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Baseline characteristics of participants in the VITamin D and OmegA-3 TriaL (VITAL): Effects on Bone Structure and Architecture

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Abstract

Vitamin D supplements are often used to benefit skeletal health, although data on effects of daily high-dose vitamin D alone on bone density and structure are lacking. The ongoing *VITamin D and OmegA-3 TriaL* (VITAL) is a double-blind, randomized, placebo-controlled trial testing effects of high-dose supplemental vitamin D_3 (cholecalciferol; 2000 IU/day) and/or omega-3 fatty acids (FAs; 1 g/day) for the primary prevention of cancer and cardiovascular disease. The study has a mean treatment period of 5 years among 25,874 U.S. men ≥50 years and women ≥55 years old from all 50 states. The ancillary study, *VITAL: Effects on Bone Structure and Architecture*, is testing effects of vitamin D_3 and/or omega-3 FAs on musculoskeletal outcomes and body composition in a subcohort of 771 participants. At in-person visits at the Harvard Catalyst Clinical and Translational Science Center (CTSC), participants completed bone density/architecture, body composition, and physical performance assessments at baseline and two-year follow-up. Baseline characteristics were evenly distributed among treatment groups, suggesting that any uninvestigated confounders will be evenly distributed; sex differences were also analyzed. Future analyses of the two-year follow-up visits will elucidate whether daily high-dose, supplemental vitamin D_3 and/or

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omega-3 FAs improve musculoskeletal outcomes, helping to advance clinical and public health recommendations.

Keywords

vitamin D; omega-3 fatty acids; bone mineral density; body composition; physical performance; sex differences

Introduction

There are high prevalences of osteoporosis and vitamin D deficiency in the U.S. Osteoporosis is the most common bone disease and is characterized by reduced bone mass, architectural deterioration, an imbalance in bone turnover, and compromised bone strength, which lead to increased fracture risk. Over 53.6 million Americans have osteoporosis or low bone mass [1]. Additionally, one in two women and one in five men aged 50 years and older will suffer an osteoporotic fracture in their remaining lifetime [2, 3]. Structural changes in bone, body composition, and clinical risk factors including vitamin D deficiency contribute to the development of osteoporosis. About 1/3 of individuals living in North America are vitamin D deficient (<20 ng/mL of 25-hydroxyvitamin D [25(OH)D]) [4]. Vitamin D deficiency is more prevalent in black individuals because of reduced activation of vitamin D after ultraviolet B radiation exposure [5, 6]. Overweight individuals are also more likely to be vitamin D deficient because vitamin D is sequestered in fat [7].

In addition to correcting low vitamin D levels, supplemental vitamin D is widely used to promote bone health, reduce fractures, and prevent functional decline. However, clinical trials and meta-analyses show inconsistent results as to whether supplemental vitamin D alone improves musculoskeletal health outcomes [8–29]. While randomized controlled trials (RCTs) provide the highest quality data, available studies are limited by designs that included supplemental calcium combined with vitamin D, vitamin D doses <1000 IU/d, bolus doses of vitamin D, studies of short duration, and/or failure to measure 25(OH)D levels.

Studies of the effects of omega-3 FAs on bone health are limited. In vitro studies have shown that omega-3 FAs suppress osteoclast formation [30], and animal studies have shown a reduction in bone resorption and some improvements in skeletal health [31–37]. However, observational and case-control studies have produced varying results [38–40], and data from large RCTs of omega-3 FAs' effects on bone mineral density (BMD) and structure are sparse and overall do not seem to show a benefit [41–43].

The *VITamin D and OmegA-3 TriaL (VITAL)* is a large, double-blind RCT testing whether high-dose supplemental vitamin D_3 (2000 IU/d) and/or omega-3 FAs (1 g/d) is effective in the primary prevention of cancer and cardiovascular disease [44]. The *VITAL: Effects on Bone Structure and Architecture* study is one of two ancillary studies evaluating effects of supplemental vitamin D alone on musculoskeletal outcomes [45]. In this study, detailed in-person assessments at the Harvard Catalyst CTSC were performed in a subcohort of participants (n=771) at baseline and two years of follow-up. The study aims to determine

whether supplemental vitamin D alone benefits BMD, bone structure, body composition, and physical performance measures. A complementary ancillary study, *VITAL: Effects on Fractures*, is determining effects of these interventions on incident fractures among the 25,874 VITAL participants nationwide. In this article, we present the baseline demographic, bone, body composition, physical performance, health and behavioral characteristics of the VITAL CTSC Bone Health subcohort by randomized treatment groups to assess the distribution among the interventions and whether there are sex differences in these baseline measures.

Materials and Methods

Overview of study design

The study design was previously described [45, 46]. VITAL is a large, randomized, 2×2 factorial, double-blind, placebo-controlled trial testing the risks and benefits of supplemental vitamin D_3 (cholecalciferol, 2000IU/d) and marine omega-3 FAs (Omacor® fish oil, eicosapentaenoic acid [EPA] + docosahexaenoic acid [DHA]; 1g/d) on cardiovascular disease and cancer. The mean length of treatment was 5 years, which ended on December 31, 2017. VITAL-Bone Health consists of two ancillary studies, *VITAL: Effects on Fractures* and *VITAL: Effects on Bone Structure and Architecture*, which build upon the resources and design of the parent VITAL study to test effects of supplemental vitamin D_3 and/or omega-3 FAs on skeletal health. In this study, *VITAL: Effects on Bone Structure and Architecture*, a subcohort of participants (n=771) completed detailed phenotyping, bone health, body composition, and physical performance assessments at baseline and two-year post-randomization at the Harvard Catalyst CTSC in Boston. The baseline visits took place between January 2012 and March 2014, and the two-year follow-up visits occurred between October 2014 and July 2016. The primary aims of this ancillary study are to determine whether supplemental vitamin D_3 and/or omega-3 FAs positively affects areal bone mineral density (aBMD) at the spine, total hip, femoral neck, and whole body as assessed by dual-energy X-ray absorptiometry (DXA), as well as biomarkers of bone remodeling. Blood samples are frozen at −80°C so that baseline and two-year follow-up bone turnover makers will be measured in the same assay. Levels of 25(OH)D, EPA and DHA will also be measured in these blood samples to assess study pill compliance and to determine the effects of the interventions on study outcomes. The secondary aim of this study is to determine whether supplemental vitamin D_3 and/or omega-3 FAs improves structure and architecture at the radius and tibia as assessed by peripheral quantitative computed tomography (pQCT). High-resolution pQCT (HR-pQCT) was also performed among a subset of participants during the two-year follow-up visits. The tertiary aim is to determine whether supplemental vitamin D_3 and/or omega-3 FAs has beneficial effects on body composition and physical function. Biomarkers of bone remodeling, pQCT, and HR-pQCT measures will be presented in future publications. Studies were approved by the Partners Human Research Committees, the Institutional Review Board of Brigham and Women's Hospital.

Study population

Women and men were eligible for the parent VITAL study if they were ≥55 years and ≥50 years old, respectively, without previous history of cardiovascular disease or cancer. Safety

exclusions included allergy to soy or fish, renal failure, hypercalcemia, hypo- or hyperparathyroidism, severe liver disease, granulomatous disease, or other serious illness. Participants were randomized after they completed a detailed consent form and a 3-month placebo run-in phase. If participants demonstrated good compliance during the placebo run-in phase (took at least 2/3 of their study pills), they were randomized into the trial. Participants agreed to limit their total personal supplemental vitamin D intake to ≤800IU/day, total supplemental calcium to ≤1200mg/day, and to refrain from taking supplemental fish oil. A total of 25,874 participants from all 50 states, including 5,107 African Americans were randomized into the trial between November 2011 and March 2014. The intervention phase of VITAL ended on December 31, 2017. Follow-up questionnaires will continue for an additional two years after the intervention phase is completed.

A subcohort of VITAL participants who lived within driving distance of Boston were enrolled into the CTSC subcohort (n=1,054). Participants were eligible for the *VITAL: Effects on Bone Structure and Architecture* ancillary study if they met requirements for the parent trial and were not on bisphosphonates within the past two years or other bone active medications including, denosumab, human parathyroid hormone, calcitonin, raloxifene, tamoxifen, or systemic estrogens within the past year. No participants were on aromatase inhibitors in the VITAL CTSC Bone Health subcohort. Of 1,054 participants in the CTSC subcohort, 771 completed bone density, body composition, and physical performance assessments.

Bone measures

Areal BMD at the lumbar spine (L1-L4), right and left hip (total hip and femoral neck), and whole body was measured using DXA (Discovery W, APEX Software Version 4.2, Hologic, Bedford, MA). Guidelines from Hologic and the International Society for Clinical Densitometry (ISCD) were followed for positioning of all DXA scans. Left and right hip measures were averaged in our analyses; when only one hip was available due to metal artifact(s), only the unaffected hip was used. T-scores were generated using the default sex and ethnicity-matched databases in the Hologic APEX Software 4.2. Z-scores were generated using the age, sex, and ethnicity-matched results from the same default databases [47]. In the DXA Hologic system, American Indians and Alaskan Natives were compared to the white database [48] and Hispanic white participants were compared to the Hispanic database [49]. Reproducibility is very good at our site [50]. Least significant change (LSC) is 0.024 g/cm^2 at the spine, 0.021 g/cm^2 at the femoral neck, 0.017 g/cm^2 at the total hip, and 0.008 g/cm^2 for males and 0.010 g/cm^2 for females at the whole body. Lumbar spine DXA scans were used to generate the Trabecular Bone Score (TBS; Version 2.1, Medimaps Group, Geneva, Switzerland). TBS is a textural analysis that can predict fracture risk independent of BMD [51]. Scores ≥1.350 signify normal microarchitecture, between 1.200-1.350 partially degraded microarchitecture, and ≤1.200 degraded microarchitecture [52, 53]. The Fracture Risk Assessment Tool (FRAX), included in the APEX Software Version 4.2, predicted 10-year probability for major osteoporotic fractures (MOF) and hip fractures in participants with low bone mass (osteopenia; T-scores from −1.1 to −2.4 at the spine, hip, or femoral neck).

When participants had internal metal (i.e. hip/knee replacements), the bone measures from the unaffected, contralateral side were used to replace the affected side to prevent metal from confounding and increasing the bone density results (n=62) [54]. When there was not an unaffected contralateral side to represent (i.e. metal in the spine, bilateral hip/knee replacements), bone measures were excluded at that site as well as at the whole body (n=27). Additionally, femoral neck measures were excluded for all participants with severe osteoarthritis at the hip (n=11). Because hip osteoarthritis elevates T-scores of the femoral neck compared to the total hip [55], if the difference between T-scores at the femoral neck and total hip was ≥1, two physicians, experienced in bone densitometry, examined the DXA images to determine whether severe hip osteoarthritis was present. Vertebrae were also excluded per the ISCD guidelines if there was more than a 1.0 T-score difference between the vertebra and adjacent vertebrae, or if there was a clear abnormality. If three or more vertebrae were excluded, the spine was not suitable for analysis. A total of 51 spine BMD measures were excluded because of spinal metal, scoliosis and/or severe degenerative disc disease. There were two participants who had bilateral breast implants who were excluded from whole body bone density and body composition analyses due to uncertain effects on bone density, fat and lean mass.

After DXA scans, all participants were sent a letter to inform them whether or not they had osteoporosis defined as a T-score ≤−2.5. There were relatively few participants (n=85; 12%) who had osteoporosis according to bone density criteria. The letters recommended that participants share the results of their bone density scans with their health care providers so that they could potentially receive treatment and/or follow-up care if needed.

Body composition measures

Body composition measures were also completed using DXA (Discovery W, APEX Software Version 4.2, Hologic, Bedford, MA). Measures include total and sub-regions of adipose and lean mass including the android and gynoid regions. Adipose tissue measures included total body fat, percent total fat, visceral adipose tissue (VAT), and fat mass index (FMI; fat mass/height^2). Measurements for lean indices included lean mass index (LMI; lean mass/height^2), appendicular lean mass (ALM), appendicular lean mass index (ALMI; appendicular lean mass/height^2), and appendicular lean mass adjusted for body mass index (ALM/BMI). Precision at our site for body composition, reported as standard deviations, is similar to other published studies [56]. The standard deviation for whole body fat mass is 0.220 kg for males and 0.245 kg for females; standard deviation for whole body lean mass is 0.230 kg for males and 0.246 kg for females.

Physical performance measures

Grip strength, the Short Physical Performance Battery (SPPB; components include walking speed, standing balance, and chair stands), and the Timed Up and Go (TUG) were assessed in the participants. **Grip strength** was measured using a JAMAR Plus + Digital Hand Dynamometer (Sammons Preston Roylan, Bolingbrook, IL) [57, 58]. Grip strength is correlated with physical activity in hip fracture patients and has been found to be inversely related to hip fracture risk [59]. Both normal, **everyday walking speed** and a **fast walking speed** were determined over 6 meters [60, 61]. Slow everyday walking speeds are correlated

with mortality, hospitalization, and disability [62–64]. **Standing balance** was measured by attempting to hold three positions (tandem, semi-tandem, and side-by-side) for 10 seconds each [65]. **Chair stands** consist of participants standing and sitting down 5 times with arms folded using a standard straight-backed chair [66]. The inability to rise from a chair is one of the strongest risk factors for hip fractures in men and can predict dependence for activities of daily living [67, 68]. By scoring normal everyday walking speed, standing balance, and chair stands on a scale of 0-4, the **composite SPPB** was determined (ranging from 0–12) to measure lower body function [63, 69]. Increases in the composite SPPB score has also been shown to be associated with improvements in physical function in hip fracture patients [70]. The **TUG** is a timed test wish consists of participants standing up from a chair, walking 3 meters, turning around, and returning to sit in the chair [71, 72]. A slow TUG has been associated with increased fracture risk [73–75].

Sarcopenia measures

Sarcopenia is characterized by a loss of muscle mass, strength, and function. There are several operational definitions of sarcopenia that include ALM, ALMI, TUG, and SPPB [62, 76–83]. Here we use the sarcopenia criteria defined by the Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium Sarcopenia Project [84]. This definition includes sex-specific cutpoints for ALM/BMI (men: ≤0.789, women: ≤0.512) and grip strength (men: <26kg, women: <16kg) to quantify low lean mass and muscle weakness, respectively. To measure muscle performance, slowness is defined as a gait speed of ≤0.8 m/s for both men and women.

Clinical factors

Participants were mailed a VITAL questionnaire at baseline, 6-months, and annually to assess risk factors that may affect bone health and body composition. The clinical factors include age, sex, race/ethnicity, BMI, education, income, alcohol use, tobacco use, physical activity (total metabolic equivalent [MET] hours/week), diet, use of medications, and history of diabetes, rheumatoid arthritis, falls, and fragility fractures.

Statistical analysis

To assess whether balance was achieved by randomization among this VITAL CTSC Bone Health subcohort, this analysis compared baseline characteristics by randomized treatment assignment. All continuous variables were first examined for normality. Means (standard deviation) or median (25^{th}, 75^{th} percentiles) are reported as appropriate. We used t-tests and analysis of variance (ANOVA) or the Wilcoxon rank sum and Kruskal Wallis tests to compare continuous variables across randomized groups and by sex. Chi-square tests were used to compare proportions, using trend tests for ordinal data. We used regression analysis to adjust for age when comparing variables by sex [85]. All analyses were generated using SAS. Results were considered statistically significant when $p<0.05$.

Results

Table 1 displays the baseline characteristics of the VITAL CTSC subcohort according to randomized treatment group. In the VITAL CTSC subcohort (n=771), 53.3% were men and

46.7% were women, with a mean age of 63.8 ± 6.1 years. The subcohort consisted of 83.4% non-Hispanic whites, 8.9% African Americans, and 3.4% Hispanics (not African American). Most participants were highly educated as 89.7% of them have attended or graduated from college or graduate school. There were no statistically significant differences in the investigated demographic characteristics among the randomized treatment groups.

The majority of factors related to bone health were also evenly distributed. The mean T-scores at the spine (−0.49±1.41), total hip (−0.53±0.90), and whole body (−0.20±1.20) were classified as normal, while the mean T-score at the femoral neck was osteopenic (−1.09±0.89). Of the 418 participants who were osteopenic, 9.6% had a hip FRAX score ≥3% or major osteoporotic fracture FRAX score ≥20%, meeting threshold for initiation of osteoporosis treatment [2]. Among the participants, 13.4% had parents with a history of hip fracture, and 8.2% had personal histories of fragility fractures. TBS, a structural measure derived from the spine BMD image, has been shown to predict fracture risk independent of BMD. Mean TBS was not equally distributed among the treatment groups (p=0.007); however, when TBS was classified into architecture status [52, 53], the distribution was similar. About 10.1% and 50.0% of participants had degraded microarchitecture and partially degraded microarchitecture, respectively.

Regarding baseline body composition characteristics, participants had a mean BMI of 28.3± 5.1 kg/m^2 and body fat percentage of 36.4%. Overall, 30.0% of participants were obese by BMI criteria, and 38.2% were obese by FMI criteria. These variables and other body composition measurements including, LMI, VAT area, and truncal fat were evenly distributed among treatment groups. According to the FNIH sarcopenia cutpoints for ALM/BMI, 25.3% of men and 25.6% of women had low lean mass [84].

Physical performance measures were also carried out at the CTSC, and all were evenly distributed among intervention groups. Overall, 98.1% of participants had a normal walking speed of >0.8 m/s [80, 86, 87], 99.4% completed the TUG test in under 12 seconds [71, 72], and 92.0% of participants were able to hold the three stances (side-by-side, semi-tandem, and tandem) for 10 seconds each [88]. However, only 72.6% of participants performed 5 consecutive chair stands faster than 11.1 seconds, a threshold determined for older adults [69]. These three tests (normal walking speed, standing balance, and chair stands) are components of the composite SPPB. A total of 94.3% of participants had a SPPB score of ≥9 out of a maximum score of 12; a score of <9 has been associated with frailty [89]. Muscle weakness, by FNIH grip strength criteria, was present in 5.2% of men and 3.7% of women [84].

With respect to other clinical risk factors, 45.7% were hypertensive, and 43.5% of participants had taken anti-hypertensive medication at some point during their lifetime. Of all participants, 10.1% had diabetes and 7.8% were currently using anti-diabetic medication. Additionally, 34.3% were currently using cholesterol-lowering medication and 8.0% were currently taking selective serotonin reuptake inhibitors (SSRIs). A total of 24.6% of participants reported one or more falls within the last year on their annual questionnaire. The only characteristic that was not equally distributed among the treatment arms was history of past smoking (p=0.021), but not current smoking (p=0.761; results not shown). Intake of

supplements and food related to vitamin D and/or omega-3 FAs are also shown in Table 1, with even distribution among intervention arms.

Table 2 shows the baseline characteristics according to sex among the VITAL bone health subcohort. No women were aged 50-54 years because of the trial's enrollment criteria; consequently, women were slightly older than men (64.4 years vs. 63.3 years old). Therefore, variables in Table 2 were adjusted for age. All race and ethnicities were similarly distributed between men and women. Education and income levels were also evenly distributed between the sexes except that there were more men who had incomes >$120,000 (35.1% vs. 23.3%).

Women had significantly lower BMD and T-scores than men at the whole body, spine, total hip, and femoral neck. Women also had lower mean TBS scores than men (1.31 vs. 1.34). More men had normal microarchitecture according to TBS (TBS ≥1.350) than women, and more women had partially degraded bone microarchitecture (TBS between 1.200 and 1.350) than men. However, there was no significant difference between men and women who had degraded microarchitecture (TBS ≤1.200). Hip FRAX scores were similar between the sexes, but women had higher major osteoporotic fracture risk than men (10.03% vs. 6.55%). Among men and women, 9.3% and 10.2%, respectively, had FRAX scores for which treatment for osteoporosis would be indicated, which is not significantly different [2].

Mean BMI was similar between men and women; however, there were more women who had normal BMI than men (33.5% vs. 20.4%), and there were more overweight men than overweight women (53.1% vs. 32.3%). No sex differences were present at the extreme BMIs, with no difference in percentages of men and women who were either underweight or obese. Women had higher body fat percentage than men (42.4% vs. 31.1%) and greater FMI (11.98 kg/m^2 vs. 8.79 kg/m^2). However, men had greater VAT areas than women (178.21 cm^2 vs.151.15 cm^2). Men also had greater lean mass than women according to LMI, ALM, ALMI, and ALM/BMI.

There were not many sex differences in physical performance measures, as men and women had similar standing-balance times, chair-stand-test times, and SPPB scores. Normal walking speed did not differ between sexes, but men had faster walking speeds than women (1.85 m/s vs. 1.75 m/s). However, women had faster TUG test times than men (7.88 s vs. 8.23 s).

Men were more likely to have a history of hypertension and to use anti-hypertensive medications. There were also more men who had diabetes and were currently taking cholesterol-lowering medications than women. Meanwhile, more women reported parents having a history of hip fractures and having a personal history of fragility fractures. There were no significant differences in use of anti-diabetic medication, rheumatoid arthritis, use of SSRIs, or number of falls in the past year between men and women.

In regards to behavioral characteristics, no sex differences were seen in smoking, physical activity by MET scores, personal use of supplemental vitamin D, or servings of dark-meat fish, or other fish and seafood. More men drank alcohol daily and used multivitamins than

women. Women used more supplemental calcium and had more servings of milk and other vitamin D-fortified foods than men.

Discussion

These analyses show that most baseline demographic, bone, body composition, physical performance, behavioral, and clinical history characteristics were evenly distributed among treatment groups in the VITAL CTSC Bone Health subcohort ($p>0.05$). Randomization was effective in distributing known musculoskeletal risk factors equally across treatment groups. The parent VITAL study also showed equal distribution among the interventions [90]. In this ancillary study, the only characteristics that were unequally distributed among a total of 67 variables were prior history of smoking and mean TBS. These risk factors will likely not affect the results of the RCT as current smoking is more likely to affect bone health and this factor was evenly distributed. Additionally, when pack-years, the average number of cigarette packs multiplied by the number of smoking years, was analyzed for past and current smokers, smoking patterns were evenly distributed among treatment groups in this ancillary study. When TBS was stratified by normal, partially degraded, and degraded microarchitecture [52, 53], there were no differences among treatment groups. The even distribution suggests that uninvestigated confounding variables will also be evenly distributed among treatment groups. Therefore, changes observed after two years of follow-up can be accredited to the treatment interventions.

Overall, this VITAL subcohort had relatively high BMD, as evidence by positive average Z-scores and average T-scores in the normal range at the spine, total hip, and total body. Overall, 8.25% of the participants had a history of a fragility fracture and 9.6% had a FRAX score in the range that one would consider therapy for osteoporosis. Only 5.2% of men and 3.7% of women had muscle weakness according to grip strength, which is similar to results of NHANES (5% of adults aged ≥60 years) [91]. While few participants had the more extreme phenotype of sarcopenia by functional measures, including grip strength, walking speed, and the SPPB, 25.3% of men and 25.7% of women had low muscle mass (ALM/BMI) according to FNIH sarcopenia criteria [84]. According to an evidence-based evaluation using the FNIH definition that included both low muscle mass (ALM/BMI) and grip strength, sarcopenia affected 1.3% of men to 2.3% of women aged ≥65 years [80]. While there are many participants with high physical performance and bone measures at baseline, the vitamin D and/or omega-3 interventions may maintain and prevent the decline of these measures vs. placebo overtime. Therefore, it is important to investigate the effects of supplemental vitamin D and/or omega-3 fatty acids on these musculoskeletal outcomes.

It is also important to investigate sex differences in this subcohort. As expected, women had lower BMD and more fragility fractures than men; they also had higher fat percentages. In addition, men were more likely to be obese and, as anticipated, have greater VAT area and lean muscle mass than women. Few sex differences existed among physical performance measures including standing balance, normal walking speed, chair stands, and the SPPB. Men did, however, show greater grip strengths and quicker fast walking speeds. There were some differences in health histories, with more men having a history of hypertension, diabetes, and use of cholesterol-lowering medications and multivitamins. Women were more

likely to use calcium supplements and have more servings of milk and other vitamin D-fortified foods suggesting possible reverse causation.

There are some limitations to this study. The majority of participants are non-Hispanic white. Although the overall VITAL cohort provided an over-sampling of non-Hispanic African Americans (20.2%), due to the regional demographics of Boston and New England, only 8.9% of the CTSC subcohort was African American. Additionally, because the VITAL CTSC subcohort required 6- to 8-hour in-person visits, participants were younger than the overall cohort (63.8 vs. 67.1 years) and overall healthier (less obese, hypertensive, diabetic, and smoked less) [90]. Despite these differences, we expect that results from *VITAL: Effects on Bone Structure and Architecture* will generate important new knowledge that will have high impact on clinical care among men and women in the U.S. Additional measures to be presented in future publications, including biomarkers of bone remodeling, pQCT, and in a subset at two-year, HR-pQCT, will allow us to determine whether supplemental vitamin D and/or omega-3 FAs have beneficial effects on bone turnover, structure, and architecture.

VITAL is one of the first RCTs to test in a primary prevention study effects of high-dose, daily supplemental vitamin D alone on bone density, structure, and architecture, as well as body composition. A parallel VITAL ancillary study is evaluating effects of supplemental vitamin D on incident fracture outcomes in the overall cohort of 25,874 adults nationwide. We have demonstrated that baseline demographic, health and musculoskeletal characteristics were evenly distributed among the randomized treatment groups and that there were sex difference in a number of these relevant variables. The ongoing VITAL-Bone Health studies will provide important information on mechanisms through which supplemental vitamin D may affect bone health and inform clinical and public health recommendations on whether vitamin D and/or omega-3 FAs supplementation should be used in the primary prevention of osteoporosis and fractures in women and men.

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Voting members of the VITAL Data and Safety Monitoring Board include Lawrence S. Cohen, MD; Theodore Colton, ScD; Mark A. Espeland, PhD; Craig Henderson, MD; Alice H. Lichtenstein, ScD; Rebecca A. Silliman, MD, PhD; and Nanette K. Wenger, MD (chair). Ex-officio members include Josephine Boyington, PhD, MPH; Rebecca B. Costello, PhD; Cindy D. Davis, PhD; Peter Greenwald, MD; Gabriela Riscuta, MD; and Harold Seifried, PhD. We would also like to acknowledge: Cindy Yu for her contributions in performing the bone density and body composition measures; Joel S. Finkelstein, MD and Mary L. Bouxsein, PhD for their roles in the HR-pQCT measures at two-years post-randomization; and Thomas Kelly, PhD for his guidance in performing the DXA whole body composition analysis. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. This work was conducted with support from Harvard Catalyst — the Harvard Clinical and Translational Science Center (NCRR and NCATS, NIH Award UL1 TR001102) and financial contributions from Harvard University and its affiliated academic healthcare centers.

Bibliography and Resources Cited

1. Wright NC, Looker AC, Saag KG, Curtis JR, Delzell ES, Randall S, Dawson-Hughes B. The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. J Bone Miner Res. 2014; 29(11):2520–6. DOI: 10.1002/jbmr.2269 [PubMed: 24771492]
2. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, Lindsay R. Clinician's Guide to Prevention and Treatment of Osteoporosis. Osteoporos Int. 2014; 25(10):2359–81. DOI: 10.1007/s00198-014-2794-2 [PubMed: 25182228]
3. Khosla S. Update in male osteoporosis. J Clin Endocrinol Metab. 2010; 95(1):3–10. DOI: 10.1210/jc.2009-1740 [PubMed: 20056806]
4. Looker AC, Johnson CL, Lacher DA, Pfeiffer CM, Schleicher RL, Sempos CT. Vitamin D status: United States, 2001–2006. NCHS Data Brief. 2011; (59):1–8. Epub 2011/05/20.
5. Harris SS. Vitamin D and African Americans. J Nutr. 2006; 136(4):1126–9. [PubMed: 16549493]
6. Moore CE, Murphy MM, Holick MF. Vitamin D intakes by children and adults in the United States differ among ethnic groups. J Nutr. 2005; 135(10):2478–85. [PubMed: 16177216]
7. Ross, AC.Taylor, CL.Yaktine, AL., Del Valle, HB., editors. Institute of Medicine. Dietary reference intakes for calcium and vitamin D. Washington DC: National Academies Press (US); 2011.
8. Sanders K, Stuart A, Williamson E, Simpson J, Kotowicz M, Young D, Nicholson G. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. JAMA. 2010; 303(18):1815–22. [PubMed: 20460620]
9. Cranney, A., Horsley, T., O'Donnell, S., Weiler, H., Puil, L., Ooi, D., Atkinson, S., Ward, L., Moher, D., Hanley, D., Fang, M., Yazdi, F., Garritty, C., Sampson, M., Barrowman, N., Tsertsvadze, A., Mamaladze, V. Evid Rep Technol Assess (Full Rep). Vol. 158. Agency for Healthcare Research and Quality (AHRQ); 2007. Effectiveness and Safety of Vitamin D in Relation to Bone Health; p. 73http://www.ahrq.gov/downloads/pub/evidence/pdf/vitamind/vitad.pdf
10. Lips P, Graafmans W, Ooms M, Bezemer P, Bouter L. Vitamin D Supplementation and Fracture Incidence in Elderly Persons: A Randomized, Placebo-Controlled Clinical Trial. Ann Intern Med. 1996; 124(4):400–6. [PubMed: 8554248]
11. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. BMJ. 2003; 326(7387):469. [PubMed: 12609940]
12. Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. Jama. 2005; 293(18):2257–64. [PubMed: 15886381]
13. Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE, Bassford T, Beresford SA, Black HR, Blanchette P, Bonds DE, Brunner RL, Brzyski RG, Caan B, Cauley JA, Chlebowski RT, Cummings SR, Granek I, Hays J, Heiss G, Hendrix SL, Howard BV, Hsia J, Hubbell FA, Johnson KC, Judd H, Kotchen JM, Kuller LH, Langer RD, Lasser NL, Limacher MC, Ludlam S, Manson JE, Margolis KL, McGowan J, Ockene JK, O'Sullivan MJ, Phillips L, Prentice RL, Sarto GE, Stefanick ML, Van Horn L, Wactawski-Wende J, Whitlock E, Anderson GL, Assaf AR, Barad D. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med. 2006; 354(7):669–83. [PubMed: 16481635]
14. Bischoff-Ferrari HA, Willett WC, Wong JB, Stuck AE, Staehelin HB, Orav EJ, Thoma A, Kiel DP, Henschkowski J. Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. Arch Intern Med. 2009; 169(6):551–61. Epub 2009/03/25. doi: 169/6/551 [pii]. DOI: 10.1001/archinternmed.2008.600 [PubMed: 19307517]
15. Avenell A, Mak JC, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures in postmenopausal women and older men. The Cochrane database of systematic reviews. 2014; 4:CD000227.doi: 10.1002/14651858.CD000227.pub4
16. DIPART. Patient level pooled analysis of 68 500 patients from seven major vitamin D fracture trials in US and Europe. BMJ. 2010; 340:b5463. Epub 2010/01/14. doi: 10.1136/bmj.b5463bmj.b5463 [PubMed: 20068257]

17. Chung M, Lee J, Terasawa T, Lau J, Trikalinos TA. Vitamin D with or without calcium supplementation for prevention of cancer and fractures: an updated meta-analysis for the U.S. Preventive Services Task Force. Ann Intern Med. 2011; 155(12):827–38. DOI: 10.7326/0003-4819-155-12-201112200-00005 [PubMed: 22184690]

18. Bischoff-Ferrari HA, Willett WC, Orav EJ, Lips P, Meunier PJ, Lyons RA, Flicker L, Wark J, Jackson RD, Cauley JA, Meyer HE, Pfeifer M, Sanders KM, Stahelin HB, Theiler R, Dawson-Hughes B. A pooled analysis of vitamin D dose requirements for fracture prevention. N Engl J Med. 2012; 367(1):40–9. Epub 2012/07/06. DOI: 10.1056/NEJMoa11096170 [PubMed: 22762317]

19. Moyer VA, on behalf of the USPSTF. Vitamin D and Calcium Supplementation to Prevent Fractures in Adults: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med. 2013; 158(9):691–6. DOI: 10.7326/0003-4819-158-9-201305070-00603 [PubMed: 23440163]

20. Newberry, S., Chung, M., Shekelle, P., Booth, MS., Liu, J., Maher, A., Motala, A., Cui, M., Perry, T., Shanman, R., Balk, E. Vitamin D and Calcium: A Systematic Review of Health Outcomes (Update) Evidence Report/Technology Assessment. Rockville, MD: Agency for Healthcare Research and Quality; 2014 Sep. Report No.: 2172014

21. Reid IR, Bolland MJ, Grey A. Effects of vitamin D supplements on bone mineral density: a systematic review and meta-analysis. Lancet. 2014; 383(9912):146–55. Epub 2013/10/15. DOI: 10.1016/s0140-6736(13)61647-5 [PubMed: 24119980]

22. Theodoratou E, Tzoulaki I, Zgaga L, Ioannidis JP. Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. BMJ. 2014; 348:g2035. Epub 2014/04/03. doi: 10.1136/bmj.g2035 [PubMed: 24690624]

23. Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. Lancet. 2007; 370(9588):657–66. Epub 2007/08/28. DOI: 10.1016/s0140-6736(07)61342-7 [PubMed: 17720017]

24. Boonen S, Lips P, Bouillon R, Bischoff-Ferrari HA, Vanderschueren D, Haentjens P. Need for additional calcium to reduce the risk of hip fracture with vitamin d supplementation: evidence from a comparative metaanalysis of randomized controlled trials. J Clin Endocrinol Metab. 2007; 92(4):1415–23. Epub 2007/02/01. DOI: 10.1210/jc.2006-1404 [PubMed: 17264183]

25. Meyer HE, Smedshaug GB, Kvaavik E, Falch JA, Tverdal A, Pedersen JI. Can vitamin D supplementation reduce the risk of fracture in the elderly? A randomized controlled trial. J Bone Miner Res. 2002; 17(4):709–15. Epub 2002/03/29. DOI: 10.1359/jbmr.2002.17.4.709 [PubMed: 11918228]

26. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med. 1997; 337(10):670–6. [PubMed: 9278463]

27. Weaver CM, Alexander DD, Boushey CJ, Dawson-Hughes B, Lappe JM, LeBoff MS, Liu S, Looker AC, Wallace TC, Wang DD. Calcium plus vitamin D supplementation and risk of fractures: an updated meta-analysis from the National Osteoporosis Foundation. Osteoporos Int. 2016; 27(1):367–76. Epub 2015/10/30. DOI: 10.1007/s00198-015-3386-5 [PubMed: 26510847]

28. Khaw KT, Stewart AW, Waayer D, Lawes CMM, Toop L, Camargo CA Jr, Scragg R. Effect of monthly high-dose vitamin D supplementation on falls and non-vertebral fractures: secondary and post-hoc outcomes from the randomised, double-blind, placebo-controlled ViDA trial. The lancet Diabetes & endocrinology. 2017; Epub 2017/05/04. doi: 10.1016/s2213-8587(17)30103-1

29. Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, Staehelin HB, Meyer OW, Theiler R, Dick W, Willett WC, Egli A. Monthly High-Dose Vitamin D Treatment for the Prevention of Functional Decline: A Randomized Clinical Trial. JAMA internal medicine. 2016; 176(2):175–83. Epub 2016/01/10. DOI: 10.1001/jamainternmed.2015.7148 [PubMed: 26747333]

30. Kasonga AE, Deepak V, Kruger MC, Coetzee M. Arachidonic acid and docosahexaenoic acid suppress osteoclast formation and activity in human CD14+ monocytes, in vitro. PloS one. 2015; 10(4):e0125145. Epub 2015/04/14. doi: 10.1371/journal.pone.0125145 [PubMed: 25867515]

31. Sun D, Krishnan A, Zaman K, Lawrence R, Bhattacharya A, Fernandes G. Dietary n-3 fatty acids decrease osteoclastogenesis and loss of bone mass in ovariectomized mice. J Bone Miner Res. 2003; 18(7):1206–16. [PubMed: 12854830]
32. Matsushita H, Barrios JA, Shea JE, Miller SC. Dietary fish oil results in a greater bone mass and bone formation indices in aged ovariectomized rats. J Bone Miner Metab. 2008; 26(3):241–7. Epub 2008/05/13. DOI: 10.1007/s00774-007-0815-3 [PubMed: 18470664]
33. Bonnet, N., Ferrari, S. New Frontiers in Skeletal Research: Bone, Fat, and Brain Connections. Bethesda, MD: Apr 27–28. 2009 A long-term diet enriched in omega-3 fatty acids improves cortical bone structure and mechanical properties in mice. Abstract#M47.
34. Sakaguchi K, Morita I, Murota S. Eicosapentaenoic acid inhibits bone loss due to ovariectomy in rats. Prostaglandins Leukot Essent Fatty Acids. 1994; 50(2):81–4. [PubMed: 8171071]
35. Yamada Y, Fushimi H, Inoue T, Matsuyama Y, Kameyama M, Minami T, Okazaki Y, Noguchi Y, Kasama T. Effect of eicosapentaenoic acid and docosahexaenoic acid on diabetic osteopenia. Diabetes Res Clin Pract. 1995; 30(1):37–42. Epub 1995/10/01. doi: 0168822795011390 [pii]. [PubMed: 8745204]
36. Reinwald S, Li Y, Moriguchi T, Salem N Jr, Watkins BA. Repletion with (n-3) fatty acids reverses bone structural deficits in (n-3)-deficient rats. J Nutr. 2004; 134(2):388–94. [PubMed: 14747677]
37. Watkins BA, Li Y, Lippman HE, Feng S. Modulatory effect of omega-3 polyunsaturated fatty acids on osteoblast function and bone metabolism. Prostaglandins Leukot Essent Fatty Acids. 2003; 68(6):387–98. Epub 2003/06/12. doi: S0952327803000632 [pii]. [PubMed: 12798659]
38. Virtanen JK, Mozaffarian D, Cauley JA, Mukamal KJ, Robbins J, Siscovick DS. Fish consumption, bone mineral density, and risk of hip fracture among older adults: The cardiovascular health study. Journal of Bone and Mineral Research. 2010; 25(9):1972–9. DOI: 10.1002/jbmr.87 [PubMed: 20572022]
39. Farina EK, Kiel DP, Roubenoff R, Schaefer EJ, Cupples LA, Tucker KL. Dietary Intakes of Arachidonic Acid and alpha-Linolenic Acid Are Associatedwith ReducedRisk of Hip Fracture in Older Adults. The Journal of nutrition. 2011; 141(6):1146–53. Epub 2011/04/22. DOI: 10.3945/jn.110.133728 [PubMed: 21508210]
40. Orchard TS, Ing SW, Lu B, Belury MA, Johnson K, Wactawski-Wende J, Jackson RD. The association of red blood cell n-3 and n-6 fatty acids with bone mineral density and hip fracture risk in the women's health initiative. J Bone Miner Res. 2013; 28(3):505–15. Epub 2012/09/29. DOI: 10.1002/jbmr.1772 [PubMed: 23018646]
41. Hutchins-Wiese HL, Picho K, Watkins BA, Li Y, Tannenbaum S, Claffey K, Kenny AM. High-dose eicosapentaenoic acid and docosahexaenoic acid supplementation reduces bone resorption in postmenopausal breast cancer survivors on aromatase inhibitors: a pilot study. Nutrition and cancer. 2014; 66(1):68–76. Epub 2013/11/28. DOI: 10.1080/01635581.2014.847964 [PubMed: 24274259]
42. Tartibian B, Hajizadeh Maleki B, Kanaley J, Sadeghi K. Long-term aerobic exercise and omega-3 supplementation modulate osteoporosis through inflammatory mechanisms in post-menopausal women: a randomized, repeated measures study. Nutrition & metabolism. 2011; 8:71. Epub 2011/10/18. doi: 10.1186/1743-7075-8-71 [PubMed: 21999620]
43. Chen JS, Hill CL, Lester S, Ruediger CD, Battersby R, Jones G, Cleland LG, March LM. Supplementation with omega-3 fish oil has no effect on bone mineral density in adults with knee osteoarthritis: a 2-year randomized controlled trial. Osteoporos Int. 2016; 27(5):1897–905. Epub 2015/12/24. DOI: 10.1007/s00198-015-3438-x [PubMed: 26694596]
44. Manson JE, Bassuk SS, Lee IM, Cook NR, Albert MA, Gordon D, Zaharris E, Macfadyen JG, Danielson E, Lin J, Zhang SM, Buring JE. The VITamin D and OmegA-3 TriaL (VITAL): Rationale and design of a large randomized controlled trial of vitamin D and marine omega-3 fatty acid supplements for the primary prevention of cancer and cardiovascular disease. Contemp Clin Trials. 2011; 33(1):159–71. Epub 2011/10/12. doi: S1551-7144(11)00245-X [pii]. DOI: 10.1016/j.cct.2011.09.009 [PubMed: 21986389]
45. LeBoff MS, Yue AY, Copeland T, Cook NR, Buring JE, Manson JE. VITAL-Bone Health: Rationale and design of two ancillary studies evaluating the effects of vitamin D and/or omega-3 fatty acid supplements on incident fractures and bone health outcomes in the VITamin D and

OmegA-3 TriaL (VITAL). Contemp Clin Trials. 2015; 41C:259–68. DOI: 10.1016/j.cct.2015.01.007

46. Manson JE, Bassuk SS, Lee IM, Cook NR, Albert MA, Gordon D, Zaharris E, Macfadyen JG, Danielson E, Lin J, Zhang SM, Buring JE. The VITamin D and OmegA-3 TriaL (VITAL): rationale and design of a large randomized controlled trial of vitamin D and marine omega-3 fatty acid supplements for the primary prevention of cancer and cardiovascular disease. Contemporary clinical trials. 2012; 33(1):159–71. DOI: 10.1016/j.cct.2011.09.009 [PubMed: 21986389]
47. Schousboe JT, Shepherd JA, Bilezikian JP, Baim S. Executive summary of the 2013 International Society for Clinical Densitometry Position Development Conference on bone densitometry. J Clin Densitom. 2013; 16(4):455–66. DOI: 10.1016/j.jocd.2013.08.004 [PubMed: 24183638]
48. Wampler NS, Chen Z, Jacobsen C, Henderson JA, Howard BV, Rossouw JE. Bone mineral density of American Indian and Alaska Native women compared with non-Hispanic white women: results from the Women's Health Initiative Study. Menopause (New York, NY). 2005; 12(5):536–44. DOI: 10.1097/01.gme.0000182161.88939.f0
49. Cauley JA. Defining Ethnic and Racial Differences in Osteoporosis and Fragility Fractures. Clinical Orthopaedics and Related Research®. 2011; 469(7):1891.doi: 10.1007/s11999-011-1863-5 [PubMed: 21431462]
50. El-Hajj, Fuleihan GE, Testa MA, Angell JE, Porrino N, Leboff MS. Reproducibility of DXA absorptiometry: a model for bone loss estimates. J Bone Miner Res. 1995; 10(7):1004–14. [PubMed: 7484275]
51. Hans D, Goertzen AL, Krieg MA, Leslie WD. Bone microarchitecture assessed by TBS predicts osteoporotic fractures independent of bone density: the Manitoba study. J Bone Miner Res. 2011; 26(11):2762–9. Epub 2011/09/03. DOI: 10.1002/jbmr.499 [PubMed: 21887701]
52. Silva BC, Boutroy S, Zhang C, McMahon DJ, Zhou B, Wang J, Udesky J, Cremers S, Sarquis M, Guo XD, Hans D, Bilezikian JP. Trabecular bone score (TBS)–a novel method to evaluate bone microarchitectural texture in patients with primary hyperparathyroidism. J Clin Endocrinol Metab. 2013; 98(5):1963–70. Epub 2013/03/26. DOI: 10.1210/jc.2012-4255 [PubMed: 23526463]
53. Schousboe JT, Vo T, Taylor BC, Cawthon PM, Schwartz AV, Bauer DC, Orwoll ES, Lane NE, Barrett-Connor E, Ensrud KE, for the Osteoporotic Fractures in Men Study Research G. Prediction of Incident Major Osteoporotic and Hip Fractures by Trabecular Bone Score (TBS) and Prevalent Radiographic Vertebral Fracture in Older Men. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2016; 31(3):690–7. DOI: 10.1002/jbmr.2713
54. Mary, K.Oates, NB.Fung, EllenSabowitz, Brian N.Shepherd, John, Warner, Sarah, editors. (ISCD) The International Society for Clinical Densitometry. Performing Body Composition Assessments with DXA. International Society for Bone Densitometry Body Composition Course Syllabus; Middletown, CT: 2012. p. 116
55. Glowacki J, Tuteja M, Hurwitz S, Thornhill TS, Leboff MS. Discordance in femoral neck bone density in subjects with unilateral hip osteoarthritis. J Clin Densitom. 2010; 13(1):24–8. Epub 2010/02/23. doi: S1094-6950(09)00268-6 [pii]. DOI: 10.1016/j.jocd.2009.09.007 [PubMed: 20171566]
56. Nowitz M, Monahan P. Short term in vivo precision of whole body composition measurements on the Horizon A densitometer. Journal of medical imaging and radiation oncology. 2017; doi: 10.1111/1754-9485.12646
57. Marino M, Gleim GW. Muscle strength and fiber typing. Clin Sports Med. 1984; 3(1):85–100. [PubMed: 6545793]
58. Ashford RF, Nagelburg S, Adkins R. Sensitivity of the Jamar Dynamometer in detecting submaximal grip effort. The Journal of hand surgery. 1996; 21(3):402–5. DOI: 10.1016/S0363-5023(96)80352-2 [PubMed: 8724469]
59. Cooper C, Barker DJ, Wickham C. Physical activity, muscle strength, and calcium intake in fracture of the proximal femur in Britain. Bmj. 1988; 297(6661):1443–6. [PubMed: 3147008]
60. Kwon S, Perera S, Pahor M, Katula JA, King AC, Groessl EJ, Studenski SA. What is a meaningful change in physical performance? Findings from a clinical trial in older adults (the LIFE-P study). J Nutr Health Aging. 2009; 13(6):538–44. [PubMed: 19536422]

61. Atkinson HH, Rapp SR, Williamson JD, Lovato J, Absher JR, Gass M, Henderson VW, Johnson KC, Kostis JB, Sink KM, Mouton CP, Ockene JK, Stefanick ML, Lane DS, Espeland MA. The relationship between cognitive function and physical performance in older women: results from the women's health initiative memory study. J Gerontol A Biol Sci Med Sci. 2010; 65(3):300–6. Epub 2009/10/01. DOI: 10.1093/gerona/glp149 [PubMed: 19789197]
62. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel JP, Rolland Y, Schneider SM, Topinkova E, Vandewoude M, Zamboni M, European Working Group on Sarcopenia in Older P. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010; 39(4):412–23. DOI: 10.1093/ageing/afq034 [PubMed: 20392703]
63. Guralnik JM, Ferrucci L, Pieper CF, Leveille SG, Markides KS, Ostir GV, Studenski S, Berkman LF, Wallace RB. Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. J Gerontol A Biol Sci Med Sci. 2000; 55(4):M221–31. [PubMed: 10811152]
64. Studenski S, Perera S, Patel K, Rosano C, Faulkner K, Inzitari M, Brach J, Chandler J, Cawthon P, Connor EB, Nevitt M, Visser M, Kritchevsky S, Badinelli S, Harris T, Newman AB, Cauley J, Ferrucci L, Guralnik J. Gait speed and survival in older adults. JAMA. 2011; 305(1):50–8. DOI: 10.1001/jama.2010.1923 [PubMed: 21205966]
65. Bijlsma AY, Pasma JH, Lambers D, Stijntjes M, Blauw GJ, Meskers CG, Maier AB. Muscle strength rather than muscle mass is associated with standing balance in elderly outpatients. Journal of the American Medical Directors Association. 2013; 14(7):493–8. Epub 2013/04/02. DOI: 10.1016/j.jamda.2013.02.001 [PubMed: 23540951]
66. Leboff MS, Hawkes WG, Glowacki J, Yu-Yahiro J, Hurwitz S, Magaziner J. Vitamin D-deficiency and post-fracture changes in lower extremity function and falls in women with hip fractures. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2008
67. Gill TM, Williams CS, de Leon CFM, Tinetti ME. The Role of Change in Physical Performance in Determining Risk for Dependence in Activities of Daily Living Among Nondisabled Community-Living Elderly Persons. Journal of Clinical Epidemiology. 50(7):765–72. DOI: 10.1016/S0895-4356(97)00065-6
68. Cawthon PM, Fox KM, Gandra SR, Delmonico MJ, Chiou CF, Anthony MS, Sewall A, Goodpaster B, Satterfield S, Cummings SR, Harris TB, Health A. Body Composition S. Do muscle mass, muscle density, strength, and physical function similarly influence risk of hospitalization in older adults? Journal of the American Geriatrics Society. 2009; 57(8):1411–9. DOI: 10.1111/j.1532-5415.2009.02366.x [PubMed: 19682143]
69. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. N Engl J Med. 1995; 332(9):556–61. Epub 1995/03/02. DOI: 10.1056/nejm199503023320902 [PubMed: 7838189]
70. Latham NK, Mehta V, Nguyen AM, Jette AM, Olarsch S, Papanicolaou D, Chandler J. Performance-based or self-report measures of physical function: which should be used in clinical trials of hip fracture patients? Archives of physical medicine and rehabilitation. 2008; 89(11):2146–55. Epub 2008/11/11. DOI: 10.1016/j.apmr.2008.04.016 [PubMed: 18996244]
71. Bischoff HA, Sthelin HB, Monsch AU, Iversen MD, Weyh A, von Dechend M, Akos R, Conzelmann M, Dick W, Theiler R. Identifying a cutoff point for normal mobility: a comparison of the timed up and go test in communitydwelling and institutionalised elderly women. Age and Ageing. 2003; 32(3):315–20. DOI: 10.1093/ageing/32.3.315 [PubMed: 12720619]
72. The Timed Up and Go (TUG) Test www.cdc.gov/steadi/materials/html: Centers for Disease Control and Prevention: 2015 [updated 3/24/2017; cited 2017 9/14/2017]. Available from: www.cdc.gov/steadi/pdf/tug_test-a.pdf.
73. Nordin E, Lindelof N, Rosendahl E, Jensen J, Lundin-Olsson L. Prognostic validity of the Timed Up-and-Go test, a modified Get-Up-and-Go test, staff's global judgement and fall history in evaluating fall risk in residential care facilities. Age Ageing. 2008; 37(4):442–8. DOI: 10.1093/ageing/afn101 [PubMed: 18515291]
74. Bauer DC. FRAX, Falls, and Fracture Prediction: Predicting the Future: Comment on "'Timed Up and Go' Test and Bone Mineral Density Measurement for Fracture Prediction". Archives of

internal medicine. 2011; 171(18):1661–2. Epub 2011/10/12. doi: 171/18/1661 [pii]. DOI: 10.1001/archinternmed.2011.495 [PubMed: 21987196]

75. Dam TT, von Muhlen D, Barrett-Connor EL. Sex-specific association of serum vitamin D levels with physical function in older adults. Osteoporos Int. 2009; 20(5):751–60. DOI: 10.1007/s00198-008-0749-1 [PubMed: 18802657]
76. Newman AB, Kupelian V, Visser M, Simonsick E, Goodpaster B, Nevitt M, Kritchevsky SB, Tylavsky FA, Rubin SM, Harris TB, Health ABCSI. Sarcopenia: alternative definitions and associations with lower extremity function. J Am Geriatr Soc. 2003; 51(11):1602–9. [PubMed: 14687390]
77. Vasunilashorn S, Coppin AK, Patel KV, Lauretani F, Ferrucci L, Bandinelli S, Guralnik JM. Use of the Short Physical Performance Battery Score to predict loss of ability to walk 400 meters: analysis from the InCHIANTI study. J Gerontol A Biol Sci Med Sci. 2009; 64(2):223–9. Epub 2009/02/03. DOI: 10.1093/gerona/gln022 [PubMed: 19182232]
78. Cawthon PM. Assessment of Lean Mass and Physical Performance in Sarcopenia. J Clin Densitom. 2015; 18(4):467–71. DOI: 10.1016/j.jocd.2015.05.063 [PubMed: 26071168]
79. Murphy RA, Ip EH, Zhang Q, Boudreau RM, Cawthon PM, Newman AB, Tylavsky FA, Visser M, Goodpaster BH, Harris TB, Health A. Body Composition S. Transition to sarcopenia and determinants of transitions in older adults: a population-based study. J Gerontol A Biol Sci Med Sci. 2014; 69(6):751–8. DOI: 10.1093/gerona/glt131 [PubMed: 24013673]
80. Dam TT, Peters KW, Fragala M, Cawthon PM, Harris TB, McLean R, Shardell M, Alley DE, Kenny A, Ferrucci L, Guralnik J, Kiel DP, Kritchevsky S, Vassileva MT, Studenski S. An evidence-based comparison of operational criteria for the presence of sarcopenia. The journals of gerontology Series A, Biological sciences and medical sciences. 2014; 69(5):584–90. DOI: 10.1093/gerona/glu013 [PubMed: 24737561]
81. von Haehling S, Morley JE, Anker SD. An overview of sarcopenia: facts and numbers on prevalence and clinical impact. J Cachexia Sarcopenia Muscle. 2010; 1(2):129–33. DOI: 10.1007/s13539-010-0014-2 [PubMed: 21475695]
82. Morley JE, Anker SD, von Haehling S. Prevalence, incidence, and clinical impact of sarcopenia: facts, numbers, and epidemiology-update 2014. J Cachexia Sarcopenia Muscle. 2014; 5(4):253–9. DOI: 10.1007/s13539-014-0161-y [PubMed: 25425503]
83. Patel HP, Syddall HE, Jameson K, Robinson S, Denison H, Roberts HC, Edwards M, Dennison E, Cooper C, Aihie Sayer A. Prevalence of sarcopenia in community-dwelling older people in the UK using the European Working Group on Sarcopenia in Older People (EWGSOP) definition: findings from the Hertfordshire Cohort Study (HCS). Age Ageing. 2013; 42(3):378–84. Epub 2013/02/07. DOI: 10.1093/ageing/afs197 [PubMed: 23384705]
84. Studenski SA, Peters KW, Alley DE, Cawthon PM, McLean RR, Harris TB, Ferrucci L, Guralnik JM, Fragala MS, Kenny AM, Kiel DP, Kritchevsky SB, Shardell MD, Dam TT, Vassileva MT. The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. J Gerontol A Biol Sci Med Sci. 2014; 69(5):547–58. DOI: 10.1093/gerona/glu010 [PubMed: 24737557]
85. Pazaris, M., Hertzmark, E., Spiegelman, D. The SAS TABLE1 Macro2013. p. 20Available from: https://cdn1.sph.harvard.edu/wp-content/uploads/sites/271/2013/11/table1.pdf
86. McLean RR, Shardell MD, Alley DE, Cawthon PM, Fragala MS, Harris TB, Kenny AM, Peters KW, Ferrucci L, Guralnik JM, Kritchevsky SB, Kiel DP, Vassileva MT, Xue QL, Perera S, Studenski SA, Dam TT. Criteria for clinically relevant weakness and low lean mass and their longitudinal association with incident mobility impairment and mortality: the foundation for the National Institutes of Health (FNIH) sarcopenia project. J Gerontol A Biol Sci Med Sci. 2014; 69(5):576–83. DOI: 10.1093/gerona/glu012 [PubMed: 24737560]
87. Cawthon PM, Peters KW, Shardell MD, McLean RR, Dam TT, Kenny AM, Fragala MS, Harris TB, Kiel DP, Guralnik JM, Ferrucci L, Kritchevsky SB, Vassileva MT, Studenski SA, Alley DE. Cutpoints for low appendicular lean mass that identify older adults with clinically significant weakness. The journals of gerontology Series A, Biological sciences and medical sciences. 2014; 69(5):567–75. DOI: 10.1093/gerona/glu023 [PubMed: 24737559]
88. Cesari M, Kritchevsky SB, Newman AB, Simonsick EM, Harris TB, Penninx BW, Brach JS, Tylavsky FA, Satterfield S, Bauer DC, Rubin SM, Visser M, Pahor M. Added value of physical

performance measures in predicting adverse health-related events: results from the Health, Aging And Body Composition Study. J Am Geriatr Soc. 2009; 57(2):251–9. Epub 2009/02/12. DOI: 10.1111/j.1532-5415.2008.02126.x [PubMed: 19207142]

89. da Camara SM, Alvarado BE, Guralnik JM, Guerra RO, Maciel AC. Using the Short Physical Performance Battery to screen for frailty in young-old adults with distinct socioeconomic conditions. Geriatrics & gerontology international. 2013; 13(2):421–8. DOI: 10.1111/j.1447-0594.2012.00920.x [PubMed: 22882512]
90. Bassuk SS, Manson JE, Lee IM, Cook NR, Christen WG, Bubes VY, Gordon DS, Copeland T, Friedenberg G, D'Agostino DM, Ridge CY, MacFadyen JG, Kalan K, Buring JE. Baseline characteristics of participants in the VITamin D and OmegA-3 TriaL (VITAL). Contemp Clin Trials. 2016; 47:235–43. DOI: 10.1016/j.cct.2015.12.022 [PubMed: 26767629]
91. Looker, AC., Wang, CY. Prevalence of reduced muscle strength in older U.S. adults: United States, 2011–2012. Statistics NCfH. , editor. Hyattsville, MD: 2015. NCHS data brief no 179

Table 1

Baseline characteristics of participants in the VITAL CTSC Bone Health subcohort, according to randomized treatment assignment

	Vitamin D and omega-3 fatty acids	**Vitamin D and placebo**	**Placebo and omega-3 fatty acids**	**Placebo and placebo**	**All**	**P-value**
Demographic characteristics						
Sex	**N= 193**	**N= 195**	**N= 195**	**N= 188**	**N= 771**	**0.77**
Male	105 (54.4%)	104 (53.3%)	98 (50.3%)	104 (55.3%)	411 (53.3%)	
Female	88 (45.6%)	91 (46.7%)	97 (49.7%)	84 (44.7%)	360 (46.7%)	
Age, mean (SD), years	63.58 (6.46)	63.73 (5.46)	63.95 (6.31)	63.91 (6.30)	63.79 (6.13)	0.93
Age group, years	**N= 193**	**N= 195**	**N= 195**	**N= 188**	**N= 771**	**0.37**
50–54	19 (9.8%)	11 (5.6%)	10 (5.1%)	13 (6.9%)	53 (6.9%)	
55–64	100 (51.8%)	106 (54.4%)	108 (55.4%)	99 (52.7%)	413 (53.6%)	
65–74	62 (32.1%)	74 (37.9%)	67 (34.4%)	64 (34.0%)	267 (34.6%)	
75+	12 (6.2%)	4 (2.1%)	10 (5.1%)	12 (6.4%)	38 (4.9%)	
Race/ethnicity	**N= 190**	**N= 193**	**N= 189**	**N= 183**	**N= 755**	**0.59**
Non-Hispanic white	155 (81.6%)	162 (83.9%)	157 (83.1%)	156 (85.2%)	630 (83.4%)	
African American	18 (9.5%)	17 (8.8%)	17 (9.0%)	15 (8.2%)	67 (8.9%)	
Hispanic (not African American)	8 (4.2%)	3 (1.6%)	6 (3.2%)	9 (4.9%)	26 (3.4%)	
Asian/Pacific Islander	5 (2.6%)	4 (2.1%)	4 (2.1%)	2 (1.1%)	15 (2.0%)	
American Indian/Alaskan Native	1 (0.5%)	1 (0.5%)	3 (1.6%)	0 (0.0%)	5 (0.7%)	
Other/Unknown	3 (1.6%)	6 (3.1%)	2 (1.1%)	1 (0.5%)	12 (1.6%)	
Education Level	**N= 193**	**N= 194**	**N= 195**	**N= 188**	**N= 770**	**0.30**
Did not complete high school	1 (0.5%)	3 (1.5%)	0 (0.0%)	5 (2.7%)	9 (1.2%)	
High school diploma or GED	20 (10.4%)	13 (6.7%)	18 (9.2%)	19 (10.1%)	70 (9.1%)	
Attended or graduated from college	67 (34.7%)	81 (41.8%)	78 (40.0%)	73 (38.8%)	299 (38.8%)	
Post-college	105 (54.4%)	97 (50.0%)	99 (50.8%)	91 (48.4%)	392 (50.9%)	
Income	**N= 165**	**N= 170**	**N= 171**	**N= 164**	**N= 670**	**0.45**
<$15,000	8 (4.8%)	11 (6.5%)	5 (2.9%)	9 (5.5%)	33 (4.9%)	
$15,000–49,999	28 (17.0%)	36 (21.2%)	32 (18.7%)	29 (17.7%)	125 (18.7%)	
$50.000–89.999	46 (27.9%)	52 (30.6%)	49 (28.7%)	37 (22.6%)	184 (27.5%)	

	Vitamin D and omega-3 fatty acids	Vitamin D and placebo	Placebo and omega-3 fatty acids	Placebo and placebo	All	P-value
$90,000–120,000	39 (23.6%)	23 (13.5%)	31 (18.1%)	33 (20.1%)	126 (18.8%)	
>$120,000	44 (26.7%)	48 (28.2%)	54 (31.6%)	56 (34.1%)	202 (30.1%)	
Bone characteristics						
Whole Body, mean (SD)						
BMD, g/cm^2	1.16 (0.14)	1.15 (0.13)	1.14 (0.13)	1.15 (0.13)	1.15 (0.13)	0.58
T-score	−0.13 (1.20)	−0.24 (1.14)	−0.28 (1.20)	−0.18 (1.27)	−0.20 (1.20)	0.66
Z-score	0.41 (0.96)	0.32 (0.92)	0.30 (0.95)	0.38 (1.04)	0.35 (0.97)	0.67
Spine, mean (SD)						
BMD, g/cm^2	1.03 (0.16)	1.02 (0.16)	1.02 (0.16)	1.03 (0.17)	1.02 (0.16)	0.86
T-score	−0.45 (1.32)	−0.53 (1.36)	−0.53 (1.40)	−0.45 (1.55)	−0.49 (1.41)	0.90
Z-score	0.70 (1.34)	0.64 (1.37)	0.65 (1.41)	0.68 (1.61)	0.67 (1.43)	0.98
Total Hip, mean (SD)						
BMD, g/cm^2	0.94 (0.14)	0.92 (0.13)	0.93 (0.15)	0.93 (0.15)	0.93 (0.14)	0.44
T-score	−0.45 (0.87)	−0.58 (0.85)	−0.54 (0.92)	−0.54 (0.94)	−0.53 (0.90)	0.55
Z-score	0.38 (0.84)	0.25 (0.86)	0.33 (0.88)	0.30 (0.94)	0.32 (0.88)	0.56
Femoral Neck, mean (SD)						
BMD, g/cm^2	0.78 (0.14)	0.76 (0.12)	0.77 (0.13)	0.77 (0.12)	0.77 (0.13)	0.22
T-score	−1.00 (0.92)	−1.17 (0.83)	−1.09 (0.91)	−1.11 (0.90)	−1.09 (0.89)	0.32
Z-score	0.24 (0.91)	0.08 (0.86)	0.18 (0.88)	0.14 (0.92)	0.16 (0.89)	0.33
TBS, mean (SD)	1.33 (0.09)	1.31 (0.10)	1.31 (0.10)	1.34 (0.09)	1.32 (0.09)	
TBS group [52, 53]	**N= 168**	**N= 173**	**N= 164**	**N= 167**	**N= 672**	**0.35**
≥1.350	66 (39.3%)	65 (37.6%)	60 (36.6%)	77 (46.1%)	268 (39.9%)	
1.200< >1.350	88 (52.4%)	87 (50.3%)	83 (50.6%)	78 (46.7%)	336 (50.0%)	
≤1.200	14 (8.3%)	21 (12.1%)	21 (12.8%)	12 (7.2%)	68 (10.1%)	
Hip FRAX, median (interquartile range)	0.90 (0.50 – 1.60)	1.00 (0.70 – 1.60]	1.00 (0.60 – 1.75)	0.90 (0.60 – 1.40)	0.90 (0.60 – 1.60)	0.61
MOF FRAX, mean (SD)	8.54 (4.52)	8.35 (3.96)	8.35 (3.56)	7.94 (3.22)	8.31 (3.86)	0.73
FRAX group	**N= 109**	**N= 109**	**N= 104**	**N= 96**	**N= 418**	**0.34**
Hip FRAX ≥3% and/or MOF FRAX ≥20%	13 (11.9%)	7 (6.4%)	8 (7.7%)	12 (12.5%)	40 (9.6%)	

	Vitamin D and omega-3 fatty acids	Vitamin D and placebo	Placebo and omega-3 fatty acids	Placebo and placebo	All	P-value
Hip FRAX< 3%, and MOF FRAX < 20%	96 (88.1%)	102 (93.6%)	96 (92.3%)	84 (87.5%)	378 (90.4%)	
Body Composition						
Anthropometric measurements, mean (SD)						
Height, in	66.97 (3.75)	67.21 (3.65)	66.34 (3.77)	66.47 (3.83)	66.75 (3.76)	0.070
Weight, lb	182.00 (35.15)	180.68 (37.67)	180.93 (39.08)	175.68 (37.62)	179.86 (37.42)	0.36
Waist, cm	98.74 (14.45)	98.86 (15.24)	99.36 (15.09)	97.30 (15.94)	98.58 (15.17)	0.59
BMI, mean (SD), kg/m^2	28.52 (5.18)	28.07 (5.31)	28.79 (5.14)	27.84 (4.93)	28.31 (5.14)	0.27
BMI group, kg/m^2	**N= 193**	**N= 195**	**N= 195**	**N= 188**	**N= 771**	**0.25**
<18.5	1 (0.5%)	0 (0.0%)	2 (1.0%)	1 (0.5%)	4 (0.5%)	
18.5–24.9	47 (24.4%)	58 (29.7%)	42 (21.5%)	54 (28.7%)	201 (26.1%)	
25–29.9	87 (45.1%)	85 (43.6%)	86 (44.1%)	76 (40.4%)	334 (43.3%)	
30–34.9	32 (16.6%)	35 (17.9%)	41 (21.0%)	45 (23.9%)	153 (19.8%)	
35+	26 (13.5%)	17 (8.7%)	24 (12.3%)	12 (6.4%)	79 (10.2%)	
Body Fat Percentage, mean (SD)	36.06 (8.59)	36.48 (8.27)	37.19 (8.62)	35.62 (8.44)	36.35 (8.48)	0.31
FMI, mean (SD), kg/m^2	10.30 (4.12)	10.22 (3.94)	10.67 (3.83)	9.88 (3.62)	10.27 (3.89)	0.26
LMI, mean (SD), kg/m^2	16.65 (2.27)	16.26 (2.41)	16.53 (2.56)	16.38 (2.51)	16.45 (2.44)	0.43
Fat Mass/Lean Mass Ratio, mean (SD)	0.63 (0.24)	0.64 (0.24)	0.66 (0.24)	0.61 (0.23)	0.63 (0.24)	0.33
VAT area, mean (SD), cm^2	167.24 (70.28)	167.22 (74.16)	168.04 (76.77)	159.90 (72.10)	165.65 (73.32)	0.68
Trunk/limb fat percent ratio, mean (SD)	1.07 (0.22)	1.04 (0.20)	1.04 (0.24)	1.05 (0.21)	1.05 (0.22)	0.38
Trunk/limb mass ratio, mean (SD)	1.24 (0.31)	1.21 (0.30)	1.21 (0.38)	1.22 (0.30)	1.22 (0.33)	0.76
Trunk Fat Mass, mean (SD), kg	15.42 (5.80)	15.39 (5.98)	15.60 (5.88)	14.58 (5.68)	15.25 (5.84)	0.33
ALM, mean (SD), kg	20.75 (4.92)	20.30 (5.12)	20.12 (5.45)	20.09 (5.33)	20.32 (5.21)	0.59
ALMI, mean (SD), kg/m^2	7.09 (1.20)	6.87 (1.26)	6.98 (1.37)	6.94 (1.32)	6.97 (1.29)	0.42
ALM/BMI, mean (SD)	0.74 (0.18)	0.73 (0.18)	0.71 (0.18)	0.73 (0.18)	0.73 (0.18)	0.29
Physical Performance						
Standing Balance Test Time, median (interquartile range), s	30.00 (30.00 – 30.00)	30.00 (30.00 – 30.00)	30.00 (30.00 – 30.00)	30.00 (30.00 – 30.00)	30.00 (30.00 – 30.00)	0.12
Normal Walking Speed, mean (SD), m/s	1.22 (0.19)	1.24 (0.20)	1.24 (0.19)	1.24 (0.20)	1.24 (0.19)	0.74
Fast Walk Speed, mean (SD), m/s	1.80 (0.27)	1.80 (0.27)	1.79 (0.28)	1.81 (0.29)	1.80 (0.28)	0.85

	Vitamin D and omega-3 fatty acids	Vitamin D and placebo	Placebo and omega-3 fatty acids	Placebo and placebo	All	P-value
Chair Stand Test, mean (SD), s	10.05 (2.54)	10.17 (2.35)	10.16 (2.36)	9.76 (2.19)	10.04 (2.37)	0.31
Grip Strength, men, mean (SD), kg	40.87 (8.50)	39.23 (8.59)	40.64 (7.80)	38.31 (9.02)	39.76 (8.53)	0.10
Grip Strength, women, mean (SD), kg	24.89 (5.18)	25.14 (4.69)	23.61 (5.64)	24.02 (4.95)	24.41 (5.16)	0.15
SPPB Score, median (interquartile range)	12.00 (11.00 – 12.00)	12.00 (11.00 – 12.00)	12.00 (11.00 – 12.00)	12.00 (11.00 – 12.00)	12.00 (11.00 – 12.00)	0.35
TUG, mean (SD), s	8.04 (1.35)	8.05 (1.21)	8.07 (1.23)	8.06 (1.23)	8.06 (1.26)	1.0
Health History						
Hypertension History	**N= 192**	**N= 193**	**N= 192**	**N= 187**	**N= 764**	**0.40**
Yes	84 (43.8%)	81 (42.0%)	96 (50.0%)	88 (47.1%)	349 (45.7%)	
Ever use of anti-hypertensive medication	**N= 193**	**N= 194**	**N= 193**	**N= 188**	**N= 768**	**0.36**
Yes	81 (42.0%)	76 (39.2%)	92 (47.7%)	85 (45.2%)	334 (43.5%)	
Current use of cholesterol-lowering medication	**N= 192**	**N= 191**	**N= 194**	**N= 186**	**N= 763**	**0.78**
Yes	71 (37.0%)	61 (31.9%)	67 (34.5%)	63 (33.9%)	262 (34.3%)	
Diabetes	**N= 191**	**N= 194**	**N= 193**	**N= 185**	**N= 763**	**0.48**
Yes	18 (9.4%)	24 (12.4%)	15 (7.8%)	20 (10.8%)	77 (10.1%)	
Current use of anti-diabetic medication	**N= 193**	**N= 195**	**N= 195**	**N= 188**	**N= 771**	**0.51**
Yes	15 (7.8%)	19 (9.7%)	11 (5.6%)	15 (8.0%)	60 (7.8%)	
Parental history of hip fracture	**N= 170**	**N= 179**	**N= 178**	**N= 177**	**N= 704**	**0.47**
Yes	20 (11.8%)	30 (16.8%)	23 (12.9%)	21 (11.9%)	94 (13.4%)	
Rheumatoid arthritis	**N= 191**	**N= 189**	**N= 195**	**N= 184**	**N= 759**	**0.55**
Yes	2 (1.0%)	6 (3.2%)	4 (2.1%)	4 (2.2%)	16 (2.1%)	
History of fragility fracture	**N= 162**	**N= 167**	**N= 163**	**N= 163**	**N= 655**	**0.76**
Yes	12 (7.4%)	17 (10.2%)	12 (7.4%)	13 (8.0%)	54 (8.2%)	
Current use of SSRIs	**N= 189**	**N= 191**	**N= 193**	**N= 186**	**N= 759**	**0.067**
Yes	9 (4.8%)	12 (6.3%)	22 (11.4%)	18 (9.7%)	61 (8.0%)	
Number of falls in the last year	**N= 125**	**N= 122**	**N= 118**	**N= 118**	**N= 483**	**0.73**
None	95 (76.0%)	96 (78.7%)	87 (73.7%)	86 (72.9%)	364 (75.4%)	
One	22 (17.6%)	17 (13.9%)	27 (22.9%)	26 (22.0%)	92 (19.0%)	
Two	4 (3.2%)	5 (4.1%)	3 (2.5%)	3 (2.5%)	15 (3.1%)	
Three or more	4 (3.2%)	4 (3.3%)	1 (0.8%)	3 (2.5%)	12 (2.5%)	

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	Vitamin D and omega-3 fatty acids	Vitamin D and placebo	Placebo and omega-3 fatty acids	Placebo and placebo	All	P-value
Behavioral Characteristics						
Leisure-time physical activity and stair climbing, total MET-hours/week, median (Interquartile range)	22.65 (9.65 – 43.70)	21.50 (7.70 – 35.60)	21.60 (8.40 – 36.00)	20.40 (6.90 – 36.90)	21.50 (7.90 – 37.10)	0.55
Smoking	**N= 193**	**N= 191**	**N= 195**	**N= 187**	**N= 766**	
Never	81 (42.0%)	84 (44.0%)	106 (54.4%)	112 (59.9%)	383 (50.0%)	
Past	98 (50.8%)	95 (49.7%)	80 (41.0%)	62 (33.2%)	335 (43.7%)	
Current	14 (7.3%)	12 (6.3%)	9 (4.6%)	13 (7.0%)	48 (6.3%)	
Alcohol use	**N= 179**	**N= 182**	**N= 184**	**N= 180**	**N= 725**	**0.26**
Never	33 (18.4%)	42 (23.1%)	40 (21.7%)	29 (16.1%)	144 (19.9%)	
Rarely to <weekly	14 (7.8%)	12 (6.6%)	15 (8.2%)	8 (4.4%)	49 (6.8%)	
1–6/week	75 (41.9%)	68 (37.4%)	63 (34.2%)	88 (48.9%)	294 (40.6%)	
Daily	57 (31.8%)	60 (33.0%)	66 (35.9%)	55 (30.6%)	238 (32.8%)	
Current use of multivitamins	**N= 179**	**N= 185**	**N= 183**	**N= 181**	**N= 728**	**0.50**
Yes	69 (38.5%)	83 (44.9%)	81 (44.3%)	83 (45.9%)	316 (43.4%)	
Current use of supplemental Vitamin D (total ≤800IU/d)	**N= 193**	**N= 195**	**N= 195**	**N= 188**	**N= 771**	**0.15**
Yes	70 (36.3%)	87 (44.6%)	92 (47.2%)	77 (41.0%)	326 (42.3%)	
Current use of supplemental calcium (total≤1200 mg/d)	**N= 193**	**N= 195**	**N= 195**	**N= 188**	**N= 771**	**0.21**
Yes	39 (20.2%)	53 (27.2%)	51 (26.2%)	38 (20.2%)	181 (23.5%)	
Intake of foods related to vitamin D and/or omega-3 fatty acids, median (interquartile range)						
Milk, servings/day	0.43 (0.07 – 1.00)	0.43 (0.07 – 1.00)	0.43 (0.13 – 1.00)	0.43 (0.07 – 1.00)	0.43 (0.07 – 1.00)	0.69
Other vitamin D-fortified foods, servings/week	0.50 (0.14 – 1.00)	0.50 (0.07 – 1.00)	0.50 (0.14 – 1.07)	0.56 (0.13 – 1.00)	0.50 (0.14 – 1.00)	0.61
Dark-meat fish, servings/week	0.93 (0.47 – 1.47)	0.93 (0.47 – 1.00)	0.93 (0.47 – 1.47)	0.93 (0.47 – 1.47)	0.93 (0.47 – 1.47)	0.58
Other fish and seafood, servings/week	0.93 (0.47 – 1.47)	0.93 (0.47 – 1.47)	0.93 (0.47 – 1.47)	0.93 (0.47 – 1.47)	0.93 (0.47 – 1.47)	0.52

Table 2

Baseline characteristics among participants in the VITAL CTSC Bone Health subcohort, according to sex and adjusted for age

Variable	Men (n=411)	Women (n= 360)	P-value
Demographic characteristics			
Age, mean (SD), years	63.28 (6.69)	64.39 (5.37)	
Age group, years	**N= 411**	**N= 360**	
50–54	12.90%	0.00%	
55–64	48.66%	59.17%	
65–74	33.57%	35.8%	
75+	4.87%	5.00%	
Race/ethnicity	**N= 403**	**N= 352**	**0.39**
Non-Hispanic white	81.38%	87.11%	
African American	10.85%	5.59%	
Hispanic (not African American)	3.78%	2.80%	
Asian/Pacific Islander	1.74%	2.25%	
American Indian/Alaskan Native	0.55%	0.83%	
Other/Unknown	1.70%	1.42%	
Education Level	**N= 411**	**N= 359**	**0.26**
Did not complete high school	1.58%	0.54%	
High school diploma or GED	8.42%	9.50%	
Attended or graduated from college	36.64%	41.48%	
Post-college	53.36%	48.48%	
Income	**N= 361**	**N= 309**	
<$15,000	5.08%	4.54%	
$15,000–49,999	16.64%	20.85%	
$50.000–89.999	24.29%	31.96%	
$90,000–120,000	18.93%	19.34%	
>$120,000	35.07%	23.31%	
Bone characteristics			
Whole Body, mean (SE)			
BMD, g/cm^2	1.22 (0.01)	1.07 (0.01)	
T-score	0.10 (0.06)	−0.56 (0.06)	
Z-score	0.46 (0.05)	0.23 (0.05)	
Spine, mean (SE)			
BMD, g/cm^2	1.08 (0.01)	0.96 (0.01)	
T-score	−0.21 (0.07)	−0.81 (0.08)	
Z-score	0.51 (0.07)	0.85 (0.08)	
Total Hip, mean (SE)			

Variable	Men (n=411)	Women (n= 360)	P-value
BMD, g/cm^2	1.00 (0.01)	0.85 (0.01)	
T-score	−0.32 (0.04)	−0.77 (0.05)	
Z-score	0.26 (0.04)	0.38 (0.05)	0.06
Femoral Neck, mean (SE)			
BMD, g/cm^2	0.82 (0.01)	0.72 (0.01)	
T-score	−0.95 (0.04)	−1.25 (0.05)	
Z-score	0.12 (0.04)	0.21 (0.05)	0.14
TBS, mean (SE)	1.34 (0.00)	1.31 (0.01)	
TBS group [52, 53]	**N= 369**	**N= 303**	
≥1.350	46.34%	30.86%	
1.200< >1.350	43.83%	58.85%	
≤1.200	9.84%	10.29%	
Hip FRAX, median (interquartile range)	1.04 (0.65 – 1.52)	1.20 (0.79 – 1.61)	0.23
MOF FRAX, mean (SE)	6.55 (0.22)	10.03 (0.22)	
FRAX group	**N= 207**	**N= 211**	**0.67**
Hip FRAX ≥3% and/or MOF FRAX ≥20%	9.26%	10.23%	
Hip FRAX < 3%, and MOF FRAX < 20%	90.74%	89.77%	
Body Composition			
Anthropometric measurements, mean (SE)			
Height, in	69.26 (0.13)	63.89 (0.14)	
Weight, lb	194.13 (1.68)	163.56 (1.80)	
Waist, cm	102.86 (0.72)	93.71 (0.77)	
BMI, mean (SE), kg/m^2	28.43 (0.25)	28.17 (0.27)	0.50
BMI group, kg/m^2	**N= 411**	**N= 360**	
<18.5	0.13%	0.83%	
18.5–24.9	20.38%	33.51%	
25–29.9	53.06%	32.32%	
30–34.9	18.46%	20.55%	
35+	7.96%	12.79%	
Body Fat Percentage, mean (SE)	31.12 (0.31)	42.38 (0.33)	
FMI, mean (SE), kg/m^2	8.79 (0.18)	11.98 (0.19)	
LMI, mean (SE), kg/m^2	17.92 (0.09)	14.76 (0.10)	
Fat Mass/Lean Mass Ratio, mean (SE)	0.49 (0.01)	0.80 (0.01)	
VAT area, mean (SE), cm^2	178.21 (3.56)	151.15 (3.82)	
Trunk/limb fat percent ratio, mean (SE)	1.17 (0.01)	0.91 (0.01)	
Trunk/limb mass ratio, mean (SE)	1.39 (0.01)	1.03 (0.01)	
Trunk Fat Mass, mean (SE), kg	15.04 (0.29)	15.50 (0.31)	0.28
ALM, mean (SE), kg	24.20 (0.15)	15.83 (0.16)	

Variable	Men (n=411)	Women (n= 360)	P-value
ALMI, mean (SE), kg/m^2	7.81 (0.04)	6.00 (0.05)	
ALM/BMI, mean (SE)	0.86 (0.01)	0.57 (0.01)	
Physical Performance			
Standing Balance Test Time, median (interquartile range), s	30.00 (30.00 – 30.00)	30.00 (30.00 – 30.00)	0.12
Normal Walking Speed, mean (SE), m/s	1.23 (0.01)	1.24 (0.01)	0.32
Fast Walk Speed, mean (SE), m/s	1.85 (0.01)	1.75 (0.01)	
Chair Stand Test, mean (SE), s	10.19 (0.12)	9.86 (0.13)	0.059
SPPB Score, median (interquartile range)	12.00 (11.00 – 12.00)	12.00 (11.54 – 12.00)	0.26
TUG, mean (SE), s	8.23 (0.07)	7.88 (0.07)	
Health History			
Hypertension History	**N= 409**	**N= 355**	
Yes	50.43%	41.46%	
Ever use of anti-hypertensive medication	**N= 410**	**N= 358**	
Yes	47.93%	39.74%	
Current use of cholesterol-lowering medication	**N= 406**	**N= 357**	
Yes	38.37%	30.50%	
Diabetes	**N= 407**	**N= 356**	
Yes	12.41%	7.61%	
Current use of anti-diabetic medication	**N= 411**	**N= 360**	**0.10**
Yes	9.25%	6.12%	
Parental history of hip fracture	**N= 373**	**N= 331**	
Yes	9.90%	17.56%	
Rheumatoid arthritis	**N= 404**	**N= 355**	**0.65**
Yes	1.83%	2.48%	
History of fragility fracture	**N= 360**	**N= 295**	
Yes	5.30%	12.06%	
Current use of SSRIs	**N= 403**	**N= 356**	**0.052**
Yes	6.18%	10.04%	
Number of falls in the last year	**N= 251**	**N= 232**	**0.24**
None	79.07%	71.07%	
One	16.95%	21.63%	
Two	2.48%	3.83%	
Three	1.50%	3.46%	
Behavioral Characteristics			
Smoking	**N= 407**	**N= 359**	**0.66**
Never	49.00%	50.81%	
Past	45.18%	43.38%	
Current	5.83%	5.80%	

Variable	Men (n=411)	Women (n= 360)	P-value
Leisure-time physical activity and stair climbing, total MET-hours/week, median (interquartile range)	22.15 (8.73 – 39.14)	19.74 (7.75 – 34.56)	0.47
Alcohol use	**N= 380**	**N= 345**	
Never	18.66%	20.54%	
Rarely to <weekly	3.64%	10.37%	
1–6/week	38.47%	43.08%	
Daily	39.22%	26.00%	
Current use of multivitamins	**N= 383**	**N= 345**	
Yes	48.20%	38.86%	
Current use of supplemental Vitamin D (total ≤800IU/d)	**N= 411**	**N= 360**	**0.90**
Yes	42.09%	43.31%	
Current use of supplemental calcium (total ≤1200 mg/d)	**N= 411**	**N= 360**	
Yes	14.43%	34.29%	
Intake of foods related to vitamin D and/or omega-3 fatty acids, median (interquartile range)			
Milk, servings/day	0.43 (0.07 – 1.00)	0.46 (0.10 – 1.00)	
Other vitamin D-fortified foods, servings/week	0.46 (0.09 – 1.00)	0.56 (0.20 – 1.05)	
Dark-meat fish, servings/week	0.93 (0.47 – 1.47)	0.93 (0.47 – 1.11)	0.071
Other fish and seafood, servings/week	0.96 (0.47 – 1.47)	0.93 (0.47 – 1.47)	0.25

* age and age-group p-value presented in Table 2 is unadjusted

Abbreviations: ALM, appendicular lean mass; ALMI, appendicular lean mass index; ALM/BMI, appendicular lean mass to body mass index ratio; BMD, bone mineral density; CTSC, Clinical and Translational Science Center; DXA, dual-energy X-ray absorptiometry; FAs, fatty acids; FMI, fat mass index; FNIH, Foundation for the National Institutes of Health; HR-pQCT, high-resolution peripheral quantitative computed tomography; LMI, lean mass index; LSC, least significant change; MET, metabolic equivalent; MOF, major osteoporotic fracture; NHANES, National Health and Nutrition Examination Surveys; pQCT, peripheral quantitative computed tomography; RCT, randomized controlled trial; SD, standard deviation; SE, standard error; SPPB, short physical performance battery; SSRIs, selective serotonin reuptake inhibitors; TBS, trabecular bone score; TUG, timed up and go; VAT, visceral adipose tissue; VITAL, VITamin D and OmegA-3 Trial.