Utility of sun-reactive skin typing and melanin index for discerning vitamin D deficiency

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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 years; 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 area under the curves for FST (0.59) and MI (forehead (0.63); hand (0.62); and 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.

$\textbf{A}$ sufficient vitamin D status is necessary for healthy skeletal growth and calcium equilibrium. However, variability in diet, skin color, geography, and sunlight exposure can 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 $\geqslant 20$ 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 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 the skin melanin content. Although MI 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). Although 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 MI 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. The study cohort comprised 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 (ref. 23). Study 2 (Clinicaltrials. gov identifier: NCT01797302) is ongoing since August 2013 and examines the cardiometabolic 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, FST, MI, 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 the subjects or their parents in response to a questionnaire (16). Classification on a scale of I–V was based on (i) subjects' degree of sunburn after the first 30–45 min of sun exposure—without sunscreen use—at the beginning of summer and (ii) 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' MI (12–15). The device was calibrated prior to use against a manufacturer-provided white calibration plate. The colorimeter's narrow-band reflectance system utilizes two high-intensity white light-emitting diodes 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 lights being reflected back, which were used to compute specific skin indices including the MI.

$$MI = 100 \times \log \frac{1}{I_{red}} \qquad (15)$$

Measurements were taken three times 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 ultraviolet radiation (facultative pigmentation), and measurements from arm were indicative of innate skin color (constitutive pigmentation).

Serum 25(OH)D. Serum 25(OH)D was measured using liquid chromatography tandem mass spectrometry assay. Assays for Study 1 participants were performed at Vitamin D, Skin, and Bone Research Laboratory at the Boston University Medical Center and those for Study 2 participants were performed at the University of Pittsburgh Medical Center Clinical Chemistry Laboratory as previously described (23,24). Vitamin D deficiency was defined as serum 25(OH)D concentration < 20 ng/ml (ref. 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 χ^2-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 MI value from the Study 1 cohort was chosen as the cutpoint for dichotomization of the MI 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 (PPV), and negative predictive value (NPV) 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. 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 the SAS Enterprise Guide version 6.1, and all tests were two-sided ($\alpha = 0.05$).

RESULTS

We studied a cross-sectional sample of 296 children enrolled in one of the 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 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%), with skin types 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 with those 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 MI and skin types IV–V). MI measurements were available in 278 children, and skin type classification was available in all children. Of the 278 children with MI measurements, 153 (55%) were vitamin D-deficient and, of the 296 children with skin type classifications, 159 (54%) were vitamin D-deficient.

Significant Correlations

MI measurements had a strong positive association with skin type at all three sites (forehead, $r = 0.66$, $P < 0.0001$; hand, $r = 0.67$, $P < 0.0001$; and upper arm, $r = 0.65$, $P < 0.0001$). Serum 25(OH)D concentrations were negatively associated with MI 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. $\geqslant 20$ ng/ml) of children stratified by skin type (I–III vs. IV–V) and skin color (MI below vs. at or above the median of Study 1 participants) is shown in **Table 2**. Rates of vitamin D deficiency were higher in children with skin types IV–V and MI at or above

Table 1. Subjects' characteristics

	All subjects; N = 296; N (%), mean ± SD, or median (25th to 75th quartile)	Study 1 subjects; N = 154; N (%), mean ± SD, or median (25th to 75th quartile)	Study 2 subjects; N = 142; n(%), mean ± SD, or median (25th to 75th quartile)	Study 1 vs. 2; P value
Age (years)	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
BMI	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 (deficient)	159 (54)	84 (55)	75 (53)	
⩾20 (non-deficient)	137 (46)	70 (45)	67 (47)	

25(OH)D, 25-hydroxyvitamin D.

the median. The proportion of vitamin D-deficient and vitamin D-non-deficient children across the skin type strata and MI strata was similar.

Prediction of Vitamin D Deficiency by Skin Type and Skin Color
The diagnostic characteristics (sensitivity, specificity, PPV, and NPV) of skin type and skin color for the prediction of vitamin D deficiency are shown in Table 3. Both MI (forehead, hand, and upper arm) and FST 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 areas under the curves for these measures are shown in Table 3.

Season, Skin Color, and Vitamin D Status
The mean serum 25(OH)D concentrations in children examined during winter/spring (January–June) were lower or trended to be lower when compared with those in 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 (MI < median, and MI ⩾ median; data
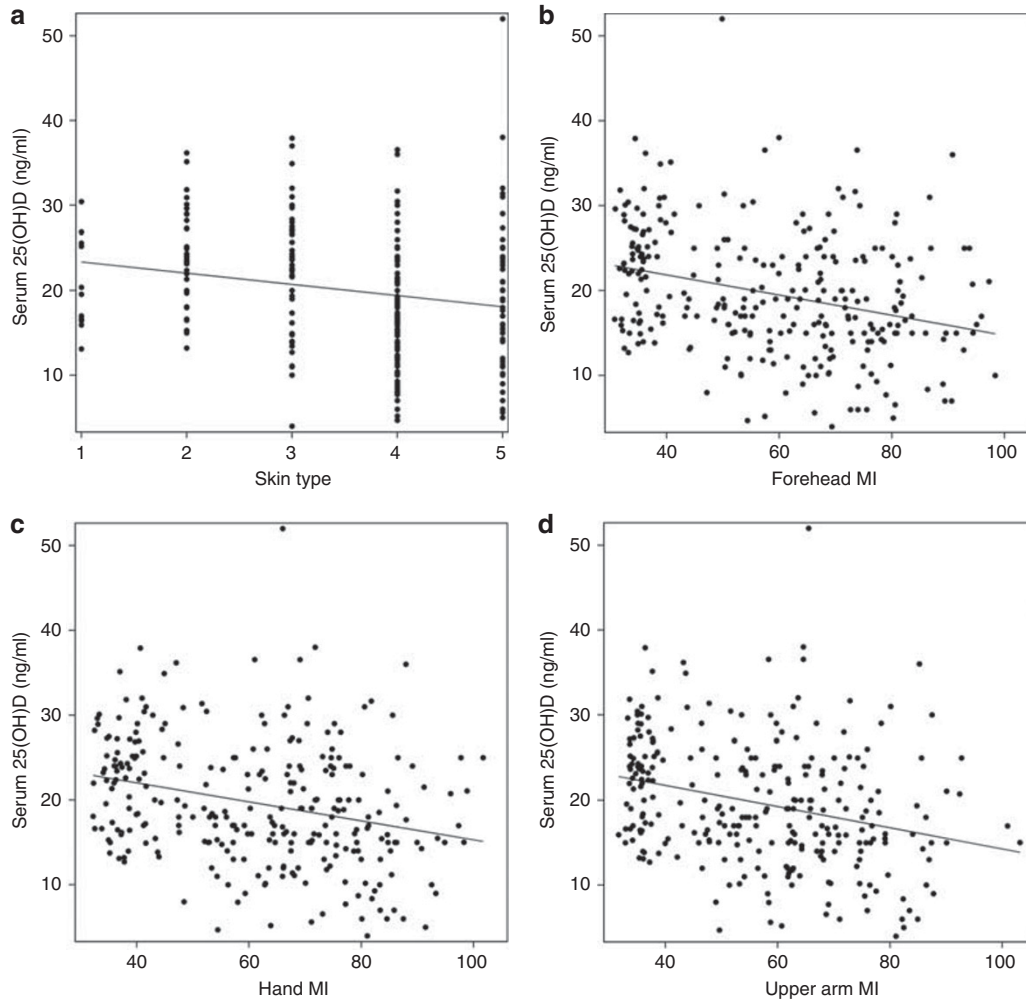
Figure 1. Serum 25(OH)D and skin color correlations: (**a**) skin type, (**b**) forehead melanin index, (**c**) hand melanin index, and (**d**) upper arm melanin index. 25(OH)D, 25-hydroxyvitamin D.

Table 2. 25(OH)D status stratified by high vs. low skin type and high vs. low MI

	Stratification; strata (N)	<20 ng/ml, deficient; n (%)	≥20 ng/ml, non-deficient; 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%)

MI, melanin index; 25(OH)D, 25-hydroxyvitamin D.
Melanin indices were dichotomized at the median of the more racially balanced Study 1 cohort.
Site (median MI (25th to 75th quartile)).
[a]Forehead (49 (35-69)).
[b]Hand (52 (38, 72)).
[c]Upper arm (48 (36, 68)).

shown in **Supplementary Table S1** online). Dark-skinned children (i.e., skin types IV–V; MI ≥ median) when compared with light-skinned children (i.e., skin types I–III; MI < 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 are shown in **Figure 3**.

DISCUSSION

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

Table 3. Prediction of 25(OH)D < 20 ng/ml between high vs. low MI and high vs. low skin type

	Se; % (95% CI)	Sp; % (95% CI)	PPV; % (95% CI)	NPV; % (95% CI)	ROC model; AUC ± SE (95% CI)
Skin types 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)

AUC, area under the curve; CI, confidence interval; MI, melanin index; NPV, negative predictive value; 25(OH)D, 25-hydroxyvitamin D; PPV, positive predictive value; Se, sensitivity; Sp, specificity.
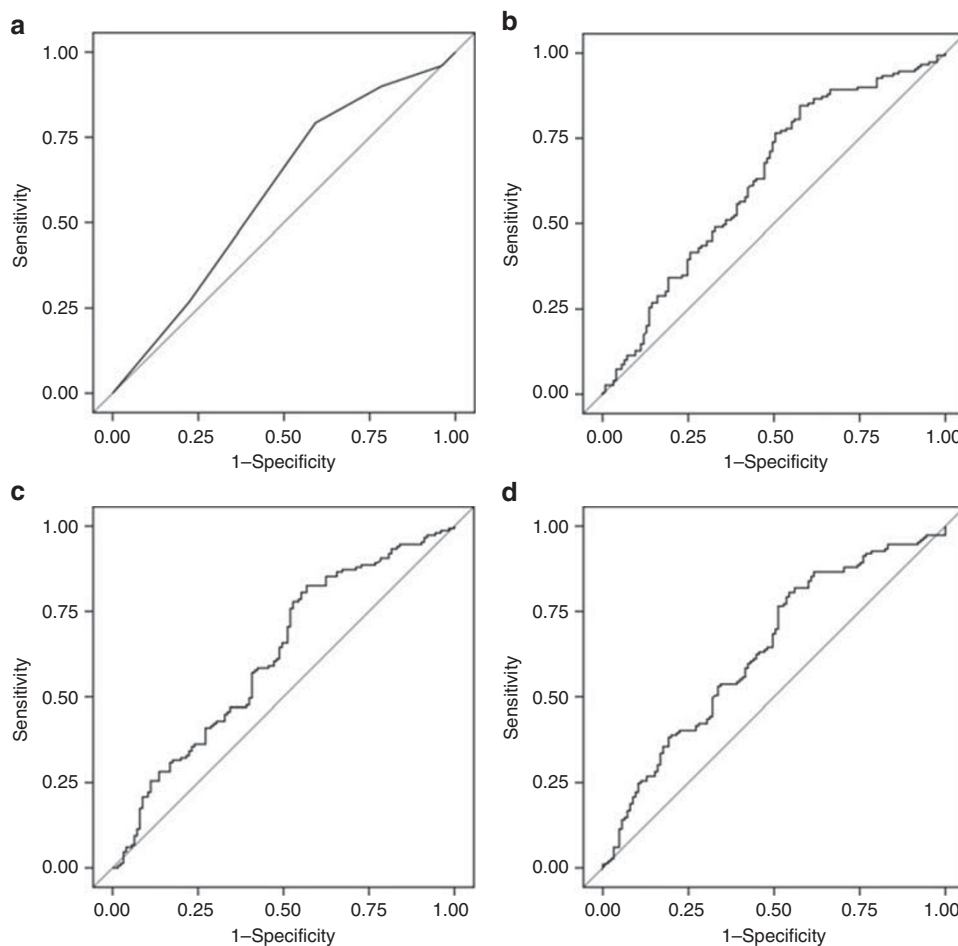

Figure 2. ROC curves (AUC (95% CI)) for discerning vitamin D deficiency by skin color: (**a**) skin types I–III vs. IV–V (0.59 (0.53, 0.66)), (**b**) forehead melanin index (0.63 (0.56, 0.70)), (**c**) hand melanin index (0.62 (0.55, 0.69)), and (**d**) upper arm melanin index (0.64 (0.57, 0.70)). AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristic.

assessment of skin color phenotypes in the context of vitamin D research.

Our findings also indicate both MI and skin type to be negatively associated with serum 25(OH)D concentrations. In addition, both MI 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 ultraviolet-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 is 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 MI in the context of vitamin D research in children and to examine their
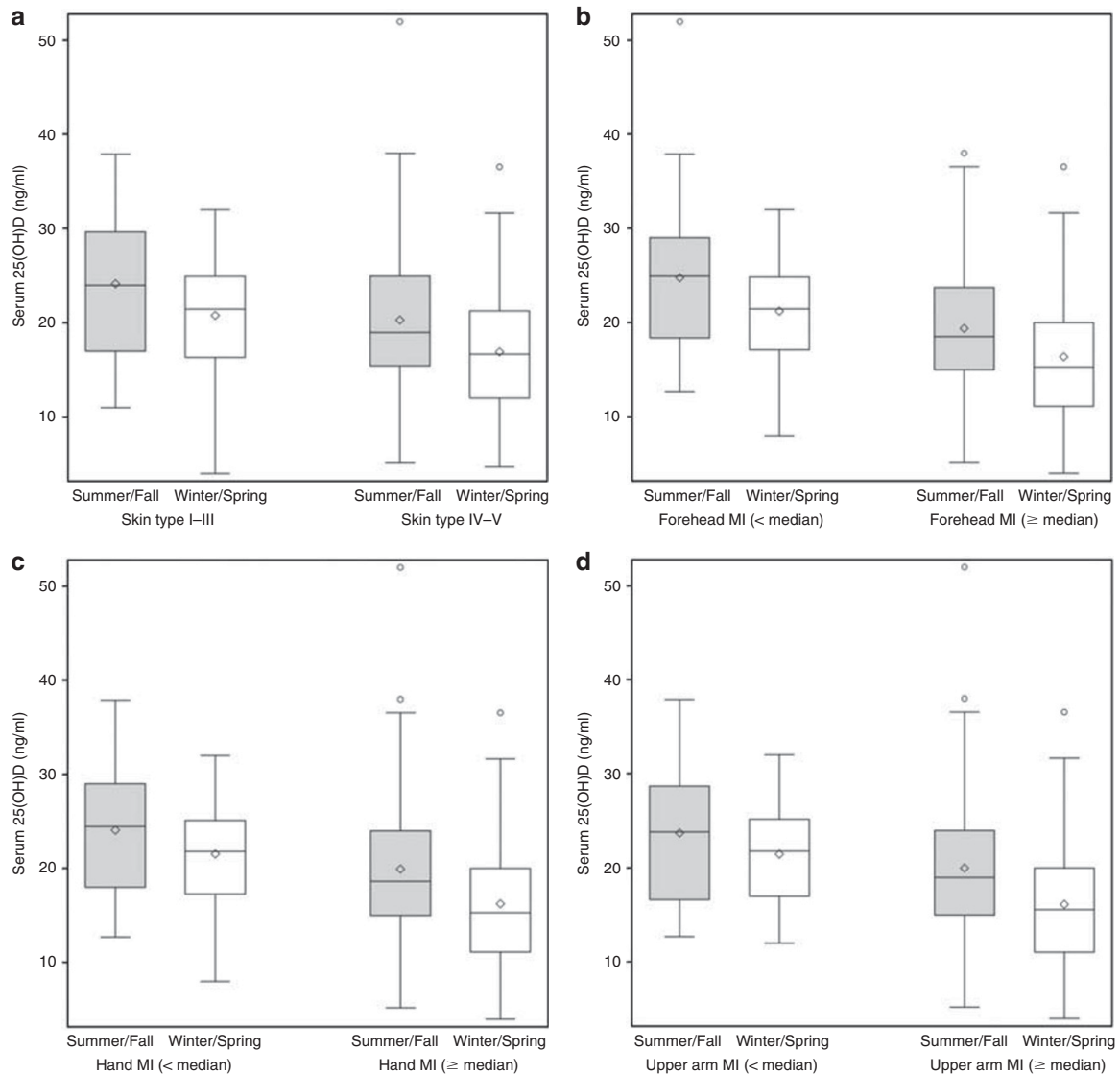
Figure 3. Box plots of the serum 25(OH)D concentrations by skin color and season: (**a**) skin types I–III vs. IV–V, (**b**) forehead melanin index (<median vs. ≥ median), (**c**) hand melanin index (<median vs. ≥ median), and (**d**) upper arm melanin index (<median vs. ≥ median). The box represents the 25th to 75th quartile range split at the median (50th percentile); means are denoted by diamonds. Shaded boxes indicate 25(OH)D concentrations during summer/fall, whereas unshaded boxes indicate 25(OH)D concentrations during winter/spring. The whiskers represent the maximum and minimum range of the data sets exclusive of outliers. Statistical outliers are shown as circles. 25(OH)D, 25-hydroxyvitamin D.

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 cutpoints of MI 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 Institute of Medicine-set threshold concentrations. The MI cutpoint was chosen from the more racially balanced Study 1 participant subset. Furthermore, it is reassuring that the chosen MI cutpoints 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 MI (Figure 1) indicates that Fitzpatrick skin type and MI may not have the same predictive value for identifying vitamin D deficiency if the study population is homogenous in skin type or MI. Fitzpatrick skin type and MI 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 with that during 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 the following: (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; (refs 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 types 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 FST, 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.* (32) collected burning and tanning histories from 18- to 30-year-old white adults and found that of 790 subjects only 41% could be classified according to the Fitzpatrick sun-reactive skin type scale; tanning response was better associated with skin color than burning response. 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 MI 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 MI 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, MI 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 whether inclusion of other determinants of vitamin D status in addition to skin color can improve the prediction of vitamin D deficiency.

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