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EDITORIALS

Vitamin D and chronic disease prevention

Multiple meta-analyses but still no magic bullet

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Vitamin D "deficiency" (circulating 25-hydroxyvitamin D concentration <30 nmol/L) has been linked to a remarkable array of chronic diseases, including bone mineral disease, autoimmunity, cancer, diabetes, and cardiovascular outcomes.[1] So plentiful are vitamin D's putative mechanistic actions that it has been whimsically invoked as an explanation for why good triumphs over evil in JRR Tolkien's *The Hobbit*.[2] Parody aside, the vitamin D literature comprises a minefield of observational data and mixed quality evidence from predominately small trials. Appropriate interpretation of the data is further muddied by seemingly endless media reports suggesting vitamin D as a panacea for chronic disease.[3 4]

Against this backdrop, two new papers bravely attempt to make sense of the existing data. Theodoratou and colleagues (doi:10.1136/bmj.g2035) highlight differences between observational data (relating circulating 25-hydroxyvitamin D to outcomes) and randomised controlled trials of supplementation.[5] Of a remarkable 137 different outcomes reportedly linked to 25-hydroxyvitamin D, only 10 had also been tested in trials, and only one (birth weight) had apparently concordant evidence of "benefit" from observational studies and trials. This pattern of findings should ring alarm bells; observational epidemiology extolled the virtues of antioxidant vitamins, only for major trials of vitamins E and C and β carotene to show null, or even some harmful, effects of supplementation on a range of outcomes.[6-8] This highlights the often underestimated problems of confounding and reverse causality that can lead to premature causal inferences in observational studies.[9] Such factors are potentially even more applicable to vitamin D; circulating concentrations can be lowered not only by lack of sun exposure (itself linked to many lifestyle circumstances) but also by inflammation, smoking, obesity, and poor diet.[10-12] Consequently, observational data linking 25-hydroxyvitamin D concentrations to any outcome can only ever be hypothesis generating.

Taking a different approach, Chowdhury and colleagues (doi:10.1136/bmj.g1903) provide a new meta-analysis of observational and trial data relating vitamin D (given alone as either the D_2 or D_3 preparation), to risk of all cause mortality.[13] Their observational analyses unsurprisingly confirmed low 25-hydroxyvitamin D to be associated with elevated risk of multiple adverse outcomes. However, their analysis of trials provides the most noteworthy finding: whereas D_2 supplementation did not seem to reduce all cause mortality (relative risk 1.04, 95% confidence interval 0.97 to 1.11), D_3 supplementation did (0.89, 0.80 to 0.99). A previous Cochrane review also reported a reduction in all cause mortality with the use of D_3, albeit of lower magnitude (relative risk 0.94, 0.91 to 0.98).[14]

The apparent degree of benefit from D_3 in the new analyses—11% lower mortality—seems remarkable, but before these results are taken as a green light for widespread D_3 supplementation, several limitations must be considered. Firstly, 14 trials contributed to the D_3 meta-analysis, totalling only 13 637 participants, and six of these were scored as being at high risk of bias. Contrast this to meta-analyses of large scale antihypertensive and statin trials,[15 16] which have an order of magnitude more participants, generally in better quality studies. Secondly, indicative of inherent uncertainty, different authors have reached somewhat differing conclusions despite exhaustive analysis on apparently overlapping datasets.[5 14 17]

Thirdly, the four studies (n=10 197) that contributed the most power to the D_3 trial meta-analyses were conducted in older people and had fractures as the primary outcome. If we accept a small benefit of vitamin D supplementation on risk of fracture, although even this has been challenged,[5 17 18] the observed reduction in mortality may have been secondary to avoidance of in-hospital complications and loss of independence in later life. Any potential reduction in mortality may therefore not be generalisable to middle aged populations. Fourthly, genetic studies investigating the causal role of vitamin D in chronic disease are sparse and inconclusive. Finally, and perhaps most importantly, vitamin D supplementation may not be without harm. Theodoratou and colleagues highlight an increased risk of hypercalcaemia in chronic kidney disease,[5] a side effect that can also occur in people without renal disease.[19 20] Thus, larger studies are still needed to rule out potential adverse effects.

We suggest three take home messages from these two new studies. Firstly, healthcare professionals should treat all

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observational data cautiously, as existing disease and associated risk factors may cause, rather than be a consequence of, low circulating 25-hydroxyvitamin D. Secondly, before widespread supplementation can be considered, new trial data are needed with a focus on potential risks as well as benefits; further reanalysis of existing data will not suffice. Fortunately, new trials are under way—for example, VITAL,[21] which has recruited 26 000 men and women and randomised them to 2000 IU D_3, omega-3 fatty acid, or placebo in a two by two factorial design. Its primary outcomes will be cancer, coronary heart disease, and stroke, and it is due to report around 2017. VITAL will also be able to assess whether any benefits of D_3 vary by baseline 25-hydroxyvitamin D concentrations. This study alone will therefore substantially increase the available D_3 trial evidence base, and, importantly, extend it to younger people.

Finally, while we wait for results of major trials, clinicians should avoid costly measurement of 25-hydroxyvitamin D in asymptomatic patients outside of bone disease related conditions.[22] Some may argue that supplementing those who are apparently "deficient" is cheap, but patients may gain false reassurance from prescription of a "protective" tablet. To improve health and prevent chronic disease, we should stick to what is proven: encourage better lifestyles in general and target established risk factors in people at elevated risk.

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