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Original Contribution

Correlates of Circulating 25-Hydroxyvitamin D

Cohort Consortium Vitamin D Pooling Project of Rarer Cancers

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Low vitamin D status is common globally and is associated with multiple disease outcomes. Understanding the correlates of vitamin D status will help guide clinical practice, research, and interpretation of studies. Correlates of circulating 25-hydroxyvitamin D (25(OH)D) concentrations measured in a single laboratory were examined in 4,723 cancer-free men and women from 10 cohorts participating in the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers, which covers a worldwide geographic area. Demographic and lifestyle characteristics were examined in relation to 25(OH)D using stepwise linear regression and polytomous logistic regression. The prevalence of 25(OH)D concentrations less than 25 nmol/L ranged from 3% to 36% across cohorts, and the prevalence of 25(OH)D concentrations less than 50 nmol/L ranged from 29% to 82%. Seasonal differences in circulating 25(OH)D were most marked among whites from northern latitudes. Statistically significant positive correlates of 25(OH)D included male sex, summer blood draw, vigorous physical activity, vitamin D intake, fish intake, multivitamin use, and calcium supplement use. Significant inverse correlates were body mass index, winter and spring blood draw, history of diabetes, sedentary behavior, smoking, and black race/ethnicity. Correlates varied somewhat within season, race/ethnicity, and sex. These findings help identify persons at risk for low vitamin D status for both clinical and research purposes.

body mass index; cohort studies; diet; dietary supplements; ethnic groups; exercise; seasons; vitamin D

Abbreviations: ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CPS-II, Cancer Prevention Study II Nutrition Cohort; HPFS, Health Professionals Follow-up Study; MEC, Multiethnic Cohort Study; NHS, Nurses' Health Study; NYU-WHS, New York University Women's Health Study; 25(OH)D, 25-hydroxyvitamin D; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; SMHS, Shanghai Men's Health Study; SWHS, Shanghai Women's Health Study; VDPP, Cohort Consortium Vitamin D Pooling Project of Rarer Cancers.

Vitamin D has established benefits for bone health and may play a preventive role in other major diseases (1), but questions persist about what constitutes optimal vitamin D status. Substantial segments of the population in the United States and globally have low vitamin D concentrations (2). Thus, it is important to understand what factors contribute to concentrations of 25-hydroxyvitamin D (25(OH)D), the major circulating metabolite of vitamin D and indicator of vitamin D status.

The major sources of circulating 25(OH)D include exposure to ultraviolet radiation (ultraviolet B, 280–315 nm) and dietary and supplemental vitamin D intake. Additional

constitutional and behavioral factors can further influence 25(OH)D status in various populations. Investigators in multiple studies have used statistical modeling to examine the relative contribution of endogenous and exogenous factors to variation in circulating 25(OH)D levels (2–26), and results from many of these studies were summarized in a 2008 International Agency for Research on Cancer report on vitamin D and cancer (27). Many studies were either small and/or lacked diversity by geographic location, age, sex, or race/ethnicity, precluding examination of a broad range of determinants according to specific subpopulations such as race/ethnicity and season of blood collection. For example, approximately half of the studies involved European countries at latitudes greater than or equal to 50°N, which is further north than anywhere in the continental United States (2–5, 8–9, 12–16, 24, 26).

In this report, we examine the correlates of circulating 25(OH)D in the large control population of the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers (VDPP). This is a geographically and demographically diverse group of men and women, including participants from US, Finnish, and Chinese cohort studies, with information on numerous factors affecting vitamin D status.

MATERIALS AND METHODS

Study design and population

Study subjects included 4,723 control participants (2,588 female and 2,135 male) from the VDPP (28). Briefly, investigators in the VDPP assayed serum or plasma samples collected prospectively in 1974–2006 for 25(OH)D and examined its association with 6 cancers (endometrial, gastric/esophageal, kidney, ovarian, pancreatic, and non-Hodgkin lymphoma), using a matched nested case-control design (28). The cohorts included in the present analysis were the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC), the Cancer Prevention Study II Nutrition Cohort (CPS-II), CLUE II (named for the slogan ''Give us a Clue to Cancer and Heart Disease''), the Health Professionals Follow-up Study (HPFS), the Multiethnic Cohort Study (MEC), the New York University Women's Health Study (NYU-WHS), the Nurses' Health Study (NHS), the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO), the Shanghai Men's Health Study (SMHS), and the Shanghai Women's Health Study (SWHS). Investigators in each cohort study received institutional review board approval from their home institution(s) to participate in the VDPP.

Measurement of circulating 25(OH)D

All plasma/serum samples were measured for 25(OH)D at Heartland Assays, Inc. (Ames, Iowa), using the DiaSorin LIAISON 25(OH) Vitamin D TOTAL Assay (29) as described in detail elsewhere (28). Batches were analyzed by cohort and included masked vitamin D standards provided by the National Institute of Standards and Technology. Interbatch coefficients of variation for these standards were 12.7% and 13.6% for level 1 (~60 nmol/L) and level 2 (~35 nmol/L) standards, respectively (28).

Correlates

Covariate data obtained closest to the time of blood draw in each cohort were cleaned and harmonized. The following potential correlates of circulating 25(OH)D were examined: alcohol use (current use, no current use, or missing data); body mass index (weight (kg)/height $(m)^2$), both continuous and categorical (<25, 25–<30, ≥ 30, or missing data); education (less than high school, completion of high school, vocational school, some college, college graduation, or graduate study); postmenopausal hormone replacement therapy (no current use, current use, or missing data); history of diabetes (no, yes, or missing data); history of high blood pressure (no, yes, or missing data); physical activity (sedentary, light activity, moderate activity, vigorous activity, or missing data); race/ethnicity (white, black, Asian, other, or missing data); smoking status (never smoker, former smoker, or current smoker); and season of blood draw (winter (January–March), spring (April–June), summer (July–September), or fall (October–December)). Potential dietary determinants of 25(OH)D concentration included vitamin D intake (IU/day, continuous), calcium intake (mg/day, continuous), milk intake (g/day, continuous), dairy food intake (g/day, continuous), fish intake (g/day, continuous), use of calcium supplements (no current use, current use, or missing data), and use of multivitamin supplements (no current use, current use, or missing data). Nutrient levels were energy-adjusted using the residuals method (30). Information on use of individual vitamin D supplements (apart from multivitamin supplements) was not available; however, the prevalence of use of vitamin D-specific supplements was less than 2% among ambulatory US adults in the 1990s (31).

Subanalyses were conducted among 4 cohorts for which investigators quantified doses of total vitamin D (dietary intake plus supplemental vitamin D, continuous) and total calcium (dietary intake plus supplemental calcium, continuous) and among 5 cohorts for which there was detailed information on eye color (blue, green/gray, brown/black, or missing data) and hair color (red, blond/light brown, brown/black, or missing data). Information on skin tone was available for only 2 cohorts, so this was not examined.

Statistical analysis

The differences in circulating 25(OH)D were examined by season, stratified by race/ethnicity and, where possible, latitude of residence. Analysis of variance was used to test whether the mean 25(OH)D concentration within season of blood draw varied by latitude (<35°N, 35°N –42°N, or >42°N) or across seasons within each racial/ethnic and latitude group. Participant characteristics were determined according to the following 25(OH)D cutpoints: <25, 25–<37.5, 37.5–<50, 50–<75, 75–<100, and ≥ 100 nmol/L, corresponding to common cutpoints used in the literature and in the VDPP site-specific analyses (28, 32–34).

Stepwise linear regression analysis was used to derive regression coefficients of correlates with continuous 25(OH)D as the outcome variable. Visual inspection of the residual Q-Q plot from the linear regression model of circulating 25(OH)D suggested departure from normality by the residuals. Using the Box-Cox procedure (35), the square-root transformation was chosen. Models with transformed and untransformed results were similar; therefore, for ease of interpretation, only the results from models using the nontransformed 25(OH)D data are presented. A backward stepwise procedure was used, allowing only variables with a P value less than or equal to 0.10 for at least 1 category to remain in the model, while retaining age, sex, cohort, and season. Stepwise procedures were conducted for all cohorts combined, for US-only cohorts, and stratified by sex, race/ethnicity, and season. Overall P values for categorical variables were calculated using the Type III Sum of Squares feature from the Proc GLM procedure in SAS (SAS Institute Inc., Cary, North Carolina).

Predictors of ''very low'' (<25 nmol/L), ''low'' (25–50 nmol/L), and ''higher'' (≥75 nmol/L) 25(OH)D concentrations were examined using multivariate polytomous logistic regression. The control group category of 50–<75 nmol/L was chosen to correspond with our site-specific analyses (28). Participants with missing information on diet (n = 258) were excluded from stepwise and polytomous regression models. All statistical analyses were conducted using SAS, version 9.1.3 or 9.2. Figures were created using R (R Foundation for Statistical Computing, Vienna, Austria (http://www.r-project.org/)).

RESULTS

Participating VDPP cohorts and control characteristics are presented in Table 1. All participants were adults; the majority were over age 50 years. In most cohorts, blood samples were collected throughout the year, except CLUE II, in which samples were collected from May to November, and ATBC, in which only 7% of samples were collected during June and August and none were collected in July.

Participants came from Finland, Shanghai, China, and all major geographic regions of the United States. Seventy-two percent of participants were white, 4% were black, 18% were Asian, and 4% were of other race/ethnicity. In the ATBC, SMHS, and SWHS cohorts, approximately 20% of the population or more had very low 25(OH)D levels (<25 nmol/L). In the CLUE II, CPS-II, and HPFS cohorts, more than 20% of the population had 25(OH)D concentrations greater than or equal to 75 nmol/L.

Figure 1 illustrates the unadjusted distributions of circulating 25(OH)D by country. Vertical lines show cutpoints used in the analyses. The distribution of 25(OH)D concentrations was slightly higher among men in the United States (Figure 1, part A) and China (Figure 1, part B) than among women in these countries. The median 25(OH)D levels among men and women in the United States were 58.4 nmol/L and 51.7 nmol/L, and in China they were 38.0 nmol/L and 33.1 nmol/L, respectively. The ATBC Study, which included only Finnish men, had the lowest vitamin D status of all cohorts (median concentration, 31.9 nmol/L) (Figure 1, part C).

Figure 2 illustrates the distribution of circulating 25(OH)D by race/ethnicity, season of blood draw, and latitude. In whites (Figure 2, part A), 25(OH)D concentrations were lowest in all seasons among persons living at latitudes greater than 42°N and highest among those living at latitudes lower than 35°N. The amplitude of seasonal differences was most marked among whites living in the North, although seasonal differences were statistically significant in each latitude stratum. In blacks (n = 188; Figure 2, part B), mean concentrations did not vary within season by 2 latitude strata, except that those living in the South (<35°N latitude) had borderline-significantly different circulating 25(OH)D according to season (P = 0.06). Among Asians (n = 871) and persons of ''other'' race/ethnicity (n = 188) (Figure 2, part C), statistically significant differences in circulating 25(OH)D were observed by season; these subgroups could not be examined by latitude because of a lack of geographic diversity.

Table 2 provides unadjusted summary data for potential correlates analyzed according to a priori 25(OH)D cutpoints. Higher percentages of black and Asian participants had 25(OH)D concentrations less than 25 nmol/L as compared with whites and persons of ''other'' race/ethnicity. The prevalence of 25(OH)D concentrations less than 25 nmol/L was highest among persons who had had blood drawn in the winter. Circulating 25(OH)D concentrations also varied by alcohol consumption, body mass index, use of hormone replacement therapy, education, history of diabetes, history of hypertension, cigarette smoking, physical activity, and use of nutritional supplements.

Results from the stepwise regression models are presented in Table 3. Variables positively associated with circulating 25(OH)D concentrations among all controls were male sex, summer blood draw (vs. fall), vigorous physical activity (vs. light activity), current alcohol use (vs. none), vitamin D intake, fish intake, and current use of calcium and multivitamin supplements (vs. no current use). Variables associated with lower circulating 25(OH)D were body mass index, winter and spring blood draw (vs. fall), history of diabetes, sedentary physical activity (vs. light activity), current smoking (vs. never smoking), and black and ''other'' race/ethnicity (vs. white). Together, these variables explained 30% of the variation in 25(OH)D concentrations. Models limited to US-only participants yielded similar findings, except that intake of milk (which is fortified with vitamin D in the United States) was a predictor while fish intake was not (data not shown).

Results from stepwise regression models stratified by sex and race/ethnicity are also shown in Table 3. Predictors in men and women varied slightly: Only the category of obesity (body mass index ≥30) was associated with significantly lower concentrations in men; a linear association with body mass index was observed among women. Associations with physical activity, smoking, vitamin use, and dietary sources varied between the sexes. In whites, who comprised 72% of the total sample population, statistically significant predictors were the same as those for the entire population. Among blacks, only male sex, summer blood

Table 1. Characteristics (%) of Participants in the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers, by Cohort

	ATBC (n = 842)	CLUE II (n = 445)	CPS-II (n = 402)	HPFS (n = 147)	MEC (n = 416)	NHS (n = 477)	NYU-WHS (n = 472)	PLCO (n = 794)	SMHS (n = 202)	SWHS (n = 526)	Total (n = 4,723)
Sex											
Male	100	35.3	46.5	100	51.9	0	0	48.4	100	0	45.2
Female	0	64.7	53.5	0	48.1	100	100	51.6	0	100	54.8
Age at blood draw, years											
≤29	0	0.9	0	0	0	0	0	0	0	0	0.1
30–39	0	5.2	0	0	0	0	6.6	0	0	0	1.1
40–49	0.2	18.2	0	2.0	0	15.1	22.9	0	15.8	26.2	9.2
50–59	60.6	28.3	1.5	24.5	13.9	41.5	41.3	19.5	20.3	25.1	30.8
60–69	39.0	28.8	39.1	32.7	35.8	43.4	29.2	62.0	33.2	48.3	41.7
70–79	0.2	16.0	53.2	40.1	39.4	0	0	18.5	30.7	0.4	15.3
80–89	0	2.7	6.2	0.7	10.8	0	0	0	0	0	1.8
Race/ethnicity											
White	100	99.8	98.0	93.9	12.5	98.3	72.2	92.6	0	0	72.3
Black	0	0.2	0.5	0	24.0	0.4	11.1	3.9	0	0	4.0
Asian	0	0	0.5	0.7	26.2	1.0	0.4	3.0	100	100	18.4
Other	0	0	1.0	2.0	37.3	0.2	4.4	0.5	0	0	4.0
Missing data	0	0	0	3.4	0	0	11.9	0	0	0	1.3
Country of residence											
United States											
Northeast	0	0	20.6	15.6[a]	0	56.2	99.6	12.6	0	0	20.0
Midwest	0	0	29.9	34.7	0	19.3	0	55.2	0	0	14.8
West	0	0	25.4	26.5	100	12.8	0.2	21.2	0	0	16.7
South	0	100	24.1	22.4	0	11.7	0.2	11.1	0	0	15.2
Finland	100	0	0	0	0	0	0	0	0	0	17.8
China	0	0	0	0	0	0	0	0	100	100	15.4

Table continues

draw, dietary calcium intake, and current multivitamin use remained in the model; all were positively associated with circulating 25(OH)D. Among Asians, male sex, summer blood draw, and current alcohol use were positively associated with 25(OH)D concentrations, while winter and spring blood draw (vs. fall), current smoking, and dietary calcium and vitamin D intakes were inversely related.

Table 4 presents results from stepwise regression analyses stratified by season of blood draw. Male sex and dietary vitamin D intake were positively associated and body mass index and black race/ethnicity were inversely associated with 25(OH)D concentrations in every season. The adjusted r^2 value for winter was 32%, whereas the summer model explained only 16% of the variation in 25(OH)D concentrations. In the winter, as opposed to the summer (when sun exposure would be expected to dominate 25(OH)D status), cigarette smoking and a high school education were inversely associated with circulating 25(OH)D concentrations and fish intake and multivitamin use were positively associated.

In the subset of 4 cohorts with data on dose of supplemental vitamin D and calcium (ATBC, CPS-II, NHS, and PLCO), both total vitamin D intake (12.7-nmol increase/1,000 IU) and fish intake (6.1-nmol/L increase per 100 g) remained in the model. The Spearman correlation between 25(OH)D and dietary vitamin D intake (all cohorts) was 0.22 ($P < 0.0001$), and for total vitamin D intake (4 cohorts) it was 0.29 ($P < 0.0001$). In the 5 cohorts with information on hair color and eye color (ATBC, HPFS, MEC, SMHS, and SWHS), these variables did not remain in the final model, and race/ethnicity remained a statistically significant predictor.

Table 5 displays predictors of 25(OH)D concentrations for the categories <25, 25–<50, and ≥75 nmol/L. The statistically significant predictors of very low 25(OH)D concentrations (<25 nmol/L) were black race/ethnicity, low vitamin D intake, female sex, obesity, sedentary behavior, and winter blood draw. Factors inversely associated with very low concentrations of 25(OH)D included Asian race/ethnicity, calcium supplement use, multivitamin use, and alcohol consumption. Predictors of 25(OH)D concentrations between 25 nmol/L and 49.9 nmol/L were similar to those for <25 nmol/L, but the associations were weaker. Vigorous physical activity was positively associated with higher 25(OH)D concentrations (≥75 nmol/L), while obesity and low dietary vitamin D intake were inversely

Table 1. Continued

	ATBC (*n* = 842)	CLUE II (*n* = 445)	CPS-II (*n* = 402)	HPFS (*n* = 147)	MEC (*n* = 416)	NHS (*n* = 477)	NYU-WHS (*n* = 472)	PLCO (*n* = 794)	SMHS (*n* = 202)	SWHS (*n* = 526)	Total (*n* = 4,723)
Latitude, degrees North											
<35	0	0	20.9	25.9	97.4	13.4	0.4	6.8	100	100	29.1
35–42	0	100	52.2	42.2	2.6	56.4	99.6	46.5	0	0	38.9
>42	100	0	26.9	32.0	0	30.2	0	46.7	0	0	32.0
Year of blood draw											
1985–1989	100	100	0	0	0	38.4	96.8	0	0	0	40.8
1990–1994	0	0	0	94.6	1.2	61.6	3.2	14.5	0	0	12.0
1995–1999	0	0	38.6	5.4	25.5	0	0	80.0	0	94.3	29.6
2000–2004	0	0	61.4	0	71.4	0	0	5.5	80.2	5.7	16.5
2005 or later	0	0	0	0	1.9	0	0	0	19.8	0	1.0
Season of blood draw											
Winter	36.9	0	16.7	15.0	24.0	25.8	26.1	22.4	17.3	21.1	22.7
Spring	27.2	33.3	19.7	27.9	27.9	27.9	19.7	28.2	26.2	22.8	26.2
Summer	10.8	47.0	41.8	34.0	27.9	24.3	24.8	24.2	18.3	15.4	24.9
Fall	25.1	19.8	21.9	23.1	20.2	22.0	29.4	25.2	38.1	40.7	26.3
25-Hydroxyvitamin D, nmol/L											
<25	36.2	3.8	4.2	2.7	11.3	5.7	12.7	4.2	18.8	24.9	14.4
25–<37.5	23.5	9.0	8.7	8.2	16.3	12.4	21.0	14.9	29.7	35.6	18.5
37.5–<50	16.6	16.2	19.2	21.1	22.1	24.5	23.1	24.7	25.2	21.9	21.2
50–<75	18.8	43.6	43.3	42.2	33.4	39.6	31.4	42.7	20.8	15.0	32.3
75–<100	4.2	20.0	18.4	19.7	12.5	14.0	10.0	10.3	5.0	2.7	10.6
≥100	0.7	7.4	6.2	6.1	4.3	3.8	1.9	3.3	0.5	0	3.1

Abbreviations: ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CPS-II, Cancer Prevention Study II Nutrition Cohort; HPFS, Health Professionals Follow-Up Study; MEC, Multi-Ethnic Cohort Study; NHS, Nurses' Health Study; NYU-WHS, New York University Women's Health Study; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; SMHS, Shanghai Men's Health Study; SWHS, Shanghai Women's Health Study.

[a] Percentages do not total 100 for this cohort because of missing data.

associated. Current use of calcium and multivitamin supplements, male sex, and summer blood draw were associated with a borderline-significantly higher likelihood of greater 25(OH)D concentrations.

DISCUSSION

In this analysis of over 4,700 men and women, low concentrations of 25(OH)D were common, especially in China and Finland. Marked variation in 25(OH)D concentrations by season of blood draw was seen among whites, especially for those living in northern latitudes, whereas less striking seasonal variation was observed in blacks and persons of ''other'' race/ethnicity. Variables that significantly predicted circulating 25(OH)D concentrations included sex, race/ethnicity, body mass index, alcohol consumption, fish intake, dietary vitamin D intake, season of blood draw, history of diabetes, physical activity, smoking status, and use of vitamin D-containing multivitamins and calcium supplements. Participants with higher 25(OH)D concentrations (≥75 nmol/L) tended to be male, to be leaner, to consume more dietary vitamin D, and to engage in vigorous physical activity.

The prevalence of very low concentrations of 25(OH)D (<25 nmol/L) in most US cohorts in this analysis was similar to national estimates of approximately 4% in older adults (36). Exceptions included the MEC, which has large proportions of African Americans and Japanese Americans, and NYU-WHS, which includes only women living at a higher latitude and in a city (New York) where ultraviolet light exposure may be further limited by tall buildings that block sunlight. The prevalence of 25(OH)D concentrations less than 25 nmol/L was 11% in MEC and 13% in NYU-WHS. Prevalences of low concentrations were higher in Finland and China than in the United States. In Finland, a country at a high northern latitude, 64% of blood samples were collected in months during which ultraviolet-induced vitamin D synthesis in the skin is very limited. By contrast, Asians living at a lower latitude in Shanghai probably absorb less ultraviolet radiation because of their somewhat darker skin pigmentation and possibly cultural practices such as avoiding direct sun exposure and wearing more

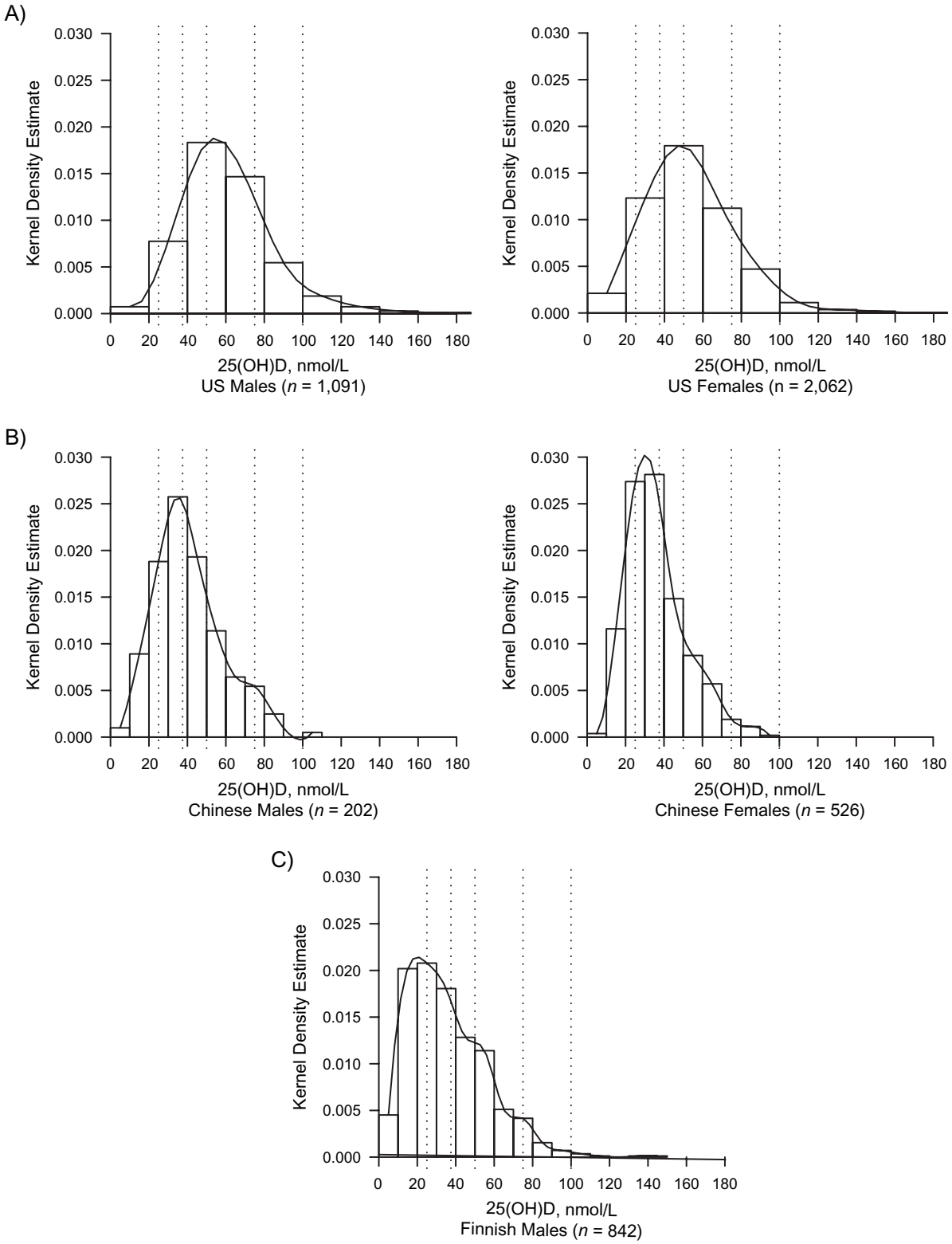

Figure 1. Distribution of circulating 25-hydroxyvitamin D (25(OH)D) concentrations by country within the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. A) Distribution of circulating 25(OH)D concentrations among US men and women. Vertical lines represent a priori cutpoints of 25, 37.5, 50, 75, and 100 nmol/L. 25(OH)D concentrations in men were statistically significantly greater than those in women ($P < 0.001$). B) Distribution of circulating 25(OH)D concentrations among men and women in Shanghai, China. 25(OH)D concentrations in men were statistically significantly greater than those in women ($P < 0.001$). C) Distribution of circulating 25(OH)D concentrations among men in Finland.

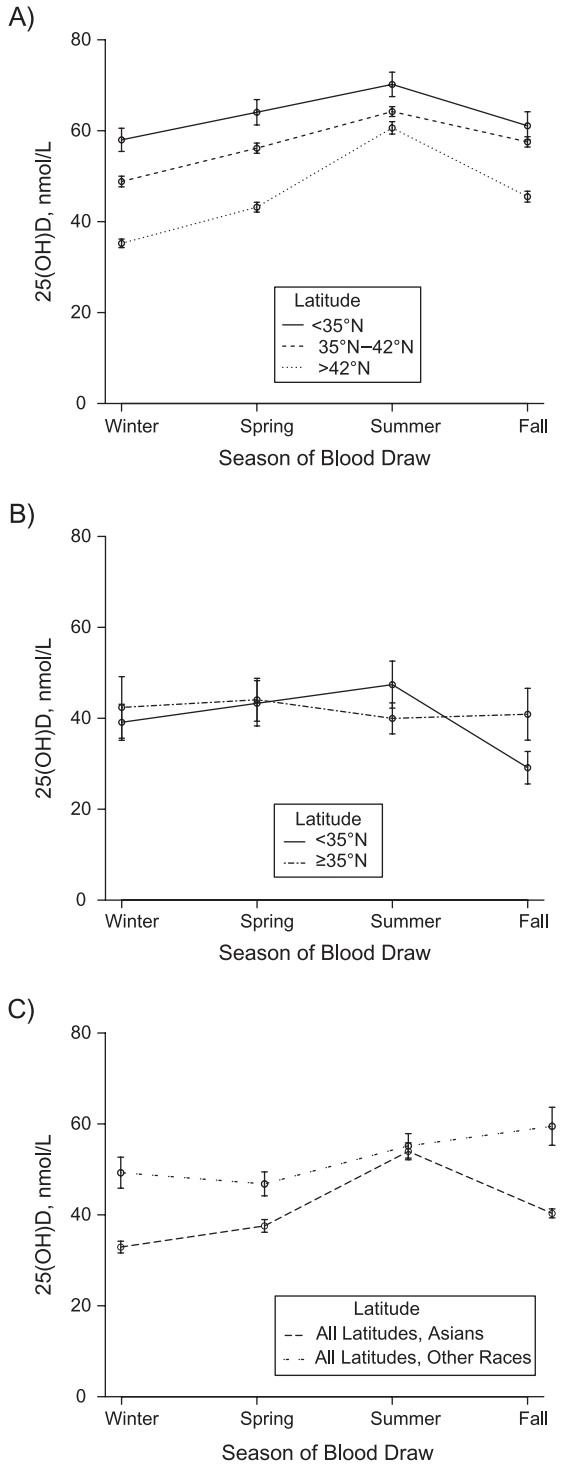

Figure 2. Mean circulating 25-hydroxyvitamin D (25(OH)D) concentrations by race/ethnicity, season, and latitude within the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. Circles represent mean values; bars represent the standard error. A) 25(OH)D concentrations among whites ($n = 3{,}415$) across seasons, within latitude categories of <35°N, 35°N–42°N, and >42°N. Differences in mean concentrations were statistically significant for all seasons at each latitude (for winter, spring, and fall, $P < 0.001$; for summer, $P = 0.0082$). Seasonal differences within latitude were also statistically significant: for <35°N, $P = 0.017$; for 35°N–42°N, $P < 0.0001$; and for >42°N, $P < 0.0001$. B) 25(OH)D concentrations among blacks ($n = 188$) across seasons, within latitude categories of <35°N and ≥35°N. Within-season 25(OH)D did not vary by latitude, but the difference within latitude across seasons was borderline-significant for latitude <35°N ($P = 0.06$), whereas no differences across season were noted for latitude ≥35°N ($P = 0.94$). C) 25(OH)D concentrations among Asians ($n = 871$) and persons of "other" race/ethnicity ($n = 188$) across seasons. The majority of Asians resided between 35°N latitude and 42°N latitude; statistically significant differences in 25(OH)D concentrations were observed across seasons ($P < 0.0001$). The majority of persons of "other" race/ethnicity resided at <35°N latitude; significant differences were observed by season ($P = 0.03$).

clothing. In both Finland and China, food is not regularly fortified with vitamin D, in contrast to the United States. The inclusion of the MEC cohort points out interesting contrasts between Asian populations in the United States and China and the potential influence of location. For example, very few persons of Japanese ancestry in the MEC (1 out of 109) had concentrations less than 25 nmol/L, which explains the lower risk of very low 25(OH)D concentrations among "Asians" after we controlled for cohort (e.g., the SWHS and SMHS) in the model. Japanese Americans in the MEC cohort are exposed to more sunlight than Chinese persons in Shanghai, and they also consume milk fortified with vitamin D. The concentration of 25(OH)D that is optimal for disease prevention is still undetermined, but concentrations of 75 nmol/L or more have been advocated (34, 37). A relatively small proportion of participants had concentrations greater than 75 nmol/L, ranging from 3% in SWHS to 27% in CLUE II, with the latter cohort having had their blood samples collected between May and November.

The strongest predictor of very low 25(OH)D concentrations in the present study was race/ethnicity, with blacks being 9 times more likely than whites to have very low vitamin D status, which is consistent with the literature (6, 7, 10, 16–18, 27). This finding is probably due in part to the higher melanin content of dark skin, which blocks pro-vitamin D_3 formation in the epidermis and dermis (38). Current multivitamin use was a particularly strong predictor of circulating 25(OH)D among blacks, providing a modifiable target for reducing vitamin D deficiency in that population.

Body mass index was an inverse correlate of circulating 25(OH)D in the entire population, which is consistent with previous reports (27, 39). Whether this is due to differences in sun exposure among persons with different body mass indices, increased clearance by a larger body-fat pool, negative feedback from higher circulating 1,25-dihydroxyvitamin D, or sequestration in fat is uncertain (40, 41). Body mass index was not a correlate of 25(OH)D among blacks and Asians in our sample, which is consistent with recent studies (18, 23, 42). Differences in dermal production and sequestration by body fat may provide one explanation (40), but more research on these complex relations is needed.

Dietary vitamin D intake and use of vitamin D-containing multivitamin supplements were strong positive predictors of 25(OH)D concentrations in most subgroups studied, which

Table 2. Distribution of Participant Characteristics According to A Priori 25-Hydroxyvitamin D Category in the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers[a]

	No. of Participants	Mean Serum 25(OH)D, nmol/L	Serum 25(OH)D Category, nmol/L					
			<25	25–<37.5	37.5–<50	50–<75	75–<100	≥100
			Mean Value					
Age at blood draw, years			58.9	59.7	61.1	62.1	62.0	61.6
Body mass index[b]			26.2	26.2	26.4	25.8	25.2	24.5
Vitamin D intake, IU/day			139	164	204	219	242	239
Dietary calcium intake, mg/day			932	890	938	966	1,011	965
Milk intake, g/day			323	237	254	265	278	293
Fish intake, g/day			32	34	34	32	30	30
			Row %					
Sex								
Male	2,135	49.2	18	17	20	32	10	3
Female	2,588	50.4	12	20	22	33	11	3
Race/ethnicity								
White	3,415	52.6	13	15	21	36	12	4
Black	188	41.1	27	26	19	19	5	3
Asian	871	41.1	20	31	23	21	5	1
Other	188	51.7	8	18	22	38	11	2
Education								
Less than high school	1,010	41.6	24	25	21	24	5	2
Completion of high school	852	51.7	11	20	21	33	12	3
Vocational school	545	41.8	24	23	21	23	6	2
Some college	1,104	52.2	12	17	20	36	12	3
College graduation	517	56.5	7	11	24	39	14	4
Graduate study	617	58.9	5	11	22	42	16	5
Season of blood draw								
Fall	1,240	48.8	14	20	22	32	10	2
Winter	1,070	40.8	26	23	21	23	6	1
Spring	1,236	48.5	15	21	21	30	10	3
Summer	1,175	60.7	4	10	20	43	16	7
Body mass index category								
<25	2,178	51.4	14	18	20	32	12	4
25–<30	1,799	49.6	14	18	22	33	10	3
≥30	717	45.6	16	21	24	29	8	1

Table continues

is consistent with previous studies of vitamin D intake and supplementation (27, 43–45). Calcium supplements often contain vitamin D, which probably explains the positive association between calcium intake and circulating 25(OH)D levels, although calcium may also spare conversion of 25(OH)D to 1,25-dihydroxyvitamin D (46). One exception was observed for Asians, among whom calcium and vitamin D intake were inversely related to 25(OH)D levels, for reasons that are unclear. This association may have been driven by different factors among Asians living in China, where supplement use is uncommon and milk is not fortified with vitamin D. Although they were statistically significant predictors, dietary vitamin D intake and total vitamin D intake were relatively weak correlates of circulating 25(OH)D.

Male sex was associated with higher circulating 25(OH)D in the stepwise models and in polytomous regression models, which is consistent with most previous reports (27). This may be due to women's higher percentage of body fat (beyond that measured through body mass index) (15), differences in amount of time spent outdoors, or sun protection behaviors (47).

Table 2. Continued

	No. of Participants	Mean Serum 25(OH)D, nmol/L	Serum 25(OH)D Category, nmol/L					
			<25	25–<37.5	37.5–<50	50–<75	75–<100	≥100
			Row %					
Physical activity								
Sedentary	1,548	44.2	20	23	22	26	8	1
Light activity	1,190	49.1	15	17	22	34	10	3
Moderate activity	783	52.4	9	18	22	37	11	3
Vigorous activity	935	56.0	10	15	19	35	15	6
History of diabetes								
No	4,352	50.2	14	18	21	32	11	3
Yes	277	44.0	16	29	20	29	5	2
History of hypertension								
No	3,308	50.2	15	18	20	33	11	3
Yes	1,357	49.1	13	19	24	32	9	3
Hormone replacement therapy (women only)								
No current use	2,018	49.7	13	21	22	31	11	3
Current use	469	56.2	5	14	23	40	13	4
Smoking status								
Never smoker	2,016	51.0	12	19	22	33	12	3
Former smoker	1,380	57.2	5	13	23	41	14	5
Current smoker	1,245	39.6	29	24	18	22	5	2
Alcohol use								
No current use	1,938	47.1	16	22	22	29	9	3
Current use	2,470	51.9	13	16	21	35	12	3
Supplemental calcium use								
No current use	2,801	49.5	16	18	20	32	10	3
Current use	793	58.1	6	10	23	40	16	4
Multivitamin use								
No current use	2,468	49.9	12	20	23	32	10	3
Current use	1,089	59.5	4	11	20	42	17	5
Dietary vitamin D intake, quintile of IU/day								
Quintile 1	753	40.8	24	18	18	28	8	3
Quintile 2	753	47.0	14	18	19	35	11	3
Quintile 3	752	50.2	11	16	22	36	11	3
Quintile 4	753	53.4	9	15	22	36	14	4
Quintile 5	752	57.7	5	11	22	40	17	4

Abbreviation: 25(OH)D, 25-hydroxyvitamin D.
[a] Summary statistics shown are unadjusted.
[b] Weight (kg)/height $(m)^2$.

Other correlates of circulating 25(OH)D concentrations observed in this study have been inconsistently associated with blood 25(OH)D concentrations in the literature. The association of alcohol intake with higher vitamin D concentrations that we observed in this study has not been seen consistently in other reports. In 1 study of elderly Americans, Jacques et al. (11) observed statistically significantly higher 25(OH)D concentrations with greater alcohol intake, but in another study of participants aged 49–75 years in which results were controlled for education and employment status, Egan et al. (6) did not. Current smoking was associated with lower circulating 25(OH)D concentrations in comparison with never smoking, which is consistent with some (2, 6, 13) but not other (10, 11, 15, 48) studies. However, no dose-response association was observed by number of cigarettes smoked per day, and smoking did not remain in the polytomous regression models. Higher 25(OH)D concentrations were observed among persons reporting

Table 3. Variables Associated With Circulating 25-Hydroxyvitamin D Concentrations (nmol/L) Among Controls in Stepwise Regression Models, Overall and by Sex and Race/Ethnicity, Cohort Consortium Vitamin D Pooling Project of Rarer Cancers[a]

	Total		Sex				Race/Ethnicity					
			Male		Female		White		Black		Asian	
	β	*P* Value	β	*P* Value	β	*P* Value	β	*P* Value	β	*P* Value	β	*P* Value
No. of controls	4,465		2,023		2,449		3,203		181		867	
Adjusted r^2	0.30		0.36		0.26		0.29		0.23		0.31	
Male sex (vs. female)	7.85	<0.001					8.20	<0.001	14.70	<0.001	9.01	0.01
Race/ethnicity		<0.0001[b]		0.0001[b]		<0.0001[b]						
White (referent)												
Other	−6.08	0.004	−7.15	0.04	−4.74	0.08						
Black	−13.53	<0.001	−11.00	0.001	−14.86	<0.001						
Asian	−0.45	0.837	4.37	0.18	−5.12	0.10						
Season of blood draw		<0.0001[b]		<0.0001[b]		<0.0001[b]		<0.0001[b]		0.26[b]		<0.0001[b]
Fall (referent)												
Winter	−7.13	<0.001	−7.89	<0.001	−6.31	<0.001	−7.54	<0.001	4.27	0.40	−8.73	<0.001
Spring	−2.18	0.010	−2.45	0.05	−1.98	0.08	−1.90	0.07	5.60	0.24	−3.96	0.01
Summer	6.80	<0.001	8.72	<0.001	6.02	<0.001	6.88	<0.001	9.38	0.048	8.52	<0.001
Body mass index[c]												
Continuous	−0.54	<0.001			−0.74	<0.001						
Categorical				0.07[b]				<0.0001[b]				
<25 (referent)												
25–<30			−0.43	0.67			−2.37	0.004				
≥30			−2.96	0.04			−7.02	<0.001				
Physical activity		<0.0001[b]		0.002[b]				<0.0001[b]				
Sedentary	−1.49	0.08	−1.83	0.11			−1.23	0.20				
Light activity (referent)												
Moderate activity	0.50	0.62	0.15	0.93			0.59	0.62				
Vigorous activity	3.37	<0.001	3.99	0.01			5.07	<0.001				
History of diabetes (yes vs. no)	−3.67	0.005	−3.20	0.07	−4.14	0.04	−5.29	0.003				
Smoking status		0.02[b]				0.001[b]		0.03[b]				0.03[b]
Never smoker (referent)												
Former smoker	0.05	0.95			0.83	0.41	0.75	0.42			−2.70	0.24
Current smoker	−3.63	0.003			−5.32	<0.001	−3.76	0.02			−5.31	0.01
Current alcohol use (vs. no current use)	2.46	0.001	3.23	0.01	1.91	0.06	2.43	0.01			3.72	0.07
Dietary calcium intake (per 100 mg)			−0.3	0.01					1.9	0.003	−0.7	0.04
Dietary vitamin D intake (per 100 IU)	1.8	<0.001	3.5	<0.001			1.8	<0.001			−3.1	0.01
Milk intake (per cup (237 mL))					2.16	<0.001						
Fish intake (per ounce (28.4 g))	0.78	0.02					0.93	0.03				
Current use of calcium supplements (vs. no current use)	4.88	<0.001	4.93	<0.001	5.87	<0.001	5.71	<0.001				
Current use of multivitamins (vs. no current use)	3.65	<0.001			5.69	<0.001	3.67	<0.001	17.56	<0.001		

[a] Results were adjusted for age, and cohort.
[b] *P* value for categorical variable.
[c] Weight (kg)/height $(m)^2$.

Table 4. Variables Associated With Circulating 25-Hydroxyvitamin D Concentrations (nmol/L) Among Controls in Stepwise Regression Models According to Season of Blood Draw, Cohort Consortium Vitamin D Pooling Project of Rarer Cancers[a]

	Season of Blood Draw							
	Winter		Spring		Summer		Fall	
	β	*P* Value	β	*P* Value	β	*P* Value	β	*P* Value
No. of controls	1,015		1,178		1,096		1,188	
Adjusted r^2	0.32		0.28		0.16		0.25	
Male sex (vs. female)	5.72	0.01	6.93	<0.001	8.98	<0.001	4.04	0.046
Race/ethnicity		0.03[b]		<0.001[b]		<0.001[b]		<0.001[b]
White (referent)								
Other	−5.85	0.14	−5.35	0.17	−11.51	0.01	3.92	0.38
Black	−11.12	0.003	−9.23	0.01	−15.21	<0.001	−16.93	<0.001
Asian	−3.06	0.46	8.96	0.05	−6.03	0.15	3.20	0.49
Education		0.13[b]						
Less than high school	−3.35	0.21						
Completion of high school	−4.82	0.05						
Vocational school	−4.38	0.11						
Some college	−0.55	0.81						
College graduation	−2.89	0.27						
Graduate study (referent)								
Body mass index[c]								
Continuous	−0.63	<0.001			−0.74	<0.001		
Categorical				0.002[b]				0.002[b]
<25 (referent)								
25–<30			−2.13	0.11			−1.00	0.44
≥30			−6.80	<0.001			−7.13	<0.001
History of diabetes (yes vs. no)			−5.30	0.04	−5.08	0.10	−5.51	0.02
Smoking status		0.26[b]		0.02[b]				0.002[b]
Never smoker (referent)								
Former smoker	−0.57	0.72	0.59	0.70			0.47	0.77
Current smoker	−4.99	0.047	−5.95	0.01			−8.56	<0.001
Current alcohol use (vs. no current use)	2.65	0.06			3.86	0.02	3.31	0.03
Dietary vitamin D intake (per 100 IU)	2.3	<0.001	2.2	<0.001	2.0	<0.001	1.2	0.03
Fish intake (per ounce (28.4 g))	2.01	0.002						
Current use of multivitamins (vs. no current use)	5.03	0.003	7.38	<0.001			5.76	0.01

[a] Results were additionally adjusted for age and cohort.
[b] *P* value for categorical variable.
[c] Weight (kg)/height $(m)^2$.

vigorous physical activity, driven primarily by associations in whites and males. A statistically significant positive association between greater physical activity and 25(OH)D concentrations was observed in only 3 (7, 17, 23) out of 7 (7, 8, 10, 11, 13, 17, 23) studies. Associations with physical activity may be a surrogate for greater sun exposure during outdoor physical activity (25, 49). Finally, a history of diabetes was associated with a significantly lower 25(OH)D concentration, even after controlling for body mass index. Two systematic reviews and meta-analyses have also shown an inverse association between vitamin D status or intake and type 2 diabetes or metabolic syndrome (50, 51), although many of the contributing studies, as in this study, were cross-sectional. This interesting finding merits further investigation.

Strengths of this study include the large sample size and the racial and geographic variability of the population. In addition, all assays were performed in a single laboratory using the same method for all assays within a period of 2–3 months. However, only 4% of the sample was black; thus, more research in this at-risk group is needed. One limitation was that few investigators had collected detailed information

Table 5. Odds Ratios for the Association Between Selected Covariates and Circulating 25-Hydroxyvitamin D Concentrations, Cohort Consortium Vitamin D Pooling Project of Rarer Cancers[a]

	Serum 25-Hydroxyvitamin D Category[b], nmol/L					
	<25		25–<50		≥75	
	OR	95% CI	OR	95% CI	OR	95 CI
Sex						
Male	1.00	Referent	1.00	Referent	1.00	Referent
Female	4.15	2.57, 6.70	1.70	1.36, 2.12	0.79	0.61, 1.03
Race/ethnicity						
White	1.00	Referent	1.00	Referent	1.00	Referent
Black	9.17	4.90, 17.18	2.53	1.60, 4.00	0.83	0.42, 1.64
Asian	0.25	0.07, 0.94	0.97	0.59, 1.59	0.74	0.40, 1.36
Other	1.00	0.44, 2.27	1.10	0.69, 1.77	0.51	0.27, 0.96
Season of blood draw						
Fall	1.00	Referent	1.00	Referent	1.00	Referent
Winter	3.23	2.43, 4.30	1.66	1.34, 2.06	0.83	0.60, 1.15
Spring	1.62	1.22, 2.14	1.23	1.01, 1.50	1.04	0.80, 1.37
Summer	0.31	0.21, 0.46	0.65	0.54, 0.80	1.22	0.95, 1.56
Body mass index[c] category						
<25	1.00	Referent	1.00	Referent	1.00	Referent
25–<30	1.04	0.83, 1.32	1.10	0.94, 1.30	0.78	0.63, 0.95
≥30	1.82	1.32, 2.50	1.60	1.29, 1.99	0.58	0.42, 0.80
Physical activity						
Sedentary	1.49	1.12, 1.98	1.16	0.95, 1.42	1.07	0.80, 1.41
Light activity	1.00	Referent	1.00	Referent	1.00	Referent
Moderate activity	0.90	0.61, 1.31	0.95	0.76, 1.19	1.01	0.74, 1.36
Vigorous activity	1.12	0.79, 1.61	0.85	0.68, 1.06	1.61	1.23, 2.12
Alcohol use						
No current use	1.00	Referent	1.00	Referent	1.00	Referent
Current use	0.61	0.46, 0.80	0.90	0.75, 1.07	1.07	0.86, 1.34
Dietary vitamin D intake, quintile of IU/day						
Quintile 1	4.67	3.12, 7.00	1.63	1.24, 2.14	0.63	0.43, 0.92
Quintile 2	3.28	2.23, 4.84	1.35	1.05, 1.73	0.70	0.51, 0.96
Quintile 3	2.12	1.43, 3.16	1.30	1.02, 1.65	0.71	0.52, 0.95
Quintile 4	1.40	0.93, 2.12	1.27	1.01, 1.61	0.74	0.56, 0.99
Quintile 5	1.00	Referent	1.00	Referent	1.00	Referent
Supplemental calcium use						
No current use	1.00	Referent	1.00	Referent	1.00	Referent
Current use	0.38	0.26, 0.56	0.76	0.61, 0.94	1.31	1.01, 1.70
Multivitamin use						
No current use	1.00	Referent	1.00	Referent	1.00	Referent
Current use	0.47	0.31, 0.70	0.71	0.58, 0.86	1.19	0.94, 1.50

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Results from a polytomous logistic regression model with mutual adjustment for the variables shown. Results were additionally adjusted for age and cohort.

[b] Reference category: 50–<75 nmol/L.

[c] Weight (kg)/height $(m)^2$.

on sun exposure, use of sunscreen or protective clothing, skin tone, or sun sensitivity, which probably accounts for a considerable proportion of the unexplained variation (i.e., ~70%) in 25(OH)D concentrations. However, race/ethnicity, physical activity, and season of blood draw served as proxies for skin tone and sun exposure to some degree.

Additional research on other sources of interindividual variability, including genetic factors (52), is needed. For pooling of the data across cohorts, the level of detail for each variable was dictated by the cohort with the least detailed information, prohibiting finer examination of some variables, such as total vitamin D intake. Although we were unable to examine the association with individual vitamin D supplements, their use was uncommon (31). We examined correlates of 25(OH)D using a cross-sectional study design. The extent to which modification of these variables would lead to changes in 25(OH)D is uncertain. In general, participants in cohort studies are more educated and of higher socioeconomic status than members of the general population; thus, results from this study are generalizable to similar populations. Even in this large pooled study of data from 10 cohorts, relatively few persons had very high concentrations of vitamin D, limiting investigation of correlates of high concentrations.

Understanding the correlates of vitamin D status has clinical, research, and public health applications. This information can help clinicians identify persons most at risk for vitamin D deficiency, who can then be screened and treated if necessary. As Table 4 shows, blacks, females, the obese, persons with low vitamin D intake, persons who are physically inactive, and persons who are not taking supplemental calcium or multivitamins are much more likely to have very low concentrations of 25(OH)D. Clinicians checking vitamin D concentrations during the winter or spring (e.g., January–June) will be less likely to overlook insufficient or deficient 25(OH)D concentrations.

These same risk factors can also be used to select at-risk individuals for clinical trials, and knowledge of correlates of circulating 25(OH)D also aids in the analysis and interpretation of observational study results. The markedly higher prevalence of very low 25(OH)D concentrations in blacks as compared with whites and among persons living in northern latitudes during less sunny months supports concern about vitamin D status in these populations and its possible impact on health outcomes.

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