Editorial

*See corresponding article on page 1088.*

# High-altitude living and vitamin D: factors associated with viral risk?

*Mona S Calvo*

Icahn School of Medicine at Mount Sinai, New York City, NY, USA; and US Food and Drug Administration, retired, Silver Spring, MD, USA



In this issue of the Journal, Beer, Herrán, and Villamor present their analyses of the 2015 nationally representative survey data measuring serum concentrations of 25-hydroxyvitamin D [25(OH)D] in Colombian women and children (1). These authors reveal an overall mean ± SE serum 25(OH)D concentration of 65.1 ± 0.4 nmol/L, a 3.1% prevalence of vitamin D deficiency (<30 nmol/L), and a clinically significant 23.9% prevalence of vitamin D insufficiency (<50 nmol/L) in this at-risk population. Pregnant women were reported to have the highest prevalence of deficiency, 6.7%, with toddlers having the highest prevalence of vitamin D insufficiency at 42.5%. The comparatively low prevalence of vitamin D deficiency for the overall population of women and children is not surprising considering Colombia is situated just below the equator. The entire country receives year-round abundant sunshine (UV and UVB) enabling cutaneous synthesis of the vitamin D precursor, cholecalciferol. Although Columbia is situated in the tropics, Colombians reside in sunny coastal cities and valleys at sea level and in mountainous areas at significantly higher altitudes. For the first time, in a nationally representative survey, the authors demonstrate that altitude is one of the strongest correlates of both vitamin D deficiency and insufficiency, showing a 4% higher prevalence in vitamin D insufficiency for every 100 m above sea level.

The importance of this finding relates to the need to add one more environmental confounder to the list of factors that influence the overall vitamin D health of a country, if wide geographic variation in altitude exists. Latitude, seasonality, and altitude influence the strength of the UVB light needed to metabolize 7-dehydrocholesterol in skin to cholecalciferol (D3), which is further metabolized in the liver to the transport or circulating metabolite 25(OH)D that is delivered to tissues, where it can be converted to the active hormonal form of the vitamin, 1,25-dihydroxyvitamin D (2). The effect of altitude needs to be considered along with latitudinal global position, usual cloud cover or pollution, concealing traditional and protective clothing, race or ethnicity, dietary practices, and other confounding factors of urban and rural dwelling when resolving the need for national public health policies and practices for vitamin D supplementation or food fortification.

Serum concentrations of 25(OH)D are recognized as the biological indicator of vitamin D status for which deficient and insufficient concentrations have been linked to greater incidence and severity of infectious microbial disease (3), especially in individuals living at higher latitudes and in cultures with limited sunlight exposure due to traditional concealing dress. Many researchers have proposed a protective role for vitamin D in influenza and other viral infections and deaths, including the novel SARS-CoV-2 virus (3–6). The interest in vitamin D's impact on viral resistance stems from its critical role in the modulation of innate and acquired immune response and the quelling of inflammation in both infectious and chronic diseases (7). Altitude has also recently been the subject of several studies exploring its relation with the Covid-19 pandemic across the world (8). The goal of this editorial is to consider how vitamin D deficiency at high altitudes reported here can help guide thinking about the possible physiologic mechanism(s) at play in recent studies reporting protective effects of high-altitude residence on the incidence and severity of the novel SARS-CoV-2 virus, the cause of the Covid-19 pandemic.

Early in the pandemic, high-altitude cities appeared to experience lower infection and mortality rates (8–11), a finding hypothesized to be due to greater UVB intensity as the mechanism underlying the protective environmental factor. Initially, analysis of the global altitudinal distribution of Covid-19 cases indicated a lower prevalence of the SARS-CoV-2 virus in high-altitude Andean inhabitants in Ecuador and Bolivia, countries bordering Colombia (9). The authors of this study suggested that high levels of UVB light at these greater elevations influence specific environmental and possibly physiologic factors impacting the virulence of SARS-CoV-2, notably the action of UVB light as a natural sanitizer of the virus, thereby decreasing its transmission. The physiologic mechanism underlying the apparent decrease in severity observed in this report remains unclear, and scientists suggest it may be related to higher vitamin D status with more intense UVB exposure at higher altitudes, which theoretically would strengthen natural immune defenses against the virus (8, 9, 11). However, a relation between altitude and viral case-fatality was not observed in another study analyzing the Peruvian Covid-19 pandemic data (10).

Could poor vitamin D status of women residing at higher altitudes be a factor contributing to the observed reduced protection against death in Covid-19 cases? On the face of it, the association of high altitude with poor vitamin D status seems contrary to what might be expected because inhabitants of

Address correspondence to MSC (e-mail: mscalvo55@comcast.net).

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high-altitude cities are exposed to stronger ultraviolet radiation (UVB), due to a thinner atmosphere filtering out less UVB than at sea level. The cold, harsh environmental conditions at these high-altitude locations, Beer, Herrán, and Villamor speculate, require year-round protective clothing, thus limiting sunlight exposure and vitamin D synthesis (1). Based on their results from the third Colombian National Nutrition Survey (2015–2016), better vitamin D status from theoretically increased UVB exposure at high elevations is not a likely physiologic mechanism in the protection against viral severity as proposed by respiratory experts (8).

It is important to note that Beer et al. only analyzed data in women and children and did not explore measures of immune response; thus, obvious limitations exist to extrapolating their findings to the Covid-19 pandemic, but they do spark interest. There is a well-established difference in SARS-CoV-2 susceptibility and mortality between males and females, with more infection and death in males (in Peru, 71% of deaths were in males); however, as altitudes of residence increase, more case-positive Peruvian women die, reducing the sex-associated protection (10). It remains to be seen if vitamin D status plays a role in this observation. Evidence concerning vitamin D protection in the Covid-19 pandemic is controversial and largely circumstantial at this time (3–6). With respect to reduced viral risk at higher altitudes, experts strongly caution against reliance on the purported protective influence of high-altitude residence until more data are available (8, 11).

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