No evidence that vitamin D is able to prevent or affect the severity of COVID-19 in individuals with European ancestry: a Mendelian randomisation study of open data, by Amin *et al*

The report from Amin *et al* concluded that the use of vitamin D supplementation for reduction of COVID-19 risks was not supported by the available data using Mendelian randomisation analysis (MRA) of UK Biobank data for Britons of European origin.[1] Their study used Genome-wide association [GWA] methodology to determine gene variant effects on baseline serum 25-hydroxyvitamin D (25(OH)D) concentrations, which were then used as surrogates for long-term vitamin D status in their MRA, without data for vitamin D intakes or sunshine exposure.[1] Though MRA studies using gene variant effects on serum 25(OH)D are common, the potential for error due to the non-linear associations of biological and health effects with serum 25(OH)D concentrations (vitamin D status) is widely recognised.[2] However, no satisfactory way has evolved for avoiding the confounding necessarily introduced by inclusion of the data lying on the upper or lower plateaus of those S-shaped relationships, but those were the datasets selected for analysis in this study.[1] This matter is important since changes in the efficacy of vitamin D are not seen in subjects with 25(OH)D values along the lower or upper plateaus of the S-shaped association curves. And, in deficiency, no health benefits are seen with supplementation in subjects on the lower plateau unless their 25(OH)D concentrations are raised onto the steep part of the association curves, from ≤25 nmol/L (=UK deficiency) to at least 50 nmol/L for bone health but to higher values for effects with higher thresholds (eg, to 80–100 nmol/L for reducing insulin resistance and type 2 diabetes mellitus (T2DM) risks, respectively).[3–5] Since gene variant effects on 25(OH)D values were reported as being much smaller than the 25–50–75 nmol/L (100%–200%–300%) increases in 25(OH)D values such thresholds require, it is unlikely that MRAs of population data can detect health effects of variation in serum 25(OH)D in subjects with 25(OH)D values <25 nmol/L unless the 25(OH)D thresholds required to affect the outcome of interest are extremely low, especially in datasets selected for baseline vitamin D deficiency.

In view of these analytical difficulties, it might be that avoiding data from the known associational plateaus for health effects of interest (ie, selecting datasets for subjects with baseline 25(OH)D values between 25 nmol/L and 110 nmol/L, even though those values only predict ~16% of current status)[6 7] might be helpful in examining long-term differences in vitamin D status as a potential determinant of health effects such as COVID-19 risks. Those 'cut-offs' for COVID-19 risks are suggested by the data analyses reported by Kaufman and colleagues for reductions in COVID-19 infection rates with increases in vitamin D status as assessed by 25(OH)D measurements made during the year before the pandemic began, using data available from a large representational American cohort study.[8]

There are many mechanistic reasons for suggesting that better vitamin D status should be protective against COVID-19 risks.[9] Furthermore, a recent study of UK Biobank data suggests that those taking vitamin D supplements over time before the pandemic began had reduced COVID-19 risks in the subsequent COVID-19 pandemic in the UK.[10] Might the authors, therefore, consider whether the modified approach to MRA for COVID-19 with genome-wide association studies (GWAS) predicted variations in vitamin D status could prove useful?

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