

# All-Source Basal Vitamin D Inputs Are Greater Than Previously Thought and Cutaneous Inputs Are Smaller<sup>1,2</sup>

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## Abstract

The magnitude of vitamin D inputs in individuals not taking supplements is unknown; however, there is a great deal of information on quantitative response to varying supplement doses. We reanalyzed individual 25-hydroxyvitamin D [25(OH)D] concentration data from 8 studies involving cholecalciferol supplementation (total sample size = 3000). We extrapolated individual study dose-response curves to zero concentration values for serum 25(OH)D by using both linear and curvilinear approaches and measured seasonal oscillation in the serum 25(OH)D concentration. The total basal input (food plus solar) was calculated to range from a low of 778 IU/d in patients with end-stage renal disease to a high of 2667 IU/d in healthy Caucasian adults. Consistent with expectations, obese individuals had lower baseline, unsupplemented 25(OH)D concentrations and a smaller response to supplements. Similarly, African Americans had both lower baseline concentrations and lower calculated basal, all-source inputs. Seasonal oscillation in 4 studies ranged from 5.20 to 11.4 nmol/L, reflecting a mean cutaneous synthesis of cholecalciferol ranging from 209 to 651 IU/d at the summer peak. We conclude that: 1) all-source, basal vitamin D inputs are approximately an order of magnitude higher than can be explained by traditional food sources; 2) cutaneous, solar input in these cohorts accounts for only 10–25% of unsupplemented input at the summer peak; and 3) the remainder must come from undocumented food sources, possibly in part as preformed 25(OH)D. *J. Nutr.* 143: 571–575, 2013.

## Introduction

It is generally understood that unsupplemented vitamin D status is the resultant of a varying and uncertain mix of cutaneous synthesis of vitamin D and ingestion of food vitamin D sources. The absolute and relative magnitudes of these sources are unknown. In various reports, particularly those evaluating associations of vitamin D input with various outcome variables, basal vitamin D status is usually measured as the serum 25-hydroxyvitamin D [25(OH)D] and the oral/food sources are estimated from published food table values. For the most part, reported food input tends to be in the range of 120–180 IU/d, though some approach 300 IU/d (1). Similarly, there is recognition of seasonal variation and the need to adjust measured values accordingly. However, the magnitude of that variation and the mechanics of the adjustment are seldom stated.

Most investigators recognize that the small input that can be attributed to usual food sources is often quite inadequate to account for measured serum 25(OH)D concentrations. The implicit conclusion is that cutaneous synthesis, while of uncertain magnitude, nevertheless accounts for much of the actual vitamin D status of most unsupplemented individuals. To many investigators,

this too seems unlikely to be a full explanation, because winter concentrations are usually well above zero and are higher than can plausibly be attributed to known food sources. The presumption that winter concentrations are sustained by a substantial adipose tissue reservoir of vitamin D has also proved unsatisfying, because when fat content has actually been measured, its vitamin D content turns out to be inadequate by itself to sustain winter levels for more than a few days (2–4).

This growing awareness of the discordance between currently identifiable sources and actual vitamin D status has led to the search for 25(OH)D in meat and poultry, thus exploring an additional, if previously undocumented, food source (5,6). Pending resolution of this latter issue and the corresponding ability to calculate basal inputs from source data, it seemed to the authors that the large amount of data accumulated over the past several years with respect to relationships between cholecalciferol inputs and steady-state serum 25(OH)D concentrations could permit reasonably accurate back-calculation of unsupplemented, basal D3 inputs (whatever their source) by using the empirically derived, quantitative relationship between input and serum 25(OH)D concentration. And by similar back-calculating from seasonal oscillation, the same holds for the endogenous (cutaneous) contribution to basal status.

Accordingly, we have analyzed the data from 2 large cohorts where the dose-response relationship was well defined and from several pharmacokinetic studies of vitamin D. We present here

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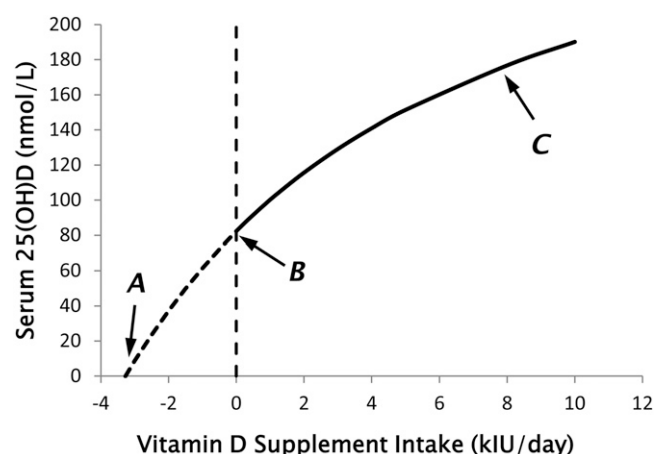
first the calculated basal and then the estimated cutaneous inputs for their participants, expressing total basal input as a function of basal vitamin D status [i.e., unsupplemented serum 25(OH)D concentration].

## Methods

**Analytical approach.** A total of 8 studies provide the data for this analysis (3,7–11; R.P. Heaney, L.A.G. Armas, C. French, unpublished data). For each, written consent had been obtained from the participants and the respective protocols approved by the cognate Institutional Review Board. Participants are described in detail in the respective papers and their demographic information is summarized in **Table 1**. For each of the studies included, the intake of cholecalciferol supplements had been ingested for a sufficiently long period of time either to allow the individual to achieve a steady-state serum concentration of 25(OH)D or for the investigators to define the time course so as to permit reliable calculation of the steady-state value (7). Thus, in included studies, that relationship had been or could be expressed as a function of the supplemental input dose. Plots of these relationships take the general form shown in **Figure 1** derived from the low end of the curve fitted to their data by Garland et al. (8), i.e., an ascending line with serum 25(OH)D at zero intake being at some non-zero, positive value, and then increasing as supplemental intake rises. In all such instances, the *x*-axis value labeled “zero” is not actually a zero intake value, but simply a zero supplement intake value.

Our approach can be succinctly summarized by noting that we assembled a group of studies providing data for the B–C segment of the curve in **Figure 1** and used that data to produce the A–B segment for each of them by extrapolation. The point where that extrapolated line crossed the *x*-axis is an estimate of the input that was derived from nonsupplement sources [i.e., the input that was supporting the measured baseline 25(OH)D concentration]. Although in this approach such a value is negative, that is simply because of the use of an arbitrary zero (i.e., zero supplement input, but not zero total input). The presumption is that at steady state, a true zero input would result in a zero value for serum 25(OH)D. Translating each data set to the right along the *x*-axis results in the extrapolated curves going through the origin, and the extent of the rightward translation required to do that is equal to basal nonsupplemented intake. In what follows, we describe the methods used for extrapolation of the respective curves to the *x*-axis.

For 6 of the included studies, the 25(OH)D response data are available for only a few cholecalciferol dose levels (basal and 1–3 treatment doses, ranging from 900 to nearly 12,000 IU/d) and thus these individual studies



**FIGURE 1** Schematic diagram of the mean relationship of serum 25(OH)D and varying daily intake of vitamin D in humans, illustrating the analytical strategy employed in this paper. This strategy consisted of assembling studies providing data in the range B–C (solid line) and extrapolating their respective curves into the region A–B (dashed line). To convert nmol/L to  $\mu\text{g/L}$ , multiply given values by 0.4. To convert kIU of vitamin D to  $\mu\text{g}$ , multiply given values by 25. 25(OH)D, 25-hydroxyvitamin D.

would most straightforwardly yield something close to a straight line when plotting serum 25(OH)D against supplement dose. However, a straight line for extrapolating to the *x*-axis [i.e., zero 25(OH)D concentrations] may not adequately reflect the common experience that at very low vitamin D status values, the 25(OH)D response to supplementation tends to be larger than when starting at higher basal levels. Accordingly, we employed a stratagem based on the fitted curve for the data of Garland et al. (8), which, with a large number of intake doses, captures the curvature often found at the low end of the input continuum. Using the curve-fitting facility of SigmaPlot V.12 (Systat Software), we fitted the data from each of the studies to the following equation, which describes the low-dose end of the intake continuum in Garland et al. (8):

$$Y = Y_0 + a(1 - \exp(-bX)),$$

in which  $Y_0$  is the measured basal serum concentration of 25(OH)D at zero supplement intake and  $X$  is the dose of the oral supplement in thousands of IUs. The variable  $a$  is the equilibrium increment in 25(OH)D

**TABLE 1** Human studies providing vitamin D response data for analysis, with estimated basal and seasonal/cutaneous inputs for each<sup>1</sup>

Study (reference)	Health status	Age	Sex (M/F)	Estimated cholecalciferol input					
				Measured 25(OH)D <sup>2</sup>			Basal		
				Response slope, nmol/L/ $\mu\text{g/d}$	Basal, nmol/L	Seasonal difference, nmol/L	Linear method	Curved method	Seasonal <sup>3</sup>
		<i>y</i>	<i>n</i>						
A (8)	Normal	47.8 ± 12.9 <sup>4</sup>	555/1018	0.746	82.3	9.05	4410	2667	485
B (9) <sup>5</sup>	Normal	66.7 ± 7.3	0/1179	0.996	71.1	5.20	2855	2051	209
C (9) <sup>6</sup>	Normal	66.6 ± 7.2	0/446	0.869	71.8	N/A	3305	2578	N/A
D (7)	Normal	38.7 ± 11.2	67/0	0.700	70.3	11.4 <sup>7</sup>	4017	2651	651
E (10)	ESRD	58.1 ± 12.1	14/6	1.400	35.7	N/A	1020	778	N/A
F (11)	Obesity	46.3 ± 12.6	23/36	0.539	57.7	N/A	4282	2095	N/A
G <sup>8</sup>	Normal	41.5 ± 10.0	12/48	0.986	46.8	7.90 <sup>7</sup>	1899	1222	320
H (3)	Normal	49.3 ± 9.7	1/16	0.631	65.0	N/A	4120	2150	N/A

<sup>1</sup> ESRD, end-stage renal disease; 25(OH)D, 25-hydroxyvitamin D.

<sup>2</sup> To convert nmol of 25(OH)D to IU, multiply the values given by 0.4.

<sup>3</sup> Maximum difference between the summer high and the winter low.

<sup>4</sup> Mean ± SD (all such values).

<sup>5</sup> Derived from the relationship of self-reported baseline vitamin D supplement intake and measured serum 25(OH)D concentration.

<sup>6</sup> Derived from the induced change in serum 25(OH)D in the vitamin D treatment arm of study B.

<sup>7</sup> Derived from the cross-winter decrease in the 25(OH)D concentration in the placebo-treated arm.

<sup>8</sup> Unpublished pharmacokinetic data of the author.

concentration, not otherwise used in the calculations that follow. The exponential constant ( $b$ ) was allowed to vary from values of 0.1 to 0.2, spanning the range of the corresponding parameter in the fitted curve in Garland et al. (8). For each data set, we solved the equation for  $Y = 0$  and reversed the sign. Because of the inevitable uncertainty in any such extrapolation, we present the results for both the linear and curved extrapolations.

Depending upon the data available in a particular study, an analogous approach was taken with respect to seasonal variation. In treatment studies with adequate year-round data, seasonal oscillation was measured on the set of entry data prior to treatment. For each study providing data for both 25(OH)D and time of year at which the basal blood sample was drawn, we fitted the data to a sine curve, as expressed in the following equation:

$$Y = Y_0 + a(\sin(2\pi X/b + c)),$$

once again using the curve-fitting facility of SigmaPlot, where  $Y_0$  is the 25(OH)D concentration around which the seasonal oscillation occurs,  $a$  is the amplitude of the oscillation [in the concentration units used to measure 25(OH)D in the study concerned],  $b$  is the number of  $x$ -axis units in one wavelength (or period), and  $c$  is the time offset (phase shift) expressed in radians. Because amplitude in a waveform is defined as the distance from the neutral point to a peak or trough, full seasonal oscillation in a given data set is given by  $2a$ .

The variables fitted using Eq. 2 were, of course, population and study specific. Accordingly, we did not pool the estimates from the various studies, because, although the wave length or period of the oscillation should be the same from study to study, the amplitude of the oscillation would not be expected to be invariant. Manifestly, that amplitude would be dependent upon latitude, the extent of solar exposure, the degree of skin pigmentation, and similar considerations and hence might well substantially vary from one population to another. However, the concern was not to find a single value to describe all seasonal variation but to estimate the magnitude of the input from endogenous synthesis, which corresponded with any particular amount of seasonal oscillation in a particular population.

For studies without year-round data but with prospective data in placebo-treated individuals, the cross-winter drop in serum 25(OH)D, when available (studies D and G), was used as a proxy for the full seasonal oscillation. In both approaches, estimating the magnitude of the seasonal input is simply a matter of dividing the seasonal variation, from high to low by the rise in serum 25(OH)D per unit vitamin D input, derived in that same population. For study A (8) and B (9), that "rise" was measured as the between-individual difference within the population, whereas for all the other studies, the rise was the mean change between basal and steady-state 25(OH)D concentrations in each individual.

**Analytical method.** Seven of the 8 studies were performed in a single center using primarily the DiaSorin Liaison assay, and in the remaining study (8), investigators used the ZRT blood spot method (ZRT Laboratory). Measurement of serum 25(OH)D was constant within any given study, hence permitting the extrapolation described in the foregoing, which is study specific.

## Results

Table 1 lists the studies analyzed, together with the sample size of each, the amplitude of the annual variation in serum 25(OH)D, and the calculated value for both total, nonsupplemented cholecalciferol input and the maximal seasonal cholecalciferol input. Figure 2 plots the relevant data from all 8 studies and shows a relatively high degree of overall pattern concordance among them. However, there are some discernible differences between them. For example, the data of study F (11) from obese individuals shows a flatter curve and a lower zero-supplement value, as would be predicted for this condition. Studies E and G (10; unpublished data of authors), both in African Americans, show

substantially lower zero-supplement values and lower calculated basal inputs, again as would be expected.

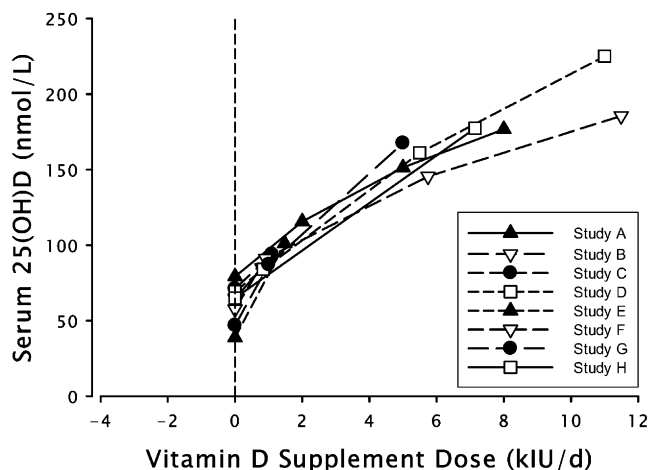
Taken together, the range of calculated, all-source, basal cholecalciferol inputs, using the linear extrapolation method (Table 1), extended from 25.5  $\mu\text{g}$  (1020 IU/d) to 110  $\mu\text{g}$  (4410 IU/d). Using the curvilinear method, the corresponding range was smaller, extending from 19.5  $\mu\text{g}$  (778 IU/d) to 66.7  $\mu\text{g}$  (2667 IU/d).

Not surprisingly, the calculated basal, all-source inputs were correlated with the measured zero-supplement value, i.e., the greater the estimated basal input, the higher the unsupplemented serum concentration, as would be predicted. Moreover, the correlation is substantially stronger for the curvilinear extrapolated values than for those based on a straight line ( $r^2 = 0.93$  vs. 0.69, respectively), suggesting that the curvilinear approach provides the better of the 2 estimates. The equation for the regression is 25(OH)D = 0.0186 (basal input) + 23.9, with units of 25(OH)D being nmol/L and basal input in IU/d.

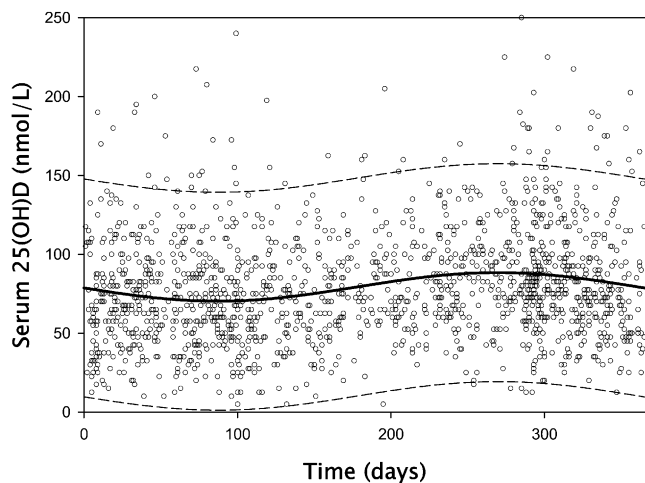
In the 2 studies providing year-round data, the amplitude ( $a$ ) of the seasonal oscillation was 4.53 and 2.60 nmol/L, with the full annual difference being 9.05 and 5.20 nmol/L, respectively. Figure 3 shows this seasonal oscillation and makes graphically apparent the relatively small contribution that seasonal synthesis makes to the total inter-individual variation in the cohorts providing data for this study. Dividing the seasonal differences by the corresponding response coefficient (Table 1) yielded mean values for maximal solar inputs amounting to 12.1 and 5.22  $\mu\text{g}$  (485 and 209 IU/d), respectively. Taking a similar approach to the cross-winter value available in studies D and G yielded estimates of seasonal input of 16.3 and 8.0  $\mu\text{g}$  (651 and 320 IU/d).

## Discussion

Perhaps the first point to note in this analysis is the magnitude of the estimated, unsupplemented, basal input, i.e., the size of the daily cholecalciferol input needed to sustain the measured basal values. This estimation necessarily involves extrapolation from measured responses produced by supplement dosing, as the inputs concerned cannot be directly measured. Simple linear extrapolation yields the higher estimate of all source cholecalciferol input. However, inspection of Figure 2 gives a clear impression of an upward convex curvature in the data to the



**FIGURE 2** Plot of the  $x$ - $y$  relationship from 8 studies (3,7–11) providing data for the B–C region of Figure 1. Data points are the mean values at each indicated dose from the studies concerned. To convert nmol/L to  $\mu\text{g}/\text{L}$ , multiply given values by 0.4. To convert kIU of vitamin D to  $\mu\text{g}$ , multiply given values by 25.



**FIGURE 3** Plot of measured 25(OH)D concentrations against day of blood draw in the participants in study A. January 1 is assigned a day value of zero. The central curvilinear line is the least squares best fit of the data to a sine wave curve, and the outer lines reflect the 95% probability range of the data. To convert nmol/L to  $\mu\text{g/L}$ , multiply given values by 0.4. To convert kIU of vitamin D to  $\mu\text{g}$ , multiply given values by 25. 25(OH)D, 25-hydroxyvitamin D.

right of the zero supplement point, a feature that was unequivocally present in the very large study of Garland et al. (8). Hence, our curvilinear extrapolation, approximating the curvature found in that study, produced estimates that, although tentative, are probably as close to the reality as current data permit.

Although seasonal variation in 25(OH)D concentration is generally recognized and widely reported, this study is the first of which we are aware that attempts to quantify that variation in terms of equivalent oral dosing. Perhaps surprising is the relative size of the seasonal oscillation, which, as Figure 3 shows, accounts for only a small fraction of inter-individual variation. Moreover, the largest relative contribution of the solar source to total basal input in any of the 8 studies was only  $\sim 25\%$  and the largest absolute contribution at the summer peak was  $12.1 \mu\text{g}$  ( $485 \text{ IU/d}$ ). By contrast, Brot et al. (12) report both a larger seasonal difference and a clear association between estimated summer sun exposure and the size of that difference. These authors, however, did not estimate the absolute production of vitamin D in their study participants. Our findings strongly suggest that however important cutaneous synthesis of vitamin D may be in theory or under ancestral conditions (and perhaps up until just a few years ago), solar synthesis is not playing a very large role in actual vitamin D status in many contemporary first-world populations. Nevertheless, it is worth noting from the data in Table 1 that the value of the seasonal input was higher in those with higher basal values, suggesting that the principal factor explaining variability of basal concentrations is, in fact, cutaneous synthesis and that food input is perhaps more constant. Thus, with low contemporary sun exposure and/or use of sunscreens, seasonal variability is not as great at a population level as perhaps it once was.

It might be objected that calculations based on seasonal oscillation do not capture the full impact of cutaneous input, because some of that input in the summer months would be stored in fat and used to support winter 25(OH)D concentrations. Although undoubtedly true to at least a limited extent, this storage and delayed utilization is probably not responsible for very much of the winter value, as shown by 3 facts: 1) measured fat vitamin D concentrations tend to be low (2–4); 2) when larger-

than-usual-maintenance doses are given orally, very little is actually stored and most is used immediately (3); and 3) as shown here, the actual maximal summer input in these cohorts was itself absolutely small, leaving little to store for later utilization.

For most of our studies, basal cholecalciferol input was calculated to be on the order of  $50 \mu\text{g}$  ( $2000 \text{ IU/d}$ ), a full order of magnitude greater than usually attributed to identifiable food sources and at least 3 times the estimated basal requirement recently published by the Institute of Medicine (13) and the German Nutrition Society (14). Because recognized food inputs of native cholecalciferol (typically  $3\text{--}4 \mu\text{g}$ ), together with the amount found here for cutaneous synthesis ( $\sim 8\text{--}12 \mu\text{g}$ ), account for  $\sim 10\text{--}15 \mu\text{g}$  ( $400\text{--}600 \text{ IU/d}$ ), this leaves an unaccounted input gap of perhaps  $40 \mu\text{g}$  ( $1600 \text{ IU/d}$ ).

The recent search for (and finding) of 25(OH)D in certain meat sources (5,6) provides an attractive possible explanation for these unexpectedly large basal input estimates and a possible candidate to fill the calculated input gap. It is important in this respect to note that the molar potency of 25(OH)D taken orally [as measured by the ability to support a given 25(OH)D concentration] is from 3 to 9 times that of native cholecalciferol (15,16), depending to some extent upon dose. Thus, the input gap of  $\sim 40 \mu\text{g/d}$  of basal vitamin D input could, in theory, be provided by as little as  $6\text{--}10 \mu\text{g/d}$  of 25(OH)D itself.

As noted above, these estimates of basal input are not consistent with the claims of the Institute of Medicine (13) and the German Nutrition Society (14), both of which assert that  $15 \mu\text{g}$  ( $600 \text{ IU/d}$ ) is sufficient to produce and sustain a serum 25(OH)D concentration of  $50 \text{ nmol/L}$  in a sun-deprived population. However, given the high level of hitherto unrecognized input from food, it still might be that  $15 \mu\text{g/d}$  of supplemental cholecalciferol could suffice to bring total input in most sun-deprived persons up to an intake sufficient to maintain  $50 \text{ nmol/L}$ . Perhaps what needs documenting is the requirement for a sun-deprived, vegan population, i.e., those almost totally dependent upon supplements. The data in this analysis indicate that that cholecalciferol requirement would be  $\sim 50 \mu\text{g}$  ( $2000 \text{ IU/d}$ ), making, of course, due allowance for inter-individual differences in efficiency of conversion of cholecalciferol to 25(OH)D and differences in body size (11). If, instead of  $50 \mu\text{g/d}$ , the target serum 25(OH)D concentration is  $80 \text{ nmol/L}$ , i.e., the amount required to ensure normal bone histology (17), our data indicate a need for cholecalciferol in sun-deprived, non-meat eaters of  $75 \mu\text{g}$  ( $3000 \text{ IU/d}$ ), a value remarkably close to our previous estimates (7).

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R.P.H. designed, analyzed, and wrote the paper; L.A.G.A. provided data and manuscript preparation; and C.F. provided data and manuscript preparation. All authors read and approved the final manuscript.

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