Public Health Nutrition: 21(11), 1971–1973 doi:10.1017/S1368980018000927

Invited Commentary

Associations of underweight and stunting with impaired vitamin D status in Ecuadorian children provides insights into the vitamin's biology

First published online 25 April 2018

Thirty years ago, Michael Holick's group showed that the low angle of penetration of sunlight into Boston, Massachusetts, USA (latitude 42°N) attenuated UVB radiation so substantially that it failed to convert 7-hydroxycholesterol, the skin precursor of vitamin D, into the vitamin itself during the winter months[1]. The Republic of Ecuador (named from the Spanish word for 'equator'), however, possesses the essence of tropical sunshine, with a near perpendicular solar angle all year round. Moreover, Ecuador, an Andean country, has an average altitude as a nation of 1117 m (3665 ft), with the capital of Quito situated at 2850 m (9350 ft). The lower gaseous density at altitude attenuates the atmospheric filtering of UVB radiation. So, from first principles, one would identify Ecuador as a propitious setting for the solar generation of vitamin D and the maintenance of adequate vitamin D status. A 2017 editorial in *Public Health Nutrition* identified four 'critical gaps' in vitamin D research at a population and community level[2]. A paper in this issue of the journal[3] addresses one of these gaps – vitamin D deficiency and its association with health risk – by providing the first evidence of vitamin D deficiency in Ecuador and assessing its associations with growth status.

Using stored samples, the authors quantified serum 25-hydroxyvitamin D (25(OH)D), a widely accepted biomarker of vitamin D status, and compared its concentration in 6–36-month-old children according to weight- and height-for-age *Z*-scores (WAZ and HAZ, respectively). Mean 25(OH)D did not differ between underweight (WAZ <− 1·0) and non-underweight children, although the prevalence of vitamin D < 42·5 nmol/l (a population-customized cut-off point) was about twice as high in children with *v.* without underweight. Mean 25(OH)D was slightly lower in children with stunting (HAZ <− 2·0) than in non-stunted children; nevertheless, the prevalence of stunting was 1·4 times higher in children with 25(OH)D < 42·5 nmol/l than in those with higher vitamin D concentrations. Blood levels of parathyroid hormone (PTH) were not related to anthropometric status and there was only a weak inverse association between PTH and 25(OH)D[3].

The paper confirms a finding from both of our groups in different settings, namely of endemic poor vitamin D status in highland populations of Latin American countries near the equator. This has been demonstrated in premenarcheal girls from Bogota, Colombia[4] and elderly Mayan Guatemalans[5]. Although Smith *et al.*[6] provided evidence for widespread vitamin D deficiency in sunny tropical countries, specifically of the South-East Asian rim, this is not necessarily the case in other areas that are sunbathed year-round, as recently shown by Robinson *et al.* in Mesoamerica and the Dominican Republic[7]. While the Ecuadorian findings on the prevalence of vitamin D deficiency are not inordinately noteworthy *per se*, a more revealing feature of the paper is the effort to draw out associations of vitamin D status with growth parameters of young children[3]. Previous investigations of vitamin D and child growth in tropical countries were conducted in school-aged children. In the Bogota School Children Cohort study, plasma 25(OH)D <50 nmol/l at the time of recruitment was associated with rapid BMI gain and, among girls, with slower growth in height over a 2·5-year follow-up period[8]. In the cross-sectional NiMeCoMeS study of Central American nations and the Dominican Republic, 25(OH)D was not associated with height- or BMI-for-age *Z*-score in children 7–12 years of age[7].

The children surveyed around Quito have the typical pattern of negligible wasting, modest underweight and abundant stunting, which characterizes low- and moderate-income countries in general[9]; as such, the sampling strategy employed to over-represent underweight children provided adequate numbers of low-WAZ and low-HAZ individuals for the desired disaggregation and modelling analyses. This opportunity first led to an exercise to find a population-specific cut-off point of 25(OH)D to define low status, based on growth measures. The analysis determined that a vitamin D concentration of < 42·5 nmol/l (rather than the conventional <50 nmol/l based on bone metabolism[10]) was the cut-off level for inadequate vitamin D status in this population. In fact, although intriguing, an approach to customize a population-specific cut-off point based on an alternative association frame is hampered for two reasons. First, it was necessary – and will always be necessary – to use the

commonly employed cut-off criteria[2,10,11] in comparing the situation in Ecuador to other locations. Second, the receiver-operating characteristic curve methodology employed to identify the new cut-off point used as the gold standards the same anthropometric measures that were later defined as outcomes or exposures in the causal inference part of the analysis. This 'double-dipping' situation, in which a cut-off point is deliberately sought to maximize the probability of finding an association, increases the chances of incurring type I error. The analytic approach is further compounded by the fact that height, the main outcome of the study, is a related correlate of the weight-for-age indicator primarily used in determining the vitamin D cut-off point.

The authors were guided by two explicit, *a priori* objectives: to 'assess whether vitamin D status differs between underweight children and normal weight children; and determine whether children with lower levels of vitamin D were more likely to be stunted than those with higher levels'. Indeed, in the design and analysis, vitamin D was the dependent variable in associations with WAZ, based on the notion that lower food intake was driving the lower vitamin status. Conversely, circulating vitamin levels constituted the independent variable in the relation to HAZ classification, suggesting that lower status was impairing bone growth. Although these assumptions are reasonable and straightforward, our entertaining the reverse causality hypotheses for the corresponding associations is worth undertaking, at least to broaden the latitude of perspectives on vitamin D biology. Hence, on the former hand (WAZ), pre-existing vitamin D deficit could itself cause inappetance and reduced food intake, becoming a driver of the lower weight; we know, however, of no systematic evidence of such a causal association in published reports. Alternatively, in older populations underweight is often associated with higher circulating 25(OH)D, purportedly due to the possibility that vitamin D, a fat-soluble vitamin, can become sequestered out of plasma into adipose tissue[12]. On the other hand (HAZ), however, having a smaller body to begin with could conceivably impair vitamin D acquisition and utilization. Plausible mechanisms would be that of a smaller body surface receiving less sun exposure. Moreover, mothers may intuitively protect a child perceived as delicate by reducing outdoor exposure and covering him/her with more clothing while outside. The putative origins of stunting, however, may intercede in vitamin D metabolism and retention. To the extent that the origin of poor linear growth may be related to environmental stress[13,14], it is feasible that such adverse exposures might similarly diminish the conversion or retention of the vitamin at the synthetic and metabolic levels. In this respect, it is of note that groups in Guatemala living under harsher and more deprived circumstances within common localities, such as rural *v.* urban elderly[5] and Mayan indigenous *v.* non-indigenous adolescents[15], had lower circulating levels of vitamin D. The lack of consistency between the associations of anthropometric indicators with PTH and those with 25(OH)D could also support non-causal interpretations of the findings.

The pragmatic and bottom-line significance of the Ecuadorian findings is that there is a heretofore unrecognized nutritional problem at a public health level. Insofar as the non-stunted and normal-weight residents of the Quito region can manifest low vitamin D status, reversing growth impairment is no guarantee for eradicating insufficient circulating concentrations of 25(OH)D, even assuming the validity of some of the scenarios of direct or reverse causality discussed for the associations. The litany of nations and settings with documentation of less than sufficient situations of endemic vitamin D status is clearly outstripping that for the countries formulating public health actions to combat it. It behoves the nutritional community now to embrace research on programmatic interventions with the vitamin to eliminate its deficiency safely and efficiently in the regions where it has been demonstrated[16,17].

Acknowledgements

Financial support: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. *Conflict of interest:* None. *Authorship:* N.W.S. and E.V. contributed equally to this commentary. *Ethics of human subject participation:* Not applicable.

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