

## Low Levels of 25-Hydroxyvitamin D Related to Increased Mortality, But Questions Remain

Melamed ML, Michos ED, Post W, Astor B. 25-Hydroxyvitamin D levels and the risk of mortality in the general population. *Arch Intern Med* 2008;168:1629–37.

### Study Overview

**Objective.** To examine whether low levels of 25-hydroxyvitamin D (25[OH]D) correlate with increased mortality in the general U.S. population.

**Design.** Observational study.

**Setting and participants.** Nationally representative sample of individuals aged  $\geq 20$  years who were part of the Third National Health and Nutrition Examination Survey (NHANES). Participants underwent laboratory testing (including measurement of 25[OH]D levels), physical examination, and interviews at baseline between 1988 and 1994 and were followed through 2000.

**Main outcome measures.** Association between 25(OH)D levels and mortality from cancer and cardiovascular disease (CVD) and all-cause mortality.

**Main results.** 13,331 individuals participated in the study, and 1806 died, including 777 from CVD (median follow-up, 8.7 years). Participants were grouped into quartiles based on laboratory values of 25(OH)D levels. Participants with 25(OH)D levels in the lowest quartile ( $< 17.8$  ng/mL) had a 26% higher adjusted rate of all-cause mortality than participants in the highest quartile (mortality risk ratio [MRR], 1.26 [95% confidence interval {CI}, 1.08–1.46]). Women, elderly persons, non-Hispanic blacks, and individuals with low socioeconomic status were more likely to fall into the lowest 25(OH)D quartile. Of participants in the lowest 25(OH)D quartile, those without CVD had a stronger association with mortality as compared with those with CVD ( $P = 0.006$  for interaction). After adjusted analyses, there were no statistically significant associations between low 25(OH)D level and mortality from cancer or CVD (MRR, 1.05 [95% CI, 0.74–1.47] and 1.20 [95% CI, 0.87–1.64], respectively).

**Conclusion.** In a nationally representative sample, low levels of 25(OH)D were associated with an increased risk of death. Further, individuals with low 25(OH)D level and no history of CVD had a stronger association with mortality than those with CVD.

### Commentary

Every few years, a new study examines the relationship between vitamin D, CVD, cancer, and mortality. While some studies have found relationships between vitamin D levels and these various outcomes [1–3], others have not [4]. A series of randomized trials have failed to conclusively establish or refute whether a relationship exists. It remains unclear whether vitamin D supplementation is beneficial, and clinicians are still unsure of whether to monitor and aggressively treat patients with low vitamin D levels.

The study by Melamed and colleagues brings certain strengths to the debate. First, the study analyzes a nationally representative group of Americans, making their findings very broadly applicable to all adults in the United States. Second, clinical and laboratory variables are detailed, which allows for relatively robust adjustments for baseline differences between participants with and without low 25(OH)D levels. Finally, the long period of follow-up between assessment of 25(OH)D levels and outcomes allows for a clearer determination of an association (ie, that vitamin D levels affect risk of mortality and not that patients dying from other causes have low vitamin D levels). Given these strengths, how much have these results moved us closer to a clear understanding of the relationship between vitamin D and death? Unfortunately, this study by Melamed and colleagues is more provocative than illuminating.

Several elements of the study raise concerns about the validity of the findings. First, the study design does not allow for assigning causality between vitamin D and mortality. In fact, given the huge baseline differences between participants with high and low 25(OH)D levels, it is just as likely that the 25(OH)D level is only a marker of some other unmeasured confounder. Because this study failed to find a clear relationship between 25(OH)D levels and CVD or cancer, alternative explanations for the association between deficient levels of vitamin D and higher mortality may be needed.

### Applications for Clinical Practice

This nationally representative study with detailed clinical data provides provocative evidence of the relationship between low vitamin D levels and an increased risk of mortality. Recent studies have cast doubt on a causal relationship;

however, the results of this study by Melamed et al may reassure those who believe that a relationship exists. For the practicing clinician, there is no reason to offer preventive vitamin D supplementation to otherwise healthy individuals to reduce the risk of CVD, cancer, or all-cause mortality.

—Review by Ashish K. Jha, MD, MPH

### References

1. Autier P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2007;167:1730–7.
2. Krause R, Buhning M, Hopfenmuller W, et al. Ultraviolet B and blood pressure. *Lancet* 1998;352:709–10.
3. Pfeifer M, Begerow B, Minne HW, et al. Effects of a short-term vitamin D(3) and calcium supplementation on blood pressure and parathyroid hormone levels in elderly women. *J Clin Endocrinol Metab* 2001;86:1633–7.
4. Hsia J, Heiss G, Ren H, et al; Women's Health Initiative Investigators. Calcium/vitamin D supplementation and cardiovascular events [published erratum appears in *Circulation* 2007; 115:e466]. *Circulation* 2007;115:846–54.

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