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Utility of Sun-reactive Skin Typing and Melanin Index for Discerning Vitamin D Deficiency

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Abstract

Background—Skin color, a vitamin D status determinant, can be assessed subjectively by Fitzpatrick sun-reactive skin typing (FST) and objectively by melanin index (MI). FST was validated against MI for discerning vitamin D deficiency [serum 25-hydroxyvitamin D (25(OH)D) <20 ng/ml] in children.

Methods—We measured FST, MI, and serum 25(OH)D in healthy, 8- to 18-year-old children from one of two vitamin D trials. MI from forehead, hand, and upper arm split at the median of the more racially-balanced study cohort and FST (I-III vs. IV-V) were used for discriminating vitamin D deficiency.

Results—A total of 296 participants (mean age, 12.3±2.3 yr; black, 208; FST IV-V, 209; 25(OH)D <20 ng/mL, 159) were studied. MI and FST had a strong positive association. Serum 25(OH)D was negatively associated with MI and FST. Sensitivity, specificity, and predictive values were similar for discriminating vitamin D deficiency between higher vs. lower MI and between FST I-III vs. IV-V. ROC AUCs for FST (0.59) and MI (forehead [0.63]; hand [0.62]; arm [0.64]) were similar.

Conclusions—FST is comparable to MI for discerning vitamin D deficiency and can be deemed as an inexpensive, useful surrogate measure of skin color in the context of vitamin D research.

Introduction

A sufficient vitamin D status is necessary for healthy skeletal growth and calcium equilibrium. However, variability in diet, skin color, geography, and sunlight exposure can

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predispose otherwise healthy children to hypovitaminosis D (1-3). Concentration of serum 25-hydroxyvitamin D [25(OH)D] is an established biomarker of vitamin D status; the Institute of Medicine defines a 25(OH)D concentration ≥20 ng/mL as sufficient for skeletal growth and development (4).

Skin color is an important determinant of vitamin D photosynthesis. Melanin pigment, the principal determinant of skin color, can compromise vitamin D photoproduction in the skin by serving as a natural filter of solar ultraviolet-B (UV-B) radiation in the epidermis (5-7). Melanin is produced by melanocytes in the epidermis and is stored in melanosomes of the stratum basale. Dark-skinned individuals have an abundance of melanin and their melanin-laden melanosomes are distributed diffusely and uniformly. On the contrary, light-skinned individuals have relatively less melanin and a sparser distribution of melanosomes (8, 9). Dark-skinned individuals, as a result of increased skin melanin content, are at a higher risk for hypovitaminosis D (10, 11).

Skin color can be quantified by reflectance photometric techniques including tristimulus colorimetry and narrow-band spectrophotometry. Narrow-band spectrophotometric devices compute melanin index (MI) as an objective measure of skin melanin content. Although melanin index can serve as an objective measure of an individual's skin color in the context of vitamin D research (12-15), the cost and effort of such measurement may pose a barrier for their widespread use. Therefore, inexpensive alternate skin color assessment techniques are needed to gain similar information with comparable effectiveness.

Fitzpatrick sun-reactive skin typing (FST) is a categorical scale of patient-reported perceptions of skin sensitivity and reactivity to sunlight exposure and has been widely used in vitamin D clinical research as an inexpensive surrogate for skin color assessment (16-18). Though it was originally devised in the treatment of psoriasis, it has been utilized in various medical contexts ranging from its role in laser hair removal to risk factors in skin cancers (16, 19-22). Skin types are categorized as I through V based on a combination of sun sensitivity (sunburn response) and reactivity (pigmentary or tanning response). Individuals with skin type I readily burn when exposed to sunlight and resist tanning on repeated exposures; those individuals with skin type V do not sunburn during sun exposure and undergo a considerable pigmentary response (sun tan) to subsequent exposures. To our knowledge, this subjective surrogate measure remains to be validated against objective measures of skin color in the context of vitamin D research in children. Therefore, we have sought to validate the utility of parent-reported, Fitzpatrick sun-reactive skin type against melanin index in discerning vitamin D deficiency.

Methods

Study Design and Participants

We conducted a cross-sectional study of healthy 8- to 18-year-old children at the Children's Hospital of Pittsburgh of University of Pittsburgh Medical Center (UPMC). Study cohort comprised of a convenience sample of children with baseline assessments collected during participation in one of two NIH-funded vitamin D clinical trials. Study 1 examined the efficacy of vitamin D supplementation in healthy 8- to 14-year-old black and white children

enrolled during October 2008 through March 2011 (23). Study 2 (Clinicaltrials.gov identifier: NCT01797302) is ongoing since August 2013 and examines the cardio-metabolic benefits of enhanced vitamin D supplementation in otherwise healthy vitamin D-deficient obese or overweight 10- to 18-year-old children. Studies were approved by the University of Pittsburgh Institutional Review Board. Parental consent and participant's assent were obtained prior to participation. Children's race was specified by their parents.

Study Measurements

Our study measurements included anthropometric measurements, Fitzpatrick sun-reactive skin type, melanin index, and serum 25-hydroxyvitamin D concentration. Children's height and weight were measured and BMI was calculated.

Fitzpatrick Sun-reactive Skin Type—Skin type was estimated by subjects' or their parents in response to a questionnaire (16). Classification on a scale of I-V was based on (a) subjects' degree of sunburn after the first 30-45 minutes of sun exposure—without sunscreen use—at the beginning of summer and (b) their respective tanning response after repeated exposures. Skin types I-III are typically associated with lighter skin tones and skin types IV-V are associated with darker skin tones (16-18): type I (easy burn, no tan); type II (easy burn, slight tan); type III (burn, then tan); type IV (no burn, good tan) and type V (never burn, marked tan).

Melanin Index—We used a hand-held dermaspectrometer (DSM II Colormeter, Cortex Technology, Hadsund, Denmark) to estimate the subjects' melanin index (12-15). The device was calibrated prior to use against a manufacturer-provided white calibration plate. The colormeter's narrow-band reflectance system utilizes two high-intensity white LEDs to reflect light onto a 7 mm^2 target area of the subjects' skin. An RGB (Red-Green-Blue) sensor determines the intensities of the red (I_{red}), green, and blue light being reflected back which were used to compute specific skin indices including the melanin index.

$$\text{Melanin Index}, MI = 100 \times \log \frac{1}{I_{\text{red}}} \quad (15)$$

Measurements were taken thrice from the forehead, the back of the hand, and inside of the upper arm and averaged. Measurements from forehead and back of the hand were reflective of skin color modified by UV radiation (facultative pigmentation) and measurements from arm were indicative of innate skin color (constitutive pigmentation).

Serum 25-hydroxyvitamin D—Serum 25(OH)D was measured by liquid chromatography tandem mass spectrometry (LC MS/MS) assay. Assays for Study 1 participants were performed at Vitamin D, Skin, and Bone Research Laboratory at Boston University Medical Center and for Study 2 participants at the UPMC Clinical Chemistry Laboratory as previously described (23, 24). Vitamin D deficiency was defined as serum 25-hydroxyvitamin D concentration <20 ng/mL (4).

Statistical Analysis

We first compared the children from the two studies on demographics and clinical characteristics using two-sample t-tests for continuous measures (or Wilcoxon Rank Sum tests for skewed data) and chi-square tests for categorical measures. We estimated the correlation among melanin measures, skin type, and serum 25(OH)D concentrations using Pearson or Spearman correlations. The median melanin index value from the Study 1 cohort was chosen as the cut-point for dichotomization of the melanin index of all participants as this subset was more racially balanced with nearly equal numbers of black and white children. The skin types were dichotomized as I-III (light-skinned) vs. IV-V (dark-skinned). We then calculated sensitivity, specificity, positive predictive value and negative predictive value for each skin measure for predicting vitamin D deficiency. Corresponding 95% confidence intervals were calculated as well. Seasonality was tested by combining seasons into a Summer/Fall group and a Winter/Spring group. Analysis of Variance (ANOVA) was used to compare the serum 25(OH)D concentrations between seasons within skin color groups and between skin color groups within seasons. Finally, we estimated the predictive value of each skin measure using logistic regression and area under the receiver operating characteristic (ROC) curve and the corresponding 95% interval. All analyses were conducted using SAS Enterprise Guide version 6.1 and all tests were two sided (α=0.05).

Results

We studied a cross-sectional sample of 296 children enrolled in one of two vitamin D clinical trials (Study 1, n=150; Study 2, n=146). Demographic characteristics, mean 25(OH)D concentrations, and vitamin D status of all participants and each of the subsamples that comprised of this cohort are shown in Table 1. The pooled cohort had a mean age of 12.3±2.3 years and majority of the children were female (55%), black (70%), skin type IV-V (71%), and vitamin D deficient (54%). The mean 25(OH)D concentration of all participants was 19.7±7.3 ng/mL. Participants from Study 2, when compared to participants from Study 1, were significantly older and had a higher representation of children who were black and who had darker skin tones (i.e. higher melanin index and skin type IV-V). Melanin index measurements were available in 278 children and skin type classification was available in all children. Of the 278 children with melanin index measurements 153 (55%) were vitamin D-deficient and of the 296 children with skin type classifications 159 (54%) were vitamin D-deficient.

Significant correlations

Melanin index measurements had a strong positive association with skin type at all three sites (forehead, r=0.66, p<0.0001; hand, r=0.67, p<0.0001; upper arm (r=0.65, p<0.0001). Serum 25(OH)D concentrations were negatively associated with melanin index measurements at the forehead (r=-0.30, p<0.0001), hand (r=-0.29, p<0.0001), and upper arm (r=-0.31, p<0.0001). Serum 25(OH)D concentrations were also negatively associated with skin type (r=-0.20, p=0.0006) (shown in Figure 1).

Vitamin D status by skin color and skin type

Vitamin D status (serum 25(OH)D <20 vs. ≥20 ng/mL) of children stratified by skin type (I-III vs. IV-V) and skin color (melanin index below vs. above the median of Study 1 participants) is shown in Table 2. Rates of vitamin D deficiency were higher in children with skin type IV-V and melanin index above the median. The proportion of vitamin D-deficient and -non-deficient children across the skin type strata and melanin index strata were similar.

Prediction of vitamin D deficiency by skin type and skin color

The diagnostic characteristics [sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV)] of skin type and skin color for the prediction of vitamin D deficiency are shown in Table 3. Both melanin index (forehead, hand, and upper arm) and Fitzpatrick sun-reactive skin type had similar diagnostic characteristics for discerning vitamin D deficiency. ROC curves comparing the degree of diagnostic accuracy for these measures are shown in Figure 2 and respective area-under-the-curves for these measures are shown in Table 3.

Season, skin color, and vitamin D status

Mean serum 25(OH)D concentrations in children examined during winter/spring (January-June) were lower or trended to be lower when compared to children who were assessed during summer/fall (July-December) within each of the respective skin type (I-III and IV-V) and skin color strata (melanin index < median, and melanin index ≥ median) (data shown in Supplemental Table S1). Dark-skinned children (i.e. skin type IV-V; melanin index ≥ median) when compared to light-skinned children (i.e skin type I-III; melanin index < median) had lower mean serum 25(OH)D concentrations during both winter/spring and summer/fall. Box-plots of the serum 25(OH)D concentrations by season and skin type or color is shown in Figure 3.

Discussion

We found Fitzpatrick sun-reactive skin type and melanin index to have similar diagnostic characteristics for distinguishing vitamin D deficiency in children. Both measures had a relatively higher sensitivity (skin type, 80%; melanin index, 77-78%) and lower specificity (skin type, 40%; melanin index, 46-48%). The positive predictive value and negative predictive value of these two measures were modest (PPV: skin type 61%, melanin index 64-65%; NPV: skin type 63%, melanin index 63-64%, respectively). In addition, we found a strong positive association between skin type and melanin index at sites representing facultative or constitutive pigmentation. These findings would indicate that both Fitzpatrick sun-reactive skin type and melanin index can be equally effective for assessment of skin color phenotypes in the context of vitamin D research.

Our findings also indicate that both melanin index and skin type to be negatively associated with serum 25(OH)D concentrations. In addition, both melanin index and skin type had a high degree of sensitivity and modest positive and negative predictive values for distinguishing vitamin D-deficient status. Together, these findings highlight the relevance of skin pigmentation as an important determinant of vitamin D status in children. The

availability of UV-B radiation is an overarching determinant for adequate vitamin D production and is driven by many variables including latitude of residence, season, atmospheric conditions, lifestyle (sun screen use, clothing, and sunlight exposure), and skin color (1-3, 11, 25, 26). In addition, dietary intake of vitamin D, adiposity, age and pubertal status are also relevant determinants of vitamin D status (24, 27-29). Therefore, it's not surprising that our prediction model that examined only "skin color" was modest at best for discerning vitamin D deficiency.

To our knowledge, this study is the first to validate Fitzpatrick sun-reactive skin type against melanin index in the context of vitamin D research in children and to examine their diagnostic accuracy for discerning vitamin D deficiency. The enrollment of a racially diverse cohort of large number of children across the skin phenotype spectrum with significant proportion of vitamin D deficiency contributed to the strength of this study. Limitations of our study are inherent to our study design—we acknowledge that our findings could vary based on the cut-points of melanin index and 25(OH)D chosen for the prediction of vitamin D deficiency. However, we have offset these limitations by using a conservative definition of vitamin D deficiency (serum 25(OH)D <20 ng/mL) based on IOM-set threshold concentrations. The melanin index cutpoint was chosen from the more racially balanced Study 1 participant subset. Furthermore, it is reassuring that the chosen melanin index cut-points were similar to the skin type stratification (I-III vs. IV-V) in categorizing the proportion of vitamin D deficiency (Table 2). Our observation of the widespread distribution of serum 25(OH)D concentrations within each of the skin types and values of melanin index (Figure 1) indicates that Fitzpatrick skin type and melanin index may not have the same predictive value for identifying vitamin D deficiency if the study population is homogenous in skin type or melanin index. Fitzpatrick skin type and melanin index may be better predictors of vitamin D deficiency in cohorts with diverse skin colors or sun-reactive skin types, as reflected in our study.

Our study design rendered the opportunity to examine the effect of season on vitamin D status by skin color. Mean serum 25(OH)D concentration was generally lower during winter/spring compared to summer/fall in both light- and dark-skinned children. Dark-skinned children had lower mean serum 25(OH)D concentration than light-skinned children during both winter/spring and summer/fall. The 25(OH)D concentrations in dark-skinned children during summer/fall were consistently lower than the 25(OH)D concentrations in light-skinned children during winter/spring. This suggests that the seasonal surge in the 25(OH)D concentrations during summer/fall in dark-skinned children was not adequate to offset their disadvantage in vitamin D photoproduction. These findings emphasize the relevance of season and skin color in the determination of vitamin D status in children and affirm our previously published findings (11, 27).

The excessive prevalence of vitamin D deficiency in our study population (serum 25(OH)D concentrations <20 ng/mL, 54%) can be ascribed to our study design and subject selection, and include: (i) enrollment of children in Study 1 only during October through March, a vulnerable period for seasonal hypovitaminosis D in Pittsburgh, PA (latitude: 40.4°N) (11, 23); (ii) inclusion of only children who were obese or overweight (mean BMI 30.6) in Study 2, a group vulnerable for hypovitaminosis D secondary to excess adiposity (27); and (iii)

overall higher representation of black children (70%) and children with skin type IV and V (70%) in the combined cohort, a group vulnerable for compromised vitamin D photosynthesis secondary to excess skin melanin content (27, 30).

When examining the utility of Fitzpatrick sun-reactive skin typing, it is necessary to acknowledge the inherent limitations of this measure. Skin phototyping is susceptible to difficulties in reproducibility due to the structure of the questions and the available responses (31). Given the limited categorical responses available, participants may have difficulty selecting from a single skin type to describe their burning and tanning responses. Rampen et al. collected burning and tanning histories from 18- to 30-year-old white adults and found that of 790 subjects only 41% of them could be classified according the Fitzpatrick sun-reactive skin type scale; tanning response was better associated with skin color than burning response (32). How the questions regarding sun sensitivity and tanning responses are interpreted can result in misclassification bias. Recall bias may also detract from reproducibility. Subjects can have difficulty remembering how long it takes for their skin to burn after an initial exposure or the timeline for their tanning response (31, 33). Fitzpatrick skin-typing is vulnerable to misclassification in Hispanics and Asians as their skin phototype is poorly correlated with their facultative and constitutive skin color (34-36). Despite these limitations, our findings of a strong positive association between skin phototyping and objective melanin index measures in a racially diverse cohort reassert the value of Fitzpatrick skin typing in the context of vitamin D research. However, further research is necessary to account for the inherent limitations of this instrument.

We conclude that Fitzpatrick sun-reactive skin type, an inexpensive surrogate measure of skin color, is comparable to melanin index in discerning vitamin D deficiency in the context of vitamin D research in cohorts of children with diverse skin colors or sun-reactive skin types. However, melanin index can provide nuanced information regarding the role of constitutive and facultative skin color for assessing vitamin D status and in determining vitamin D requirements (15, 37). Future studies are warranted to examine if inclusion of other determinants of vitamin D status in addition to skin color can improve the prediction of vitamin D deficiency.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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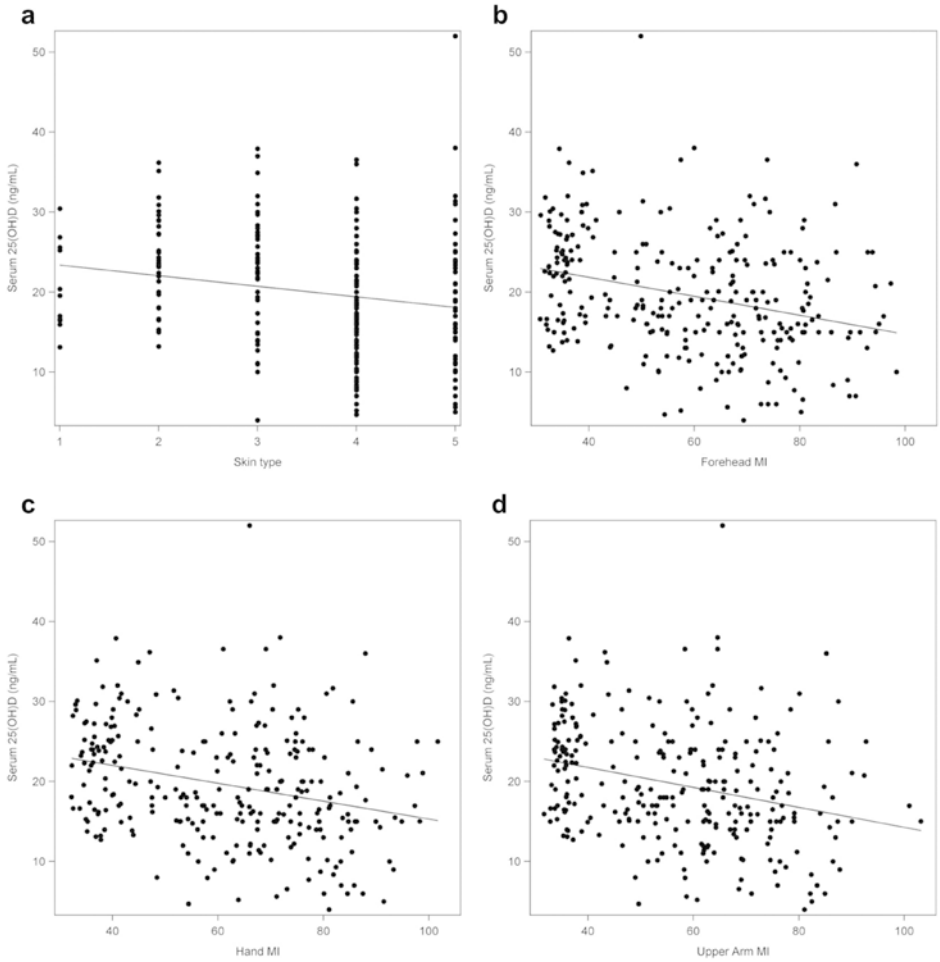

Figure 1.

Serum 25(OH)D and skin color correlations: (**a**) skin type, (**b**) forehead melanin index, (**c**) hand melanin index, and (**d**) upper arm melanin index.

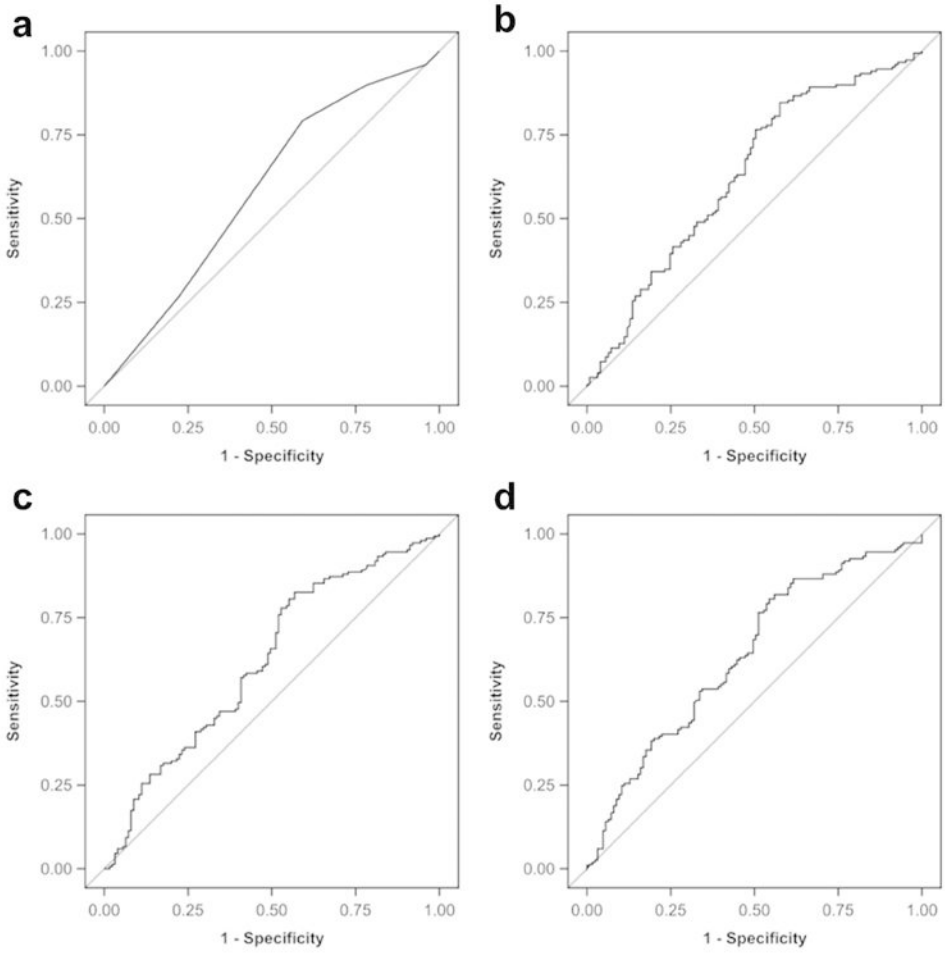

Figure 2.

ROC curves [AUC (95% CI)] for discerning vitamin D deficiency by skin color: (**a**) skin type I-III vs. IV-V [0.59 (0.53, 0.66)], (**b**) forehead melanin index [0.63 (0.56, 0.70)], (**c**) hand melanin index [0.62 (0.55, 0.69)], and (**d**) upper arm melanin index [0.64 (0.57, 0.70)].

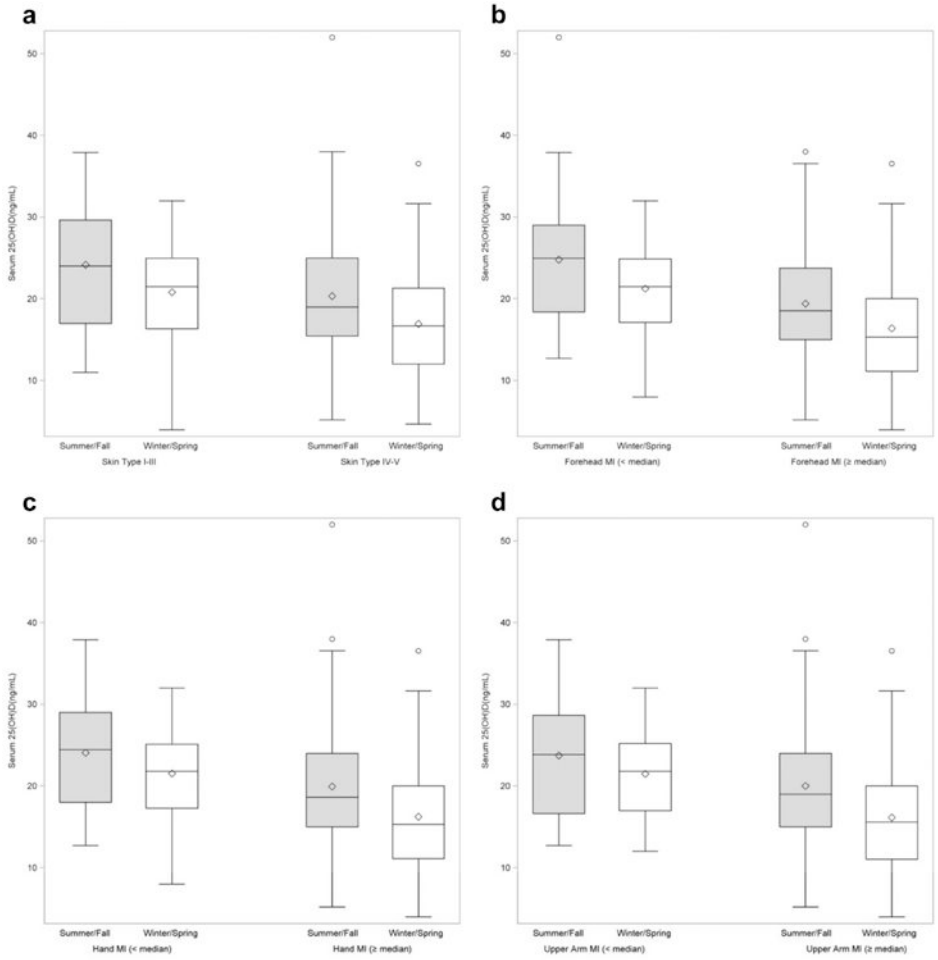

Figure 3.

Box-plots of the serum 25(OH)D concentrations by skin color and season: (**a**) skin type I-III vs. IV-V, (**b**) forehead melanin index (<median vs. ≥median), (**c**) hand melanin index (<median vs. ≥median), and (**d**) upper arm melanin index (<median vs. ≥median). The *box* represents the 25th-75th quartile range split at the median (50th percentile); means are denoted by diamonds. Shaded boxes indicate summer/fall 25(OH)D concentrations while unshaded boxes indicate winter/spring 25(OH)D concentrations. The *whiskers* represent the maximum and minimum range of the datasets exclusive of outliers. Statistical outliers are shown as circles.

Table 1

Subjects' characteristics

	All Subjects	Study 1 Subjects	Study 2 Subjects	Study 1 vs 2
	N=296; n (%), Mean ± SD, or Median (25th-75th quartile)	N=154; n (%), Mean ± SD, or Median (25th-75th quartile)	N=142; n (%), Mean ± SD, or Median (25th-75th quartile)	P value
Age (yr)	12.3 ± 2.3	11.3 ± 1.9	13.4 ± 2.1	<0.0001
Male	134 (45)	76 (49)	58 (41)	0.14
Race				<0.0001
Black	208 (70)	83 (54)	125 (88)	
White	82 (28)	71 (46)	11 (8)	
Other	6 (2)	0	6 (4)	
Ethnicity				
Hispanic	14 (5)	2 (1)	12 (8)	
Weight (kg)	63.8 ± 25.1	48.8 ± 18.5	80.1 ± 20.8	<0.0001
Height (cm)	154.6 ± 13.3	148.8 ± 13.1	160.9 ± 10.4	<0.0001
Body mass index	25.9 ± 7.4	21.5 ± 5.8	30.6 ± 5.8	<0.0001
Skin type				<0.0001
I (easy burn, no tan)	11 (4)	10 (6)	1 (1)	
II (easy burn, slight tan)	32 (11)	27 (18)	5 (4)	
III (burn, then tan)	44 (15)	31 (20)	13 (9)	
IV (no burn, good tan)	136 (46)	63 (41)	73 (51)	
V (never burn, marked tan)	73 (24)	23 (15)	50 (35)	
Melanin index				
Forehead	59.3 (39.3 - 73)	49.1 (35.1 - 68.8)	65 (53.4 - 75.5)	<0.0001
Hand	63.2 (43.2 - 75.2)	52.3 (38 - 72.5)	67.7 (57.3 - 76.8)	<0.0001
Upper arm	58 (38.8 - 69)	47.6 (36 - 67.6)	62.3 (53 - 72)	<0.0001
Mean serum 25(OH)D ng/mL	19.7 ± 7.3	19.4 ± 7.2	20 ± 7.4	0.46
Serum 25(OH)D ng/mL				0.77
<20 ng/mL (deficient)	159 (54)	84 (55)	75 (53)	
≥20 ng/mL (non-deficient)	137 (46)	70 (45)	67 (47)	

Table 2

25(OH)D status stratified by high vs. low skin type and high vs. low melanin index

	Stratification	<20 ng/ml, deficient	≥20 ng/mL, non-deficient
	Strata (N)	**n (%)**	**n (%)**
Skin type	I-III (87)	32 (37%)	55 (63%)
	IV-V (209)	127 (61%)	82 (39%)
Forehead MI	MI < median[a] (94)	34 (36%)	60 (64%)
	MI ≥ median[a] (184)	119 (65%)	65 (35%)
Hand MI	MI < median[b] (90)	33 (37%)	57 (63%)
	MI ≥ median[b] (188)	120 (64%)	68 (36%)
Upper arm MI	MI < median[c] (94)	35 (37%)	59 (63%)
	MI ≥ median[c] (183)	117 (64%)	66 (36%)

Melanin indices were dichotomized at the median of the more racially-balanced Study 1 cohort

Medians: site [MI (25^{th}-75^{th} quartile)];

[a] forehead [49 (35, 69)];

[b] hand [52 (38, 72)];

[c] upper arm [48 (36, 68)]

Table 3

Prediction of 25(OH)D <20ng/mL between high vs. low melanin Index and high vs. low skin type

	Se	Sp	PPV	NPV	ROC Model
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	AUC ± SE (95% CI)
Skin Type I-III vs IV-V	80 (74, 86)	40 (32, 48)	61 (54, 67)	63 (53, 73)	0.59 ± 0.033 (0.53, 0.66)
Forehead MI	78 (71, 84)	48 (39, 57)	65 (58, 72)	64 (54, 74)	0.63 ± 0.034 (0.56, 0.70)
Hand MI	78 (72, 85)	46 (37, 54)	64 (57, 71)	63 (53, 73)	0.62 ± 0.034 (0.55, 0.69)
Upper arm MI	77 (70, 84)	47 (38, 56)	64 (57, 71)	63 (53, 73)	0.64 ± 0.034 (0.57, 0.70)

Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; SE, standard error