our tests will be two-tailed. If physical function is not distributed approximately normal, we will attempt to assess the outcome using appropriate transformations, or bootstrapping simulations[61]. We are aware race and compliance may be partially confounded. As a final sensitivity analysis, we will assess if any observed relationships are mediated by compliance with the protocol. Next secondary outcomes data collected will be used to test the hypotheses about racial differences. Preliminarily, we will assess if the distributional assumptions of the outcomes of the ANCOVA model are met. If not, we will attempt to delimit an appropriate transformation, or employ bootstrapping. To assess the racial effects, the change of these outcomes by intervention group and race will be assessed, controlling for the baseline levels. Both the interactive (with group) and the main effects of race and group will be assessed. In addition, we will assess if the race effects are mediated by compliance. We will not control for the Type-I error rate inherent in multiple testing of multiple outcomes. Rather, for any relationship declared statistically significant, the reader will be alerted to the preliminary nature of the findings, the multiple testing issues and the requirement for replication. The results of these analyses will provide invaluable information regarding the process and functional forms and, potentially, the causal pathways of the intervention process. For example, one important analysis will enter 'level of compliance to the intervention' into the analysis, allowing for a 'per protocol' analysis of the results.

Power Estimate: The sample size of n = 84 per group is based directly on our findings in the MEASUR-UP study, which used the same diet treatments, study population, and primary outcome as in the present Aim 1. In MEASUR-UP, the SPPB score for WL-Pro changed by +2.4 units over the course of the study, while the WL-Control group experienced an increase of +0.9 units. The pooled standard deviation of these changes is 1.7. Thus, the MEASUR-UP study observed a standardized difference of 0.88 = (2.4 – 0.9)/1.7. Differences of this magnitude have been labeled as 'large' in the power analysis literature. Assuming equivalent effect sizes observed in the MEASUR-UP study, an overall sample size of 100 (evenly divided between groups), and a Type-I error rate of 0.05 (two tailed), the power of our design is greater than 99% to declare significance for the effect size observed in the pilot. At 80% power, this design is powered to detect a difference in change scores in the SPPB of 0.96, or a standardized difference of 0.57.

Analysis Plan for the supplemental protocol:
Aim 1: Feasibility-Recruitment capability: Proportion of participants recruited will be calculated as the number of participants deemed potentially eligible and contacted for enrollment divided by the total number of

participants enrolled. Feasibility of recruitment hypothesis: ≥35% of participants approached for recruitment will agree to participate

Feasibility-Retention: Retention proportion retention will be computed by dividing the number of retained subjects at the end of the intervention by the total number randomized into the study.

Retention hypothesis: ≥80% of participants will remain in the study for the duration of the trial

We will calculate the rate of retention and its respective confidence intervals overall and by group. While non-powerful, we will assess if these rates differ by chi-square test of proportion and Poisson regression respectively. In a series of sensitivity tests, we will assess if retention overall was impacted by demographic and high risk variables.

Feasibility-Intervention Tools: Records of intervention tools and time spent to administer them will be used for post-study analysis of intervention tool effectiveness.

Acceptability-Satisfaction: participant satisfaction of intervention delivery, overall experience, and outcomes will be assessed using a Likert scale and open-ended questions.

Aim 2 and 3: This design is a two-armed feasibility trial, with replicate measures at three time points: baseline, three, and six months. Since subjects are randomized to either HR-WL-Protein or HR-WL-Control, and the groups are presumed equal at baseline, we will employ mixed models, analyze under an Intent to Treat (ITT) criteria, and control for baseline and assess the impact of Time, Treatment Group and the interaction of these variables on the outcomes. Controlling for the individual baseline values for the particular outcomes, the trajectories over time and differences in those trajectories will be assessed. Following the statistical principles section from the International Conference on Harmonization, we will select covariates (e.g., age, race, number of comorbidities) for the primary models a priori, but we also will conduct auxiliary sensitivity analyses that evaluate whether potential group imbalances bias the treatment effect estimate. These analyses will be performed using conventional testing for confounding. As defined, the overall test of the intervention effect will be the joint effect of group and group*time on 2 df assessing an overall effect of group, and if this group effect is constant over time. If significant, follow-up tests will assess where group differences lie. In particular, we note that if the time by group interaction is rejected, we will test if the groups differ at the end of 6 months (a test of effect at the completion of the intervention). We will carefully examine model assumptions, including the distribution of model residuals, additively, linearity, and influential observations, and will, if necessary, re-parameterize the models or transform the outcomes accordingly.

Privacy, Confidentiality, and Information Security

Lists of Data Reviewed and/or Collected for Screening/Recruitment and Conduction of Study:

- Demographics: age, race, gender, weight, height, marital status, education, employment status, living arrangements, socioeconomic and smoking status
- Diagnosis of pre-diabetes
- Mini Cog
- Hand-grip strength
- Weight
- Height
- Physical Function – Short physical performance battery, 6-minute walk, 30 second chair stand, 8 foot up and go
- Physical activity – Actigraph and wear log
- CT-scan of the thigh

- Isokenetic knee extensor peak torque
- Three-day food record
- Protein checklist
- Nutrition Literacy Questionnaire
- Food Security Questionnaire
- Intervention Evaluation Questionnaire
- 24-hour dietary recall
- Biological Markers – routing chemistries, HgA1C, GFR, and fasting glucose
- Quality of life questionnaires – SF-36, POMS, CES-D, Perceived Stress Scale, and the Pittsburgh Sleep Questionnaire, Trial Marking Test, Frustration Discomfort Scale, SWL, Hopkins Verbal Learning Test, Symbol Digital Modalities Form, Grooved Pegboard, and Cantab.
- Body Composition – BodPod
- Waist circumference measures
- Medical History Questionnaire

The Personal Health Information that will be obtained, used, and/or shared for this study includes:

Identifier(s)	Source(s) of Health Information
☒ Names	☒ Medical history & physical exam information
☒ All geographic subdivisions smaller than a State, including street address, city, county, precinct, and zip code. Describe: Address of participants will be collected	☐ Photographs, videotapes, audiotapes, or digital or other images
☒ All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, visit or treatment dates, etc.; and all ages over 89, Describe: Dates to be collected include date of birth and date of visits.	☒ Biologic specimens (e.g., blood, tissue, urine, saliva). Describe: plasma will be collected at all times points for routine chemistries (HgA1C, GFR, and fasting glucose).
☒ Telephone numbers	☒ Progress notes
☐ Fax numbers	☒ Diagnostic / Laboratory test results
☐ Electronic mail addresses	☐ Operative reports
☒ Social Security Numbers	☒ Imaging (x-ray, CT, MRI, etc.)
☒ Medical record numbers	☐ Discharge summaries
☐ Health plan beneficiary numbers	☒ Survey / Questionnaire responses
☒ Account numbers	☐ Billing records
☐ Certificate and/or license numbers	☐ HIV testing or infection records

Identifier(s)	Source(s) of Health Information
☐ Vehicle identifiers and serial numbers, including license plate numbers	☐ Sickle cell anemia information
☒ Device identifiers and serial numbers	☒ Alcoholism or alcohol use information
☐ Web Universal Resource Locators (URLs)	☒ Drug abuse information
☐ Internet Protocol (IP) address numbers	☒ Mental health (not psychotherapy) notes
☐ Biometric identifiers, including finger & voice prints	☒ Psychological test results
☐ Full-face photographic images and any comparable images	☐ Genetic testing
☒ Any other unique identifying number, linked study ID, characteristic, or code, describe: a unique study ID will be assigned to each participant.	☒ Other, describe: Questionnaires include: Mini-Cog, SF-36, POMS, CES-D, Perceived Stress Scale, and the Pittsburgh Sleep Questionnaire, Frustration Discomfort, SWL. Three-day food records and protein checklists will be collected. Functional assessment, Short Physical Performance Battery, Isokenetic knee extensor peak torque, 6-minute walk, 30 second chair stand, 8-foot up and go. Cognitive testing: Symbol Digit Modalities; Hopkins Verbal Learning Test; Trail Making Test; CANTAB.

Several types of data will be collected over the course of the study. As described under the Request for Waiver or Alteration of Informed Consent and Waiver of HIPAA Authorization for Research, PHI to be collected during recruitment activities includes name, age, medical history, address, telephone number, social security number, date of birth, HbA1c, fasting blood glucose, and history of alcoholism or drug abuse. Other data to be collected over the course of the study (as described in the HIPAA authorization) include name; address; phone number; social security number; Physical Function; Physical activity; Three-day food record; Protein checklist; muscle quality (isokinetic knee extension peak torque and CT-scan of the thigh); hand-grip strength, body composition; quality of life and cognitive status; cognitive testing; Biological Markers including plasma for HgA1c, fasting blood glucose, and GFR, and account numbers (for Veterans who have bank accounts, payment will be issued via direct deposit, which requires a Vendorizing Coversheet that asks for account information and VA Form 10-7078 to be obtained). Additionally, a unique study ID will be assigned to each participant. Sources of health information include medical history and physical exam information, progress notes in CPRS, laboratory test results, survey responses, dietary intake including food and beverages and mental health notes. This information will be used for research purposes only.

1. Data and/or Specimen Acquisition:

Data for this study will be collected through (*check all that apply*):

☒ **Prospective data and/or specimen collection obtained from participants. Provide description of processes:** Potential participants identified will be sent an introductory letter signed by the PI that describes the study and informs them that they will be called regarding participation. In the letter, potential participants

will be given an “opt-out” number to call in order to decline participation and/or further contact regarding participation. Five business days after the mailing, Veterans who have not called the study number to decline participation will be called by a study staff member to request their participation in the research study (see telephone screen script). In the telephone contact, the study staff member will inform the Veteran that he/she was selected for recruitment because he/she is an older Veteran who is obese and has met the criteria for prediabetes on a recent screening.
Any Veteran who contacts or is contacted by study staff will be told that their participation is voluntary, and they may choose not to answer any questions that they find too sensitive. Also, Veterans will be told that their participation will not affect their care at the VA. The study staff member will explain the study in detail, including compensation. No study procedures will begin until formal, written informed consent has been obtained. Participants will come to the Duke Center for Living and will be consented for study participation. Following consent, participants will be screened for pre-diabetes (fasting blood draw). Participants who qualify as being pre-diabetic and meet other eligibility criteria will return to the Center for Living to complete the remaining assessments (function, body composition, quality of life, dietary intake, isokinetic knee extensor peak torque (Cybex)). Finally, on a third visit they will report to Durham VAMC radiology for a CT-Scan. These assessments will be completed again at the 3-month midpoint and 6-month endpoint.

☐ Retrospective data collection and/or specimens obtained from medical chart review/data access.
Describe how data will be obtained (e.g., fileman, CDW, etc.):

☐ Retrospective data collection and/or specimens obtained from an IRB-approved data and/or specimen repository. Indicate the repository source including name, VA location, and IRB number: .
Note: for data and/or specimens obtained from a VA approved data repository, a Data Use Agreement (DUA) must be executed prior to obtaining data and/or specimens. See VHA Handbook 1200.12 for further information.

2. Level of Data:

The following level(s) of data will be acquired/maintained for this study (*check all that apply*):
☒ Identified (e.g., names, addresses or other identifiers included)
☒ Coded (direct and/or all identifiers removed, but study code/ID included)
De-Identified (all HIPAA 18 and study ID/code removed):
☐ Verified Statistically
OR
Verified by Absence or Removal of HIPAA 18 and study ID
☐ Limited Data Set
☐ Other: Describe:

3. Location of Data and/or Specimens, and Data Retention Plan:

A.
Data and/or Specimen Location: All PHI data will be stored on the VA server at S:\GRECC\Grecc Research\Bales\Valor Up that is encrypted, password-protected, and only accessible to Dr. Bales and her study staff. All hard copy data, including, but not limited to, consent form, HIPAA authorization form, and survey responses will be stored in a locked file cabinet in a locked office suite at the Duke Aging Center Nutrition Laboratory, Room 00505. Data will be entered using VPN access by the VA Research team.

The study team will employ REDCap (Research Electronic Data Capture) hosted within VIREC for data entry. Key components of this activity include data entry screen programming and database testing and validation.

The database will include study default parameters and ranges for database, protocols, users, and access rights. Access and data entry to the database will be controlled by login permissions, and the database will be backed up daily, with full backups occurring weekly, and quarterly backups retained for perpetuity.

A second excel spreadsheet database will be created to electronically track participants through all components of the study including screening. This tracking will contain identifiable data, including the key that links participants to study identification numbers; other data collected in the course of the study will be kept separately from identifying information. This database will be stored on the VA server S:\GRECC\Grecc Research\Bales\Valor UP. that is encrypted, password-protected, and only accessible to Dr. Bales and her study staff.

Plasma specimens will be stored in the -80 degree freezer at the Duke Center for Living. Specimens, as outlined above, will be coded when stored.

Data will be also be placed at the VA Informatics and Computing Interface (VINCI; http://vaww.vinci.med.va.gov/vincicentral/VINCIWorkspace.aspx). The VA Informatics and Computing Infrastructure is a partnership between the VA Office of Information Technology and the Veterans' Health Administration Office of Research and Development. Researchers and operations staff can use VINCI to access data and statistical analysis tools in a virtual working environment through a certified VHA network computer using the VA Intranet or Virtual Private Network (VPN).

B. Data Retention Plan

☒ Research records will be maintained and destroyed according to the National Archives and Records Administration, Records Schedule Number: DAA-0015-2015-0004. Records destruction, when authorized, will be accomplished using the then current requirements for the secure disposal of paper and electronic records. Currently, destruction of research records (see DAA-0015-2015-0004, section 7.6 "Research Investigator Files" for materials included in research records) is scheduled for 6 years after the cut-off (the cut-off is the completion of the research project) and may be retained longer if required by other federal agencies. Records will not be destroyed without pre-notification to the facility records manager.

☐ Other data retention plan, describe:

4. **Data Access and Data Recipients:** Only members of our DVAMC research team will have access to identifiers and coded data. Our statistician, Carl Pieper will have access to the de-identified data.

   All VA research personnel who have access to VHA records are instructed, in accordance with VA policy, on the requirements of Federal privacy and information laws and regulations, VA regulations and policies, and VHA policy. All study personnel who are VA employees working within the VA system have fulfilled all required HIPAA and other VA security and privacy policy training requirements and have agreed to follow guidelines pertaining to the protection of patient data. All research staff sign VA Rules of Behavior, and all study staff are up-to-date with VHA Privacy Policy Training and the VA Office of Cyber and Information Security Awareness Training Course. The data security and privacy procedures summarized in that course include logging off or locking the computer when walking away from it; no sharing of access codes, verify codes or passwords; not allowing anyone else to use the computer under one's password; and disposing of sensitive information using VA-approved methods (e.g., shredder bins).

   Access to study data will be removed for all study personnel when they are no longer part of the research team.

5. Data and/or Specimen Transportation and/or Transmission for all data and/or specimens involved in the study:

I. ☐ Data and/or specimens will not be transported or transmitted outside of Durham VAMC environment.

II. ☐ Data and/or specimens will be transported BETWEEN sites that are under the auspices of the Durham VA Medical Center.

III. ☐ Data and/or specimens will be transmitted to other VA sites using the following method(s):

A. Data

☐ Data are de-identified and thus will be sent via unencrypted e-mail or unencrypted disk (encryption is optional).

☐ Data are coded or contain identifiers and thus will be sent

Other, describe:

B. Specimens

☐ Specimens are de-identified and thus will be sent via standard carrier (tracking is optional).

☐ Specimens are coded or contain identifiers and thus will be sent via VA-authorized carrier with tracking.

☐ Other, describe:

IV. ☒ Data and/or specimens will be transported to non-VA/VHA sites (e.g., academic affiliates, laboratories, etc.) using the following method(s):

A. Data

☐ Data are de-identified and thus will be sent via unencrypted e-mail or unencrypted CD.

☒ Data are coded or contain identifiers and thus will be sent via FIPS 140-2 encrypted hard drive/flash drive using VA—approved carrier with tracking.

☐ Data are coded or identified and will be uploaded to sponsor website using electronic case report form (eCRF)

☒ Other, describe: Data will be stored at the Duke Aging Center Nutrition Laboratory. Data will only be transferred to the VA if the Durham Office of Research and Development deem it necessary. In this event, data will be transferred using a FIPS 140-2 encrypted hard drive/flash drive and walked over to the VA by a member of the research team

B. Specimens

☐ Specimens are de-identified and thus will be sent via standard carrier (tracking is optional) or will be hand-delivered by research study personnel. Specify method of delivery:

☒ Specimens are coded and thus will be sent via VA-approved carrier with tracking or will be hand-delivered by research study personnel. Specify method of delivery: Specimens will be analyzed through the Duke Molecular Physiology Institute. Co-Investigator, Dr. Kim Huffman, will oversee the transfer of specimens from the Duke Center for Living to the Duke Molecular Physiology Institute. Specimens will be hand-delivered by members of the research team.

☒ Other, describe: Specimens will be stored at the Duke Center for Living in a secured building that requires badge access to enter.

In accordance with the HIPAA and the Privacy Act, for any coded or identifiable data or specimens released from the Durham VAMC (with the exception of Limited Data Sets), an Accounting of Disclosure (AOD) will be maintained (e.g., in a database or spreadsheet) that includes the participant's name, date of the disclosure, description of the nature of the Individually Identifiable Information (III) disclosed, purpose of each disclosure, and the name and address of the person/agency to whom the disclosure was made.

C. ☒ Local DVAMC memorandum "Authorization to Use, Process, Store, or Transmit VA Sensitive Information Outside VA Owned or Managed Facilities" has been pre-filled out for each study team member who may transport the data and/or specimens off-site. This (these) forms are included with the IRB materials.

D. ☒ Containers (e.g., briefcase, bin) are labeled with the following notice (label placed on the outside of container) in accordance with VHA Directive 6609:

NOTICE!!!

Access to these records is limited to: AUTHORIZED PERSONS ONLY.

Information may not be disclosed from this file unless permitted by all applicable legal authorities, which may include the Privacy Act; 38 U.S.C. §§ 5701, 5705, 7332; the Health Insurance Portability and Accountability Act; and regulations implementing those provisions, at 38 C.F.R. §§ 1.460 – 1.599 and 45 C.F.R. Parts 160 and 164. Anyone who discloses information in violation of the above provisions may subject to civil and criminal penalties.

V. ☐ We will communicate with veterans enrolled as participants in this research study through Myhealthe.va.gov .

6. Risk Mitigation Strategies:

At each level of data management and for each subject contact, strict adherence to VHA policy will be observed regarding HIPAA, IRB, and other VHA patient quality controls. A unique code number will be assigned to each participant. The key to the code will be kept in a password-protected file on a secured network S:\GRECC\Grecc Research\Bales\Valor Up We will employ REDCap (Research Electronic Data Capture) hosted within VIRECfor data entry. Key components of this activity include data entry screen programming and database testing and validation. The database will include study default parameters and ranges for database, protocols, users, and access rights. Access and data entry to the database will be controlled by login permissions, and the database will be backed up daily, with full backups occurring weekly, and quarterly backups retained for perpetuity.

As previously described, a second excel spreadsheet database will be created to electronically track participants through all components of the study including screening. This tracking will contain identifiable data, including the key that links participants to study identification numbers; other data collected in the course of the study will be kept separately from identifying information. This database will be stored on a Duke secured computer server S:\GRECC\Grecc Research\Bales\Valor Up that is encrypted, password-protected, and only accessible to Dr. Bales and her study staff.

These procedures will protect the identity of all patients and providers as pertains to any reports generated from this study. The individuals responsible for data safety and monitoring will be Drs. Bales, Starr, McDonald, Huffman, and Pieper.

☐ Data are fully de-identified (stripped of HIPAA 18 and study ID/code) before being shared outside of Durham VAMC.
☐ Specimens are fully de-identified (stripped of HIPAA 18 and study ID/code before being shared outside of Durham VAMC.
☒ Direct identifiers will be maintained separately from data and or specimens by using a code to "identify" subjects. In a separate database (i.e., a "linking" or "cross-walk" database) this code will be linked to identifying subject information.
☐ Other, specify:

7. Suspected Loss of VA Information:

Should any incident such as theft or loss of data, unauthorized access of sensitive data or non-compliance with security controls occur it will be immediately reported according to VA policy. All incidents regarding information security/privacy incidents will be reported to the ISO and PO within 1 hour of acknowledgement of issue and done so using the VHADUR Research Events Report e-mail group (VHADURResearchEventReport@va.gov).

8. Reporting of Results:

☒ Reporting of results, such as in scientific papers and presentations, will never identify individual subjects. Data will be presented in aggregate and individual-level data will not be published.
☐ Other results reporting plan, describe:

9. Future Use of Data:

☐ Data will be retained for future use. This is described elsewhere in the protocol and is noted in the HIPAA authorization.
- ☐ Future Use of data is optional (i.e., not required by the research subject).
- ☐ Future Use of data is required for participation in the study.

☒ No future use of data is currently planned.

10. Use of Mail Merge Technology

☒ Mail merge programs will be used to generate letters and/or address labels for mailings to potential or already enrolled research subjects. The study team is aware that to reduce risk of mail merge related privacy incidents, use of mail merge programs requires a 25% accuracy check to verify that (potential) research subject name and mailing address are properly "matched". If discrepancies are found, a 100% accuracy check is required before letters may be mailed.

11. Use of Non-Standard Software

☒ I do NOT intend to use any new specialized software (i.e. Software that's not already approved OR installed) in this study.

☐ I intend to use specialized software that has not already been installed and it has been approved for use by the VA Technical Reference Model (TRM) Group.
(Note: All new software must be approved by TRM before it can be installed on VA systems.)

☐ I intend to use previously installed software on my VA computer.

12. Use of Cloud Computing Services

☒ Cloud computing services will NOT be used in this study.

☐ Cloud computing services WILL be used in this study as described below and have been approved nationally by the VA Chief Information Officer (CIO). (Note: ONLY cloud computing services that have been approved nationally may be used.)

References

1. Affairs USDoV. Close to 25 percent of VA patietns have diabetes. http://www.va.gov/health/NewsFeatures/20111115a.asp. Published 2015. Accessed June 1, 2017.
2. Breland JY, Phibbs CS, Hoggatt KJ, et al. The Obesity Epidemic in the Veterans Health Administration: Prevalence Among Key Populations of Women and Men Veterans. *Journal of general internal medicine.* 2017;32(Suppl 1):11-17.
3. Alley DE, Ferrucci L, Barbagallo M, Studenski SA, Harris TB. A research agenda: the changing relationship between body weight and health in aging. *J Gerontol A Biol Sci Med Sci.* 2008;63(11):1257-1259.
4. Short KR, Vittone JL, Bigelow ML, Proctor DN, Nair KS. Age and aerobic exercise training effects on whole body and muscle protein metabolism. *American journal of physiology Endocrinology and metabolism.* 2004;286(1):E92-101.
5. Melton LJ, 3rd, Khosla S, Crowson CS, O'Connor MK, O'Fallon WM, Riggs BL. Epidemiology of sarcopenia. *J Am Geriatr Soc.* 2000;48(6):625-630.
6. Costamagna D, Costelli P, Sampaolesi M, Penna F. Role of Inflammation in Muscle Homeostasis and Myogenesis. *Mediators Inflamm.* 2015;2015:805172.
7. Porter Starr KN, McDonald SR, Bales CW. Obesity and Physical Frailty in Older Adults: A Scoping Review of Lifestyle Intervention Trials. *J Am Med Dir Assoc.* 2014.
8. Cheng FW, Gao X, Bao L, et al. Obesity as a risk factor for developing functional limitation among older adults: A conditional inference tree analysis. *Obesity (Silver Spring).* 2017.
9. Menke A, Rust KF, Fradkin J, Cheng YJ, Cowie CC. Associations between trends in race/ethnicity, aging, and body mass index with diabetes prevalence in the United States: a series of cross-sectional studies. *Ann Intern Med.* 2014;161(5):328-335.
10. Cannon CP, Kumar A. Treatment of overweight and obesity: lifestyle, pharmacologic, and surgical options. *Clin Cornerstone.* 2009;9(4):55-68; discussion 69-71.
11. Ross R. The challenge of obesity treatment: avoiding weight regain. *CMAJ.* 2009;180(10):997-998.
12. Tzankoff SP, Norris AH. Effect of muscle mass decrease on age-related BMR changes. *Journal of applied physiology: respiratory, environmental and exercise physiology.* 1977;43(6):1001-1006.
13. Elia M, Ritz P, Stubbs RJ. Total energy expenditure in the elderly. *Eur J Clin Nutr.* 2000;54 Suppl 3:S92-103.
14. Villareal DT, Apovian CM, Kushner RF, Klein S. Obesity in older adults: technical review and position statement of the American Society for Nutrition and NAASO, The Obesity Society. *Am J Clin Nutr.* 2005;82(5):923-934.
15. Weinheimer EM, Sands LP, Campbell WW. A Systematic Review of the Separate and Combined Effects of Energy Restriction and Exercise on Fat-free Mass in Middle-aged and Older Adults: Implications for Sarcopenic Obesity. *Nutr Rev.* 2010;68(7):375-388.
16. Kalyani RR, Metter EJ, Ramachandran R, Chia CW, Saudek CD, Ferrucci L. Glucose and insulin measurements from the oral glucose tolerance test and relationship to muscle mass. *J Gerontol A Biol Sci Med Sci.* 2012;67(1):74-81.

17. Houston DK, Nicklas BJ, Ding J, et al. Dietary protein intake is associated with lean mass change in older, community-dwelling adults: the Health, Aging, and Body Composition (Health ABC) Study. *Am J Clin Nutr.* 2008;87(1):150-155.
18. Josse AR, Atkinson SA, Tarnopolsky MA, Phillips SM. Increased Consumption of Dairy Foods and Protein during Diet- and Exercise-Induced Weight Loss Promotes Fat Mass Loss and Lean Mass Gain in Overweight and Obese Premenopausal Women. *J Nutr.* 2011;141(9):1626-1634. Epub 2011 Jul 1620.
19. Sahni S, Mangano KM, Hannan MT, Kiel DP, McLean RR. Higher Protein Intake Is Associated with Higher Lean Mass and Quadriceps Muscle Strength in Adult Men and Women. *J Nutr.* 2015;145(7):1569-1575.
20. McLean RR, Mangano KM, Hannan MT, Kiel DP, Sahni S. Dietary Protein Intake Is Protective Against Loss of Grip Strength Among Older Adults in the Framingham Offspring Cohort. *J Gerontol A Biol Sci Med Sci.* 2016;71(3):356-361.
21. Bradlee ML, Mustafa J, Singer MR, Moore LL. High-Protein Foods and Physical Activity Protect Against Age-Related Muscle Loss and Functional Decline. *J Gerontol A Biol Sci Med Sci.* 2017.
22. Symons TB, Schutzler SE, Cocke TL, Chinkes DL, Wolfe RR, Paddon-Jones D. Aging does not impair the anabolic response to a protein-rich meal. *Am J Clin Nutr.* 2007;86(2):451-456.
23. Pennings B, Groen B, de Lange A, et al. Amino acid absorption and subsequent muscle protein accretion following graded intakes of whey protein in elderly men. *Am J Physiol Endocrinol Metab.* 2012;302(8):E992-999.
24. Symons TB, Sheffield-Moore M, Wolfe RR, Paddon-Jones D. A moderate serving of high-quality protein maximally stimulates skeletal muscle protein synthesis in young and elderly subjects. *J Am Diet Assoc.* 2009;109(9):1582-1586.
25. Casperson SL, Sheffield-Moore M, Hewlings SJ, Paddon-Jones D. Leucine supplementation chronically improves muscle protein synthesis in older adults consuming the RDA for protein. *Clinical Nutrition.* 2012;31(4):512-519.
26. Koopman R, Verdijk L, Manders RJF, et al. Co-ingestion of protein and leucine stimulates muscle protein synthesis rates to the same extent in young and elderly lean men. *American Journal of Clinical Nutrition.* 2006;84(3):623-632.
27. Volpi E, Kobayashi H, Sheffield-Moore M, Mittendorfer B, Wolfe RR. Essential amino acids are primarily responsible for the amino acid stimulation of muscle protein anabolism in healthy elderly adults. *Am J Clin Nutr.* 2003;78(2):250-258.
28. Dillon EL, Sheffield-Moore M, Paddon-Jones D, et al. Amino Acid Supplementation Increases Lean Body Mass, Basal Muscle Protein Synthesis, and Insulin-like Growth Factor-I Expression in Older Women. *J Clin Endocrinol Metab.* 2009;94(5):1630-1637.
29. Phillips SM, Tang JE, Moore DR. The role of milk- and soy-based protein in support of muscle protein synthesis and muscle protein accretion in young and elderly persons. *J Am Coll Nutr.* 2009;28(4):343-354.
30. McGregor RA, Cameron-Smith D, Poppitt SD. It is not just muscle mass: a review of muscle quality, composition and metabolism during ageing as determinants of muscle function and mobility in later life. *Longevity & healthspan.* 2014;3(1):9.
31. Sakuma K, Yamaguchi A. Molecular mechanisms in aging and current strategies to counteract sarcopenia. *Curr Aging Sci.* 2010;3(2):90-101.
32. Beasley JM, LaCroix AZ, Neuhouser ML, et al. Protein intake and incident frailty in the Women's Health Initiative observational study. *J Am Geriatr Soc.* 2010;58(6):1063-1071. Epub 2010 May 1067.
33. Porter Starr KN, Pierper CR, Orenduff M, et al. Improved function with enhanced protein intake per meal: A pilot study of weight reduction in frail, obese older adults. *J Gerontol A Biol Sci Med Sci.* 2015;In Press.

34. Smith GI, Yoshino J, Kelly SC, et al. High-Protein Intake during Weight Loss Therapy Eliminates the Weight-Loss-Induced Improvement in Insulin Action in Obese Postmenopausal Women. *Cell Rep.* 2016;17(3):849-861.
35. Kitabchi AE, McDaniel KA, Wan JY, et al. Effects of High-Protein Versus High-Carbohydrate Diets on Markers of β-Cell Function, Oxidative Stress, Lipid Peroxidation, Proinflammatory Cytokines, and Adipokines in Obese, Premenopausal Women Without Diabetes: A randomized controlled trial. *Diabetes Care.* 2013;36(7):1919-1925.
36. Stentz FB, Brewer A, Wan J, et al. Remission of pre-diabetes to normal glucose tolerance in obese adults with high protein versus high carbohydrate diet: randomized control trial. *BMJ Open Diabetes Research & Care.* 2016;4(1).
37. Richard C, Cristall L, Fleming E, et al. Impact of Egg Consumption on Cardiovascular Risk Factors in Individuals with Type 2 Diabetes and at Risk for Developing Diabetes: A Systematic Review of Randomized Nutritional Intervention Studies. *Canadian journal of diabetes.* 2017.
38. Tabak AG, Herder C, Rathmann W, Brunner EJ, Kivimaki M. Prediabetes: a high-risk state for diabetes development. *Lancet.* 2012;379(9833):2279-2290.
39. Locher JL, Goldsby TU, Goss AM, Kilgore ML, Gower B, Ard JD. Calorie restriction in overweight older adults: Do benefits exceed potential risks? *Exp Gerontol.* 2016;86:4-13.
40. Griffith DM, Metzl JM, Gunter K. Considering intersections of race and gender in interventions that address US men's health disparities. *Public health.* 2011;125(7):417-423.
41. Newton RL, Jr., Griffith DM, Kearney WB, Bennett GG. A systematic review of weight loss, physical activity and dietary interventions involving African American men. *Obes Rev.* 2014;15 Suppl 4:93-106.
42. Chao SY, Zarzabal LA, Walker SM, et al. Estimating diabetes prevalence in the Military Health System population from 2006 to 2010. *Military medicine.* 2013;178(9):986-993.
43. Centers for Disease Control and Prevention. The State of Aging and Health in America 2013. Atlanta, GA: Centers for Disease Control and Prevention, US Dept of Health and Human Services; 2013.
44. Whitt-Glover MC, Kumanyika SK. Systematic review of interventions to increase physical activity and physical fitness in African-Americans. *Am J Health Promot.* 2009;23(6):S33-56.
45. DeLany JP, Jakicic JM, Lowery JB, Hames KC, Kelley DE, Goodpaster BH. African American women exhibit similar adherence to intervention but lose less weight due to lower energy requirements. *Int J Obes.* 2014;38(9):1147-1152.
46. Voils CI, Grubber JM, McVay MA, et al. Recruitment and Retention for a Weight Loss Maintenance Trial Involving Weight Loss Prior to Randomization. *Obes Sci Pract.* 2016;2(4):355-365.
47. Stumvoll M, Meyer C, Mitrakou A, Gerich JE. Important role of the kidney in human carbohydrate metabolism. *Medical hypotheses.* 1999;52(5):363-366.
48. Stumvoll M, Meyer C, Mitrakou A, Nadkarni V, Gerich JE. Renal glucose production and utilization: new aspects in humans. *Diabetologia.* 1997;40(7):749-757.
49. Morris C, O'Grada C, Ryan M, et al. Identification of differential responses to an oral glucose tolerance test in healthy adults. *PloS one.* 2013;8(8):e72890.
50. McDonald SR, Porter Starr KN, Mauceri L, et al. Meal-based enhancement of protein quality and quantity during weight loss in obese older adults with mobility limitations: Rationale and design for the MEASUR-UP trial. *Contemp Clin Trials.* 2015;40:112-123.
51. Human energy requirements: report of a joint FAO/ WHO/UNU Expert Consultation. *Food and nutrition bulletin.* 2005;26(1):166.
52. Miller GD. Improved nutrient intake in older obese adults undergoing a structured diet and exercise intentional weight loss program. *J Nutr Health Aging.* 2010;14(6):461-466.53. Nicholson NR. A review of social isolation: an important but underassessed condition in older adults. *J Prim Prev*. 2012;33(2-3):137-152.

54. Berg-Weger M, Morley JE. Editorial: Loneliness and Social Isolation in Older Adults during the COVID-19 Pandemic: Implications for Gerontological Social Work. *J Nutr Health Aging*. 2020;24(5):456-458.
55. Boreskie KF, Hay JL, Duhamel TA. Preventing Frailty Progression during the COVID-19 Pandemic. *J Frailty Aging*. 2020;9(3):130-131.
56. Porter Starr KN, Miller MG, Mitchell N, and Bales CW. Nutrition, function, and quality of life in older adults socially isolated due to the COVID-19 pandemic: A focus on telehealth interventions. In: *Integrated Science: Multidisciplinary and Interdisciplinary in Health.* Vol. III. Springer. In press.
57. Jiménez-Pavón D, Carbonell-Baeza A, Lavie CJ. Physical exercise as therapy to fight against the mental and physical consequences of COVID-19 quarantine: Special focus in older people. *Prog Cardiovasc Dis*. 2020;S0033-0620(20)30063-3.
58. Belanger MJ, Hill MA, Angelidi AM, et al. Covid-19 and disparities in nutrition and obesity. *N Engl J Med.* 2020 https://doi.org/ 10.1056/NEJMp2021264
59. Bock D. *Multivariate Statistical Methods in Behavioral Research.* New York City: McGraw-Hill; 1973.
60. Anderson T. *An Introduction to Mutlivariate Statistical Analysis.* New York City: Wiley; 1984.
61. Efron B. *The Jackknife, the Bootstrap, and Other Resampling Plans.* Philadelphia, Pa: Society for Industrial and Applied Mathematics; 1982.