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New Meta-Analysis Suggests 'Threshold' Effect for Vitamin D and CVD

Lisa Nainggolan | Nov 16, 2012

BOSTON — A new meta-analysis has found a linear, inverse association between cardiovascular disease risk and vitamin-D levels up to a certain point, but then a possible "threshold" effect [1].

Dr Lu Wang (Brigham and Women's Hospital, Boston, MA) and colleagues say in their review that the majority of earlier meta-analyses, as well as this one, have found an association between low circulating vitamin-D levels and increased risk of cardiovascular events. But the dose-response curve has not previously been fully determined, with some research suggesting a U-shaped curve between the two.

"The dose–response curve indicated that the association was generally linear across the range of vitamin D from 20 to 60 nmol/L," they state in their paper, published online November 13, 2012 in *Circulation: Cardiovascular Quality and Outcomes*. "More prospective studies and randomized clinical trials are needed to further clarify the association between vitamin D >60 nmol/L and CVD risk and to assess the causality of observed associations," they note.

Findings on Dose-Response Will Help Inform Future Trials

Wang and colleagues say that with widespread attention to a possible role of vitamin D in the prevention of CVD, it was becoming increasingly important to further evaluate the dose–response association between the two and "to determine the optimal vitamin-D level that may confer potential cardiovascular benefits."

They searched MEDLINE and EMBASE from 1966 through February 2012 for prospective studies that assessed the association of 25(OH)-vitamin D concentrations with CVD risk and included 19 independent studies with 6123 CVD cases in 65 994 participants.

In a comparison of the lowest with the highest vitamin-D categories, the pooled relative risk was 1.52 for total CVD, 1.42 for CVD mortality, 1.38 for coronary heart disease, and 1.64 for stroke. And "these associations remained strong and significant when analyses were limited to studies that excluded participants with baseline CVD and were better controlled for season and confounding," they observe.

They also assessed the linearity of the dose–response association between vitamin D and CVD risk. The latter increased across decreasing 25(OH)-vitamin D below about 60 nmol/L, with a relative risk of 1.03 per 25-nmol/L decrement in 25(OH)-vitamin D.

And although there was considerable heterogeneity between individual studies, stratified analysis found that the inverse association was consistent in various study subgroups, too, they note.

A stronger association was found in studies with <10 years of follow-up than in those with longer follow-up, however, "which may reflect changes in 25(OH)-vitamin D over longer periods of time or the competing risks for fatal and nonfatal diseases in older populations," they observe.

But in eight studies that examined 25(OH)-vitamin D >65 nmol/L, six found no significant change in the risk of CVD, suggesting a possible threshold effect.

"Our meta-analysis of prospective observational studies allows an evaluation of the dose–response association between vitamin D and CVD risk over a broad range of vitamin-D levels, which will not only complement findings from ongoing randomized trials but also help to inform future trials that test the effect of vitamin-D supplements on CVD in terms of the optimal doses," they conclude.

Wang et al report no conflicts of interest.

References

1. Wang L, Song Y, Manson JE, et al. Circulating 25-hydroxy-vitamin d and risk of cardiovascular disease. A meta-analysis of prospective studies. *Circ Cardiovasc Qual Outcomes* 2012; DOI:10.1161/CIRCOUTCOMES.112.967604. Available at: http://circoutcomes.ahajournals.org. Abstract

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