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Bone Mineral Acquisition in Healthy Asian, Hispanic, Black, and Caucasian Youth: A Longitudinal Study*

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ABSTRACT

Ethnic and gender differences in bone mineral acquisition were examined in a longitudinal study of 423 healthy Asian, black, Hispanic, and white males and females (aged 9–25 yr). Bone mass of the spine, femoral neck, total hip, and whole body was measured annually for up to 4 yr by dual energy x-ray absorptiometry. Age-adjusted mean bone mineral curves for areal (BMD) and volumetric (BMAD) bone mineral density were compared for the 4 ethnic groups. Consistent differences in areal and volumetric bone density were observed only between black and nonblack subjects. Among females, blacks had greater mean levels of BMD and BMAD at all skeletal sites. Differences among Asians, Hispanics, and white females were significant for femoral neck BMD, whole body BMD, and whole body bone mineral content/height ratio, for which Asians had significantly lower values; femoral neck BMAD in Asian and white females was lower than that in Hispanics. Like the females, black males had consistently greater mean values than nonblacks for all BMD and BMAD measurements. A few differences were also observed among nonblack male subjects. Whites had greater mean total hip BMD, whole body BMD, and whole body bone mineral content/height ratio than Asian and Hispanic males; Hispanics had lower spine BMD than white and Asian males. The tempo of gains in BMD varied by gender and skeletal site. In females, total hip, spine, and whole body BMD reached a plateau at 14.1, 15.7, and 16.4 yr, respectively. For males, gains in BMD leveled off at 15.7 yr for total hip and at age 17.6 yr for spine and whole body. Black and Asian females and Asian males tended to reach a plateau in BMD earlier than the other ethnic groups. The use of gender- and ethnic-specific standards is recommended when interpreting pediatric bone densitometry data. (*J Clin Endocrinol Metab* **84:** 4702–4712, 1999)

PEAK BONE mass is a key determinant of skeletal health throughout life. Approximately 60% of the risk of osteoporosis can be explained by the amount of bone mineral acquired by early adulthood; subsequent bone loss accounts for the remaining risk (1). Recognition of the pivotal importance of peak bone mass has led to a proliferation of pediatric bone studies. This research has been directed at identifying determinants of optimal bone accretion (2) and risk factors for early osteopenia (3). Children and young adults with a variety of chronic disorders face an increased risk of osteopenia and osteoporosis (3). The skeletal health of these young patients is best assessed with bone densitometry, but age- and puberty-adjusted standards are needed to interpret their results. The need for pediatric reference data has provided a further impetus to examine bone mineral acquisition in healthy youth.

Despite the proliferation of pediatric research in the past decade (2, 4–24), several aspects of bone mineral acquisition remain controversial. The timing of peak bone mass is disputed; some studies conclude that bone mass is maximal by age 20 yr (4–8, 14–17), whereas other reports indicate measurable bone mineral gains into the third decade (9, 18). In part, these differences may reflect small sample sizes or cross-sectional (10–19, 23) *vs.* longitudinal design (4–9). The tempo of bone mineral accrual has been shown to vary by skeletal site, with gains continuing longer at whole body than at hip or spine (6, 7, 9). Ethnic differences in bone mass have been observed in some (20, 22, 24), but not all (11, 12), studies. Similarly, there are discrepancies concerning the magnitude of gender differences in bone mass. These controversies have persisted in part because of a relative paucity of data from males and nonwhites. Variability in reported ethnic or gender differences also results when different noninvasive methods are used to assess bone mineral. Finally, the influence of exercise, diet, and other lifestyle variables on bone mineral acquisition is debatable (2, 8, 16). In some studies, activity and calcium intake have been estimated to make a 5–10% difference in bone mass (5, 8, 9), whereas others have found no significant correlation (4). These divergent findings may be explained by the lack of standardized instruments to quantitate diet and activity and a paucity of longitudinal bone accrual studies.

Perhaps the most debated issue in pediatric bone research is the optimal technique for determining bone mass in growing children. Dual energy x-ray absorptiometry (DXA) is widely accepted as the preferred method for assessing bone mass in children because of its speed, precision, availability, and modest radiation exposure (25). Despite these advantages, DXA is limited because it does not measure volumetric

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bone density. By convention, bone mass is reported as bone mineral content (BMC; grams) or areal bone density (BMD; grams per cm^2), terms that are strongly influenced by bone size (26, 27). As a result, DXA may overestimate true bone mass in larger individuals and underestimate bone mass in smaller individuals. Several investigators have derived models to estimate volumetric bone density to reduce the influence of bone size on DXA measurements (4, 5, 13, 27). Although the validity of these models remains controversial (26, 28, 29), they provide a reasonable approach to adjusting for bone size. Quantitative computed tomography (QCT) circumvents the measurement artifacts associated with DXA by measuring volumetric bone mineral density directly. However, QCT is not widely available and requires considerably higher radiation exposure than DXA (25). Furthermore, published pediatric norms for QCT (20, 30) are more limited than those for DXA. Quantitative ultrasound is emerging as an attractive method to evaluate pediatric bone mineral because it is portable, inexpensive, and requires no ionizing radiation (25). Quantitative ultrasound has not supplanted DXA, however, because this technique is less precise (25) and pediatric reference data are limited (31, 32).

This longitudinal study was designed to examine the influence of gender and ethnicity on bone mineral acquisition in healthy youths and young adults (aged 9–25 yr). A total of 423 black, Asian, Hispanic, and white males and females had measurements of bone mass made by DXA at study entry and yearly thereafter for up to 4 yr. Growth, pubertal development, diet, and exercise were monitored during this period as well. Normative curves for areal (BMD) and volumetric bone mineral apparent density (BMAD) at the spine, proximal hip, and whole body have been modeled from these longitudinal data.

Subjects and Methods

Subjects

A convenience sample of healthy youth was recruited from the community through advertisements and personal contact (21, 22). Individuals with a history of medical conditions or use of medications affecting bone mineral were excluded. Subjects were encouraged to return annually for a total of four visits or until they had reached age 26 yr. Recruitment occurred between May 1992 and February 1996; data collection ended in February 1997. The cohort at entry included 103 non-Hispanic whites, 103 Hispanics, 103 Asians, and 114 non-Hispanic blacks, aged 8.8–25.9 yr; 230 females and 193 males were enrolled as previously reported (22). For simplicity, ethnicity and race will be used as interchangeable terms, and the groups will be referred to as white, Hispanic, Asian, and black. A total of 280 subjects completed 2 visits; 189 were studied 3 times, and 113 were evaluated 4 times. Subjects who completed fewer than 4 visits included those who refused, relocated, or reached age 26 yr during the study period; in addition, subjects who were recruited late in the study did not complete all visits because funding had terminated.

Clinical assessment

All assessments performed at study entry were repeated at each annual follow-up visit (21, 22). In brief, height was measured using a wall-mounted stadiometer, and weight was determined with a balance beam using a standardized protocol. Pubertal stage was estimated with a self-assessment instrument using Tanner classifications of breast development in females and genital development in males (33). Calcium/protein ratio was assessed using the NCI Food Questionnaire (34). Habitual physical activity was determined from a structured interview directed at recall of recreational exercise during the previous 12 months.

Bone densitometry

Bone mineral was measured by DXA (QDR 1000W, software version 6.10, Hologic, Inc., Waltham, MA) in the pencil beam mode. Regions of interest included the lumbar spine (L2–L4), left proximal femur (femoral neck and total hip), and whole body. A standardized protocol was employed for analysis of the proximal hip to reduce measurement inconsistencies that may result from changes in femoral neck geometry during growth (22). BMC (grams) and BMD (grams per cm^2) were determined by Hologic, Inc., software. BMAD (grams per cm^3), an estimate of volumetric bone density, was calculated as previously described (4, 27). Spine BMAD was derived using the formula BMC $\div$ $(\text{area})^{1.5}$; femoral neck BMAD was calculated from the expression BMC $\div$ $(\text{area})^2$. The expression whole body BMC $\div$ height (cm) was calculated to adjust for whole body bone size. In our laboratory, the *in vivo* coefficient of variation for replicate measurements of BMD in adolescents and young adults is 0.6% at all skeletal sites studied.

The study protocol was approved by the Stanford University administrative panel on human subjects in medical research. Written consent was obtained from all participants and from the parents of subjects under age 18 yr.

Statistical models and methods

We used several biostatistical techniques to model the bone mineral percentile curves. A mixed effects model was employed to allow inclusion of all data from each subject despite irregularly spaced measurements or missing values (35). The model also adjusts for measurement errors and other random fluctuations. Semiparametric regression models were used to permit flexible modeling of the curves using splines (36). After inspection of the data, we selected knots (ages) where shifts in the bone acquisition curves were greatest. A piecewise cubic polynomial model was applied between adjacent pairs of knots, with constraints built in to force the adjacent cubic polynomial to join up smoothly. Robust nonparametric smoothing techniques were used to provide estimates of the SD as a function of age (37). A detailed description of these modeling techniques is provided in the references (35–37).

Fitting the models

The models were fit by maximum likelihood estimation that incorporates estimates of random error between and within individuals in a single model. This method adjusts for highly correlated repeated measurements from single individuals, thus allowing examination of fixed effects (such as ethnicity). We used the linear mixed effects software in SPlus (version 4.3) for this modeling and fit separate models for males and females (38).

Age-adjusted mean and SD curves were produced for areal BMD of the spine, femoral neck, total hip, and whole body. Curves for spine and femoral neck BMAD and whole body BMC/height ratio were also generated as estimates of volumetric bone density. For the bone measurements at each site, we tested whether models varied by ethnic group. Where significant ethnic differences in mean bone mass were observed, separate curves were created. If differences between two or more racial groups were not significant, data were pooled to maximize the number of subjects in the reference curves.

Modeling the tempo of bone acquisition

To examine gender and ethnic differences in the tempo of bone mineral acquisition, we applied a simpler statistical model than that used to create the SD curves. Analysis was designed to estimate the age at which bone accrual reached a plateau, and a simple linear model of bone mineral acquisition rates was used between age 9 yr and the age at which bone acquisition leveled off. We used a grid-search technique to localize the age at plateau and then tested the validity of that assumption using a bootstrap technique (39). For each ethnicity and gender, we determined the age at which bone acquisition plateaus, the mean bone mineral achieved by that age, and the rate of bone acquisition (the slope of the curve between age 9 yr and the age at plateau).

All measures of bone mass increased with age except femoral neck BMAD, which appeared to decline transiently during midpuberty. To explore the reason for this change, we plotted both femoral neck BMC

and area curves, obtained by smoothing the observed data. These curves were scaled to fit on the same axes, and the curves and their derivatives were compared.

Results

Clinical characteristics

Entry data for the age, height, weight, pubertal stage, dietary intake, and physical activity of the study subjects have been published previously (21, 22). Two changes were made in the original cohort after the initial report; 1 black male subject was subsequently excluded because of a skeletal contracture, and 1 Hispanic female was added to the cohort. Subjects were asked to return annually for up to 4 visits or until age 26 yr. Of 423 subjects studied at baseline, 280 subjects completed 2 visits, 189 were studied 3 times, and 113 were evaluated 4 times.

Tables 1 and 2 summarize the number of subjects studied at each age and the mean anthropometric and bone mineral data. Data from all visits for each subject are included. Bone mineral results for each subject are also superimposed on the age-adjusted curves (Figs. 1 and 2) to show the ethnic distribution by age and to display the individual variability in bone mineral acquisition rates. Participants ranged in age from 9–25 yr at entry. Of the 230 females, 17% were prepubertal or in early puberty, 35% were at midpuberty, and 48% were pubertally mature. Among the 193 males, 28% were in pre- or early puberty, 33% were midpubertal, and 39% had reached sexual maturity. The mean age for each pubertal group did not differ by ethnicity. There were also no ethnic differences in mean weight, height, or body mass index (BMI) for males or females until late puberty. Among the mature females, Hispanics were shorter than whites; black and Hispanic females had greater BMI than Asian and white females. Asian males weighed less than white males at maturity, but did not have significant differences in BMI. A few ethnic differences in diet were also observed. The mean calcium/protein and calcium/energy ratios were greater in white than in Asian or black females; white males consumed more calcium per g protein than Asian males in early and late puberty (22). There were no significant differences in habitual weight-bearing physical activity between ethnic groups.

Racial differences in bone mineral data

Mean and SD curves for spine bone density (BMD) by age are shown for females (Fig. 1) and males (Fig. 2). Mean BMD for black females was approximately 10% greater than mean BMD in nonblacks. Differences among white, Hispanic, and Asian females were not significant, and data from these three groups were combined. Like the females, black males had greater areal bone density at the spine than all nonblack subjects; however, white and Asian males had greater mean spine BMD than Hispanics. The difference between blacks and whites was approximately 3% at the spine (Fig. 2).

Age-adjusted mean and SD curves for BMD and BMAD for all other skeletal sites are provided at the study web site (http://www-stat.stanford.edu/pediatric-bones). This site has been designed to provide a standard deviation or z-score for BMD or BMAD if age, gender, race/ethnicity, and densitometry data (BMC, BMD, and bone area) are entered.

TABLE 1. Summary of clinical characteristics by age—females[a,b,c]

Age	9–11 yr (n = 55)		11–13 yr (n = 84)		13–15 yr (n = 99)		15–17 yr (n = 86)		17–19 yr (n = 65)		19–21 yr (n = 50)		21–23 yr (n = 51)		23–26 yr (n = 57)	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Tanner stage[d]																
Pre-early puberty	43	78	22	26	2	2	0	0	0	0	0	0	0	0	0	0
Mid-puberty	12	22	61	73	76	76	49	57	26	40	7	14	7	14	1	2
Maturity	0	0	1	1	22	22	37	43	39	60	44	86	44	86	56	98
Height (cm)	141.2 ± 8.4		153.7 ± 8.0		161.0 ± 6.9		162.3 ± 5.5		161.9 ± 6.4		162.0 ± 5.7		163.3 ± 6.0		163.6 ± 6.7	
Weight (kg)	37.8 ± 11.3		47.8 ± 12.0		58.3 ± 14.2		61.5 ± 14.0		60.2 ± 12.6		61.2 ± 11.3		59.6 ± 9.3		62.6 ± 11.2	
L_{2-4} BMD (g/cm^2)	0.728 ± 0.098		0.843 ± 0.142		1.002 ± 0.135		1.060 ± 0.123		1.078 ± 0.104		1.085 ± 0.115		1.065 ± 0.118		1.074 ± 0.117	
L_{2-4} BMAD (g/cm^3)	0.136 ± 0.013		0.142 ± 0.019		0.158 ± 0.018		0.164 ± 0.018		0.166 ± 0.014		0.166 ± 0.017		0.162 ± 0.019		0.164 ± 0.022	
TH BMD (g/cm^2)	0.746 ± 0.097		0.846 ± 0.141		0.967 ± 0.135		0.981 ± 0.133		0.981 ± 0.110		0.975 ± 0.111		0.975 ± 0.113		0.956 ± 0.125	
FN BMD (g/cm^2)	0.707 ± 0.099		0.782 ± 0.127		0.893 ± 0.146		0.922 ± 0.155		0.907 ± 0.109		0.883 ± 0.114		0.880 ± 0.106		0.873 ± 0.114	
FN BMAD (g/cm^3)	0.168 ± 0.023		0.166 ± 0.026		0.182 ± 0.030		0.189 ± 0.038		0.187 ± 0.028		0.180 ± 0.027		0.176 ± 0.027		0.174 ± 0.028	
WB BMD (g/cm^2)	0.827 ± 0.076		0.904 ± 0.094		0.904 ± 0.101		1.045 ± 0.095		1.059 ± 0.075		1.076 ± 0.070		1.072 ± 0.073		1.088 ± 0.078	
WB BMC (g)	1140 ± 366		1547 ± 428		2021 ± 460		2179 ± 462		2189 ± 402		2219 ± 346		2208 ± 309		2308 ± 383	
WB BMC/ht (g/cm)	8.00 ± 2.22		9.99 ± 2.42		12.50 ± 2.55		13.42 ± 2.79		13.49 ± 2.20		13.74 ± 1.96		13.51 ± 1.72		14.10 ± 2.18	

[a] Numbers derived from data gathered from 230 females examined for one to four annual visits.
[b] Except for Tanner stage, numbers represent mean ± SD.
[c] L_{2-4}, lumbar spine, second through fourth vertebrae; FN, femoral neck; TH, total hip; WB, whole body; BMD, bone mineral density; BMAD, bone mineral apparent density; BMC, bone mineral content.
[d] Based on self-reported breast stage.

TABLE 2. Summary of clinical characteristics by age—males[a,b,c]

Age	9–11 yr (n = 48)		11–13 yr (n = 75)		13–15 yr (n = 78)		15–17 yr (n = 70)		17–19 yr (n = 63)		19–21 yr (n = 47)		21–23 yr (n = 40)		23–26 yr (n = 35)	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Tanner stage[d]																
Pre-early puberty	39	81	42	56	14	18	1	1	0	0	0	0	0	0	0	0
Mid-puberty	9	19	33	44	58	74	42	60	35	56	10	21	2	5	3	9
Maturity	0	0	0	0	6	8	27	39	28	44	37	79	38	95	32	91
Height (cm)	139.9 ± 8.5		149.4 ± 8.7		161.8 ± 9.3		171.0 ± 8.1		174.3 ± 7.0		174.7 ± 7.3		175.6 ± 5.5		172.2 ± 8.8	
Weight (kg)	36.4 ± 8.7		43.9 ± 9.5		53.6 ± 12.2		61.1 ± 10.0		65.5 ± 9.6		72.6 ± 17.2		71.0 ± 10.0		74.6 ± 15.0	
L_{2-4} BMD (g/cm^2)	0.672 ± 0.066		0.720 ± 0.082		0.819 ± 0.131		0.964 ± 0.150		1.027 ± 0.123		1.047 ± 0.149		1.041 ± 0.132		1.037 ± 0.149	
L_{2-4} BMAD (g/cm^3)	0.125 ± 0.011		0.124 ± 0.012		0.129 ± 0.014		0.142 ± 0.017		0.146 ± 0.015		0.149 ± 0.017		0.148 ± 0.020		0.148 ± 0.022	
TH BMD (g/cm^2)	0.776 ± 0.080		0.838 ± 0.087		0.918 ± 0.134		1.025 ± 0.153		1.053 ± 0.119		1.064 ± 0.156		1.043 ± 0.152		1.026 ± 0.170	
FN BMD (g/cm^2)	0.737 ± 0.070		0.784 ± 0.083		0.841 ± 0.112		0.935 ± 0.133		0.972 ± 0.124		0.965 ± 0.157		0.945 ± 0.144		0.916 ± 0.136	
FN BMAD (g/cm^3)	0.172 ± 0.023		0.169 ± 0.019		0.163 ± 0.020		0.171 ± 0.020		0.172 ± 0.022		0.169 ± 0.026		0.168 ± 0.029		0.165 ± 0.028	
WB BMD (g/cm^2)	0.812 ± 0.053		0.869 ± 0.059		0.929 ± 0.091		1.021 ± 0.099		1.071 ± 0.089		0.885 ± 0.148		1.117 ± 0.102		1.128 ± 0.107	
WB BMC (g)	1058 ± 264		1350 ± 296		1738 ± 451		2163 ± 464		2383 ± 398		2531 ± 508		2575 ± 419		2599 ± 511	
WB BMC/ht (g/cm)	7.50 ± 1.51		9.00 ± 1.62		10.69 ± 2.23		12.59 ± 2.30		13.64 ± 1.98		14.44 ± 2.52		14.64 ± 2.20		15.03 ± 2.50	

[a] Numbers derived from data gathered from 193 males examined for one to four annual visits.
[b] Except for Tanner stage, numbers represent mean ± SD.
[c] L_{2-4}, lumbar spine, second through fourth vertebrae; FN, femoral neck; TH, total hip; WB, whole body; BMD, bone mineral density; BMAD, bone mineral apparent density; BMC, bone mineral content.
[d] Based on self-reported genital stage.

Figure 3 summarizes ethnic differences in areal and volumetric bone mineral densities at all skeletal sites. For each measure of BMD or BMAD, the analysis determined whether there was a shift upward or downward in the mean levels for Asians, blacks, or Hispanics compared with the mean level for the white cohort. The *dashed line* represents the mean level of age-adjusted BMD or BMAD for the white cohort, and the *horizontal bar*s indicate the mean level (±SE) for males and females in each ethnic group. Among females (*right column*), blacks had significantly greater mean values for all measures of bone mineral at all skeletal sites. As estimated volumetric (BMAD) as well as areal (BMD) bone mineral densities were significantly greater in black females, the observed differences could not be attributed simply to racial differences in bone size. Differences in the mean bone mineral levels between the nonblack groups at some sites reached statistical significance but were more modest than black-white differences. Asian females had significantly lower femoral neck BMD, whole body BMD, and whole body BMC/height ratio than Hispanic and white subjects. Femoral neck BMAD in Asian and white females was lower than that in Hispanics.

As in females, black males had greater mean BMD and BMAD at all sites than nonblacks (Fig. 3). Some ethnic differences in mean bone mineral curves were also found among the nonblack groups. Spine BMD was greater in whites and Asians than in Hispanics (Fig. 2); whites also had greater mean total hip BMD, whole body BMD, and whole body BMC/height ratio than Asian and Hispanic males.

The magnitude of change in areal bone density during puberty was greater than the change in estimated volumetric bone density. In females, BMD increased approximately 50% at the spine (Fig. 1), 25% at the femoral neck, 30% at the total hip, and 30% for the whole body between ages 9–18 yr. Males showed gains of similar or slightly greater magnitude from 9–18 yr (Fig. 2). Spine BMAD increased by approximately 20% in females and males, and no net increase in femoral neck BMAD occurred during adolescence.

The tempo of bone mineral acquisition

All measures of bone mineral increased with age except for femoral neck BMAD, which varied in midadolescence but did not increase significantly between early and late adolescence. Femoral BMAD values declined transiently between ages 10–13 yr in females and between ages 13–15 yr in males. To explore the reason for this change, we compared the changes in femoral neck BMC and area curves. The transient decrease in femoral BMAD coincided with more rapid gains in femoral neck area than in BMC, resulting in a transient decline in the ratio of BMC to (area).[2] The subsequent rise in femoral BMAD occurred as gains in femoral neck area leveled off and BMC continued to increase (data not shown).

To examine the effects of gender and ethnicity on the tempo of bone mineral acquisition, we used a simpler statistical model as described in *Materials and Methods*. For males and females in each racial group, we estimated the inflection point at which gains in BMD reached a plateau, the mean BMD value at that age, and the rate (slope) of bone mineral acquisition from early puberty until the plateau was reached. Data for spine BMD are shown in Fig. 4. For the entire female

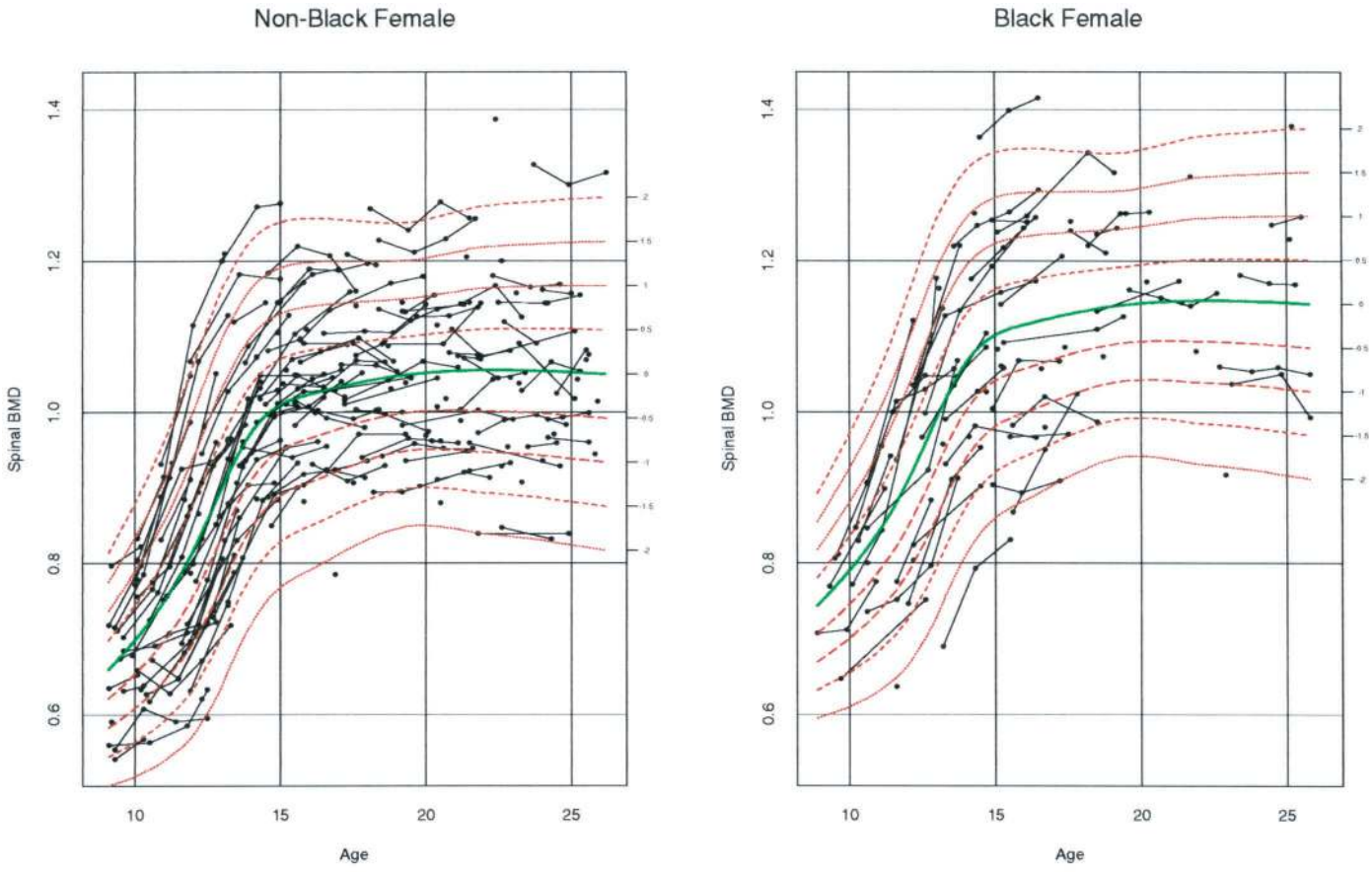

FIG. 1. Spine BMD for females by age. Mixed effects and semiparametric models were used to create the mean curves, and robust nonparametric smoothing techniques were employed for estimations of SD and by age. Mean BMD was significantly greater in black (*right panel*) *vs.* nonblack (Asian, Hispanic, and white) subjects (*left panel*). The *solid line* represents the mean level for age, and the *dashed lines* indicate the SD as indicated.

cohort, total hip, spine, and whole body BMD reached a plateau at ages 14.1, 15.7, and 16.4 yr, respectively. Black and Asian females tended to reach this plateau earlier than white and Hispanic females. For males, the plateau in total hip BMD was observed at 15.7 yr, whereas spine and whole body BMD leveled off at age 17.6 yr. Asian males tended to reach maximal BMD earlier than the mean at total hip and spine.

The ethnic differences in mean BMD at the plateau were similar in magnitude to the mean differences observed for the age-matched curves (Fig. 3). Blacks had significantly greater areal bone densities than nonblacks at the spine, total hip, and whole body. For black females, the mean spine and hip bone density was approximately 0.06 gm/cm^2 greater than the mean for all females; for whole body, the difference was 0.05 gm/cm^2. Black males achieved a mean BMD that was approximately 0.025, 0.03, and 0.05 gm/cm^2 greater for spine, whole body, and total hip, respectively, than the mean for all males (data not shown).

Discussion

This is the first report of longitudinal change in bone density in healthy, ethnically diverse youth. A primary goal of this study was to determine whether there were racial or gender-related differences in the tempo and magnitude of bone mineral acquired during adolescence. We found that blacks had greater mean BMD and BMAD at all sites than nonblacks. For a few measures of bone mineral, we found significant differences among Asian, Hispanic, and white subjects as well. As racial differences were found in volumetric (BMAD) as well as areal (BMD) bone density, the observed differences in bone mineral could not be attributed solely to ethnic differences in bone size. As expected, BMD increased rapidly at all skeletal sites during the early teen years and reached a plateau by late adolescence. Bone mineral acquisition accelerated and plateaued earlier in females than males. Asian males and females and black females tended to reach a plateau earlier than others. Spine BMAD and whole body BMC/ht ratio also increased during puberty; by contrast, there were no significant gains in femoral neck BMAD between early and late adolescence.

The combination of statistical methods used to generate the bone mineral curves optimized the information to be gained from our longitudinal data. The mixed effects model allowed the inclusion of data from all subjects regardless of the number of study visits and the variable intervals between visits. The model made appropriate adjustments for measurement errors and for inclusion of multiple data points from the same individual. Cubic regression splines permitted flexible modeling of the bone acquisition curves through adolescence, when the velocity of gains vary considerably.

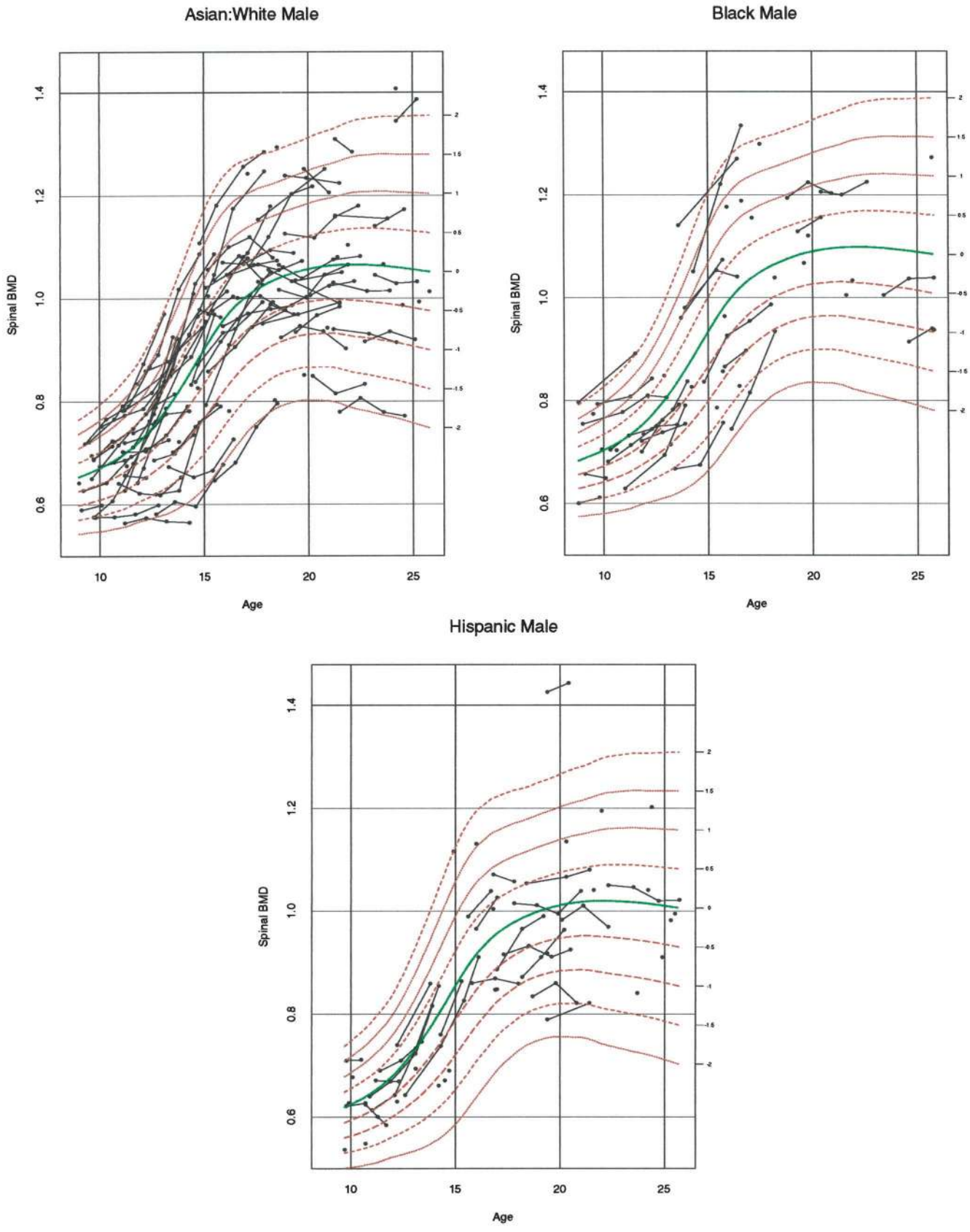

FIG. 2. Spine BMD for males by age. The curve for black males was significantly greater than the mean levels of all nonblacks; Asian and white males had greater mean spine BMD than Hispanics. Mean and SD curves are shown.

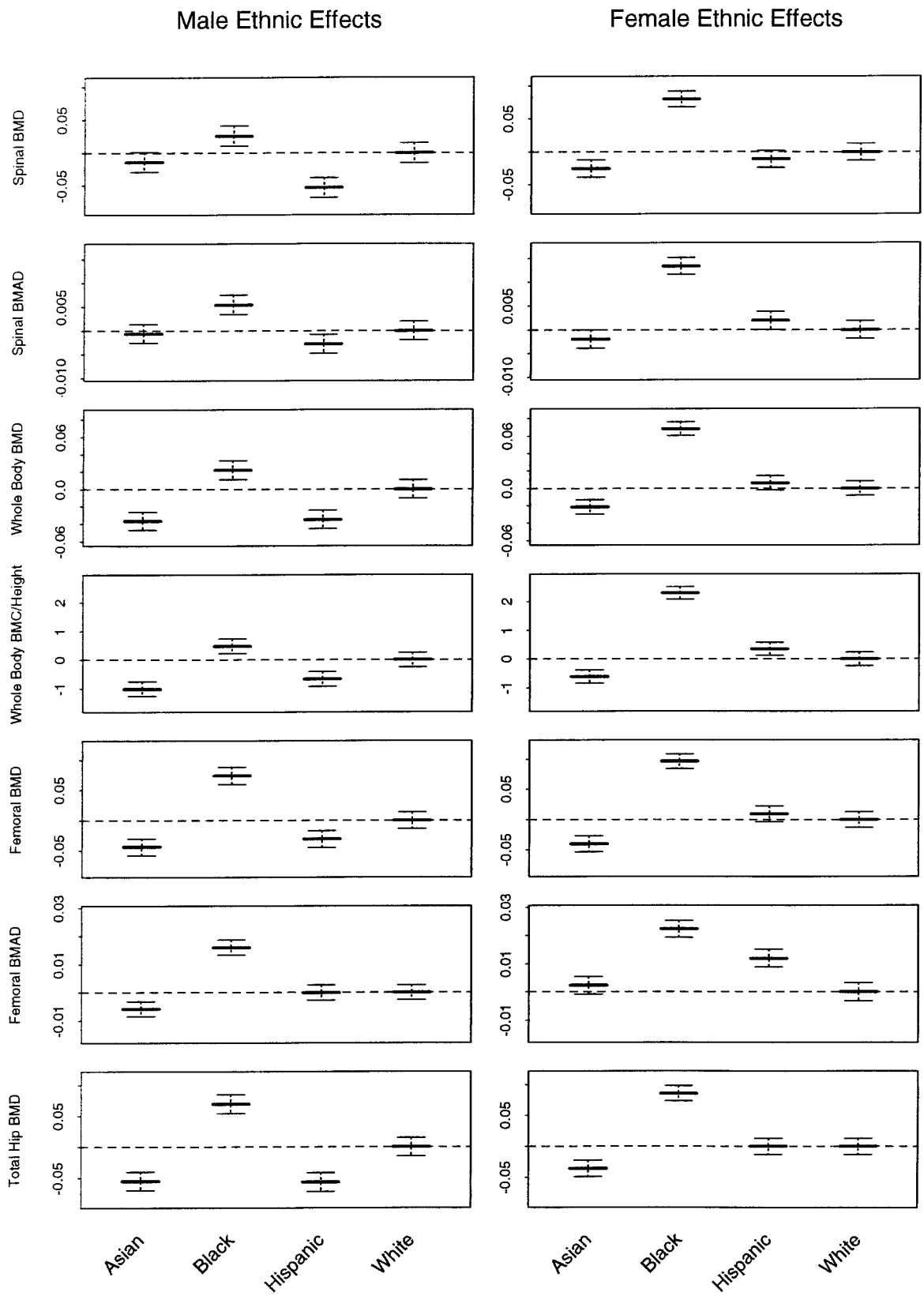

FIG. 3. Ethnic differences in areal (BMD; grams per cm^2) and volumetric bone mineral density (BMAD; grams per cm^3) in healthy 9- to 25-yr-olds. The *dashed line* represents the mean level of the curve (z-score = zero) for age-adjusted bone mineral in white subjects. The *solid lines* and *error bars* designate the mean (±SE) levels of the bone mineral curves for Asian, black, Hispanic, and white in males (*left column*) or females (*right column*). Differences from the mean are expressed in grams per cm^2 (for BMD) and grams per cm^3 (for BMAD).

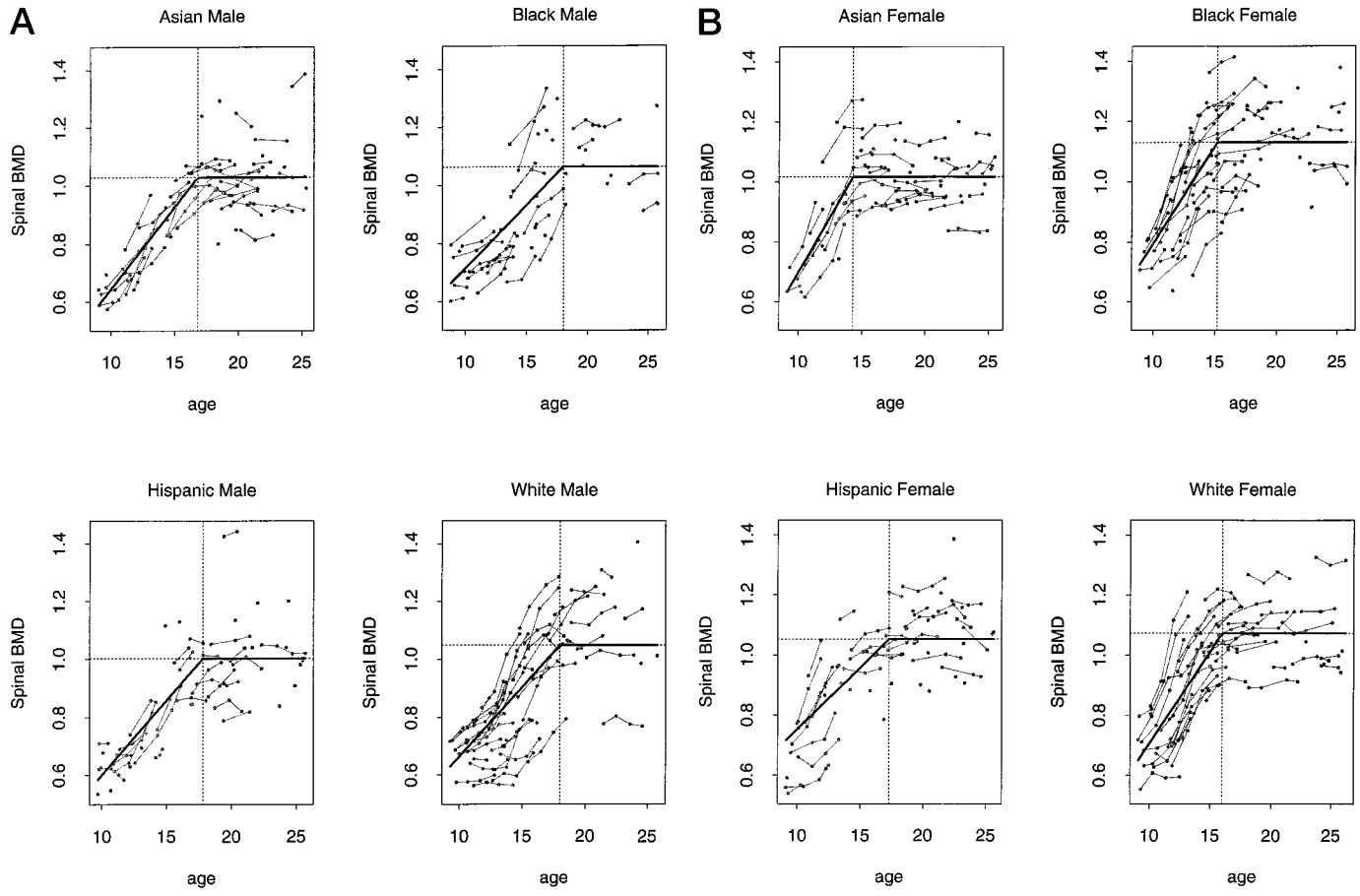

FIG. 4. Gender differences in the tempo of bone acquisition at the spine in males (A) and females (B). The age and mean BMD at the time gains in bone mineral plateaued were estimated by bootstrapping as described in *Materials and Methods*. *Interconnected dots* represent serial data from individual subjects.

We used robust nonparametric smoothing to estimate the magnitude of the SD. We found that the SD from the mean was not fixed but, rather, increased with age. Maximum likelihood estimations allowed us to examine the effect of ethnicity by adjusting for the repeated measurements taken from the same subject.

We found that blacks had significantly greater areal and volumetric bone density than nonblacks (Hispanic, Asian, and white) at all skeletal sites. For example, mean spine BMD for age was approximately 10% greater in black females and 3% greater in black males. Several previous studies from our group (22) and others (11, 20, 24, 40–42) observed that black American youths have 5–23% more bone mass than whites depending upon skeletal site, age, and gender. Significant differences have not been found between black and white South African youths (12). The differences we observed in bone mass between blacks and whites could not be attributed entirely to racial differences in bone size, because blacks also had greater estimated volumetric bone density (BMAD). Gilsanz *et al.* also found that QCT measurements of volumetric bone density at the spine were greater in blacks than whites (20, 42). By contrast, they observed no racial difference in femoral shaft cortical bone density, although blacks had greater cross-sectional area in that region (20, 42). Data from cross-sectional studies indicated that racial differences in bone mass increase during puberty because black adolescents gain more bone mineral in late adolescence (20, 22, 42). However, one longitudinal study found that bone mass increased more in black than in white children, aged 8–10 yr (24). We were unable to determine whether there were racial differences in the rates of bone accrual at differing ages because the statistical approach used assumed the shape of the bone mineral curves to be similar for all groups.

We observed fewer significant differences in bone mineral among Asian, Hispanic, and white subjects, and the magnitude of these differences was more modest than that of the black *vs.* nonblack differences. Asian females had lower mean femoral neck BMD, whole body BMD, and whole body BMC/height ratio than whites and Hispanics; femoral neck BMAD in Asian and white females was lower than that in Hispanics. Among males, spine BMD was lower in Hispanics than in Asian or whites. Total hip BMD, whole body BMD, and whole body BMC/height ratio were also greater in whites than in Hispanic or Asian males. The few differences we observed between Hispanic and white cohorts contrast with data of McCormick *et al.* (11), showing no significant differences in spine BMD (corrected for body weight) between Hispanic and white children (11). Once again, the discrepant findings may reflect differences in cohort size, cross-sectional *vs.* longitudinal study design, or the statistical

tests applied. In our study, Asian youths had lower measures of bone mineral at some sites than their white American counterparts, similar to findings from several adult studies (43). Some of the apparent differences in BMD between Asians and Caucasians can be explained by racial differences in bone size and body weight (21, 22, 43). We speculate that the Westernized diet and activity patterns of our largely American-born Asian cohort attenuated ethnic differences in bone size and geometry (44), thus reducing differences in areal bone density between Asians and whites.

We found more ethnic differences in bone mineral in this longitudinal study than we found at baseline in this cohort (21, 22). At study entry, differences between blacks and whites were not observed at all skeletal sites and pubertal stages (22). Mean BMD and BMAD for Asian, Hispanic, and white subjects were similar until late puberty, when Asian males had lower whole body BMD and BMC/height ratio than whites (22). Several factors may explain the apparent increase in ethnic differences in the current study. Firstly, the dataset used for longitudinal analyses was larger, increasing our power to detect small differences. Secondly, we applied a mixed effects model for this study compared with the regression models used for the cross-sectional data analysis. Finally, the bone mineral data presented here are adjusted only for age, whereas our earlier studies controlled for several confounding variables, such as height, weight, and pubertal stage. Although the latter approach corrected for appropriate genetic and lifestyle factors, this reduced our power to detect small ethnic differences.

We found that gender, but not ethnicity, had a significant influence on the timing of bone mineral acquisition. Gains in bone mineral plateaued earlier in females than in males. There was a tendency for Asian youth to reach a plateau earlier than blacks, whites, and Hispanics at some sites, but these differences were not significant. Our conclusions about the tempo of bone mineral acquisition are generally consistent with findings from studies in predominantly white youth in the U.S. and abroad (4–11, 13–17, 23). In a longitudinal study of Canadian youth, Bailey *et al.* found that peak gains in spine, femoral neck, and whole body BMC occurred at 13 yr in females and 14.4 yr in males, approximately 1 yr after peak height velocity (45). Lu *et al.* found that spine BMD plateaued at ages 15.7 and 17.4 yr in Australian females and males, respectively, similar to our estimates of 15.7 and 17.6 yr (7). Most studies have concluded that females and males attain 95–100% of their peak bone mass by the late teen years (6, 14–17, 19). However, Recker *et al.* found that women gained 5% and 12% in spine and whole body BMD, respectively, during the decade between ages 20–29 yr (9). We had insufficient numbers of older subjects to address the timing of peak bone mass.

Our data support the conclusion that pubertal gains in areal bone density largely reflect increases in bone size rather than changes in true volumetric bone mineral density (4, 13, 26). Between early and late adolescence, BMD increased dramatically at all sites. By contrast, gains in estimated BMAD at the spine were more modest, and there was no net increase in femoral neck BMAD. These findings support prior studies showing that estimated volumetric bone density increases at the spine, but not at the femoral neck or shaft, during adolescence (4, 5, 13). The changes we observed in BMAD are also consistent with QCT data, indicating pubertal gains in both size and volumetric density of vertebrae, whereas the volumetric bone density of the femoral shaft does not change (26, 30). The transient decrease that we observed in femoral neck BMAD during early puberty has not been reported previously, perhaps because earlier studies were cross-sectional or because mixed effect modeling was not used to analyze the data.

We acknowledge several limitations of this study. The cohort studied was a convenience sample, which may not be representative of all American youth. Despite a reasonably large cohort size at study entry, the number of subjects in each age, ethnicity, and gender group at baseline was limited because of the spectrum of age and ethnicity. Furthermore, the cohort size was diminished by attrition in subsequent years, particularly among nonwhite participants. Attrition rates of 43–51% have been observed in studies of black adults (46, 47). Retaining teens in a clinical study is even more challenging because of their mobility, dependence upon parental cooperation, and competing social and academic interests. Finally, it was beyond the scope of this paper to address the influence of lifestyle variables on longitudinal gains in bone mineral. Studies in predominantly white cohorts indicate that calcium intake or physical activity may account for as much as 5–10% of the variance in bone mineral accrual among children (1, 8, 16) or young adults (9). Furthermore, common lifestyle patterns may contribute to genetic factors to produce ethnic differences in bone mass. In a study of black and white adults, Ettinger *et al.* found that correcting for body size, composition, diet, physical activity, endocrine function, and markers of bone metabolism reduced, but did not eliminate, racial differences in peak bone mass (48). We found few ethnic differences in lifestyle in this cohort at study entry, and these variables were weak predictors of bone mineral (23). However, we intend to extend our analyses of these data to explore the correlation between diet and activity and longitudinal changes in bone mass.

Despite these weaknesses, we believe that the bone mineral curves from this study provide valuable reference norms. To date, DXA manufacturers have included little or no pediatric data in their software, making it difficult to interpret scans in younger patients. There are several published studies in predominantly white cohorts (6, 10, 13–19, 23), but few reports of Hispanic or black youth (11, 20). The only bone mineral data from Asian American youth to date were collected from our study group (21, 22). The sample size of 423 subjects makes this one of the larger studies and the only reported longitudinal study to include ethnically diverse youth. The statistical approach used to model the bone mineral curves allowed inclusion of both cross-sectional and longitudinal data. We provide gender- and ethnic-specific curves for most skeletal sites, including total hip. The use of gender-specific reference data is particularly important, because adolescent differences in the tempo of bone gain may lead to the overdiagnosis of osteopenia in males (6, 49). It is equally important to use ethnic-specific reference standards, because mean differences in bone mineral between blacks and nonblacks approximate 5–10%, the equivalent of 0.5–1.0 SD. Bone mineral data are presented in terms of both areal

(BMD) and estimated volumetric (BMAD) mineral density to allow adjustments for bone size. The reference data presented here can be used without modification when interpreting bone scans obtained on the Hologic, Inc., 1000W in the pencil beam mode. When interpreting studies collected using other densitometers or software versions, it will be necessary to correct for systematic differences (50).

There is continued debate about the best method to adjust for body size and pubertal stage when interpreting pediatric DXA scans (23, 51). Our bone mineral data are presented by chronological age rather than pubertal stage to facilitate their use when pubertal stage is not available. Furthermore, the statistical model used to create the bone mineral curves required a continuous variable. However, we recognize that it may be appropriate to adjust for pubertal stage or skeletal age rather than chronological age when evaluating data from youths with premature or delayed maturation (1). For children with significant growth retardation, it may also be helpful to compare estimates of volumetric bone density (BMAD) to reduce the influence of bone size (5, 13, 27). Other investigators have suggested that BMD be adjusted for weight (11), lean body mass (52), or height (23) to correct for differences in body size. Molgaard *et al.* proposed that whole body BMD be replaced by measurements of bone area corrected for height and of BMC corrected for bone area and height (23). Regardless of the method used to adjust for body size, our data suggest that gender and ethnic differences in bone mass are sufficient to justify the use of sex- and race-specific reference data when interpreting pediatric bone mineral.

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References

1. **Hui SL, Slemenda CW, Johnston CC.** 1990 The contribution of bone loss to post menopausal osteoporosis. Osteop Int. 1:30–34.
2. **Bonjour JP.** 1996 Bone mineral acquisition in adolescence. In: Marcus R, Feldman D, Kelsey J, eds. Osteoporosis. San Diego: Academic Press; 465–476.
3. **Bachrach LK.** 1996 Osteopenia in childhood and adolescence. In: Osteoporosis. Marcus R, Feldman D, Kelsey J, eds. San Diego: Academic Press; 785–800.
4. **Katzman DK, Bachrach LK, Carter DR, Marcus R.** 1991 Clinical and anthropometric correlates of bone mineral acquisition in healthy adolescent girls. J Clin Endocrinol Metab. 73:1332–1339.
5. **Kroger H, Kotaniemi A, Kroger L, Alhava E.** 1993 Development of bone mass and bone density of the spine and femoral neck: a prospective study of 65 children and adolescents. Bone Miner. 23:171–182.
6. **Theintz G, Buchs B, Rizzoli R, Slosman D, Clavien H, Sizonenko PC, Bonjour J-PH.** 1992 Longitudinal monitoring of bone mass accumulation in healthy adolescents: evidence for a marked reduction after 16 years of age at the levels of lumbar spine and femoral neck in female subjects. J Clin Endocrinol Metab. 75:1060–1065.
7. **Lu PW, Briody JN, Ogle GD, et al.** 1994 Bone mineral density of total body, spine, and femoral neck in children and young adults: a cross-sectional and longitudinal study. J Bone Miner Res. 9:141–1457.
8. **Slemenda CW, Reister TK, Sui SL, Miller JZ, Christian JC, Johnston Jr CC.** 1994 Influences on skeletal mineralization in children, and adolescents: evidence of varying effects of sexual maturation and physical activity. J Pediatr. 125:201–207.
9. **Recker RR, Davies KM, Hinders SM, Heaney RP, Stegman MR, Kimmel DB.** 1992 Bone gain in young adult women. JAMA. 268:2403–2408.
10. **Southard RN, Morris JD, Maha JD, Hayes JR, Torch MA, Sommer A, Zipf WB.** 1991 Bone mass in healthy children: measurement with quantitative DXA. Radiology. 179:735–738.
11. **McCormick DP, Ponder SW, Fawcett HD, Palmer JL.** 1991 Spinal bone mineral density in 335 normal and obese children and adolescents: evidence for ethnic and sex differences. J Bone Miner Res. 5:507–513.
12. **Patel DN, Pettifor JM, Becker PJ, Grieve C, Leschner K.** 1992 The effect of ethnic group on appendicular bone mass in children. J Bone Miner Res. 7:263–272.
13. **Lu PW, Cowell CT, Lloyd-Jones SA, Briody JN, Howman-Giles R.** 1996 Volumetric bone mineral density in normal subjects, aged 5–27 years. J Clin Endocrinol Metab. 81:1586–1590.
14. **Faulkner RA, Bailey DA, Drinkwater DT, McKay HA, Arnold C, Wilkinson AA.** 1996 Bone densitometry in Canadian children 8–17 years of age. Calcif Tissue Int. 59:344–351.
15. **Sabatier J-P, Guaydier-Souquieres G, Laroche D, et al.** 1996 Bone mineral acquisition during adolescence and early adulthood: a study in 574 healthy females 10–24 years of age. Osteop Int. 6:141–148.
16. **Boot AM, De Ridder MAJ, Pols HAP, Krenning EP, de Muinck Keizer-Schrama MPF.** 1997 Bone mineral density in children and adolescents: relation to puberty, calcium intake, and physical activity. J Clin Endocrinol Metab. 82:57–62.
17. **Young D, Hopper JL, Nowson CA, et al.** 1995 Determinants of bone mass in 10- to 26-year-old females: a twin study. J Bone Miner Res. 10:558–567.
18. **Teegarden D, Proulx WR, Martin BR, et al.** 1995 Peak bone mass in young women. J Bone Miner Res. 10:711–715.
19. **Matkovic V, Jelic T, Wardlaw GM, et al.** 1994 Timing of peak bone mass in Caucasian females and its implication for the prevention of osteoporosis. J Clin Invest. 93:799–808.
20. **Gilsanz V, Skaggs DL, Kovanlikaya A, Sayre J, Loro ML, Kaufman F, Korenman SG.** 1998 Differential effect of race on the axial and appendicular skeletons of children. J Clin Endocrinol Metab. 83:1420–1427.
21. **Bhudhikanok GS, Wang M-C, Eckert K, Matkin C, Marcus R, Bachrach LK.** 1996 Differences in bone mineral in young Asian and Caucasian Americans may reflect differences in bone size. J Bone Miner Res. 11:1545–1556.
22. **Wang M-C, Aguirre M, Bhudhikanok GS, Kendall CG, Kirsch S, Marcus R, Bachrach LK.** 1997 Bone mass and hip axis length in healthy Asian, black, Hispanic, and white American youths. J Bone Miner Res. 12:1922–1935.
23. **Molgaard C, Thomsen BL, Prentice A, Cole TJ, Michaelsen KF.** 1997 Whole body bone mineral content in healthy children and adolescents. Arch Dis Child. 76:9–15.
24. **Nelson DA, Simpson PM, Johnson CC, Barondess DA, Kleerekoper M.** 1997 The accumulation of whole body skeletal mass in third- and fourth-grade children: effects of age, gender, ethnicity, and body composition. Bone. 20:73–78.
25. **Genant HK, Engelke K, Fuerst T, et al.** 1996 Noninvasive assessment of bone mineral and structure: state of the art [Review]. J Bone Miner Res. 11:707–730.
26. **Seeman E.** 1998 Editorial: growth in bone mass, and size–are racial and gender differences in bone mineral density more apparent than real? J Clin Endocrinol Metab. 83:1414–1419.
27. **Carter DR, Bouxsein ML, Marcus R.** 1992 New approaches for interpreting projected bone densitometry data, J Bone Miner Res. 7:137–145.
28. **Mazess RB, Barden H, Mautalan C, Vega E.** 1994 Normalization of spine densitometry. J Bone Miner Res. 9:541–548.
29. **Cummings SR, Marcus R, Palermo L, Ensrud KE, Genant HK, Study of Osteoporotic Fractures Research Group.** 1994 Does estimating volumetric bone density of femoral neck improve the prediction of hip fracture? A prospective study. J Bone Miner Res. 9:1429–1432.
30. **Gilsanz V, Boechat I, Roe TF, Loro ML, Sayre JW, Goodman WG.** 1994 Gender differences in vertebral body sizes in children and adolescents. Radiology. 190:673–677.
31. **Jaworski M, Lebiedowski M, Lorenc RS, Trempe J.** 1995 Ultrasound bone measurement in pediatric subjects. Calcif Tissue Int. 56:368–371.
32. **Mughal MZ, Ward K, Qayyum N, Langton CM.** 1997 Assessment of bone status using the contact ultrasound bone analyzer. Arch Dis Child. 76:535–536.
33. **Duke PM, Litt IF, Gross RT.** 1980 Adolescents' self-assessment of sexual maturation. Pediatrics. 66:918–920.
34. **Block G, Hartman AM, Dresser CM, Carroll MD, Gannon J, Gardner L.** 1986 A data-based approach to diet questionnaire design and testing. Am J Epidemiol. 124:453–469.
35. **Diggle P, Liang K, Zeger S.** 1994 Analysis of longitudinal data. Oxford: Oxford Science.
36. **Hastie T, Tibshirani R.** 1990 Generalized additive models. New York: Chapman, and Hall.
37. **Cleveland W.** 1979 Robust locally-weighted regression and smoothing scatterplots. J Am Stat Soc. 74:829–836.
38. **Pinheiro J, Bates D.** 1995 Mixed effects models, methods, and classes for S and Splus. Madison: Department of Statistics, University of Wisconisn.
39. **Efron B, Tibshirani R.** 1993 An introduction to the bootstrap. New York: Chapman and Hall.
40. **Li J-Y, Specker BL, Ho ML, Tsang RC.** 1989 Bone mineral content in black and white children 1 to 6 years of age. Am J Dis Child. 143:1346–1349.
41. **Bell NH, Shary J, Stevens J, Garza M, Gordon L, Edwards J.** 1991 Demonstration that bone mass is greater in black than in white children. J Bone Miner Res. 6:719–723.
42. **Gilsanz V, Roe TF, Mora S, Costin G, Goodman WG.** 1991 Changes in

vertebral bone density in black girls and white girls during childhood and puberty. N Engl J Med. 325:1597–1600.
43. **Cundy T, Cornish J, Evans MC, Gamble G, Stapleton J, Reid IR.** 1995 Sources of interracial variation in bone mineral density. J Bone Miner Res. 10:368–373.
44. **Greulich WW.** 1976 Some secular changes in the growth of American-born and native Japanese children. Am J Phys Anthropol. 45:553–568.
45. **Bailey DA, Faulkner RA, McKay HA.** 1996 Growth, physical activity, and bone mineral acquisition. Exercise Sports Sci Rev. 24:233–266.
46. **Blumenthal DS, Sung J, Coates R, Williams J, Liff J.** 1995 Recruitment and retention of subjects for a longitudinal cancer prevention study in an inner-city black community. Health Serv Res. 30:197–205.
47. **Psaty BM, Cheadle A, Koepsell TD, et al.** 1994 Race and ethnicity–specific characteristics of participants lost to follow-up in a telephone cohort. Am J Epidemiol. 140:161–171.
48. **Ettinger B, Sidney S, Cummings SR, et al.** 1997 Racial differences in bone density between young adult black and white subjects persist after adjustment for anthropometric, lifestyle, and biochmical differences. J Clin Endocrinol Metab. 82:429–434.
49. **Leonard MB, Propert KJ, Zemel BS, Stallings VA, Feldman HI.** 1999 Discrepancies in pediatric bone mineral density reference data: potential for misdiagnosis of osteopenia. J Pediatr. 135:182–188.
50. **Genant HK.** 1995 Universal standardization for dual x-ray absorptiometry: patient and phantom cross-calibration results. J Bone Miner Res. 10:997–998.
51. **Prentice A, Parsons TJ, Cole TJ.** 1994 Uncritical use of bone mineral density in absorptiometry may lead to size-related artifacts in the identification of bone mineral. Am J Clin Nutr. 60:837–842.
52. **Robinson TL, Snow-Harter C, Taaffe DR, Gillis D, Show J, Marcus R.** 1995 Gymnasts exhibit higher bone mass than runners despite similar prevalence of amenorrhea and oligomenorrhea. J Bone Miner Res. 10:26–35.