Vitamin D: Ten Beliefs

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To the editor

We commend the authors on their comprehensive review investigating the use of vitamin D supplementation across many clinical outcomes.[1] However, we disagree with their conclusions that the current literature supports only a beneficial effect of vitamin D supplementation on fracture risk. As the authors correctly point out, observational studies of vitamin D are subject to important limitations since, in general, a decreased level of vitamin D is a marker of poor health. Consequently, bias due to confounding is likely to be an important limitation of observational vitamin D studies. Further, since many diseases lead to a decrease in time outside and reduced sun exposure, reverse causation may likewise plague such studies. While randomized controlled trials (RCT) are usually less susceptible to these forms of bias, vitamin D is off-patent. Therefore RCTs of vitamin D supplementation are often small and limited to short follow-up periods, due to cost constraints.

Given this lack of high-quality observational and RCT evidence, we elected to investigate whether vitamin D influences the risk of MS and coronary artery disease (CAD) using Mendelian randomization (MR). This approach allows for an assessment of lifelong exposure to decreased vitamin D on risk of disease that is uninfluenced by reverse causation and less susceptible to bias due to confounding. This is because MR uses the genetic determinants of vitamin D status as proxies for vitamin D level and since genetic variants are randomized at meiosis, MR retains many of the advantages of an RCT. While our MR analyses supported a causal role of vitamin D in the MS etiology (OR = 2.02, 95 % CI = 1.65–2.46, $p = 7.72 \times 10^{-12}$),[2] they did not support an important effect of vitamin D on CAD risk (OR = 0.99, 95 % CI = 0.84–1.17, $p = 0.93$).[3]

We concluded that vitamin D supplementation may be an important form of primary prevention for MS, which warrants further investigation by clinical trials. Restricting a systematic review of the effects of vitamin D to observational studies and RCTs ignores relevant information provided by MR. As this field progresses, we believe that a discussion of MR analyses in future reviews of vitamin D is worth consideration. Given the paucity of high-quality RCT data, MR may present the best evidence to support, or contradict, a role for vitamin D in disease susceptibility.

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