Hypertension, Pulse, and Other Cardiovascular Risk Factors and Vitamin D Status in Finnish Men

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BACKGROUND
Debate exists about the relationship between hypovitaminosis D and cardiovascular (CVD) risk.

METHODS
This study investigated baseline (n = 2,271) 25-hydroxyvitamin D (25(OH)D) and baseline and 4 year (n = 1,957) CVD risk in a cohort of Finnish middle-aged male smokers.

RESULTS
The prevalences of measured hypertension, high pulse rate, diabetes, and coronary heart disease were 63%, 16%, 5%, and 10% at baseline and were 64%, 20%, 6%, and 16% at 4 years after baseline. The mean 25(OH)D was 41 ± 18 nmol/L. At baseline, systolic blood pressure ($\beta = -0.048$; $P = 0.02$), and pulse rate ($\beta = -0.043$; $P = 0.04$) were both associated with lower 25(OH)D levels but not coronary heart disease or diabetes prevalence. On remeasuring CVD risk 4 years after baseline, the only significant association with baseline 25(OH)D levels was high pulse rate ($\beta = -0.077$; $P = 0.001$). In addition, a higher 25(OH)D level at baseline was associated with a change in pulse rate ($\beta = -0.055$; $P = 0.01$). These trends for hypertension (baseline) and high pulse rate (baseline and 4 years after baseline) were also seen on adjusted categorical analysis ($P_{trend} < 0.05$).

CONCLUSIONS
Vitamin D deficiency at baseline was associated with hypertension in Finnish male smokers, but not after 4 years. These results are consistent with recent findings in other large cohort studies with measured blood pressure. Change in pulse rate over time continued to be significantly associated with lower 25(OH)D baseline levels; this new finding should be investigated further.

Keywords: blood pressure; coronary heart disease; diabetes; hypertension, pulse/heart rate; vitamin D status; 25(OH)D.

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Vitamin D is a steroid prohormone either synthesized in the skin after UV exposure or achieved through supplemental or dietary intake. Although there is strong evidence for its role in maintaining bone and muscle health, there has been recent debate[1] about the role of vitamin D deficiency in cardiovascular (CDV) conditions[2] based on conflicting results. Cross-sectional studies have consistently shown associations of hypertension with lower 25-hydroxyvitamin D (25(OH)D) baseline levels, but recent findings in large cohorts with measured rather than self-reported blood pressure have not found this association to be persistent over time.[3] To our knowledge, there have been no large, well-documented, prospective studies that have investigated measured hypertension and pulse rate (a measure of heart health) over time and compared this concurrently with coronary heart disease (CHD) and diabetes outcomes. As such, we investigated these relationships in a population of Finnish male middle-aged smokers with well-documented lifestyle, dietary, and medical data: the Alpha-Tocopherol and Beta-Carotene (ATBC) study cohort.[4]

Thus the aims of this study were to investigate the following:

1. The association between baseline 25(OH)D levels and measured blood pressure (systolic blood pressure (SBP) and diastolic blood pressure (DBP)) and pulse rate as well as diabetes and CHD prevalence measured at baseline. These measures were adjusted for confounding by lifestyle, medical conditions, and diet (n = 2,271).
2. The association between baseline 25(OH)D and measured blood pressure, pulse rate, diabetes, and CHD prevalence (n = 1,957) 4 years after baseline, with adjustment for confounding as above.

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3. The association between baseline 25(OH)D and change in measured blood pressure levels and pulse rates 4 years after baseline, with adjustment for confounding as above.

METHODS

All subjects were selected from the ATBC study, which was a randomized, double-blind, placebo-controlled primary prevention trial undertaken to determine whether supplementation with α-tocopherol, β-carotene, or both would reduce the incidence of lung and other cancers in male smokers. The rationale, design, and methods of the study, as well as the characteristics of the participants, have been described in detail previously.[4] The study subjects were male smoker control subjects, aged 50–69 years, residing in southwestern Finland (latitude 60°N–63°N). The exclusion criteria included history of cancer or other serious diseases; the use of vitamin E, vitamin A, or β-carotene supplements in excess of predefined doses; and treatment with anticoagulant agents.

A total of 2,271 study subjects had fasting serum samples collected only during the prerandomization baseline visit and stored at −70 °C (baseline). No other follow-up blood samples were collected in this cohort.

The hypovitaminosis rates and baseline predictors of 25(OH)D levels of this study population (n = 2,271) have also been previously described. These predictors are season, geographical location, physical activity, missing teeth, and fish and alcohol intake.[5]

Through baseline questionnaires, all study participants provided information on general characteristics, lifestyle (including smoking, alcohol intake, physical activity), and medical history on diabetes and heart disease (history of CHD and angina pectoris), all of which were self-reported, as well as usual dietary intake over the 12 months before enrollment, which was assessed by a self-administered comprehensive food frequency questionnaire. Dietary vitamin D intake was assessed from food sources and vitamin supplement intake. Nutrient intake was estimated through linkage with the food composition database of the Finnish National Public Health Institute. Height, weight, SBP and DBP, and pulse were measured by trained nurses at baseline and yearly for up to 9 years. Blood pressure was measured from the right arm with a mercury sphygmomanometer under standardized conditions. The lower of 2 measurements at least 1 minute apart was recorded.

The average annual dropout rate up to 4 years was 4%; thus at 4 years after baseline, data on CVD risk were available on the remaining 1,957 subjects.

The 4-year follow-up data on diabetes and CHD were based on hospital discharge records. Diagnoses of codes 410–414 from the International Classification of Diseases, 9th Revision were considered CHD. If participants had diabetes or CHD at baseline, they were considered as having the disease at the 4-year follow-up.[4] All serum 25(OH)D data from the cancer substudies of the original ATBC study were assayed using radioimmunoassay methods, with the exception of 1 substudy that also used the direct enzyme-linked immunosorbent assay kit (IDS, Boldon, Tyne and Wear, UK) and the recent multisite investigation that used a chemiluminescence assay (DiaSorin, Stillwater, MN). Intra- and inter-batch coefficients of variation for all assays ranged 5.3%–16.5% and 8.4%–16.5%, respectively.[5]

Statistical analysis

Hypertension was defined as measured SBP ≥ 140 mm Hg and DBP ≥ 90 mm Hg. High pulse/heart rate was defined as ≥ 84 beats/minute, as defined in the Framingham study.[6] Regression diagnostics were performed on all variables for both linear and categorical analyses. There were no significant interactions between 25(OH)D and CDV variables in these data.

In all analyses, age (years); education level; week of blood draw; laboratory of 25(OH)D assay; number of years smoked; number of cigarettes smoked per day; body mass index (kg/m^2); intakes of energy (kcal), alcohol, dietary D, and calcium; and CVD risk, as appropriate, were entered as confounders in adjusted models. In addition, further adjustment was made by known predictors of 25(OH)D in this population[5] (i.e., season, geographical location, physical activity, missing teeth, and fish and alcohol intake). Linear trends in the logistic regression analyses were assessed using the continuous values of the variable in a likelihood ratio test.[7] All statistical analyses were performed using the SPSS 16 statistical package (SPSS, Chicago, IL).

The study was approved by the institutional review boards of the US National Cancer Institute and the National Public Health Institute of Finland, with written informed consent obtained from each participant before randomization.

RESULTS

Forty-five percent of the population had 25(OH)D levels < 37 nmol/L, and 69% had levels < 50nmol/L. The mean baseline 25(OH)D level was 41 ± 18 nmol/L.[5] The prevalences of hypertension, high pulse rate, diabetes, and CHD were 63%, 16%, 5%, and 10%, respectively, at baseline and 64%, 20%, 6%, and 16%, respectively, 4 years after baseline. Baseline serum 25(OH)D level was significantly associated with SBP (β = −0.048; P = 0.02) and pulse rate (β = −0.043; P = 0.04) but not with DBP(β = −0.028; P = 0.19) in linear regression models. Similar associations between 25(OH)D levels and CDV factors after adjustment for confounding were seen when 25(OH)D levels were stratified as <25, ≥25–37, ≥37–50, ≥50–80, ≥80 nmol/L. In particular, significant trends for SBP (P_{trend} = 0.01) and pulse rate (P_{trend} = 0.04) were reported. Low baseline 25(OH)D levels were not significantly associated with diabetes or CHD at baseline (Table 1). When dietary vitamin D was used as the independent variable, no significant associations were found with any cardiovascular variable considered (data not shown).

Four years after baseline, there was no association found between baseline 25(OH)D levels and hypertension, CHD, or diabetes prevalence. In contrast, the association of 25(OH)D levels at baseline with high pulse rate (≥84 beats/minute) remained very significant after 4 years of follow-up

Table 1. Association between baseline vitamin D and blood pressure, pulse, diabetes, and coronary heart disease (CHD) at baseline (n = 2,271)

		High SBP ≥140 mm Hg (n = 1,224)		High DBP ≥90 mm Hg (n = 1,028)		High pulse ≥84 beats/minute (n = 334)		Hypertension SBP ≥140 or DBP ≥90 mm Hg (n = 1,427)		Diabetes (n = 104)		CHD (n = 222)	
		OR (95% CI)[a]	OR (95% CI)[b]	OR (95% CI)[a]	OR (95% CI)[b]	OR (95% CI)[a]	OR (95% CI)[b]	OR (95% CI)[a]	OR (95% CI)[b]	OR (95% CI)[a]	OR (95% CI)[b]	OR (95% CI)[a]	OR (95% CI)[b]
Baseline 25(OH)D, nmol/L	No.												
≥25	505	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
25 ≥ 37	517	0.9 (0.7–1.2)	1.0 (0.8–1.3)	1.1 (0.8–1.4)	1.1 (0.9–1.5)	0.7 (0.5–1.0)	0.7 (0.5–1.0)	0.9 (0.7–1.1)	1.0 (0.8–1.1)	1.3 (0.7–2.4)	1.2 (0.6–2.2)	0.6 (0.4–1.0)	0.6 (0.4–1.0)
37 ≥ 50	541	0.8 (0.6–1.0)	0.8 (0.6–1.0)	0.7 (0.6–0.9)	0.7 (0.6–1.0)	0.7 (0.5–0.9)	0.6 (0.4–0.9)	0.7 (0.6–1.0)	0.8 (0.6–1.0)	1.1 (0.6–1.9)	1.0 (0.5–2.0)	0.9 (0.6–1.3)	0.8 (0.5–1.2)
50 ≥ 80	560	0.7 (0.6–0.9)	0.7 (0.5–0.9)	0.9 (0.7–1.1)	0.9 (0.7–1.1)	0.7 (0.5–1.0)	0.7 (0.5–1.0)	0.7 (0.6–0.9)	0.8 (0.6–1.0)	1.0 (0.6–1.9)	1.0 (0.5–2.0)	1.2 (0.8–1.7)	1.2 (0.8–1.8)
≥80	148	0.8 (0.6–1.2)	0.8 (0.5–1.2)	0.8 (0.6–1.2)	0.9 (0.6–1.3)	0.7 (0.4–1.2)	0.7 (0.4–1.1)	0.7 (0.6–1.3)	0.9 (0.6–1.1)	1.1 (0.5–2.7)	1.2 (0.4–3.2)	0.9 (0.5–1.7)	0.8 (0.4–1.7)
P_{trend}		0.01	0.01	0.03	0.07	0.04	0.05	0.03	0.05	0.92	0.96	0.26	0.30

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; OR, odds ratio; SBP, systolic blood pressure; 25(OH)D, 25 hydroxyvitamin D.

[a]Crude OR and 95% CI (i.e., with no adjustment for confounding).

[b]Adjusted for age, education level, week of blood draw, laboratory of 25(OH)D analysis, number of years smoked, number of cigarettes smoked per day, alcohol intake, body mass index, and intakes of energy and calcium.

Table 2. Association between low baseline vitamin D and blood pressure, pulse, diabetes, and coronary heart disease (CHD) 4 years after baseline (n = 1,957)

		High SBP ≥140 mm Hg (n = 1,073)		High DBP ≥90 mm Hg (n = 731)		High pulse ≥84 beats/minute (n = 397)		Hypertension SBP ≥140 or DBP ≥90 mm Hg (n = 1,203)		Diabetes (n = 121)		CHD (n=306)	
		OR (95% CI)[a]	OR (95% CI)[b]	OR (95% CI)[a]	OR (95% CI)[b]	OR (95% CI)[a]	OR (95% CI)[b]	OR (95% CI)[a]	OR (95% CI)[b]	OR (95% CI)[a]	OR (95% CI)[b]	OR (95% CI)[a]	OR (95% CI)[b]
Baseline 25(OH)D, nmol/L	No.												
≥25	439	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
25 ≥ 37	451	1.1 (0.8–1.4)	1.2 (0.9–1.5)	0.9 (0.7–1.2)	0.8 (0.6–1.1)	0.8 (0.6–1.1)	0.8 (0.6–1.1)	1.1 (0.8–1.5)	1.2 (0.9–1.6)	1.1 (0.6–1.9)	1.0 (0.5–1.7)	0.9 (0.6–1.3)	0.9 (0.6–1.4)
37 ≥ 50	466	1.0 (0.8–1.3)	1.0 (0.7–1.3)	0.8 (0.6–1.1)	0.7 (0.6–1.0)	0.7 (0.5–0.9)	0.7 (0.5–1.0)	1.0 (0.8–1.3)	1.0 (0.7–1.3)	1.0 (0.6–1.7)	0.9 (0.5–1.6)	0.9 (0.7–1.4)	1.0 (0.6–1.4)
50 ≥ 80	470	0.9 (0.7–1.2)	0.9 (0.7–1.2)	0.8 (0.6–1.0)	0.7 (0.6–1.0)	0.6 (0.5–0.9)	0.7 (0.5–0.9)	0.9 (0.7–1.2)	0.9 (0.7–1.2)	0.9 (0.5–1.6)	0.9 (0.5–1.6)	1.0 (0.7–1.4)	1.1 (0.7–1.6)
≥80	131	1.0 (0.7–1.4)	0.9 (0.6–1.4)	0.7 (0.5–1.1)	0.7 (0.4–1.0)	0.6 (0.4–1.0)	0.6 (0.4–1.1)	1.1 (0.7–1.6)	1.0 (0.6–1.5)	1.0 (0.4–2.3)	1.0 (0.4–2.4)	1.1 (0.7–1.9)	1.3 (0.7–2.2)
P_{trend}		0.52	0.32	0.02	0.03	0.003	0.02	0.58	0.36	0.77	0.67	0.69	0.41

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; OR, odds ratio; SBP, systolic blood pressure; 25(OH)D, 25 hydroxyvitamin D.

[a]Crude OR and 95% CI (i.e., with no adjustment for confounding).

[b]Adjusted for age, education level, week of blood draw, laboratory of 25(OH)D analysis, number of years smoked, number of cigarettes smoked per day, alcohol intake, body mass index, and intakes of energy and calcium.

(Table 2). These categorical data at 4 years after baseline were also confirmed in linear regression analyses: pulse ($\beta = -0.077$; $P = 0.001$); SBP ($\beta = -0.009$; $P = 0.69$).

Similarly, when change in either SBP or DBP levels or pulse rate (4 years after baseline minus baseline values) was analyzed, only a higher 25(OH)D at baseline was associated with a reduced pulse rate ($\beta = -0.055$; $P = 0.01$) between baseline and 4 years after baseline: for every 18.2 nmol/L increase in serum 25(OH)D at baseline (which is equivalent to 1 SD of the 25(OH)D distribution), there was a decrease of 1 beat per minute in pulse 4 years after baseline.

DISCUSSION

Hypertension at baseline was associated with lower 25(OH)D levels in this population of middle-aged Finnish male smokers, but there was no significant association of hypertension at 4-year follow-up (with base-line 25(OH)D levels).

These baseline results were consistent with previous studies and meta-analyses that investigated associations between low 25(OH)D levels and hypertension cross-sectionally.[1–3] More important, this analysis did not find a statistically significant association between low 25(OH)D levels and hypertension at 4-year follow up, which is consistent with the 4 prospective studies that also found this lack of association.[3] Similar to this study, these studies all compared baseline 25(OH)D levels with measured blood pressure over time.[8–11] The only prospective studies that have reported an association between lower 25(OH)D levels at baseline and hypertension over time have based these results on self-reported rather than measured blood pressure and did not adjust for dietary vitamin D and many other lifestyle factors and comorbidities.[12,13] In addition, meta-analysis results from randomized control trials of 25(OH)D and hypertension have been null.[14]

Although hypertension was not associated with baseline 25(OH)D 4 years after baseline, it is pertinent that there was a very significant inverse relationship between 4-year pulse rate and baseline 25(OH)D. The only other known investigation of pulse/heart rate and hypovitaminosis[15] was conducted on 2 consecutive National Health and Nutrition Examination Survey (NHANES) cross-sectional data sets (NHANES lll and NHANES 2001–2006). This analysis showed similar associations of baseline 25(OH)D levels with hypertension and pulse rate with similar adjustment for confounding to our study (but no control for dietary factors). It should be noted that this NHANES analysis, although large and measured at 2 points in time, was not prospective (i.e., there was no follow-up of study subjects).

Thus, to our knowledge there have been no prospective studies investigating the association between change in pulse/heart rate over time and baseline 25(OH)D levels. Our findings of an association between low 25(OH)D levels and a high pulse rate are consistent with the results of 2 early small clinical trials that showed that vitamin D reduces heart rate.[16,17] Studies *in vivo* and *in vitro* have postulated mechanisms for vitamin D-mediated reduction of heart function that may have more to do with a direct effect on the heart, possibly through a negative correlation between vitamin D signalling in cardiomyocytes and sympathetic regulation of heart rate, than renoprotective effects that contribute to development of arterial hypertension.[15,18]

In contrast with our findings for CHD and diabetes, some previous epidemiological studies have found an association between low serum vitamin D and diabetes[19] and CHD prevalence and death.[20] However, as with the hypertension literature, the results of intervention trials with 25(OH)D have been inconclusive.[1,2,19,20] Our null findings for the association between 25(OH)D levels and CHD and diabetes risk may be because of the self-reported nature of the disease conditions at baseline or because of the low rates of these conditions in this population. There is an urgent need for large randomized control trials to clarify the conflicting literature for these conditions.

Important limitations of our study include lack of information on antihypertensive drug use and the reliance upon self-report of diabetes and CHD status at baseline. However, most studies that have used self-reported diabetes and CHD report good validation with medical reports. In addition, it could be hypothesized that at the time of this study's inception, very few Finnish persons took blood pressure medication (as was also reported in the Norwegian study that was conducted during a similar time period[9]).

We also acknowledge that in this analysis we do not have data on hours of sunlight per day, albumin, vitamin D binding protein, parathyroid hormone levels, and liver and renal function. However, when these existing data were adjusted for predictors of low 25(OH)D[5] (i.e., season, geographical location, physical activity, missing teeth, and fish and alcohol intake), there were no differences in the results. We cannot rule out possible reverse causality (i.e., men with greater CVD symptoms may be outdoors less for activity and sun UVB exposure, which would decrease their 25(OH)D)) or underlying medical conditions that were unmeasured and that may simultaneously lower 25(OH)D and increase pulse. The strengths of this study are that we were able to measure change in measured blood pressure and pulse over time and can relate this to baseline vitamin D status in a large cohort of men who have well-documented medical and lifestyle factors (including both diabetes and CHD risk).

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DISCLOSURE

The authors declared no conflict of interest.

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