Investigation of Sex Differences in Hip Structure in Peripubertal Children

Adrian Sayers, Michele Marcus, Carol Rubin, Michael A. McGeehin, and Jonathan H. Tobias

Academic Rheumatology (A.S., J.H.T.), Clinical Science at North Bristol, University of Bristol, Bristol BS10 5NB, United Kingdom; Department of Epidemiology (M.M.), Rollins School of Public Health, Emory University, Atlanta, Georgia 30322; and National Center for Environmental Health (M.M., C.R., M.A.M.), Centers for Disease Control and Prevention, Atlanta, Georgia 30333

Context: There is evidence that sex differences in hip structure are increased during puberty, possibly as a consequence of associated changes in body composition.

Objectives: The objective of the study was to explore relationships between sex, puberty, hip structure, and body composition.

Design/Setting: The design was a longitudinal birth cohort study: The Avon Longitudinal Study of Parents and Children.

Participants: Participants included 3914 boys and girls (mean age 13.8 yr).

Outcome Measures: Measures included dual-energy x-ray absorptiometry-derived femoral neck width (FNW), cortical thickness (CT), bending strength [cross-sectional moment of inertia (CSMI)], section modulus, buckling ratio (BR), and femoral neck and total hip bone mineral density.

Results: FNW, CT, and CSMI were higher in boys, whereas BR was lower in girls ($P < 0.001$). Differences in hip structure were studied according to puberty (self-completion Tanner stage questionnaires). FNW, CT, and CSMI were higher in Tanner stage IV/V *vs.* I/II, particularly in boys ($P < 0.001$, puberty-sex interaction). BR was lower in Tanner stage IV/V, particularly in girls ($P = 0.008$, puberty-sex interaction). Adjusting for height, fat mass, and lean mass resulted in differential attenuation in the sexes, such that CT attenuated by about 80% and about 40% in boys and girls, respectively ($P = 0.004$, puberty-sex interaction for adjusted CT, Tanner stages I/II *vs.* IV/V). The difference in BR showed little attenuation after adjustment.

Conclusion: During puberty, hip-bending strength increases, particularly in boys, due to their greater FNW, reflecting changes in height, fat mass, and lean mass. In contrast, BR falls during puberty, particularly in girls, reflecting their smaller FNW relative to CT, involving mechanisms partly independent of height and body composition. **(*J Clin Endocrinol Metab* 95: 3876–3883, 2010)**

Sexual dimorphism in skeletal development is well recognized. At the hip, these differences have been reported to emerge during puberty and comprise largely greater periosteal apposition in boys, leading to greater femoral neck width (FNW) and bending strength (1). More rapid periosteal bone formation in boys, leading to greater cortical bone size, has also been reported at the midfemur (prepubertal children and young adults combined) (2), midtibia (peripubertal children) (3), and distal tibia and femoral neck (18 yr olds) (4). In terms of possible sex differences in endosteal apposition, a previous study based on metacarpal radiogrametry suggested that en-

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2009-2446 Received November 16, 2009. Accepted April 27, 2010.
First Published Online May 19, 2010

Abbreviations: ALSPAC, Avon Longitudinal Study of Parents and Children; BMD, bone mineral density; BR, buckling ratio; CSA, cross-sectional area; CSMI, cross-sectional moment of inertia; CT, cortical thickness; DXA, dual-energy x-ray absorptiometry; FN, femoral neck; FNW, FN width; pQCT, peripheral quantitative computed tomography; SM, section modulus; TH, total hip.

docortical bone formation is more rapid during puberty in girls (5). On the other hand, 18-yr-old males were found to have greater cortical thickness (CT) of the distal tibia by peripheral quantitative computed tomography (pQCT) compared with age-, height-, and weight-matched females (4). A further study suggests that puberty acts to increase cortical bone mass in girls by increasing cortical density rather than thickness (6).

Sexual dimorphism in skeletal development may be more pronounced during puberty (3, 5), suggesting a role of sex hormones in their generation, as supported by correlations between sex steroid levels and changes in endocortical and periosteal surfaces during puberty (7). Rapid changes in fat and lean mass, which are thought to play a major role in bone mass acquisition in childhood (8–10), may also contribute to any relationship between puberty and sexual dimorphism. Consistent with this suggestion, sex differences in hip structure that emerged during the adolescent growth spurt largely disappeared after adjusting for height and lean mass (1). On the other hand, it is clear that sexual dimorphism of the skeleton is evident before the onset of puberty (11), suggesting that some components are independent of puberty.

Taken together, these studies suggest that sex differences in hip structure become more pronounced during puberty and are at least partly explainable by those in body composition. Here we report a cross-sectional study intended to examine these relationships in more detail in a large population-based cohort of peripubertal children. Specifically we investigated whether associations between pubertal stage and dual-energy x-ray absorptiometry (DXA)-derived measures of hip structure differ between boys and girls and whether these differences are explained by those in body composition.

Subjects and Methods

Study population

The Avon Longitudinal Study of Parents and Children (ALSPAC) study is a geographically based birth cohort study investigating factors influencing the health, growth, and development of children. All pregnant women resident within a defined part of the former county of Avon in southwest England with an expected date of delivery between April 1991 and December 1992 were eligible for recruitment, of whom about 14,000 were enrolled (12) (http://www.alspac.bristol.ac.uk). ALSPAC is a relatively homogenous population in ethnic terms, approximately 97% of subjects being Caucasian. Ethical approval was obtained from the ALSPAC Law and Ethics Committee and relevant local ethics committees. Data in ALSPAC are collected by self-completion postal questionnaires sent to parents, linkage to computerized records, abstraction from medical records, and examination of the children at research clinics.

Measurement of hip structure

All children attending the research clinic at age 13.8 yr were offered a left hip DXA scan on a GE Lunar Prodigy (Madison, WI). As well as generating total hip (TH) and femoral neck (FN) bone mineral density (BMD; g/cm^2), each scan was analyzed using the manufacturer's automated advanced hip analysis software, which generated a range of structural parameters at the site of minimum FN width. This method has recently been validated against volumetric quantitative computed tomography in adults (13). In the present study, rather than use values derived from adult populations, bone conversion factors (*i.e.* assumed average calcium content of bone tissue) were based on sex- and puberty-specific measures of cortical BMD obtained from tibial pQCT scans as previously reported (6). Geometric indices consisted of FNW (mm), cortical cross-sectional area (CSA; cm^2), and CT (mm). Derived biomechanical strength indices comprised buckling ratio (BR; 0.5FNW divided by CT); cross-sectional moment of inertia (CSMI; cm^4), which reflects resistance to bending; and section modulus (SM; cm^3), which is CSMI adjusted for size by dividing by FN radius.

Confounders

Total body fat and lean mass were measured using DXA (GE Lunar Prodigy). Height was measured using a Harpenden stadiometer (Holtain Ltd., Crymych, UK), and weight was measured to the nearest 50 g using the Tanita body fat analyzer (model TBF 305; Tanita, Arlington Heights, Illinois). Pubertal status was assessed by self-report on a postal questionnaire at an average age of 13.1 yr. Diagrams and descriptions of the five Tanner stages of pubertal development were included in the questionnaires, and participants were asked to check which stage most closely matched their current stage. Pubertal status was assigned based on pubic hair self-ratings in girls and boys (to aid comparability between the sexes, pubic hair ratings were used in isolation).

Statistical methods

Descriptive statistics are presented as means and SD and medians and interquartile ranges. The effect of sex and puberty was estimated using simple linear regression in which puberty was introduced as a categorical element into the linear predictor. The significance of each interaction was assessed using the partial F test based and nominal significance set at $P < 0.05$; if there was no evidence of an interaction between sex and puberty, a more parsimonious model was fitted without an interaction term. Adjustment for confounders was performed by the addition of confounders into the right-hand side of the linear predictor and comparing the parameter estimates of the models before and after adjustment. All figures are plotted with means and 95% confidence intervals. All missing data were treated as missing at random, and complete case analysis was performed in analyses. Analyses were conducted using STATA 9.2 (Stata Corp. College Station, TX).

Results

The Teen Focus 2 research clinic was conducted at mean age of 13.8 yr. A total of 11,351 young people were invited, of whom 6,147 attended, and 6053 subsequently

TABLE 1. Demographic descriptive statistics

	Sex	Mean (SD)	25th (%)	50th (%)	75th (%)
Age (yr)	Male	13.85 (0.18)	13.74	(13.82)	13.92
	Female	13.86 (0.20)	13.75	(13.84)	13.94
Height (cm)	Male	165.13 (8.51)	159.15	(165.30)	170.70
	Female	162.24 (6.21)	158.20	(162.20)	166.40
Weight (kg)	Male	54.74 (11.64)	46.60	(53.10)	61.40
	Female	54.60 (10.63)	47.60	(53.00)	60.20
Total body fat mass (kg)	Male	11.08 (7.67)	5.64	(8.54)	14.40
	Female	16.39 (7.68)	10.79	(14.87)	20.12
Total body lean mass (kg)	Male	41.09 (7.13)	35.88	(40.67)	46.02
	Female	35.35 (4.11)	32.64	(35.10)	37.97

Data show means (SD), median, and lower and upper quartile thresholds (males, n = 1820; females, n = 2094).

underwent total body and hip DXA scans; 162 hip DXAs were rejected due to poor quality of the image. A total of 3914 individuals had complete DXA and covariate information, on whom the present analysis is based. Boys who underwent hip DXA scans were taller and had a lower fat mass but greater lean mass compared with girls (Table 1). Girls were more advanced in puberty compared with boys, as reflected by the proportion in different Tanner stages: 35.5, 27.6, and 36.9% boys *vs.* 16.0, 22.9, and 61.1% girls in Tanner stage I/II, III, and IV/V, respectively. Ages were similar across each sex and pubertal stage (Table 2).

BMD results

In unadjusted analyses, Tanner stage I/II girls had lower FN and TH BMD compared with boys, FN BMD was equal in Tanner stage III boys and girls yet lower at the TH region, and FN and TH BMD was lower in Tanner stage IV/V girls compared with boys (Table 3). After adjusting for height, fat mass, and lean mass, FN BMD was similar in both sexes at Tanner stage I/II but was now higher in mid- and late pubertal girls compared with boys (Table 4). A similar pattern was also observed for TH BMD (Table 4). To evaluate the net effect of puberty in boys and girls, BMD differences were analyzed between Tanner stage I/II and IV/V. In unadjusted analyses, the difference in FN BMD between early and late pubertal children was more marked in girls, and in adjusted analyses the difference between early and late pubertal children was greater in girls compared with boys (Table 5). A similar pattern of differences was also observed for TH BMD (Table 5).

TABLE 2. Age distribution by pubertal status

	Tanner stage		
	I+II	III	IV+V
Boys			
n	646	503	671
Age (yr)	13.85 (0.19)	13.83 (0.17)	13.84 (0.19)
Girls			
n	336	480	1278
Age (yr)	13.86 (0.19)	13.85 (0.19)	13.86 (0.20)

Descriptive statistics of age (years) by pubertal status, presented as means (SD). Pubertal status is defined by Tanner stages I–V.

Hip geometry

FNW was greater in boys compared with girls in early, mid-, and late pubertal children (Table 3 and Fig. 1). After adjusting for height, fat mass, and lean mass, FNW was still greater in boys compared with girls, but the difference was partially attenuated (Table 4 and Fig. 2). In terms of the overall effect of puberty, in unadjusted analyses, the difference in FNW between early and late pubertal children was more marked in boys, but after adjustment these differences were largely attenuated (Table 5). Similar results were obtained for CSA, with pronounced effects of sex and puberty observed in unadjusted analyses, which were largely, but not completely, attenuated in adjusted models.

CT was greater in early, mid-, and late pubertal boys compared with girls (Table 3 and Fig. 1). After adjustment for height, fat mass, and lean mass, CT was similar in early pubertal boys and girls but greater in mid- and late pubertal girls compared with boys (Table 4 and Fig. 2). In unadjusted analyses, the difference in CT between early and late pubertal children was greater in boys, and in contrast in adjusted analyses, the difference between early and late pubertal children was greater in girls (Table 5).

Hip strength

CSMI was higher in early, mid-, and late pubertal boys compared with girls (Table 3 and Fig. 1). After adjustment for fat mass, lean mass, and height, these sex differences were partially attenuated (Table 4 and Fig. 2). In unadjusted analyses, the difference in CSMI between early and late pubertal children was greater in boys compared with girls, and although the differences in CSMI between early and late pubertal children were largely attenuated by adjustment for fat mass, lean mass, and height, a small sex difference in favor of boys persisted (Table 5). Similar results were obtained for SM with the exception that in

TABLE 3. Unadjusted mean hip structural parameters by sex and Tanner stage

		Boys		Girls		Sex difference	Pub-sex
	Puberty	Mean (SD)	(95% CI)	Mean (SD)	(95% CI)	($P \leq$)	($P \leq$)
FN-BMD (g/cm^2)	I+II	0.93 (0.10)	(0.92, 0.94)	0.89 (0.11)	(0.88, 0.90)	0.0001	0.0001
	III	0.96 (0.10)	(0.95, 0.97)	0.96 (0.11)	(0.95, 0.97)	0.4707	
	IV+V	1.02 (0.12)	(1.01, 1.03)	1.01 (0.11)	(1.00, 1.02)	0.1058	
Total hip-BMD (g/cm^2)	I+II	0.95 (0.11)	(0.95, 0.96)	0.90 (0.11)	(0.89, 0.92)	0.0001	0.0001
	III	0.99 (0.11)	(0.98, 1.00)	0.97 (0.11)	(0.96, 0.99)	0.1057	
	IV+V	1.05 (0.13)	(1.04, 1.06)	1.02 (0.11)	(1.01, 1.02)	0.0001	
Minimum width at neck (mm)	I+II	29.05 (2.52)	(28.88, 29.23)	27.13 (2.19)	(26.88, 27.37)	0.0001	0.0001
	III	29.89 (2.57)	(29.69, 30.09)	27.54 (2.22)	(27.34, 27.75)	0.0001	
	IV+V	31.72 (2.37)	(31.55, 31.89)	27.96 (2.04)	(27.84, 28.09)	0.0001	
CSA (cm^2)	I+II	0.24 (0.04)	(0.24, 0.25)	0.22 (0.04)	(0.21, 0.22)	0.0001	0.0001
	III	0.26 (0.04)	(0.26, 0.27)	0.24 (0.04)	(0.23, 0.24)	0.0001	
	IV+V	0.30 (0.05)	(0.30, 0.30)	0.24 (0.03)	(0.24, 0.25)	0.0001	
CT (mm)	I+II	1.69 (0.19)	(1.68, 1.71)	1.61 (0.22)	(1.59, 1.63)	0.0001	0.0001
	III	1.78 (0.21)	(1.76, 1.80)	1.76 (0.23)	(1.74, 1.78)	0.1281	
	IV+V	1.93 (0.25)	(1.91, 1.94)	1.78 (0.22)	(1.77, 1.79)	0.0001	
CSMI (cm^4)	I+II	1.51 (0.44)	(1.47, 1.54)	1.16 (0.34)	(1.11, 1.20)	0.0001	0.0001
	III	1.70 (0.51)	(1.66, 1.74)	1.33 (0.39)	(1.29, 1.36)	0.0001	
	IV+V	2.16 (0.57)	(2.12, 2.19)	1.40 (0.35)	(1.37, 1.42)	0.0001	
Minimum SM (cm^3)	I+II	0.96 (0.21)	(0.94, 0.98)	0.80 (0.19)	(0.78, 0.82)	0.0001	0.0001
	III	1.06 (0.23)	(1.04, 1.08)	0.91 (0.21)	(0.89, 0.93)	0.0001	
	IV+V	1.28 (0.27)	(1.26, 1.30)	0.95 (0.19)	(0.94, 0.96)	0.0001	
Maximum BR	I+II	9.25 (1.32)	(9.14, 9.35)	9.02 (1.35)	(8.88, 9.16)	0.0118	0.0001
	III	9.01 (1.31)	(8.90, 9.13)	8.33 (1.36)	(8.21, 8.45)	0.0001	
	IV+V	8.82 (1.35)	(8.72, 8.92)	8.31 (1.30)	(8.23, 8.38)	0.0001	

Unadjusted mean values, SD, and 95% confidence intervals (CIs) of hip structural components by sex and pubertal status in children at Tanner stage I+II, III, and IV+V. *P* values are shown for the pairwise sex difference at pubertal stages I+II, III, and IV+V (Sex difference), and the puberty-sex interaction term as analyzed across all three pubertal stage groupings (Pub-sex).

adjusted analyses, no sex difference was observed in comparing results between early and late pubertal children (Table 5).

BR was lower in early, mid-, and late pubertal girls compared with boys (Table 3 and Fig. 1). In adjusted analyses the observed sex differences in BR were greater than in unadjusted analyses (Table 4 and Fig. 2). In unadjusted analyses, BR was lower in late *vs.* early pubertal children, this difference being greater in girls. After adjustment, this difference partially attenuated in boys but not girls, with the result that differences in BR between early and late pubertal children according to sex became greater (Table 5).

Discussion

In this cross-sectional analysis of sexual dimorphism of hip structure in 3914 peripubertal children, important sex differences were seen in hip geometry. For example, boys had wider FNs and thicker cortices, resulting in greater CSA as well as a higher bending strength reflected by CSMI, which was approximately 35% greater compared with girls. Sex differences in FNW and CSMI were greater in late *vs.* early pubertal children, but this effect was largely attenuated by adjusting for height, fat mass, and lean mass. Profound changes in fat mass, and lean mass take place during puberty, which differ significantly according to sex, and skeletal development is thought to be closely related to lean mass in particular (14, 15). Therefore, the increase in sex differences in bone size after puberty that we observed may have arisen from functional adaptation of the skeleton to associated changes in body composition. Consistent with this possibility, Forwood *et al.* (1), who examined DXA-derived indices of hip structure in a longitudinal study of 70 boys and 68 girls, likewise found that observed sex differences in CSA, FNW, and SM were attenuated by adjusting for height and lean mass. A strong association between changes in muscle mass and sex differences in cortical bone size at puberty has also been observed at the femur, tibia, and forearm (9, 10, 16). Evidence from a prospective study of changes in hip structure of 83 boys and girls that peak accrual of lean mass during puberty precedes that of SM is consistent with the possibility that such bone changes during puberty occur secondary to increased muscle forces (17). On the other hand, in a recent prospective study of tibial structure across puberty as assessed by pQCT in girls, growth in muscle cross-sectional area peaked 1 yr after that of tibial outer dimensions (18).

Our observation that parameters related to FN size and bending strength were greater in early pubertal boys compared with girls in unadjusted analyses is also consistent

TABLE 4. Adjusted mean hip structural parameters by sex and Tanner stage

	Puberty	Boys Mean (95% CI)	Girls Mean (95% CI)	Sex difference ($P \leq$)	Pub-sex ($P \leq$)
FN-BMD (g/cm^2)	I+II	0.95 (0.94, 0.96)	0.95 (0.94, 0.96)	0.8849	0.001[a]
	III	0.95 (0.94, 0.95)	0.99 (0.98, 1.00)	0.0001	
	IV+V	0.93 (0.93, 0.94)	1.03 (1.02, 1.03)	0.0001	
Total hip-BMD (g/cm^2)	I+II	0.97 (0.96, 0.98)	0.96 (0.95, 0.98)	0.7126	0.001[a]
	III	0.96 (0.96, 0.97)	1.01 (1.01, 1.02)	0.0001	
	IV+V	0.96 (0.95, 0.97)	1.04 (1.04, 1.05)	0.0001	
FNW (mm)	I+II	29.72 (29.60, 29.84)	28.38 (28.22, 28.54)	0.0010	0.001[c]
	III	29.55 (29.42, 29.69)	28.22 (28.08, 28.35)	0.0010	0.139[b]
	IV+V	29.63 (29.50, 29.76)	28.29 (28.20, 28.39)	0.0010	
CSA (cm^2)	I+II	0.25 (0.25, 0.25)	0.24 (0.24, 0.24)	0.0001	0.001[a]
	III	0.25 (0.25, 0.26)	0.25 (0.25, 0.26)	0.3528	
	IV+V	0.26 (0.26, 0.26)	0.25 (0.25, 0.25)	0.0001	
CT (mm)	I+II	1.72 (1.71, 1.74)	1.71 (1.69, 1.73)	0.3682	0.001[a]
	III	1.75 (1.73, 1.77)	1.82 (1.81, 1.84)	0.0001	
	IV+V	1.78 (1.76, 1.80)	1.81 (1.80, 1.83)	0.0030	
CSMI (cm^4)	I+II	1.63 (1.60, 1.65)	1.46 (1.43, 1.49)	0.0001	0.001[a]
	III	1.61 (1.59, 1.64)	1.49 (1.46, 1.52)	0.0001	
	IV+V	1.70 (1.67, 1.73)	1.48 (1.46, 1.49)	0.0001	
Minimum SM (cm^3)	I+II	1.02 (1.01, 1.03)	0.95 (0.93, 0.97)	0.0001	0.001[a]
	III	1.02 (1.00, 1.03)	0.99 (0.98, 1.01)	0.0136	
	IV+V	1.06 (1.04, 1.07)	0.99 (0.98, 1.00)	0.0001	
Maximum BR	I+II	9.28 (9.17, 9.38)	8.88 (8.73, 9.02)	0.0001	0.001[a]
	III	9.08 (8.96, 9.19)	8.20 (8.08, 8.32)	0.0001	
	IV+V	9.01 (8.88, 9.13)	8.22 (8.14, 8.30)	0.0001	

Mean values and 95% confidence intervals (CIs) of hip structural components by sex and pubertal status in children at Tanner stage I+II, III, and IV+V, adjusted for fat mass, lean mass, and height. *P* values are shown for the pairwise sex difference at pubertal stages I+II, III, and IV+V (Sex difference) and the puberty-sex interaction term as analyzed across all three pubertal stage groupings (Pub-sex).

[a] For FNW, *P* value for puberty-sex interaction.

[b] For FNW, *P* value for puberty-sex interaction term was greater than 0.05, so *P* values under the Pub-sex column instead show overall and puberty effects.

[c] For FNW, *P* value for puberty-sex interaction was less than 0.05, so *P* value under the Pub-Sex column instead shows overall sex effect.

with findings from Forwood *et al.* (1). In the present study, sex differences before puberty were partly attenuated by adjusting for height fat and lean mass but were still present. These findings suggest that the wider FNs of boys compared with girls cannot be accounted for entirely by puberty and/or functional adaptation to differences in fat or lean mass. However, changes in hormonal milieu, which precede clinical puberty, may explain a proportion

TABLE 5. Differences between high and low pubertal stage by sex

		Unadjusted			*P* (≤)	Adjusted			*P* (≤)
	Sex	Δ	(95% CI)	*P* (≤)	Pub-sex	Δ	(95% CI)	*P* (≤)	Pub-sex
FN-BMD (g/cm^2)	Male	0.088	(0.076, 0.100)	0.001	0.001	−0.013	(−0.025, −0.001)	0.039	0.001
	Female	0.118	(0.105, 0.132)	0.001		0.080	(0.068, 0.092)	0.001	
Total-BMD (g/cm^2)	Male	0.095	(0.083, 0.108)	0.001	0.044	−0.011	(−0.023, 0.002)	0.095	0.001
	Female	0.114	(0.100, 0.128)	0.001		0.078	(0.066, 0.090)	0.001	
FNW (mm)	Male	2.668	(2.421, 2.915)	0.001	0.001	0.045	(−0.176, 0.266)	0.691	0.116
	Female	0.834	(0.560, 1.109)	0.001		−0.194	(−0.409, 0.022)	0.078	
CSA (cm^2)	Male	0.058	(0.054, 0.062)	0.001	0.001	0.009	(0.005, 0.012)	0.001	0.715
	Female	0.029	(0.024, 0.033)	0.001		0.010	(0.006, 0.013)	0.001	
CT (mm)	Male	0.232	(0.208, 0.256)	0.001	0.001	0.052	(0.027, 0.076)	0.001	0.004
	Female	0.171	(0.144, 0.197)	0.001		0.101	(0.077, 0.125)	0.001	
CSMI (cm^4)	Male	0.653	(0.605, 0.700)	0.001	0.001	0.074	(0.036, 0.111)	0.001	0.025
	Female	0.240	(0.187, 0.292)	0.001		0.016	(−0.021, 0.052)	0.396	
Minimum SM (cm^3)	Male	0.319	(0.296, 0.342)	0.001	0.001	0.039	(0.020, 0.058)	0.001	0.871
	Female	0.151	(0.125, 0.177)	0.001		0.041	(0.023, 0.059)	0.001	
Maximum BR	Male	−0.425	(−0.568, −0.282)	0.001	0.008	−0.269	(−0.432, −0.105)	0.001	0.001
	Female	−0.714	(−0.874, −0.555)	0.001		−0.654	(−0.813, −0.495)	0.001	

Δ Represents the difference between means of hip structural components for Tanner stage I/II and IV/V and 95% confidence intervals (CIs), by sex. Results are shown for unadjusted and adjusted (for height, fat and lean mass) hip variables. *P* values are shown for the difference between Tanner stages I/II and IV/V in boys and girls separately and for the difference between the extent of gain between males and females based on the puberty-sex interaction term (Pub-sex).

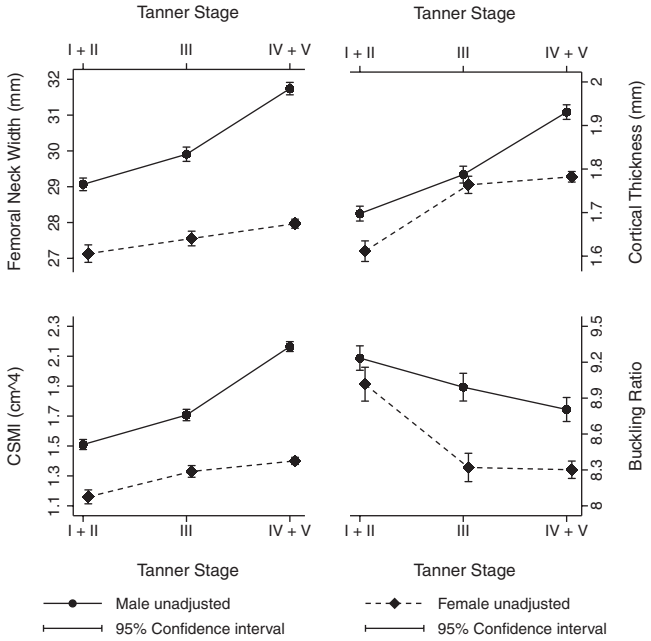

FIG. 1. Mean and 95% confidence intervals of unadjusted hip structural parameters in boys (n = 1820) and girls (n = 2094) stratified by pubertal status.

of the sex differences observed. Consistent with the present findings, we recently reported that humeral width relative to its length is greater in prepubertal boys compared with girls in this cohort (11). Similarly, previous radiogrametry studies observed wider bones in boys compared with girls at all stages of development (5, 19).

Whereas CSMI was greater in boys, we found that BR was lower in girls. Unlike CSMI, the sex differences in BR

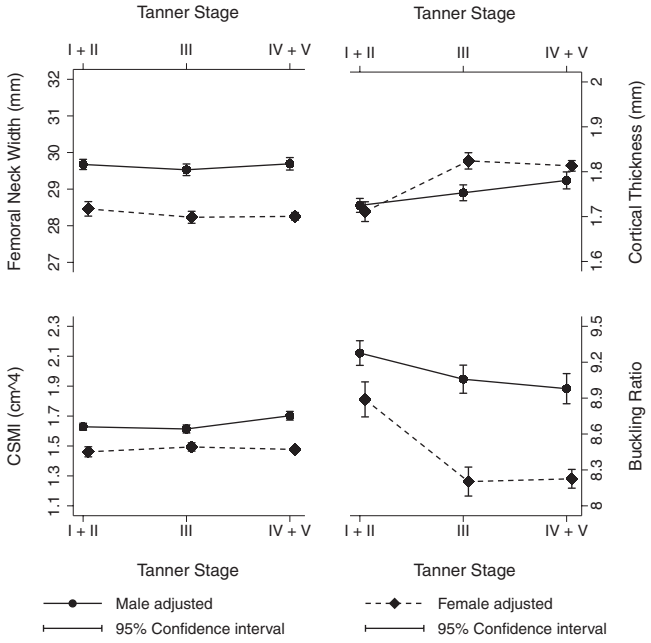

FIG. 2. Mean and 95% confidence intervals of height and fat and lean mass adjusted hip structural parameters in boys (n = 1820) and girls (n = 2094) stratified by pubertal status.

was small in early pubertal boys and girls but became more pronounced as puberty progressed. These differences in BR reflect the fact that in boys, puberty leads to a greater increase in bone diameter relative to CT. Interestingly, these differences were more marked in models adjusted for height and lean and fat mass, in which the difference in CT and BR between early and late puberty was approximately twice as great in girls compared with boys. This finding of greater sex differences in adjusted models suggests that maturational status affects bone development independently of growth, possibly reflecting a direct influence of sex steroids on cellular activity of the skeleton.

We are not aware of any previous study reporting sex differences in BR in childhood at the hip or any other skeletal site. Because BR represents a ratio between FNW and CT, the lower BR in girls is at least partly accounted for by sex differences in periosteal growth. In addition, slower endocortical expansion in girls may have contributed to sex differences in BR that we observed, reflecting differences in the rate of endocortical remodeling and/or endosteal apposition. Consistent with this possibility, a previous radiogrametry study of metacarpal bones revealed evidence of endosteal apposition in pubertal girls (5). However, equivalent changes were not observed in a previous pQCT study of the midtibia (3), possibly reflecting the fact that endocortical changes during puberty are site specific. As for possible influences of sex steroids on endosteal apposition, our findings are also consistent with evidence that rising estrogen levels in pubertal girls have been found to correlate with endosteal apposition as assessed by tibial pQCT (7). This effect of rising estrogen levels in late pubertal girls on endocortical surfaces appears to be mirrored by gains in trabecular bone mass, as reflected by equivalent associations observed in ALSPAC between sex, puberty, and size-corrected spinal BMD (20). Finally, constitutional factors might exist that affect both the age of onset of puberty and hip structure, so associations that we observed between hip structure and pubertal stage are not necessarily a direct result of hormonal differences.

Although we observed that bending strength was clearly higher in late pubertal boys, BR was lower in late pubertal girls implying greater cortical stability, suggesting that greater endocortical apposition in late and postpubertal girls due to increased estrogen exposure can compensate biomechanically for their lower periosteal apposition compared with boys. However, although BR has been found to be superior to measures of bending strength in predicting hip fractures in the elderly, cortical instability may be less important in determining skeletal strength in children, in whom intact internal trabecular structure is expected to make an important contribution to resisting buckling (21, 22). Nonetheless, in analyses of the rela-

tionship between hip geometry and fracture risk in ALSPAC, CSMI and BR showed equivalent albeit weak associations with past history of any fracture (results not shown). Although these results suggest that hip strength around the time of puberty may be equivalent in both sexes, presumably, estrogen depletion after the menopause results in reversal of these gains in endocortical bone during puberty in girls, suggesting that the high fracture risk in elderly women compared with men (23) has its antecedents in these differences in bone structure, which appear to be established during puberty if not before (24).

In the present study, we used secondary sex characteristics as assessed by Tanner stage questionnaire to compare how maturational changes at puberty affect hip structure in boys and girls. This approach is well suited to analyzing sex differences in hip structure related to sex steroid exposure, as exemplified by the greater reduction in endosteal expansion in peripubertal girls that we observed, assumed to be related to rising estrogen levels. However, one limitation of analyzing sex differences according to puberty is that children in distinct Tanner stages may differ in other important ways that we have not been able to adjust for. In addition, when comparing boys and girls of the same age, even after adjusting for Tanner stage, girls are likely to be more advanced in terms of their skeletal maturation, as suggested by observations that girls reach peak height velocity at a slightly earlier Tanner stage as compared with boys (25).

A further weakness of this study is our use of DXA-derived measures of bone structure, which has limitations in predicting three-dimensional properties such as CSMI from two-dimensional projected DXA images (13). Whereas the same assumption for the relative proportion of trabecular to cortical bone at the femoral neck was used as in adults, bone mineralization has previously been found to vary in relation to both sex and maturational status, which we attempted to correct for based on previously published literature. However, the values used were derived from a distinct population that was approximately 2 yr younger than ours (6) and obtained at the tibia rather than the hip. In addition, because this data analysis is cross-sectional, within-individual changes in hip structure throughout puberty may not be the same as comparing individuals of the same age at different pubertal stages.

In conclusion, on examining hip structure in a large cohort of peripubertal children, we found evidence of sexual dimorphism in hip development, characterized by greater CSMI in boys but lower BR in girls. The former differences appeared to result from more rapid periosteal bone growth in boys established in early childhood and subsequently increased throughout puberty. The lower BR in girls reflected their narrower FNs relative to CT, which we attribute to slower rates of both periosteal and endocortical expansion. Although sex differences in bending differences were mainly accounted for by those in height and fat and lean mass, those in BR were largely independent of these factors, suggesting that other factors such as sex steroids make an important contribution to sexual dimorphism of hip structure around the time of puberty.

Acknowledgments

We are extremely grateful to all the families who took part in this study; the midwives for their help in recruiting them; and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists, and nurses. This publication is the work of the authors who serve as guarantors for the contents of this paper. The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Address all correspondence and requests for reprints to: Professor J. H. Tobias, Academic Rheumatology, Avon Orthopaedic Centre, Southmead Hospital, Bristol BS10 5NB, United Kingdom. E-mail: jon.tobias@bristol.ac.uk.

The U.K. Medical Research Council, the Wellcome Trust, and the University of Bristol provide core support for ALSPAC. Salary support for A.S. is provided by Wellcome Trust Grant 079960. Hip DXA scans were funded by a grant from the Vivienne and Sam Cohen Charitable Trust.

Disclosure Summary: The authors have nothing to disclose.

References

1. **Forwood MR, Bailey DA, Beck TJ, Mirwald RL, Baxter-Jones AD, Uusi-Rasi K** 2004 Sexual dimorphism of the femoral neck during the adolescent growth spurt: a structural analysis. Bone 35:973–981
2. **Högler W, Blimkie CJ, Cowell CT, Kemp AF, Briody J, Wiebe P, Farpour-Lambert N, Duncan CS, Woodhead HJ** 2003 A comparison of bone geometry and cortical density at the mid-femur between prepuberty and young adulthood using magnetic resonance imaging. Bone 33:771–778
3. **Kontulainen SA, Macdonald HM, Khan KM, McKay HA** 2005 Examining bone surfaces across puberty: a 20-month pQCT trial. J Bone Miner Res 20:1202–1207
4. **Nieves JW, Formica C, Ruffing J, Zion M, Garrett P, Lindsay R, Cosman F** 2005 Males have larger skeletal size and bone mass than females, despite comparable body size. J Bone Miner Res 20:529–535
5. **Garn SM** 1972 The course of bone gain and the phases of bone loss. Orthop Clin North Am 3:503–520
6. **Kontulainen SA, Macdonald HM, McKay HA** 2006 Change in cortical bone density and its distribution differs between boys and girls during puberty. J Clin Endocrinol Metab 91:2555–2561
7. **Wang Q, Alén M, Nicholson PH, Halleen JM, Alatalo SL, Ohlsson C, Suominen H, Cheng S** 2006 Differential effects of sex hormones on peri- and endocortical bone surfaces in pubertal girls. J Clin Endocrinol Metab 91:277–282
8. **Foley S, Quinn S, Jones G** 2009 Tracking of bone mass from child-

hood to adolescence and factors that predict deviation from tracking. Bone 44:752–757
9. **Fricke O, Sumnik Z, Tutlewski B, Stabrey A, Remer T, Schoenau E** 2008 Local body composition is associated with gender differences of bone development at the forearm in puberty. Hormone Res 70:105–111
10. **Macdonald H, Kontulainen S, Petit M, Janssen P, McKay H** 2006 Bone strength and its determinants in pre- and early pubertal boys and girls. Bone 39:598–608
11. **Clark EM, Ness AR, Tobias JH** 2007 Gender differences in the ratio between humerus width and length are established prior to puberty. Osteoporos Int 18:463–470
12. **Golding J, Pembrey M, Jones R, ALSPAC Study Team** 2001 ALSPAC—the Avon Longitudinal Study of Parents and Children. I. Study methodology. Paediatr Perinat Epidemiol 25:74–87
13. **Prevrhal S, Shepherd JA, Faulkner KG, Gaither KW, Black DM, Lang TF** 2008 Comparison of DXA hip structural analysis with volumetric QCT. J Clin Densitom 11:232–236
14. **Rauch F, Bailey DA, Baxter-Jones A, Mirwald R, Faulkner R** 2004 The 'muscle-bone unit' during the pubertal growth spurt. Bone 34:771–775
15. **Schoenau E, Frost HM** 2002 The "muscle-bone unit" in children and adolescents. Calcif Tissue Int 70:405–407
16. **Högler W, Blimkie CJ, Cowell CT, Inglis D, Rauch F, Kemp AF, Wiebe P, Duncan CS, Farpour-Lambert N, Woodhead HJ** 2008 Sex-specific developmental changes in muscle size and bone geometry at the femoral shaft. Bone 42:982–989
17. **Jackowski SA, Faulkner RA, Farthing JP, Kontulainen SA, Beck TJ, Baxter-Jones AD** 2009 Peak lean tissue mass accrual precedes changes in bone strength indices at the proximal femur during the pubertal growth spurt. Bone 44:1186–1190
18. **Xu L, Nicholson P, Wang Q, Alén M, Cheng S** 2009 Bone and muscle development during puberty in girls: a seven-year longitudinal study. J Bone Miner Res 24:1693–1698
19. **Virtama P, Helela T** 1969 Radiographic measurements of cortical bone: variations in a normal population between 1 and 90 years of age. Acta Radiol 293(Suppl):S1–S110
20. **Tobias JH, Steer CD, Vilarino-Güell C, Brown MA** 2007 Estrogen receptor α regulates area-adjusted bone mineral content in late pubertal girls. J Clin Endocrinol Metab 92:641–647
21. **Kaptoge S, Beck TJ, Reeve J, Stone KL, Hillier TA, Cauley JA, Cummings SR** 2008 Prediction of incident hip fracture risk by femur geometry variables measured by hip structural analysis in the study of osteoporotic fractures. J Bone Miner Res 23:1892–1904
22. **Rivadeneira F, Zillikens MC, De Laet CE, Hofman A, Uitterlinden AG, Beck TJ, Pols HA** 2007 Femoral neck BMD is a strong predictor of hip fracture susceptibility in elderly men and women because it detects cortical bone instability: the Rotterdam Study. J Bone Miner Res 22:1781–1790
23. **Cooper C** 1989 Osteoporosis—an epidemiological perspective: a review. J Royal Soc Med 82:753–757
24. **Wang Q, Cheng S, Alén M, Seeman E** 2009 Bone's structural diversity in adult females is established before puberty. J Clin Endocrinol Metab 94:1555–1561
25. **Sherar LB, Baxter-Jones AD, Mirwald RL** 2004 Limitations to the use of secondary sex characteristics for gender comparisons. Ann Hum Biol 31:586–593