Vitamin D deficiency is associated with many adverse health outcomes, including several kinds of bone diseases, more than a dozen types of cancer, multiple autoimmune diseases, and type 2 diabetes. It also seems to be very prevalent. A recent review by Holick found the prevalence of vitamin D deficiency—defined as 25-hydroxyvitamin D (25[OH]D) <20 ng/mL—to be 40%-100% of elderly American and European men and women still living in the community and 42% of 15- to 49-year old black females throughout the United States.\(^1\) These results were all in higher-risk groups (risk factors for vitamin D deficiency include older age and darker skin pigmentation). Surprisingly, 32% of healthy students, physicians, and residents at a Boston hospital were found to be vitamin D deficient, despite drinking a glass of milk, taking a multivitamin daily, and eating salmon at least once a week (all of which are dietary sources of vitamin D).\(^2\) Altogether, the high prevalence of vitamin D deficiency, even in healthy adults with high dietary vitamin D intake, coupled with the many adverse health outcomes associated with it, make it a high priority for research.

**Behavioral and Environmental Contribution to Vitamin D Status**

The primary source of vitamin D is exposure to sunlight, which produces vitamin D metabolites in the skin. Production of vitamin D in the skin decreases with increased age, decreased time spent outdoors, use of sun block, darker skin pigmentation (which acts as a natural sun block), increased clothing coverage of skin, and a more oblique (slanted) angle of the sun (eg, winter season, high latitude, low altitude, and early or late time of day). Secondary sources of vitamin D are dietary intake of vitamin D rich foods and vitamin D supplements. These sources become more important at times when the zenith angle of the sun is oblique, such that very few solar ultraviolet B (UV-B) photons reach the earth, allowing little or no vitamin D synthesis (eg, November to February in latitudes further north than Atlanta, Georgia).

**Genetic Contribution to Vitamin D Status**

There is a moderately strong genetic component to levels of 25[OH]D. Residual heritability estimates range from 0.23 in Hispanics from the San Luis Valley, Colo., and 0.28 in African Americans from Los Angeles, Calif., to 0.41 in Hispanics from San Antonio, Tex.\(^3\) These heritability estimates are comparable to that reported in the Framingham Heart Study (0.29),\(^4\) which is composed of white individuals. Although 1 linkage analysis\(^5\) and at least 1 candidate gene study\(^3\) have been conducted, no genome-wide association (GWA) studies of vitamin D have been published thus far.

**Genetic Architecture of Vitamin D Status**

Like many phenotypic traits, the determinants of vitamin D levels are complex and likely involve multiple genes with both independent (genetic heterogeneity) and interacting effects, as well as gene-environment interactions. Determining the genetic architecture of vitamin D status will be a critical next step in better understanding individual variation in levels of vitamin D and in identifying individuals at increased risk for vitamin D deficiency.

**Analytic Approaches**

Machine learning approaches, such as random forests, can screen large amounts of genetic data and take into account gene-gene and gene-environment interaction effects as well as main effects without requiring model specification. These methods will be particularly useful in elucidating the genetic architecture of levels of vitamin D.

**Future Research**

Research is underway at the University of Wisconsin-Madison to determine the genetic architecture of vitamin D status using innovative measures of behavioral and environmental factors and results from 2 unpublished GWA studies, along with the machine learning approaches described above, with 300 participants from the Survey of the Health of Wisconsin (SHOW).

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**References**


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