

Can Vitamin D Deficiency Break Your Heart?

To the Editor: We congratulate Hoang et al¹ from the Cooper Center Longitudinal Study on their article reporting a significant association between low serum 25-hydroxyvitamin D [25(OH)D] levels and depression among the largest group of individuals in whom this potential link has been explored to date. The fact that this study was done as part of a medical student summer research program makes it even more impressive. In the same issue of *Mayo Clinic Proceedings*, Chamberlain et al² report that among a cohort of patients with preexisting cardiovascular (CV) disease, depression independently predicted hospitalization and all-cause mortality over a 17-year follow-up period. We have recently documented strong independent associations between low vitamin D levels and adverse CV events,³⁻⁵ and some meta-analyses show that vitamin D supplementation appears to significantly lower all-cause mortality,⁶ whereas others do not.⁷ Thus, it is biologically plausible that vitamin D deficiency-induced depression may, in part, be responsible for increased CV risk associated with low vitamin D levels. Additionally, the tendency for depressed patients to stay indoors and be

physically inactive (both risk factors for vitamin D deficiency) may lead to low vitamin D levels, which, in turn, are associated with increased CV risk.² Although the study from Hoang et al¹ demonstrates that the association between low 25(OH)D levels was independent of physical activity, we were surprised that these Cooper Center Longitudinal Study data were also not corrected for precisely measured levels of cardiorespiratory fitness.

Vitamin D deficiency, besides being associated with depression, appears to increase the risk of developing inflammation, insulin resistance, diabetes, and atherosclerosis, and also activates the renin-angiotensin-aldosterone system, which predisposes to hypertension and left ventricular hypertrophy.³⁻⁵ All of these consequences of vitamin D deficiency, including depression, can adversely affect CV health and longevity (Figure).

An abnormally low vitamin D level, as defined by a serum 25(OH)D level less than or equal to 20 ng/mL, is present in 42% of the overall American adult population, 82% of black individuals, and 69% of the Hispanic population.³ The average 25(OH)D level in adults is 20 ng/mL⁸; a long-term daily intake of an additional 100 IU of vitamin D will increase this level by only about 1 ng/mL.³⁻⁵ Thus, supplementing the diet by the 600 to 800 IU

daily as recommended by the Institute of Medicine's new guidelines⁹ would be expected to raise adult Americans' mean vitamin D levels to 26 to 28 ng/mL, which is still in the insufficient range (<30 ng/mL). Recently, the Endocrine Society clinical practice guidelines¹⁰ suggested doses of 1000 to 2000 IU of vitamin D₃ daily, which are much more likely to achieve a 25(OH)D level of at least 30 ng/mL.

Insufficient vitamin D causes musculoskeletal pain and weakness, and supplementing low 25(OH)D levels back into the normal ranges has been shown unequivocally to improve integrity and strength of bones and muscles and to reduce falls.^{4,5} Large randomized controlled trials are under way, and these should help to determine whether raising low vitamin D levels will also reduce risks for CV events, depression, and death. These results are not expected for several years (at least 3 years and possibly 5 years or more), and in the meanwhile it seems prudent to recommend a daily intake of 1500 to 2000 IU of vitamin D₃ for most American adults. Recent data, including those from *Mayo Clinic Proceedings*,^{1,2} suggest that measuring vitamin D levels and normalizing deficiencies may be especially important for individuals with a history of depression and/or CV disease.

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2. Chamberlain AM, Vickers KS, Colligan RC, Weston SA, Rummans TA, Roger VL. Associations of preexisting depression and anxiety with hospitalization in patients with cardiovascular disease. *Mayo Clin Proc.* 2011;86(11):1056-1062.

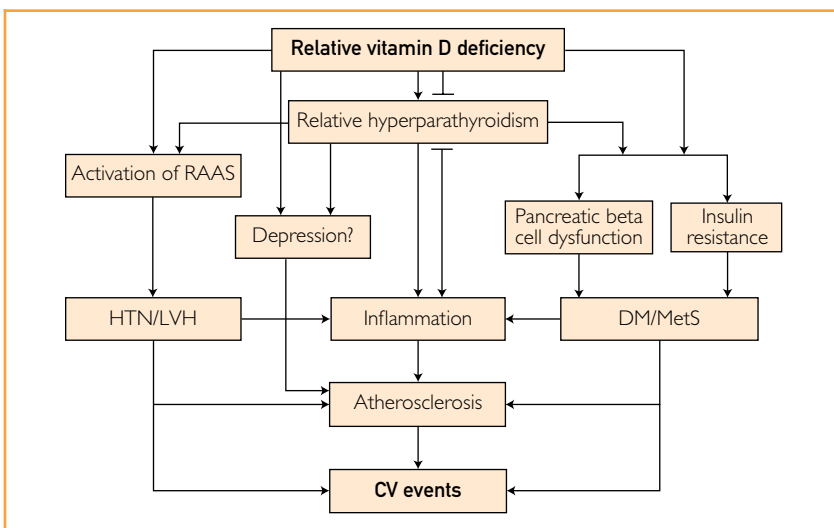


FIGURE. Potential mechanisms for CV effects of vitamin D deficiency. CV = cardiovascular; DM = diabetes mellitus; HTN = hypertension; LVH = left ventricular hypertrophy; MetS = metabolic syndrome; RAAS = renin-angiotensin-aldosterone system. From *J Am Coll Cardiol*,⁵ with permission.

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Predicting Recurrent Depression Using Vitamin D Levels?

To the Editor: I read the report of Hoang et al¹ on low 25-hydroxyvitamin D and depression with great interest. Of note, recently published guidelines on evaluation of vitamin D deficiency do not call for screening of persons with prior or current depression.² A plausible clinical application of the findings of this study—if confirmed, especially in multiracial cohorts—would be to obtain 25-hydroxyvitamin D levels in patients with a history of depression and treat when indicated, in hope of preventing new episodes of depression.

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In reply: We thank O'Keefe et al for their interest in our report on the association between serum hydroxyvitamin D and current depressive symptoms.¹ Lack of cardiorespiratory fitness (CRF) has been associated with depressive symptoms. For example, previous studies from the Aerobics Center Longitudinal Study found a significant inverse dose-response relationship between maximal CRF and depressive symptoms.^{2,3} The current study focused on depressive symptoms and their relationship to serum hydroxyvitamin D from a psychiatric perspective. Physical activity has been used as a covariate by other similar studies exploring the relationship between vitamin D and depression.^{4,5} In our report, we controlled for physical activity, or exercise, which represents a modifiable behavior that was statistically significant in its inverse relationship to depressive symptoms in this study.¹ In sensitivity analyses that included CRF in the model, the relationship between vitamin D and depression was essentially unchanged.

We applaud O'Keefe et al's thoughtful review of the potential mechanisms linking depression, vitamin D, and cardiovascular disease. The idea that low vitamin D levels may be, in part, responsible for the association between depression and cardiovascular disorders is interesting and worthy of further investigation.

Kolade noted that guidelines for vitamin D deficiency do not call for screening vitamin D levels in the setting of current or prior depression. The idea of using vitamin D screening and, when necessary, supplementation to prevent depression relapse is very interesting and warrants further study.

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Sustained Blood Pressure—Lowering Actions of Subcutaneous B-Type Natriuretic Peptide (Nesiritide) in a Patient With Uncontrolled Hypertension

To the Editor: Hypertension continues to be an important public health problem, with a substantial proportion of patients failing to achieve optimal blood pressure (BP) control.