O bservational studies have mostly found a strong association of low plasma 25-hydroxyvitamin D (25(OH)D), usually used to measure vitamin D status, with increased risk of coronary heart disease, stroke, and cardiovascular death.\textsuperscript{1-3} However, recent Mendelian randomization studies and randomized intervention trials do not support a causal association of 25(OH)D or vitamin D supplementation with cardiovascular disease.\textsuperscript{4-8} This discrepancy has been ascribed to failures to account either for confounding or reverse causation in observational studies or for the nonlinear relationships in genetic studies and inappropriate recruiting of vitamin D replete individuals to vitamin D supplementation trials.


In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Qi et al\textsuperscript{9} present a comprehensive report on the association of 25(OH)D and other biomarkers of vitamin D status on coronary heart disease. Using the Nurses’ Health Study in a nested case–control design with 382 cases and 575 controls and 20-year follow-up, they show independent associations of VDBP (vitamin D–binding protein) with coronary heart disease and an interaction of 25(OH)D with parathyroid hormone on risk of coronary heart disease (Figure). However, 25(OH)D was not independently associated with coronary heart disease. In essence, this report claims that reality may be more complex than claiming that low 25(OH)D is a risk factor for coronary disease (Figure). The main limitation of these findings is that this is an observational study that cannot escape residual confounding; therefore, causal claims cannot be substantiated beyond reference to biological plausibility. Other limitations include the modest sample size and the relatively high mean levels of 25(OH)D in the population studied. In addition, there are no immediate consequences for clinical practice. Most importantly, we are all awaiting investigations of the biomarkers with regard to risk of coronary heart disease. Further studies are needed to investigate these hypotheses and any potential consequences for clinical practice. In conclusion, the study by Qi et al highlights that other biomarkers of vitamin D status could be independently associated with risk of coronary heart disease and that there could be potential interactions of the biomarkers with regard to risk of coronary heart disease. Further studies are needed to investigate these hypotheses and any potential consequences for clinical practice. Most importantly, we are all awaiting the randomized intervention of vitamin D supplementation to be published in the near future (eg, ViDA [The Vitamin D Assessment], CAPS [Clinical Trial of Vitamin D3 to Reduce Cancer Risk in Postmenopausal Women], VITAL [Vitamin D

\[Naive\ model\ of\ the\ association\ of\ 25(OH)D\ with\ coronary\ heart\ disease\]

\[\text{25(OH)D} \rightarrow \text{Coronary heart disease}\]

\[Models\ proposed\ by\ Qi\ et\ al.\]

\[\text{25(OH)D} \rightarrow \text{VDBP} \rightarrow \text{Coronary heart disease}\]

Biological activity of vitamin D $\rightarrow$ PTH, parathyroid hormone; and VDBP, vitamin D–binding protein.

Figure. Proposed models for the association of biomarkers of vitamin D status with risk of coronary disease. 25(OH)D indicates 25-hydroxyvitamin D; PTH, parathyroid hormone; and VDBP, vitamin D–binding protein.

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Vitamin D and Risk of Cardiovascular Disease

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and Omega-3 Trial], DO-HEALTH [Vitamin D - Omega3 - Home Exercise - Healthy Ageing and Longevity Trial], and FIND [Finnish Vitamin D Trial]). These randomized trials will provide us with definitive answers as to whether vitamin D supplementation will reduce cardiovascular disease or not and whether vitamin D is causally related to cardiovascular disease.

References


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