

**VITamin D and OmegA-3 TriaL: Effects on Bone Structure and Architecture (VITAL)**

NCT01747447

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## Study Protocol

**VIT**amin D and **OmegA**-3 **TriAL** (**VITAL**) is a randomized, placebo-controlled study examining whether vitamin D<sub>3</sub> (cholecalciferol) and omega-3 fatty acids prevent cancer and cardiovascular disease. VITAL participants (n = 25,871) were randomized to receive either both 200 IU/day vitamin D<sub>3</sub> and 1 g/day omega-3 fatty acids, vitamin D<sub>3</sub> and placebo, omega-3 fatty acids and placebo, or both placebo pills. Males ≥ 50 years of age and females ≥ 55 years of age were included if they had no history of cardiovascular disease or cancer, other than nonmelanoma skin cancer, at the time of enrollment. Participants with serious medical conditions such as renal failure or cirrhosis, were excluded. Throughout the duration of the trial, individuals could not exceed more than 800 IU/d of vitamin D, which is the US Recommended Dietary Allowance for older adults [1, 2].

From the VITAL Cohort, 1,054 participants were enrolled in the Harvard Clinical and Translational Science Center (CTSC) sub-cohort. These individuals lived within driving distance of the CTSC. Participants in the bone density sub-cohort were recruited from the CTSC sub-cohort and had not been on bisphosphonates in the past two years. Additionally, these participants were not taking denosumab, calcitonin, tamoxifen, raloxifene, or other bone active medications. These participants had bone density and body composition measurements, as well as physical performance tests at baseline (n = 771) and 2-year follow-up (n = 687) [3, 4].

Participants underwent Dual-energy X-ray absorptiometry (DXA; Discovery W, APEX Software Version 4.2, Hologic, Bedford, MA, USA) to measure areal bone mineral density at the lumbar spine, total hip, femoral neck, and whole body as well as adipose tissue measurements and lean tissue measurements [3]. In addition, participants received peripheral quantitative computed tomography (pQCT; XCT 3000; Stratec Medizintechnik GmbH, Birkenfeld,

Germany) scans at baseline (n = 677) and 2-year follow-up (n = 600) to measure changes in volumetric bone mineral density (vBMD), cortical thickness, and measures of bone strength at both the radius and tibia [4]. At two-year follow-up, a subset of participants had high-resolution peripheral quantitative computed tomography (HR-pQCT) scans [3].

### **Statistical Analysis Plan**

This study utilized the intention-to-treat principle. In its design, the study had power to detect differences in aBMD of 1.03% at the spine, 1.22% at the femoral neck, and 0.42% in the whole body. These differences were based on a projected sample size of 600 and 10% loss to follow-up. The actual differences came to 0.91% at the spine, 1.08% at the femoral neck, and 0.37% in the whole body with 771 participants enrolled [4].

To compare continuous variables across the different subgroups, we used *t* tests and analysis of variance (Wilcoxon rank sum and Kruskal-Wallis tests). To compare proportions, we used chi-square tests. Analyses were conducted using SAS (SAS Institute, Cary, NC, USA). A *p* value greater than 0.5 was considered significant in the analyses. Results were reported as mean (standard deviation) or median (25<sup>th</sup>, 75<sup>th</sup> percentiles). The primary analysis looked at the effects of vitamin D versus placebo on measures of bone health [4].

## References

- 1 Manson JE, Cook NR, Lee IM, et al. Vitamin D supplements and prevention of cancer and cardiovascular disease. *N Engl J Med*. 2019; 380(1): 33– 44.
- 2 Institute of Medicine Committee to Review Dietary Reference Intakes for Vitamin D, Calcium. The National Academies Collection: Reports funded by National Institutes of Health. In AC Ross, CL Taylor, AL Yaktine, HB Valle, eds. *Dietary reference intakes for calcium and vitamin D*. Washington, DC: National Academies Press (US) National Academy of Sciences; 2011.
- 3 Donlon CM, LeBoff MS, Chou SH, et al. Baseline characteristics of participants in the VITamin D and OmegA-3 TriaL (VITAL): effects on bone structure and architecture. *Contemp Clin Trials*. 2018; 67: 56– 67.
- 4 LeBoff MS, Chou SH, Murata EM, Donlon CM, Cook NR, Mora S, Lee IM, Kotler G, Bubes V, Buring JE, Manson JE. Effects of Supplemental Vitamin D on Bone Health Outcomes in Women and Men in the VITamin D and OmegA-3 TriaL (VITAL). *J Bone Miner Res*. 2020; 35(5): 883-893.