Relation of Serum 25-Hydroxyvitamin D to Heart Rate and Cardiac Work (from the National Health and Nutrition Examination Surveys)†

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Vitamin D may protect against cardiovascular disease, but its association with cardiac function is unclear. The aim of this study was to examine the associations of serum 25-hydroxyvitamin D (25[OH]D) with heart rate, systolic blood pressure, and the rate–pressure product (RPP). Data analyses were carried out on 27,153 participants aged ≥20 years, with measurements of serum 25(OH)D, heart rate (from radial pulse), and systolic blood pressure, in the National Health and Nutrition Examination Surveys (NHANES) carried out from 1988 to 1994 and from 2001 to 2006. RPP was calculated as heart rate times systolic blood pressure. Results were adjusted for age, gender, race or ethnicity, body mass index, physical activity, tobacco smoking, co-morbidities, and blood pressure treatment. Compared to participants with 25(OH)D ≥35 ng/ml, the adjusted mean ± SE heart rate was significantly ($p < 0.001$) higher, by 2.1 ± 0.6 beats/min, in participants with 25(OH)D <10.0 ng/ml, while mean systolic blood pressure was 1.9 ± 0.8 mm Hg higher ($p < 0.05$) for participants with 25(OH)D <10.0 ng/ml and 1.7 ± 0.6 mm Hg higher ($p < 0.01$) for those with 25(OH)D of 10.0 to 14.9 ng/ml. As a consequence, adjusted mean RPP was 408 ± 110 beats/min · mm Hg higher ($p < 0.001$) for participants with 25(OH)D <10.0 ng/ml and 245 ± 80 beats/min · mm Hg higher ($p < 0.01$) for participants with 25(OH)D of 10.0 to 14.9 ng/ml, compared to those with 25(OH)D ≥35 ng/ml. In conclusion, these results show that low serum 25(OH)D levels are associated with increased heart rate, systolic blood pressure, and RPP and suggest that low vitamin D status may increase cardiac work. Vitamin D intervention studies are required to confirm these findings. **(Am J Cardiol 2010;105:122–128)**

Epidemiologic evidence is accumulating rapidly of an inverse association between vitamin D status and risk for cardiovascular disease. Recent cohort studies have shown that low baseline blood levels of 25-hydroxyvitamin D (25[OH]D) predict increased risk for cardiovascular disease[1–4] and confirmed earlier case control studies reporting inverse associations between serum 25(OH)D and myocardial infarction[5] and stroke.[6] The mechanisms for these inverse associations are still unclear. Receptors to 1,25-dihydroxyvitamin D have been identified in cardiac and vascular smooth muscle,[7,8] and animal studies have shown that vitamin D deficiency results in cardiac hypertrophy.[9] Hypertension also may be involved, as inverse associations have been observed between 25(OH)D levels and blood pressure.[10,11]

Because vitamin D affects cardiac and vascular function, we decided to examine in the National Health and Nutrition Examination Surveys (NHANES), which are representative samples of the US population, whether vitamin D status, as measured by serum 25(OH)D, is related to heart rate and also to the heart rate–systolic pressure product (RPP),[12] which is a measure of cardiac work and cardiac oxygen demand and is correlated with myocardial blood flow in healthy volunteers.[13,14] We included participants from NHANES III and NHANES 2001-2006 to assess consistency between the surveys and to increase the sample size so that we could do subgroup analyses of the association between serum 25(OH)D and measures of cardiovascular function.

Methods

The data reported in this paper come from NHANES III and NHANES 2001-2006, which are cross-sectional surveys representative of the US civilian noninstitutionalized population carried out by the National Center for Health Statistics of the Centers for Disease Control and Prevention from 1988 to 1994 and twice yearly from 2001 to 2006, respectively. A stratified, multistage sampling design was used to recruit participants from household clusters, with oversampling of non-Hispanic blacks and Mexican Americans. Participants were initially interviewed at home, before visiting mobile centers, where they underwent extensive physical examinations. Full details have been published of

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all survey methods, including sampling, interviews at home, examinations at mobile centers, laboratory measurements of blood samples, ethical approval, and informed consent.[15,16]

Participants were initially interviewed at home, where information was collected on a wide range of variables, including age, gender, race or ethnicity (self-assigned as non-Hispanic white, non-Hispanic black, Mexican American, or other). Participants were asked about current tobacco smoking, if they were currently taking prescribed medicines for high blood pressure, and the number of times a range of common physical activities were undertaken in leisure time during the previous month.[15,16] Metabolic equivalents were assigned for each physical activity, and participants aged ≥60 years were classified as doing moderate or vigorous activities if the metabolic equivalent for any activity was ≥3.0 or ≥6.0, respectively, while those aged 20 to 59 years were similarly classified if the metabolic equivalent for any activity was ≥3.5 or ≥7.0, respectively.[17]

Participants were defined as having cardiovascular disease if they reported that doctors had ever told them they had had heart attacks or strokes or if they had pain or discomfort in their chest consistent with angina defined by the Rose criteria (asked only of subjects aged ≥40 years in the 2001 to 2006 surveys)[18] and as having diabetes if they had ever been told by doctors that they had diabetes or were currently taking diabetes medications.

Physical measurements were carried out on most participants at mobile examination centers.[15,16] Participants were dressed in underpants and disposable light clothing and slippers while being weighed on electronic scales in pounds, which were converted to kilograms. Standing height was measured with a fixed stadiometer to the nearest millimeter. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Blood pressure was measured at the mobile examination centers by physicians with mercury sphygmomanometers using a standard protocol. Up to 3 blood pressure measurements were collected from each participant while in the sitting position and averaged after excluding the first measurement if >1 measurement was collected. Systolic blood pressure was defined as the point at which the first Korotkoff sound was heard, and diastolic blood pressure was the level of mercury 2 mm below the point at which the last sound was heard. Radial pulse was measured by physicians for 15 seconds and multiplied by 4 from 1988 to 1994 and for 30 seconds and multiplied by 2 from 2001 to 2006, to convert to beats per minute. Pulse rate (beats/min) and systolic blood pressure (mm Hg) were multiplied to calculate the RPP as an indirect measure of myocardial work.[12]

Blood samples collected during the examination were centrifuged, aliquoted, frozen to −70°C on site, and shipped on dry ice to central laboratories, where they were stored at −70°C until analysis.[15,16] Serum 25(OH)D was measured by a radioimmunoassay kit after extraction with acetonitrile (DiaSorin, Inc., Stillwater, Minnesota) by the National Center for Environmental Health of the Centers for Disease Control and Prevention (Atlanta, Georgia). Serum 25(OH)D concentrations ranged from 2.0 to 90.1 ng/mL after excluding 1 subject with value of 160.3 ng/ml.

A total of 16,573 adults from 1988 to 1994 and 14,542 from 2001 to 2006 aged ≥20 years attended mobile examination centers. Data in this report are restricted to 27,153 non-Hispanic white, non-Hispanic black, and Mexican-American adults aged ≥20 years who attended the mobile examination centers (n = 14,671 from 1988 to 1994 and n = 12,482 from 2001 to 2006), after excluding those of other races or ethnicities (n = 662 from 1988 to 1994 and n = 565 from 2001 to 2006), those who had no serum 25(OH)D measurements (n = 762 from 1988 to 1994 and n = 856 from 2001 to 2006) or very high serum 25(OH)D (n = 1 from 1988 to 1994), and those who did not have systolic blood pressure or pulse rate measurements (n = 477 from 1988 to 1994 and n = 639 from 2001 to 2006).

Table 1
Number and percentage of participants by level of demographic variables, body mass index, and leisure physical activity, for participants in National Health and Nutrition Examination Surveys, 1988 to 1994 and 2001 to 2006

Variable	NHANES		Both Surveys (n = 27,153)
	1988–1994 (n = 14,671)	2001–2006 (n = 12,482)	
Men	6,925 (47%)	6,051 (48%)	12,976
Women	7,746 (53%)	6,431 (52%)	14,177
Age (years)			
20–29	3,073 (21%)	2,409 (19%)	5,482
30–39	2,940 (20%)	2,084 (17%)	5,024
40–49	2,292 (16%)	2,146 (17%)	4,438
50–59	1,635 (11%)	1,612 (13%)	3,247
60–69	2,072 (14%)	1,825 (15%)	3,897
≥70	2,659 (18%)	2,406 (19%)	5,065
Race/ethnicity			
Non-Hispanic white	6,414 (44%)	6,867 (55%)	13,281
Non-Hispanic black	4,139 (28%)	2,507 (20%)	6,646
Mexican	4,118 (28%)	3,108 (25%)	7,226
Body mass index (kg/m^2)			
<25	5,720 (39%)	3,753 (31%)	9,473
25–29	5,163 (35%)	4,408 (36%)	9,571
≥30	3,758 (26%)	4,035 (33%)	7,793
Physical activity (times/month)			
Inactive	3,255 (22%)	5,282 (42%)	8,537
Moderate (1–11)	4,095 (28%)	1,642 (13%)	5,737
Moderate (≥12)	5,064 (35%)	2,067 (17%)	7,131
Vigorous (1–11)	1,471 (10%)	1,568 (13%)	3,039
Vigorous (≥12)	786 (5%)	1,923 (15%)	2,709
Smoking status			
Never	7,172 (49%)	6,351 (53%)	13,523
Ex-smoker	3,701 (25%)	3,351 (28%)	7,052
≤19 cigarettes/day	2,135 (15%)	1,233 (10%)	3,368
≥20 cigarettes/day	1,593 (11%)	1,015 (8%)	2,608
Serum 25(OH)D (ng/ml)			
<10.0	549 (4%)	1,019 (8%)	1,568
10.0–14.9	1,783 (12%)	1,894 (15%)	3,677
15.0–19.9	2,676 (18%)	2,378 (19%)	5,054
20.0–24.9	2,686 (18%)	2,656 (21%)	5,342
25.0–29.9	2,372 (16%)	2,215 (18%)	4,587
30.0–34.9	1,918 (13%)	1,236 (10%)	3,154
≥35.0	2,687 (18%)	1,084 (9%)	3,771
Cardiovascular disease*	1,321 (15%)	1,145 (14%)	2,466
Diabetes mellitus	1,219 (8%)	1,239 (10%)	2,458
Blood pressure medication	2,383 (16%)	2,882 (23%)	5,265

* For participants aged ≥40 years.

Table 2
Mean differences in measures of cardiovascular function among categories of 25-hydroxyvitamin D, compared to reference category (≥35.0 ng/ml), for participants aged ≥20 years in the National Health and Nutrition Examination Survey, 1988 to 1994 and 2001 to 2006, adjusted for age, gender, and race or ethnicity

Variable and Survey Period	25(OH)D Category (ng/ml)							p Value (Wald's F)
	<10.0	10.0–14.9	15.0–19.9	20.0–24.9	25.0–29.9	30.0–34.9	≥35.0 Reference	
	Difference (vs 25[OH]D ≥35.0 ng/ml)							
Heart rate (beats/min)								
1988–1994	3.0 ± 0.8§	1.8 ± 0.5‡	0.9 ± 0.4	0.6 ± 0.4	0.2 ± 0.4	0.1 ± 0.4	73.9 ± 0.4	0.0023
2001–2006	3.0 ± 0.5§	2.3 ± 0.4§	1.5 ± 0.5‡	0.2 ± 0.4	−0.2 ± 0.6	0.4 ± 0.6	71.6 ± 0.4	<0.0001
Both periods*	3.0 ± 0.4§	2.0 ± 0.4§	1.1 ± 0.3§	0.4 ± 0.3	0.01 ± 0.3	0.3 ± 0.3	72.8 ± 0.3	<0.0001
Systolic blood pressure (mm Hg)								
1988–1994	2.8 ± 0.8§	1.8 ± 0.6‡	1.5 ± 0.5‡	1.4 ± 0.4‡	0.4 ± 0.6	0.1 ± 0.6	125.3 ± 0.4	0.0007
2001–2006	3.7 ± 0.9§	3.5 ± 0.7§	1.5 ± 0.7†	0.9 ± 0.6	0.7 ± 0.6	−0.01 ± 0.7	123.3 ± 0.5	<0.0001
Both periods*	3.3 ± 0.6§	2.3 ± 0.4§	1.2 ± 0.4‡	0.9 ± 0.4†	0.4 ± 0.4	−0.04 ± 0.4	124.6 ± 0.3	<0.0001
Rate-pressure product (beats/min · mm Hg)								
1988–1994	574 ± 113§	366 ± 86§	233 ± 70‡	178 ± 68†	64 ± 72	27 ± 72	9,267 ± 61	0.0001
2001–2006	674 ± 83§	566 ± 63§	318 ± 65§	110 ± 64	39 ± 64	62 ± 84	8,776 ± 53	<0.0001
Both periods*	629 ± 68§	434 ± 56§	247 ± 50§	125 ± 49†	32 ± 51	42 ± 56	9,058 ± 45	<0.0001

Data are expressed as mean ± SE.
* Also adjusted for survey period.
† $p < 0.05$, ‡ $p < 0.01$, and § $p < 0.001$ versus reference category (25[OH]D ≥35 ng/ml).

Table 3
Mean differences in heart rate among categories of 25-hydroxyvitamin D, compared with reference category (≥35.0 ng/ml), for participants aged ≥20 years in the National Health and Nutrition Examination Surveys, 1988 to 1994 and 2001 to 2006, adjusted for age, gender, race or ethnicity, and survey period, by subgroups*

Variable	25(OH)D Category (ng/ml)							p Value (Wald's F)
	<10.0	10.0–14.9	15.0–19.9	20.0–24.9	25.0–29.9	30.0–34.9	≥35.0 Reference	
	Difference in Heart Rate vs 25(OH)D ≥35.0 ng/ml (beats/min)							
Age (years)								
20–39	1.9 ± 0.6‡	1.8 ± 0.5§	0.7 ± 0.5	0.6 ± 0.5	0.3 ± 0.4	0.5 ± 0.5	73.4 ± 0.4	0.0043
40–59	5.1 ± 0.8§	3.2 ± 0.7§	2.2 ± 0.6§	1.0 ± 0.6	0.6 ± 0.6	0.3 ± 0.6	72.5 ± 0.5	<0.0001
≥60	2.8 ± 0.8§	1.6 ± 0.6‡	1.0 ± 0.5†	0.1 ± 0.4	−0.4 ± 0.4	0.1 ± 0.5	72.1 ± 0.4	0.0005
Race/ethnicity								
Non-Hispanic white	3.6 ± 0.9§	3.3 ± 0.6§	1.9 ± 0.4§	0.8 ± 0.4†	0.7 ± 0.3†	0.8 ± 0.4	72.7 ± 0.3	<0.0001
Non-Hispanic black	2.5 ± 0.7§	1.3 ± 0.7	0.2 ± 0.6	−0.8 ± 0.7	−0.4 ± 0.7	−0.5 ± 0.9	73.2 ± 0.6	<0.0001
Mexican American	1.1 ± 0.9	0.3 ± 0.5	−0.02 ± 0.5	−0.03 ± 0.5	−1.6 ± 0.6‡	−0.7 ± 0.6	73.6 ± 0.5	0.0002
Body mass index (kg/m^2)								
<25	3.6 ± 0.7§	2.2 ± 0.5§	1.4 ± 0.5‡	0.7 ± 0.4	−0.4 ± 0.4	0.3 ± 0.5	72.1 ± 0.3	<0.0001
25–29	1.3 ± 0.7	0.7 ± 0.5	0.1 ± 0.5	−1.0 ± 0.5	−0.8 ± 0.4†	−0.4 ± 0.5	72.9 ± 0.4	0.0030
≥30	1.8 ± 0.8†	0.8 ± 0.7	−0.1 ± 0.6	0.02 ± 0.7	0.2 ± 0.7	−0.01 ± 0.8	75.5 ± 0.6	0.039
Physical activity								
Inactive	1.2 ± 0.6	0.2 ± 0.5	0.3 ± 0.5	−0.9 ± 0.5	−1.5 ± 0.5‡	−0.5 ± 0.6	75.0 ± 0.5	<0.0001
Moderate	2.6 ± 0.8‡	1.5 ± 0.5‡	0.1 ± 0.4	0.2 ± 0.4	−0.03 ± 0.4	0.2 ± 0.4	73.9 ± 0.4	0.0071
Vigorous	2.9 ± 1.0‡	2.8 ± 0.7§	1.7 ± 0.6‡	0.8 ± 0.5	0.6 ± 0.5	0.4 ± 0.6	69.5 ± 0.4	<0.0001
Smoker								
Never	2.9 ± 0.5§	2.1 ± 0.5§	1.3 ± 0.4§	0.6 ± 0.4	0.3 ± 0.4	0.1 ± 0.4	72.7 ± 0.3	<0.0001
Former	3.0 ± 0.8§	2.0 ± 0.7‡	0.9 ± 0.6	−0.02 ± 0.6	−0.2 ± 0.6	0.4 ± 0.6	72.2 ± 0.5	0.0011
Present	3.1 ± 0.8§	1.6 ± 0.7†	1.1 ± 0.6	1.0 ± 0.6	0.1 ± 0.6	1.0 ± 0.7	73.8 ± 0.5	0.0067
Cardiovascular disease (age ≥40 years)	3.8 ± 1.4‡	1.9 ± 1.1	3.1 ± 1‡	1.8 ± 1.0	0.2 ± 0.9	0.3 ± 1.2	71.1 ± 0.9	0.0027
Diabetes	3.6 ± 1.2‡	1.8 ± 1.1	2.6 ± 1.1†	1.1 ± 1.1	1.5 ± 1.2	0.9 ± 1.2	74.4 ± 0.9	0.0098
Blood pressure medication	3.7 ± 1.0§	1.5 ± 0.8†	1.8 ± 0.6‡	0.3 ± 0.6	0.3 ± 0.6	0.1 ± 0.7	71.8 ± 0.5	0.0002

Data are expressed as mean ± SE.
* See Table 1 for number of participants in each subgroup.
† $p < 0.05$, ‡ $p < 0.01$, and § $p < 0.001$ versus reference category (25[OH]D ≥35 ng/ml).

Statistical analyses were carried out using SUDAAN version 10.0.0 (RTI International, Research Triangle Park, North Carolina) to correct standard errors for any design effect arising from clustered sampling. Sampling weights were not used in analyses to weight up to the US population, because data from 4 NHANES random samples were com-

Table 4
Mean difference in rate–pressure product between categories of 25-hydroxyvitamin D, compared to reference category (≥35.0 ng/ml), for participants aged ≥20 years in the National Health and Nutrition Examination Survey, 1988 to 1994 and 2001 to 2006, adjusted for age, gender, race or ethnicity, and survey period, by subgroups*

Variable	25(OH)D Category (ng/ml)							p Value (Wald's F)
	<10.0	10.0–14.9	15.0–19.9	20.0–24.9	25.0–29.9	30.0–34.9	≥35.0 Reference	
	Difference in RPP vs 25(OH)D ≥35.0 ng/ml (beats/min · mm Hg)							
Age (years)								
20–39	493 ± 89§	419 ± 68§	221 ± 63§	156 ± 68†	112 ± 59	89 ± 63	8,279 ± 54	<0.0001
40–59	919 ± 127§	679 ± 113§	463 ± 101§	255 ± 92‡	167 ± 97	108 ± 109	8,909 ± 75	<0.0001
≥60	607 ± 154§	359 ± 112‡	179 ± 90†	69 ± 93	−89 ± 90	−20 ± 98	10,023 ± 76	<0.0001
Race/ethnicity								
Non-Hispanic white	688 ± 134§	666 ± 97§	370 ± 67§	223 ± 62§	155 ± 62†	103 ± 71	9,105 ± 57	<0.0001
Non-Hispanic black	552 ± 128§	333 ± 118‡	143 ± 117	−31 ± 128	−46 ± 136	30 ± 175	9,146 ± 104	<0.0001
Mexican American	477 ± 139§	247 ± 92‡	132 ± 83	64 ± 80	−150 ± 99	−58 ± 96	8,935 ± 82	<0.0001
Body mass index (kg/m^2)								
<25	596 ± 118§	337 ± 87§	183 ± 73†	132 ± 77	−23 ± 62	−4 ± 70	8,730 ± 50	<0.0001
25–29	298 ± 120†	185 ± 78†	66 ± 77	−138 ± 77	−124 ± 74	−71 ± 87	9,223 ± 65	0.0003
≥30	448 ± 132‡	277 ± 120†	46 ± 106	56 ± 114	−49 ± 134	−16 ± 135	9,607 ± 104	0.0001
Physical activity								
Inactive	414 ± 120§	210 ± 98†	185 ± 96	−79 ± 97	−170 ± 91	−47 ± 106	9,481 ± 85	<0.0001
Moderate	540 ± 120§	345 ± 77§	103 ± 67	146 ± 67†	28 ± 70	37 ± 73	9,223 ± 57	<0.0001
Vigorous	565 ± 154§	487 ± 100§	230 ± 92†	85 ± 80	82 ± 83	13 ± 87	8,374 ± 62	<0.0001
Smoker								
Never	647 ± 93§	459 ± 70§	271 ± 58§	149 ± 64†	93 ± 67	22 ± 71	8,968 ± 54	<0.0001
Former	722 ± 159§	368 ± 109‡	195 ± 97†	68 ± 94	−65 ± 93	47 ± 101	9,325 ± 76	<0.0001
Present	567 ± 117§	497 ± 99§	313 ± 97‡	211 ± 90†	92 ± 92	167 ± 100	8,938 ± 92	<0.0001
Cardiovascular disease (≥40 years)	589 ± 232†	305 ± 206	528 ± 199‡	212 ± 183	−61 ± 181	13 ± 230	9,702 ± 162	0.0031
Diabetes	546 ± 237†	333 ± 186	355 ± 175†	108 ± 174	103 ± 196	53 ± 189	10,050 ± 146	0.032
Blood pressure medication	539 ± 190‡	292 ± 145†	176 ± 113	−41 ± 122	−122 ± 121	−50 ± 136	10,115 ± 101	0.0005

Data are expressed as mean ± SE.
* See Table 1 for number of participants in each subgroup.
† $p < 0.05$, ‡ $p < 0.01$, and § $p < 0.001$ versus reference category (25[OH]D ≥35 ng/ml).

bined. PROC CROSSTAB was used to compare distributions of categorical variables, and PROC REGRESS was used to calculate adjusted means and mean differences between subgroups.

Results

Table 1 lists the distribution of variables for demographic status, BMI, lifestyle, medical disease status, and serum 25(OH)D septile by NHANES survey period. Compared to the 1988 to 1994 survey, participants in the 2001 to 2006 survey were older and more likely to have BMIs ≥30 kg/m^2, to report doing vigorous physical activity, to have diabetes, and to be taking blood pressure medications but less likely to smoke tobacco. Participants in the 2001 to 2006 surveys were distributed more toward the low vitamin D categories compared to those in the 1988 to 1994 survey ($p < 0.0001$). However, there was no difference between survey periods in the proportion who were male or had cardiovascular disease.

Table 2 lists mean levels of cardiovascular function by septile of 25(OH)D, adjusted for age, gender, and race or ethnicity, for each NHANES survey period and for the 2 periods combined. Pulse rate and systolic blood pressure each increased with decreasing vitamin D level for each survey period. As a consequence, the RPP also increased in a stepwise fashion as vitamin D decreased within each survey period, so the adjusted mean value for the lowest vitamin D category (<10 ng/ml) was 629 beats/min · mm Hg higher compared to that for the highest vitamin D category (≥35 ng/ml) for the combined survey periods. These associations remained significant ($p < 0.05$) in the NHANES III data (1988 to 1994) after also adjusting for season (data not shown). Similar adjustment of the 2001 to 2006 data was not possible because month of interview has not been released publically.

Subgroup analyses were carried out to determine the consistency of the inverse association between vitamin D status, adjusting for demographic variables, and survey period. Significant (Wald's F $p < 0.05$) inverse associations between 25(OH)D category and pulse rate occurred in all subgroup levels for age, ethnicity, BMI, leisure physical activity, and tobacco smoking and among participants with cardiovascular disease, those with diabetes, and those who were receiving treatment for hypertension, although there appeared to be a reverse J-shaped association among Mexican Americans (Table 3). Significant inverse associations between 25(OH)D category and RPP were also seen in all subgroups (Table 4), with participants in the lowest 25(OH)D septile (<10.0 ng/ml) consistently having significantly higher RPPs ($p < 0.05$) than those in the highest septile (≥35.0 ng/ml). The inverse association between vitamin D and systolic blood pressure was less consistent and

Table 5
Mean measurements of cardiovascular function for participants aged ≥40 years in the National Health and Nutrition Examination Survey, 1988 to 1994 and 2001 to 2006, by level of lifestyle risk factor, adjusted for age, gender, race or ethnicity, survey period, cardiovascular disease, diabetes, hypertension treatment, and other variables in table (n = 15,932)

Lifestyle Risk Factor	n	Pulse Rate (beats/minute)		Systolic Blood Pressure (mm Hg)		RPP (beats/min · mm Hg)	
		Mean	Difference	Mean	Difference	Mean	Difference
25(OH)D (ng/mL)							
<10.0	894	75.2 ± 0.5	2.1 ± 0.6§	134.2 ± 0.7	1.9 ± 0.8†	10,078 ± 93	408 ± 110§
10.0–14.9	2,090	74.0 ± 0.3	0.9 ± 0.4	134.1 ± 0.5	1.7 ± 0.6‡	9,916 ± 56	245 ± 80‡
15.0–19.9	2,998	73.6 ± 0.3	0.5 ± 0.4	132.6 ± 0.4	0.3 ± 0.5	9,762 ± 47	92 ± 69
20.0–24.9	3,272	72.9 ± 0.2	−0.2 ± 0.4	132.6 ± 0.4	0.3 ± 0.5	9,670 ± 45	−0.1 ± 63
25.0–29.9	2,791	72.6 ± 0.3	−0.5 ± 0.4	131.9 ± 0.4	−0.4 ± 0.6	9,570 ± 41	−100 ± 68
30.0–34.9	1,854	73.0 ± 0.4	−0.1 ± 0.4	131.8 ± 0.5	−0.5 ± 0.6	9,629 ± 65	−42 ± 68
≥35.0*	2,033	73.1 ± 0.3	0	132.3 ± 0.4	0	9,670 ± 54	0
Body mass index (kg/m†)							
<25*	4,975	72.6 ± 0.2	0	130.9 ± 0.3	0	9,493 ± 43	0
25–29	6,117	72.7 ± 0.2	0.1 ± 0.2	133.0 ± 0.3	2.1 ± 0.4§	9,659 ± 39	166 ± 48§
≥30	4,840	74.8 ± 0.2	2.2 ± 0.3§	134.0 ± 0.3	3.1 ± 0.4§	10,017 ± 35	524 ± 48§
Physical activity (times/month)							
Inactive*	5,519	74.5 ± 0.2	0	133.3 ± 0.3	0	9,923 ± 40	0
Moderate (1–11)	3,305	73.8 ± 0.3	−0.7 ± 0.3†	133.0 ± 0.3	−0.3 ± 0.4	9,809 ± 48	−114 ± 47†
Moderate (≥12)	4,630	72.7 ± 0.2	−1.8 ± 0.3§	132.2 ± 0.3	−1.1 ± 0.5†	9,602 ± 39	−320 ± 52§
Vigorous (1–11)	1,198	71.7 ± 0.4	−2.8 ± 0.4§	131.6 ± 0.6	−1.7 ± 0.6‡	9,465 ± 67	−457 ± 77§
Vigorous (≥12)	1,280	70.3 ± 0.3	−4.2 ± 0.4§	131.8 ± 0.5	−1.5 ± 0.5‡	9,282 ± 53	−641 ± 60§
Tobacco Smoking							
Never smoker*	7,326	72.8 ± 0.2	0	133.0 ± 0.3	0	9,688 ± 36	0
Ex-smoker	5,479	73.1 ± 0.2	0.3 ± 0.2	132.1 ± 0.3	−1.0 ± 0.4†	9,649 ± 36	−39 ± 41
≤19 cigarettes/day	1,560	73.9 ± 0.3	1.1 ± 0.4‡	132.6 ± 0.6	−0.5 ± 0.6	9,782 ± 60	95 ± 63
≥20 cigarettes/day	1,567	75.7 ± 0.4	3.0 ± 0.4§	133.1 ± 0.5	0.03 ± 0.5	10,062 ± 69	374 ± 67§

Data are expressed as mean ± SE.
* Reference group.
† $p < 0.05$, ‡ $p < 0.01$, and § $p < 0.001$ versus reference group.

was not significant ($p > 0.05$) in some subgroups (participants with cardiovascular disease or diabetes, those taking blood pressure medication, and those with BMIs <30 kg/m^2; data not shown).

Table 5 lists mean levels of measures of cardiovascular function by septile of serum 25(OH)D and other lifestyle variables associated with cardiovascular function (BMI, leisure physical activity, and tobacco smoking) from fully adjusted multivariate models that contained all of these variables plus demographic, disease (cardiovascular and diabetes), and hypertension treatment variables. These analyses were restricted to participants aged ≥40 years who had full information on all variables, including cardiovascular disease. Adjusted mean pulse rate was significantly ($p < 0.001$) higher, by 2.1 beats/min, in participants with 25(OH)D levels <10.0 ng/ml compared to those with levels ≥35 ng/ml, while mean systolic blood pressure was significantly ($p < 0.05$) higher in participants with 25(OH) levels <15 ng/ml compared to the highest vitamin D group. As a consequence, mean RPP was significantly higher ($p < 0.01$) for participants with 25(OH)D levels <15 ng/ml compared to those with levels ≥35 ng/ml. The adjusted mean RPP for participants with 25(OH)D <10 ng/ml (10,078 beats/min · mm Hg) was similar to that for participants with BMIs ≥30 kg/m^2 (10,017 beats/min · mm Hg) and that smoking ≥20 cigarettes per day (10,062 beats/min · mm Hg). The adjusted mean difference in RPP between the highest and lowest vitamin D categories (408 beats/min · mm Hg) was similar to that between the highest and lowest tobacco-smoking categories (374 beats/min · mm Hg), although smaller than the difference between the highest and lowest categories for BMI (524 beats/min · mm Hg) and physical activity (641 beats/min · mm Hg).

Discussion

We have shown that low vitamin D status is associated with increased heart rate, systolic blood pressure, and RPP (a measure of cardiac work), adjusting for covariates, in large cross-sectional surveys representative of the US population. The inverse association between vitamin D status and RPP was observed in all age groups ≥20 years and in all 3 racial and ethnic groups (non-Hispanic whites, non-Hispanic blacks, and Mexican Americans).

The finding of an inverse association between vitamin D status and heart rate is consistent with the results of 2 clinical trials showing that vitamin D reduces heart rate.[19,20] This suggests that vitamin D may have a direct effect on the heart, possibly through a negative correlation between vitamin D signaling in cardiomyocytes and sympathetic system regulation of heart rate. This is supported by evidence that 1,25-dihydroxyvitamin D_3 regulates the production of tyrosine hydroxylase, the rate-limiting enzyme in the catecholamine biosynthetic pathway, and raises the possibility that the vitamin D hormonal system may modulate functions of the peripheral and central catecholaminergic sys-

tem.[21] A direct effect of vitamin D on cardiac function is supported by echocardiographic studies in humans showing that vitamin D increases diastolic and end-systolic diameter and increases fractional fiber shortening[22,23] and by animal evidence showing that vitamin D deficiency alters heart morphology and adversely affects cardiac function.[9] Furthermore, the inverse association between vitamin D status and systolic blood pressure, seen in both survey periods (Table 2) and previously reported for NHANES III,[11] suggests that vitamin D also affects vascular function and is consistent with clinical research showing that vitamin D beneficially influences vascular resistance and endothelial function.[24]

The inverse association between vitamin D status and RPP, which does not appear to have been described previously, suggests that vitamin D deficiency may increase cardiac work and cardiac oxygen demand, because studies in healthy human volunteers have shown that RPP is correlated with myocardial blood flow.[13,14] The increased RPP value seen in smokers (Table 5) is consistent with previous studies reporting higher values in smokers[25] or from taking nicotine[26] and suggests that the RPP measure of cardiac work in the NHANES samples is valid. Although the mean differences in RPP among 25(OH)D categories are relatively small, they are similar in size to those among categories of other cardiovascular risk factors, particularly tobacco smoking (Table 5), suggesting that they are biologically relevant.

A previous cohort study of coronary patients in Italy, which found that RPP at rest is inversely associated with survival, may not be applicable to healthy subjects, because measurements in the Italian study were collected after myocardial infarctions and before discharge, when patients were recuperating.[27] Another cohort study of patients referred for exercise testing found that RPP did not predict cardiovascular mortality.[28] However, in healthy subjects, because heart rate[29] and systolic blood pressure[30] predict cardiovascular mortality, it is probable that their product, the RPP measure, will also predict mortality.

Thus, our findings are likely to have clinical and public health significance. Adjusted mean pulse rates and RPP measures for subjects with serum 25(OH)D levels <10.0 ng/ml were similar for those who smoked ≥ 20 cigarettes per day, were inactive, or had BMIs ≥ 30 kg/m^2 (Table 5). In subjects with previous cardiovascular disease, those with serum 25(OH)D levels <20.0 ng/ml had increased heart rates and RPP values compared with those with levels ≥ 35 ng/ml (Tables 3 and 4). Final multivariate models showed increased RPP values in participants with 25(OH)D levels <15.0 ng/ml (Table 5). Data from the latest available NHANES surveys (2001 to 2006), weighted for sampling probabilities, indicate that a substantial proportion of the US population aged ≥ 20 years (56% of non-Hispanic blacks, 25% of Mexican Americans, and 10% of non-Hispanic whites) have 25(OH)D levels <15.0 ng/ml.

Our study had some limitations. There may have been drift in the laboratory assays of 25(OH)D between the 2 6-year survey periods, although any effect from this will have been minimized by adjusting for survey period in our analyses. The measurements of pulse rate, systolic blood pressure, and serum 25(OH)D were made on a single occasion for each participant. This is likely to have resulted in measurement error, which, if random, is likely to have weakened observed associations between cardiovascular function and vitamin D status. The RPP value is derived from heart rate and systolic blood pressure rather than a direct measure of cardiac work and myocardial blood flow. Another limitation was the cross-sectional study design, which could not separate cause and effect. It is possible that another lifestyle variable (besides physical activity and obesity) associated with vitamin D status was confounding the association between vitamin D and cardiac function, although the consistency of the inverse associations of serum 25(OH)D with heart rate and RPP across all subgroups (Tables 3 and 4) suggests that this is unlikely.

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