Published in final edited form as:

JAMA. 2013 July 10; 310(2): 153–155. doi:10.1001/jama.2013.7229.

Race/Ethnicity, Serum 25-Hydroxyvitamin D, and Heart Disease

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A growing body of observational evidence had suggested that low 25-hydroxyvitamin D (25[OH]D) concentrations may be a key biological predictor of increased rates of coronary heart disease (CHD).[1] Because low serum 25(OH)D concentrations are more common and more severe among racial/ethnic minority groups, which are also affected by higher rates of CHD and CHD risk factors, low vitamin D was being heralded as a potential modifiable contributor to racial/ethnic disparities in cardiovascular health.[2] However, the causal link between 25 (OH)D concentrations and CHD remains uncertain.[3,4] Additionally, the potential clinical implications of low serum 25(OH)D concentrations, the pathological mechanisms through which vitamin D may modulate CHD, and whether these factors differ across racial/ethnic groups are unclear.

To date, the literature on vitamin D and CHD has been limited due to larger studies being observational in nature. Randomized interventions are smaller, shorter in duration, and only address CHD surrogates. Previous studies have also been inconsistent in defining vitamin D status, in defining and determining cardiovascular outcomes, in the use of baseline 25 (OH)D concentrations, and in adjusting for seasonal variations in vitamin D concentrations.[1] Further, in an attempt to address racial/ethnic influences on possible vitamin D–related health outcomes, the literature is limited by the lack of detailed patient-level information and adequate numbers of diverse populations.

In this issue of *JAMA*, Robinson-Cohen and colleagues[5] conducted a well-designed investigation to assess the association of serum 25(OH)D concentrations with time to first adjudicated CHD event across multiple racial groups and to provide information to help unravel the complex associations between race/ethnicity, 25(OH)D, and CHD. The authors analyzed data from 6436 diverse racial/ethnic study participants in a community-based prospective cohort, the Multi-Ethnic Study of Atherosclerosis (MESA). From 2000 to 2002, participants between 45 and 84 years of age without known cardiovascular disease at baseline were enrolled from 6 sites. Detailed demographic, clinical, and laboratory data were obtained and for the present analysis participants had a mean follow-up of 8.5 years. The

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Norris reports receiving grant support from the National Institutes of Health; and payment for lectures and consulting from Abbott, Amgen, Davita, and Takeda. Dr Williams reported no disclosures.

participants included 38% white, 28% black, 22% Hispanic, and 12% Chinese individuals who completed detailed interviews including estimated vitamin D intake to complement the measurement of 25(OH)D concentrations and in-person examinations assessing CHD risk factors. During the follow-up period, 361 study participants developed an incident CHD event (including myocardial infarction, angina, or CHD death).

Robinson-Cohen et al estimated the relative hazard of CHD using 3 different Cox proportional hazards regression models. The first model included demographic data; the second model added likely potential confounding variables such as body mass index, smoking status, educational attainment, family income, physical activity, and vitamin D intake; and the third model added possibly confounding or mediating variables including diabetes status, systolic blood pressure, chronic kidney disease, antihypertensive and lipid-lowering medications, cholesterol and triglyceride levels, and C-reactive protein concentrations. In the fully adjusted third model, each 10-ng/mL decrement in serum 25(OH)D concentrations was associated with a significant 15% greater overall risk of incident CHD. However, the investigators noted substantial differences among racial/ethnic groups regarding the association between 25(OH)D concentrations and CHD, with a 26% greater risk of incident CHD among white participants and a 76% greater risk among Chinese participants. Unexpectedly, there was no significant association between 25(OH)D concentrations and CHD risk among black or Hispanic participants.

In this study the lowest mean baseline serum 25(OH)D concentrations were found in black participants (19.2 ng/mL), moderately low 25(OH)D concentrations in Hispanic (24.6 ng/mL) and Chinese participants (26.7 ng/mL), and adequate levels (≥30 ng/mL) in white participants (30.1 ng/mL). Based on these baseline findings, it might be anticipated that if the serum concentration of 25(OH)D was a strong predictor of CHD, the relationship would be most pronounced in black participants who had the lowest 25(OH)D concentrations at baseline. However, these findings did not support the anticipated relationship between low 25(OH)D and increased CHD across all racial/ethnic groups.

Prior studies in nonwhite populations have shown variable findings.[4] In a recent 3-month, double-blind, randomized trial of nearly 300 black patients, each 1-ng/mL increase in plasma 25-hydroxyvitamin D led to a significant 0.2-mm Hg reduction in systolic blood pressure ($P = .02$), but the study did not assess CHD events.[6] By contrast a double-blind, placebo-controlled study of 90 racial/ethnically diverse patients (ethnicity: 62% Hispanic; race: white 31%, black 18%, Asian 24%, other 27%) with CHD and vitamin D deficiency (<20 ng/mL) found no difference in surrogate markers of cardiovascular health (such as blood pressure, endothelial function, circulating adhesion molecules, or serum proinflammatory cytokines) among participants receiving 50 000 IU of oral ergocalciferol for 12 weeks compared with those receiving placebo, despite a 22-ng/mL greater increase in serum 25(OH)D in the active treatment group.[7]

The article by Robinson-Cohen et al raises several important questions about the relationship between serum concentration of 25(OH)D and CHD. One question is whether seasonal variability in 25(OH)D concentrations might vary across racial/ethnic groups and influence previously reported findings. While it is possible that seasonal changes may magnify racial/

ethnic differences in 25(OH)D concentrations, this seems unlikely in this study for 2 reasons: (1) the lack of evidence of a different pattern of 25(OH)D concentration and CHD when annualized 25(OH)D data were used and (2) the lack of evidence of an association in race-specific quintiles in which very low levels of 25(OH)D (ie, below 10 ng/mL in black participants and 16 ng/mL in Hispanic participants) would be expected to be associated with increased CHD events.

A second question is whether racial/ethnic differences in the relationship between serum 25(OH)D and CHD may be driven by differential regulation of parathyroid hormone (PTH). Although Robinson-Cohen et al did not report detailed data on PTH across racial/ethnic groups, it remains plausible given previous findings of racial/ethnic differences in the PTH/vitamin D axis across groups with African Americans having the highest PTH levels.[8] The relevance of this is increased by the established importance of calcium/PTH/vitamin D in the regulation of blood pressure and vascular tone.[9] A pursuit for a more detailed exploration of the racial differences in the relationship of vitamin D and PTH modulation with CHD risk is warranted.

A third question is whether racial/ethnic variations in vitamin D–mediated cellular activation/metabolism (ie, the vitamin D receptor [VDR], vitamin D binding protein, or other related factors) might contribute to the observed racial differences between 25(OH)D concentrations and CHD risk association. Vitamin D binding protein polymorphisms show strong ethnic variations, and darker pigmented African, African American, and Asian populations are more likely to carry the GC-1F form of vitamin D binding protein, whereas white populations more frequently exhibit the GC-1S form.[10] While such biological adaptations may protect against the lower 25 (OH)D concentrations associated with increased melanin and reduced conversion of previtamin D to vitamin D by sunlight, their clinical implications remain unclear. In VDR knockout mice, the absence of cellular recognition of vitamin D results in cardiomyocyte hypertrophy, up-regulated renin angiotensin system activity, and increased expression of matrix metalloproteinases[11]; all of these factors have been implicated in increased CHD risk. Preliminary findings from Artaza and colleagues[11] suggest that 1,25-dihydroxyvitamin D may affect CHD susceptibility by promoting cardiomyocyte differentiation through negative modulation of the Wnt signaling pathway. However, racial/ethnic differences have not yet been elucidated in these and other key pathways, which may play an important role in the influence of vitamin D on cardiovascular health.[12] The data presented by Robinson-Cohen et al raise the possibility that differences in up- or down-regulation of these pathways may possibly underlie the racial/ethnic differences found in the MESA cohort.

In conclusion, this large, well-designed, multiethnic study adds important insights to the complex relationships among race/ethnicity, 25(OH)D concentrations, and CHD risk. The heterogeneity of the findings underscores the importance of exploring racial differences in clinical research and of not immediately generalizing results from ethnically homogeneous populations to other groups that may differ by race/ethnicity, sex, or age. Although the pooled data demonstrated a significant association between 25(OH)D and CHD, the subgroup analyses revealed marked differences underscoring the importance of examining

such cohorts by race/ethnicity and thereby potentially discovering sociocultural or biological mediators that may affect cardiovascular health.

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