IMPORTANCE  Prevention of osteoporosis in adulthood begins with optimizing bone health in early life. The longitudinal association between growth and bone accretion during childhood is not fully understood.

OBJECTIVES  To assess the acquisition of whole-body (WB) and skeletal site–specific bone mineral content (BMC) relative to linear growth in a healthy, diverse, longitudinal cohort of children, adolescents, and young adults and to test for differences related to sex and African American race.

DESIGN, SETTING, AND PARTICIPANTS  This investigation was a mixed longitudinal study with annual assessments for up to 7 years at 5 US clinical centers. Participants were healthy children, adolescents, and young adults. The study dates were July 2002 through March 2010. The dates of the analysis were June through December 2016.

MAIN OUTCOMES AND MEASURES  Anthropometrics, BMC, and body composition via dual-energy x-ray absorptiometry. The superimposition by translation and rotation (SITAR) analysis method was used to define the mean trajectories for height, WB lean soft tissue, appendicular lean soft tissue, and WB and skeletal site–specific BMC acquisition and to measure the age and magnitude of peak velocity for each parameter. The SITAR modeling was performed separately by sex and self-reported race.

RESULTS  Among 2014 healthy children, adolescents, and young adults (1022 [50.7%] female and 479 [23.8%] African American) aged 5 to 19 years at study entry, the mean age of peak height velocity was 13.1 years (95% CI, 13.0-13.2 years) in African American boys vs 13.4 years (95% CI, 13.3-13.4 years) in non-African American boys (difference, −0.3 years; 95% CI, −0.4 to −0.1 years) and 11.0 years (95% CI, 10.8-11.1 years) in African American girls vs 11.6 years (95% CI, 11.5-11.6 years) in non-African American girls (difference, −0.6 years; 95% CI, −0.7 to −0.5 years). Age of peak acquisition of WB BMC was 14.0 years (95% CI, 13.8-14.1 years) in African American boys vs 14.0 years (95% CI, 13.8-14.1 years) in non-African American boys (difference, −0.0 years; 95% CI, −0.2 to 0.2 years) and 12.1 years (95% CI, 12.0-12.3 years) in African American girls vs 12.4 years (95% CI, 12.3-12.5 years) in non-African American girls (difference, −0.3 years; 95% CI, −0.4 to −0.1 years). At age 7 years, children had acquired 69.5% to 74.5% of maximal observed height but only 29.6% to 38.1% of maximal observed WB BMC. Adolescents gained 32.7% to 35.8% of maximal observed WB BMC during the 2 years before and 2 years after peak height velocity. Another 6.9% to 10.7% of maximal observed WB BMC occurred after linear growth had ceased. In the group at highest risk for fracture, non-African American boys, peak fracture incidence occurred approximately 1 year before peak height velocity.

CONCLUSIONS AND RELEVANCE  In this longitudinal study, height gains substantially outpaced gains in BMC during childhood, which could contribute to fracture risk. A significant proportion of bone is accrued after adult height is achieved. Therefore, late adolescence represents a potentially underrecognized window of opportunity to optimize bone mass.
The bone mass achieved by young adulthood is a critically important determinant of lifelong bone health. A significant proportion of peak bone mass is acquired during adolescence. Although linear growth and bone acquisition are coordinated, they do not occur at exactly the same pace. It has previously been hypothesized that a lag between skeletal expansion and skeletal mineralization may contribute to an epidemiologically observed increase in fracture risk in childhood. However, few pediatric studies have contained sufficiently detailed longitudinal measurements to characterize the difference in pace between gains in height and gains in bone throughout childhood, adolescence, and young adulthood. The strong associations between bone mineral content (BMC) accrual and lean soft tissue (LST) are also important to consider. Moreover, the association between growth, body composition, and BMC accrual may be specific to the particular skeletal site and may vary with sex and race. We and others have previously demonstrated differences in skeletal development in African American children compared with non-African American children. The degree to which sex- and race-related differences in adult bone density are attributable to differences in the timing and magnitude of developmental gains in bone mass remains unknown.

Therefore, the present study aimed (1) to assess the acquisition of whole-body (WB) and skeletal site-specific BMC relative to linear growth, WB LST, and appendicular LST (aLST) (reflecting mostly skeletal muscle in the limbs) between ages 5 and 20 years in a healthy, diverse, longitudinal cohort and (2) to test for differences related to sex and African American race. We used innovative techniques that have significantly increased the feasibility of such investigations.

Methods

Study Sample

The Bone Mineral Density in Childhood Study (BMDCS) was a mixed longitudinal investigation of 2014 children enrolled at 5 US centers who were evaluated between July 2002 and March 2010. The dates of the analysis were June through December. Participants (aged 5–19 years at study entry) were evaluated annually for up to 7 years. Inclusion and exclusion criteria were specified to obtain a healthy sample of children without medical problems known to adversely influence bone health. Height and body mass index of each participant at study entry were required to be between the 3rd and 97th percentiles for age and sex.

The protocol was approved by the institutional review boards at each clinical center (The Children’s Hospital of Philadelphia, Cincinnati Children’s Hospital Medical Center, Creighton University, Children’s Hospital Los Angeles, and Columbia University) and the data coordinating center (Clinical Trials and Survey Corporation). Consent was obtained from the parent or guardian for participants younger than 18 years, and assent was obtained from participants. Written informed consent was obtained from study participants 18 years or older.

Fracture

Participants were asked whether they had experienced a fracture in the previous year. This question was asked at each follow-up visit.

Statistical Analysis

Characteristics of the cohort were summarized with parametric or nonparametric statistics as appropriate. We used a growth modeling approach called superimposition by translation and rotation (SITAR), which generates a shape-invariant model with a single fitted curve. Models with different df were tested empirically and evaluated with respect to an epidemiologically observed increase in fracture risk in childhood. However, few pediatric studies have contained sufficiently detailed longitudinal measurements to characterize the difference in pace between gains in height and gains in bone throughout childhood, adolescence, and young adulthood. The strong associations between bone mineral content (BMC) accrual and lean soft tissue (LST) are also important to consider. Moreover, the association between growth, body composition, and BMC accrual may be specific to the particular skeletal site and may vary with sex and race. We and others have previously demonstrated differences in skeletal development in African American children compared with non-African American children. The degree to which sex- and race-related differences in adult bone density are attributable to differences in the timing and magnitude of developmental gains in bone mass remains unknown.

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to goodness of fit. For each individual and for each dimension of growth (height, WB and skeletal site-specific BMC acquisition, WB LST, and aLST), 3 parameters were estimated as random effects for each individual that correspond to key features of variation in growth. These parameters included size (individuals can be larger or smaller than average), tempo (the timing of the adolescent spurt can be earlier or later than average), and velocity (the duration of the adolescent spurt can be more or less rapid than average). By design, SITAR permits inclusion of individuals with missing data and reduces complex growth curves into these 3 clinically meaningful parameters that can be compared across individuals and groups. We tested models with 4 to 8 $d_f$ and used visualization, along with the Bayesian information criterion, to identify the best model. Results were used to estimate the age and magnitude of peak velocity for each individual participant. As in previous investigations from the BMDCS, we fit separate models for African American and non-African American children. We used the standard error of the tempo parameter in the sex- and race-stratified SITAR models as an estimate of the standard error of age of peak height velocity (PHV), and we used the standard error of the velocity parameter as a proportional standard error for peak velocity. Summary statistics were used to perform sex-stratified $t$ tests to assess the difference between African Americans and non-African Americans for each parameter. We report unadjusted $P$ values and indicate those that meet the Bonferroni-adjusted $P$ value threshold of less than 0.0028 (0.05 divided by 18 sex-stratified comparisons).

The difference in growth velocity parameters by race (African American vs non-African American) was assessed using 2-sample $t$ tests for girls and boys separately. We expressed the magnitude of BMC and LST parameters at the age of PHV relative to maximal observed value before 20 years or the value at age 20 years, whichever was greater (referred to as maximal observed value) because the age of PHV serves as a common point of reference. We estimated the proportion of maximal observed BMC and LST that is acquired during the following 2 periods of interest: (1) during the 2 years before and 2 years after PHV and (2) after peak height (linear growth velocity <1 cm/y) was achieved. Pearson product moment correlation analyses were used to investigate the association between the size, tempo, and velocity parameters obtained by SITAR in each of the dimensions of growth. To understand the association between pubertal timing and SITAR parameters, we visualized these parameters with the cohort stratified into previously defined categories of age of pubertal onset (within the BMDCS cohort, <25th percentile, 25th to <75th percentile, and ≥75th percentile). Analysis of variance was used to evaluate the association of the age of peak velocity and peak velocity in each parameter with the category of pubertal timing. To understand how observed trajectories of linear growth and bone acquisition may relate to fracture vulnerability, we calculated the annualized incidence of any fracture in each year of life by sex and race.

All analyses were conducted using R (version 3.1.3), including the SITAR extension package. Statistical significance was taken as a 2-sided $P$ value of less than .05.

## Results

### Sample Characteristics

The sample consisted of 2014 healthy children, adolescents, and young adults (1022 [50.7%] female and 479 [23.8%] African American), who completed a mean of 5 annual visits each (eTable 1 in the Supplement). These visits represent a range of pubertal stages, with 5001 of 10 695 (46.8%) visits occurring in postpubertal (Tanner V) adolescents.

### SITAR Trajectories

The mean trajectory curves are shown in Figure 1A (for magnitude of attained BMC and LST) and Figure 1B (for velocity of BMC and LST) by sex and race. As expected, older boys were taller and had more BMC and LST than older girls. For boys, peak velocity in all parameters occurred later and was greater in magnitude. Across childhood, the absolute amount of both BMC and LST was greater in African American children and adolescents compared with non-African American children and adolescents despite overall similar heights.

### Estimates of the Age and Magnitude of Peak Velocities

As summarized in Table 1 and Table 2, the mean age of PHV occurred significantly earlier in African American boys compared with non-African American boys (13.1 vs 13.4 years) (difference, −0.3 years, 95% CI, −0.4 to −0.1 years) and significantly earlier in African American girls compared with non-African American girls (11.0 vs 11.6 years) (difference, −0.6 years, 95% CI, −0.7 to −0.5 years). Age of peak acquisition of WB BMC was similar in African American boys compared with non-African American boys (14.0 vs 14.0 years) (difference, −0.0 years; 95% CI, −0.2 to 0.2 years). Age of peak acquisition of WB BMC was significantly younger in African American girls compared with non-African American girls (12.1 vs 12.4 years) (difference, −0.3 years; 95% CI, −0.4 to −0.1 years), and a similar pattern was observed at all skeletal sites. Model-derived estimates of peak velocity of WB BMC accrual lagged behind PHV by 0.6 to 0.9 years in boys and by 0.8 to 1.2 years in girls in this cohort (Figure 2). Figure 2 also shows that, before the age of peak velocity in each parameter, the relative pace of linear growth is faster than the relative pace of WB BMC accrual. For example, at age 7 years, height velocity is 62.9% to 76.3% of PHV, but WB BMC velocity is 27.8% to 31.9% of peak WB BMC velocity. In eFigure 1 in the Supplement, a consequence of this discrepancy is shown, namely, that the proportion of maximal observed value is larger for height than for bone. For example, at age 7 years, children had acquired 69.5% to 74.5% of maximal observed height but only 29.6% to 38.1% of maximal observed BMC. Also, both African American and non-African American boys at age 10 years have achieved 79.0% and 78.2%, respectively, of maximal observed height but only 41.2% and 39.7%, respectively, of maximal observed BMC.

Age at which peak velocity for the acquisition of each parameter occurs is shown in eFigure 2 in the Supplement. Overall, peak gains in total hip and femoral neck BMC occurred before peak gains in WB BMC, lumbar spine, and dis-
tal one-third radius. Peak gains in the ultradistal radius occurred last (Tables 1 and 2 and eFigure 2 in the Supplement).

We also examined the acquisition of these parameters relative to a common reference, PHV (Table 3, Figure 2, and
The timing and magnitude of peak acquisition in height, WB LST, and aLST show similar high correlations with site-specific BMC accrual (Pearson $r$ range, 0.72-0.88 [$P < .001$] for all parameters).

With respect to sexual maturation, we found that, in both girls and boys, earlier pubertal timing was associated with younger age of peak velocity as well as more rapid velocity; this pattern was consistent across growth parameters tested (eFigure 3 in the Supplement). Rates of fracture were highest in non-African American boys and overall lower in African American children (eFigure 4 in the Supplement). For the highest-risk group, non-African American boys, fracture rates were highest at approximately age 12.5 years before the age of PHV (13.4 years).

**Discussion**

We describe the timing and magnitude of peak acquisition in height, WB LST, aLST, WB and skeletal site-specific BMC...
acquisition, and puberty stage in a contemporary, multi-center, multiethnic cohort of healthy children, adolescents, and young adults. First, we report race-specific differences in the age and magnitude of peak gains in height, LST, and WB and skeletal site-specific BMC acquisition. Second, we demonstrate that, in the 2 years before and 2 years after PHV, adolescents gained approximately one-third of their observed maximal BMC. Through childhood, children have gained

In each panel, the solid vertical line indicates the age of PHV, and the dashed vertical line indicates the age of peak WB BMC acquisition. The ages at which peak velocity in each of these parameters occurs, along with the lag between the 2, are also given. The 2 years before and 2 years after the PHV are shaded in gray.

PBMCV indicates peak (whole-body) bone mineral content velocity.

Table 3. Percentage of Maximal Observed Value in Height, Lean Mass, and Whole-Body and Site-Specific Bone Mineral Content (BMC) at the Mean Age of Peak Height Velocity, by Sex and Self-reported Race

<table>
<thead>
<tr>
<th>Variable</th>
<th>% of Maximal Observed Value</th>
<th>African American Girls (n = 233)</th>
<th>Non-African American Girls (n = 789)</th>
<th>African American Boys (n = 246)</th>
<th>Non-African American Boys (n = 746)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height</td>
<td></td>
<td>90.4</td>
<td>90.1</td>
<td>90.3</td>
<td>90.0</td>
</tr>
<tr>
<td>WB LST</td>
<td></td>
<td>67.8</td>
<td>68.5</td>
<td>63.4</td>
<td>63.8</td>
</tr>
<tr>
<td>aLST</td>
<td></td>
<td>70.9</td>
<td>72.4</td>
<td>65.0</td>
<td>65.0</td>
</tr>
<tr>
<td>BMC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WB</td>
<td></td>
<td>58.3</td>
<td>60.2</td>
<td>56.7</td>
<td>58.8</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td></td>
<td>50.3</td>
<td>49.9</td>
<td>50.8</td>
<td>48.2</td>
</tr>
<tr>
<td>Total hip</td>
<td></td>
<td>64.4</td>
<td>65.4</td>
<td>59.6</td>
<td>57.7</td>
</tr>
<tr>
<td>Femoral neck</td>
<td></td>
<td>71.4</td>
<td>70.0</td>
<td>66.7</td>
<td>66.0</td>
</tr>
<tr>
<td>Distal one-third radius</td>
<td></td>
<td>68.3</td>
<td>68.2</td>
<td>61.5</td>
<td>63.5</td>
</tr>
<tr>
<td>Ultradistal radius</td>
<td></td>
<td>55.8</td>
<td>56.5</td>
<td>52.0</td>
<td>52.5</td>
</tr>
</tbody>
</table>

Abbreviations: aLST, appendicular lean soft tissue; WB, whole body; WB LST, whole-body lean soft tissue.
substantially less BMC relative to height, which may contribute to their increased incidence of fracture. Similar to previous analyses in this cohort,16 we observe this increased incidence of fracture before PHV most clearly in non-African American boys. Our analyses reveal strong associations between trajectories of both height and LST acquisition with BMC accrual. Most important, we illustrate the extended acquisition of bone that occurs well after the cessation of linear growth in both girls and boys.

Our results show similarities with another seminal study of the timing of peak bone mineral accrual. Specifically, the Saskatchewan Pediatric Bone Mineral Accrual Study was a 6-year longitudinal investigation, beginning in 1991, of 113 children of mostly white race who were aged 8 to 14 years at enrollment.17,18 The age of PHV estimates were similar to those obtained in the BMDCS for non-African American participants. The investigators found that adolescents had attained approximately 90% of adult height and approximately 60% of adult WB BMC by the time of their PHV, estimates that are also similar to those obtained in the BMDCS in non-African American participants. We show that earlier puberty is associated with more rapid physical maturation (eFigure 3 in the Supplement). It has long been known that the timing and magnitude of the velocity curve differs between children who are early, typical, and late maturing,19; this phenomenon is captured well by the SITAR models. The present study adds substantially to this previous work in that it provides a more contemporary assessment of skeletal development and, most important, includes both estimates in African American children and at multiple skeletal sites.

We also observed sex- and race-specific differences in the acquisition of BMC and LST. These differences recapitulate patterns observed in the BMDCS and in other diverse cohorts.20,21 Overall, as expected, girls had lower BMC and LST than boys after peak linear growth, and peak acquisition of BMC and LST occurred sooner. With respect to race in both girls and boys, despite having similar heights, African American girls and African American boys had more WB LST, aLST, and BMC than their non-African American counterparts. In African American girls and boys, peak gain in height, WB LST, and aLST occurred earlier than in their non-African American counterparts; in African American girls, consistent differences were observed for BMC as well. Multiple previous studies have also demonstrated race-specific effects on bone development. For example, in a cross-sectional study,22 differences in cancellous vertebral bone density were significantly greater in African American girls in late puberty (34% vs 11% increase from prepubertal values). Our longitudinal study adds to these cross-sectional observations and suggests that race-specific differences in trajectories of BMC and LST acquisition may underlie the increased fracture prevalence among children16 and the higher rates of osteoporosis and hip fracture among adults of white race23 compared with African Americans.

To better understand determinants of bone health across the life span, we modeled the acquisition of BMC at various skeletal sites. This finding is important because skeletal sites can differ in many ways, including their exposure to weight-bearing forces and the relative contribution of cortical and trabecular bone to DXA estimates of aBMD. We found that, although growth patterns at specific sites were correlated, the timing of peak bone mineral accrual and the cessation of BMC acquisition differed by skeletal site (eFigure 2 in the Supplement). For total hip and femoral neck, the mean BMC accrual approached zero by age 20 years, particularly for female participants (i.e., there was evidence of a cessation of BMC gain and the beginning of loss in early adulthood at these sites rich in trabecular bone) (Figure 1). Other investigations have shown that trabecular bone loss can occur in young adulthood, especially from the predominantly trabecular bone of the lumbar spine.24 In contrast, even after linear growth ceases, young adults continue to gain cortical bone, and cortical bone loss may not occur until the fourth or fifth decade of life.25,26 The persistence of BMC acquisition in the distal one-third radius that we observed after age 20 years in the BMDCS (Figure 1) may reflect ongoing gains in cortical bone.

Similar to previous investigations,17 we identified a lag between the acquisition of height and the acquisition of BMC relative to maximal observed values (Figure 2 and eFigure 1 in the Supplement). One possible consequence of this lag is that the proportional load borne by cortical bone decreases around the time of PHV, a period that corresponds to some investigations to peak epidemiological incidence of fracture.27 Most important, we found that in childhood, well before PHV, children gain height more rapidly than they accrue BMC. The slower rate of BMC relative to height acquisition in childhood may explain the epidemiological observation that the window of fracture vulnerability may begin many years before PHV. Indeed, we observed that, on average, in non-African American boys (the group that experienced the most fractures) the highest incidence of fracture was at approximately age 12.5 years, before the mean PHV. The lag typically observed between gains in height and bone may be due to the expansion in cortical thickness, cross-sectional area, and density that continues even after the cessation of linear growth.24,28 However, differences in lag do not appear to explain race-specific variations in fracture rates.

Strengths and Limitations
The present study has several important strengths and limitations. By design, the cohort is approximately 24% African American, which permits analysis of African American-specific associations. Although we used self-reported race, our group has previously shown that such report is associated with genetic ancestry.6 Use of the novel SITAR modeling strategy is another advantage because SITAR readily accommodates the range in the number and timing of measurements that can occur in a longitudinal study. In addition, by reducing the dimensionality of complex growth curves, SITAR facilitates the investigation of the influence of clinical covariates or even therapeutic interventions29 on growth. Inclusion of more participants in the third and fourth decades of life would likely improve the SITAR model fitting in late adolescence. We used DXA to estimate site-specific BMC. While DXA may not capture important dimensions of bone quality, DXA-based assessments are also used in clinical practice to evaluate bone health. However, future studies using newer imaging techniques...
should be undertaken. Also, it would be informative to extend these longitudinal observations into adulthood to explicitly evaluate the influence of developmental parameters on osteoporosis and fracture.

Conclusions

In summary, in a longitudinal cohort, we report sex and race differences in the size, tempo, and velocity of WB and skeletal site-specific BMC accrual. Consistent with historical reports in children of almost exclusively European descent, we found that all adolescents gained a substantial proportion of maximal observed BMC during pubertal growth. However, despite the clear importance of linear growth to bone health, we also found that, even after linear growth has ceased, approximately 6.9% to 10.7% of maximal observed WB BMC is accrued in late adolescence. We also found that, for many years before PHV, bone accretion proceeds at a modest pace compared with gains in height, which may contribute to the increased vulnerability to fracture that we observed, particularly in non-African American boys. A detailed understanding of sex and race associations, as well as the developmental timing of BMC accrual, is critical for the development of rational strategies to optimize peak bone mass.¹

REFERENCES


