Reply to 'The emerging evidence for non-skeletal health benefits of vitamin D supplementation in adults'

Roger Bouillon, Despoina Manousaki, Cliff Rosen, Katerina Trajanoska, Fernando Rivadeneira and J. Brent Richards

We thank Grant et al. for their interest in our recently published Review on vitamin D supplementation (Bouillon, R. et al. The health effects of vitamin D supplementation: evidence from human studies. *Nat. Rev. Endocrinol.* **18**, 96–110 (2022)[1]). Considering the well-accepted hierarchy of evidence, our Review dealt with large randomized clinical trials (RCTs) published from 2017 to 2020 and Mendelian randomization studies, and deliberately did not review observational studies. Grant et al., however, use several observational studies and post hoc analyses to argue the benefits of high serum concentrations of 25-hydroxyvitamin D (25OHD) on hypertension, breast cancer or type 2 diabetes mellitus (T2DM) (Grant, W.B. et al. The emerging evidence for non-skeletal health benefits of vitamin D supplementation in adults. *Nat. Rev. Endocrinol.* https://doi.org/10.1038/s41574-022-00646-x (2022)[2]).

The D2d study of individuals with prediabetes concluded that 4,000 IU of vitamin D per day did not decrease the progression of prediabetes into T2DM in the intention to treat analysis[3]. In their Correspondence, Grant et al. discuss data from a post hoc analysis of this RCT[2]. We clearly mentioned in our Review that in this same post hoc analysis, a reduction in the progression from prediabetes to T2DM was found in participants with continuously high serum concentrations of 25OHD (>100 nmol/l) throughout the trial[1]. This interesting observation should guide a follow up trial, however, it is certainly not sufficient to change clinical practice for patients with prediabetes.

Grant et al. cite data on breast cancer incidence in three different cohorts of women, concluding that women with the highest serum concentrations of 25OHD had a lower risk of breast cancer than women with the lowest 25OHD[2]. Many other observational studies, however, generated discordant results[4]. Moreover, the VITAL (Vitamin D and Omega-3 trial) and ViDA (Vitamin D Assessment study) RCTs did not find a lower breast cancer rate after long term vitamin D supplementation in much larger groups of participants[5,6]. Similarly, several Mendelian randomization studies could not confirm an effect of genetically lowered serum concentrations of 25OHD on breast cancer risk[1].

A very large number of Mendelian randomization studies looked at the health consequences of genetically lowered serum concentrations of 25OHD in the general population and did not generally identify any health benefits of high vitamin D status (for example, cancer or cardiovascular events)[1]. However, four independent Mendelian randomization studies found an increased risk of genetically lowered serum concentrations of 25OHD for youth or adult-onset multiple sclerosis[1]. As Grant et al. propose in their Correspondence[2], Mendelian randomization studies have limitations. For example, most Mendelian randomization studies to date cannot predict large differences in serum concentrations of 25OHD and they have not tested for non-linear effects. However, they are the only way to evaluate the lifelong health consequences of decreased vitamin D levels. Of note, methodological advances testing the nonlinear effects of decreased vitamin D using Mendelian randomization have shown that vitamin D deficiency increases all-cause mortality, adding further evidence to the importance of correcting vitamin D deficiency[7].

The large RCTs thus conclude that vitamin D supplementation of vitamin D replete individuals does not generally generate measurable health benefits[1]. We agree that these studies included too few participants with severe vitamin D deficiency to validate the potential extra skeletal benefits of correcting vitamin D deficiency. While awaiting studies dealing with such questions, we suggest to follow the major guidelines, which unanimously recommend correction of vitamin D status in individuals with severe (serum levels of 25OHD <30 nmol/l) or modest (<50 nmol/l) vitamin D deficiency[8].

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Competing interests
The authors declare no competing interests.