Comment on Weller "Sunlight: Time for a Rethink?"

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In a recent publication in the *Journal of Investigative Dermatology* Weller reviewed the evidence for two mechanisms by which solar UV reduces risk of disease: by inducing vitamin D synthesis and by liberation of nitric oxide (NO) [1]. The manuscript outlined the evidence that while solar UVB exposure increased serum 25-hydroxyvitamin D [25(OH)D] concentrations and people with higher concentrations were healthier, clinical trials have found little benefit from vitamin D supplementation. On the other hand, photomobilization of NO from cutaneous stores has been found to reduce risk of cardiovascular disease. However, the available evidence suggests that the health benefits of adequate vitamin D provision are much stronger than reported in Weller's review.

The evidence that solar UVB and vitamin D reduces both incidence and mortality for many types of cancer comes from over 7000 publications listed at pubmed.gov, using various approaches: ecological, observational, randomized controlled trials (RCTs), and mechanistic studies [2]. The ecological studies clearly show very strong inverse correlations between indices of solar UVB dose and incidence and mortality rates for about 20 types of cancer [2]. A recent meta-analysis of vitamin D RCTs found that daily, but not interval, vitamin D supplementation from before cancer diagnosis in adults over 70 years of age reduced mortality rates by about 12% [3]. A recent study in Japan of the 36% of immunoactive-P53-antibody positive digestive tract cancers showed that their survival rates increased five-fold with vitamin D supplementation [4].

For COVID-19, a 2024 meta-analysis of data from 16 peer reviewed reports found a 60% reduced incidence of COVID-19 and a 70% reduced need for intensive care with vitamin D supplementation [5].

For the risks of type 2 diabetes mellitus, a reanalysis of the D2d trial data for progression from prediabetes to diabetes by achieved 25(OH)D found a 70% reduced rate of progression from prediabetes to diabetes in those in the vitamin D treatment arm achieving, and maintaining, serum 25(OH)D values of 125-150 nmol/L in comparison to those achieving values of 50-74 nmol/L [6]. These findings are supported by data from two other studies, while supplementation also increased regression to normoglycaemia by 30%.

The problem with most vitamin D RCTs is that they follow the guidelines for pharmaceutical drugs, not nutrients [7]. In drug trials, the only source of the drug is in the trial, the control group does not receive any of the drug, there is generally a linear dose-response relationship, and the outcome is examined by intention to treat. These trial designs do not work well for nutrients, including vitamin D. For vitamin D, for example, serum 25(OH)D concentration should be measured prior to enrollment and trials should enroll those with low concentrations; vitamin D doses should be high enough to raise achieved concentrations to levels known to be associated with health benefits and achieved concentrations should be used in the

analyses. In many previous vitamin D RCTs, unfortunately, many participant groups have had mean 25(OH)D concentrations around 75 nmol/L, have been given low vitamin D doses, have been permitted to take additional vitamin D, whether in treatment or control arms, and data analyses were by intention to treat. These confounding factors have resulted in few RCTs of vitamin D findings significant benefits of vitamin D supplementation, even for health benefits well supported by other studies.

An example of a well-designed trial of vitamin D supplementation carried out using appropriate principles was made in Iran to study pregnancy outcomes [8]. Two hospitals were involved; one was the control with no vitamin D supplementation, the other gave pregnant women enough vitamin D to raise serum 25(OH)D concentrations from a mean of 28 nmol/L to a mean of 53 nmol/L. Those in the supplemented group were found to have significantly reduced risks of gestational diabetes, pre-eclampsia, and preterm delivery in comparison to those unsupplemented.

An analysis of outcomes of the many UK Biobank participants, of whom 29,107 (6.5%) died during a median follow-up period of 11.8 years,[9] showed that self-reported vitamin D supplement use was significantly associated with a 10% lower all-cause mortality rate. Furthermore, regular vitamin D supplement users had significantly lower mortality rates by 11% for cancer and by 29% for respiratory disease, than nonusers, respectively, though their reduced cardiovascular disease mortality was not significant. Similarly, significant 34% risk reductions of COVID-19 infections were seen in UK Biobank supplement users, independent of baseline or genetically determined vitamin D status, in the later COVID-19 pandemic [10].

For those wishing to learn more about what has been established regarding vitamin D, its mechanisms of action and biological effects, the Fifth Edition of Feldman and Pike's Vitamin D was published in 2024 (https://shop.elsevier.com/books/feldman-and-pike-s-vitamin-d/hewison/978-0-323-91386-7) with 106 chapters by leading vitamin D researchers that cover all aspects of vitamin D metabolism and health effects.

We agree that the health benefits of sunlight require additional research and analysis. We also accept that the emerging evidence that photomobilization of NO from cutaneous stores has shown benefits for several health outcomes. However, we think that the health benefits of vitamin D from sunlight, diet, and supplements have been under appreciated due in large measure to the fact that most vitamin D RCTs have been based on guidelines for pharmaceutical drugs rather than for nutrients.

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