Serum 25-Hydroxyvitamin D Levels Are Strongly Related to Systolic Blood Pressure But Do Not Predict Future Hypertension

Rolf Jorde, Yngve Figenschau, Nina Emaus, Moira Hutchinson, Guri Grimnes

Abstract—Vitamin D receptors have been detected in vascular smooth muscle cells, and 1,25-dihydroxyvitamin D inhibits the renin mRNA expression. Epidemiological studies show an inverse relation between serum 25-hydroxyvitamin D levels and blood pressure, and low serum 25-hydroxyvitamin D levels are reported to be predictors of future development of hypertension. This may indicate an important role for vitamin D in blood pressure regulation. In the present study, 25-hydroxyvitamin D was measured in sera collected in 1994 from 4125 subjects who did not use blood pressure medication, and thereafter measurement was repeated in 2008 for 2385 of these subjects. In sera from 1994 there was a significant decrease in age, body mass index, and systolic blood pressure and a significant increase in physical activity score across increasing 25-hydroxyvitamin D quartiles. After adjusting for sex, age, body mass index, and physical activity, the difference in systolic blood pressure between the lowest and highest serum 25-hydroxyvitamin D quartiles was 3.6 mm Hg. After adjustment for confounders, serum 25-hydroxyvitamin D from 1994 did not predict future hypertension or increase in blood pressure, nor was there any significant association between change in serum 25-hydroxyvitamin D from 1994 to 2008 and change in blood pressure. Our results do not support a causal role for vitamin D in blood pressure regulation, and large randomized clinical trials, preferably including subjects with hypertension and/or low serum 25-hydroxyvitamin D levels, are greatly needed to clarify whether vitamin D supplementation affects the blood pressure. (Hypertension. 2010;55:792-798.)

Key Words: blood pressure ■ epidemiology ■ human ■ hypertension ■ vitamin D

There has been a great focus on the relation between mineral metabolism and blood pressure since the early reports on lower calcium intake and lower serum calcium levels in hypertensive compared with normotensive subjects.1–3 In experimental animal models of hypertension, calcium supplementation consistently lowers blood pressure,4,5 whereas the effect in humans is less pronounced.6,7 Vitamin D, which is of vital importance for the calcium metabolism, is produced locally in the skin by the sun. Thus, ultraviolet B exposure transforms 7-dehydrocholesterol in the skin to previtamin D, which is rapidly converted to vitamin D. To a minor extent, humans also acquire vitamin D from the diet, in particular, from fatty fish and supplements. To become biologically active, vitamin D has to be hydroxylated first in the liver to 25-hydroxyvitamin D (25[OH]D) and thereafter in the kidneys to 1,25-dihydroxyvitamin D.8 Vitamin D increases the intestinal calcium absorption and could thereby have an indirect effect on blood pressure. In addition, receptors for vitamin D have been found recently in a number of tissues not directly related to calcium metabolism, such as vascular smooth muscle cells and the renin-producing juxtaglomerular cells.9,10 Vitamin D may, therefore, also have a more direct role in blood pressure regulation, which has been substantiated in several epidemiological studies.11,12 Thus, in cross-sectional studies, the serum level of 25(OH)D, which is the storage form of vitamin D in the body and the metabolite used to evaluate the subject’s vitamin D status, and the serum level of 1,25-dihydroxyvitamin D, which is the active form of vitamin D, appear to be inversely associated with blood pressure.13–16 Furthermore, low serum 25(OH)D levels have been reported to predict future hypertension.17,18 Ultraviolet B irradiation, which causes an increase in serum 25(OH)D levels, appears to lower blood pressure in hypertensive subjects, whereas ultraviolet A irradiation, which does not increase the serum 25(OH)D levels, has no effect on the blood pressure.19 This may indicate a causal relation between serum 25(OH)D and blood pressure, and, if so, one would expect that an altered serum 25(OH)D level would be associated with a corresponding change in blood pressure.

In Tromsø, in north Norway, health surveys have been performed 6 times since 1974.20 Serum 25(OH)D was deter-
minded both in the fourth 1994–1995 and the sixth 2008 surveys, giving us the opportunity to test the cross-sectional relation between serum 25(OH)D and blood pressure, the predictive value of serum 25(OH)D regarding future hypertension, and the relation between change in serum 25(OH)D and change in blood pressure over time.

Methods

Study Population

The Tromsø Study, conducted by the University of Tromsø in cooperation with the National Health Screening Service, is a longitudinal, population-based multipurpose study focusing on lifestyle-related diseases. The fourth survey in 1994–1995 (“1994” in the following, for simplicity) was performed in 2 phases, and all of the residents in the Tromsø municipality ≥25 years of age were invited to participate in the first phase of the study. A total of 27,158 persons participated, providing an attendance rate of 77% among eligible inhabitants. All men aged 55 to 74 years, all women aged 50 to 74 years, and a 5% to 10% sample of the remaining age groups between 25 and 84 years were preselected to a second phase of the survey, and 7965 persons, or 78% of those invited, attended. Sera from this second phase were stored for later analyses. In the sixth Tromsø Study, performed in 2008, 19,762 subjects were invited and 12,984 attended.

Measurements

In both surveys, the participants filled in questionnaires on medical history, blood pressure medication, and lifestyle factors, including vitamin D supplementation and use of cod liver oil during the last 14 days, as well as smoking. Blood pressure was measured as described previously in detail with an automatic device (Dinamap Vital Signs Monitor 1846, Critikon Inc). A physical activity score was calculated, and height and weight were measured as described previously.

Blood samples were drawn in a nonfasting state. Serum parathyroid hormone was analyzed in 2001 in a subgroup of participants from the fourth Tromsø Study using an automated clinical chemical analyzer (Immulite 2000), with a reference range of 1.1 to 6.8 pmol/L for those ≤50 years of age and 1.1 to 7.5 pmol/L for those >50 years of age. Sera from the second phase of the fourth Tromsø Study were stored at −70°C and, after a median storage time of 13 years, thawed in March 2008, and analyzed for 25(OH)D, whereas sera from the sixth Tromsø Study were analyzed subsequently within 3 days. 25-Hydroxyvitamin D3 was measured by immunometry (ECLA) using an automated clinical chemistry analyzer (Modular E170, Roche Diagnostics). According to the producer, the assay has, for total analytic precision, a coefficient of variation ≤7.8%, as judged in any of 3 different concentrations (48.6, 73.8, 177.0 nmol/L). The cross-reactivity with 25-hydroxyvitamin D2 was <10%, and the analytic sensitivity was 10 nmol/L. Five subjects had 25(OH)D below the detection limit, and their values were set to 5 nmol/L. At present, the laboratory has no reference values for 25(OH)D, but the manufacturer provides a population-based reference range of 27.7 to 107.0 nmol/L for adults as a guideline. This analysis has been approved by the Norwegian Accreditation Authority. With this method, we have found smokers to have 15% to 20% higher serum 25(OH)D levels than nonsmokers, which we have not found when measuring serum 25(OH)D with other immunologic or liquid chromatography-mass spectrometry methods (data not shown). For this discrepancy we have at present no explanation and have, therefore, decided to exclude smokers from the present analysis.

Statistics

Normal distribution was evaluated with visual inspection of histograms and determination of skewness and kurtosis. All of the variables used as dependent variables were considered normally distributed. Linear trends across serum 25(OH)D quartiles were tested with linear regression with use of covariates as described in the tables. In these analyses, we adjusted for month of blood sampling with the use of dummy variables. ANCOVA was used to calculate adjusted means of systolic and diastolic blood pressures.

Comparison between values from 1994 and 2001 were done with the paired Student t test or with the χ2 test. To evaluate change in blood pressure status, the subjects were classified in the following 3 categories: (1) normotensive, systolic blood pressure <140 mm Hg and diastolic blood pressure <90 mm Hg; (2) increased blood pressure, systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg (but not hypertensive, as defined below); and (3) hypertensive, systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥95 mm Hg and/or using blood pressure medication.

A logistic regression model was used to calculate odds ratios with 95% CIs for change in blood pressure category from 1994 to 2008. Linear regression models were used testing 25(OH)D from 1994 as a continuous variable for the prediction of systolic blood pressure in 2008. Correlations were evaluated with Pearson correlation coefficient (r). Evaluations of change in serum 25(OH)D versus change in blood pressure were done using both unadjusted serum 25(OH)D values and z scores for serum 25(OH)D values calculated within each month in 1994 and 2008 to eliminate effects of season and storage. Unless otherwise stated, all of the data are expressed as mean±SD. All of the tests were 2 sided, and P<0.05 was considered statistically significant. Statistical analyses were performed with SPSS version 15.0 (SPSS Inc).

Ethics

The study was recommended by the Regional Committee for Medical and Health Research Ethics, North Norway. Each participant gave a written informed consent before the examinations.

Results

Cross-Sectional Study

Among the 7965 subjects who attended the second phase of the fourth Tromsø Study, 7168 subjects had valid 25(OH)D measurements. A total of 2337 of these subjects were current smokers and, thus, were excluded. Among the remaining 4831 subjects, 698 were on blood pressure medication, and in 8 subjects the date of examination was lacking, leaving 4125 subjects for the cross-sectional analysis. The characteristics of all of these subjects according to serum 25(OH)D quartiles are shown in Table 1. A total of 32.2% of the subjects had been taking vitamin D supplements or cod liver oil during the last 14 days. Subjects taking vitamin D supplements and/or cod liver oil had a mean serum 25(OH)D level of 57.0±17.4 nmol/L, and subjects not taking vitamin D supplements had a mean level of 50.7±16.0 nmol/L (P<0.001). However, vitamin D supplementation status did not affect the relation between serum 25(OH)D and blood pressure and was, therefore, not included in the following model. With increasing serum 25(OH)D quartiles, there was a significant decrease in age, body mass index (BMI), and systolic blood pressure and an increase in physical activity score. The same was seen if stratifying for age above or below 60 years (data not shown). There was a nonsignificant decrease in diastolic blood pressure across the serum 25(OH)D quartiles (P=0.052). After adjusting for sex, age, BMI, and physical activity score, the differences in systolic and diastolic blood pressures between the lowest and the highest serum 25(OH)D quartiles were 3.6 and 1.0 mm Hg, respectively. Figures 1 and 2 show serum 25(OH)D in relation to systolic and diastolic blood pressure, respectively. Serum parathyroid hormone was measured in 1887 subjects, and, as expected, there was a significant
levels in the 4125 subjects from the Tromsø Study in 1994. The
Figure 1.
Figure 2.
Longitudinal Study
Among the 4125 subjects from the fourth Tromsø Study in 1994, 2450 had valid serum 25(OH)D measurements in the sixth Tromsø Study in 2008. Among these, 39 subjects were now current smokers and, thus, were excluded and a further 26 had incomplete data sets, leaving 2385 for the longitudinal analysis. Their characteristics in 1994 and 2008 are shown in Table 2. Compared with values from 1994, there was in 2008 a significant increase in BMI, serum 25(OH)D, and systolic blood pressure and a significant decrease in diastolic blood pressure. The samples from 1994 and 2008 were measured with the same 25(OH)D assay and during the same time frame. Therefore, the most likely explanation for the 3% higher levels in the samples from 2008 is an effect of storage time frame. Therefore, the most likely explanation for the 3% difference in those who moved to a lower blood pressure category in those in the lower serum 25(OH)D quartiles in 1994 than in those in the highest quartile, but this was not significant tendency for a larger increase in blood pressure from 1994 to 2008 in those with higher serum 25(OH)D levels in 1994. However, if only including subjects not using blood pressure medication in 1994 or in 2008, the change in blood pressure from 1994 to 2008 was almost identical in all of the serum 25(OH)D quartiles from 1994 (Table 3).

Table 1. Characteristics of All 4125 Subjects Included in the Cross-Sectional Analysis From the Fourth Tromsø Study and According to Serum 25(OH)D Quartile

<table>
<thead>
<tr>
<th>Serum 25(OH)D Quartile, nmol/L</th>
<th>Men/Women</th>
<th>Age, y*</th>
<th>Serum Parathyroid Hormone, pmol/L†</th>
<th>BMI, kg/m²‡</th>
<th>Physical Activity Score*</th>
<th>Systolic Blood Pressure, mm Hg*</th>
<th>Diastolic Blood Pressure, mm Hg*</th>
<th>Adjusted Systolic Blood Pressure, mm Hg†</th>
<th>Adjusted Diastolic Blood Pressure, mm Hg†</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;41.4</td>
<td>339/691</td>
<td>60.3±10.7</td>
<td>3.2±2.5</td>
<td>25.9±4.5</td>
<td>2.8±2.5</td>
<td>146.8±22.8</td>
<td>83.4±13.1</td>
<td>144.7±20.8</td>
<td>83.0±12.8</td>
</tr>
<tr>
<td>41.4 to 51.5</td>
<td>400/641</td>
<td>59.1±10.5</td>
<td>3.0±1.4</td>
<td>26.3±3.9</td>
<td>3.2±2.6</td>
<td>143.5±21.8</td>
<td>82.6±12.6</td>
<td>143.7±19.8</td>
<td>83.1±12.2</td>
</tr>
<tr>
<td>51.6 to 62.6</td>
<td>426/667</td>
<td>58.5±9.9</td>
<td>2.6±1.1</td>
<td>26.1±3.6</td>
<td>3.3±2.6</td>
<td>141.8±21.5</td>
<td>81.0±13.0</td>
<td>142.4±19.8</td>
<td>82.6±12.2</td>
</tr>
<tr>
<td>≥62.6</td>
<td>377/644</td>
<td>57.6±9.9§</td>
<td>2.5±1.4§</td>
<td>25.5±3.3§</td>
<td>3.6±2.7§</td>
<td>139.1±19.9</td>
<td>80.6±11.8</td>
<td>141.1±20.5§</td>
<td>82.0±12.5§</td>
</tr>
<tr>
<td>All subjects§</td>
<td>1542/2583</td>
<td>58.9±10.3</td>
<td>2.9±1.4</td>
<td>26.2±3.9</td>
<td>3.2±2.6</td>
<td>142.8±21.7</td>
<td>82.2±12.7</td>
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<td></td>
</tr>
</tbody>
</table>

*Data are mean±SD.
†Number of subjects according to increasing serum 25(OH)D quartiles: 555, 499, 478, and 355.
‡Data were adjusted for sex, age, BMI, and physical activity score.
§P<0.001 (trend across serum 25(OH)D quartiles, linear regression with sex, age, BMI, physical activity score, and month of examination as possible covariates).
||Mean serum 25(OH)D was 52.7±16.7 nmol/L.

Using the same cutoffs for serum 25(OH)D quartiles as in the cross-sectional study, there was, across increasing serum 25(OH)D quartiles from 1994, a decrease in systolic blood pressure measured in 2008 (Table 3). There was a nonsignificant tendency for a larger increase in blood pressure from 1994 to 2008 in those with higher serum 25(OH)D levels in 1994. However, if only including subjects not using blood pressure medication in 1994 or in 2008, the change in blood pressure from 1994 to 2008 was almost identical in all of the serum 25(OH)D quartiles from 1994 (Table 3). There were slightly more subjects who started blood pressure medication and moved to a higher blood pressure category in those in the lower serum 25(OH)D quartiles in 1994 than in those in the highest quartile, but this was not statistically significant. This was the case when all of the subjects were analyzed together regardless of blood pressure status at baseline, when only subjects who were normotensive at baseline were included, and when subjects with elevated
levels below the serum 25(OH)D 10th and fifth percentiles (<34.1 nmol/L and <29.6 nmol/L, respectively) were tested separately. However, they did not differ significantly from the rest of the cohort, nor were the results significantly different if subjects with serum 25(OH)D levels above the 90th or the 95th percentiles (>73.7 nmol/L and >81.5 nmol/L, respectively) were chosen as the reference group (data not shown).

Using serum 25(OH)D from 1994 as a continuous variable, serum 25(OH)D was a significant negative predictor for systolic blood pressure in 2008 if adjusting only for month of blood sampling and sex but not when age and other covariates were included (Table 5). The positive strongest predictor of systolic blood pressure in 2008 was, as expected, systolic blood pressure in 1994 (Table 5). Serum 25(OH)D from 1994 as a continuous variable was also a significant negative predictor of elevated blood pressure in 2008 and hypertension in 2008 after adjusting for age, sex, and month of examination but not when BMI was included in the model (data not shown). Serum 25(OH)D from 1994 was not a significant predictor of diastolic blood pressure in 2008, regardless of which covariates were included in the model (data not shown).

There was a significant correlation between serum 25(OH)D from 1994 and 2008 (r=0.40; P<0.001). This correlation increased slightly to r=0.43 (P<0.001) when using the serum 25(OH)D z scores from 1994 and 2001. There were no significant correlations between change in serum 25(OH)D (value in 2008 minus value in 1994) and


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<tbody>
<tr>
<td></td>
<td>Systolic Blood Pressure, mm Hg*</td>
<td>Diastolic Blood Pressure, mm Hg*</td>
<td>Systolic Blood Pressure, mm Hg*</td>
</tr>
<tr>
<td>All 2385 subjects</td>
<td>143.1±21.0</td>
<td>82.6±12.4</td>
<td>149.2±25.1</td>
</tr>
<tr>
<td>&lt;41.4</td>
<td>172/360</td>
<td>137.8±17.2</td>
<td>78.4±10.7</td>
</tr>
<tr>
<td>41.4 to 51.5</td>
<td>227/372</td>
<td>132.6±15.9</td>
<td>77.2±10.0</td>
</tr>
<tr>
<td>51.6 to 62.6</td>
<td>254/391</td>
<td>131.5±14.3</td>
<td>77.5±9.8</td>
</tr>
<tr>
<td>&gt;62.6</td>
<td>200/429</td>
<td>130.4±14.7</td>
<td>76.9±9.3</td>
</tr>
<tr>
<td>P for trend†</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>P for trend‡</td>
<td>&lt;0.01</td>
<td>NS</td>
<td>NS</td>
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Subjects not using blood pressure medication in 2008

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<tbody>
<tr>
<td></td>
<td>Systolic Blood Pressure, mm Hg*</td>
<td>Diastolic Blood Pressure, mm Hg*</td>
<td>Systolic Blood Pressure, mm Hg*</td>
</tr>
<tr>
<td>All 2385 subjects</td>
<td>137.8±17.2</td>
<td>78.4±10.7</td>
<td>147.7±26.3</td>
</tr>
<tr>
<td>&lt;41.4</td>
<td>114/231</td>
<td>132.6±15.9</td>
<td>77.2±10.0</td>
</tr>
<tr>
<td>41.4 to 51.5</td>
<td>153/244</td>
<td>131.5±14.3</td>
<td>77.5±9.8</td>
</tr>
<tr>
<td>51.6 to 62.6</td>
<td>167/250</td>
<td>130.4±14.7</td>
<td>76.9±9.3</td>
</tr>
<tr>
<td>&gt;62.6</td>
<td>137/308</td>
<td>130.4±14.7</td>
<td>76.9±9.3</td>
</tr>
<tr>
<td>P for trend†</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>P for trend‡</td>
<td>&lt;0.01</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>
change in systolic or diastolic blood pressures ($r = -0.018$ and $-0.012$, respectively). If using change in $z$ score for 25(OH)D, the corresponding correlations with change in blood pressure were $r = 0.004$ and $r = 0.017$, respectively. These associations did not improve in a multiple linear regression model with age, sex, and change in BMI as covariates (data not shown).

### Discussion

In the present study we have confirmed the cross-sectional association between serum 25(OH)D and blood pressure, but we did not find serum 25(OH)D to be a significant predictor of future hypertension, nor was there an association between change in serum 25(OH)D and change in blood pressure. To our knowledge the latter has not been reported before.

Regarding the cross-sectional relation between serum 25(OH)D and systolic blood pressure, this has convincingly been demonstrated by Scragg et al.\(^{13}\) in a study including 12,644 subjects. In their study, the difference in systolic blood pressure between those in the highest and lowest serum 25(OH)D quartiles was 3.0 mm Hg, which is almost identical to that reported by us. On the other hand, the association between serum 25(OH)D and diastolic blood pressure appears to be much weaker and not significant after adjustment for BMI in our study or in the studies by Scragg et al.\(^{13}\) and by Schmitz et al.\(^{16}\)

A further indication of a relation between serum 25(OH)D levels and blood pressure appeared from 2 recent publications by Forman et al.\(^{17,18}\) on serum 25(OH)D levels and risk of incident hypertension. In their study from 2007 that included 18,111 subjects with measured serum 25(OH)D values and 115,919 subjects with predicted 25(OH)D values, subjects with vitamin D deficiency had, during a follow-up period of 4 to 16 years, more than double the risk of developing hypertension compared with subjects with normal 25(OH)D levels. This was confirmed in a subsequent study in 2008 that included 14,848 women using a nested case-control design.\(^{18}\)

However, one important weakness of these 2 studies, as pointed out by the authors, was the lack of blood pressure measurements at baseline. As shown in our study, one of the strongest predictors of future hypertension is of course a high blood pressure at baseline, which, again, is strongly and inversely correlated to the serum 25(OH)D levels. Accordingly, among subjects that at baseline do not have a diagnosis of hypertension, those with a low serum 25(OH)D level will still have a higher blood pressure than those with a normal 25(OH)D level and, therefore, will be more likely to be diagnosed with hypertension at a later stage.

In contrast to the 2 studies by Forman et al.\(^{17,18}\) we did not find low serum 25(OH)D levels from 1994 to predict a later increase in blood pressure or the development of hypertension, regardless of how a low serum 25(OH)D level or

### Table 4. Development of Elevated Blood Pressure or Hypertension in 2008 According to Blood Pressure Category and Serum 25(OH)D Quartile in 1994

<table>
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<tr>
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</thead>
<tbody>
<tr>
<td>N % OR (95% CI)*</td>
<td>Elevated Blood Pressure and/or Hypertensive in 2008</td>
<td>Hypertensive in 2008</td>
<td>Hypertensive in 2008</td>
</tr>
<tr>
<td>&lt;41.4</td>
<td>532 35.2 1.01 (0.78 to 1.32)</td>
<td>250 55.6 1.22 (0.87 to 1.72)</td>
<td>28.4 1.15 (0.79 to 1.68)</td>
</tr>
<tr>
<td>41.4 to 51.5</td>
<td>599 33.7 1.06 (0.83 to 1.37)</td>
<td>318 52.2 1.12 (0.92 to 1.55)</td>
<td>27.4 1.15 (0.80 to 1.64)</td>
</tr>
<tr>
<td>51.6 to 62.6</td>
<td>625 33.3 1.12 (0.87 to 1.43)</td>
<td>333 53.8 1.17 (0.86 to 1.61)</td>
<td>26.1 1.10 (0.77 to 1.57)</td>
</tr>
<tr>
<td>&gt;62.6 (reference)</td>
<td>629 29.3 1.06 (0.80 to 1.39)</td>
<td>367 48.2 1.21 (0.88 to 1.67)</td>
<td>23.4 1.07 (0.74 to 1.57)</td>
</tr>
</tbody>
</table>

*OR indicates odds ratio.
*Covariates in logistic regression model include sex, age, BMI in 1994, and physical activity score in 1994.

### Table 5. Standardized $\beta$-Coefficients From Linear Regression Models With Systolic Blood Pressure in 2008 as the Dependent Variable

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
<th>Model 5</th>
<th>Model 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum 25(OH)D 1994, nmol/L*</td>
<td>-0.05†</td>
<td>-0.05†</td>
<td>-0.03</td>
<td>-0.02</td>
<td>-0.02</td>
<td>0.003</td>
</tr>
<tr>
<td>Sex (men: 1; women: 2)</td>
<td>-0.02</td>
<td>-0.05†</td>
<td>-0.05‡</td>
<td>-0.05‡</td>
<td>-0.05‡</td>
<td>-0.07§</td>
</tr>
<tr>
<td>Age 1994, y</td>
<td>0.33§</td>
<td>0.32‡</td>
<td>0.29‡</td>
<td>0.20§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI 1994, kg/m²</td>
<td>0.09§</td>
<td>0.08§</td>
<td>-0.01</td>
<td>-0.01</td>
<td></td>
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<tr>
<td>Physical activity score 1994</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure score 1994, mm Hg</td>
<td>0.042§</td>
<td></td>
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$r^2$ 0.01 0.01 0.11 0.12 0.12 0.27

*Data were adjusted for month of blood sampling with dummy variables.
†$P<0.05$.
‡$P<0.01$.
§$P<0.001$.
hypertension was defined. A reason for this discrepancy could be differences in study design, because we had measured blood pressure values both in 1994 and 2008, and on both occasions the examinations carried out and the questionnaires used were almost identical. In our analyses, we adjusted for relevant confounders like age, sex, BMI, season, and physical activity, after which any apparent trend for decreased risk of hypertension across increasing 25(OH)D quartiles became statistically nonsignificant. When baseline blood pressure from 1994 was included in the analysis, any relation between serum 25(OH)D and future blood pressure disappeared completely.

If there is a causal relation between serum 25(OH)D levels and blood pressure, a change in serum 25(OH)D levels should be accompanied by a change in blood pressure. This was not seen in our study, not even in a simple correlation analysis. One objection to this finding could be that we had only 2 time points. However, the high correlation between the serum 25(OH)D levels from 1994 and 2008 suggests that these serum values do give a fair indication of the individual’s vitamin D status.

Our results are, therefore, not in favor of a causal relation between serum 25(OH)D and blood pressure. However, there are many indications that vitamin D is involved in blood pressure regulation, the most important being the demonstration that 1,25-dihydroxyvitamin D inhibits the renin mRNA expression. This issue is unlikely to be solved by observational studies and has to be settled by randomized, placebo-controlled clinical intervention studies. So far, only a few such studies have been published, and a recent review found 8 studies that could be included in a meta-analysis. When these studies were combined, there appeared to be a significant reduction in diastolic blood pressure of 3.1 mm Hg in subjects given vitamin D compared with the placebo group and a nonsignificant reduction in systolic blood pressure of 3.6 mm Hg. The effect was more pronounced with unactivated than activated vitamin D, and the effect was only seen in subjects with elevated blood pressure at baseline. In line with this, Pilz et al also concluded in their review that most studies favor a lowering of arterial blood pressure by vitamin D but that more randomized, controlled trials are greatly needed.

Our study has some limitations. Although we included 2385 subjects in the longitudinal study, we cannot exclude that a larger number would have disclosed an association between serum 25(OH)D and future hypertension. Because the difference in systolic blood pressure between those in the highest and lowest serum 25(OH)D quartiles was only 3 mm Hg, and even if assuming that this difference was because of vitamin D alone, it is conceivable that any effect of vitamin D on the development of hypertension would be small. We only had 2 measurements of serum 25(OH)D and blood pressure. Preferably there should have been a series of measurements to truly see changes over time. We did not have a detailed food frequency questionnaire for the evaluation of vitamin D intake, nor did we have a measure of habitual solar exposure.

On the other hand, our study does have some strengths. We used measured 25(OH)D levels and not predicted ones, and we found a very strong relation between systolic blood pressure and serum 25(OH)D at baseline, which adds external validity to the results. We made adjustments for relevant confounders, and the observation time was long and similar in all of the subjects. In particular, we demonstrated the importance of measuring the blood pressure at baseline.

**Perspectives**

We were not able to find a relation between change in serum 25(OH)D levels and change in blood pressure nor that serum 25(OH)D levels predict future hypertension. To decide the importance of vitamin D and blood pressure, intervention studies should be performed. Because it is unlikely that vitamin D will have a marked blood pressure–reducing effect, it is important to include a large group of subjects and preferably subjects with increased blood pressure and low serum 25(OH)D levels. Considering the prevalence of vitamin D deficiency worldwide, even a modest effect on blood pressure would be of considerable clinical importance. Therefore, such studies should have a high priority in future vitamin D research.

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**Disclosures**

None.

**References**


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