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# Bone Health in Boys with Autism Spectrum Disorder

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## Abstract

**Objectives:** To examine bone mass in children and adolescents with autism spectrum disorder (ASD).

**Study Design:** Risperidone-treated 5 to 17 year-old males underwent anthropometric and bone measurements, using dual-energy x-ray absorptiometry (DXA) and peripheral quantitative computed tomography (pQCT). Multivariable linear regression analysis models examined whether skeletal outcomes differed among participants with (n=30) versus without ASD (n=156).

**Results:** After adjusting for potential covariates, having ASD was associated with significantly lower trabecular bone mineral density and bone strength at the radius, and with marginally lower total body less head bone mineral content ($p<0.09$). No differences at the lumbar spine were observed.

**Conclusions:** ASD are associated with lower bone mass. Future studies should investigate interventions to optimize skeletal health in ASD.

### Keywords

Bone mass; autism; risperidone

## Introduction

Autism spectrum disorders (ASD) are prevalent developmental conditions characterized by deficits in socio-emotional processing and are associated with significant impairment (Association, 2013). Importantly, their persistence into adulthood and the challenges in assisting individuals with ASD lead independent and fulfilling lives have been increasingly recognized. For instance, due to associated features such as restricted range of interest/

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Compliance with Ethical Standards

**Ethical approval:** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent:** Written informed consent was obtained from parents or legal guardians of all individual participants and assent was obtained from the participants.

activities, dietary peculiarities, and social skills deficit, concerns about lifestyle practices of individuals with ASD and their health impact have arisen (Cashin, Buckley, Trollor, & Lennox, 2016; Hategan, Bourgeois, & Goldberg, 2016). This may be compounded by the fact that many patients require treatment with psychotropics, which themselves can adversely affect health (Aman et al., 2005; Calarge et al., 2013; Calarge, Xie, Fiedorowicz, Burns, & Haynes, 2012).

One particular area of interest is skeletal health. Children and adolescents with ASD may fail to accrue bone mass as expected, for any number of reasons. First, they often have sensory sensitivities and aversion to certain flavors or textures, restricting their intake of nutritious foods. Second, they may be placed on restrictive diets (e.g., gluten-free casein-free diets) due to perceived therapeutic benefits (Hediger et al., 2008). Third, they may receive medications, including psychotropics, that interfere with bone metabolism. In addition, they may not engage in adequate physical activity, due to social isolation or lack of interest. Such failure to optimize peak bone mass could place children and adolescents with ASD at an increased risk for fracture, given that bone mass accrued by early adulthood is a major determinant of bone mass later in life (“Osteoporosis prevention, diagnosis, and therapy,” 2001).

Several, albeit not all, studies conducted in patients with ASD have found low bone mass and increased fracture risk (Hediger et al., 2008; Mouridsen, Rich, & Isager, 2012; Neumeyer et al., 2017; Neumeyer, Gates, Ferrone, Lee, & Misra, 2013; Neumeyer et al., 2015). However, these studies are limited in number and sample size. Additionally, except for one (Neumeyer et al., 2017), they have not taken advantage of state-of-the-art technology, such as peripheral quantitative computed tomography (pQCT), to isolate trabecular from cortical bone (Pitukcheewanont & P., 2005). Trabecular bone is more metabolically active and, thus, susceptible to fractures (Pitukcheewanont & P., 2005). Moreover, these studies did not include a psychiatrically-ill control group to determine if the differences found are specific to ASD or are better accounted for by the presence of general psychopathology (Hediger et al., 2008; Mouridsen et al., 2012; Neumeyer et al., 2017; Neumeyer et al., 2013; Neumeyer et al., 2015).

Thus, we compiled data from four independent studies to examine skeletal health in children and adolescents with ASD in comparison to patients with other psychiatric disorders (Calarge, Schlechte, Burns, & Zemel, 2015). Bone mass was evaluated using dual-energy x-ray absorptiometry (DXA) as well as pQCT. We hypothesized that trabecular bone mass will be lower in patients with ASD.

## Methods

### Participants:

Data from four studies were combined in this analysis to maximize sample size (Table 1). Three studies included children and adolescents who had been taking risperidone for at least six or twelve months. The fourth consisted of a longitudinal observational study that included, among others, six children who had initiated treatment with risperidone within the prior month (Bahr et al., 2015). In all four studies, chronic medical or neurological

conditions, concurrent treatment with more than one antipsychotic medication, and the use of medications that affect bone metabolism led to exclusion. Importantly, no participant was on gluten-free casein-free diet.

All the studies were approved by the local Institutional Review Board. After study description, written consent from parents or legal guardians and assent was obtained from the participants.

## Procedures:

At study entry, height and weight were measured following standard procedures (Calarge et al., 2012). The medical and pharmacy records were reviewed to document all psychotropic treatments, including the start and stop date of each drug as well as its dosage (Calarge, Nicol, Schlechte, & Burns, 2014).

A best-estimate diagnosis, following the Diagnostic and Statistical Manual of Mental Disorders [DSM-IV-TR, (Association, 2000)], was generated based on a review of the psychiatric record, supplemented by a standardized interview of the parent using the Diagnostic Interview Schedule for Children (except in Study 2) (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000), the Child Behavior Checklist (Achenbach & Rescorla, 2001), and a clinical interview conducted by a child psychiatrist (CAC).

Daily calcium and vitamin D intake during the week prior to enrollment was estimated using the 2004 Block Kids Food Frequency Questionnaire (Block et al., 2000), and physical activity was assessed (except in Study 2) by asking the parent to compare the child's usual level of physical activity to their peers', using a 5-point Likert scale (Slemenda, Miller, Hui, Reister, & Johnston, 1991).

Following the same protocol described previously (Calarge et al., 2015), a pQCT scan was obtained at the 4% site of the nondominant radius (rich in trabecular bone) to estimate volumetric bone mineral density (vBMD). A Stratec XCT-2000 scanner, software version 6.0 (Stratec, Inc., Pforzheim, Germany), was used. Trabecular vBMD was measured as the mean density of the 85% central area of the bone's cross-section (Calarge et al., 2015). Bone strength index (BSI) was computed as follows BSI ($mg^2/mm^4$) = Total Area $mm^2$ * (Total Density $mg/cm^3)^2$, where Total Area is the total cross sectional area at the ultra-distal radius and Total Density is the total vBMD at the ultra-distal radius. BSI incorporates both material and geometric properties of the skeletal site, as captured by pQCT. We conducted a test-retest study and an inter-rater reliability study of pQCT measurements at the ultra-distal radius site (4%) comparing two technicians. Each reliability study consisted of 5 children or adolescents tested twice, within a few minutes, with forearm repositioning. For the test-retest study, the precision error was calculated as root-mean-square coefficient of variation of duplicate measurements (Baim et al., 2008; Bonnick et al., 2001). Reproducibility (i.e., % coefficient of variation) was 1.81% for trabecular vBMD and 3.76% for total cross-sectional area. Inter-rater reliability was calculated using intraclass correlation coefficient (ICC) (Walter, Eliasziw, & Donner, 1998). The ICC for trabecular vBMD and total cross-sectional area were >0.994 (95% CI ranging between 0.880–0.999). pQCT scans were rated as having no movement, mild movement (i.e., having minor streaks but no break in the cortical rim or

soft tissue), moderate movement (i.e., having breaks in the cortical rim but without displacement), or severe movement (i.e., having significant displacement of the cortical rim). Scans compromised by moderate to severe movement were rejected. In addition, a Hologic QDR DELPHI-4500A DXA unit (Hologic, Inc., Bedford, MA; Studies 1 and 2) or a Hologic Discovery A unit (Studies 3 and 4) was used to estimate bone mineral content (BMC) and areal bone mineral density (aBMD) in the lumbar spine vertebrae L1 through L4 (LS) or of the total body less head (TBLH). The two DXA units were cross-calibrated and quality-control and calibration of the equipment were performed daily (Calarge et al., 2015). A precision study was conducted by two technicians, with each scanning 15 different participants, three times. The average of the least significant change (LSC), at 95% confidence level, were: LSC of the lumbar spine: 0.0295 g/cm$^2$, LSC of the total hip: 0.0235 g/cm$^2$, LSC of the femoral neck: 0.033 g/cm$^2$. While each of the four studies acquired at least one bone scan, the scan type and skeletal site varied (Table 1).

### Data Analysis:

Body mass index (BMI) was computed as weight/height$^2$ (kg/m$^2$) and age-sex-specific height and BMI Z-scores were generated based on the 2000 Centers for Disease Control and Prevention normative data (Ogden et al., 2002).(Ogden et al., 2002) Age-sex-height-race-specific Z-scores for LS and TBLH BMC and aBMD were generated following the Bone Mineral Density in Childhood Study (Zemel et al., 2011).

Because only one participant with ASD and having a bone scan was a girl and given that BMD is under a strong sex effect, we restricted the analyses to boys.

Differences among the participants with ASD and those without were compared using the Wilcoxon rank-sum test for continuous variables and chi square or Fisher's Exact test for categorical ones. Multivariable linear regression analysis examined the association between the two clinical groups and skeletal outcomes, adjusting for relevant covariates. All hypothesis tests were two-tailed with a significance level of $p < 0.05$ and analyses utilized procedures from SAS version 9.3 for Windows (SAS Institute Inc., Cary, NC).

## Results

### Participants

One hundred eighty six boys contributed to this analysis. Their demographic and clinical data are presented in Tables 2 and 3, for the entire sample and divided by ASD diagnosis. Several differences emerged, including participants with ASD being more sexually mature, less physically active, more likely to be taking multivitamins, which probably accounts for their larger daily intake of vitamin D, and more likely to have taken SSRIs.

### ASD and pQCT-Based Bone Measures

After adjusting for age ($p<0.006$), height and BMI Z-scores ($p>0.50$ and $p=0.0002$, respectively), and SSRI use ($\beta= -11.4$, SE=6.0, $p<0.07$), having a diagnosis of ASD was associated with a significantly lower trabecular vBMD at the ultradistal radius ($\beta= -23.9$, SE=8.2, $p=0.004$, Cohen's d=0.68). Adjusting additionally for physical activity ($p<0.05$),

dietary calcium and vitamin D intake (both p>0.50), and duration of risperidone treatment (p>0.50) reduced slightly the sample size but did not alter the results substantially (SSRIs effect: β= −13.5, SE=6.2, p<0.04 and ASD effect: β= −21.6, SE=8.7, p<0.02, Cohen's d=0.64). Substituting Tanner stage for age yielded comparable findings (ASD effect: β= −23.2, SE=8.0, p<0.005, Cohen's d=0.67). Given that the prevalence of disruptive behavior disorders and anxiety disorders were lower in patients with ASD, we repeated the analyses adjusting for these disorders. The findings did not change substantially and neither disorder was significantly associated with trabecular vBMD (both p values >0.70).

Similarly, after adjusting for age (p<0.0001), height and BMI Z-scores (p>0.70 and p=0.0002, respectively), and SSRI use (p>0.10), having ASD was associated with a lower bone strength index (β= −4.95, SE=1.85, p<0.009, Cohen's d=0.62). Adjusting for physical activity (p=0.0004), dietary calcium and vitamin D intake (both p>0.80), and duration of risperidone treatment (p>0.80) again did not significantly change the findings (β= −4.43, SE=2.03, p<0.04, Cohen's d=0.56). Again, substituting Tanner stage for age yielded comparable findings (β= −4.17, SE=1.93, p<0.04, Cohen's d=0.50) as did adjusting for the presence of disruptive behavior disorders and anxiety disorders, which were not significantly associated with bone strength index (both p values >0.60).

### ASD and DXA-Based Bone Measures

After adjusting for age (p>0.20), height and BMI Z-scores (p>0.10 and p<0.002, respectively), physical activity (p>0.10), dietary calcium and vitamin D intake (p>0.10), duration of risperidone treatment (p>0.70), and SSRI use (β= −0.46, SE=0.23, p<0.06, Cohen's d=0.75), an ASD diagnosis was associated with lower TBLH BMC, although this failed to reach statistical significance (β= −0.56, SE=0.32, p=0.09, Cohen's d= 0.92). It was also not significantly associated with TBLH aBMD (β= −0.47, SE=0.35, p>0.10, Cohen's d=0.69).

Similarly, after adjusting for age (p<0.02), height and BMI Z-scores (both p<0.0001), physical activity (p<0.07), dietary calcium intake (p>0.90), dietary vitamin D intake (β=0.0011, SE=0.0006, p<0.07), duration of risperidone treatment (p>0.50), and SSRI use (β= −0.22, SE=0.17, p>0.10, Cohen's d=0.25), having ASD was not associated with LS aBMD (β= −0.30, SE=0.25, p>0.20, Cohen's d=0.34). It was also not associated with LS BMC (β= −0.17, SE=0.23, p>0.40, Cohen's d=0.21).

## Discussion

ASD is associated with a number of behaviors and treatments that could hamper bone mass accrual. Indeed, we found significantly lower trabecular bone mass in participants with ASD, as compared to youth with other psychiatric disorders, suggesting that the findings may be specific to ASD and are not merely accounted for by psychopathology or psychotropics.

Non-traumatic fractures disproportionately involve skeletal sites rich in trabecular bone (e.g., distal radius, hip, vertebrae). Trabecular bone is more metabolically active and, therefore, susceptible to the impact of hormonal, metabolic, and iatrogenic factors

(Pitukcheewanont & P., 2005). As such, bone imaging techniques that allow disentangling trabecular from cortical bone may be particularly useful when examining skeletal health. Unlike DXA which generates a bi-dimensional image of the bone (overlaying cortical and trabecular bone), pQCT separates the two, while using a comparable amount of radiation (Pitukcheewanont & P., 2005; Specker & Schoenau, 2005). As expected, we did find a significantly lower trabecular vBMD at the ultradistal radius in patients with ASD, of moderately large effect size. This translated also into a significantly lower bone strength index. Lower bone mass in the upper extremity is consistent with lower second metacarpal bone cortical thickness as described in younger children with ASD (Hediger et al., 2008). Our results are also consistent with findings from a recent study using high-resolution pQCT, where participants with ASD exhibited lower trabecular thickness, compressive stiffness, and failure load at the ultradistal radius, compared to typically-developing controls (Neumeyer et al., 2017). Additionally, radius trabecular vBMD was numerically lower in participants with ASD, although this difference was not statistically significant, likely due to the small sample size.

DXA is the preferred method for assessing BMC and aBMD for clinical use (Baim et al., 2008). Specifically, Using DXA, the International Society for Clinical Densitometry recommends obtaining a lumbar spine and a whole body DXA scan when assessing skeletal health in children (Baim et al., 2008). Having ASD was associated with a much lower TBLH BMC and aBMD (Cohen's d= 0.92 and 0.69, respectively). This failed to reach statistical significance, however, primarily due to the small sample size given that only two of the smaller studies collected a whole-body DXA scan (Table 1). In contrast, the differences between the two groups at the lumbar spine were small.

The lumbar spine is estimated to contain around 60% trabecular bone while the whole body contains around 20% (Nilas & Christiansen, 1988). At the ultra-distal radius, pQCT estimates virtually 100% of the true vBMD (Pitukcheewanont & P., 2005; Specker & Schoenau, 2005). The fact that trabecular bone mass was much lower at the radius in participants with ASD but not at the lumbar spine may suggest site specific effects in ASD (i.e., weight- vs. non-weight-bearing bone). Of interest, however, this is different from what has been reported by Neumeyer at al., where significant differences in bone mass between ASD and healthy controls were found both at the lumbar spine and the hip (Neumeyer et al., 2013). Importantly, both studies used the Bone Mineral Density in Childhood Study database to generate sex-age-height-race/ethnicity-specific Z-scores. However, while the mean height-adjusted Z-scores at the lumbar spine were less than zero in children with and without ASD in the Neumeyer at al. study, the mean Z-scores in our participants were above zero (Table 4). This suggests differences in the characteristics of the participants enrolled in the two studies.

Importantly, the differences we found in bone mass across participants with and without ASD were significant despite accounting for anthropometric characteristics, physical activity, dietary intake of calcium and vitamin D, and psychotropic use. This suggests that alternative pathways may be involved, although lifestyle factors (e.g., dietary practices and physical activity) cannot be completely ruled out given the limitations of self-report for assessing these variables.

The novel findings from this study should be interpreted in light of certain limitations. First, the study is cross-sectional and restricted to boys treated with risperidone. Future, prospective studies could more decisively draw conclusions about factors that contribute to low bone mass in this population, in the absence of antipsychotic treatment. In addition, the diagnosis of ASD did not include the use of standardized methods, such as the autism diagnostic observation schedule. Moreover, using state-of-the-art methods to track dietary intake and physical activity would capture these variables more accurately. We controlled for vitamin D intake but it would have been more helpful to measure serum vitamin D concentration. Future studies should also include females and a more ethnically and racially diverse participants.

In sum, bone mass is reduced in patients with ASD compared to psychiatric controls. This remains the case after accounting for potential confounders. Thus, future studies should investigate interventions to optimize skeletal health in ASD, particularly in light of evidence showing increased fracture risk in youth and adults with ASD (Neumeyer et al., 2013).

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**Table 1:**

Description of Studies Contributing Data to the Main Analysis.

| Study | Sample Size | | Age Range | Study Description | pQCT | DXA | |
|---|---|---|---|---|---|---|---|
| | No-ASD | ASD | | | 4% Site | LS | TBLH |
| Study 1 | 103 | 18 | 7 to 17 years | Cross-sectional observational study in participants who had received risperidone for at least six months to examine the skeletal effects of risperidone | X | X | --- |
| Study 2 | 4 | 2 | 10 to 18 years | Cross-sectional observational study in participants who had received risperidone for at least one year to examine the skeletal effects of antipsychotics | X | X | --- |
| Study 3 | 45 | 10 | 5 to 17 years | Randomized placebo-controlled trial of calcium and vitamin D supplementation in participants who had received risperidone for at least one year and exhibited hyperprolactinemia (only baseline data used in this analysis) | X | --- | X |
| Study 4 | 4 | 0 | 5 to 16 years | Longitudinal observational study of largely antipsychotic-naïve participants to examine the effect of risperidone on the gut microbiota. Six participants initiated treatment with risperidone within the prior month (only baseline data used in this analysis) | --- | --- | X |

pQCT: Peripheral quantitative computed tomography. DXA: Dual-energy x-ray absorptiometry.

LS: Lumbar spine. TBLH: Total body less head.

**Table 2:**

Demographic and Clinical Characteristics of the Entire Sample and Split Based on ASD Diagnosis (mean±std, unless noted otherwise)

| | Entire Sample n=186 | No-ASD n=156 | ASD n=30 | Statistic | p-value |
|---|---|---|---|---|---|
| Age, yrs | 11.7±2.8 | 11.6±2.9 | 12.5±2.6 | Wilcoxon = 3239.0 | 0.11 |
| Tanner Stage (%) I/II/III/IV/V | 36/19/12/17/17 | 43/13/13/20/11 | 23/27/20/10/20 | Fisher's Exact | **0.04** |
| Race/Ethnicity, n (%) | | | | Fisher's Exact | 0.20 |
| White | 154 (83) | 126 (81) | 28 (93) | | |
| African American | 22 (12) | 21 (14) | 1 (3) | | |
| Hispanic | 6 (3) | 6 (4) | 0 | | |
| Other | 3 (2) | 2 (1) | 1 (3) | | |
| Height Z-score[a] | 0.18±0.97 | 0.14±0.95 | 0.33±1.06 | Wilcoxon = 3007.0 | 0.46 |
| BMI Z-score [a] | 0.55±1.00 | 0.55±1.01 | 0.50±1.02 | Wilcoxon = 2832 | 0.92 |
| Testosterone, ng/dL[b] | 182.9±205.6 | 189.4±209.3 | 152.4±187.6 | Wilcoxon = 2240.0 | **0.91** |
| Physical Activity | 2.4±1.2 | 2.6±1.1 | 1.6±1.2 | Wilcoxon = 1540.5 | **0.0001** |
| Dietary Calcium Intake, mg/day | 1021±373 | 1007±373 | 1097±371 | Wilcoxon = 2610 | 0.25 |
| Dietary Vitamin D Intake, IU/day | 280±151 | 269±247 | 340±255 | Wilcoxon = 2627 | *0.22* |
| Multivitamin Use, n (%) | 35 (19) | 23 (15) | 12 (40) | $\chi^2$= 10.37 | **0.0013** |
| Bone Fractures, n (%)[c] | 40 (23) | 35 (24) | 5 (18) | $\chi^2$= 0.55 | 0.46 |
| Age at Bone Fracture, yrs | 7.2±4.4 | 7.4±4.6 | 5.5±2.9 | Wilcoxon = 56.0 | 0.51 |

ASD: Autism Spectrum Disorder.

[a]Age-sex-specific body mass index (BMI) Z-scores generated based on the 2000 Centers for Disease Control and Prevention normative data.

[b]Total testosterone was measured in 161 participants. It was detectable in 133 No-ASD and 28 ASD participants.

[c]Data missing for 14 participants.

Significant results ($p<0.05$) are bolded and marginally significant results ($p<0.10$) are bolded and italicized.

**Table 3:**

Psychiatric Characteristics of the Entire Sample and Split Based on ASD Diagnosis (mean±std, unless noted otherwise)

| | Entire Sample n=186 | No-ASD n=156 | ASD n=30 | Statistic | p-value |
|---|---|---|---|---|---|
| ADHD, n (%) | 170 (91) | 143 (92) | 27 (90) | $\chi^2$= 0.09 | 0.77 |
| DBD, n (%) | 171 (92) | 147 (94) | 24 (80) | $\chi^2$= 6.87 | **0.0088** |
| Depressive Disorder, n (%) | 9 (5) | 9 (6) | 0 | Fisher's Exact | 0.36 |
| Anxiety Disorder, n (%) | 60 (32) | 56 (36) | 4 (13) | $\chi^2$= 5.86 | **0.016** |
| Tic Disorder, n (%) | 39 (21) | 34 (22) | 5 (17) | $\chi^2$= 0.40 | 0.53 |
| Pharmacotherapy | | | | | |
| MPH Use, n (%) | 133 (72) | 116 (74) | 17 (57) | $\chi^2$= 0.90 | **0.049** |
| MPH Tx Duration, yrs¶ | 4.1±2.8 | 5.9±0.2 | 4.8±0.5 | Wilcoxon = 2685 | **0.66** |
| SSRI, n (%) | 88 (47) | 64 (41) | 24 (80) | $\chi^2$= 15.33 | **<0.0001** |
| SSRI Tx Duration, yrs¶ | 2.0±1.8 | 1.2±0.1 | 2.5±0.3 | Wilcoxon = 3905.5 | **<0.0001** |
| Risperidone Tx Duration, yrs¶ | 2.8±2.0 | 2.9±0.2 | 3.5±0.4 | Wilcoxon = 3186.5 | 0.16 |

ADHD: attention deficit hyperactivity disorder, DBD: disruptive behavior disorder, ASD: Autism Spectrum Disorder, MPH Tx: treatment with psychostimulants, SSRI Tx: treatment with selective serotonin reuptake inhibitors.

¶: Results for the two clinical groups are reported as least squares means and standard error, given that the analyses are adjusted for age.

Significant results ($p<0.05$) are bolded.

**Table 4:**

Skeletal Measures for the Entire Sample and Split Based on MPH Treatment Status

| | | Entire Sample | No-ASD | ASD | Statistic | p-value |
|---|---|---|---|---|---|---|
| **Dual-Energy X-ray Absorptiometry-Based Measures** | | | | | | |
| LS BMC Z-score, n=140 | Unadjusted Mean Values ± Std | 0.12±0.91 | 0.19±0.87 | −0.20±1.03 | Wilcoxon = 1236.0 | ***0.07*** |
| | LSMeans ± SE | --- | 0.15±0.08 | 0.01±0.20 | F=0.40 | 0.53 |
| LS aBMD Z-score, n=140 | Unadjusted Mean Values ± Std | 0.26±1.01 | 0.32±1.00 | −0.06±1.01 | Wilcoxon = 1272.0 | 0.11 |
| | LSMeans ± SE | --- | 0.31±0.08 | 0.11±0.21 | F=0.72 | 0.40 |
| TBLH BMC Z-score, n=46 | Unadjusted Mean Values ± Std | 0.18±0.76 | 0.27±0.76 | −0.26±0.66 | Wilcoxon = 119.0 | ***0.05*** |
| | LSMeans ± SE | --- | 0.18±0.10 | −0.06±0.21 | F=1.02 | 0.3188 |
| TBLH aBMD Z-score, n=46 | Unadjusted Mean Values ± Std | 0.30±0.80 | 0.38±0.83 | −0.12±0.48 | Wilcoxon = 127.0 | ***0.08*** |
| | LSMeans ± SE | --- | 0.28±0.11 | 0.09±0.24 | F=0.51 | 0.48 |
| **Peripheral Quantitative Computed Tomography-Based Measures** | | | | | | |
| Trabecular vBMD, $mg/cm^3$, n=151 | Unadjusted Mean Values ± Std | 202±39 | 327±55 | 302±47 | Wilcoxon = 1227.0 | **0.001** |
| | LSMeans ± SE | --- | 205.2±3.2 | 181.3±7.4 | F=8.54 | **0.004** |
| Strength Index, $mg^2/mm^4$, n=151 | Unadjusted Mean Values ± Std | 23.1±11.3 | 23.6±11.6 | 20.7±9.1 | Wilcoxon = 1645.0 | 0.20 |
| | LSMeans ± SE | --- | 23.9±0.72 | 18.9±1.7 | F=7.14 | **0.0084** |

LS: lumbar spine, BMC: bone mineral content, aBMD: areal bone mineral density, TBLH: total body less head, vBMD: volumetric bone mineral density, LSMeans: least squares means and standard errors (refer to text for details about the models), Std: standard deviation.

Age-sex-height-race-specific Z-scores for LS and TBLH BMC and aBMD were generated following the Bone Mineral Density in Childhood Study (Zemel et al. 2011).

Significant results ($p<0.05$) are bolded and marginally significant results ($p<0.10$) are bolded and italicized.