JIM Letter to the Editor

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Regarding: Low vitamin D is a marker for poor health and increased risk for disease: But causality is still unclear in most cases

To the Editor,

In a recent editorial, Peter Bergman stated that whether associations between low 25-hydroxyvitamin D [25(OH)D] concentrations and poor health are causally linked was unclear in most cases [1]. His statement was based on the consideration of vitamin D randomized controlled trials (RCTs). However, as discussed at length in a recent review, most vitamin D RCTs have been poorly designed, conducted, and analyzed [2], having been based on guidelines for pharmaceutical drugs rather than on nutrients. Heaney outlined guidelines for trials of nutrients such as vitamin D in 2014 [3]. These guidelines include, for vitamin D, that serum 25(OH)D concentrations of the proposed participants must be measured, and only subjects with low values should be included, that vitamin D doses used must raise 25(OH)D concentrations to values associated with reduced risk in observational studies, and that, therefore, achieved concentrations must be measured. However, most vitamin D RCTs have included many participants with relatively high 25(OH)D concentrations, have used too low vitamin D doses, and did not base their analyses on individual participant 25(OH)D concentrations.

Also overlooked in the editorial is that Mendelian randomization (MR) studies have now demonstrated the causality of vitamin D in reducing risk of several types of disease. In MR studies, data for alleles of genes involved in the vitamin D pathway are used to estimate genetic variations in serum 25(OH)D (genome-wide association studies) using perhaps 100,000 participants and have then examined health outcomes with those gene variants in large study populations. The assumption is that, because individuals are randomized into study groups by the genetic variants they carry, bias due to confounding and reverse causation is avoided [4]. The Hyppönen group, using MR analyses of findings stratified by baseline 25(OH)D concentration (i.e., non-linear analyses), has shown many significant effects of vitamin D in participants with low 25(OH)D concentrations. This methodology has already demonstrated causality for several health outcomes in their hands, including cardiovascular disease, dementia, and all-cause mortality rates, using data from the UK Biobank [4] as well as for hypertension, multiple sclerosis, and type 2 diabetes mellitus by others that they cite [4].

RCTs and MR studies have not supported the causality of vitamin D in the reducing risk of cancers. However, the evidence from observational studies and geographical ecological studies, as well as an understanding of the mechanisms involved, provides sufficient evidence for causality when considered by Hill's criteria for causality in a biological system [5, 6]. It should also be noted that the Vitamin D and Omega-3 Trial (VITAL) [7] had serious shortcomings including that the mean 25(OH)D concentration for those in the vitamin D treatment arm with 25(OH)D data was 30 ng/mL, that the vitamin D dose was 2000 IU/d but that all participants were permitted to take up to 600–800 IU/d vitamin D and to receive solar UVB, and that outcomes were not analyzed in terms of achieved 25(OH)D concentrations. Nevertheless, secondary analyses did find significant reductions for cancer incidence for those with a BMI <25 kg/m^2 and overall reductions in the cancer mortality rate when the earliest years of data were omitted.

Conflict of interest statement

WBG receives funding from Bio-Tech Pharmacal, Inc. (Fayetteville, AR). BJB has no conflict of interests to declare.

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