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Longitudinal changes in calcaneal quantitative ultrasound measures during childhood

M. Lee,

Lifespan Health Research Center, Department of Community Health, Wright State University Boonshoft School of Medicine, 3171 Research Blvd., Dayton, OH 45420, USA. Department of Pediatrics, Wright State University Boonshoft School of Medicine, Dayton, OH, USA

R. W. Nahhas,

Lifespan Health Research Center, Department of Community Health, Wright State University Boonshoft School of Medicine, 3171 Research Blvd., Dayton, OH 45420, USA

A. C. Choh,

Lifespan Health Research Center, Department of Community Health, Wright State University Boonshoft School of Medicine, 3171 Research Blvd., Dayton, OH 45420, USA

E. W. Demerath,

Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN, USA

D. L. Duren,

Lifespan Health Research Center, Department of Community Health, Wright State University Boonshoft School of Medicine, 3171 Research Blvd., Dayton, OH 45420, USA

W. C. Chumlea,

Lifespan Health Research Center, Department of Community Health, Wright State University Boonshoft School of Medicine, 3171 Research Blvd., Dayton, OH 45420, USA. Department of Pediatrics, Wright State University Boonshoft School of Medicine, Dayton, OH, USA

R. J. Sherwood,

Lifespan Health Research Center, Department of Community Health, Wright State University Boonshoft School of Medicine, 3171 Research Blvd., Dayton, OH 45420, USA. Department of Pediatrics, Wright State University Boonshoft School of Medicine, Dayton, OH, USA

B. Towne,

Lifespan Health Research Center, Department of Community Health, Wright State University Boonshoft School of Medicine, 3171 Research Blvd., Dayton, OH 45420, USA. Department of Pediatrics, Wright State University Boonshoft School of Medicine, Dayton, OH, USA

R. M. Siervogel, and

Lifespan Health Research Center, Department of Community Health, Wright State University Boonshoft School of Medicine, 3171 Research Blvd., Dayton, OH 45420, USA. Department of Pediatrics, Wright State University Boonshoft School of Medicine, Dayton, OH, USA

S. A. Czerwinski

Lifespan Health Research Center, Department of Community Health, Wright State University Boonshoft School of Medicine, 3171 Research Blvd., Dayton, OH 45420, USA

M. Lee: miryoung.lee@wright.edu

Abstract

Summary—This longitudinal study examined how calcaneal quantitative ultrasound (QUS) measures change during childhood while taking into account skeletal maturation, body mass index (BMI), and physical activity. The study reported sex differences in QUS growth curves and an inverse relationship between BMI and speed of sound (SOS) measures.

Introduction—The aim of this study was to examine how calcaneal QUS parameters change over time during childhood and to determine what factors influence these changes.

Methods—The study sample consisted of a total of 192 Caucasian children participating in the Fels Longitudinal Study. A total of 548 calcaneal broadband ultrasound attenuation (BUA) and SOS observations were obtained between the ages of 7.6 and 18 years. The best fitting growth curves were determined using statistical methods for linear mixed effect models.

Results—There are significant sex differences in the pattern of change in QUS parameters ($p<0.05$). The relationship between QUS measures and skeletal age is best described by a cubic growth curve in boys and a linear pattern among girls. Boys experience their most rapid growth in BUA and SOS in early and late adolescence, while girls experience constant growth throughout childhood. Adiposity levels were significantly associated with the changes in SOS among boys ($p<0.001$) and girls ($p<0.01$), indicating that children with higher BMI are likely to have lower SOS over time compared to children with lower BMI. For girls, physical activity levels showed positive associations with changes in QUS measures ($p<0.05$).

Conclusion—This study documents significant sex differences in the pattern of change in QUS measures over childhood and adolescence. Our study also shows significant influences of adiposity and physical activity on the pattern of change in QUS measures during childhood.

Keywords

Calcaneal quantitative ultrasound; Children; Longitudinal study; Skeletal health

Introduction

Accrual of peak bone mass at the end of adolescence or early in adulthood lays the foundation for bone to manage the various challenges to the skeleton over one's lifetime [1, 2]. Studies of peak bone mass and childhood bone accrual have been mostly based on areal bone mineral density (aBMD) collected using dual energy X-ray absorptiometry (DXA). There are, however, a number of other non-invasive techniques including quantitative computed tomography (QCT) and quantitative ultrasound sonometry (QUS) to quantify

bone health. While DXA provides measures of aBMD and bone mineral content (BMC), it is subject to bone size problems in growing children. QCT is used to assess volumetric BMD and geometry, and peripheral QCT (pQCT) provides advantages over QCT with less radiation exposure. However, both QCT and pQCT are less available for use in children compared to DXA. QUS measurements correlate well with aBMD and with bone quality measures [3–5]. Many epidemiologic studies and meta-analyses conducted on adults demonstrate the predictive ability of QUS, particularly calcaneal QUS parameters, for future non-spine fracture even across different QUS devices [6–8]. In children, QUS at the calcaneus predicts the risk of osteopenia or fragility fracture [9, 10]. The advantages of portable, non-expensive, safe, and radiation-free QUS measures are well recognized in adults, but unfortunately its utility is less well-known in children [4, 5, 11].

Based on cross-sectional data, age and sex-specific reference data for QUS measures at the calcaneus and other skeletal sites are available for clinical use to assess bone health in children [12–15]. There are also a few longitudinal studies using QUS conducted among children, but those studies mainly focus on treatment effects in pediatric patients with chronic diseases such as arthritis or growth-related disorders (as reviewed by Baroncelli) [5, 16–18]. As a result, studies examining serial changes in QUS measures among healthy children are relatively scarce [19, 20]. Moreover, available longitudinal studies have not adequately considered inter-individual differences in skeletal maturation during childhood and their influence on serial QUS measures [19, 20]. Consequently, additional information that characterizes changes in bone development while accounting for individual variation in serial QUS measures is much needed. A better characterization of the patterns of change in QUS measures of healthy, maturing children would facilitate the broader use of QUS to assess pediatric skeletal health without the risk of undue radiation exposure.

Using serial data from children participating in the Fels Longitudinal Study (FELS), the purpose of this study is to examine how QUS measures change over time during childhood, while taking into account factors such as obesity, physical activity, and skeletal maturation.

Methods

Study sample

The sample consists of a subset of children who are participants in the Fels Longitudinal Study. Details of the Fels Longitudinal Study have been published previously [21, 22]. Briefly, the Fels Longitudinal Study, which began in 1929, is an ongoing study of human growth, development, and aging. Almost all of the participants are Caucasian (~98%) and were recruited without regard to health status.

Between 1999 and 2006, 227 children were seen for Fels Longitudinal Study visits. Of these children, three did not have calcaneal QUS measurements. Study participants with chronic conditions such as diabetes mellitus, arthritis, asthma, or who were taking glucocorticoid-related medications that could possibly influence bone metabolism were excluded ($n=32$) for the present study. This resulted in a sample of 192 children (98 boys and 94 girls). Anthropometric characteristics and calcaneal QUS measurements of the excluded participants were not significantly different from the included except that physical activity

levels were slightly higher in the excluded participants ($p<0.05$). Each included participant had from one to seven measurements between the ages of 7.6 and 18 years; 64 children (24 boys and 40 girls) had one examination, 25 children (14 boys and 11 girls) had two examinations, 34 children (19 boys and 15 girls) had three examinations, 35 children (24 boys and 11 girls) had four examinations, 16 children (eight boys and eight girls) had five examinations, 14 children (six boys and eight girls) had six examinations, and four children (three boys and one girl) had seven examinations. There were a total of 548 examinations with a median of three visits per participant.

Signed informed consent was obtained from participants' parents/guardians, and assent was obtained from each participant. All protocols and procedures were approved by the Wright State University Institutional Review Board.

Calcaneal quantitative ultrasound measurements

Calcaneal QUS measures were collected twice on each participant's self-reported dominant heel using the gel-based Sahara[®] bone sonometer (Hologic, Inc., Waltham, MA, USA). Average values of each QUS parameter (BUA (decibels per megahertz) and SOS (meters per second)) were used for analysis. The literature suggests that BUA and SOS may exhibit distinct structural properties of bone. BUA is more related to structural parameters such as connectivity and porosity of the skeleton as well as bone density, while SOS is more influenced by bone mineral mass and elasticity [23, 24]. Approximately 92% of participants reported their right leg as dominant throughout the study period. Quality control was performed daily by the direct apposition of the phantom into the transducers of bone sonometer. The coefficients of variation for BUA and SOS were 5.30% and 0.35%, respectively.

Other measurements

Skeletal maturity assessment of the hand-wrist (FELS method) was used to determine skeletal maturity at each visit [25]. The FELS method is used to calculate an individual's skeletal age based on an X-ray of the left hand and wrist taken at each visit. The FELS method, developed using approximately 14,000 serial radiographs, is a bone-specific approach that recognizes individual variation in the order of chondrification and ossification of diaphyses and centers of ossification in epiphyses, the order of epiphyseodiaphyseal fusion, and the size and shape of bones [25]. Skeletal age is a good physiological indicator of accelerated or delayed skeletal development compared to one's chronological age and sex [25]. Body weight and height were measured according to standard anthropometric methods [26]. Body weight (kilograms) was recorded to 0.1 kg without shoes or any heavy clothing, and height (centimeters) was measured to 0.1 cm without shoes. Body mass index (BMI; kilograms per square meter) was calculated from weight and height. BMI percentile values (BMI%) were calculated based on 2000 Centers for Disease Control and Prevention (CDC) Growth Charts in US children [27] for the illustration of examples. Self-assessed habitual physical activity levels for sport were collected using the Baecke Questionnaire of Habitual Physical Activity [28] modified for children [29]. This modified questionnaire has been validated and was determined to be a moderately reliable instrument for physical activity in children between 7 and 19 years old [29]. The sport activity score was calculated based on

three questions including two open questions asking about the intensity of activity (metabolic equivalents) and frequency of involvement in sports in school and outside school. These questions are: (1) Since your last visit, what sports did you play in school? (2) Since your last visit, what sports or physically active games did you play outside of school? (3) When you play sports or games, do you sweat?

Statistical analysis

Using Student's *t* test, differences in descriptive characteristics including QUS measures between boys and girls were tested within each age stratum. The pattern of change in response with chronological age or skeletal age was investigated, by sex, using the linear mixed model.

In general, a linear mixed model has the form:

$$y_{ij} = \sum \beta_k x_{ijk} + \sum b_{ri} z_{ijr} + e_{ij}$$

where *i*, *j*, *k*, and *r* index the participants, observation times, fixed effects, and random effects, respectively; *y_{ij}* are the QUS outcome measures (BUA or SOS); *x_{ijk}* are potentially time-varying covariates with corresponding parameters *β_k*; *z_{ijr}* are potentially time-varying random effects with corresponding participant-specific parameters *b_{ri}* which are independent between participants and normally distributed with mean 0 and variance matrix *G* within participants; and *e_{ij}* are normally distributed within participant with mean 0 and variance matrix *σ²R_i*.

The following three-step method [30, 31] was used for fitting a linear mixed model for each QUS outcome, by sex. First, a maximal fixed effects model was specified. This model included all plausible predictor time-varying variables, namely a cubic polynomial in chronological age or skeletal age (each centered at 8 years), quadratic polynomials in BMI (centered at the sex-specific 50th percentile at chronological age 8 years) and physical activity level (centered at the sex-specific median value), and interactions between the timing variable (age or skeletal age) and each of BMI and physical activity. BUA was log-transformed in order to achieve normality of the residuals and multiplied by 100 to improve the numerical stability of the estimates. Due to the high correlation between timing variables (chronological age or skeletal age) and height (*r*>0.80), height was not considered in the models. Second, given the maximal mean model, the best covariance structure was determined based on the Akaike information criterion (AIC) [32]. Each candidate covariance structure was defined by a specification for the random effects and for the residual error. We considered random polynomial terms, as well as three residual variance structures (independence, autocorrelation, and autocorrelation with measurement error). Finally, given the covariance structure with the smallest AIC, a comparison was made between cubic, quadratic, and linear trends for each sex, with non-significant covariates (BMI, physical activity, and their interactions with age or skeletal age) dropped from the model.

In all models, parameters were allowed to vary by sex. All longitudinal analyses were performed using PROC MIXED implemented in SAS version 9.2 (SAS Inc., Cary, NC, USA). The level of statistical significance was set at $\alpha=0.05$.

Results

Participant characteristics

There were no significant sex differences in chronological age, skeletal age, and anthropometric measurements at the time of first visit. Furthermore, there were no significant sex differences in QUS measures at the first visit.

Anthropometric data, skeletal age, sport activity, and QUS data for the study participants by chronological age groups and sex are shown in Tables 1 and 2. There were no significant differences between the sexes in skeletal age within any age group. Boys had significantly greater height than girls after age 14 years and significantly greater weight after age 16 years. However, mean BMI values were not significantly different between boys and girls at any age. Up to age 10 years, mean sport activity levels were significantly higher for boys than for girls, but these levels were not significantly different at older ages. BUA and SOS measures did not differ by sex within any age group (Table 2).

Estimation of QUS measures across chronological age

Table 3 summarizes the fixed effects regression coefficients and standard error (SE) from the final models for BUA and SOS using chronological age as a timing variable. There were significant differences ($p<0.001$) between sexes in the pattern of change in BUA over time. In particular, boys display a cubic growth curve, while girls have a linear growth curve. The patterns of longitudinal change in SOS differ from those in BUA. We found significant linear trend for SOS among boys and cubic trend for SOS among girls. There were also significant sex differences ($p<0.05$) in the pattern of change in SOS over time. It appears that the sex-specific pattern of change in QUS measures over time differs between boys and girls when chronological age is used as the timing variable.

BMI was negatively associated with SOS in both boys and girls while BMI was positively associated with BUA in boys (but with a smaller effect compared to SOS). In addition, physical activity was positively related to calcaneal QUS measures only in girls. There was also no evidence for a significant interaction effect between adiposity status or physical activity and the age variables on QUS measures.

Estimation of QUS measures across skeletal age

Table 4 shows the fixed effects regression coefficients from the final models for both QUS parameters using skeletal age as a timing variable. The fixed effect estimates from the final mixed effect models were used to describe the estimated individual fitted growth pattern and covariate effects (i.e., BMI and physical activity) in Figs. 1 and 2. Similar to the previous analysis based on chronological age, there were significant sex differences in the pattern of change in BUA and SOS (all p values <0.01). However, the mixed effect models based on skeletal age as a timing variable resulted in more consistent sex-specific patterns of change

in BUA and SOS measures. In particular, boys have a cubic growth pattern for both BUA and SOS and girls exhibit linear growth in both. This suggests that boys exhibit a more rapid increase in both BUA and SOS during early and late skeletal development, while girls maintain a relatively constant rate of increase in BUA and SOS throughout their skeletal development. Covariates (i.e., BMI and physical activity) were significantly related to BUA and SOS in a manner similar to the results based on chronological age. The effect of BMI was illustrated in Figs. 1 and 2 using examples (solid and dotted black lines). Higher BMI was negatively associated with both BUA and SOS for both boys and girls. The relationship between BMI and BUA for boys appears to change with age in Fig. 1, but that is because the lines represent constant BMI percentile, which corresponds to increasing BMI with age. For the other cases (BUA for girls and SOS for both sexes), a child with age-specific 50th BMI percentile (solid line) would have higher BUA or SOS than an overweight child with age-specific 85th BMI percentile (dotted line) over time (see Figs. 1 and 2). Among girls, sport activity is positively related to QUS measures regardless of the timing variable used. For example, girls with higher BMI (85th percentile, dotted line) and lower physical activity scores (15th percentile, or 2.00 on a scale of 1–5) have lower mean SOS than girls with lower BMI (50th percentile) and higher physical activity score (50th percentile, or 2.67; see Fig. 2b).

Covariance structures

For both BUA and SOS, the best covariance structures included random intercept and slope terms for individual variation regardless of timing variables used. This indicates that participants vary significantly in their mean and rate of change (velocity), but not in their curvature (acceleration) in BUA and SOS. For BUA, variation among individuals' curves remains fairly constant with increasing skeletal age (see Fig. 1). For SOS, the random intercepts and slopes were positively correlated with each other, indicating that individuals with low SOS tend to have a slower rate of increase and those with higher SOS tend to have a faster rate of increase (see Fig. 2). Thus, differences between individuals tend to become greater later in childhood.

Discussion

The main purpose of this paper was to describe the pattern of within-individual change in QUS measures assessed serially in children over the course of growth and maturation. The results of this study indicate that, in general, calcaneal QUS measures increase over time and there are significant sex differences in the pattern of age-related change in BUA and SOS. Also, our results suggest that the age-related changes become more apparent and consistent when skeletal maturation is also considered. We note that changes in BMI are significantly associated with BUA in boys and SOS in both boys and girls over the course of childhood. Additionally, our finding suggests that habitual physical activity is positively related to QUS measures in girls. Our study is unique in that few longitudinal studies have examined changes in QUS parameters over childhood using more than two examinations per participant. Furthermore, to our knowledge, our study is the first study to demonstrate a longitudinal negative relationship between childhood BMI and calcaneal QUS parameters.

During childhood growth and development, bone grows in size and in length through bone modeling and remodeling in order to adapt to rapid increases in physiological loads due to changes in body composition [2]. Various assessment techniques including DXA and QCT are available to assess bone mineral accrual in children. While DXA is the gold standard method for measurement of areal BMD, it has limited utility due to the fact that bone size is increasing in growing children. On the other hand, QCT or pQCT assess volumetric or “true” trabecular or cortical BMD and structural parameters in growing children with fewer problems. However, QCT or pQCT are less readily available and more costly in tracking childhood bone health in general. Even though there are limitations associated with QUS technology, such as diverse incompatible QUS devices, QUS measurements are especially interesting to pediatricians and researchers due to a few advantages in the evaluation of pediatric skeletal status or bone health in clinical practice or at the population level, namely no radiation, ease of use, and portability [5]. Calcaneal QUS assessment is the most studied modality among the various QUS techniques (transverse or axial transmission) utilized at different skeletal sites. Compared to phalangeal QUS or tibial QUS measurements, calcaneal QUS values are more consistently related to bone density and overall fracture incidence in adults [6, 8] and in children [9, 10, 33]. This may be due to the fact that the calcaneus as a weight-bearing bone consists of more than 90% trabecular bone with relatively small cortical thickness [4]. Therefore, calcaneal QUS measures seem to be less dependent on increased cortical thickness due to increases in bone size or due to augmented mechanical forces (mainly pressure) during growth [5].

Bone mass measured by aBMD changes during growth and maturation [34–39]. While there are no age effects reported in cross-sectional QUS studies of children [12, 40, 41], longitudinal studies have demonstrated that QUS measures track during growth and puberty [19, 20, 42]. Wang et al. found that changes in calcaneal BUA were significantly correlated with age-related changes in aBMD or volumetric BMD in 258 pubertal girls, while no significant relationship was observed between tibial shaft SOS and DXA [33]. It is also interesting to note that QUS measures are still increasing in late adolescence in both boys and girls. The age or range of age where bone mineral accumulation reaches its maximum (i.e., peak bone mass) differs by skeletal sites and often varies by how bone is measured. While peak bone mass at the femoral neck is reported to be achieved by late adolescence, some studies reported that peak bone mass in other skeletal sites is not likely to be achieved until the late twenties [1]. Therefore, the lack of a late-adolescent plateau of the BUA and SOS measures in our study may not be surprising. Also, it is not easily comparable to other studies since very few longitudinal studies are available to report the peak or maximum values of QUS measures in children and young adults [20, 33]. It is likely that our results, in accordance with pediatric reference data reported by Baroncelli [5], suggest that the maximum measures of calcaneal QUS measures, like peak bone mass, will be achieved after late adolescence. However, further longitudinal studies based on larger sample sizes or different ethnic/racial populations will help our understanding of “peak QUS measures” over the course of growth and development.

We found significant sex differences in the pattern of change in QUS measures, showing that, for instance, boys demonstrate increased growth in BUA and SOS concurrent with early and late adolescence, while girls experience more constant growth throughout skeletal

development. Others have reported inconsistent results concerning sex differences in QUS measures [15, 43, 44]. However, our results seem to be similar to studies by Wunsche et al. [41] and others [19]. In a large cross-sectional study of German children, Wunsche et al. reported age-related linear increase in calcaneal BUA values in girls while between age 10 and 14 years, there was an apparent plateau or no change in BUA values for boys [41]. Vignolo et al. noted that amplitude-dependent SOS values significantly accelerated in late puberty in boys and increased constantly in peri- and post-pubertal girls. This may due to a different tempo of maturation and longitudinal growth between males and females as previously suggested [41, 45]. While in our study cross-sectional analyses of BUA and SOS showed no significant sex difference within each age group (Table 2), we observed significant sex differences in our longitudinal analysis as previously reported in other longitudinal studies [19, 20, 42]. Collectively, these results highlight the limitations of cross-sectional studies in explaining longitudinal processes.

Accounting for biological maturation is necessary to control for individual differences in the timing or tempo of maturation especially in a longitudinal study of children [46]. Somatic maturation indicators such as peak height velocity have been used previously in longitudinal studies of bone mass using aBMD [45], but not in studies of QUS measures. In our study, we have used skeletal age as a timing indicator to adjust for skeletal maturational differences among individuals, instead of using skeletal maturation or pubertal stage as a covariate (e.g., relative skeletal age) in an analysis using chronological age as a timing variable as other studies have done [15, 19, 42, 44]. Mean skeletal ages across different age groups were not significantly different between boys and girls, although the mean values in girls tend to be higher than those in boys suggesting the faster rate of skeletal maturation in girls (Table 1). It appears that use of skeletal age as a timing variable seems to reduce variance in QUS measures, allowing for time trends to be better identified.

Skeletal development during childhood is influenced by many factors including body composition, lifestyle factors, co-morbidities, and genetics [2, 22, 34, 47]. In this study, we found an important serial association between BMI, used as a surrogate marker for adiposity, and lower QUS measures. BMI has been recommended by experts as a screening measure to identify at-risk children for overweight and obesity in populations. There are, however, several limitations to note when using BMI as a surrogate for adiposity [48, 49]. For instance, BMI is not a direct measure of total body fat and changes in BMI during adolescence do not necessarily correspond with changes in fat mass. However, in overweight and obese adolescents, changes in BMI-for-age seem to reflect more of the relative increase in fat mass rather than in fat-free mass, particularly in girls [50]. High childhood BMI tracks well into adulthood, and high levels of BMI correlate well with high adiposity and concurrent health risk (e.g., cardiovascular risk) in general [51, 52]. The mean SOS for overweight children, based on CDC BMI percentile, seems to be lower than the mean SOS for normal weight children, even after adjusting for concurrent physical activity levels (Fig. 2). Our finding is similar to a recent report by Falk et al.[53] who reported that only tibial SOS, not radial SOS, was significantly reduced in overweight boys compared with normal weight boys aged between 9 and 12 years old. Inconsistent research results exist on the effect of obesity or body mass on bone during growth. Some studies show increased bone mass in obese children [54, 55], while others report no difference or decreased bone

mass (e.g., decreased total body bone mineral apparent density) after adjusting for body size or weight [44, 56, 57]. Similarly, not all studies have reported beneficial effects of obesity on bone changes measured using QUS [53, 57–59]. This may be associated with technical differences among different QUS devices and with whether adjustment for body size or heel width for calcaneal measurement was carried out in these studies. Our findings were not significantly changed when we adjusted for heel width or sex-specific stature-forage (i.e., stature z-scores) in our analyses (data not shown). In addition, the effect of body mass appears to be parameter specific [59]. Obese children tend to show advanced growth and maturation possibly resulting in larger bone size and bone mass, compared with normal weight children [54]. However, obese children are also exposed to adverse lifestyle factors such as reduced physical activity possibly resulting in decreased or insufficient muscular strength to sustain their body weight against fracture [60, 61]. Given the increase in the prevalence of childhood obesity, our results demonstrating negative longitudinal associations between BMI and calcaneal QUS measures, particularly SOS, in both boys and girls warrant further investigation.

In the current study, patterns of change in QUS measures were dependent on physical activity level in girls but not in boys. Our finding of higher BUA and SOS accrual in girls reporting higher levels of physical activity longitudinally is encouraging. However, it is not clear why there is sex-specific benefit of sport activity (measured using questionnaire) on calcaneal QUS measures in our study. While there is a non-linear trend (higher activity in middle childhood and lower activity in early and late childhood) in reported activity level over time, the reported activity levels in boys were not significantly different from those in girls in our study ($p>0.05$). Experimental studies in mice have shown that external weight-bearing forces stimulate bone formation and bone remodeling and change the distribution of bone mass to accommodate the mechanical forces during the period of bone acquisition [62]. The literature suggests beneficial effects of physical activity or exercise on bone mass accrual in children [34, 63]. However, it is also suggested that the influence of physical activity on bone mass accrual may be age dependent, skeletal site specific, and sex specific [38, 64–66]. For example, Weeks et al. found that physical activity measures from accelerometry have shown positive association with hip, spine, and total body BMC in pre-pubertal boys, but only with total body BMC in pre-pubertal girls [38]. The beneficial impact of physical activity or exercise on QUS measures seems to be less consistent [44, 58, 64]. Other studies have also reported that daily physical activity had no significant influence on phalangeal or calcaneal QUS [44, 58]. Exercise intervention studies have reported that jumping exercises result in a significant difference in bone mass and QUS measures during childhood between intervention and control groups, particularly in boys [64].

Previously published serial studies of QUS measures over childhood have been limited by a relative shortness in follow-up duration. Furthermore, changes in measuring devices (QUS) during previous longitudinal studies have further limited their usefulness in examining longitudinal changes. Throughout our study period, we have used a single QUS device to measure BUA and SOS. A few limitations should be noted in our study. Among other lifestyle factors, dietary intake in children was not measured during the study period. However, dietary intake of calcium and vitamin D has not been correlated with QUS

measures in several studies [18, 44, 58, 67]. Physical activity levels were collected using a questionnaire on habitual activity rather than using a direct assessment of activity (e.g., accelerometer). However, Treuth et al. demonstrated that the sport activity index used as the measure of habitual physical activity in our study was correlated with physical activity measured by accelerometer [29]. Given the inconsistent influence of daily or habitual physical activity on QUS measures (as suggested in the literature), we can conclude that there is a minimal effect of physical activity on QUS measures of the calcaneus particularly in boys. Finally, our study results are valid for non-Hispanic white children and may not necessarily be generalizable to other ethnic/racial populations.

Monitoring changes in bone health during childhood is of great interest in children with clinical needs, as well as in healthy children. Any deviation in the pattern of change, or any disorder during childhood that influences bone accrual, may play an important role in determining risk for osteoporosis and fracture in later life. Like other measurement modalities (e.g., DXA), QUS measurements in children suffer from a number of technical problems including different QUS devices and limited current understanding of the bone tissue properties assessed [5, 68]. Given that QUS assessment is portable, radiation free, easily administered, and of low cost, it is feasible to use QUS, especially calcaneal QUS measures, to screen for reduced bone mass, and to monitor bone changes in pediatric offices in healthy children or children with clinical needs. As reviewed by Guglielmi et al. [69], the current literature suggests that QUS measures can be used to differentiate children with fractures and non-fractures and to identify children with lower bone mass based on existing limited studies. Our study shows that calcaneal QUS measurements allow safe and probably accurate assessment of skeletal health during growth and development. Moreover, our findings suggest that calcaneal QUS measures are amenable to examination of sex-specific longitudinal changes in skeletal growth and are potentially relevant in a clinical setting. In summary, we found that calcaneal BUA and SOS follow a non-linear growth trajectory in boys and a linear growth pattern in girls during childhood. Our results also indicate that obesity may be negatively associated with QUS (specifically SOS) measures in boys and girls.

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Fig. 1.

Growth patterns of BUA. Data for BUA for boys and girls are plotted against skeletal age as the timing variable. The *gray lines* represent predicted longitudinal changes for each participant derived from mixed models. The *solid and dotted black lines* represent patterns of change in BUA based on two examples. **a** Boys. The *solid black line* is the fitted mean line for a boy who has BMI at the 50th percentile according to CDC 2000 growth charts over time. The *dotted line* is for a boy who has BMI at the 85th percentile over time. **b** Girls. The *solid black line* is the fitted mean line for a girl who reports her activity level at the girl-specific median value (2.67). The *dotted line* is for a girl who reports her sport activity level at the 15th centile value (2.00).

Fig. 2.

Growth patterns of SOS. Data for SOS for boys and girls are plotted against skeletal age as the timing variable. The *gray lines* represent predicted longitudinal changes for each participant derived from mixed models. The *solid and dotted black lines* represent patterns of change in SOS based on two examples. **a Boys.** The *solid black line* is the fitted mean line for a boy who has BMI at the 50th percentile according to CDC 2000 growth charts over time. The *dotted line* is for a boy who has BMI at the 85th percentile over time. **b Girls.** The *solid black line* is the fitted mean line for a girl who has BMI at the 50th percentile and reports her activity level at the girl-specific median value (2.67). The *dotted line* is for a girl who has BMI at the 85th percentile and reports her activity level at the 15th centile value (2.00)

Table 1

Description of study participants ($n=192$) by age group and sex

Groups	N_{obs}^a (548)	Skeletal age (year)	Weight (kg)	Stature (m)	BMI (kg/m ²)	Sport activity
Boys						
<9 years	29	8.41 (1.02)	29.63 (7.91)	1.32 (0.07)	16.82 (3.03)	3.04 (0.66)*
9 age<10	24	10.11 (1.43)	35.61 (11.79)	1.39 (0.07)	18.13 (4.61)	2.94 (0.58)*
10 age<11	26	10.86 (1.63)	39.78 (13.92)	1.43 (0.07)	19.14 (5.35)	2.96 (0.76)
11 age<12	38	11.91 (1.45)	42.18 (12.02)	1.49 (0.07)	18.85 (4.02)	2.79 (0.76)
12 age<13	33	12.94 (1.41)	49.84 (14.09)	1.55 (0.09)	20.39 (4.28)	2.90 (0.84)
13 age<14	30	14.19 (1.11)	58.61 (17.46)	1.64 (0.07)	21.63 (5.63)	3.08 (0.79)
14 age<15	38	14.84 (1.05)	65.93 (17.02)	1.71 (0.07)*	22.44 (5.33)	2.95 (0.75)
15 age<16	27	16.03 (1.27)	66.76 (12.46)	1.76 (0.05)*	21.50 (3.80)	2.93 (0.76)
16 age<17	25	17.06 (0.96)	73.76 (17.18)*	1.78 (0.06)*	23.37 (5.44)	2.84 (0.45)
17 years	32	17.72 (0.38)	73.70 (16.11)*	1.81 (0.06)*	22.59 (4.74)	2.74 (0.53)
Girls						
<9 years	26	8.70 (1.39)	29.94 (7.51)	1.31 (0.06)	17.23 (2.88)	2.41 (0.46)*
9 age<10	22	9.63 (1.19)	32.98 (9.08)	1.38 (0.08)	17.06 (3.00)	2.56 (0.50)*
10 age<11	23	11.04 (1.05)	38.84 (10.15)	1.45 (0.06)	18.24 (3.84)	2.84 (0.61)
11 age<12	17	12.09 (0.92)	46.96 (12.89)	1.51 (0.08)	20.32 (4.23)	2.71 (0.57)
12 age<13	22	13.00 (0.83)	52.33 (15.19)	1.56 (0.07)	21.19 (5.07)	2.76 (0.54)
13 age<14	29	13.80 (1.10)	51.86 (11.31)	1.60 (0.06)	20.16 (3.96)	3.00 (0.71)
14 age<15	28	15.38 (1.34)	59.92 (12.94)	1.65 (0.06)*	22.07 (4.10)	2.85 (0.73)
15 age<16	25	16.41 (1.26)	61.64 (10.04)	1.65 (0.06)*	22.80 (3.57)	2.89 (0.83)
16 age<17	22	17.34 (0.98)	63.20 (11.63)*	1.65 (0.07)*	23.31 (4.48)	2.70 (0.85)
17 years	32	17.83 (0.47)	65.37 (15.94)*	1.65 (0.06)*	24.36 (6.69)	2.68 (0.68)

* $p < 0.05$ (significant sex difference within age group)^aNumber of observations within age group. The total number of observation from the 192 study participants was 548

Table 2QUS measures of study participants ($n=192$) by age group and sex

Groups	BUA (dB/MHz)		SOS (m/s)	
	Boys	Girls	Boys	Girls
<9 years	60.31 (14.16)	56.22 (11.05)	1,565.82 (20.84)	1,561.72 (16.00)
9 age<10	61.67 (9.56)	58.40 (10.97)	1,567.89 (24.28)	1,564.00 (22.09)
10 age<11	69.96 (16.74)	62.67 (16.46)	1,571.91 (25.18)	1,562.52 (25.08)
11 age<12	67.73 (15.65)	63.39 (13.90)	1,569.48 (26.34)	1,568.61 (26.53)
12 age<13	69.04 (22.53)	70.28 (17.78)	1,567.50 (32.39)	1,573.41 (29.00)
13 age<14	73.83 (20.70)	70.51 (14.67)	1,573.94 (35.45)	1,572.96 (28.69)
14 age<15	69.47 (18.65)	75.29 (13.76)	1,565.38 (30.23)	1,575.74 (25.36)
15 age<16	75.48 (14.68)	78.20 (13.88)	1,580.82 (25.74)	1,576.65 (30.45)
16 age<17	76.31 (18.40)	77.82 (17.19)	1,570.96 (31.71)	1,575.82 (32.03)
17 years	79.91 (18.88)	88.69 (26.69)	1,577.23 (35.27)	1,592.85 (43.89)

The total number of observation in QUS data from the 192 study participants was 548. The numbers of observations within each age and sex group are listed in Table 1

Table 3

Estimated fixed effects regression coefficients (SE) for prediction of BUA and SOS by chronological age

Variable	Males		Females	
	Estimate (SE)	<i>p</i> value	Estimate (SE)	<i>p</i> value
BUA				
Intercept	399.68 (4.25)	<0.0001	400.70 (3.07)	<0.0001
Age ^a	10.37 (3.01)	<0.001	4.37 (0.54)	<0.0001
Age ²	-2.02 (0.70)	0.005	–	NS
Age ³	0.14 (0.05)	0.003	–	NS
BMI ^a	-0.64 (0.78)	0.414	–	NS
BMI ²	0.09 (0.04)	0.032	–	NS
Sport activity ^a	–	NS	4.17 (1.69)	0.015
SOS				
Intercept	1,567.92 (3.27)	<0.0001	1,566.72 (4.22)	<0.0001
Age ^a	2.38 (0.71)	0.001	-1.83 (3.11)	0.557
Age ²	–	NS	1.42 (0.72)	0.049
Age ³	–	NS	-0.10 (0.05)	0.040
BMI ^a	-4.57 (0.89)	<0.0001	-2.93 (0.81)	<0.001
BMI ²	0.22 (0.05)	<0.0001	0.12 (0.04)	0.002
Sport activity ^a	–	NS	3.89 (1.86)	0.038

BUA was log-transformed and multiplied by 100

NS not significant

^a Age was centered at 8 years. BMI was centered at its sex-specific median at age 8 years, and sport activity was centered at its sex-specific median. BMI and sport activity are both time-varying variables

Table 4

Estimated fixed effects regression coefficients (SE) for prediction of BUA and SOS by skeletal age

Variable	Males		Females	
	Estimate (SE)	<i>p</i> value	Estimate (SE)	<i>p</i> value
BUA				
Intercept	398.04 (4.31)	<0.0001	399.91 (3.34)	<0.0001
Skeletal age ^a	14.54 (2.52)	<0.0001	4.07 (0.53)	<0.0001
Skeletal age ²	-3.01 (0.56)	<0.0001	–	NS
Skeletal age ³	0.20 (0.04)	<0.0001	–	NS
BMI ^a	-0.94 (0.82)	0.255	–	NS
BMI ²	0.09 (0.04)	0.033	–	NS
Sport activity ^a	–	NS	4.28 (1.84)	0.021
SOS				
Intercept	1,564.99 (4.35)	<0.0001	1,563.14 (3.29)	<0.0001
Skeletal age ^a	9.94 (2.98)	0.001	3.24 (0.77)	<0.0001
Skeletal age ²	-2.11 (0.68)	0.002	–	
Skeletal age ³	0.14 (0.04)	0.001	–	
BMI ^a	-4.47 (0.96)	<0.0001	-2.96 (0.90)	0.001
BMI ²	0.20 (0.05)	<0.001	0.12 (0.04)	0.004
Sport activity ^a	–	NS	4.07 (2.06)	0.049

BUA was log-transformed and multiplied by 100

NS not significant

^a Skeletal age was centered at 8 years. BMI was centered at its sex-specific median at age 8 years, and sport activity was centered at its sex-specific median. BMI and sport activity are both time-varying variables