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An eight-year longitudinal analysis of physical activity and bone strength from adolescence to emerging adulthood: The Iowa Bone Development Study

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Abstract

Purpose—Most pediatric physical activity and bone health research has focused on the period immediately around puberty; few have addressed bone structural strength outcomes. This study assessed the magnitude and consistency of the longitudinal relationships between device-measured vigorous physical activity (VPA) and structural bone strength outcomes across adolescence to emerging adulthood.

Method—Participants with three to five bone scans between 11–19 yr were studied ($n=439$, 220 females, 1838 records). DXA scans of the hip (hip structural analysis) and pQCT scans of the tibia were obtained. Outcomes included femoral neck (NN) section modulus (Z), NN cross-sectional area (CSA), tibial bone strength index (BSI), and tibial torsion strength (pSSI). Sex-specific bone mixed growth models were developed using Biological Age (BA; chronological age – best estimate of Peak Height Velocity age estimated via Mirwald equation) as the time variable, and height, weight, and device-measured VPA as time-varying covariates. Models also included the VPA-BA interaction.

Results—Individual-centered VPA and the VPA-BA interaction were significantly, positively associated ($p<0.05$) with BSI, pSSI, Z, and CSA in males and females, indicating accumulative effects of VPA throughout maturation and beyond.

Conclusion—Bone remains responsive to the mechanical loading of PA throughout adolescence and into emerging adulthood. Attention should be placed on promoting bone-strengthening PA after the pre-pubertal years when adult exercise patterns are likely formed.

Introduction

Bone mass and bone structural strength predict fracture risk throughout the lifespan. Physical activity (PA) is important in the accrual of bone mass and the development of bone strength; particularly, activities done at a high rate and intensity (20,21). Activities that provide a mechanical load to the lower body skeleton can be captured with hip-worn accelerometers calibrated to vigorous-intensity PA (VPA). The research evidence indicates the influence of PA on bone is maturity-dependent; that is, bone mass is accrued at a higher rate during the years surrounding Peak Height Velocity (PHV), and that bone responds optimally to PA during these early adolescent years (approximately age 9–14 yr) (2,3,18).

While pre- and early-puberty are important times to focus on bone strengthening behaviors due to how quickly bone is growing, continuing the focus into later adolescence and

adulthood may also be important since accrual of bone is not complete until early adulthood (9). In addition, much of the epidemiological work completed on bone health is cross-sectional. Few studies have longitudinally examined the association of PA and bone especially throughout the entire period of bone accrual (22). Additionally, few studies have addressed bone structural strength outcomes (21,22). Gabel and colleagues (9) found 4% to 6% greater bone strength outcomes in the most active adolescents (~60 minutes per day of moderate- and vigorous-intensity PA, MVPA) versus the least active (<30 minutes per day of MVPA) up to nine years post PHV. Similarly, a previous analysis of Iowa Bone Development Study (IBDS) participants showed that boys and girls with the highest PA trajectories across childhood and adolescence had significantly greater bone strength outcomes at age 17 yr when compared to those with the lower PA trajectories (13). Late adolescence and early adulthood is understudied in the bone-health literature, yet it is a critical period when bone continues to accrue, while simultaneously PA participation, particularly VPA participation, declines (2,13). Equally important, late adolescent PA tracks into adulthood, suggesting a key time when adult PA patterns are developed (4).

Of the studies that have examined the relationship between PA and bone health into late adolescence, few have used structural outcomes obtained via Peripheral Quantitative Computed Tomography (pQCT), objective measures of PA, and a clear measure of physical development (9,13). Historically, bone research was completed using measures of bone mass and density (via Dual Energy X-ray Absorptiometry, DXA). Research shows, however, the importance of bone structure, in addition to mass, on the bone's ability to resist fracture (21). For example, pQCT-derived structural variables that estimate bone's resistance to compressive and torsional forces are good indicators of fracture risk (14). When studying the intricate relationships between PA and health outcomes, a precise measure of PA (i.e., device-measured PA), specifically bone-loading VPA, is also necessary. Finally, as indicated earlier, PA and bone development are maturity-dependent (21). Thus, having valid, repeated measurements of bone structure, PA, and physical development are essential to fully understand the influence of PA on bone health. Therefore, the purpose of this study was to assess the magnitude and consistency of the longitudinal associations between device-measured VPA and structural bone strength outcomes (via pQCT and DXA with Hip Structural Analysis, HSA) using the IBDS cohort. We specifically focused on the entire adolescent period (11–19 yr), and assessed the accumulative effects of mean VPA across adolescence, as well as change from the mean at each measurement period. We hypothesized that the benefits of VPA on bone structural strength accumulated and persisted across the entire period of adolescence and emerging adulthood.

Methods

The Iowa Bone Development Study (IBDS) included children recruited at age 5 yr from the Iowa Fluoride Study, a birth cohort of over 1,000 children born in one of eight Iowa hospitals (16). Participants in the IBDS were recruited between 1998 and 2001. Additional information on study design and participant demographics has been reported previously (10,11,12,13).

The current analysis used data from five clinical exams with bone imaging and PA measures collected at ages 11, 13, 15, 17, and 19 yrs. Participants were included in analysis if they had bone imaging and accelerometer measures at least three times from age 11 to 19 yr (N=1,838 measurements; n = 220 females with 946 records; n = 219 males with 898 records; participants with serious chronic conditions, such as diabetes, Crohn's disease, cerebral palsy or lupus (n = 11) were excluded). Approval for this study was obtained from the University of Iowa Institutional Review Board for human subjects. Parents provided written informed consent; participants provided assent at ages 11–17 and consent at age 19.

Physical Activity Exposure Variables

Physical activity was measured utilizing ActiGraph 7164 accelerometers at ages 11 and 13, GT1M models at age 15, and the GT3X+ at ages 17 and 19. Movement counts recorded using the different models of the ActiGraph monitors are highly correlated with one another ($r = 0.99$) (15,19). In our study, movement counts were collected in 1-minute epochs at ages 11 and 13, and 5-second epochs (reintegrated into 1-minute epochs using ActiLife software) at ages 15, 17 and 19. Participants were asked to wear the monitors at the right hip (on an elastic belt or clip) during all waking hours for five consecutive days, including weekend days, except during bathing and swimming. Participants were included in analyses if they wore the accelerometer for three to five days, for at least ten hours per day, for at least three measurement periods (n=220 females, 219 males). Accelerometer data were analyzed using the Evenson approach, which utilizes cut points to predict minutes of VPA ($> 4,012$ counts per minute). When compared to indirect calorimetry, the VPA cut point has excellent classification accuracy (ROC-AUC = 0.83) (6). Time spent in VPA (minutes per day) was used in the analyses since this intensity of activity requires high impact or high muscle forces both of which place osteogenic strain on the bone (1). With hip-worn accelerometry, non-osteogenic VPA, such as during cycling and swimming, is not measured.

Bone Strength Structural Outcomes

Bone strength structural outcomes were assessed at each measurement period during clinical visits to the University of Iowa General Clinical Research Center or Clinical Research Unit. The Hologic QDR 4500A DXA (Delphi upgrade, software V.12.3 in fan beam mode) model was utilized for hip region. Global Regions of Interest were used to determine the boundaries of hip images, which were confirmed by trained technicians. Structural geometry was estimated using the Hip Structural Analysis (HSA) program (Hologic Apex 3.0 software). The HSA program determined the narrowest part of the femoral neck (NN), where the NN Cross-Sectional Area (CSA, cm^2) and NN Section Modulus (Z, cm^3 , a measure of bending strength), were computed and used in analysis.

Additional bone structural strength measures were estimated via pQCT using the Stratec XCT 2000/3000 (software V.6.2). Polar Strength Strain Index (pSSI, mm^3), which is a measure of tibial torsional strength, was estimated at the 38% (cortical) site, and Bone Strength Index (BSI, mg^2/mm^4), which is a measure of bones compressive strength, was estimated at the 4% (trabecular) site. pQCT scans were acquired using a voxel size of 0.4 mm, 2.2 mm tomographic slice thickness, and a scan speed of 20 mm/s. BSI was calculated with the formula: $\text{BSI (mg}^2/\text{mm}^4) = \text{total area (mm}^2) \times \text{total density (mg/mm}^3)^2$. Cortmode

2 with a threshold of 480 mg/cm^3 was used to measure pSSI. Bending and torsional strength are related to bone structure, and are important measures for injury risk. Analyses of the metaphyseal cross-section at 4% found total bone using interactive contour search mode 3 with the threshold set just above soft tissue density at 169 mg/cm^3 . These measures are important because two bones with the same Cortical Area (cm^2), yet differences in bone structure, have different resistance to bending (cm^4). The bone with its mass further from the neutral axis will have a greater bending strength than the one with its mass closer to the neutral axis (11).

Anthropometry

During the clinic visit, research nurses measured height (cm) using a Harpenden stadiometer (Holtain, UK) and weight (kg) using a Healthometer physician's scale (Continental, Bridgeview, IL, USA). Biological Age (BA; chronological age at measurement time period – best estimate of age at PHV) was estimated at each visit from age 11 to 17 using age, sex, seated height, and leg length and the Mirwald and colleagues' (17) predictive equations. The Mirwald equation has a Standard Error of the Estimate (SEE) of 0.49 yr for boys and 0.50 yr for girls, respectively. The PHV age estimate has higher precision when measurements used in the equation are taken closer to actual PHV age. Since we had multiple PHV age estimates, to increase precision, the best estimate was determined as the calculated PHV age that was closest in absolute value to chronological age at time of measurement - in most cases, age 11 or 13 for girls and 13 or 15 for boys (17).

Statistical Methods

Sex-specific descriptive statistics (mean, standard deviation, median, interquartile range) were calculated for anthropometric, VPA, and bone strength outcomes. Differences in VPA between males and females were formally tested using t-tests. Sex-specific mixed effects growth models were developed using up to five repeated measurements. Participants were aligned by maturity (BA) to better describe growth patterns. Models included random intercept and slope for BA as the time variable, and cubic polynomials for BA as fixed effect to describe non-linear growth pattern over long study period, weight, and height were included as time varying covariates. Then VPA was added to the models as the main time varying predictor of interest. Two variables were created for each time varying covariate: mean value over time for the individual and change from this mean value at each assessment. This was done to disaggregate within-individual and between-individual differences (5,9). Mean value over time for the individual was centered using the sex-specific mean value from all sample records. Centering the individual mean allows for meaningful interpretation of model intercept values (5). SAS 9.4 software was used for the analysis; MIXED procedure was applied for model building. Model fit was assessed using residual plots. To demonstrate the importance of VPA for bone strength, we developed bone growth trajectories for typical male and female participants based on our models (Figure 1) – these trajectories correspond to mean values for all independent variables in the mixed models for bone outcomes, except VPA. For VPA we looked at the distributions of mean VPA and estimated 25th and 75th percentiles as representing relative low and relative high levels of VPA overtime. VPA change was set as the mean level for each wave of assessment.

Results

Participants were, on average, 11.2 yr at the first visit used in the analysis, and 19.7 yr at the last visit. Please note that the U.S. Physical Activity Guidelines define children and adolescents as 17 yr or younger and adults as 18 yr and older (1). Participant characteristics, including anthropometry, bone structural outcomes, and VPA are presented in Table 1. Males had a median of 16.9 min/day of VPA at age 11 and 9.2 min/day at age 19. Females had a median of 8.0 min/day of VPA at age 11 and 3.8 min/day at age 19. VPA was significantly different between males and females across all measurement periods (p-values < 0.001 for age 11, 13, 15, and 17 yr; p-value < 0.01 for age 19 yr). Values across study assessments (height, weight, and bone strength outcomes) indicate non-linear patterns of growth over this long study period, therefore inclusion of cubic polynomials for BA in our models was needed to adequately describe such growth for bone strength outcomes.

Table 2 shows the two-level multivariable growth models for pQCT derived bone strength outcomes. Table 3 shows the two-level multivariable growth models for DXA measured femoral neck strength outcomes, estimated via HSA. The mixed models had random intercepts and slopes for participants, with cubic polynomial time variables using BA to describe growth over time. Weight, height and VPA were included using variables for between- and within-individual differences. Between-individual differences in VPA or mean VPA variable, as well as the interaction between mean VPA and BA, were statistically significant predictors for BSI, pSSI, NN Section Modulus, and NN Cross-Sectional Area for males and females. Within-individual difference in VPA or VPA (change) was included in final models if at least marginally significant (p-value < 0.1).

Figure 1 represents the sex-specific growth models and highlights the differences in bone outcomes between the 25th and 75th percentiles for mean VPA (across all measurement periods) with light gray lines showing actual trajectories of the participants. While the bone outcomes are continually increasing with age, those in the 75th percentile for mean VPA begin with better bone outcomes, and increase at a greater rate. The differences are more pronounced in males when compared to females. Importantly, all four bone outcomes were higher in those who accumulated more VPA across adolescence.

BSI across adolescence by level of mean VPA is shown in Panel A. For both males and females, those in the 75th percentile for mean VPA had greater bone bending strength at the distal tibia than those in the 25th percentile. Similarly, Panel B illustrates the positive effects of mean VPA on pSSI, a measure of torsional strength of the distal tibia. The effect of mean VPA on section modulus (Z), which estimates the bending strength of the proximal femur, is shown in Panel C, and also increases with greater mean VPA. Lastly, Panel D displays CSA, which estimates compressive strength at the proximal femur. Those in the 75th percentile have greater CSA than those in the 25th percentile.

Discussion

The purpose of this study was to assess the longitudinal associations between device-measured PA and structural bone strength outcomes throughout adolescence and into

emerging adulthood (19 yr). The study modeled growth for four bone outcomes aligned on maturity (BA), adjusting for height and weight, prior to examining the relationship of VPA to bone strength. On average, accumulating 5 minutes per day more VPA (to reach mean VPA levels) was associated with up to 3.0% greater bone structural outcomes by age 19 in males, and up to 5.1% greater bone structural outcomes in females. Although the addition of 5 minutes per day of “extra” VPA does not seem like much in a typical 960 minute waking day, the low amount of VPA that we report, especially in females, indicates a significant public health challenge ahead. When looking at VPA percentiles across the cohort, for average female participants an increase in mean VPA from the 25th percentile to the 75th percentile would result in a relative increase in bone strength that ranged from 2.5 – 5.4% at age 11 and 3.8 – 6.2% at age 19. For males, the predicted increases from the 25th percentile to the 75th percentile ranged from 3.6 – 6.7% at age 11 and 5.0 – 6.3 % at age 19. A general assumption in the literature is that a 3% difference is likely to be clinically meaningful (22) suggesting that there is much to be gained by promoting VPA for bone health throughout adolescence.

The dose-response findings that we report are in agreement with previous work on adolescents, including our own work. For example, previous IBDS data showed significant relationships between PA and bone strength, despite decreasing PA throughout adolescence (13). Similarly, in a review of effects of PA interventions on bone strength, mass and structure, interventions reported significantly greater gains in the intervention groups with 20 to 36 minutes of high-impact PA per week, ranging from 3% to 5% over seven to eight months, when compared to regular physical education participation (21). Additionally, observational studies showed a significant contribution of PA to bone strength in both boys and girls, with 2% to 12% of the variance explained by VPA, MVPA or loaded PA (21). Gabel and colleagues (9) studied participants from adolescence to emerging adulthood (age 9 to 20 yr) and found that adolescents in the highest quartile for MVPA (~60 minutes per day) had 4% to 6% greater bone strength outcomes than those in the lowest quartile (<30 minutes per day) throughout the measurement period. While this analysis (9) did not distinguish between MVPA and VPA, a separate analysis from the same study suggested that increasing the number of bouts of VPA per day, but not total volume, was associated with greater bone strength (8). As a side note, we initially ran analyses using both MVPA and VPA. The VPA models consistently explained more of the variability in bone outcomes.

Finally, our modeling approach examined mean VPA across all measurement periods, as well as change from the mean at each measurement period. Previous work from the IBDS indicates that PA patterns track at a moderate- to high-level ($r=0.41-0.63$) across childhood and adolescence (7), suggesting that the most active (or least active) participants at age 11 yr stay that way as they age. Notably, the significant interaction between mean VPA and BA suggests accumulative effects. The differences in bone structural outcomes between the most active and least active participants across the entire measurement period were greater with increasing BA, that is, with increasing age. Thus, greater attention should be placed on promoting bone-strengthening VPA throughout adolescence, rather than focusing solely on the period of PHV. Post PHV may be a particularly important time since PA patterns track from adolescence into adulthood (4), i.e., the type of bone-strengthening VPA that adolescents engage in is likely to be the type they will do as adults.

Strengths of the current study included the use of hip-worn ActiGraph accelerometers to measure PA and a valid method for estimating PHV (17). The study also utilized both HSA from DXA and pQCT to measure bone structural strength. Limitations of the study included a fairly homogenous sample of individuals born in Iowa, thus limiting generalizability to other geographical areas, or populations with more diverse, ethnic/racial variability. Additionally, other behavioral factors that can impact bone health were not included in analysis, including dietary and genetic factors.

Conclusions

This study demonstrated the accumulative impact of VPA on bone strength outcomes throughout adolescence and into emerging adulthood. We showed the importance of VPA across adolescence and the accumulative effects on bone. Greater attention should be given to promoting bone-strengthening PA throughout adolescence and emerging adulthood to maximize bone strength and reduce fracture risk.

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Figure 1.

Growth models for Bone Strength Index (BSI, Panel A), Tibia Torsion Strength (pSSI, Panel B), Femoral Neck (NN) Section Modulus (Panel C), and NN Cross-Sectional Area (CSA, Panel D) aligned by Biological Age. BSI measured at the 4% site, and pSSI measured at the 38% site via Peripheral Quantitative Computed Tomography. NN Section Modulus and NN CSA measured via Hip Structural Analysis using Dual Energy X-Ray Absorptiometry. The red lines represent the 25th percentile for mean VPA across adolescence, and the green lines

represent the 75th percentile for mean VPA across adolescence, highlighting their differences.

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Table 1.

Participant Characteristics by Sex and Age

Males	Age 11 (n=197)	Age 13 (n=208)	Age 15 (n=192)	Age 17 (n=165)	Age 19 (n=130)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	11.2 (0.3)	13.3 (0.4)	15.4 (0.3)	17.5 (0.4)	19.7 (0.6)
BA (years)	-2.4 (0.8)	-0.4 (0.9)	1.7 (0.8)	3.9 (0.8)	6.0 (1.0)
Height (cm)	148.9 (7.6)	163.1 (9.2)	175.3 (7.8)	178.9 (7.6)	179.9 (7.4)
Weight (kg)	45.0 (12.9)	58.3 (15.8)	71.2 (16.9)	79.8 (18.7)	84.6 (20.5)
BSI 4%	60.6 (14.1)	76.4 (17.5)	103.9 (27.7)	133.3 (31.2)	146.5 (32.8)
pSSI 38%	1,009.6 (261.2)	1,401.2 (361.0)	1,788.2 (428.9)	2,048.8 (448.2)	2,176.0 (469.2)
NN Section Modulus	0.95 (0.26)	1.30 (0.35)	1.80 (0.45)	2.17 (0.51)	2.30 (0.53)
NN Cross-Sectional Area	2.41 (0.42)	2.92 (0.54)	3.65 (0.72)	4.17 (0.80)	4.33 (0.84)
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
VPA (min/day)	16.9 (10.8, 29.3) *	12.4 (8.2, 22.8) *	7.1 (3.0, 14.4) *	6.7 (3.3, 15.0) *	9.2 (4.0, 20.0) **
Females	Age 11 (n=204)	Age 13 (n=204)	Age 15 (n=189)	Age 17 (n=187)	Age 19 (n=162)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	11.2 (0.3)	13.3 (0.4)	15.3 (0.3)	17.5 (0.4)	19.7 (0.6)
BA (years)	-0.5 (0.6)	1.5 (0.7)	3.5 (0.7)	5.8 (0.7)	8.0 (0.8)
Height (cm)	149.3 (7.5)	160.8 (6.6)	164.9 (6.5)	166.0 (6.5)	166.4 (6.7)
Weight (kg)	44.3 (12.5)	55.9 (14.6)	61.6 (14.7)	66.2 (15.9)	69.5 (19.0)
BSI 4%	54.1 (13.6)	73.3 (20.0)	90.4 (22.3)	98.8 (23.9)	101.2 (24.0)
pSSI 38%	961.2 (228.4)	1,229.5 (275.4)	1,404.1 (316.1)	1,502.1 (337.0)	1,544.4 (333.1)
NN Section Modulus	0.87 (0.24)	1.19 (0.30)	1.37 (0.35)	1.48 (0.37)	1.52 (0.36)
NN Cross-Sectional Area	2.23 (0.40)	2.77 (0.52)	3.08 (0.56)	3.24 (0.60)	3.28 (0.59)
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
VPA (min/day)	8.0 (4.3, 14.0)	6.1 (3.0, 11.7)	3.4 (1.3, 9.0)	3.6 (1.5, 9.0)	3.8 (1.2, 11.4)

SD – standard deviation; IQR – interquartile range; BA – biological age (chronological age – age at Peak Height Velocity); VPA – vigorous-intensity physical activity; BSI – Bone Strength Index estimated via pQCT of the tibia; pSSI – tibia torsion strength estimated via pQCT of the tibia; NN – femoral neck (DXA - Hip Structural Analysis)

* significant difference between males and females, p-value < 0.001

** significant difference between males and females, p-value < 0.01.

Table 2.

Two-Level Multivariable Growth Model for Peripheral Quantitative Computed Tomography Bone Strength Outcomes

Outcome	Effect	Estimate	Standard Error	p-value	Estimate	Standard Error	p-value
		Males			Females		
BSI 4%	Intercept	83.3821	1.1519	<0.0001	68.3867	1.3325	<0.0001
	BA	9.0474	0.7495	<0.0001	3.8108	0.9145	<0.0001
	BA * BA	1.0221	0.0855	<0.0001	0.5790	0.1738	0.0009
	BA * BA * BA	-0.1644	0.0118	<0.0001	-0.0839	0.0118	<0.0001
	Height (mean)	0.0917	0.1313	0.4859	-0.0924	0.1471	0.5307
	Height (change)	0.2404	0.1272	0.0593	0.5426	0.1443	0.0002
	Weight (mean)	0.3621	0.0668	<0.0001	0.5264	0.0675	<0.0001
	Weight (change)	0.3563	0.0664	<0.0001	0.4824	0.0589	<0.0001
	VPA (mean)	0.4455	0.1125	0.0001	0.4480	0.1230	0.0003
	BA * VPA (mean)	0.0701	0.0257	0.0066	0.0662	0.0229	0.0040
	VPA (change)	0.0880	0.0343	0.0107	0.0994	0.0350	0.0047
	pSSI 38%	1529.811	15.1515	<0.0001	1226.756	12.7973	<0.0001
	BA	65.4781	6.6746	<0.0001	3.8402	7.8124	0.6232
	BA * BA	5.3788	0.7733	<0.0001	8.5348	1.4333	<0.0001
	BA * BA * BA	-1.0258	0.0906	<0.0001	-0.7611	0.0934	<0.0001
	Height (mean)	9.6296	1.7846	<0.0001	12.4675	1.5874	<0.0001
	Height (change)	16.3860	1.0856	<0.0001	18.3087	1.2460	<0.0001
	Weight (mean)	8.7001	0.8996	<0.0001	8.8557	0.7176	<0.0001
	Weight (change)	4.6302	0.5929	<0.0001	3.4657	0.4750	<0.0001
	VPA (mean)	7.4167	1.5830	<0.0001	5.2987	1.3712	0.0001
	BA * VPA (mean)	0.7182	0.2521	0.0045	0.7594	0.2004	0.0002

BA – biological age; BSI – Bone Strength Index estimated via pQCT of the tibia; pSSI – tibia torsion strength estimated via pQCT of the tibia; height (mean), weight (mean), and VPA (mean) were sample centered individual over-time mean variables; height (change), weight (change), and VPA (change) were measures of change from individual mean variables. VPA (change) is included in final models if at least marginally significant (p-value < 0.1).

* indicates interaction.

Table 3.

Two-Level Multivariable Growth Model for Dual Energy X-ray Absorptiometry Hip Femoral Neck Strength Outcomes

Outcome	Effect	Estimate	Standard Error	p-value	Estimate	Standard Error	p-value
		Males			Females		
NN Section Modulus	Intercept	1.4715	0.0167	<0.0001	1.2369	0.0179	<0.0001
	BA	0.0777	0.0112	<0.0001	-0.0400	0.0123	0.0012
	BA * BA	0.0146	0.0012	<0.0001	0.0167	0.0024	<0.0001
	BA * BA * BA	-0.0023	0.0002	<0.0001	-0.0013	0.0002	<0.0001
	Height (mean)	0.0144	0.0020	<0.0001	0.0144	0.0020	<0.0001
	Height (change)	0.0174	0.0019	<0.0001	0.0249	0.0020	<0.0001
	Weight (mean)	0.0081	0.0010	<0.0001	0.0104	0.0009	<0.0001
	Weight (change)	0.0078	0.0010	<0.0001	0.0068	0.0008	<0.0001
	VPA (mean)	0.0063	0.0016	0.0001	0.0059	0.0017	0.0004
	BA * VPA (mean)	0.0012	0.0004	0.0009	0.0008	0.0003	0.0023
	VPA (change)	0.0009	0.0005	0.0663			
NN Cross-Sectional Area	Intercept	3.1768	0.0268	<0.0001	2.8318	0.0273	<0.0001
	BA	0.1130	0.0169	<0.0001	-0.0371	0.0174	0.0334
	BA * BA	0.0197	0.0019	<0.0001	0.0212	0.0032	<0.0001
	BA * BA * BA	-0.0034	0.0003	<0.0001	-0.0019	0.0002	<0.0001
	Height (mean)	0.0186	0.0031	<0.0001	0.0149	0.0033	<0.0001
	Height (change)	0.0245	0.0028	<0.0001	0.0362	0.0028	<0.0001
	Weight (mean)	0.0148	0.0016	<0.0001	0.0199	0.0015	<0.0001
	Weight (change)	0.0120	0.0015	<0.0001	0.0146	0.0011	<0.0001
	VPA (mean)	0.0106	0.0026	<0.0001	0.0092	0.0028	0.0012
	BA * VPA (mean)	0.0016	0.0006	0.0039	0.0012	0.0004	0.0041
	VPA (change)	0.0028	0.0008	0.0003			

BA – biological age; NN – femoral neck (DXA - Hip Structural Analysis); height (mean), weight (mean), and VPA (mean) were sample centered individual over-time mean variables; height (change), weight (change), and VPA (change) were measures of change from individual mean variables. VPA (change) is included in final models if at least marginally significant (p-value < 0.1).

* indicates interaction.