A Novel Approach Localizes the Association of Vitamin D Status With Insulin Resistance to One Region of the 25-Hydroxyvitamin D Continuum

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ABSTRACT

Vitamin D status has been implicated in insulin resistance, type 2 diabetes mellitus, and hypertension, but the range of vitamin D status values over which the association can be found is unknown. Our objective was to define this range in a cohort of nondiabetic adult Canadians. We used a regression modeling strategy, first adjusting insulin-response variables and systolic and diastolic blood pressure for BMI, waist circumference, weight, age, and sex. The resulting residuals were regressed against serum 25-hydroxyvitamin D [25(OH)D] concentration using successive 40% data blocks ranging from the 0th to the 60th percentile of 25(OH)D values. All of the predictor variables were significantly associated with each of the dependent variables, with BMI and waist circumference accounting for >98% of the explained variance. The vitamin D association was localized to the serum 25(OH)D range extending from 40 to 90 nmol/L (16–36 mg/L). We conclude that vitamin D status is inversely associated with insulin responsiveness and blood pressure. Consistent with the threshold response characteristic typical of nutrients, the association was strongest in a circumscribed region of the range of 25(OH)D values. There was no association at 25(OH)D values >80–90 nmol/L (32–36 mg/L), indicating that the vitamin D association applied principally to values below that level. The differences observed, if they can be further confirmed in prospective studies, are of a magnitude that would be clinically important.


Introduction

A large and rapidly growing literature suggests that vitamin D status is a factor in various chronic conditions such as autoimmune disorders and cardiovascular disease (1). Of the several suggested extraskeletal activities of vitamin D, perhaps the best attested is insulin resistance. Increased insulin resistance is found associated with low vitamin D status in a variety of observational study designs (2–22), including population-based studies in countries as geographically diverse as Norway (20), Australia (17), and the United States (5,19). Low vitamin D status is predictive of incident metabolic syndrome (5,10,17), the features of which include insulin resistance and hypertension. That this association is most likely causal has been shown by several recently published randomized, controlled trials evaluating vitamin D effects on insulin resistance (23–25) as well as blood pressure (BP) (26–28).

The BP association has a clear basis in biology because evidence from vitamin D knockout mice indicates that hypertension is a consequence of vitamin D deprivation (29).

Although more sophisticated mathematical models are potentially available, all of the observational studies of which we are aware have used a simple linear (or sometimes logarithmic) relationship between vitamin D status and the various indices of insulin responsiveness or BP. Such models explicitly assume that the association is operative across the full range of vitamin D intakes. This is arguably not the best analytic strategy because nutrient responses tend to be sigmoidal, with response reaching a plateau at some point within the plausible intake range (30,31). To our knowledge, no study to date has sought specifically to find the “sensitive” segment of the vitamin D status range or to focus its analysis on that range.

As with insulin response, large population studies looking for associations between vitamin D and BP have yielded inconsistent results (32–38). This inconsistency could be because the actual effect is small (39), resulting in a correspondingly low power to detect a real association. Or, as we hypothesize here for both insulin and BP, results of large observational studies may have been influenced by a failure to
use an analytic strategy that corresponds to the unique features of nutrient response (30,31).

Thus, although the association is reasonably well established, existing data do not provide information on the range of vitamin D status values over which it is operative, nor how much vitamin D is sufficient to produce the reported difference in insulin responsiveness or BP. In this article, we report the results of application of an analytic strategy specifically designed to fit sigmoid curves. The predictor variable was 25-hydroxyvitamin D [25(OH)D]8, and the outcome variables were fasting plasma insulin, homeostatic model assessment–insulin resistance (HOMA-IR) (40), insulin responsiveness (QUICKI) (41), and both systolic and diastolic BP.

Methods

Subjects

We had the opportunity to examine this matter in a hitherto untapped database developed by a not-for-profit Canadian health foundation, Pure North S’Energy Foundation (PNSF), located in Calgary, Alberta. This foundation was created to address health issues among workers in the Canadian oil and gas industry (and their families). Its program includes promoting such outcomes as healthy weight and improved nutrition among its members. Membership is voluntary and without cost. Participants are recruited into the foundation’s program typically through their employers. Foundation enrollment consists of gathering health information from participants through a questionnaire and interview, making anthropometric measurements, and providing both blood and urine samples for analysis. For this study, data were obtained for members enrolled from October 2007 through December 2011. The list on the left gives the sorting criteria for each level of sample generation, and the designations “Yes” and “No” in the boxes to the right refer to the number of individuals meeting or not meeting that criterion, respectively. HOMA-IR, homeostasis model assessment–insulin resistance; 25(OH)D, 25-hydroxyvitamin D.

![Diagram](https://via.placeholder.com/150)

**Figure 1** Generation of the analysis sample from the total adult cohort enrolled in the Pure North S’Energy Foundation (PNSF) program during the period October 2007 through December 2011. The list on the left gives the sorting criteria for each level of sample generation, and the designations “Yes” and “No” in the boxes to the right refer to the number of individuals meeting or not meeting that criterion, respectively. HOMA-IR, homeostasis model assessment–insulin resistance; 25(OH)D, 25-hydroxyvitamin D.

All statistical analyses were performed using IBM SPSS Statistics version 20. Variables that were appreciably skewed to the right [HOMA-IR, insulin, glucose, and 25(OH)D] were log transformed before incorporation into the various models. This transformation effectively normalized all 4 variables. Sex was coded as a 0/1 variable. All variables of interest were analyzed separately for men and women.
Multiple linear models were generated for the dataset as a whole as well as for men and women separately. Values of the 5 dependent variables (or their log, transforms) were adjusted for BMI, waist circumference, weight, age, and sex using a linear regression model. Modeling was confined to cases for which there were valid values for all of the involved variables. Values for the dependent variables, adjusted for BMI, waist, sex, age, and weight, were plotted against the log, transform of 25(OH)D using first the locally weighted scatterplot smoothing (LOESS) method, and then a method similar to LOESS, but reporting actual slopes for sequential data blocks. To do this, we performed a series of linear regressions using data blocks comprising 40% of the fully adjusted residual values for the dependent variables from the entire dataset (≈1646 records per block), stepping them up from the lowest 25(OH)D value by 5 percentage increments. The output of this exercise was a series of values for the coefficient for the natural logarithm (ln)25(OH)D term in the bivariate linear regression equations for each of the dependent variables. This approach, as noted, is similar to that used by LOESS, with the exception of the fact that we assumed a quasigmoid pattern for the underlying relationship between the outcome variable and vitamin D status, whereas LOESS is model free. Coefficients with $P < 0.05$ were considered statistically significant.

## Results

Pertinent features of the analyzable members of the cohort are set forth in Table 1. There were 2406 males and 1710 females, with ages spanning a range from 18 to 95 y, BMI ranging from 14.7 to 55.5 kg/m$^2$, and serum 25(OH)D values ranging from 10.0 to 361.0 nmol/L (4 to 144 μg/L). Thus, the individuals in this cohort exhibited values that were approximately coextensive with the range of values for these variables in the general population. As would be expected, the men had larger body size than the women. For all variables except age, the values for men and women differed significantly, which is not surprising given the large sample sizes. Overall, however, the sex-related differences were small. Nevertheless, the differences justified treating sex as a cofactor in the subsequent analyses.

Table 2 presents the numbers of individuals in the cohort who had values above the upper reference limit for fasting insulin and systolic BP (120 pmol/L and 140 mm Hg, respectively), arrayed by 25(OH)D quartile. It shows a significant excess of individuals with elevated values at the lowest vitamin D status quartile. Contrasting the lowest and highest quartiles, the RR (95% CI) for an elevated fasting insulin value was 2.08 (1.31–3.29; $P < 0.01$) and for elevated BP, 1.36 (1.08–1.71; $P < 0.01$). However, because of the strong interrelationship of obesity and waist circumference, on the one hand, with both BP and insulin responsiveness on the other, the relative excess of values at the lower vitamin D status quartiles would likely have been influenced by factors such as obesity in those same quartiles. It was necessary, therefore, to dissect out an independent effect (if any) for 25(OH)D after adjusting for the recognized and strongly influential body size and fat distribution variables.

Table 3 sets forth the resulting multiple linear regression models for the 5 dependent variables of interest, using the entire dataset, with sex entered as a cofactor and including ln25(OH)D. Stepwise methods were used, but for each dependent variable except ln(insulin), the same set of predictor variables was found to be statistically significant (Table 3), although not always in the same order. These were BMI, waist circumference, weight, age, sex, and ln25(OH)D. These 5 variables accounted for almost one fourth of the total variance for the 3 insulin-related outcome variables (insulin, HOMA-IR, and QUICKI), and for approximately one fifth of the variance of the BP variables. For the insulin-related dependent variables, BMI and waist circumference alone accounted for almost 98% of the explained variance, more or less as expected. The coefficients for ln25(OH)D in these models, together with their 95% CIs, are also shown in Table 3. Except for QUICKI, the sign of the coefficient for all models was negative, indicating an inverse correlation. For QUICKI, which measures insulin sensitivity rather than resistance, the sign was positive. The coefficients of ln25(OH)D in these models were for the most part statistically highly significant ($P < 0.001$) for all outcome variables except systolic BP, for which $P = 0.09$.

These analyses establish an independent association of vitamin D status with the dependent variables in this cohort, both in men and women. As would be expected, the relative excess of values at the lower vitamin D status quartiles would likely have been influenced by factors such as obesity in those same quartiles. It was necessary, therefore, to dissect out an independent effect (if any) for 25(OH)D after adjusting for the recognized and strongly influential body size and fat distribution variables.
accounting for ~2% of their variance. But strictly linear models, as their name suggests, generally presume that the relationship, if any, prevails across the full range of the data analyzed. Significant departures from this assumption could appreciably alter, and even obscure, an underlying relationship. Because the underlying hypothesis for nutrients is that the response is approximately sigmoid shaped and because sigmoid curves have 2 flat regions at low- and high-exposure values (with the transition being sandwiched between them), we first developed LOESS plots such as Figure 2 [InHOMA-IR on ln25(OH)D]. This plot shows, in the middle of the ln25(OH)D range, a clear offset between low and high ln25(OH)D values. It is this offset that we explored in the subsequent analyses. The evident smallness of the offset in Figure 2 (relative to the range of the HOMA-IR values) is a graphic reflection of the relative smallness of the contribution of ln25(OH)D to the total variance (as shown in Table 3).

In this analysis, we prepared a set of residuals, adjusting the raw values of the outcome variables for BMI, waist, age, sex, and weight. We then repeated the modeling exercise by regressing these residuals against ln25(OH)D, using a series of 40% contiguous data blocks, stepping up from the 0th percentile for serum 25(OH)D through the 60th percentile. For each iteration, we determined the value of the fitted coefficient of the 25(OH)D variable and its 95% confidence limits. Figure 3 shows the values for the resulting ln25(OH)D coefficients for ln(HOMA-IR), QUICKI, systolic BP, and diastolic BP as the dependent variables. In each case, these coefficients are plotted at the midpoints of the 25(OH)D data ranges evaluated. [A curve very similar to that of HOMA-IR was produced for ln(insulin) (not shown).] Coefficients significantly different from 0 are marked with an asterisk.

The patterns evident in Figure 3 show that there was indeed a statistically significant correlation between vitamin D status and each of the outcome variables, but that it was confined to only a portion of the serum 25(OH)D continuum, consistent with the sigmoid model. In regions either lower or higher, the coefficients were smaller (and for HOMA-IR and systolic BP were not statistically different from 0). However, in the response region, the absolute magnitude of the coefficients increased, reaching values that were 2 to 7 times greater than those produced using the full range of serum 25(OH)D values (i.e., those shown in Table 3). This pattern is what would be predicted for a relationship that was embedded in a continuum but applicable in only a portion of its range.

For all 5 outcome variables, the third and fourth data blocks [i.e., 25(OH)D values between 42 and 82 nmol/L] produced the numerically largest value for the coefficient of ln25(OH)D. For systolic BP, the earlier and later blocks produced 0 or near 0 values, indicating the absence of any association of ln25(OH)D with outcome at those 25(OH)D concentrations. For the others, particularly diastolic BP, there was a strong suggestion of a vitamin D effect beginning in the lowest quantiles evaluated.

Figure 4 shows the quantitative offset between the values of the 4 dependent variables of Figure 3, below and above the transition zone. This mode of presenting the data displays the underlying inverse sigmoid character of the relationship and corresponds directly to the LOESS plot (Fig. 1). In each case, the heavy horizontal lines represent the mean values for the residuals for the 4 dependent variables (after adjusting for BMI, weight, waist circumference, sex, and age), plotted over the ranges over which there was no significant association of ln25(OH)D with outcome at those 25(OH)D concentrations. For the others, particularly diastolic BP, there was a strong suggestion of a vitamin D effect beginning in the lowest quantiles evaluated.

Table 4 presents the set of maximum coefficients for the vitamin D term derived from the various models for all 5

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**Table 3. Multiple regression models for insulin response and blood pressure.**

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Significant predictor variables</th>
<th>R² for model</th>
<th>Coefficient for ln25(OH)D</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ln(insulin)</td>
<td>BMI, waist, sex, ln25(OH)D</td>
<td>0.262</td>
<td>-0.084 (±0.117 to -0.051)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ln(HOMA-IR)</td>
<td>BMI, waist, age, sex, ln25(OH)D</td>
<td>0.274</td>
<td>-0.075 (±0.112 to -0.038)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QUICKI</td>
<td>BMI, waist, age, sex, ln25(OH)D</td>
<td>0.238</td>
<td>+0.0029 (±0.00143 to 0.0037)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>BMI, waist, age, sex, ln25(OH)D</td>
<td>0.227</td>
<td>-0.755 (±1.63 to +0.123)</td>
<td>0.092</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>BMI, waist, age, sex, ln25(OH)D</td>
<td>0.184</td>
<td>-1.480 (±2.12 to -0.84)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

1 BP, blood pressure; HOMA-IR, homeostasis model assessment–insulin resistance; ln, natural logarithm; QUICKI, quantitative insulin sensitivity check index; 25(OH)D, 25-hydroxyvitamin D.
2 Mean (95% CI).
3 Probability that the confidence interval for the coefficient for ln25(OH)D includes 0.
dependent variables, together with the data ranges over which the magnitude of the coefficient was found to be maximal. Because some of the variables had been log-transformed, actual effect size over the ranges where the association is detectable is nonlinear. Nevertheless, the aggregate effects across the cognate transition zones can be estimated from the difference between the 2 steady-state values in the plots of Figure 4. For insulin, the total magnitude of the vitamin D–related difference was $212.0 \text{ pmol/L}$, $20.37$ for HOMA-IR, $+0.023$ for QUICKI, $-2.56 \text{ mm Hg}$ for systolic BP, and $-3.96 \text{ mm Hg}$ for diastolic BP ($P < 0.001$ for all).

Discussion
These analyses add further support to the hypothesis that vitamin D status contributes significantly to the maintenance of glucose homeostasis and normal BP in free-living North American adults. Its effect is much smaller than the effects of fatness and fat distribution, both of which could easily obscure the vitamin D effect in cross-sectional studies. The data summarized in Table 3 (which is how this issue is usually approached) effectively established the role of vitamin D status as an independent predictor, at least for this cohort. Although we could have stopped there, the subsequent segmented analysis added new information to the description of the vitamin D effect. It resulted in substantially improved sensitivity, permitting both localization of the association to the operative exposure range and better estimation of its true magnitude than would have been possible using ordinary linear modeling methods (with their typical assumption of monotonic relationships between variables across the span of analyzed values). This latter point is illustrated clearly for systolic BP, which exhibited only a marginal significance ($P = 0.09$) when the entire range of 25(OH)D values was used to generate a model (Table 3). By contrast, when the focus was confined to the middle of the 25(OH)D range, the absolute value of the coefficient of ln25

![Figure 3](https://advances.nutrition.org/)

**Figure 3** Plots of the coefficients of the ln25(OH)D term in bivariate regression equations using as dependent variables the residuals for ln(HOMA-IR), QUICKI, systolic BP, and diastolic BP derived after fitting to a multivariate model using BMI, waist circumference, age, sex, and weight. For each plot, the points represent the computed coefficients for successive 40% data blocks stepping upward from the lowest 25(OH)D value by increments of 5 percentiles. Error bars are 1 SEM. Asterisks designate coefficient values that are significantly different from 0. Note that the x-axis values are plotted at the midpoint of the ranges over which the relationships were calculated. The boundaries of those ranges extend upward and downward by $\approx 20 \text{ nmol/L}$. BP, blood pressure; D25, 25-hydroxyvitamin D; HOMA-IR, homeostasis model assessment–insulin resistance; In, natural logarithm; QUICKI, quantitative insulin sensitivity check index; 25(OH)D, 25-hydroxyvitamin D.
(OH)D increased substantially and became clearly significant ($P = 0.015$).

The recently published study of Gagnon et al. (17) contained a LOESS plot of the risk of incident metabolic syndrome against vitamin D status, showing a clear offset at \(25(OH)D\) values ranging from \(\geq 50 \text{ nmol/L}\) to \(\geq 100 \text{ nmol/L}\), very similar to where we found the maximum association for our 5 dependent variables. As with our data, \(25(OH)D\) concentration explained \(\approx 1\%\) of the variance in risk of the outcome variable (incident metabolic syndrome) (17).

Although our study represents what is, to our knowledge, the first explicit modeling of observational data using the sigmoid character of nutrient response, it must be recognized that such a model is implicit in the process involved in setting intake requirements and is explicitly diagrammed, for example, in Chapter 1 of Willett’s Nutritional Epidemiology (42). A decision that \(X\) mg/d of a particular nutrient is sufficient to meet the average needs is equivalent to saying that the benefit produced by the nutrient is maximized at this intake and that further increases produce no additional health benefit, i.e., the curve has reached the upper flat region of its sigmoid shape. For example, the Institute of Medicine decision that a vitamin D status of \(50 \text{ nmol/L} (20 \mu g/L)\) was sufficient (43) was tantamount to saying that the transition from inadequate to adequate had occurred at \(<50 \text{ nmol/L} (20 \mu g/L)\).

Other recent reports using variants of a segmental analysis analogous to ours have found results congruent with those described here. Hyppönen and Power (14) using a “broken-stick” method, instead of assuming linearity of response, reported a statistically significant negative association between

**Figure 4** Plots of quasi-integrals of the data in Figure 2 showing the underlying inverse sigmoid character of the relationship between vitamin D status and HOMA-IR, insulin, and BP. In each plot, the heavy horizontal lines represent the flat portions of the sigmoid curve above and below the transition zone (together with their 95% CI, the horizontal dashed lines). The heavy diagonal dashed line represents the transition and is an approximation, as the data indicate only that the transition occurs somewhere in the range of \(40–90 \text{ nmol/L} (16–36 \mu g/L)\). BP, blood pressure; HOMA-IR, homeostasis model assessment–insulin resistance; QUICKI, quantitative insulin sensitivity check index; \(25(OH)D\), 25-hydroxyvitamin D.

<table>
<thead>
<tr>
<th>Outcome Variable</th>
<th>Maximum Coefficient$^2$</th>
<th>(25(OH)D), range</th>
</tr>
</thead>
<tbody>
<tr>
<td>(ln[Insulin])</td>
<td>(-0.246 (,-0.403\text{ to }-0.0892))</td>
<td>(49.4–87.2)</td>
</tr>
<tr>
<td>(ln[HOMA-IR])</td>
<td>(-0.218 (,-0.369\text{ to }-0.067))</td>
<td>(42.4–82.1)</td>
</tr>
<tr>
<td>QUICKI</td>
<td>(+0.00901 (0.0234–0.0157))</td>
<td>(49.4–87.2)</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>(-4.99 (,-8.93\text{ to }-1.050))</td>
<td>(49.4–87.2)</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>(-3.40 (,-5.928\text{ to }-0.8716))</td>
<td>(42.4–82.1)</td>
</tr>
</tbody>
</table>

$^1$ BP, blood pressure; \(ln\), natural logarithm; \(25(OH)D\), \(QUICKI\), quantitative insulin sensitivity check index; 25-hydroxyvitamin D.  
$^2$ Point estimate (95% CI).
vitamin D status and hemoglobin A1c, with a break point at 
\(\sim 65 \text{ nmol/L}\). Larsen et al. (28), in a randomized, controlled trial, found an inverse effect on BP at 25(OH)D values mainly
<80 nmol/L. Both inflection points are within the range of vi-
tamin D status values where we found an association between
25(OH)D and the insulin and BP variables. Further, these
findings, together with those presented here, are consist-
tent with the recommendation from the systematic review
by Cavalier et al. (44) that serum 25(OH)D be maintained at >75 nmol/L.

The very recent study of Belenchia et al. (25) provides
strong corroboration of the findings that we report here. Us-
ing a randomized, controlled trial design in 35 obese adoles-
cents and administering a vitamin D dose of 4000 IU/d, these
investigators increased serum 25(OH)D from 47 to 95 nmol/L
and found a significant decrease in HOMA-IR (−1.63) and
a significant increase in QUICKI (+0.016). These changes are
very similar to those we observed in adults and span precisely
the region of the 25(OH)D continuum in which our associa-
tion occurs.

A principal strength of our study lies not so much in the
relationship that we found (which is to some extent con-
firmatory), but in the additional inferential power conferred
by the segmented analysis, permitting in observational studies
better localization of the effect transition than has heretofore
been possible. In this dataset, that transition lies somewhere
in the 25(OH)D range of 40–90 nmol/L. To localize it more
precisely would have required smaller percentile blocks,
which in turn would have required a much larger sample size
if we were to have adequate power within each block. In
any case, these data provide information concerning the serum
25(OH)D concentration that must be achieved to ensure the
cognitive effects. In this cohort and with this analytic approach,
our results suggest that that value must be at least as high as 80
nmol/L (32 µg/L).

A second strength is seen by way of contrast with usual
studies of such associations, which report estimated changes
in some endpoint variable per some arbitrary amount of
change in the predictor variable, e.g., a decrease of 1 mm
Hg in systolic BP for each 10 nmol/L increase in serum
25(OH)D. That approach clearly assumes not only linearity,
but independence of the response and the basal exposure,
i.e., that any 10-nmol/L increase will produce the specified
response, irrespective of starting level. That is clearly not
valid for a sigmoid type of response. By contrast, the approach
we have taken here yields the total response produced, not by a
constant unit quantity of the independent variable, but by the
full transition from inadequate to adequate.

A weakness of the study lies in its observational character
and the corresponding inability to attribute a causal role to
vitamin D status, at least from these data alone. However,
given that there are randomized trial data showing an effect of
vitamin D on both HOMA-IR (23–25) and BP (26–28), the
concordant evidence from this study strongly suggests that el-
levating vitamin D status to a 25(OH)D level of at least 80
nmol/L would be expected to result in small but useful im-
provements in both glucose homeostasis and BP control.

It must also be noted that we did not attempt to evaluate the
linearity of the relationship between the confounders
(e.g., BMI, waist) and the endpoint variables as we did for vi-
tamin D. For them, there is no a priori reason to doubt that
linearity, which is usually assumed in the literature on this
topic. Nevertheless, that assumption is not evidence of possi-
ble underlying nonlinearity nor that some nonlinear method
would not have removed more of the variance in the endpoint
variables. Finally, the database on which these analyses are
based did not include values for serum leptin or other cy-
tokines associated with obesity and insulin resistance.
Hence, we were unable to explore these possibly mechanistic
associations.

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Director, Peter Faris, Biostatistician (Alberta Health Services).
All authors have read and approved the final manuscript.

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