1-1-2023

Comment on: Association between vitamin D and cardiovascular health: Myth or fact? A narrative review of the evidence

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Letter to the Editor

WOMEN'S HEALTH

Women's Health
Volume 19: 1–2

DOI: 10.1177/17455057231175310
journals.sagepub.com/home/whe
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Comment on: Association between vitamin D and cardiovascular health: Myth or fact? A narrative review of the evidence

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Keywords
causality, Hill's criteria, Mendelian randomization, myocardial infarction, observational study, randomized controlled trial, vitamin D supplementation

Date received: 7 March 2023; accepted: 25 April 2023

To the Editor:

The recent review in *Women's Health* by Ahmadieh and Arabi[1] examined the evidence regarding the association between vitamin D and cardiovascular health and concluded that the suggestion that vitamin D supplementation could reduce risk of cardiovascular disease (CVD) in deficiency is "a myth." Their conclusion was based on the The VITamin D and OmegA-3 TriaL (VITAL) study, a randomized controlled trial (RCT)[2] which failed to find that vitamin D supplementation reduced CVD risks because of several fallacies in the design.[3] In this letter, we explain why this RCT failed and what evidence supports a causal role of vitamin D in reducing the risk of CVD.

The strongest evidence that vitamin D reduces the risk of CVD is a Mendelian randomization (MR) study based on CVD data from the large UK Biobank cohort.[4] MR studies are more informative than RCTs in this regard because they use results from genome-wide association analysis to assign participants to genetically predicted increases in serum 25-hydroxyvitamin D [25(OH)D] concentrations. This methodology randomizes participants with respect to other factors that affect serum 25(OH)D concentrations such as diet, supplementation, and ultraviolet B exposure. That MR study provided data from 44,519 CVD cases and 251,269 controls and examined by nonlinear MR after stratification into 10 ranges of baseline serum 25(OH)D. There was an L-shaped association between genetically predicted increases in serum 25(OH)D across those strata and CVD risk (P nonlinear$=0.007$), where CVD risk decreased steeply as baseline 25(OH)D concentrations increased to 25 nmol/L and leveled off toward a plateau as baseline 25(OH)Ds neared 50 nmol/L. These findings are similar to those for 25(OH)D concentration and subsequent risk of CVD reported by a Danish observational study of risk of ischemic heart disease, myocardial infarction, and early death as a function of seasonally adjusted serum 25(OH)D concentrations,[5] and as shown in Figure 3 of that article, significant risk was most marked with baseline 25(OH)Ds of <25 nmol/L.

The VITAL study participants who provided 25(OH)D values had a mean serum 25(OH)D concentration of 78 nmol/L and were given 2000 IU/d vitamin D_3 in the treatment arm.[2] In addition, all participants were given the choice of taking up to 600-800 IU/d of vitamin D_3 without reporting it. Notably, of 25,871 participants, there were only 34 with major CVD events in both vitamin D treatment and control arms with 25(OH)Ds <50 nmol/L, and 218 in the treatment arm and 216 in the control arm with 25(OH)D concentration >50 nmol/L. This RCT was designed *circa* 2010 and based on guidelines for trials of pharmaceutical drugs, not nutrients. Heaney outlined guidelines for nutrients in 2014.[6] As applied to vitamin D, those guidelines call for basing the RCT on serum 25(OH)D concentrations, not vitamin D doses. A recent review highlighted that very few vitamin D RCTs found, or could have found, beneficial effects of vitamin D as they were not suitably designed, conducted, or analyzed.[3]

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Another way to evaluate the causality of vitamin D status and health outcomes is through the application of Hill's criteria for causality in a biological system.[7] The criteria appropriate for vitamin D include strength of association, consistency, temporality, biological gradient, plausibility, coherence, experiment, and analogy. An analysis of the evidence for vitamin D reducing the risk of CVD by Hill's criteria was reported in 2014[8] when it could be concluded that all criteria were satisfied except for experimental verification. With the recent MR study,[4] this additional criterion for causality of CVD has now been satisfied.

A well-designed large observational study provided strong evidence that vitamin D supplementation reduces CVD risks.[9] This was a retrospective, observational, nested case–control study of patients (N=20,025) with low 25(OH) D concentrations (<50 nmol/L) who received care at the U.S. Veterans Health Administration from 1999 to 2018. Patients were divided into 3 groups: Group A (untreated, concentrations ⩽ 50 nmol/L), Group B (treated to concentrations 52-74 nmol/L), and Group C (treated to concentrations ⩾ 75 nmol/L). Among that cohort, the risk of myocardial infarction was significantly lower in Group C than in Group B (hazard ratio=0.65, 95% CI 0.49-0.85, P=0.002) or in Group A (hazard ratio=0.73, 95% CI 0.55-0.96), P=0.02).

Additional support for the protective role of vitamin D supplementation comes from the fact that CVD mortality rates are about 25% higher in winter than those in summer as discussed in a recent review of the factors affecting the seasonality of CVD incidence and CVD mortality rates[10] where seasonal changes in temperature and serum 25(OH)D concentrations and elevated parathyroid hormone concentrations were discussed in detail. While the evidence regarding temperature is strong, so is that for vitamin D, and which is more important in particular situations may depend on how much exposure there is to cold temperatures or to extreme heat.

In conclusion, numerous studies have provided substantial data regarding the protective role of higher 25(OH) D concentrations for CVD. To convince the medical view, it may be necessary to conduct an RCT with severely vitamin D-deficient elderly participants with significant CVD risk factors, giving those in the treatment arm vitamin D_3 of 4000 IU/d and not permitting any participant to take additional vitamin D supplements, and measure serum 25(OH)D concentrations at least once a year.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Yes.

Author contribution(s)

William B Grant: Conceptualization; Supervision; Writing – original draft; Writing – review & editing.

Fatme Al Anouti: Investigation; Writing – review & editing.

Barbara J Boucher: Investigation; Writing – review & editing.

Acknowledgements

Not applicable.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Competing interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: W.B.G. receives funding from Bio-Tech Pharmacal, Inc. (Fayetteville, AR, USA). The other authors have no conflicts of interest to declare.

Availability of data and materials

Not applicable.

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