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Correspondence

# Difficulties in designing randomised controlled trials of vitamin D supplementation for reducing acute cardiovascular events and in the analysis of their outcomes

## Correspondence to the editor, IJC Heart & Vasculature

The question of whether vitamin D supplementation may reduce the risk of acute cardiovascular events remains under debate. The recent study by Nudy et al. found no evidence of benefit of vitamin D supplementation for reducing those in a meta-analysis of older randomised controlled trial [RCT] data, but the authors noted many problems likely to have confounded analyses of the available data [1]. These problems included wide variations in dosages given, in duration of follow up, the lack of standardisation of the 25-hydroxyvitamin D [25(OH)D] assay data from different laboratories and the fact that it was not possible to analyse outcomes using individual participant data [IPD]. Many RCTs did not have adequate power for detection of cardiovascular disease [CVD] health benefits and none had been carried out in subjects selected as deficient. Together, these factors made it impossible, as the authors concluded, for the study to have been able to detect whether supplementation reduced CVD outcomes from the analyses made. If the authors purpose in this report was to warn others of the unsuitability of much RCT data for use in meta-analyses seeking evidence of CVD risk reduction, they have clearly succeeded. However readers should be aware, especially those considering carrying out further trials for CVD health benefits, that there several more factors that should, ideally, be addressed in future RCTs for CVD outcomes if they are to be adequate for providing definitive answers on whether vitamin D supplementation induces any CVD risk reductions.

The major additional factor to consider arises from the authors' comment that 'a linear relationship does not exist between baseline 25(OH)D and vitamin D supplementation effect on CVD' [1,2], since vitamin D provision does not have linear associations with its effects. Instead there are S shaped associations, both for the association of serum 25(OH)D with intake and for the associations of various outcomes with vitamin D status [serum 25(OH)D concentrations] [2]. Analyses of data for entire cohorts without considering the range of 25(OH)D values within each cohort means that in deficient subjects where vitamin D doses were not large enough to raise 25(OH)D values from the lower plateau of the S curve onto the steep slope of the 'S', and in 'replete' subjects with initial 25(OH)D values on the upper plateau of the relevant S shaped curves, beneficial health outcomes should not be expected [2]. To avoid these confounding factors subjects could be selected as being deficient at baseline; alternatively, outcomes could be examined using IPD so that they can be assessed for subjects with different degrees of insufficiency/deficiency at baseline, a technique that has revealed benefits not apparent in initial overall analyses, as first shown for upper respiratory tract infections, and in other condition subsequently [3–5].

Other potential confounders of outcomes in trials of vitamin D supplementation include non-supplemental vitamin D provision in RCT subjects due to exposure to sunshine, self-supplementation and from food, and the interactions of other nutrients with vitamin D efficacy [6]. Additional calcium supplementation has featured in many RCTs on bone health and, in large amounts, calcium has healed rickets in D deficient children though this phenomenon remains under debate; increasing supplemental calcium intakes in adults are suspected of having adverse effects on CVD outcomes [though similar increases in dietary calcium intakes are not] [7–9]. Magnesium is essential for the normal function of enzymes, including those in the vitamin D axis [7] and signalling pathways, but deficiency is common across the developed world [10]. Vitamin A in excess, as is increasingly common in the developed world, inhibits the actions of vitamin D experimentally both *in vivo* and *in vitro* and has been found in some human RCT data [11]. Unfortunately, despite these well understood interactions, relevant data are not collected routinely in vitamin D RCTs.

The very long natural history of CVD, starting with increases in risk markers in childhood and progressing over the lifespan, with increasingly irreversible fibrosis in arterial walls following the chronic inflammatory changes that characterise this disorder, suggests that very long RCTs might be needed for detection of reduction in its progression. The increases in inflammatory plaque disruption and the risks this leading to acute cardiovascular events should, however, be reducible, if not reversible, as it is with adequate treatment with statins, since vitamin D inhibits secretion of the destructive matrix-metalloproteinases in large amounts by infiltrating macrophages that leads to disruption of increasingly unstable plaque [12,13]. Ideally, therefore, control and test subjects studied in RCTs for CVD risk reduction should have comparable pathological changes in their arteries and it may become possible to assess this as new markers of CVD severity evolve.

Adequate long-term RCT data for the effects of correcting vitamin D deficiency on CVD risks, allowing for the factors noted by Nudy et al. [1], and those mentioned above, are increasingly unlikely to be carried out, especially in subjects selected as deficient since leaving control subjects with deficiency un-supplemented over time is considered unethical. It is possible, however, that data from long-term observational population studies, may provide relevant data. For example, public health data from countries with effective food fortification programmes, such as Finland, may reveal reductions in atheromatous disease risks with higher vitamin D status that are independent of earlier dietary interventions in Finland [such as the very successful North Karelia project

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[*www.who.int/chp/about/integrated_cd/index2.html], and of continuing medical interventions, before too long as it is now 10 years since deficiency was virtually eliminated in Finland and 10–20 years may be long enough to induce vitamin D-related cardiovascular risk reductions [14,15].

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