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EDITORIALS

Do vitamin D supplements help prevent respiratory tract infections?

A clinically useful effect remains uncertain despite hints in a new analysis

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Vitamin D supplementation is a hot topic, provoking passionate arguments for and against widespread supplementation. Recently in *The BMJ* we discussed the evidence, concluding that vitamin D supplements should not be taken by adults to prevent non-musculoskeletal disease.[1] Three months later comes a meta-analysis by Martineau and colleagues (doi:10.1136/bmj.i6583), concluding that prevention of acute respiratory tract infection is a "major new indication for vitamin D supplementation."[2] Given the short time between articles, why are the conclusions so different? Is this really a major new development, providing the long sought reliable evidence of benefits of vitamin D on a non-skeletal outcome in the general population? Or is it yet another hypothesis about vitamin D supplementation that needs testing in adequately powered randomised controlled trials?

Eight trial level meta-analyses have examined this topic since 2012, with conflicting findings: three reported benefits and five no consistent benefits from vitamin D.[3-10] Martineau and colleagues extend this work by analysing individual patient data from 25 randomised controlled trials with acute respiratory tract infection as an outcome, involving 11 321 participants of all ages, some with existing chest disease. The headline result is a 12% reduction in the odds of an acute respiratory tract infection from supplementation.

There are reasons for viewing the headline result cautiously. In absolute terms, the primary result is a reduction from 42% to 40% in the proportion of participants experiencing at least one acute respiratory tract infection. It seems unlikely that the general population would consider a 2% absolute risk reduction sufficient justification to take supplements. Furthermore, the definition of acute respiratory tract infection varied between studies, consisting of a mixture of diverse conditions such as acute otitis media, laboratory confirmed influenza, self reported colds, parent reported colds or chest infections, or radiograph confirmed pneumonia. It is difficult to know whether a reduction in this mixture of conditions is applicable to the general population and how it should be interpreted clinically.

The meta-analysis includes individual patient data from 25 studies, which is an impressive achievement. Obtaining and analysing individual patient data for meta-analyses is difficult and time consuming. However, the selection of trials was sometimes unclear. A table of excluded trials with reasons for their exclusion would have been helpful.[11 12] Conversely, prospective data collection was one of the authors' inclusion criteria,[13] but they also included two trials that collected data retrospectively.[14-16] The differing conclusions to the previous systematic reviews, may be in part due to methodological differences such as these, as occurs in other overlapping meta-analyses of vitamin D supplements.[17 18]

As in previous reviews, there is noticeable heterogeneity in the trial results (authors' figure 2). Individual patient data analyses allow exploration of heterogeneity to a much greater degree than trial level analyses. The authors found potentially important factors modifying the response to supplementation: those with 25-hydroxyvitamin D levels less than 25 nmol/L and those receiving daily or weekly doses rather than bolus dose, had greater benefits, although vitamin D status was only available for less than 40% of trial participants. Although not statistically significant, there could be a clinically relevant interaction with age: in table 2 the benefits from vitamin D appear largely confined to the smallest subgroup of children aged 1.1-15.9 years (n=1079, absolute risk reduction 13%). In the three other larger subgroups (≤1 years n=5571, 16-65 years n=3051, >65 years n=1232), the absolute reductions were small and statistically non-significant, ranging from 0-3%.

Should these results change clinical practice? Probably not. The results are heterogeneous and not sufficiently applicable to the general population. We think that they should be viewed as hypothesis generating only, requiring confirmation in well designed adequately powered randomised controlled trials. Several very large such randomised controlled trials of vitamin D supplements will report on the effects on respiratory infections within the next few years. These trials have not targeted individuals with very low serum concentrations of vitamin D, and there is still a need for trials in these population groups. We

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consider that current evidence does not support the use of vitamin D supplementation to prevent disease, except for those at high risk of osteomalacia, currently defined as 25-hydroxyvitamin D levels less than 25 nmol/L.

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