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Vitamin D and Cardiovascular Disease

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OPINION

Vitamin D has received widespread attention for its potential role in preventing cardiovascular disease (CVD) and type 2 diabetes mellitus. Several epidemiological studies have suggested that individuals with low blood levels of vitamin D have increased risks of heart disease, stroke, hypertension, and diabetes. Yet the revised 2011 Institute of Medicine report for intake of calcium and vitamin D, which was guided by skeletal health alone, concluded that the evidence that vitamin D prevents CVD, diabetes, or other cardiometabolic outcomes was inconsistent and inconclusive and did not meet criteria for establishing a cause and effect relationship.[1,2] This finding was consistent with an earlier systematic review conducted by the Agency for Healthcare Research and Quality (AHRQ) in 2009. [3] Ongoing clinical trials seek to address the effects of vitamin D supplementation on CVD and other nonskeletal outcomes.

VITAMIN D LEVELS IN US, PREVALENCE OF VITAMIN D DEFICIENCY AND CURRENT DIETARY GUIDELINES

Based on bone health, recommended dietary allowances (covering requirements of ≥97.5% of the population) for vitamin D are 600 IU/d for individuals aged 1 to 70 years and 800 IU/d for those older than 70 years, corresponding to a serum 25-hydroxyvitamin D level of 20 ng/mL or greater (≥50 nmol/L) under conditions of minimal sun exposure. [2]

Vitamin D is synthesized in the skin as a pro-hormone in response to ultraviolet light and is also absorbed from the gastrointestinal tract. Both sources are activated in the liver to 25(OH)D and in the kidney to 1,25-dihydroxyvitamin D[1,25$(OH)_2$D]; the 25(OH)D level has a half-life of 2–3 weeks and is a measure of vitamin D status.[4] Extra-renal activation of vitamin D occurs in a number of tissues which may affect inflammation and innate immunity.[5–9] The National Health and Nutrition Examination Survey (NHANES) indicated that vitamin D "insufficiency" exists in more than half of US middle-aged and older women[10] and more than a third of similarly aged men,[5,11] although there has been recent debate about what constitutes vitamin D deficiency and sufficiency.[12]

Despite lack of consensus on the definition and prevalence of vitamin D insufficiency in the United States[1,2], some estimates suggest nonetheless that at least one third of middle-aged and older Americans have such insufficiency[5,13]. The elderly are particularly vulnerable, at least in part due to reduced physical and outdoor activity. [14–19] African-American individuals are also particularly vulnerable, in part because darkly pigmented skin is less able to synthesize vitamin D in response to solar radiation and because blacks tend to have

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lower dietary and supplemental vitamin D intakes than whites.[20,21] Obese individuals are also at above-average risk, presumably because of decreased bioavailability of this fat-soluble vitamin.[22–24] Given the aging population and rising obesity prevalence,[25] low vitamin D status is an increasingly important public health issue.

VITAMIN D AND CARDIOVASCULAR DISEASE

There are gaps in knowledge in terms of understanding the role of vitamin D in the prevention of cardiovascular disease. Data from laboratory studies, ecologic studies[26,27], epidemiologic investigations [28–31] suggest a protective effect for vitamin D against CVD. Mechanisms by which vitamin D may prevent these diseases are shown in Figure 1. [32]

The vitamin D receptor is expressed in cells throughout the vascular system. Many cell types, including vascular smooth muscle cells, endothelial cells, and cardiomyocytes, produce 1α-hydroxylase, which converts 25-hydroxyvitamin D to calcitriol, the natural ligand of the vitamin D receptor. Calcitriol has been shown to inhibit vascular smooth muscle cell proliferation, regulate the renin-angiotensin system, decrease coagulation, and exhibit anti-inflammatory properties.

Observational and ecological studies

Ecological studies have suggested higher cardiovascular disease mortality during the winter and in regions with less solar UV-B exposure. Some, but not all, observational studies suggest an inverse association between 25-hydroxyvitamin D levels and clinical cardiovascular disease events. The AHRQ report identified 4 relevant observational studies. The Framingham Offspring Study [29] and the Health Professionals Follow-up Study[28] found significant inverse associations between 25-hydroxyvitamin D levels and incident cardiovascular disease events. However, a closer look at the former study indicated that the relationship between 25-hydroxyvitamin D and cardiovascular disease was nonlinear and reached a plateau between 20 and 30 ng/mL, with a suggestion of slightly increased risk at higher 25-hydroxyvitamin D levels. In addition, the Third National Health and Nutrition Examination Survey (NHANES III) found no significant association between serum 25-hydroxyvitamin D and cardiovascular disease mortality, although persons in the lowest quartile had a 26% increase in total mortality. [34] The NHANES III analysis suggested a similar U-shaped relationship for 25-hydroxyvitamin D, with increased total mortality not only at low (<20 ng/mL) but also at high (>50 ng/mL) levels. Other observational studies have shown mixed results. [35] Although the observational evidence is suggestive of increased risks associated with low levels of serum 25-hydroxyvitamin D, confounding by obesity and behavioral factors cannot be excluded. Although measures of serum 25-hydroxyvitamin D are considered useful markers of vitamin D exposure, correlation between these levels and health outcomes in observational studies do not prove causation. Possible confounders exist such as obesity (due to depositioin primarily in adipose tissue), sun exposure, physical activity (correlated with time outdoors) and nutritional status. Other factors such as ethnicity, skin pigmentation and medications may also affect serum 25-hydroxyvitamin D levels.

Randomized trials

There is a paucity of randomized controlled trials of vitamin D and cardiovascular disease events and absence of any trials with cardiovascular disease as the primary prespecified outcome. [2,3] A British trial that tested 100 000 IU of vitamin D_3 or placebo every 4 months (equivalent to ~833 IU/d) for up to 5 years, with cardiovascular disease as a secondary outcome, showed null results. In a small 1-year Australian trial, vitamin D (1000 IU/d) added to calcium supplementation vs. calcium alone was associated with a nonsignificantly

lower risk of ischemic heart disease events and no difference in the risk of stroke. When data from these 2 trials were combined, the pooled relative risk (RR) for cardiovascular disease was 0.90 (95% confidence interval [CI], 0.77–1.05) for vitamin D. [35] The recently published Randomised Evaluation of Calcium or Vitamin D (RECORD) trial showed no effects of vitamin D on all cause and vascular-disease mortality but tested only 800 IU of vitamin D daily.[36,37] postmenopausal women were randomly assigned to a daily combination of calcium (1000 mg) and low-dose vitamin D_3 (400 IU) or to placebo and followed for a mean of 7 years—found that the intervention did not reduce risk for cancer, coronary heart disease, or stroke, [38,39] but its effect on blood levels of 25-hydroxyvitamin D [25(OH)D], the major circulating vitamin D metabolite, was small. In a pooled analysis of 3 trials of combination calcium plus vitamin D vs placebo, including the Women's Health Initiative (WHI), the RR for cardiovascular disease was 1.04 (95% CI, 0.92–1.18).[35] Thus, the conclusion of both the IOM Committee [2] and recent systematic reviews [3,35] was that the evidence was inconsistent and insufficient to prove a cause and effect relationship between vitamin D and CVD. There have thus far been no completed prospective randomized trials of vitamin D and incident cardiovascular disease at doses adequate to produce meaningful changes in 25(OH)D levels or designed to assess CVD as a primary prespecified outcome.

VITAMIN D AND CVD RISK FACTORS

There is evolving data about the possible relationship of vitamin D with CVD risk factors, some of which are summarized in this section. Figure 2 summarizes hypothesized mechanisms underlying the interrelationships among vitamin D deficiency and several CVD risk factors.

Vitamin D and inflammation

Vitamin D may attenuate inflammation. VDR signaling inhibits proliferation of T-cells,[40,41] and transcription of inflammatory cytokines.[42,43] $1,25(OH)_2D$ inhibits lymphocyte proliferation and production of antibodies and lymphokines. Vitamin D may induce an inhibitory effect of LPS-driven monokine production.[44] Combined with VDR-mediated inhibition of dendritic cell maturation,[45–48] vitamin D in T-cells suppresses Th1-driven inflammatory responses, while promoting a Th2 regulatory phenotype.[49] In 2 cohorts, 25(OH)D levels were inversely associated with CRP[50] and interleukin 6 (IL6),[30,51] while another study found suppression of TNF-α concentrations.[52] Vitamin D treatment reduced disease severity in patients with rheumatoid arthritis,[53,54] psoriasis,[55–57] and scleroderma.[58] Two trials analyzed vitamin D therapy on CRP in special populations[59,60] with mixed results: the first study showed no effects on C-reactive protein or fibrinogen with vitamin D supplementation in elderly individuals.[59] The latter showed a 50% reduction in CRP in participants with kidney disease when given a vitamin D analogue.[60] Clarification of conflicting data regarding vitamin D and inflammation is needed.

Vitamin D and blood pressure

Vitamin D may affect the renin-angiotensin system,[61] exert beneficial effects on vascular smooth muscle cells,[5,62] the endothelium, [63,64–67] and cardiomyocytes.[68] VDR knockout mice have elevated circulating levels of renin and angiotensin II and develop hypertension.[61] A similar phenotype occurs in mice lacking the 1α-hydroxylase gene.[69] Injection of mice with $1,25(OH)_2D$ analogs suppresses renin production *in vivo*,[70] and negatively regulates the expression of the angiotensinogen gene.[71,72] Small human studies have reported cross-sectional associations between vitamin D and renin activity.[73,74] A recent trial of vitamin D supplementation showed a 14 mmHg decrease in SBP. in patients with type 2 diabetes.[75] However, blood pressures findings in other randomized trials have been inconsistent.[2,76]

Vitamin D and insulin resistance

Vitamin D deficiency is associated with impaired glucose tolerance and reduced insulin turnover and insulin sensitivity.[77–80] Furthermore, vitamin D repletion improves glucose clearance in vitamin D-deficient animals independent of other nutritional factors.[77] Human studies also support the association between vitamin D and insulin sensitivity. Chiu et al. reported a positive correlation between 25(OH)D and insulin sensitivity indices in healthy volunteers, after multivariate analyses that included potential covariates of age, sex, ethnicity, body mass index, waist-hip ratio, systolic and diastolic blood pressure and season.[81] Among 5,677 adults in New Zealand, 25(OH)D levels were lower among individuals diagnosed with impaired glucose tolerance compared to controls, after matching for age, sex and ethnicity.[82] In the Framingham Offspring Study, plasma 25(OH)D levels in the lowest compared to highest tertile were associated with a 1.6% higher fasting plasma glucose, a 9.8% higher fasting insulin, and a 12.7% higher HOMA-IR index (homeostasis model assessment of insulin resistance).[83] In a prospective study among 524 adults, baseline 25(OH)D levels were inversely associated with fasting insulin and HOMA-IR 10 years later.[84]

VITAMIN D AND TYPE 2 DIABETES

The role of calcitriol in the synthesis and secretion of insulin and regulation of calcium trafficking in beta islet cells, and its effects on insulin action have been established in both rodent models and cell culture. [2] Although some observational studies have shown an inverse relationship between higher vitamin D intake or serum 25-hydroxyvitamin D and risk of type 2 diabetes, a systematic review and meta-analysis [85] with a large body of observational evidence and 6 intervention studies with vitamin D supplementation found generally neutral results. Studies published after the IOM report[2] have shown mixed results; there was either a higher risk of prediabetes in individuals (NHANES III) with 25-hydroxyvitamin D levels below 18 ng/mL[86] or no association between serum 25-hydroxyvitamin D and risk of type 2 diabetes in a Canadian population or in the WHI. Randomized trials of vitamin D supplementation and risk of type 2 diabetes have had inconsistent results. In the Randomised Evaluation of Calcium or vitamin D (RECORD) trial, there was no effect of 800 IU/d of vitamin D_3 supplementation (with or without 1000 mg of calcium carbonate) on incident diabetes over 2 to 5 years (fracture was the primary outcome variable and diabetes outcomes were self-reported). [86]

In separate studies of vitamin D supplementation with 4000 IU/d or 120 000 IU every 2 weeks in South Asian overweight women and obese men, respectively, insulin sensitivity significantly improved compared with placebo.[87] However, another study in overweight adults in Germany found no relationship between vitamin D supplementation (3300 IU/d) with glucose metabolism during weight loss.[88] In a post hoc analysis of a trial testing the effects of 3 years of supplementation with 700 IU of vitamin D and 500 mg of calcium daily on bone health, individuals with impaired fasting glucose were found to have a lower increase in fasting glucose levels and less insulin resistance compared with placebo controls.[89] In patients with established type 2 diabetes, vitamin D has not been shown to improve insulin resistance or glucose metabolism.[2] Thus, the overall evidence from clinical trials and observational research[2,3,85,86,90] is insufficient to establish a causal relationship between vitamin D supplementation and type 2 diabetes prevention.

VITAMIN D AND STATIN-INDUCED MYALGIAS

There is also evidence for the relationship of vitamin D deficiency to statin myopathy.[91–93] One study[93] reported resolution of myalgia after restoring vitamin D levels in vitamin D-deficient individuals. The authors speculated that patients with concurrent vitamin D

deficiency may reflect a reversible interaction between vitamin D deficiency and statins on skeletal muscle. It has been hypothesized that a potential mechanism may be via the induction of CYP enzymes by vitamin D, as vitamin D is known to activate CYP3A4 [94,95] which may help in the metabolism of certain statins, [96] In addition, hydroxylated vitamin D derivatives may also possess 3-hydroxy-3-methyl-glutaryl-Coenzme A (HMG-CoA) reductase activity.[97] However, data from the Treating to New Targets (TNT) trial have suggested no relationship between vitamin D levels and statin-induced myalgias. [98] These data remain hypothesis-generating and no large scale randomized data exist yet in this regard.

SUMMARY

There is biological plausibility for a role of vitamin D in the prevention of cardiovascular disease and diabetes, but less so than would be anticipated relative to the current popularity of the supplement in the U.S. There is currently insufficient data to inform nutritional requirements. No large-scale randomized trials have been completed with cardiovascular disease or diabetes as the primary prespecified outcomes. Although the observational evidence is suggestive of increased risks associated with low levels of serum 25-hydroxyvitamin D, confounding by obesity and behavioral factors cannot be excluded. More research is needed to elucidate whether higher intakes of vitamin D (between the recommended dietary allowance and the tolerable upper intake level) or serum 25-hydroxyvitamin D levels in the range of 20 to 50 ng/mL influence cardiovascular disease or diabetes risk. New randomized trials assessing the role of supplementation with vitamin D in cardiovascular disease and type 2 diabetes prevention are in progress, such as the Vitamin D and Omega-3 trial (VITAL, NCT01169259), the Vitamin D, Insulin Resistance and Cardiovascular Disease trial (NCT00736632) and the Vitamin D Supplementation and Metabolism in Vitamin D Deficient Elderly trial (NCT01145703). Because of the involvement of the authors of this chapter in the first trial, the next section briefly describes the design of the ongoing VITAL trial.[33]

ONGOING RESEARCH

The Vitamin D and Omega-3 (VITAL) Trial

VITAL is one of the ongoing trials seeking to address the role of vitamin D and marine omega-3 fatty acids in the primary prevention of cancer and CVD. It is a randomized, double-blind, placebo-controlled clinical trial among 20,000 U.S. men and women without cancer or CVD at baseline, who are selected on age only (men aged ≥50 and women aged ≥55), with an oversampling of blacks. Blacks are at higher risk of vitamin D deficiency and are also at higher risk for certain cancers (e.g., prostate cancer) [99] and cardiovascular events (e.g., stroke) [21], as well as mortality from CVD [21], so it is critical to test the effect of vitamin D supplementation in this group. In a 2×2 factorial design, participants will be randomized to vitamin D_3 (cholecalciferol; 2000 IU/day) with or without marine omega-3 fatty acids (Omacor® fish oil, EPA + DHA, 1 g/d) supplements (or placebos) independently. The mean treatment period will be 5 years.

Intervention

With regard to the vitamin D_3 dose of 2000 IU/day, careful review of the literature suggested that this dose provides the best balance of efficacy and safety. We sought to obtain a large-enough difference in vitamin D status between the treatment and placebo groups to detect benefits for the primary endpoints of cancer and CVD. VITAL was designed in 2008, when the recommended dietary intakes set by the Institute of Medicine (IOM), were 400 IU/day for adults aged 50–70 and 600 IU/day for adults aged >70.[100] In 2011, the IOM released RDAs for these age groups of 600 IU/day and 800 IU/day,

respectively.[2] These RDAs correspond to a serum 25(OH)D level of 50 nmol/L and are sufficient for the maintenance of bone health in at least 97.5% of the North American population. Nevertheless, accumulating data suggest that vitamin D intakes above these RDAs may be necessary for maximal health benefits. In a review of studies of serum 25(OH)D in relation to various outcomes, including colorectal cancer, falls, fractures, physical functioning, and dental health, Bischoff-Ferrari et al. [101] found that advantageous 25(OH)D levels began at 75 nmol/L, and optimal levels were between 90–100 nmol/L. The average older individual requires an oral vitamin D_3 intake of at least 800–1000 IU/day to achieve a serum 25(OH)D of 75 nmol/L. [102] Among postmenopausal women in the Women's Health Initiative, 400 IU/day of vitamin D_3 was estimated to have raised median plasma 25(OH)D from 42.3 to only 54.1 nmol/L. [38,103] In addition, a study by Aloia et al. [104] showed a nonlinear dose-response relation between serum 25(OH)D and vitamin D intake, with the rate of increase in serum levels slowing at higher levels of intake. Extrapolation of the Women's Health Initiative data, along with consideration of the Aloia et al. findings, suggest that 2000 IU of vitamin D_3 would be required to reach the postulated optimal value of 90 nmol/L in the active vitamin D group in VITAL. The difference in achieved 25(OH)D levels between the active treatment and placebo groups is expected to be approximately 50 nmol/L. A secondary arm will test omega-3 fatty acids on the same outcomes.

Study design

Baseline blood samples will be collected in at least 80% of participants (n=16,000), with follow-up blood collection in about 6000 participants. A summary of the study design is provided in Figure 3 adapted from Manson et al.[33]

Follow-up questionnaires every 6 months will assess treatment compliance (plasma biomarker measures will also assess compliance in a random sample of participants), use of non-study drugs or supplements, occurrence of endpoints, and cancer and vascular risk factors. Endpoints will be confirmed by medical record review by a committee of physicians blinded to treatment assignment and deaths will be ascertained through the National Death Index-Plus and other sources. Ancillary studies, including clinic visits for in-depth phenotyping of 1000 participants, will make use of the randomized design to investigate whether these agents affect risk for diabetes and glucose intolerance; hypertension; cognitive decline; depression; osteoporosis and fracture; physical disability and falls; asthma and other respiratory diseases; infections; rheumatoid arthritis, systemic lupus erythematosus, thyroid diseases, and other autoimmune disorders, among others.

CONCLUSION

Despite biological plausibility for a role of vitamin D in the prevention of cardiovascular disease and diabetes, randomized trial data need to be completed before there is sufficient data to inform nutritional requirements. Other emerging hypotheses such as the potential relationship between circulating vitamin D levels and statin-induced myalgias require further corroboration.

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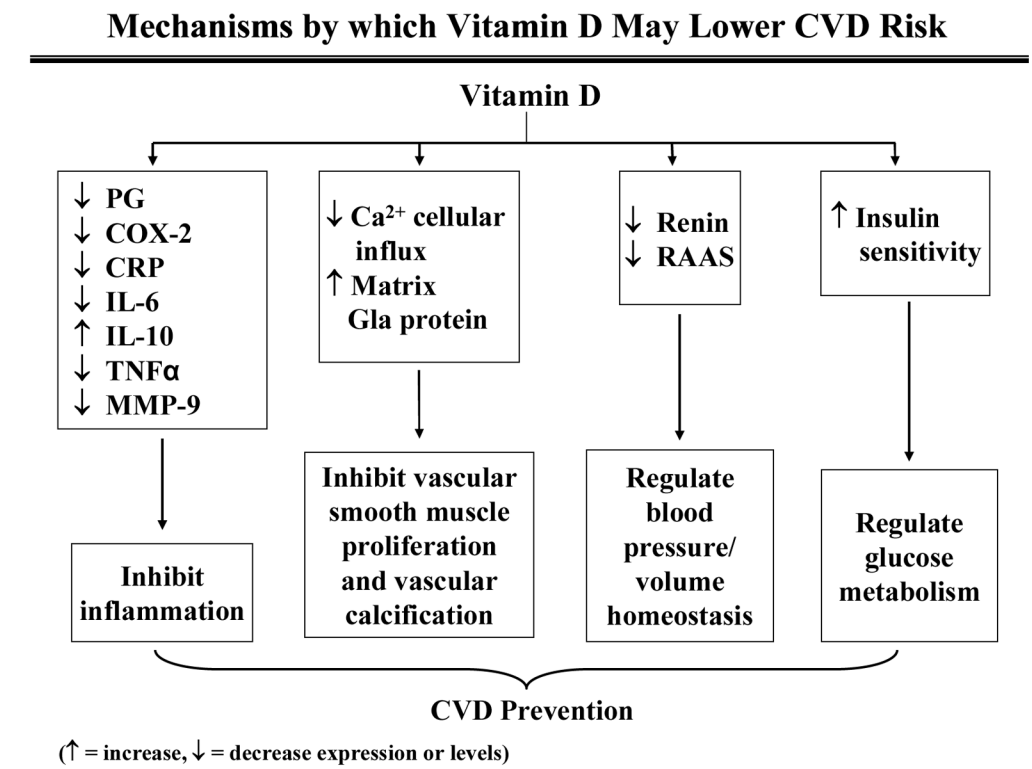

Figure 1.

Mechanisms by which vitamin D may impact CVD. Adapted from Manson et al, 2012.[33] PG, prostaglandin; COX-2, cyclooxygenase-2 ; CRP, C-reactive protein ; IL-6, interleukin-6 ; IL-10, interleukin-10 ; TNF-a, tumor necrosis factor-a, MMP-9, matrix metalloproteinase-9; RAAS, renin-angiotension-aldosterone system.

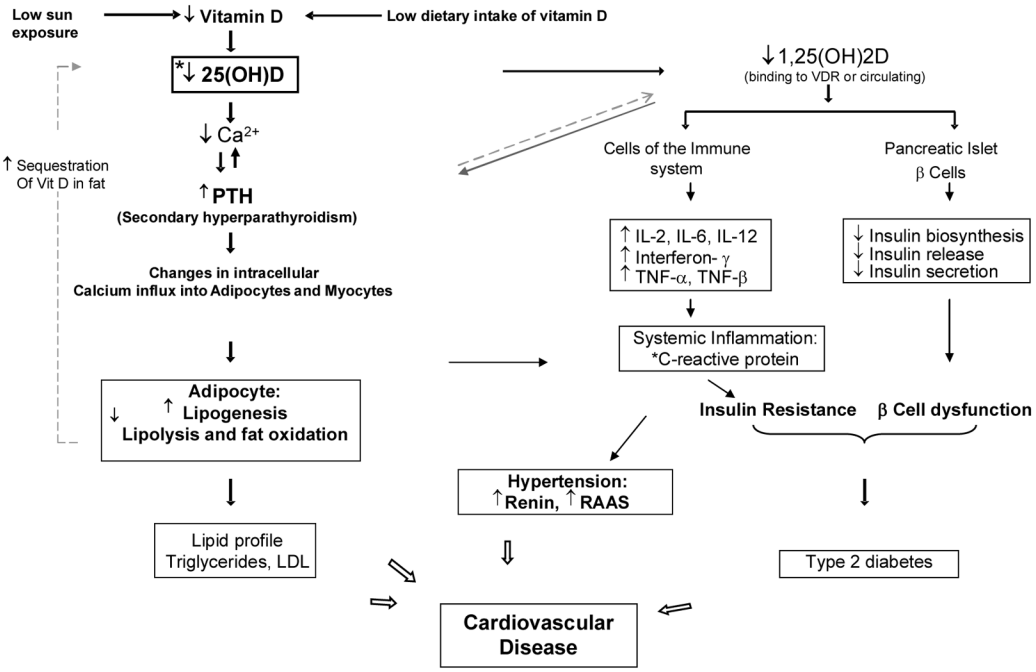

Figure 2.
Hypothesized mechanisms underlying the interrelationships among vitamin D deficiency, cardiovascular disease risk factors such as insulin resistance, hypertension and diabetes.

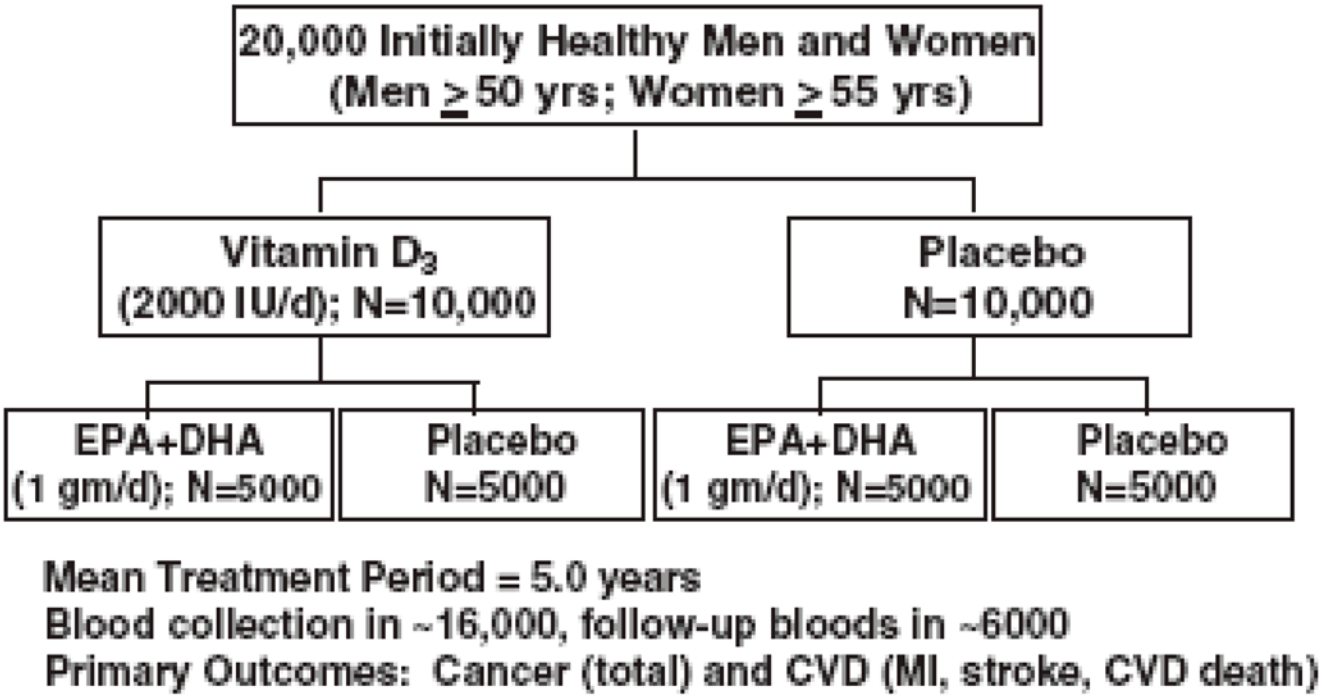

Fig. 3.
The *VIT*amin D and Omeg*A*-3 Trial (VITAL) design.