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# Incorporating Nutrition, Vests, Education, and Strength Training (INVEST) in Bone Health: Trial Design and Methods

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## Abstract

**Background:** Achievement of 5-10% weight loss (WL) among older adults living with obesity considerably improves prognosis of health-related outcomes; however, concomitant declines in bone mineral density (BMD) limit overall benefit by increasing fracture risk. Declines in mechanical loading contribute to WL-associated BMD loss, with pilot data signaling the addition of external weight replacement (via weighted vest use) during intentional WL mitigates bone loss at weight bearing sites to a similar degree as resistance exercise training (RT). Definitive data in support of weighted vest use as a potential strategy to mitigate WL-associated bone loss in this population are needed.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**Methods:** In the Incorporating Nutrition, Vests, Education, and Strength Training (INVEST) in Bone Health trial (NCT04076618), 192 older adults (60-85 years) who are overweight (BMI≥27 kg/m$^2$) with at least one obesity-related risk factor or obese (BMI=30-40 kg/m$^2$) will be randomly assigned to participate in one of three 12-month intervention groups: WL alone, WL + weighted vest use (WL+VEST), or WL+RT. The primary aim is to determine the effects of WL+VEST compared to WL alone and WL+RT on indicators of bone health and subsequent fracture risk.

**Discussion:** Determining effective, translatable strategies that minimize bone loss during intentional WL among older adults holds public health potential. The INVEST in Bone Health trial offers an innovative approach for increasing mechanical stress during intentional WL in the absence of RT. If successful, findings from this study will provide evidence in support of a scalable solution to minimize bone loss during intentional WL among older adults with obesity.

### Keywords

Bone mineral density; obesity; older adults; weight loss

## 1. Introduction

Over the next 10 years, half of Americans aged ≥65 years are projected to be classified as obese.[1] Older adults living with obesity are more likely to experience comorbidities, disability, and a reduced quality of life compared to their normal weight counterparts.[2] Intentional weight loss (WL) improves several obesity-related comorbidities; however, a significant concern associated with prescribing WL in this population is the concomitant loss of bone. Randomized controlled trial data show that 10% WL is accompanied by approximately 2% bone loss.[3] Intentional WL leads to decreased bone mineral density (BMD), which may compound age-expected BMD declines, thereby increasing an individual's fracture risk.[4–6] Importantly, fractures in older adults are often the precursor of disability, loss of independence, reduced quality of life, and mortality.[7–10] These observations underscore the pressing need to identify WL interventions capable of reducing excess adiposity while preserving BMD in this population.

Our group recently showed that resistance training (RT) provides an effective stimulus for minimizing WL-associated bone and muscle loss (while augmenting fat mass loss) compared to WL alone or WL plus aerobic training.[11,12] However, RT was not able to fully prevent WL-induced bone and muscle loss, and its effectiveness was related to exercise compliance. Exercise compliance in older adults is a relevant concern since they are less likely to achieve recommended guidelines to preserve bone health during WL.[13,14] Additionally, needing a fitness center membership, being familiarized with RT, and having proper supervision, limits the scalability of RT. Thus, identification of alternative strategies capable of providing mechanical stress in the absence of traditional exercise are warranted and hold significant public health promise.

Weighted vests provide a feasible and practical option for maintaining an individual's mechanical load during intentional WL by allowing an individual to replace lost weight externally. Previous studies demonstrated that wearing weighted vests during exercise increases dual energy x-ray absorptiometry (DXA) acquired areal BMD (aBMD) and bone

turnover, while maintaining lean body mass and muscle strength, among weight stable older adults.[15–21] We recently demonstrated that this approach is feasible and efficacious in reducing WL-associated aBMD loss by increasing bone formation, and may influence muscular power.[22,23] However, direct comparison of the effects of weighted vest use during WL on bone health outcomes has yet to be compared with RT.

The primary purpose of the Incorporating Nutrition, Vests, Education, and Strength Training (INVEST) in Bone Health trial is to compare the effects of WL alone with WL plus weighted vest (WL+VEST) or WL+RT on bone density and fracture risk indicators. Our primary aim is to determine the effects of WL+VEST compared to WL alone and WL+RT on 12-month change in total hip volumetric BMD (vBMD), which is sensitive to age-and treatment-related changes, yet less susceptible to obesity and WL-induced measurement error than DXA-acquired aBMD.[24–26] We expect that, despite similar WL (~10%), participants in the WL+VEST will display attenuated losses of total hip trabecular vBMD versus WL alone and that loss in total hip trabecular vBMD will be no greater in WL+VEST compared to WL+RT.

## 2. Methods

### 2.1.1 Overview

The INVEST in Bone Health trial is designed to compare the effects of WL, WL+VEST, and WL+RT on indicators of bone health and subsequent fracture risk in older adults with obesity. The current trial is approved by the Wake Forest University Institutional Review Board (IRB No. 00058279) and is registered on clinicaltrials.gov (NCT04076618). Prior to completing any data collection, all participants will provide written informed consent and complete a HIPAA authorization form.

### 2.1.2 Participant characteristics and eligibility

The INVEST in Bone Health trial will recruit 192 relatively healthy older (60-85 years) men and women (targeting 40% men and 25% African American participants) who are either obese (body mass index [BMI]=30-40 kg/m$^2$) or overweight (BMI=27.0-30.0 kg/m$^2$) plus at least one of the following risk factors: 1) elevated waist circumference (>35 inches in women, >40 inches in men); 2) diabetes; 3) hypertension; 4) dyslipidemia; 5) or other obesity-related comorbidities, to take part in a three-group randomized 12-month WL intervention. Specific participant inclusion and exclusion criteria are displayed in Table 1 and were selected to identify individuals most likely to benefit from the intervention and to protect those who may be at risk for experiencing adverse events while participating in the study.

### 2.1.3 Participant recruitment and screening

Participants will be recruited via written advertisements (e.g., newspapers and flyers) in addition to targeted mailings (e.g., email and postal notecards). The screening process includes an initial phone screen followed by three in-clinic screening visits (SV; see assessment timeline in Table 2). Those responding to recruitment materials will be contacted via phone to undergo a series of initial screening questions to determine participant

eligibility, potential interest for being enrolled in the intervention, and if eligible, will schedule the first of three in-clinic screening visits (SV1). During SV1, following an overnight fast (≥10 hr) participants will be asked to provide information regarding their background, demographics, medical history, and medications, and then undergo a series of medical assessments. The medical assessments include blood pressure and pulse recordings, height and weight measures to determine BMI, the Center for Epidemiologic Studies Depression Scale (CES-D),[27] Montreal Cognitive Assessment (MoCA),[28] and a blood draw (blood cell count and metabolic panel). Participants that remain eligible following SV1 will then complete SV2 where physical performance assessments will be performed (see below), as well as a series of DXA scans to screen for osteoporosis. The last of the three SVs (SV3) will also follow an overnight fast (≥10hr) and the participant will be asked to provide a urine sample and blood draw, complete a resting metabolic rate test, lower extremity strength tests, quantitative computed tomography scans of the hip and spine and complete fatigue and pain questionnaires.

#### 2.1.4 Randomization

Those meeting the eligibility criteria will be randomized via a web-based randomization system, stratified by sex using permuted blocks with random block sizes. Participants will be assigned to one of the three study interventions: 1) WL alone; 2) WL + weighted vest intervention (WL+VEST); or 3) WL + structured resistance training (WL+RT). A brief description of each intervention group is displayed in Table 3.

## 2.2 Study Interventions

### 2.2.1 Familiarization with study interventions

During SV1, participants will perform a brief set of movement tasks (e.g., leg extension, raise hands above head) to ensure they are capable of performing the exercises prescribed in the WL+RT group. If the participant can properly execute each movement, they will be asked to complete a three day dietary familiarization where they will be provided the OPTAVIA® Optimal Weight 4 & 2 & 1 Plan® (Medifast, Inc., Baltimore, MD) guide along with sample meal plans, dietary intake trackers, a sampling of meal replacement products, and product satisfaction forms. Participants will also be asked to follow the OPTAVIA® Optimal Weight 4 & 2 & 1 Plan® dietary program for a three-day period. We have used this dietary prescription previously, demonstrating feasibility of use in our population as well as ensuring similar nutrition (e.g., protein, calcium, and vitamin D) across all treatment groups.[22,29,30] The participants are requested to complete this dietary familiarization over the week following SV1 to determine their willingness to adhere to the diet plan. Additionally, participants will discuss the forms (e.g., intake trackers and satisfaction) when they return for SV2. At the completion of SV2, participants will be provided an unloaded vest and be asked to wear it for 8 hours a day, during their most active time, for a three-day period. When returning for SV3, participants will report on their willingness to wear the vest for the required time (8hr/day) over 12 months if randomized to that intervention group.

### 2.2.2 Weight loss intervention (WL, provided to all groups)

Each participant enrolled in the INVEST in Bone Health study will undergo a nutritionally complete, hypocaloric WL program designed to result in ~10% body weight loss over the 12-month intervention. Body weight will be measured and recorded at all group sessions to provide additional feedback and to increase motivation, and the official study weights will occur at baseline, six and 12 months. If the study registered dietitian (RD) notices that a participant is struggling with the WL prescription, additional one on one counseling sessions will be held to improve compliance. Additionally, if a participant is experiencing WL too quickly (>0.9 kg per week), the RD may adjust the participant's caloric intake to decrease the rate of WL.

The WL intervention consists of a partial meal replacement (MR) program and group education sessions led by the study RD. These classes are based in state-of-the-art methods for promoting WL grounded in the group dynamics literature, social cognitive theory, and strategies that optimize self-regulation.[31–33] All participants will be asked to follow the OPTAVIA® Optimal Weight 4 & 2 & 1 Plan®, a nutritionally complete, reduced calorie (1100-1300 calories per day) WL meal plan. The meal plan consists of consuming four MRs, two self-prepared "lean and green" meals, and one healthy snack per day. Each MR is about 90-110 calories, 10-15g protein, is fortified with at least 20% of the daily value for 24 vitamins and minerals (including calcium and vitamin D), and contains GanadenBC30 probiotic cultures. For the twice daily self-prepared "lean and green" meals and one healthy snack per day, participants will be responsible for purchasing and preparing the ingredients on their own or, on occasion, can choose to use one of OPTAVIA's alternative pre-packaged options (i.e. Flavors of Home® for the "lean and green" meal or an OPTAVIA snack for the healthy snack). Each "lean and green" meal will consist of 5-7 oz. lean protein, three servings of non-starchy vegetables and up to two servings of healthy fat. The healthy snack will consist of a self-selected serving of fruit, dairy, or grain/starch. Participants will be guided by the study RD on their food purchasing and preparation and will be encouraged to consume only what is approved from the menu.

Once a participant has met or exceeded the intervention goal of 10% total WL at three consecutive group weigh-ins, they will be provided the option to transition to the Lean & Green Life™ maintenance plan. This plan provides a calorie prescription based upon an individual's total energy expenditure and monitoring of body weight. Participants will gradually increase their daily calories and decrease the number of MRs consumed through a transitional period. At the end of this transitional period, participants will be recommended to consume three OPTAVIA MRs, two "lean and green" meals, and meet the remainder of their remaining caloric needs with "Healthy 100's" options (i.e. whole food and beverage options derived from the Diabetes Exchange List that contain approximately 100 calories).

In addition to receiving dietary counseling, all participants will be asked to attend behavioral counseling group sessions led by the RD. These group sessions will be held weekly for the first six months and transition to bi-weekly sessions for the last six months of the intervention. This component of the intervention was designed to provide guidance towards making healthier food choices while teaching effective long-term behavioral habits to promote WL and prevent weight regain.[34] The sessions will emphasize healthy strategies for

self-monitoring diet and weight and achieving the recommended 150 minutes of aerobic exercise per week.[35,36] Participants will be encouraged to achieve the 150 minutes per week and can do so in an individualized manner. To ensure dietary adherence, participants will be requested to track their food and beverage intake daily for the first three months and will transition to less frequent reporting as the study continues. Intake reports will be assessed by the study RD and additional feedback and encouragement will be provided if necessary. At six and 12 months participants will be asked to complete program evaluation to provide feedback on the WL program (e.g., product satisfaction, potential future usage, and product preferences).

#### 2.2.3 Weight loss plus weighted vest intervention (WL + VEST)

In addition to the WL component described above, participants in the WL+VEST group will receive a weighted vest to wear for the duration of the 12-month intervention (HyperWear®, Austin, TX, Figure 1). The vest will be appropriately sized for each participant, will fit comfortably over or under clothing, will not interfere with upper body movement, and allow for full chest expansion without restricting an individual's breathing. Unloaded vests weigh approximately two pounds and can be increased in $1/8^{th}$ pound increments (56.7 grams) by adding weighted blocks into the vest pockets. Participants will be asked to wear the vest on a daily basis, progressing to a goal of eight hours per day during the most active part of their day. Initially, participants will receive the vest unloaded but will be provided additional weights (up to a maximum weight of 10% of their starting body weight) to match each participant's rate of WL based on weekly (first six months) and biweekly (final six months) body weight assessments. The vest design contains a quadrant (front and back with left and right sides) loading system allowing for the added weights to be distributed in a balanced manner. To monitor vest wear time, intervention staff will periodically embed a small accelerometer into one of the vest pockets during the group sessions, and participants will also keep a daily log to record the time worn. Intervention staff will monitor and discuss the accelerometer output and daily logs with participants at each group session and intervene when necessary to enhance compliance.

#### 2.2.4 Weight loss plus resistance exercise training (WL+RT)

In addition to the WL intervention mentioned above, the third group will complete a structured resistance training intervention designed to induce whole-body musculoskeletal adaptations. Exercise sessions will include the following exercises: leg press, knee extension and flexion, chest press, seated row, overhead press, triceps extension, and bicep curl and will be completed on exercise machines (Nautilus Inc., Vancouver, WA). The resistance exercise sessions will take place on three non-consecutive days per week for the duration of the 12-month intervention and will be supervised by trained intervention staff. The training prescriptions will be designed based off each individual's one-repetition maximum (1RM), designated as the maximum amount of weight lifted for each exercise through a complete range of motion in a controlled manner. Resistance exercise sessions will progress in an individualized manner to minimize soreness and allow participants to become familiar with each exercise. The overall training goal is for each participant to complete three sets of 10-12 repetitions at 70-75% 1RM for each exercise. Following each set, participants will rest for approximately one minute. When a participant is able to complete ≥12 repetitions for

two of the three sets at two consecutive resistance exercise sessions, the resistance for that exercise will be increased. Prior to each resistance exercise session, participants will complete a brief warm-up (e.g., 5-10 minutes walking or cycling) and complete each exercise session with a cool-down period consisting of light stretching.

## 2.3 Study assessments timeline

Study assessments will be collected at baseline (SV1, SV1A, SV2, SV3); following the six-month intensive WL phase, between weeks 22-26 (FV1, FV2); and after the six-month reduced contact phase, between weeks 50-54 (FV3, FV4). The assessments include a series of questionnaires, physical exams and physical performance tasks, radiology and imaging tests, and phlebotomy.

## 2.4 Primary outcome measure

The INVEST in Bone Health trial is powered to detect group differences in our primary outcome variable of 12-month change in total hip trabecular vBMD measured from quantitative computed tomography (QCT) scans at baseline, six, and 12 months with the primary contrast looking at change over 12 months. QCT scans collected at the six-month timepoint allow for further examination of bone outcomes following the intensive WL phase.

### 2.4.1 Quantitative computed tomography (QCT) scanning protocol

A helical QCT scan including the femurs and lumbar spine will be performed at baseline, six, and 12 months via a 64-slice scanner (PET/CT GE Discovery MI). The scan will cover from the top of L1 through three cm below the mid-shaft of both femurs. Each scan will be acquired with a standard field of view of 50 cm and a tube voltage of 120 kV, with a standard reconstruction and secondary reconstruction using a bone algorithm. The Mindways Model 3 solid bone mineral calibration phantom will be imaged in every scan and quality assurance procedures of the CT system will be performed regularly according to manufacturer guidelines.

### 2.4.2 Volumetric BMD (vBMD) acquisition and assessment

Volumetric BMD (vBMD) of the total hip, femoral neck, and lumbar spine will be obtained via QCT Pro™ software (Mindways, Austin, TX). The software automatically segments the proximal femur to provide total hip trabecular, cortical, and integral vBMD. Additionally, the proximal femur is also divided into compartments to measure trabecular, cortical, and integral vBMD of the femoral neck. Elliptical regions of interest are automatically placed within a mid-vertebral slice at each vertebral level to obtain lumbar spine trabecular vBMD. The CT Hounsfield units (HU) are calibrated using the bone mineral phantom to derive aqueous potassium phosphate density measures of vBMD in mg/cm$^3$. Elasticity-density relationships will be used to derive subject-specific material properties from vBMD measurements for inclusion in finite element models.[37–39]

## 2.5 Secondary outcome measures

### 2.5.1 Cortical thickness acquisition and assessment

Variable cortical thickness across the surface of the proximal femur and spine will be obtained using validated algorithms that accurately measure thicknesses as small as 0.3 mm from clinical CT scans (Stradview, Cambridge University, UK).[40–42] A mathematical model constrained by a global cortical density and out-of-plane blur is fit to HU intensities measures from a line normal to the cortical surface that passes through the soft tissue, cortex, and trabecula. Point clouds of the inner and outer cortex surfaces are output, as well as cortical thickness measurements (~14,000/femur; ~3,000/vertebrae). A mapping approach will be applied to assign subject-specific cortical thickness to each node of the cortical shell elements in the finite element (FE) models as previously performed.[40]

### 2.5.2 Finite element (FE) model derived bone strength

Subject-specific FE models of the proximal femur and lumbar spine will be developed using mesh morphing.[43–45] Thin-plate spline radial basis function interpolation and a relaxation algorithm will be used to morph an existing FE model to a subject-specific geometry. Atlases will be obtained from existing human body models such as the Global Human Body Models Consortium (GHBMC) or the Total Human Model for Safety.[43–47] Homologous landmarks from analogous locations on the atlas and subject-specific geometries will be used to derive an interpolation function and coefficients to morph the atlas FE model nodal coordinates. Homologous landmarks are collected using image segmentation and registration to derive atlas and subject-specific point clouds.[48] The subject-specific FE models will incorporate vBMD-derived material properties and variable cortical thicknesses. Bone strength will be estimated through simulation of the following experimental tests: single-limb stance, sideways fall, and a quasi-static uniaxial vertebral compression test.[46,47] The peak fracture force, or bone strength, will be defined as the peak force recorded between the impactor and femoral head or vertebral body.

### 2.5.3 Regional fat and muscle cross-sectional areas

Abdominal subcutaneous and visceral fat cross-sectional areas will be measured from a CT slice centered at the L3 level. Muscle area and intermuscular fat will be measured at the mid-thigh defined as the midpoint between the superior aspect of the greater trochanter and the inferior aspect of the lateral condyle measured on the anterior-posterior scout of the femur. Muscle and fat areas will be semi-automatically segmented from CT using Mimics software (v23, Materialise, Leuven, Belgium) with fat and muscle thresholds set at −190 to −30 HU and −29 to 150 HU, respectively. Segmentations will be manually refined as needed.

### 2.5.4 Dual energy x-ray absorptiometry (DXA) derived measures

Total body, total hip, femoral neck, lumbar spine, and distal radius areal BMD will be determined by DXA (iDXA, GE Medical Systems, Madison, WI). Coefficient of variations (CV) from repeated measurements for the hip and spine regions are both <2%. Additional DXA-acquired parameters include trabecular bone scores (TBS; %CV: 3.3), which will be obtained from the lumbar spine scans; total body fat mass (%CV: 1.3); total body lean mass

(%CV: 0.9); appendicular lean mass, measured from the whole-body scan comprising the bone free lean body mass of the upper and lower extremities; and visceral fat area, measured from the whole-body scan in a five cm wide region across the entire abdomen proximal of the iliac crest at a level approximately corresponding to L4. All scans will be performed and analyzed by trained technicians certified by the International Society of Clinical Densitometry. Daily quality control scans will be performed with the manufacturer provided calibration phantom.

### 2.5.5 $D_3$-Creatine ($D_3Cr$) dilution method for measuring muscle mass

A direct measure of muscle mass will be obtained using the $D_3$-Creatine ($D_3Cr$) dilution method described previously.[49] In brief, participants ingest a 30 mg oral dose of deuterated creatine, and three to six days later provide a fasted, morning urine sample that is not the first morning void. From the urine sample, $D_3Cr$, $D_3$-creatinine, unlabeled creatine, and unlabeled creatinine will be analyzed by liquid chromatography-mass spectrometry and quantities will be included in an algorithm used to determine total body creatine pool size, thereby permitting skeletal muscle mass estimation in accordance with an established algorithm.[50]

### 2.5.6 Physical function and muscular strength

Physical function will be assessed via: 1) the expanded Short Physical Performance Battery (SPPB),[51] consisting of five repeated chair stands, standing balance (semi- and full-tandem stands and a single leg stand for 30 seconds), a four meter walk to assess usual gait speed, and a narrow four meter walk test of balance (walking at usual pace within lines of tape spaced 20 cm apart); 2) the fast 400 meter walk test,[52] consisting of 10 laps of a 40 meter course (20 meters out and 20 meters back); 3) the timed up and go (TUG) test,[53] requiring an individual to rise from a chair, walk three meters, turn around, walk back to the chair and sit down; and 4) stair climbing time, by capturing the fastest time a participant can climb 12 steps. Muscular strength will be measured via: 1) isokinetic dynamometry (Biodex®, Shirley, NY) of the dominant knee extensors at 60 degrees per second, where the peak torque (Nm) value will be obtained; and 2) grip strength dynamometry, measured in both hands using a Jamar Hydraulic Hand Dynamometer (Performance Health, Warrenville, IL) with the mean value of two trials from the stronger hand included in analyses.

### 2.5.7 Biomarkers of bone turnover and metabolism

Blood samples will be collected on all participants at baseline, six, and 12 months in the morning via venipuncture following an overnight fast (≥10 hours). Prior to the blood draw, participants will be requested to refrain from completing physical activity for at least 24 hours before providing the sample. After centrifugation for 15 minutes at 4°C (plasma) and 10 minutes at room temperate (serum), aliquots of plasma and serum will be stored at −70°C locally until batch analyses will be completed following study completion. Per international recommendation,[54] biomarkers of bone turnover, Procollagen Type 1 N-Terminal Propeptide (P1NP) and C-Terminal Telopeptide of Type 1 Collagen (CTX), will be measured by technicians in the ELISA Core laboratory. Key regulators of bone metabolism will also be assessed using the sampling and analytic methods described above (interleukin-6, leptin,

insulin-like growth factor 1, sclerostin), or sent to a standard clinical laboratory for processing (estradiol, parathyroid hormone, vitamin D, cortisol).

## 2.6 Sample size and statistical power

The INVEST in Bone Health trial is powered using co-primary hypotheses, with a conservative Bonferroni correction implemented, resulting in a total sample size of 192 participants (64 per group) necessary to achieve optimal statistical power. Based on our preliminary data[23] for the WL+VEST intervention preserving total hip aBMD as well as the effect size estimates generated from an 18 month trial of WL versus WL+RT on total hip vBMD,[12] we anticipate a 3% decrease (~0.300g/cm$^3$ total hip vBMD) in the WL+VEST group compared to a 5.5-6.0% decrease in WL alone. Assuming 12-month group differences in total hip vBMD between 0.0076-0.009 g/cm$^3$, we will have at least 80% power to detect a statistically significant difference for the primary outcome assuming common group standard deviations of 0.0127 g/cm$^3$ and using a 2-sided test expecting <15% dropout. Despite not having total hip trabecular vBMD pilot data, total hip vBMD is highly correlated with total hip trabecular vBMD, with previous research demonstrating enhanced sensitivity of the trabecular region.[55,56] Thus, the enrolled sample size of the INVEST in Bone Health trial will provide adequate power for total hip trabecular vBMD as our primary outcome measure.

We expect that the change in total hip trabecular vBMD for the WL+VEST will be noninferior to the change observed within WL+RT. The noninferiority margin for the difference in 12-month total hip vBMD changes is −4% or −0.0115 g/cm$^3$, as used previously.[57] Assuming equivalence between WL+VEST and WL+RT (12-month mean of 0.291g/cm$^3$), a baseline sample size of 64 per group provides 87% power to establish noninferiority between WL+VEST and WL+RT. This analysis assumes the same SD of change (0.0127g/cm$^3$) as the alternative co-hypothesis, a conservative attrition rate (<15%), and the Type I error rate is 0.0125, based on the convention of using 0.025 for a one-sided test being further divided in half due to co-primary hypotheses.

Given the challenges associated with establishing and forecasting noninferiority boundaries for exploratory outcomes, the analyses for the second aim will focus on the three group comparisons of WL, WL+VEST, and WL+RT. Based on the above baseline sample size of 64 per intervention arm, we will have 80% power to detect relatively modest effect sizes (variance of means/within-group variance) of 0.085–0.090 with similar attrition rates assumed above, assuming an F-test and a 0.05 Type I error rate.

## 2.7 Statistical analyses

Statistical analyses will be completed using SAS v9.4 (SAS Institute, Cary, NC) and R software (R Program, Vienna, Austria). The primary aim for comparisons of total hip trabecular vBMD will be tested using a mixed model fit using the change in total hip trabecular vBMD at 12 months versus the treatment effect indicator for each of the three groups, adjusted for visit (six or 12 months), visit × treatment interaction, sex (to account for randomization strata) and baseline value. A contrast statement will test change in total hip

trabecular vBMD at 12 months in WL versus WL+VEST, and a statistically significant difference will be established at $p<0.025$. Non-inferiority comparisons between WL+VEST and WL+RT will be determined based on whether the lower bound of the one-sided confidence interval for the estimated 12-month treatment effect of WL+VEST versus WL +RT overlaps the −4.0% non-inferiority boundary for total hip trabecular vBMD. This will be performed using $\alpha=0.0125$ to account for co-primary hypotheses as well as for using a 1-sided alternative hypothesis. Tests for both co-primary hypotheses will be based on different contrast statements within the same statistical model. These analyses will be repeated examining the short-term effect at six months of both interventions as exploratory analyses.

Regarding our secondary outcome measures, the analytic models will mirror the model used in the primary aim, with the exception that comparisons will focus on comparisons among the three group mean differences. All outcomes will be assessed at six and 12 months, and while means at both visit time points will be estimated, the 12-month treatment effect will be of primary interest. Treatment effects for changes in outcome variables are compared using a mixed model fit with treatment group, visit, and treatment × visit interaction, adjusted for sex and baseline values of the outcome. Tests will be performed using contrast statements at 12 months (primarily) and six months (secondarily), and we will use the partial F-test $p<0.05$ for significance. Significant comparisons for secondary outcomes will further use pairwise comparisons of all three groups at each visit using an adjusted significance value (0.05/3 groups) of $p<0.0167$.

## 2.8 Descriptive data and potential covariates

Potential covariates will be monitored across the study intervention. If covariates are found to be unbalanced between groups, and related to study outcomes, these variables will be included as covariates in exploratory, secondary statistical analyses. Demographic data will be recorded based on participant self-report at baseline only, and medical information on prior and existing co-morbidities and hospitalizations will also be collected by self-report. This information will be used to assess 10 year major osteoporotic and hip fracture risk using the FRAX tool.[58] Medication and current supplement use will be recorded by having participants bring in medications and supplements during an in-clinic visit. Standing height without shoes will be measured to the nearest 0.1 cm using a stadiometer and body mass will be measured to the nearest 0.1 kg using a calibrated and certified balance beam scale and used to calculate BMI. Waist, hip, and thigh circumference will be measured to the nearest 0.1 cm with a Gulick-II spring-retractable steel tape. Resting metabolic rate will be measured in the morning after an overnight fast by indirect calorimetry using the Weir equation.[59] Accelerometry will be used to objectively assess physical activity over a seven-day period at baseline, six and 12 months using a triaxial accelerometer and inclinometer.[60] Additional questionnaires assessing fatigue,[61] pain,[62] physical activity,[63] and intervention-specific adherence self-efficacy[64] will be measured. Adverse events will be assessed and recorded by asking participants to complete a health status questionnaire during assessment visits and specified intervention sessions, and spontaneously reported adverse events will also be collected and reported by intervention staff.

## 3.0 Discussion

The purpose of the INVEST in Bone Health trial is to understand the effects of a nutritionally complete, hypocaloric WL program compared to WL+VEST and WL+RT on indicators of bone health and subsequent fracture risk in older adults who are overweight or obese. Specifically, INVEST aims to identify whether replacing an individual's WL with external load via a weighted vest reduces WL-induced losses in BMD. We expect that despite demonstrating similar WL between groups (~10% body mass), participants in the WL+VEST group will display smaller losses in total hip trabecular vBMD than WL alone, and the changes will be no greater in the WL+VEST compared to WL+RT. Further, we hypothesize that participants in the WL+VEST and WL+RT will demonstrate improvements in fracture-related risk factors compared to WL alone.

Despite the notion that resistance exercise may optimize intentional WL outcomes, few older adults meet current resistance exercise guidelines,[65] thus challenging the translatability of RT as an effective strategy to counter bone loss consequences of WL and providing impetus to identify feasible, alternate load-based approaches. The INVEST in Bone Health trial study was designed to specifically address this concern. To our knowledge, this will be the first trial to compare the efficacy of WL+VEST and WL+RT on minimizing WL-induced bone loss and fracture risk. If successful, findings may ultimately translate into a more appealing alternative for maintaining bone during WL and would provide impetus for future work both in research and commercial sectors to design more convenient and scalable loading devices. Importantly, the WL+VEST may provide unique advantages that WL+RT does not. For example, the ability to specifically adjust the weighted vest in 1/8$^{th}$ pound (56.7 grams) increments permits an individual to apply great precision for paralleling the amount of body weight lost, a factor that is predictive of the quantity of bone loss.[66] Further, the build and versatility of the vest allows an individual to decide whether the vest is worn above or beneath clothing, and can be worn without restricting an individual's upper body movement and breathing patterns, thereby conferring practical utility. Importantly, our group recently identified that WL+VEST is a safe and feasible approach for use during a WL intervention in older adults, with pilot data showing individuals were willing to wear the vest over six hours per day over the course of six months, with few reported adverse events.[22] These observations further indicated that WL+VEST appeared to help preserve lower extremity muscular power, reduce the loss of hip aBMD, and increase bone formation markers over a 22-week pilot trial, but warrant further evaluation.[22,23] In addition, previous work in weight stable older adults has also reported favorable results. For example, Roghani et al.[15] reported that six weeks of three days per week walking (30 min) with weighted vest use (~4-8% body weight) resulted in greater calcium phosphorus levels and balance, greater decreases in fat mass, and a larger increase in fat free mass compared to walking with no external load and controls. Additionally, following 32-weeks of weighted vest exercise in weight stable older women, Jessup et al.[16] noted that despite observing a 5% decrease in body weight, femoral neck aBMD significantly increased in the vest users. Aside from these observations, the current literature collectively supports the ability of weighted vest use to enhance muscle and bone outcomes.[15–23] Therefore, the results of this trial may alter current

guidelines for intentional WL in older adults by providing an innovating, yet translatable, avenue for disrupting expected WL-associated declines in bone loss.

### 3.1 Strengths and limitations

The INVEST in Bone Health trial provides a novel, fully powered comparison between WL +VEST, WL+RT, and WL alone, which may lead to a strategy that maintains mechanical stress during WL while avoiding the common barriers associated with physical activity.[13,14] Additionally, the implementation of a WL-intensive phase (first six months) followed by a reduced-contact phase will provide insight into whether WL+VEST can be implemented effectively in a practical setting. The use of weekly and biweekly group sessions to provide informed dietary choices and strategies for maintaining WL may lessen the likelihood that participants will experience weight regain when transitioning out of the active intervention. Lastly, by measuring several biomarkers of bone turnover and metabolism as well as the distal radius (a non-load bearing skeletal site), the study is poised to expand our knowledge of the systemic mechanisms (beyond mechanical un/loading) underlying WL-associated bone loss.

Despite these strengths, the trial contains potential limitations. One limitation could be encouraging the participants to achieve 150 minutes of aerobic exercise per week in addition to the completing the requisite procedures associated with the trial arm. It is possible that not all participants may achieve this guideline, and different forms of aerobic exercise can result in various quantities of mechanical stress (e.g., running versus cycling), nevertheless this quantity of exercise reflects current recommendations.[35,36] However, we are also measuring self-reported and objective physical activity and should these covariates be unbalanced, secondary statistical analyses will be adjusted accordingly. An additional limitation could be the requirement for participants to travel to our site for resistance exercise sessions, whereas alternative forms of resistance exercise (e.g., exercise bands) could be implemented at their residence. Importantly, the resistance training program was designed to gradually introduce older adults to this modality of exercise while providing the requisite mechanical stress, which may not be achievable with exercise bands. Moreover, despite using targeted recruitment to minimize risks, as with any exercise intervention there is a possibility for injury. While our preliminary data suggest that poor adherence to WL or the WL+VEST is unlikely, it is possible that this could occur, or that there is variation within the study for adherence to WL or WL+VEST. Such variation in adherence to WL+VEST may allow for exploratory analyses to determine the dose-response relationship between WL+VEST and changes in bone health.

## 4. Conclusion

Effective strategies capable of minimizing bone loss during intentional WL in older adults need to be identified and implemented. Exercise appears to provide a robust stimulus, but more specifically, the mechanical stress mediated through resistance exercise has demonstrated superior results when compared to aerobic exercise or WL alone. Few older adults meet current physical activity guidelines, thus identification of novel approaches to maintain bone during intentional WL periods are needed. The INVEST in Bone Health trial

offers an innovative approach for providing mechanical stress during intentional WL in the absence of exercise. If successful, findings offer the potential to challenge current exercise prescriptions and offer a novel and practical approach for maintaining bone mass during WL in older adults with obesity, while providing insight into the mechanisms governing treatment response.

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**Fig. 1.**
HyperWear® Hyper Vest Pro Weight Vest.

**Table 1.**

Particiipant Inclusion and Exclusion Critieria

| Criteria | Inclusion Criteria | Exclusion Criteria | Assessment |
|---|---|---|---|
| Age | Age 60-85 years | | Self-report |
| Obesity status | BMI=30-40 kg/m$^2$<br>If BMI 27.0-30.0 kg/m$^2$-AND ≥1 of the following risk factors:1) elevated waist circumference (>35 inches in women, >40 inches in men); 2) diabetes; 3) hypertension; 4) dyslipidemia; 5) or other obesity-related comorbidities | Weight greater titan 450 lbs. (DXA/CT limit) | Measured on scale |
| Functional status | | Dependent on cane or walker: >2 falls (injurious on non-injurious) in past year | Self-report |
| Weight Status | No weight loss of >5% in past 6 months | Any contraindications for participation in voluntary weight loss | Self-report |
| Lifestyle Behaviors | | Smoker (>1 cigarette/d or 4/week within year); Drag abuse or excessive alcohol use (>14 drinks/week) | Self-report |
| Physical status | | Participation in regular resistance training and/or > 20 mins per day of moderate intensity aerobic exercise on > days/week in past 6 months | Self-report |
| Cognitive status | | Evidence of cognitive impairment (MoCA score <22) | Questionnaire |
| Orthopedic status | No self-disclosed contraindications for safe and optimal participation in exercise training/vest use. | Osteoporosis (any of the below):<br>Self-reported and on prescription medication.<br>Self-reported prior spine, hip, wrist, or shoulder fracture after age 40 (except when caused by trauma or fall from height).<br>T-score ≤ −2.5 at total hip, femoral neck, lumbar spine, distal radius scan at screening visit.<br>Chronic back/shoulder/knee pain with current or past (within 1 year) prescription medication use for at least 3 months.<br>Severe, diagnosed arthritis (osteoarthritis, rheumatoid arthritis, or gout) with current or past (within 1 year) prescription medication use for at least 3 months.<br>Past (ever) or planned (next 12 months) back surgery.<br>Past (6 months prior) or planned (next 12 months) joint replacement surgery; or past (ever) bilateral hip replacement surgery. | Self-report on Medical History form, or medication use or DXA scan |
| Co-morbidity/ health status | Approved for participation by Study Coordinator | Uncontrolled hypertension (BP>160/90 mmHg)<br>Current or recent past (within 1 year): severe symptomatic heart disease, uncontrolled angina, stroke, chronic respiratory disease requiring oxygen, neurological or hematological disease; cancer (except non-melanoma skin cancer), requiring treatment for at least 3 months in past year.<br>Low vitamin D (<20 ng/mL), abnormal kidney or liver function (2x upper limit of normal), eGFR<45 mL/min/1.73 m$^2$. Anemia (Hb< 13 g/dL in men/< 12 g/dL in women); Uncontrolled diabetes (fasting glucose >140 mg/dl) | BP measurement<br>Self-report on Medical History Form<br>Metabolic panel/CBC screening blood test |
| Medication use | | Use of growth hormones, weight loss medications, oral steroids, insulin, or prescription osteoporosis medications in the past year. | Self-report on Medical History Form |
| Technology Status | Willing to complete online/ electronic study forms and participate in virtual group sessions, as needed | No home computer, laptop, or tablet with reliable home internet OR no smartphone (touchscreen enabled phone) with reliable unlimited mobile internet. | Self-report |
| Research participation | Willing to provide informed consent; agree to all study procedures and assessments; Able to provide own transit to assessment/intervention visits | Involved in another behavioral/intervention research study or weight loss program; Unable<br>to tolerate diet, vest, or CT scan (claustrophobia).<br>Judged unsuitable for the trial for any reason by clinic staff | Self-report |

**Table 2.**

INVEST in Bone Health Trial Assessment Timeline

| **INVEST Measurements** | **SV1** | **SV1A** | **SV2** | **SV3** | **INT** | **FV1** | **FV2** | **INT** | **FV3** | **FV4** |
|---|---|---|---|---|---|---|---|---|---|---|
| Participant Status | fasted | | | fasted | | | fasted | | | fasted |
| Weeks | −6 to 0 | | | | 1-24 | 22-26 | | 25-52 | 50-54 | |
| Location | WFSM or WFU | Phone | WFU | WFSM | WFSM or WFU | WFU | WFSM | WFSM or WFU | WFU | WFSM |
| **Questionnaires** | | | | | | | | | | |
| Phone Screener | | | | | | | | | | |
| Consent/HIP AA | • | | | | | | | | | |
| Demographics | • | | | | | | | | | |
| Medical history | • | • | | | | | | | | |
| Medications | • | • | • | •• | | • | •• | | • | •• |
| Depression (CES-D) | • | • | | •• | | | •• | | | •• |
| Cognitive Assessment (MoCA) | • | | | | | | | | | • |
| Pittsburgh Fatigability Scale | | | | •• | | | •• | | | •• |
| PROMIS Pain Intensity and | | | | •• | | | •• | | | •• |
| Fatigue | | | | | | | | | | |
| CHAMPS physical activity | • | • | | •• | | | •• | | | •• |
| Adverse Events | | | • | •• | •• | • | •• | •• | • | •• |
| **Physical Exams and Physical Performance Measures** | | | | | | | | | | |
| Vital signs | | • | | • | | • | • | | • | • |
| Anthropometrics | | | | • | | • | | | • | |
| eSPPB | | | | • | | • | | | • | |
| Hand Grip Test | | | | • | | • | | | • | |
| RMR | | | | | • | | • | | | • |
| Activity Monitor - thigh | | | | • | | • | | | • | |
| Activity Monitor - in vest | | | | | | | | • | | |
| 400-meter Walk – fast | | | | • | | • | | | • | |
| TUG | | | | • | | • | | | • | |
| Biodex | | | | | • | | • | | | • |
| Stair climb | | | | • | | • | | | • | |
| **Musculoskeletal Assessments** | | | | | | | | | | |
| DXA | | | • | | | • | | | • | |
| QCT | | | | • | | | • | | | • |
| $D_3C_r$ Muscle mass | | | | • | | | • | | | • |
| **Phlebotomy** | | | | | | | | | | |
| CBC | • | | | | | | | | | |
| Metabolic Panel | • | | | | | | | | | |

| INVEST Measurements | SV1 | SV1A | SV2 | SV3 | INT | FV1 | FV2 | INT | FV3 | FV4 |
|---|---|---|---|---|---|---|---|---|---|---|
| Vitamin D | | | | • | | | | | | |
| Plasma/Serum Storage | | | | • | | • | | | | • |
| **Other** | | | | | | | | | | |
| Run-in instructions | • | | • | | | | | | | |
| Participant Satisfaction | | | | | | | | •• | | •• |
| Self-Efficacy | | | | | •• | | | •• | | •• |
| Adherence monitoring | | | | | • | | | • | | |

SV=screening visit, INT=intervention, FV=follow up visit, WFSM=Wake Forest School of Medicine, WFU=Wake Forest University, eSPPB=extended short physical performance battery, RMR=resting metabolic rate, TUG=timed up and go, DXA=dual energy x-ray absorptiometry, QCT=computed tomography, $D_3C_r$-Deuterated creatine dilution method for directly measuring muscle mass, CBC=complete blood count. Occurrence of assessment indicated by •, collected via phone indicated by •• Phone screening will be completed prior to SV1

**Table 3.**

Intervention Components by Treatment Group

| Intervention Component | Intensive WL Phase (Months 1-6) | Reduced Contact WL Phase (Months 7-12) |
|---|---|---|
| Weight Loss (WL) only | Weekly behavioral-based group sessions: 10% WL goal following national obesity treatment guidelines | Biweekly behavioral-based group sessions; 10% WL goal following national obesity treatment guidelines |
| WL + Weighted Vest | WL + 8 hours/day weighted vest use titrated weekly to adjust for achieved WL (up to 10% baseline weight) | WL + 8 hours/day weighted vest use titrated biweekly to adjust for achieved WL (up to 10% baseline weight) |
| WL + Resistance Training (RT) | WL + 3 days/week progressive, structured RT | |

Abbreviations: WL- weight loss, RT- resistance training.