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Update on the vitamin D and omega-3 trial (VITAL)☆

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Abstract

Despite continued appreciation of the potential role of vitamin D and omega-3 fatty acids in the prevention of cancer and cardiovascular disease (CVD), there remain no completed large-scale, randomized trials of these agents for the primary prevention of cancer or CVD in a population that has not been selected on the basis of elevated risk. The vitamin D and omega-3 trial (VITAL) is a 2 × 2 factorial randomized, double-blind, placebo-controlled trial of the benefits and risks of vitamin D (vitamin D_3 [cholecalciferol], 2000 IU/d) and marine omega-3 fatty acids (Omacor® fish oil, a 1 g/d) in the primary prevention of cancer and CVD among 25,875 men and women, aged ≥50 and ≥55 years, respectively. Randomization began in November 2011 and was completed in March 2014. This report will describe the rationale for the trial and currently available randomized trial data, summarize related ongoing large-scale trials, and provide a brief overview of study design, and an update on randomization milestones, racial/ethnic diversity, biorepository activities, in-depth phenotyping of a subcohort, and ancillary studies.

Keywords

Cancer; Cardiovascular disease; Cholecalciferol; Primary prevention; Omega-3 fatty acids; Vitamin D; Randomized controlled trial

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1. Introduction

1.1. Current randomized trial data for vitamin D and omega-3 fatty acid supplementation in the prevention of cancer and CVD

Whether vitamin D and marine omega-3 fatty acid supplements prevent cancer and CVD remains unclear. Prospective observational data related to vitamin D status and *total cancer* are limited [1–3] and inconsistent [4] with no large-scale prevention trial of vitamin D with cancer as the primary pre-specified outcome having been completed. Cancer incidence and mortality has been assessed in four vitamin D trials [5–9], however results have not clearly supported a chemoprotective effect. In the largest of these trials, the Women's Health Initiative (WHI) conducted among >36,000 postmenopausal women, daily calcium (1000 mg) plus low-dose vitamin D_3 (400 IU) did not reduce cancer incidence, although a protective effect against cancer mortality was suggested over the 7 year follow-up [7,8]. With regard to site-specific cancers, in the British [5] [(2686 older adults randomized to 100,000 IU of vitamin D_3 or placebo (one capsule every 4 months)] and the WHI [10] trials, vitamin D did not reduce colorectal cancer incidence, although nonsignificant reductions in colorectal cancer mortality were found. Only the WHI has been large enough to examine breast cancer as a separate secondary endpoint, showing no significant effect on incidence or mortality [8]. Additional large trials are needed to evaluate both total cancer and type-specific cancers. Indeed, a report published by the Institute of Medicine in 2011 [11] concluded that large randomized trials of vitamin D are necessary for a definitive assessment of its effect on site-specific cancers.

There are few randomized trials of vitamin D and CVD events and no trials with CVD as the primary prespecifed outcome. In a British trial [5], there were nonsignificant treatment-associated reductions in the 5 year incidence of non-fatal or fatal CHD and CVD events. A 1-year trial in Australia investigated the effect of vitamin D supplementation (1000 IU/d) added to calcium supplementation (1000 mg/d) on the risk for falls in 302 elderly women [12]. Compared with calcium alone, vitamin D supplementation was associated with a lower rate of ischemic heart disease (1.3% *vs.* 2.0%) and a similar rate of stroke (both 2.0%). Combining the data from these two trials yielded a RR for CVD of 0.90 (0.77–1.05) [13]. In the WHI, the combination of calcium and low-dose vitamin D did not affect the incidence of CHD [14] or stroke [14] or mortality from these outcomes [15]. A 2011 meta-analysis of randomized trials of vitamin D administered with or without calcium found no significant effects for the outcomes of MI (six trials; RR = 1.02) or stroke (six trials; RR = 1.05) [16]. Taken together, currently available randomized trial data do not provide evidence that supplemental vitamin D confers protection from CVD, at least not at the relatively low doses tested to date.

With regard to omega-3 fatty acids and cancer risk, results of observational studies regarding a role for marine omega-3 fatty acids in protecting against the development of total or site-specific cancers continue to be equivocal [17] and there are no large randomized trials of marine omega-3 fatty acids for the primary prevention of cancer in a general population. Two large but unblinded trials in secondary prevention or high CVD risk settings—GISSI [18] in Italy, which tested the effect of 3.5 years of EPA + DHA (1 g/d)

supplementation in 11,324 recent MI patients, and JELIS [19] in Japan, which tested the effect of 4.6 years of EPA (1.8 g/d) supplementation in 18,645 hypercholesterolemic patients on statins—found that supplementation neither increased nor decreased incidence of total cancer. JELIS also reported neutral results for breast, colorectal, and lung cancer. Because of the higher background intake of fish in Asia, one might expect attenuated effects of supplementation in this cohort compared with a U.S. population. However, results of several non-Asian trials conducted either in special populations (e.g., people with diabetes) or for secondary prevention of CVD, and which tested 400–1000 mg/d of EPA + DHA, have all reported null findings for cancer incidence [20–24]. Despite considerable laboratory evidence for cardiovascular protective effect, there are similarly no large randomized trials of marine omega-3 fatty acids for the primary prevention of CVD in a general population. The open-label GISSI [18] and JELIS [19] trials, conducted in patients with prior MI or with hypercholesterolemia, respectively, found that marine omega-3 fatty acid supplements reduced the risk for subsequent total CVD or coronary events by a significant ~20%. The placebo-controlled GISSI-HF trial also found that fish oil reduced fatal CVD by 10% (1–19%) [20]. However, more recent trials [21–23,25,26] of high-risk or post-MI patients testing moderate doses of EPA+DHA have all reported null results for CVD risk reduction. Three of these trials [23,25,26] however, were substantially underpowered to detect significant small to modest benefits on CVD outcomes [24]. In addition, the prevalence of use of medications such as statins, β-blockers, and angiotensin-converting enzyme inhibitors was much higher in recent trials, so there may have been little opportunity for fish oil supplements to provide additional cardiovascular benefit [24]. Indeed, a stratified analysis from one of these trials found a significant reduction in CVD risk among nonusers of statins but not in users [27], suggesting that these medications can mask treatment benefits. In GISSI, however, there was no similar effect modification [28]. A recent and comprehensive meta-analysis of randomized trials assessing omega-3 supplementation in secondary prevention [29] concluded that fish oil did not prevent incident CVD events. However, this meta-analysis has been criticized for several reasons [30,31], including the use of an overly strict adjustment for multiple comparisons; failure to stratify by statin use; inclusion of studies with insufficient omega-3 dosing; and insufficient consideration of nutrient status as assessed by blood measures of omega-3s.

1.2. Ongoing randomized trials of vitamin D

To our knowledge, VITAL is the largest randomized trial of vitamin D in the U.S., and it is the only large trial worldwide with racial/ethnic diversity and an appreciable number of black participants. At least three other large trials [32–34] are in the planning or recruitment stage (Table 1). In contrast to VITAL, the study populations in these trials will be less racially/ethnically diverse and will include few if any blacks, limiting the ability to study the effect of vitamin D in this group; the number of blood samples that will be collected or whether any in-clinic visits will be conducted is unclear; and, in two trials, intermittent bolus dosing of vitamin D, which can be associated with wide fluctuations in blood levels of active vitamin D and is not reflective of more constant physiologic exposures, will be used. Results from trials with weekly, monthly, or quarterly dosing may be misleading, especially for nonskeletal outcomes [35]. Several midsized trials (n = 2100–5500) [22,36–40] are also

underway (only one is in the U. S. is focused on cancer prevention [38]) but will have limited power to examine cancer and/or CVD outcomes compared to the larger trials.

1.3. Ongoing randomized trials of marine omega-3 fatty acids

In a study of cardiovascular events in diabetes (ASCEND) [41], 15,000 British adults with diabetes have been randomized to marine omega-3 fatty acids (1 g/d) and/or aspirin in a factorial design and are being followed for 5–7 years for incident CVD. However, results in diabetic populations may not apply to general populations. The DO-HEALTH trial [39] in Europe is testing the effect of 3 years of EPA + DHA supplementation (1 g/d) on physical performance, fracture, and other outcomes in 2100 older adults but will have limited power to assess cancer and CVD endpoints. There are no completed, ongoing, or planned randomized clinical trials in the U.S. (or elsewhere) of marine omega-3 fatty acid supplements for the primary prevention of cancer or CVD in a general population selected only on the basis of age and not on the basis of other vascular risk factors such as diabetes or high cholesterol.

2. Materials and methods

2.1. Overview of study design

VITAL is a 2 × 2 factorial randomized, double-blind, placebo-controlled trial of the benefits and risks of vitamin D (vitamin D_3 [cholecalciferol], 2000 IU/d) and marine omega-3 fatty acids (Omacor® fish oil, a 1-g capsule containing eicosapentaenoic acid [EPA; 465 mg] + docosahexaenoic acid [DHA; 375 mg) in the primary prevention of cancer and CVD among 25,875 men and women, aged ≥50 and ≥55, respectively [42]. Participants were recruited throughout the U.S., and blacks were oversampled. After successful completion of a 3-month placebo run-in, participants were randomized to vitamin D, fish oil, both active agents, or both placebos (Fig. 1).

2.2. Recruitment update

VITAL employed a 3-stage screening process to assemble the cohort. Our goal was to randomize at least 20,000 individuals, including 5000 blacks. To reach this goal, we used both a mail-based and community-based approach. We mailed an initial screening questionnaire to age-eligible U.S. adults, identified largely from commercially available mailing lists with high minority group representation, followed up on responses to media reports about VITAL, and conducted direct mailings to communities with a high percentage of blacks. We also invited participants in one of our previously completed trials [43] to consider participating in VITAL. Of the 401,605 persons who returned the initial screening questionnaire sent to 9.9 million adults, 160,404 were willing and eligible to receive a second-stage screening questionnaire. Of the 55,902 persons who returned this questionnaire, 39,430 were willing and eligible to enter the run-in phase of the study. Of this group, 25,875 persons, including 5108 blacks, successfully completed a 3-month placebo run-in and were randomized into the trial. The first participants were randomized in November 2011 and randomization was completed in March 2014.

2.3. Follow-up and compliance

The first participants to be randomized have received their 6-month (interim), 1-year (full-length), 18-month (interim) and 2-year (full-length) study questionnaires. Data from the first ~7100 participants indicate high response and compliance rates to date: 97% of participants returned their year 1 questionnaire and >90% are continuing to take their study capsules. Plasma biomarker measures also assessed compliance in a random sample of participants. We measured serum 25(OH)D concentrations in baseline samples (n = 150) using two assays: (1) Quest's liquid chromatography-tandem mass spectrometry (LC-MS/MS) with both 25(OH)D_2 and D_3 quantitated and summed to give the total 25 (OH)D, and (2) Abbott ARCHITECT chemiluminescent microparticle immunoassay (CMIA) at Atherotech. QC blinded replicates were included. Total 25(OH)D levels in blinded duplicates were highly correlated both within ($r \geq 0.94$) and between ($r = 0.88$) assay methods. Coefficients of variation (CVs) were 4 to 5% for both assays. These preliminary results demonstrate high quality of the assays with a high correlation of 25(OH)D levels between methods. In addition, examination of the difference between baseline and 1-year samples, comparing the intervention and placebo arms suggests excellent compliance.

2.4. Blood specimen collection

Baseline blood samples were collected during the run-in from all participants willing to provide a sample (N = ~17,000). Blood specimens will also be collected at trial years 1–4 from a randomly selected subset of 6000 of these participants. A blood collection kit, including a freezer pack, overnight courier air bill, and informed consent form (specific to the collection, storage, and use of blood samples) was mailed to each willing participant. Some participants had their blood drawn by their healthcare provider, while others had their blood drawn by Examination Management Services, Inc. (EMSI), a nationwide company that provides phlebotomy and specimen-collection services, in their homes or at a local blood-drawing facility. Participants were asked to return blood samples to our laboratory within 24 h of venipuncture. The samples were centrifuged to separate plasma, serum, red blood cells, and buffy coat; these components were stored in nitrogen freezers (−170 °C) within 30–36 h of venipuncture. Identical procedures are being used for the follow-up blood collections. Blood levels of 25(OH)D and EPA + DHA, as well as calcium and PTH, will be assayed in all baseline and follow-up samples.

2.5. In-depth subcohort phenotyping

A subcohort of 1000 VITAL participants is receiving detailed health assessments at a Clinical Translational Science Center (CTSC) site in Boston before randomization and at 2 years. Baseline visits began in January 2012 and concluded in March 2014. To date 1054 participants have completed baseline CTSC visits and 2-year follow-up examinations are under way. Participants undergo a physical examination including direct assessment of blood pressure, height, weight, hip and waist circumference and physical performance. Participants also provide fasting blood and urine samples, undergo oral glucose tolerance testing, cognitive and mood assessment, spirometry, bone density testing, body composition measurement, and echocardiography. These in-clinic visits provide a valuable opportunity for face-to-face contact with a subset of the cohort, allowing for in-depth phenotyping and

in-person validation of the remote assessment methods in the main trial and ancillary studies.

2.6. Ancillary studies

In addition to testing vitamin D and omega-3 supplementation for cancer and CVD prevention, VITAL, with its diverse study population, wealth of questionnaire data on health, large repository of blood samples, and clinical data gathered in the CTSC, also represents a valuable resource for ancillary studies on vitamin D and omega-3 fatty acids. The racial/ethnic diversity of the cohort will enable an exploration of the effects of vitamin D not only in white but also nonwhite (particularly black) individuals, an area deemed to be of high priority by the IOM and other scientific organizations. As shown in Table 2, 18 ancillary grant applications that will use and build on data from VITAL have received funding.

3. Conclusion

The purported health benefits of vitamin D and marine omega-3 fatty acids are receiving increasing attention in both the medical literature and the popular press. However, current data are inconclusive as to whether supplementation with these agents reduces the risk for cancer, CVD, and other non-skeletal illnesses in the general population. VITAL will test the efficacy of vitamin D (vitamin D_3 [cholecalciferol], 2000 IU/d) and marine omega-3 fatty acids (Omacor® fish oil, a 1 g/d) for the prevention of cancer and CVD in a multiethnic primary prevention population. The study includes the collection and storage of baseline blood specimens in the majority of the cohort and follow-up specimens in a subgroup of participants. In depth phenotyping in a subgroup and several well-integrated ancillary studies will examine the investigation of multiple clinical, biochemical, and genetic hypotheses. The results of VITAL are expected to inform individual decisions, clinical recommendations, and public health guidelines.

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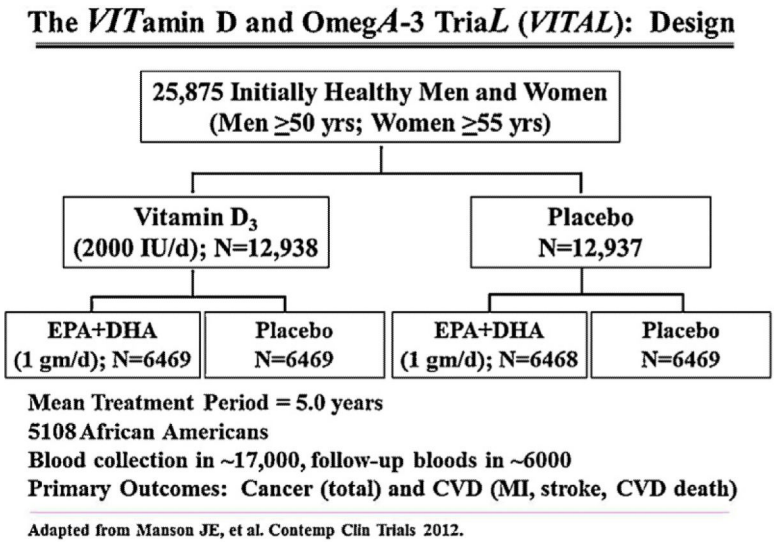

Fig. 1.

Factorial design of the vitamin D and omega-3 trial.

Table 1

Several ongoing large-scale randomized trials ($n \geq 10{,}000$ participants) of vitamin D supplementation worldwide.

Trial, Location	Sample Size	Age range	Treatment duration	Vitamin D intervention	Primary endpoints	No. of blood collections	Recruitment status
VITAL, U.S.	26,000	≥50 M ≥55 F	5 years	2000IU/d	Cancer; CVD	Baseline: 17,000 Follow-up: 6000	Recruitment completed
D-Health, Australia	25,000	60-79	5 years	60,000IU/month (bolus)	Total mortality; cancer	Limited	Recruiting
Finnish vitamin D trial (FIND), Finland	18,000	≥60 M ≥65 F	5 years	1600 IU/d or 3200IU/d	Cancer; CVD	Unclear	Recruiting
Vitamin D and longevity (VIDAL), U.K.	20,000	65-84	5 years	100,000IU/month (bolus)	Total mortality; cancer	Unclear	2-yr feasibility trial in 1600 adults is ongoing

Table 2

Ancillary studies in VITAL (NIH – funded unless otherwise noted).

Cognitive function	In-clinic protocol
Diabetes	Blood pressure
Hypertension	Height, weight, waist, hip
2D echocardiogram	Fasting bloods & 2-h OGTT
Respiratory diseases	Urine collection
Autoimmune disorders	Spirometry
Fractures	Physical performance
Bone imaging	Cognitive function
Depression/mood	Mood/depressive symptoms
Infections	2D echocardiogram
Diabetic nephropathy	DXA/bone microarchitecture
Atrial fibrillation	
Anemia	
Macular degeneration	
Dry eye syndrome	Pending (under review)
Mammographic density	Vitamin D genomics
Magnesium & vitamin D	HTN-related nephropathy
Racial/ethnic differences	Heart failure
Vitamin D/adiposity (AHA)	Telomere biology