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Clinical Research Article

Race-neutral Pediatric Reference Ranges for Bone Mineral Density Predict Prospective Fractures in Childhood

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Abstract

Introduction: Race-specific reference ranges for pediatric areal bone mineral density (BMD) are widely used, but the value of race-based clinical algorithms has been questioned. We developed race-neutral pediatric reference ranges for areal BMD and bone mineral apparent density (BMAD) and compared race-specific vs race-neutral Z-scores in their ability to predict prospective fractures.

Material and Methods: This secondary analysis of the Bone Mineral Density in Childhood Study used longitudinal BMD data of the spine, hip, forearm, and total body less head and BMAD from dual-energy x-ray absorptiometry (DXA) scans. Race/ethnicity, dietary calcium, physical activity, and prospective fractures were assessed by questionnaire. Race-neutral reference ranges and height-for-age Z-score adjustment equations were created using the lambda-sigma-mu method. Race-neutral and race-specific Z-scores were compared using linear mixed-effect modeling. Cox proportional hazard modeling was used to test whether race-neutral Z-scores associated with fracture.

Results: Race-neutral BMD and BMAD Z-scores were 0.5 to 0.7 SD greater than race-specific Z-scores for Black children but only ∼0.1 SD lower for children from other race/ethnicity groups. Growth and lifestyle factors modified group differences. One SD increase in race-neutral Z-scores was associated with a 12% to 18% reduced risk of fracture.

Conclusion: We present the first race-neutral pediatric reference ranges for BMD and BMAD that are weighted to be representative of the US population and demonstrate that these Z-scores associate with fracture risk. Adoption of these new reference ranges should be considered, with thoughtful implementation for patients previously monitored with race-specific reference ranges, especially among children who identify as Black.

Key Words: BMD, BMAD, children, fracture

Numerous studies have reported higher areal bone mineral density (BMD) in African Americans compared to other racial and ethnic groups of US children (1, 2) and adults (3). Accordingly, 2 International Society of Clinical Densitometry Pediatric Positions conferences in 2007 and 2013 (4-6) concluded that BMD reference ranges for children should be age-, sex-, and race-specific. Following this recommendation, the National Institute of Child Health and Human Development's Bone Mineral Density in Childhood Study (BMDCS) published separate reference ranges for Black and non-Black children in 2007 and 2011 (2, 7).

In health care and biomedical research, the use of race-based categories has come under scrutiny as a potential source of health disparities (8-10). Race and ethnicity are social constructs of group identity that capture an array of behavioral, social, political, economic, and environmental factors that

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influence health outcomes. Although racial and ethnic identity may also overlap with population ancestry, it is not possible to separate genetic vs nongenetic bases for most complex traits. Therefore, the use of racial categories in biomedical research and practice needs to be carefully evaluated in terms of whether it confers harm or benefit and how it impacts interpretation of findings.

In contrast to BMD, national growth charts for height, weight, and body mass index are race-neutral, despite known differences in growth, maturation, and obesity prevalence between race and ethnicity groups (11-14). Accordingly, here we present race-neutral reference ranges for BMD representative of the race/ethnicity distribution of the US population. Consistent with the prior race-specific reference ranges, we characterized the association of height Z-scores with BMD and bone mineral apparent density (BMAD) Z-scores, to provide a method for adjusting for short-for-age or tall-for-age status in the interpretation of BMD during childhood. In addition, we compared these new race-neutral curves to the previously published race-specific reference curves in order to (1) quantify the magnitude of the effect of changing to race-neutral reference ranges on specific groups, (2) test whether race/ethnicity differences are diminished when biological and behavioral factors known to be associated with bone mineral accrual in children are considered, and (3) determine whether race-neutral and race-specific Z-scores associate with prospective fracture risk, a clinically relevant outcome.

Methods

Design

This is a secondary analysis of data from the National Institute of Child Health and Human Development Bone Mineral Density in Childhood Study, a mixed longitudinal study of healthy children conducted between 2002 and 2009 (2, 7). Children were enrolled at 5 clinical centers in the United States: Cincinnati Children's Hospital Medical Center (Cincinnati, OH), Los Angeles Children's Hospital (Los Angeles, CA), The Children's Hospital of Philadelphia (Philadelphia, PA), Creighton University (Omaha, NE), and Columbia University (New York, NY). Inclusion/exclusion criteria at enrollment [Supplementary Table S1 (15)] were consistent with identifying a group of healthy children with growth within the normal range (±2 SD) for height, weight, and body mass index who did not have medical conditions or medication use that would affect growth, nutritional status, or bone density. Children with a history of >2 fractures if age <10 years or >3 fractures if age ≥ 10 years were excluded. Children remained in the study if they did not meet eligibility criteria (medical conditions or medication use) at a later visit, but their results were excluded in the creation of reference ranges if certain eligibility criteria were not met [Supplementary Fig. S1 (15)].

The first wave of recruitment enrolled males 6 to 16 years and females 6 to 15 years of age, who were measured annually for up to 6 years (7 visits). A second recruitment wave in the fourth year included children who were 5 years and 19 years. This group was measured annually for 3 years. In all, 2014 children were enrolled, and the full age range encompassed 5 to 23 years.

The institutional review board at each institution reviewed and approved the protocol. We obtained written informed consent from legal guardians if study participants were <18 years of age and from study participants for ages ≥ 18 years. Assent was obtained from study participants <18 years of age.

Methods

Self-identified race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White) and ethnicity (Hispanic or Latino—yes, no, or unknown) was obtained by questionnaire using the categories designated by the National Institutes of Health at that time. If more than 1 category for race or "unknown" was selected or the question was declined; then individuals were categorized as "other/mixed race." Height and weight were measured using standard techniques with study participants wearing light clothing and shoes removed. Z-scores for height (HAZ), weight (WAZ), and body mass index were calculated using the Centers for Disease Control and Prevention 2000 growth charts (16).

BMD measurements were obtained using Hologic (Marlborough, MA) dual energy X-ray absorptiometers (QDR4500A, QDR4500W, and Delphi A models) and analyzed centrally (J.A.S.) using Hologic Discovery 12.3 software at baseline and Apex 2.1 software at follow-up with the compare feature. We measured the lumbar spine, proximal femur, forearm, and whole body using standardized positioning and scan acquisition techniques. Scans were inspected for movement or other artifacts and excluded if these were present. Outcomes included BMD of the spine, total hip, femoral neck, distal one-third radius, ultradistal radius, and total body less head (TBLH BMD) and spine BMAD. BMAD was calculated as $[(\sum \text{L1 to L4 bone mineral content [BMC]})/(\text{L1 area}^{1.5} + \text{L2 area}^{1.5} + \text{L3 area}^{1.5} + \text{L4 area}^{1.5})]$ (17). Body composition was obtained from whole body scans; appendicular lean soft tissue mass index (ALMI), excluding bone, was calculated (sum of lean soft tissue mass of the arms and legs) and expressed as Z-scores relative to age and sex (13).

Dietary calcium intake (mg/day) was estimated with a 45-item semiquantitative food frequency questionnaire developed by Block Dietary Data Systems (Berkeley, CA) as previously described (18, 19) and compared to the Dietary Reference Intake for calcium (20). Physical activity (hours/week) was estimated using a 37-item modified questionnaire from Slemenda (21). From the list of activities, we derived an estimate of high-impact physical activity based on time spent in physical activities with a ground reaction force greater than 2 times body weight involving sprinting, turning, or jumping actions (22). Data on fractures in the prior year were elicited by questionnaire.

Statistical Analyses

Race-neutral reference ranges were estimated using the lambda-mu-sigma method, and the Box Cox Cole Green distribution family was selected (23). Analyses were conducted using the Generalized Additive Models for Location Scale and Shape function in R (version 4.2.1, R Foundation for Statistical Computing, Vienna, Austria). Sample weights were applied (White: 10; Black: 6; Hispanic: 15; Asian: 7; other: 12) so that the representation of race and ethnicity groups was similar to the 2017-2018 National Health and Nutrition Examination Survey (24): 49% non-Hispanic White; 13% non-Hispanic Black; 26% Hispanic; 5% Asian; 7% Pacific Islander, Native American, and other. These weights were selected to approximate the current race/ethnicity distribution in the United States. Males and females were analyzed separately. The age-specific L (power for the Box-Cox transformation), M (median) and S (SD) values were used to create reference percentiles using equation 1:

$$\text{BMD centile} = \text{M}\ (1 + \text{LSZ})^{1/\text{L}}$$

where Z is the Z-score that corresponds to a given percentile. Individual Z-scores were then calculated using equation 2:

$$\text{Z} = [((\text{X}/\text{M})^{\text{L}})\text{–}1]/\text{L}\bullet\text{S}$$

where X is the measured BMD. All ages were used to generate the curves. As there were few individuals older than age 20 years of age, the reference ranges were restricted to ages 5 to 20 years.

Additional analyses were performed using Stata v. 16.1. We assessed differences in race-neutral BMD Z-scores according to self-identified race and ethnicity using mixed-effects models to account for the multiple observations per person. Sample weights were not applied for these analyses since the goal was to examine actual values. We then adjusted for lifestyle factors, linear growth, and body composition (calcium intake, high-impact physical activity, HAZ, and ALMI-Z) known to be associated with BMD in a stepwise manner to assess whether race/ethnicity differences in BMD Z-scores were attenuated or eliminated after adjustment for these factors.

The effects of shorter ($\text{HAZ} < -1$ SD), average (HAZ within ± 1 SD), or taller stature ($\text{HAZ} > 1$ SD) on BMD Z-scores were examined by mixed-effects regression analysis to account for the multiple observations per person. We present the R^2 value to characterize the variance in BMAD and BMD Z-scores explained by HAZ. Bootstrapping was used to estimate the standard error for the R^2 value. To further inspect this relationship, we repeated the analysis within subgroups based on age (5-9.9, 10-14.9, and ≥15 years), since linear growth velocity is variable across childhood. We then used sex-specific regression models with age group by HAZ interactions to test for potential age-specific associations between HAZ and BMD outcomes (excluding BMAD and ultradistal radius BMD Z-scores since these outcomes were not associated with HAZ). Sample weights (as described earlier) were included in these latter models to develop age- and sex-specific HAZ adjustment equations [as previously described (2, 25)] representative of the US population. The adjustment method involves predicting the age- and sex-specific BMD Z-score based on HAZ. The HAZ-adjusted BMD outcome is calculated as:

$$\text{Predicted Z-score} = \text{a} + \text{b}^{*}\text{HAZ (age and sex specific)}$$

$$\begin{aligned}&\text{HAZ adjusted Z-score}\\&\quad = \text{BMD for age Z-score–Predicted Z-score}\end{aligned}$$

Lastly, we assessed if each of the BMD Z-scores associated with the risk of prospective fractures over the 7-year observational period using Cox proportional hazard models to estimate hazard ratios (HRs). Bootstrapping was used to obtain 95% confidence intervals (CIs) for the HRs. This involved generating 1000 bootstrapped datasets by random sampling with replacement and fitting Cox proportional hazard models for race-neutral and race-specific BMAD Z-scores and BMD Z-scores and HAZ-adjusted Z-scores within each dataset. To determine whether the race-neutral Z-scores were more strongly associated with fracture risk, we calculated the difference in HRs (race-specific Z-score minus race-neutral Z-score) for each of the 1000 bootstrapped datasets. The empirical distribution of these differences was then used to calculate the 95% CIs for the difference in HRs. These analyses were conducted in R, version 4.3.1.

Results

The study enrolled 2104 individuals with a total of 10 722 observations over the 7-year observation period (63% completed 7 visits and 95% of participants completed 3 or more visits). For this study, we excluded 634 observations on 219 study participants because they did not meet certain inclusion criteria at postbaseline visits [Supplementary Fig. S1 (15)]. We next removed scans that did not pass quality control review—motion artifact and interfering factors—resulting in sample sizes of 9847 to 10 032 scans per skeletal site for the 2104 participants. Baseline characteristics of this analytical cohort are provided in Table 1.

The overall composition of the race/ethnicity identity in the sample based on the 10 032 observations was 48% White,

Table 1. Baseline characteristics

Factor	Category	Baseline visit
n		2014[a]
Age, mean (SD)		11.3 (4.4)
Sex (%)	Male	992 (49.3)
	Female	1022 (50.7)
Tanner stage (%)	1	906 (45.0)
	2	205 (10.2)
	3	162 (8.0)
	4	213 (10.6)
	5	410 (20.4)
	Not done	118 (5.9)
Self-reported race (%)	American Indian or Alaskan	4 (0.2)
	Asian or Pacific Islander	129 (6.4)
	Black	479 (23.8)
	Hispanic	336 (16.7)
	White	953 (47.3)
	Mixed/other	113 (5.6)
Physical activity, hours/week, mean (SD)		
Total		16.5 (13.8)
High impact		4.4 (5.2)
Dietary calcium intake		
mg/day, mean (SD)		911.2 (552.4)
Percent of recommended intake, %[b]		76 (0.5)
Height Z-score, mean (SD)		0.14 (0.82)
BMI Z-score, mean (SD)		0.33 (0.82)
Appendicular lean soft tissue mass index Z-score, mean (SD)		0.00 (1.00)

Abbreviation: BMI, body mass index.

[a] Of this total, n = 1554 enrolled in year 1 and n = 460 enrolled in year 4.

[b] Recommended calcium intake based on the Institute of Medicine, Dietary Reference Intakes for Calcium and Vitamin D (Washington, DC: The National Academies Press; 2011).

22% Black, 16% Hispanic, 7% Asian, and 6% other/mixed race. Children who self-identified as Black were overrepresented in the sample because the initial study goal was to generate separate reference curves for Black and non-Black children. Sample weights were applied so that the resulting representation of groups was similar to the 2017-2018 National Health and Examination Survey as follows: White: 49%; Black: 14%; Hispanic: 25%; Asian: 5%; other: 7%.

The sex-specific reference curves for BMD of the spine, total hip, femoral neck, distal one-third radius, ultradistal radius, TBLH, and BMAD are shown in Fig. 1A-1C and Supplementary Fig. S2A-2D (15). Lambda-mu-sigma values and −2 SD, median, and +2 SD values are provided in Table 2 and Supplementary Table S2 (15).

The race-specific and race-neutral Z-scores comparisons are illustrated in Fig. 2 [and Supplementary Fig. S3 (15)]. On average, the difference in Z-scores between the race-neutral curves and the race-specific curves was −0.1 SD for all race/ethnicity groups except the group that self-identified as Black; for this group, race-neutral Z-scores were 0.5 to 0.7 SD greater than race-specific Z-scores [Supplementary Table S3 (15)]. Consistent with these results, the prevalence of low BMD Z-scores (BMD $Z < -2$) did not change significantly for most race/ethnicity groups (less than 1 percentage point). However, for the group that identified as Black [Supplementary Table S4 (15)], the change was statistically significant ($P \leq .002$) at all skeletal sites. For example, the prevalence of low spine BMD was 2.5% using race-specific Z-scores but was 1% using race-neutral Z-scores.

We considered whether the differences in race-neutral Z-scores by race/ethnicity groups might be attributable to growth, body composition, or lifestyle factors. We compared adjusted mean (95% CI) Z-scores for race/ethnicity groups from models with the sequential addition of the following covariates: no covariates; calcium intake, time spent in high-impact physical activity, HAZ, and ALMI-Z. Results are shown in Fig. 3 [and Supplementary Fig. S4 (15)]. For all race/ethnicity groups, there were no appreciable changes in adjusted mean Z-scores when calcium intake and physical activity were included in the models. The addition of ALMI-Z to models with the other covariates had the largest effect on reducing BMD and BMAD Z-score differences between race/ethnicity groups, and the adjusted means from the full model were closer to 0 than the unadjusted means. For the Black group, the adjusted means for all Z-scores remained higher than for other groups.

Given the known association between height and DXA measures of BMD, we used sex-specific regression analysis to examine the association of HAZ with BMD and BMAD Z-scores for the entire cohort and by age group (<10 years, 10-14.9 years, and ≥15 years). Explained variances (R^2) across all ages were highest for TBLH BMD-Z ($R^2 = 0.19$ for females and 0.17 for males) but were lower for other skeletal sites. The R^2 values for BMAD and ultradistal radius BMD Z-scores across all ages and for individual age groups were negligible, ranging from 0.01 for spine BMAD-Z and ultradistal radius to 0.10 for spine BMD-Z. The variance in TBLH BMD-Z explained by HAZ was greatest for children less than age 10 years ($R^2 = 0.33$ for females and 0.30 for males) and was lower for older age groups ($R^2 = 0.23$ for males and females 10-14.9 years; $R^2 = 0.06$ for females and 0.08 for males ≥15 years). For other skeletal sites, the R^2 values ranged from 0.01 to 0.16 in children <10 years and 0.02 to 0.17 for children 10 to 14.9 years and was extremely low in those ≥ 15 years, ranging from 0.04 to 0.00 (Supplementary Table S5). Because of the age trends, we developed age- and sex-specific equations to predict spine, total hip, femoral neck, distal one-third radius, and TBLH BMD Z-scores with HAZ (Table 3). The difference between the BMD for age Z-score and the HAZ-predicted BMD Z-score (HAZ-adjusted Z-score) represents the degree to which low (or high) BMD for age Z-score might be attributable to shorter stature. For example, for a boy of age 10.2 years with height = 127.5 cm, HAZ = −1.88, spine BMD = 0.43 g/cm^2, and spine BMD-for-age Z = −2.52, his HAZ-predicted spine BMD Z would be [0.005 + (−1.88 * 0.335) = − 0.63] and his HAZ-adjusted spine BMD Z would be [−2.52 − (−0.63)] = −1.89. This example illustrates that performing HAZ adjustment of BMD Z-scores in children with shorter stature can change the classification of their BMD from lower than expected for age and sex (here, −2.52) to within the expected range (here, −1.89).

Figure 4 and Supplementary Fig. S5 (15) show the distributions of BMD for age Z-scores and HAZ-adjusted BMD Z-scores for groups with shorter (HAZ < −1), average (HAZ −1 to +1), or taller (HAZ >+1) stature across 3 age groups. The HAZ-adjusted BMD Z-scores have values close to 0 ± 1, in alignment with children with average stature for their age.

Lastly, we used prospectively collected fracture information to assess the risk of fracture associated with race-neutral Z-scores and race-specific Z-scores. For participants ≤ 20 years (for whom Z-scores could be computed), 221 study participants reported a total of 264 fractures over the 7401 annual follow-up study visits; 183 individuals reported 1 fracture, and 81 reported 2 or more fractures. Sixty-two percent of fractures occurred in males. Most fractures occurred in the forearm (35%), hand (27%), or foot (11%). The majority occurred during sport activities (48%) [Supplementary Table S6 (15)]. Results of the Cox proportional hazard models indicated that a 1 SD increase in race-neutral spine BMAD, spine BMD, and distal one-third radius BMD Z-score associated with 12% to 18% reduced risk of fracture (HR: 0.82, 95% CI: 0.76, 0.91; HR: 0.88, 95% CI: 0.82, 0.99; and HR: 0.86, 95% CI: 0.78, 0.98, respectively) (Table 4). Race-neutral TBLH, total hip, femoral neck, and ultradistal radius BMD Z-scores also were not significantly associated with fracture risk. A 1 SD increase in race-specific spine BMAD Z-score was associated with an 13% reduction in fracture risk (HR: 0.87, 95% CI: 0.80, 0.98). Race-neutral HAZ-adjusted BMD Z-scores for the spine, total hip, femoral neck, and distal one-third radius were significantly associated with fracture risk, with HRs ranging from 0.83 to 0.88 (Table 4), whereas only race-specific HAZ-adjusted spine BMD Z-score associated with fracture (HR: 0.87, 95% CI: 0.80, 0.97). The difference in HRs between race-neutral and race-specific Z-scores was significant for spine BMD, spine BMAD, and distal one-third radius and HAZ-adjusted femoral neck and distal one-third radius BMD. The HRs for HAZ-adjusted spine BMD did not differ for the race-neutral and race-specific Z-scores (Table 4).

Discussion

We generated the first race-neutral Z-scores for BMD and BMAD for children ages 5 to 20 years of age representative of the race/ethnicity distribution of the US population and showed the differences between race-neutral vs race-specific

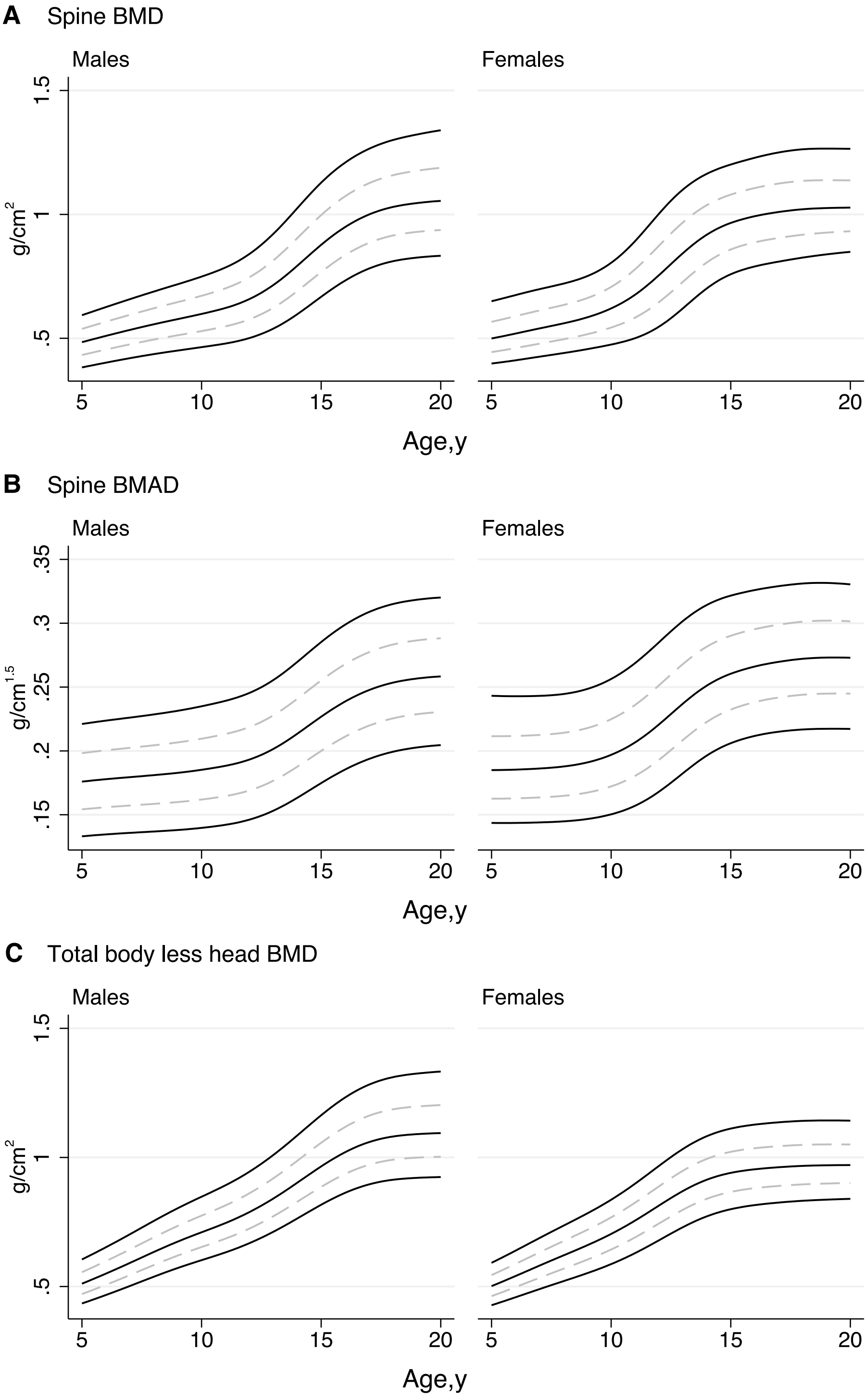

Figure 1. Reference ranges for race-neutral Z-scores for (A) spine BMD, (B) spine BMAD, and (C) total body less head BMD. Shown are the curves for −2 SD, −1 SD, the median, + 1 SD, and +2 SD.

Abbreviations: BMAD, bone mineral apparent density; BMD, bone mineral density.

Z-scores in this cohort. This comparison is important for understanding the interpretation of Z-scores with the adoption of race-neutral reference ranges. For example, when interpreting newly obtained race-neutral BMD Z-scores in patients monitored previously with race-specific BMD Z-scores, there are likely to be shifts in Z-scores due to a change in reference range. For most subgroups, this shift will be a modest change (0.1 Z-score units), but for children who identify as Black, the shifts are likely to be large (0.5 or more Z-score units). For children who identify as Black, this shift should not be interpreted as an improvement in bone health; it represents how an individual child's BMD compares to the general population, rather than how it compares to their peers who identify as Black, a group who, on average, have higher BMD than other subgroups of the general population. For patients who identify as Black and are currently being

Table 2. LMS values and reference ranges for BMD of the spine, total body less head, total hip, femoral neck, distal one-third radius, and ultradistal radius and spine bone mineral apparent density

Age	Males					Females				
	L	S	−2 SD	Median (M)	+2 SD	L	S	−2 SD	Median (M)	+2 SD
Spine BMD										
5.0-5.9	0.685	0.109	0.392	0.497	0.610	−0.542	0.122	0.405	0.509	0.662
6.0-6.9	0.647	0.111	0.411	0.522	0.642	−0.400	0.123	0.419	0.530	0.687
7.0-7.9	0.609	0.112	0.428	0.545	0.673	−0.258	0.123	0.433	0.550	0.709
8.0-8.9	0.570	0.115	0.444	0.567	0.704	−0.113	0.123	0.448	0.571	0.734
9.0-9.9	0.530	0.117	0.458	0.588	0.733	0.038	0.127	0.465	0.601	0.774
10.0-10.9	0.490	0.121	0.471	0.610	0.766	0.195	0.138	0.486	0.645	0.844
11.0-11.9	0.453	0.126	0.489	0.638	0.810	0.348	0.149	0.520	0.713	0.947
12.0-12.9	0.417	0.131	0.518	0.684	0.878	0.466	0.148	0.581	0.800	1.055
13.0-13.9	0.380	0.135	0.566	0.752	0.971	0.512	0.134	0.663	0.884	1.136
14.0-14.9	0.338	0.133	0.632	0.835	1.078	0.475	0.119	0.734	0.945	1.185
15.0-15.9	0.287	0.128	0.702	0.915	1.172	0.378	0.112	0.777	0.981	1.215
16.0-16.9	0.223	0.122	0.760	0.977	1.240	0.242	0.109	0.800	1.002	1.240
17.0-17.9	0.150	0.119	0.799	1.017	1.285	0.078	0.108	0.818	1.016	1.258
18.0-18.9	0.070	0.118	0.820	1.039	1.312	−0.110	0.105	0.833	1.024	1.265
19.0-19.9	−0.015	0.118	0.830	1.051	1.332	−0.319	0.101	0.844	1.027	1.265
Total body less head BMD										
5.0-5.9	−0.236	0.083	0.451	0.530	0.628	−0.146	0.082	0.443	0.521	0.615
6.0-6.9	−0.278	0.084	0.484	0.570	0.677	−0.010	0.084	0.474	0.561	0.663
7.0-7.9	−0.319	0.084	0.520	0.613	0.728	0.110	0.086	0.505	0.601	0.712
8.0-8.9	−0.360	0.085	0.555	0.654	0.779	0.205	0.087	0.536	0.640	0.759
9.0-9.9	−0.402	0.085	0.587	0.692	0.826	0.270	0.088	0.569	0.681	0.809
10.0-10.9	−0.443	0.086	0.617	0.728	0.870	0.298	0.089	0.607	0.729	0.866
11.0-11.9	−0.484	0.086	0.649	0.766	0.917	0.279	0.089	0.654	0.784	0.933
12.0-12.9	−0.526	0.087	0.689	0.813	0.976	0.201	0.088	0.705	0.843	1.001
13.0-13.9	−0.567	0.087	0.737	0.871	1.046	0.065	0.086	0.753	0.894	1.060
14.0-14.9	−0.608	0.088	0.790	0.934	1.125	−0.110	0.083	0.787	0.929	1.099
15.0-15.9	−0.650	0.088	0.841	0.994	1.199	−0.288	0.082	0.809	0.948	1.121
16.0-16.9	−0.691	0.089	0.881	1.042	1.260	−0.440	0.080	0.821	0.958	1.132
17.0-17.9	−0.732	0.089	0.906	1.072	1.299	−0.560	0.079	0.829	0.965	1.139
18.0-18.9	−0.774	0.090	0.918	1.087	1.319	−0.656	0.078	0.835	0.969	1.143
19.0-19.9	−0.815	0.091	0.923	1.093	1.329	−0.741	0.077	0.838	0.970	1.143
Total hip BMD										
5.0-5.9	1.281	0.093	0.485	0.599	0.708	−0.132	0.097	0.472	0.572	0.696
6.0-6.9	1.155	0.098	0.510	0.636	0.759	−0.095	0.098	0.493	0.598	0.729
7.0-7.9	1.030	0.103	0.533	0.671	0.808	−0.059	0.100	0.511	0.623	0.762
8.0-8.9	0.909	0.107	0.552	0.701	0.853	−0.022	0.104	0.526	0.647	0.797
9.0-9.9	0.793	0.112	0.568	0.726	0.892	0.014	0.110	0.540	0.674	0.840
10.0-10.9	0.683	0.116	0.582	0.750	0.930	0.050	0.120	0.560	0.712	0.903
11.0-11.9	0.586	0.120	0.601	0.779	0.975	0.087	0.128	0.592	0.767	0.989
12.0-12.9	0.506	0.124	0.630	0.821	1.038	0.123	0.131	0.639	0.835	1.081
13.0-13.9	0.448	0.127	0.673	0.882	1.123	0.160	0.128	0.691	0.897	1.153
14.0-14.9	0.411	0.130	0.725	0.954	1.221	0.196	0.123	0.729	0.938	1.193
15.0-15.9	0.392	0.131	0.772	1.018	1.307	0.232	0.121	0.749	0.961	1.216
16.0-16.9	0.387	0.132	0.806	1.065	1.368	0.269	0.122	0.756	0.973	1.233
17.0-17.9	0.391	0.132	0.827	1.092	1.404	0.305	0.123	0.758	0.980	1.243
18.0-18.9	0.398	0.132	0.835	1.103	1.417	0.342	0.123	0.759	0.980	1.241
19.0-19.9	0.402	0.132	0.834	1.103	1.417	0.378	0.120	0.758	0.975	1.227

(*continued*)

Table 2. Continued

Age	Males					Females				
	L	S	−2 SD	Median (M)	+2 SD	L	S	−2 SD	Median (M)	+2 SD
Femoral neck BMD										
5.0-5.9	0.262	0.101	0.461	0.567	0.691	−0.770	0.090	0.466	0.551	0.669
6.0-6.9	0.271	0.105	0.485	0.601	0.737	−0.670	0.095	0.476	0.569	0.697
7.0-7.9	0.280	0.108	0.507	0.634	0.782	−0.571	0.100	0.488	0.589	0.728
8.0-8.9	0.289	0.112	0.525	0.661	0.821	−0.470	0.105	0.500	0.610	0.761
9.0-9.9	0.298	0.115	0.539	0.685	0.856	−0.364	0.111	0.514	0.636	0.801
10.0-10.9	0.307	0.119	0.552	0.707	0.890	−0.252	0.117	0.534	0.670	0.853
11.0-11.9	0.316	0.123	0.569	0.734	0.930	−0.134	0.123	0.562	0.716	0.920
12.0-12.9	0.324	0.126	0.591	0.769	0.980	−0.018	0.129	0.596	0.770	0.996
13.0-13.9	0.333	0.130	0.622	0.816	1.046	0.085	0.132	0.628	0.821	1.067
14.0-14.9	0.342	0.133	0.659	0.870	1.122	0.170	0.135	0.652	0.859	1.118
15.0-15.9	0.351	0.136	0.694	0.923	1.196	0.235	0.136	0.666	0.882	1.147
16.0-16.9	0.360	0.138	0.723	0.967	1.258	0.282	0.137	0.673	0.894	1.163
17.0-17.9	0.369	0.140	0.741	0.996	1.301	0.312	0.137	0.676	0.900	1.169
18.0-18.9	0.378	0.142	0.747	1.008	1.321	0.328	0.136	0.678	0.900	1.167
19.0-19.9	0.386	0.144	0.743	1.008	1.324	0.335	0.134	0.677	0.896	1.158
Distal one-third radius BMD										
5.0-5.9	0.510	0.077	0.363	0.426	0.494	0.168	0.079	0.357	0.418	0.489
6.0-6.9	0.307	0.077	0.382	0.447	0.520	0.347	0.077	0.376	0.441	0.512
7.0-7.9	0.115	0.078	0.399	0.467	0.545	0.513	0.077	0.394	0.463	0.536
8.0-8.9	−0.050	0.079	0.416	0.487	0.570	0.671	0.078	0.409	0.482	0.558
9.0-9.9	−0.176	0.080	0.431	0.505	0.593	0.830	0.079	0.423	0.501	0.581
10.0-10.9	−0.254	0.081	0.445	0.521	0.616	0.992	0.082	0.439	0.525	0.612
11.0-11.9	−0.283	0.084	0.459	0.541	0.642	1.147	0.085	0.462	0.558	0.651
12.0-12.9	−0.264	0.088	0.477	0.566	0.678	1.274	0.084	0.492	0.595	0.693
13.0-13.9	−0.214	0.090	0.503	0.600	0.722	1.333	0.080	0.525	0.628	0.725
14.0-14.9	−0.150	0.089	0.538	0.641	0.769	1.296	0.074	0.552	0.650	0.744
15.0-15.9	−0.086	0.084	0.578	0.684	0.810	1.160	0.069	0.573	0.666	0.757
16.0-16.9	−0.026	0.078	0.616	0.719	0.841	0.946	0.067	0.588	0.678	0.769
17.0-17.9	0.030	0.073	0.643	0.744	0.860	0.671	0.066	0.598	0.686	0.778
18.0-18.9	0.083	0.071	0.659	0.760	0.876	0.344	0.066	0.604	0.691	0.786
19.0-19.9	0.140	0.071	0.669	0.772	0.889	−0.022	0.067	0.606	0.693	0.792
Ultradistal radius BMD										
5.0-5.9	0.033	0.099	0.228	0.278	0.338	−0.423	0.112	0.221	0.274	0.346
6.0-6.9	−0.132	0.104	0.233	0.285	0.352	−0.454	0.114	0.223	0.277	0.353
7.0-7.9	−0.291	0.108	0.238	0.293	0.366	−0.473	0.114	0.228	0.284	0.362
8.0-8.9	−0.424	0.111	0.243	0.301	0.380	−0.442	0.113	0.234	0.291	0.369
9.0-9.9	−0.503	0.113	0.249	0.309	0.392	−0.324	0.113	0.239	0.296	0.374
10.0-10.9	−0.511	0.115	0.254	0.315	0.402	−0.108	0.116	0.240	0.302	0.382
11.0-11.9	−0.449	0.119	0.257	0.321	0.413	0.174	0.124	0.242	0.311	0.396
12.0-12.9	−0.312	0.126	0.259	0.331	0.430	0.483	0.134	0.247	0.329	0.423
13.0-13.9	−0.093	0.136	0.264	0.345	0.455	0.779	0.138	0.260	0.355	0.457
14.0-14.9	0.175	0.144	0.274	0.368	0.487	1.001	0.134	0.281	0.383	0.486
15.0-15.9	0.428	0.146	0.291	0.397	0.523	1.103	0.124	0.306	0.408	0.508
16.0-16.9	0.606	0.141	0.315	0.430	0.558	1.078	0.115	0.328	0.427	0.524
17.0-17.9	0.688	0.134	0.342	0.460	0.588	0.933	0.109	0.343	0.438	0.534
18.0-18.9	0.700	0.126	0.368	0.486	0.613	0.693	0.106	0.353	0.444	0.542
19.0-19.9	0.676	0.120	0.388	0.504	0.630	0.398	0.105	0.358	0.446	0.545

(*continued*)

Table 2. Continued

Age	Males					Females				
	L	S	−2 SD	Median (M)	+2 SD	L	S	−2 SD	Median (M)	+2 SD
Spine bone mineral apparent density										
5.0-5.9	0.779	0.125	0.134	0.177	0.222	−0.255	0.131	0.144	0.185	0.243
6.0-6.9	0.751	0.126	0.135	0.179	0.225	−0.179	0.131	0.144	0.186	0.243
7.0-7.9	0.723	0.126	0.136	0.180	0.227	−0.103	0.131	0.144	0.187	0.244
8.0-8.9	0.696	0.127	0.137	0.182	0.230	−0.026	0.131	0.146	0.189	0.246
9.0-9.9	0.668	0.128	0.139	0.184	0.233	0.050	0.133	0.148	0.194	0.252
10.0-10.9	0.641	0.129	0.141	0.187	0.237	0.127	0.134	0.153	0.201	0.262
11.0-11.9	0.613	0.129	0.144	0.190	0.242	0.203	0.134	0.162	0.213	0.277
12.0-12.9	0.585	0.128	0.149	0.197	0.250	0.279	0.129	0.175	0.229	0.294
13.0-13.9	0.558	0.126	0.158	0.207	0.262	0.356	0.121	0.190	0.245	0.309
14.0-14.9	0.530	0.123	0.169	0.220	0.278	0.432	0.114	0.202	0.256	0.319
15.0-15.9	0.502	0.120	0.180	0.233	0.292	0.508	0.109	0.209	0.264	0.324
16.0-16.9	0.475	0.117	0.190	0.244	0.304	0.585	0.106	0.214	0.268	0.328
17.0-17.9	0.447	0.115	0.197	0.251	0.312	0.661	0.105	0.216	0.271	0.330
18.0-18.9	0.420	0.113	0.201	0.255	0.317	0.738	0.105	0.217	0.273	0.332
19.0-19.9	0.392	0.112	0.204	0.258	0.319	0.814	0.104	0.217	0.273	0.331

Abbreviations: BMD, bone mineral density; LMS, lambda-mu-sigma.

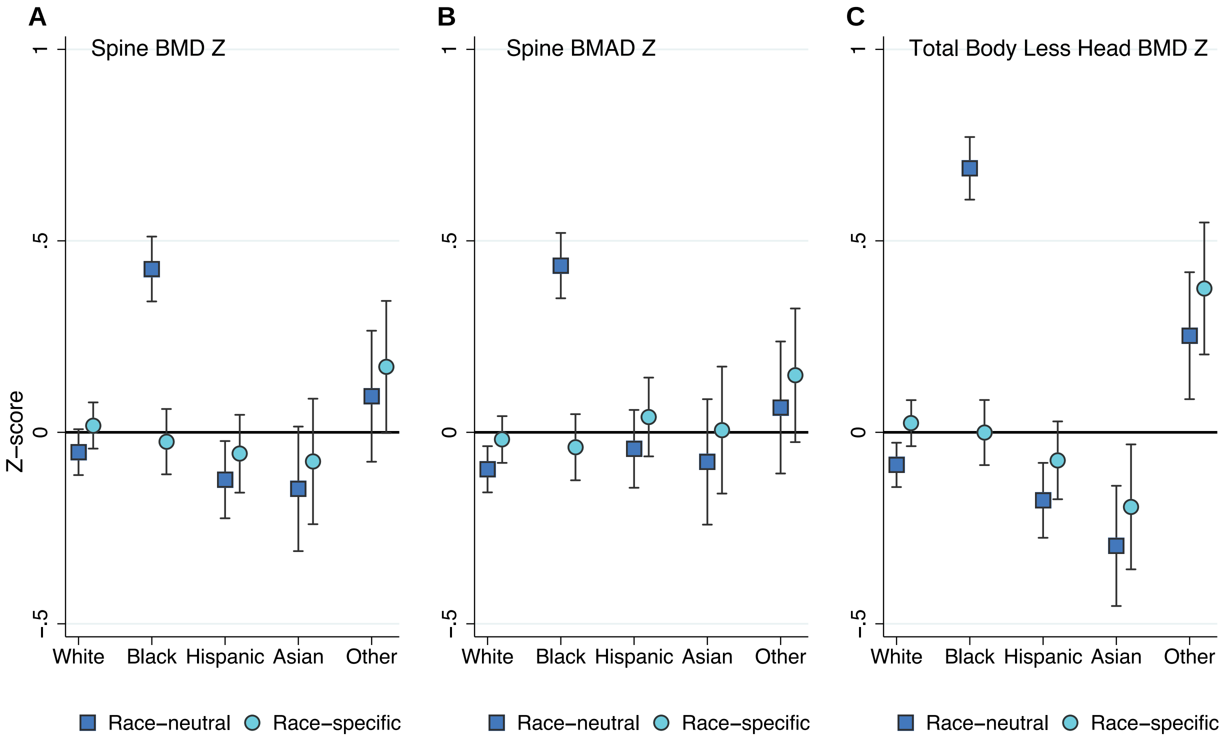

Figure 2. Distributions of race-specific and race-neutral Z-scores by race/ethnicity groups for (A) spine BMD, (B) spine BMAD, and (C) total body less head BMD. Shown are the mean values and 95% confidence intervals.

Abbreviations: BMAD, bone mineral apparent density; BMD, bone mineral density.

monitored, calculation of both previous and new BMD measurements with race-neutral reference data would aid in the interpretation of longitudinal changes.

BMD in childhood is influenced by numerous factors, including growth, lean mass, diet, weight-bearing physical activity, and health-related factors (26, 27). The BMDCS cohort was selected based on overall good health; data for children who were exposed to medications or other factors at follow-up that might adversely affect their bone density were excluded from this analysis. We examined subgroup

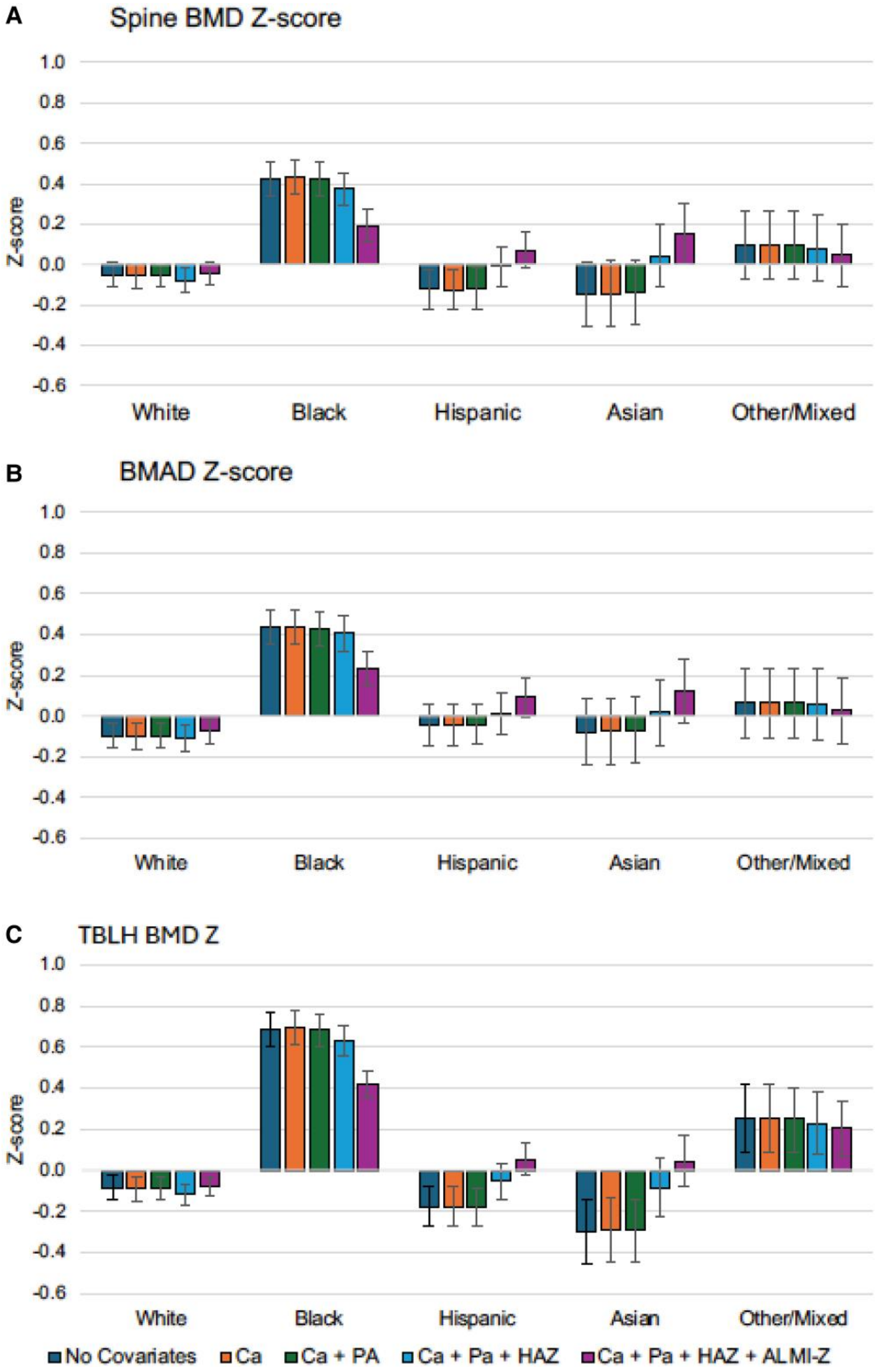

Figure 3. Mean race-neutral Z-scores by race/ethnicity groups without adjustment and with sequential adjustment for calcium intake, high-impact physical activity, HAZ, and ALMI-Z for (A) spine BMD, (B) spine BMAD, and (C) total body less head BMD.

Abbreviations: ALMI-Z, appendicular lean soft tissue mass index Z-score; BMAD, bone mineral apparent density; BMD, bone mineral density; HAZ, height-for-age Z-score.

differences in race-neutral BMD and BMAD Z-scores adjusted for calcium intake, weight-bearing physical activity, height status (HAZ), and appendicular lean soft tissue mass index Z-score (ALMI-Z). Calcium intake and physical activity did not have an appreciable effect on subgroup differences, whereas HAZ, and especially ALMI-Z, reduced the race/ethnicity group differences in BMD and BMAD Z-scores, but large differences remained between the Black group vs all other groups. Other unmeasured modifiable and nonmodifiable factors, such as genetics, may contribute to these differences. Although genome-wide association studies have identified genetic markers associated with BMD,

Table 3. HAZ prediction equations for BMD of the spine, total body less head, total hip, femoral neck, and distal one-third radius

Z-score	Age range	Males	Females
Spine BMD	5-5.9	−0.071 + (HAZ * 0.442)	−0.145 + (HAZ * 0.531)
	6-6.0	−0.034 + (HAZ * 0.405)	−0.060 + (HAZ * 0.491)
	7-7.0	−0.039 + (HAZ * 0.375)	0.005 + (HAZ * 0.483)
	8-8.9	−0.015 + (HAZ * 0.469)	−0.014 + (HAZ * 0.550)
	9-9.9	−0.046 + (HAZ * 0.389)	−0.056 + (HAZ * 0.500)
	10-10.9	0.005 + (HAZ * 0.335)	−0.179 + (HAZ * 0.540)
	11-11.9	−0.081 + (HAZ * 0.399)	−0.224 + (HAZ * 0.616)
	12-12.9	−0.112 + (HAZ * 0.464)	−0.132 + (HAZ * 0.588)
	13-13.9	−0.142 + (HAZ * 0.526)	−0.071 + (HAZ * 0.414)
	14-14.9	−0.107 + (HAZ * 0.520)	−0.008 + (HAZ * 0.303)
	15-15.0	−0.015 + (HAZ * 0.290)	−0.044 + (HAZ * 0.241)
	16-16.9	−0.034 + (HAZ * 0.249)	−0.013 + (HAZ * 0.240)
	17-17.9	−0.042 + (HAZ * 0.228)	−0.017 + (HAZ * 0.192)
	18-18.9	−0.035 + (HAZ * 0.256)	−0.045 + (HAZ * 0.176)
	19-19.9	−0.018 + (HAZ * 0.253)	−0.031 + (HAZ * 0.140)
Total body less head BMD	5-5.9	−0.090 + (HAZ * 0.704)	−0.228 + (HAZ * 0.879)
	6-6.0	−0.071 + (HAZ * 0.666)	−0.094 + (HAZ * 0.736)
	7-7.0	−0.064 + (HAZ * 0.715)	−0.003 + (HAZ * 0.720)
	8-8.9	−0.029 + (HAZ * 0.744)	0.000 + (HAZ * 0.682)
	9-9.9	−0.027 + (HAZ * 0.669)	−0.097 + (HAZ * 0.622)
	10-10.9	−0.058 + (HAZ * 0.591)	−0.188 + (HAZ * 0.639)
	11-11.9	−0.117 + (HAZ * 0.591)	−0.256 + (HAZ * 0.708)
	12-12.9	−0.128 + (HAZ * 0.550)	−0.150 + (HAZ * 0.620)
	13-13.9	−0.139 + (HAZ * 0.556)	−0.081 + (HAZ * 0.494)
	14-14.9	−0.111 + (HAZ * 0.553)	−0.029 + (HAZ * 0.388)
	15-15.0	−0.032 + (HAZ * 0.327)	−0.039 + (HAZ * 0.371)
	16-16.9	−0.022 + (HAZ * 0.244)	−0.045 + (HAZ * 0.323)
	17-17.9	−0.026 + (HAZ * 0.236)	−0.015 + (HAZ * 0.316)
	18-18.9	−0.047 + (HAZ * 0.321)	−0.013 + (HAZ * 0.355)
	19-19.9	−0.007 + (HAZ * 0.285)	−0.011 + (HAZ * 0.302)
Total hip BMD	5-5.9	−0.039 + (HAZ * 0.124)	−0.182 + (HAZ * 0.515)
	6-6.0	0.046 + (HAZ * 0.121)	−0.036 + (HAZ * 0.365)
	7-7.0	−0.013 + (HAZ * 0.149)	0.010 + (HAZ * 0.317)
	8-8.9	−0.011 + (HAZ * 0.329)	0.000 + (HAZ * 0.259)
	9-9.9	−0.012 + (HAZ * 0.330)	−0.052 + (HAZ * 0.333)
	10-10.9	−0.046 + (HAZ * 0.275)	−0.129 + (HAZ * 0.406)
	11-11.9	−0.041 + (HAZ * 0.280)	−0.202 + (HAZ * 0.531)
	12-12.9	−0.098 + (HAZ * 0.355)	−0.108 + (HAZ * 0.492)
	13-13.9	−0.101 + (HAZ * 0.377)	−0.048 + (HAZ * 0.353)
	14-14.9	−0.084 + (HAZ * 0.369)	−0.021 + (HAZ * 0.264)
	15-15.0	0.015 + (HAZ * 0.149)	−0.025 + (HAZ * 0.241)
	16-16.9	−0.028 + (HAZ * 0.109)	−0.031 + (HAZ * 0.222)
	17-17.9	−0.013 + (HAZ * 0.104)	−0.001 + (HAZ * 0.198)
	18-18.9	−0.001 + (HAZ * 0.107)	−0.024 + (HAZ * 0.213)
	19-19.9	−0.040 + (HAZ * 0.180)	−0.035 + (HAZ * 0.138)
Femoral Neck BMD	5-5.9	−0.047 + (HAZ * 0.250)	−0.145 + (HAZ * 0.512)
	6-6.0	0.009 + (HAZ * 0.206)	−0.093 + (HAZ * 0.490)
	7-7.0	−0.015 + (HAZ * 0.300)	0.038 + (HAZ * 0.432)
	8-8.9	−0.015 + (HAZ * 0.461)	−0.029 + (HAZ * 0.356)
	9-9.9	−0.038 + (HAZ * 0.443)	−0.067 + (HAZ * 0.399)
	10-10.9	−0.051 + (HAZ * 0.379)	−0.130 + (HAZ * 0.426)

(*continued*)

Table 3. Continued

Z-score	Age range	Males	Females
	11-11.9	−0.042 + (HAZ * 0.337)	−0.202 + (HAZ * 0.509)
	12-12.9	−0.093 + (HAZ * 0.352)	−0.095 + (HAZ * 0.465)
	13-13.9	−0.094 + (HAZ * 0.348)	−0.045 + (HAZ * 0.316)
	14-14.9	−0.073 + (HAZ * 0.342)	0.004 + (HAZ * 0.216)
	15-15.0	−0.004 + (HAZ * 0.147)	−0.037 + (HAZ * 0.208)
	16-16.9	−0.023 + (HAZ * 0.107)	−0.023 + (HAZ * 0.194)
	17-17.9	0.011 + (HAZ * 0.059)	0.000 + (HAZ * 0.175)
	18-18.9	−0.003 + (HAZ * 0.064)	−0.042 + (HAZ * 0.179)
	19-19.9	−0.047 + (HAZ * 0.106)	−0.014 + (HAZ * 0.140)
One-third radius BMD	5-5.9	−0.011 + (HAZ * 0.284)	−0.184 + (HAZ * 0.641)
	6-6.0	−0.033 + (HAZ * 0.357)	−0.063 + (HAZ * 0.410)
	7-7.0	−0.042 + (HAZ * 0.391)	0.043 + (HAZ * 0.436)
	8-8.9	−0.052 + (HAZ * 0.432)	−0.014 + (HAZ * 0.413)
	9-9.9	0.003 + (HAZ * 0.440)	−0.088 + (HAZ * 0.477)
	10-10.9	−0.054 + (HAZ * 0.388)	−0.146 + (HAZ * 0.435)
	11-11.9	−0.076 + (HAZ * 0.429)	−0.212 + (HAZ * 0.543)
	12-12.9	−0.114 + (HAZ * 0.483)	−0.099 + (HAZ * 0.501)
	13-13.9	−0.110 + (HAZ * 0.491)	−0.069 + (HAZ * 0.370)
	14-14.9	−0.104 + (HAZ * 0.349)	−0.020 + (HAZ * 0.253)
	15-15.0	−0.006 + (HAZ * 0.179)	−0.029 + (HAZ * 0.183)
	16-16.9	0.021 + (HAZ * −0.022)	−0.016 + (HAZ * 0.116)
	17-17.9	−0.009 + (HAZ * 0.004)	−0.007 + (HAZ * 0.163)
	18-18.9	−0.033 + (HAZ * 0.009)	−0.021 + (HAZ * 0.268)
	19-19.9	0.036 + (HAZ * −0.053)	0.011 + (HAZ * 0.216)
	15-15.0	−0.004 + (HAZ * −0.008)	0.013 + (HAZ * −0.033)
	16-16.9	0.035 + (HAZ * −0.180)	0.004 + (HAZ * −0.045)
	17-17.9	0.022 + (HAZ * −0.201)	0.002 + (HAZ * 0.014)
	18-18.9	−0.028 + (HAZ * −0.191)	−0.041 + (HAZ * 0.063)
	19-19.9	0.051 + (HAZ * −0.109)	0.022 + (HAZ * 0.010)

Abbreviations: BMD, bone mineral density; HAZ, height-for-age Z-score.

osteoporosis, and fracture (28-36), to date they explain only a small portion of the variability in these bone outcomes (37). However, family studies suggest a strong heritable component to BMD with heritability estimates of 60% to 80%, much of which remains to be characterized (38-40). Indeed, persistently greater BMD Z-scores among children who identify as Black may represent yet to be defined genetic potential for higher BMD, and initial observations reflect this hypothesis (41, 42).

The development of peak bone mass, the maximum bone density accrued during childhood, adolescence, and young adulthood, is thought to be an important determinant of the long-term risk of osteoporosis later in adulthood (26, 43). A simulation study estimated that, at the population level, a 10% increase in peak bone mass delays the onset of osteoporosis later in life by 13 years (44). In this regard, race-specific curves may be of value for mechanistic investigations of the progression toward expected peak bone mass and the potential impact of achieving expected peak bone mass on lifelong fracture risk. While we show that race-neutral Z-scores are better predictors of childhood fracture than race-specific Z-scores in a healthy cohort, their ability to predict lifelong fracture is unknown. Use of race-specific Z-scores in childhood may help discriminate early life factors associated with osteoporosis later in life. Highlighting the importance of osteoporosis in Black women, the Women's Health Study found that even though the relative risk of fracture was lower in Black women compared to other race/ethnicity groups, the age-adjusted annualized rate of fractures among Black women was greater than many other morbidities, such as invasive breast cancer, stroke, and coronary heart disease (45). Further research is needed to determine whether use of race-specific curves in assessing bone health in Black children provides greater insight into early determinants of osteoporosis in adulthood.

During childhood, especially during the peripubertal years, areal BMD measurement by DXA is influenced by height; children who are shorter for age have lower areal BMD-for-age Z-scores than children who are taller for age. An ideal adjustment method is one that would capture the variability in BMD Z-score due to stature such that groups of taller and shorter children would have Z-score values close to 0 ± 1. We examined the relationship of HAZ to BMD and BMAD Z-scores across different age ranges and found that (1) spine BMAD and ultradistal radius Z-scores are not associated with height; and (2) for children ≥ 15 years of age, the associations with

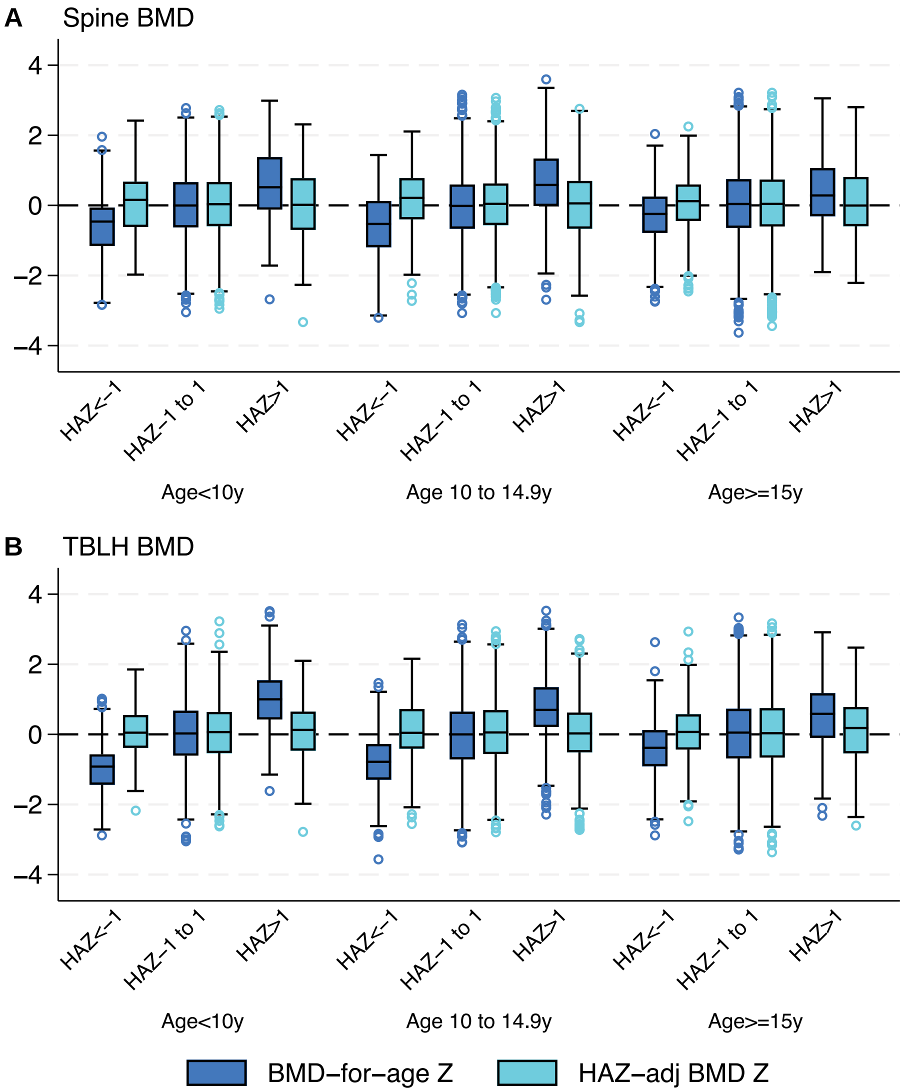

Figure 4. Race-neutral BMD-for-age Z-scores compared to height-for-age adjusted BMD Z-scores for (A) spine BMD and (B) total body less head BMD. Abbreviation: BMD, bone mineral density.

HAZ are negligible for all measures except for TBLH BMD. We generated sex- and age-specific HAZ adjustment equations that first predict what an individual's BMD Z-score would be based on their HAZ, and the difference between their measured BMD for age Z-score and their HAZ-predicted Z-score is an indicator of the degree to which their shorter or taller stature affects their bone density Z-score. Although we did not find significant associations between HAZ and BMD Z-scores at older ages, we included prediction equations for older children to assist in calculating HAZ adjustment in children who may have delayed puberty and short stature. Importantly, this statistical model is based on children with normal growth patterns. The use of these prediction equations for children with extreme values for HAZ is beyond the scope of these statistical models and may yield spurious results.

One of the primary goals of BMD evaluation is to identify individuals at greatest risk of fracture and who could potentially benefit from fracture prevention interventions. However, few large studies have examined the relationship between BMD/BMAD Z-scores and prospective fractures. Crabtree et al studied the association of fracture risk with spine and whole-body BMD in a cohort of 450 children, of whom 40% had sustained a low-trauma fracture. They found that spine BMAD performed best in predicting fracture (46). In a large birth cohort with whole-body BMC/BMD measured at age 9.9 years, Clark et al demonstrated that BMC adjusted for body size predicted fractures in the following 2 years (47). We showed that race-neutral Z-scores for spine BMAD and distal one-third radius were most strongly associated with fracture risk, with HRs that were significantly lower than race-specific Z-scores—a 1 SD increase in Z-score was associated with a 14% to 18% reduced risk of fracture. The point estimates for HRs were stronger for race-neutral HAZ-adjusted BMD Z-scores (0.83-0.88). For the race-specific Z-scores, only spine BMAD and HAZ-adjusted spine BMD Z-scores associated with prospective fracture. With the exception of spine BMD Z-score, the race-neutral Z-scores were better predictors of fracture. Interestingly, TBLH BMD Z-score was not associated with fracture risk, even though this scan type is recommended by the International Society of Clinical Densitometry Pediatric Position (5, 6).

Table 4. HRs and 95% CIs for incident fracture (bootstrapping with 100 reps)

	Race-neutral				Race-specific				HR Comparison[a]	
	HR	95% CI	*P*-value	n Obs	HR	95% CI	*P*-value	n observations	Difference in HR	95% CI for difference
BMD for age Z										
Spine BMD	**0.88**	(0.82, 0.99)	.028	7359	0.93	(0.86, 1.06)	.221	7359	0.05	(0.03, 0.08)
Spine BMAD	**0.82**	(0.76, 0.91)	.001	7359	**0.87**	(0.80, 0.98)	.022	7359	0.05	(0.03, 0.07)
Total body less head BMD	0.93	(0.86, 1.05)	.203	7207	1.02	(0.94, 1.16)	.761	7207	0.09	(0.07, 0.12)
Total hip BMD	0.90	(0.82, 1.01)	.105	7357	0.98	(0.88, 1.11)	.755	7357	0.08	(0.05, 0.11)
Femoral neck BMD	0.89	(0.81, 1.01)	.060	7357	0.97	(0.88, 1.11)	.632	7357	0.08	(0.05, 0.12)
One-third radius BMD	**0.86**	(0.78, 0.98)	.034	7314	0.94	(0.84, 1.07)	.392	7314	0.07	(0.05, 0.11)
Ultradistal radius BMD	0.91	(0.83, 1.04)	.199	7320	0.97	(0.88, 1.11)	.714	7320	0.06	(0.04, 0.08)
HAZ-adjusted BMD Z[b]										
Spine BMD	**0.85**	(0.77, 0.95)	.007	7300	**0.87**	(0.80, 0.97)	.020	7345	0.02	(0.00, 0.04)
Spine BMAD[c]										
Total body less head BMD	0.90	(0.81, 1.01)	.098	7148	0.94	(0.84, 1.06)	.376	7193	0.04	(0.01, 0.07)
Total hip BMD	**0.88**	(0.79, 0.98)	.050	7298	0.92	(0.81, 1.01)	.198	7343	0.04	(0.00, 0.05)
Femoral neck BMD	**0.87**	(0.79, 0.97)	.030	7298	0.92	(0.82, 1.04)	.214	7343	0.05	(0.03, 0.08)
One-third radius BMD	**0.83**	(0.75, 0.94)	.009	7255	0.89	(0.79, 1.00)	.091	7300	0.05	(0.03, 0.08)
Ultradistal radius BMD[c]										

Bold values are statistically significant ($P \leq .05$) hazard ratios.
Abbreviations: BMAD, bone mineral apparent density; BMD, bone mineral density; CI, confidence interval; HAZ, height-for-age Z-score; HR, hazard ratio.
[a] HR using race-specific Z-scores minus HR using race-neutral Z-score.
[b] HAZ-adjusted BMD Z-score calculated for individuals up to age 19.9 years, whereas BMD-for-age Z-scores include individuals up to 20 years of age.
[c] HAZ adjustment not required for spine BMAD or ultradistal radius.

The race-neutral HAZ-adjusted distal one-third radius BMD Z-score had the second strongest HR (0.80; 95% CI 0.71, 0.91). Given these findings, the high prevalence of forearm fractures in children, the lower likelihood of medical and other artifacts in this scan region (eg, continuous glucose monitors, gastrostomy tubes, body piercings, spinal rods), and the lower burden of radiation exposure, forearm scans should be considered more frequently for bone health assessment in children and interpreted using race-neutral reference ranges, with the caveat that performance of forearm scans in predicting fracture in youth with chronic illness associated with increased fracture risk has not been tested.

This study had several limitations. The BMDCS was conducted at 5 centers throughout the United States but is not geographically representative of the country. It is unknown whether these reference ranges are applicable to children living outside the United States. All scans were acquired on Hologic bone densitometers, and the BMD results are not directly comparable to those acquired on devices from other manufacturers. Fracture data were by self-report and not verified from medical records. Also, study participants were excluded if they were at risk of fracture due to other health concerns, so the generalizability of these findings to children at greater risk is unknown. The strengths of the study far outweigh its limitations. The reference curves and HAZ adjustment method were based on over 10 000 DXA measurements along with growth, body composition, dietary calcium intake, and physical activity information among healthy children following a standardized protocol and quality assurance procedures. These reference ranges are applicable for all children, including those of multiracial identity who represent a growing percentage of children in the US population (48).

Conclusions

This is the first report of race-neutral pediatric reference ranges, weighted to be representative of the race/ethnicity distribution of the US population. Comparisons of race-neutral reference ranges with previous race-specific reference ranges demonstrated that BMD and BMAD Z-scores were modestly different for most race/ethnicity groups, but race-neutral Z-scores were higher for children who identify as Black. These findings are relevant for children who are currently being monitored longitudinally if switching from race-specific to race-neutral reference ranges for Z-scores calculations. In addition, we demonstrated that differences between race/ethnicity groups were partially but not completely modified by growth and body composition measures associated with BMD. Importantly, we demonstrated that race-neutral Z-scores, especially those that are adjusted for height status, are significantly associated with fractures in childhood.

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Disclosures

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Data Availability

All data collected by the Bone Mineral Density in Childhood Study are available through the Eunice Kennedy Shriver National Institute of Child Health and Human Development Data and Specimen Hub (https://dash.nichd.nih.gov/explore/dataset). Supplementary material is available at https://figshare.com/s/d20df8cbae8a2e25dcfe.

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