Ultrasonographic Measurements of Joint Cartilage Thickness in Healthy Children: Age- and Sex-Related Standard Reference Values

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ABSTRACT. ***Objective.*** Loss of joint cartilage may be an early feature of chronic inflammatory joint diseases like juvenile idiopathic arthritis (JIA). Conventional radiography usually detects only late changes such as joint space narrowing and bone erosion rather than early inflammatory changes. Joint cartilage is easily visualized with high-frequency ultrasonography (US), but age- and gender-related normal standard reference values should be established before US measurement of cartilage thickness becomes standard procedure in the clinic.

Methods. A cross-sectional study of bilateral grey-scale US cartilage thickness of the knee, ankle, wrist, and second metacarpophalangeal (MCP) and second proximal interphalangeal (PIP) joints was performed in 394 (215 boys/179 girls) healthy Danish Caucasian children aged between 7 and 16 years.

Results. Cartilage thickness differed significantly between sexes ($p < 0.001$ for all joints), boys having thicker cartilage than girls. Cartilage thickness clearly decreased with increasing age in both sexes. A formula for calculating sex-specific cartilage thickness at different ages in childhood is suggested. No difference between the right and left side of the investigated joints was observed.

Conclusion. Using US, we established age- and sex-related normal reference intervals for cartilage thickness of the knee, ankle, wrist, and MCP and PIP joints in 7- to 16-year-old children, and designed a formula for calculating hyaline cartilage thickness in all age groups throughout childhood. (J Rheumatol First Release September 1 2010; doi:10.3899/jrheum.100101)

Key Indexing Terms:
ULTRASONOGRAPHY CARTILAGE REFERENCE INTERVAL
CHILDREN JUVENILE IDIOPATHIC ARTHRITIS

Hyaline cartilage covering the subchondral bone enables smooth joint mobility with only discrete friction, and in weight-bearing joints it absorbs the forces of compression[1,2]. Throughout growth, the cellular concentration becomes progressively less, and in the adult hyaline articular cartilage, chondrocytes constitute less than 2% of the total volume, with more than 70% composed of water[3].

Magnetic resonance imaging (MRI) has been described as a reliable and reproducible tool for assessing the thickness and volume of articular cartilage *in vivo*[4,5], and age-related changes of the articular cartilage of the knee have been reported[6,7]. With use of high-frequency ultrasonography (US), joint cartilage, due to its high content of water, is easily visualized as an anechoic structure[8,9,10,11]. Early features of cartilage erosion and thinning can be detected as a blurring and obliteration of the normally sharp margins of the cartilage surface[12]. Thus, consecutive, standardized US assessments of cartilage thickness in target joints could be an important supplement to clinical monitoring of the disease and adjustment of treatment in patients with juvenile idiopathic arthritis (JIA).

In previous studies we validated US measurement of joint cartilage thickness in a pediatric setting, and variability was found to be low[10]. We also found a good level of agreement between cartilage thickness measured by MRI and US[11]. However, use of MRI for measuring cartilage thickness in patients with JIA is reported to be hampered by the absence of normal age-related reference values[13,14].

Unlike rheumatoid arthritis (RA) in adults, subchondral bone erosions are not frequently observed in JIA. On the other hand, degradation of cartilage could be anticipated in JIA since joint space narrowing is a result of longterm duration of disease activity in JIA[15,16].

Articular cartilaginous changes during the disease course

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in JIA are not well described. The previous absence of noninvasive, accurate means of articular cartilage estimation partly explains why such knowledge has been limited. We aimed to establish standard age- and gender-related US reference values for joint cartilage thickness in healthy children.

MATERIALS AND METHODS

Joint cartilage thickness was measured by US in the knee, ankle, wrist, second metacarpophalangeal (MCP), and second proximal interphalangeal (PIP) joints on both the right and the left extremity in 394 healthy Caucasian children. A total of 3940 joints were investigated.

The children were recruited from Risskov municipal school, Aarhus, Denmark. We invited all 758 registered pupils to participate in the study. Informed consent was obtained from 422 pupils and their parents.

A total of 419 pupils met inclusion criteria, as ascertained by questionnaire. The criteria were age between 6 and 16 years; no history of joint trauma, swelling, tenderness, or previous surgical intervention in the joints; no known chronic diseases, including musculoskeletal disease; and no intake of medicine influencing growth or bone metabolism, including corticosteroids. The children underwent clinical evaluation and joint examination to assure clinical normality of their joints before the US investigation. No sport activities were allowed on the day of examination. Twenty-three children were not present at school on the examination days and 3 children declined the US examination. Only one child aged less than 7 years was examined and the child's data were excluded from the analysis. Among the 393 children, 214 were boys and 179 girls.

Ultrasonography. All US examinations and measurements of cartilage thickness were based on a European League Against Rheumatism (EULAR) standard scan[17] and the anatomical positions of the US probes were as described[10,11] (Table 1). The investigations were performed by one investigator experienced in musculoskeletal US (AHS). We used conventional B-mode on a real-time EUB-6500 CFM scanner (Hitachi, Tokyo, Japan), equipped with a linear 6–13 MHz transducer (d-THI, frequency 14 MHz, dynamic range 65).

The pressure on the probe was adjusted to a level just below visible deformation on the anatomical structure. Scanner settings were uniform for all measurements. We performed 2 cartilage thickness measurements for each joint of the right- and left-side extremities. The US image acquisition time was about 20–30 minutes for most of the children, for some of the youngest up to 40 minutes. All measurements were obtained blinded, and US images and cartilage thickness measurements for each child were stored on DVD for later entry into a database.

Knee and ankle joints. For cartilage thickness measurement of the knee, the child was placed in a supine position with the knee maximally flexed, and a suprapatellar transverse scan was performed according to EULAR guidelines[17]. Cartilage thickness was measured corresponding to the midline of the intercondylar notch. With the child still in a supine position, the ankle joint was examined with the plantar surface of the foot resting on the examination bed (90° knee flexion), and an anterior longitudinal scan between the first and second metatarsal bone was obtained. The anterior demarcation of the cartilage on the medial part of the dome of the talus was identified. From this point, a distance of 5 mm in the proximal direction was measured and the cartilage thickness was measured perpendicularly to the bone surface as described[10,11].

Wrist and finger joints. Wrist cartilage thickness was measured with the child in supine position and with both hands palm-side down on the examination bed and placed to the side of the body. A dorsal, longitudinal scan of the articulating surface of the radial and scaphoid bones was obtained[17].

With the child still in the same position, the cartilage thickness of the second MCP and the second PIP joints was obtained from a transversal dorsal scan with the MCP and PIP joints flexed 90°[17].

Table 1. Cartilage thickness in 8- and 15-year-old boys and girls, shown as mean (mm), 95% confidence interval (CI) and 95% predicted interval (PI).

Joint, Age Group, 8- and 15-yr-old	Mean, mm	95% CI	95% PI
		Boys	
Knee			
8	3.96	3.86 to 4.06	3.14 to 4.78
15	3.47	3.38 to 3.56	2.65 to 4.28
Ankle			
8	1.14	1.09 to 1.18	1.10 to 1.18
15	0.88	0.83 to 0.92	0.84 to 0.92
Wrist			
8	2.00	1.91 to 2.09	1.95 to 2.04
15	1.18	1.10 to 1.26	1.14 to 1.23
MCP			
8	1.45	1.40 to 1.49	1.41 to 1.48
15	0.71	0.67 to 0.75	0.67 to 0.74
PIP			
8	0.89	0.86 to 0.92	0.85 to 0.93
15	0.59	0.56 to 0.62	0.55 to 0.63
		Girls	
Knee			
8	3.60	3.50 to 3.71	2.71 to 4.50
15	2.87	2.74 to 3.00	1.98 to 3.77
Ankle			
8	0.99	0.96 to 1.03	0.67 to 1.32
15	0.78	0.73 to 0.83	0.46 to 1.10
Wrist			
8	1.71	1.63 to 1.79	1.05 to 2.37
15	0.96	0.86 to 1.05	0.30 to 1.62
MCP			
8	112	1.09 to 1.16	0.83 to 1.42
15	0.53	0.48 to 0.57	0.23 to 0.82
PIP			
8	0.80	0.77 to 0.82	0.58 to 1.01
15	0.44	0.40 to 0.47	0.22 to 0.65

Statistical analysis. The association between joint cartilage thickness and age was analyzed by linear regression using the average (of right and left joint) thickness as dependent variable and age as independent variable. Boys and girls were first analyzed separately. In order to compare the slopes, they were then analyzed together with gender and the interaction between gender and age serving as additional, independent variables. At the end, an analysis was performed without the interaction. The results are described by the estimated slopes [with a 95% confidence interval (CI)] and by the estimated thickness for both an 8-year-old and a 15-year-old child [with a 95% CI and 95% prediction interval (PI)].

The correlations between the residuals (the deviation between the estimated lines and the observed thickness) are calculated in order to investigate whether the joint thickness correlates with age. Random data variation is described by the standard deviation of the means: SD_{line} and by the standard deviation within a child SD_{within}, i.e., variation between right and left.

Significance was set at 5% ($p < 0.05$) in all calculations. All statistics were performed using the Stata version 10 statistical package.

Ethics. Our study was conducted in accord with the Helsinki II Declaration and approved by the local Ethical Committee. Prior informed consent was obtained from all parents and children. On the day of examination, confirmation of participation was sought, and if the child declined to participate, this was fully accepted.

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RESULTS

Figures 1 and 2 show mean cartilage thickness results with 95% CI and predicted 95% intervals (PI). Values within the predicted 95% CI serve as standard reference values.

Table 1 shows the cartilage thickness for boys and girls aged 8 and 15 years to illustrate the difference in cartilage thickness between healthy children at each end of the age interval studied. All examined joints exhibited a statistically significant difference ($p < 0.001$ for all joints) in cartilage thickness between the sexes, boys having thicker cartilage than girls regardless of age (Table 2). In all examined joints, the cartilage thickness decreased with increasing age, regardless of gender (Table 3). An analysis using the natural, logarithmically transformed thickness as dependent variable was also performed, but the estimated thickness in this model was almost the same as in the previous model in the range from 7 to 16 years. The only difference in the 2 models was that the prediction interval narrows because the thickness decreases and because the random variation in this model is relative (Tables 3A and 3B).

No difference was observed between the right and left side of the investigated joints (Table 4).

At the level of an individual child, a boy as well as a girl, a positive correlation was observed between the thickness of cartilage measured in each of the various joints (knee, ankle, wrist, and finger joint; data not shown). Calculation of cartilage thickness at other ages than those investigated here is possible using the formula below. Given the estimate of the thickness y_8 for an 8-year-old child, the slope ß and the standard deviation of the residual SD_{line}, an estimate of the thickness yx for a x-year-old child can be calculated as: $y_x = y_8 + ß*(x - 8)$; and a 95% PI can be calculated as: $y_8 + ß*(x - 8) \pm 1.96*SD_{line}$.

Since the number of boys and girls is large and this uncertainty of the estimated line is small compared to SD_{line}, the uncertainty of the estimated line has not been taken into account in the formula above. A 95% PI for the differences between the thickness of the right and left joint of a child can be calculated as: $\pm 2.77*SD_{within}$ (Table 4).

Assuming common slopes for boys and girls, the esti-

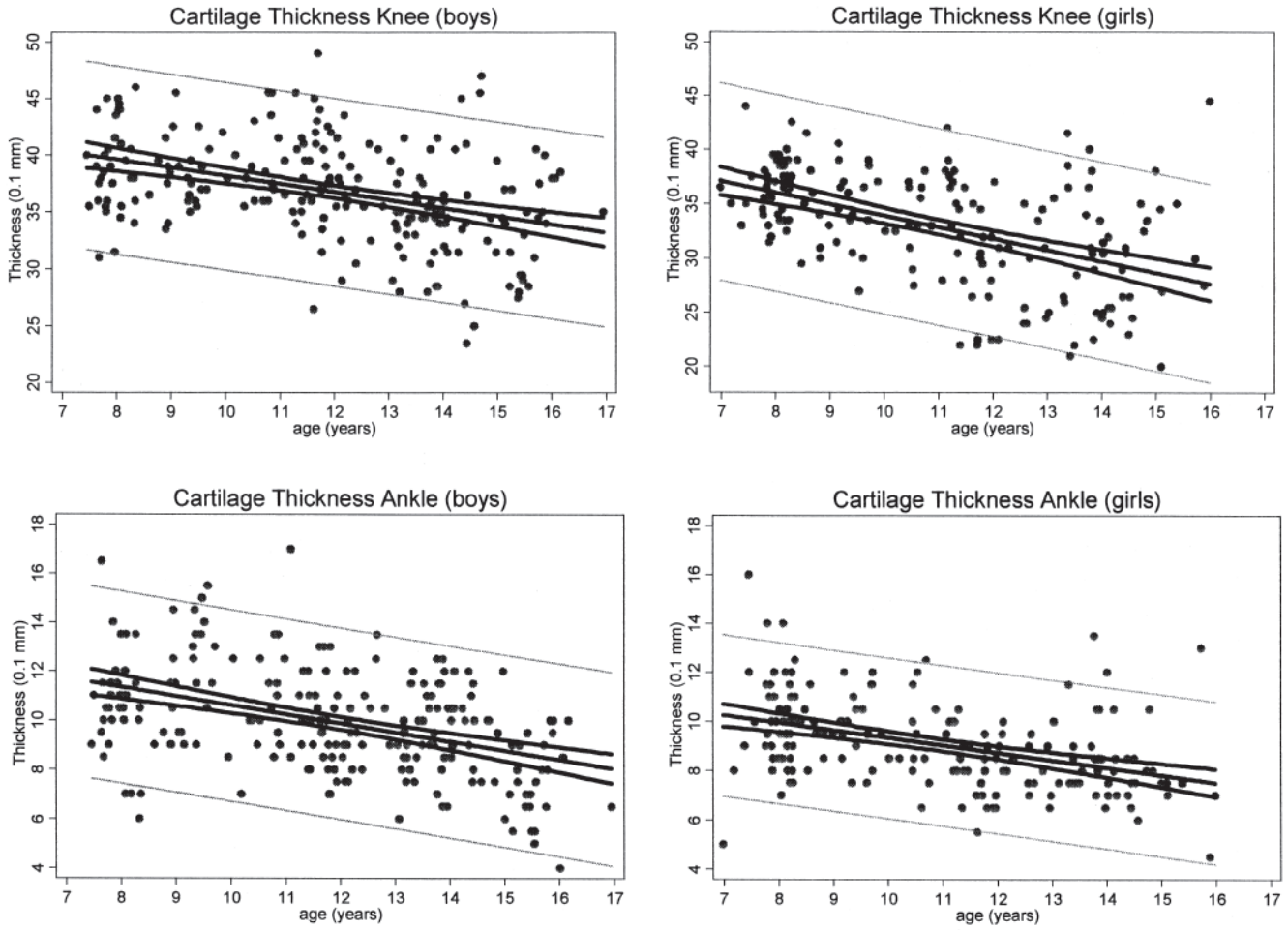

Figure 1. Cartilage thickness measures in the knees and ankles of healthy boys and girls. Mean cartilage thickness along with 95% confidence interval (3 solid black lines, mean is the solid center line) and predicted 95% confidence interval (grey lines).

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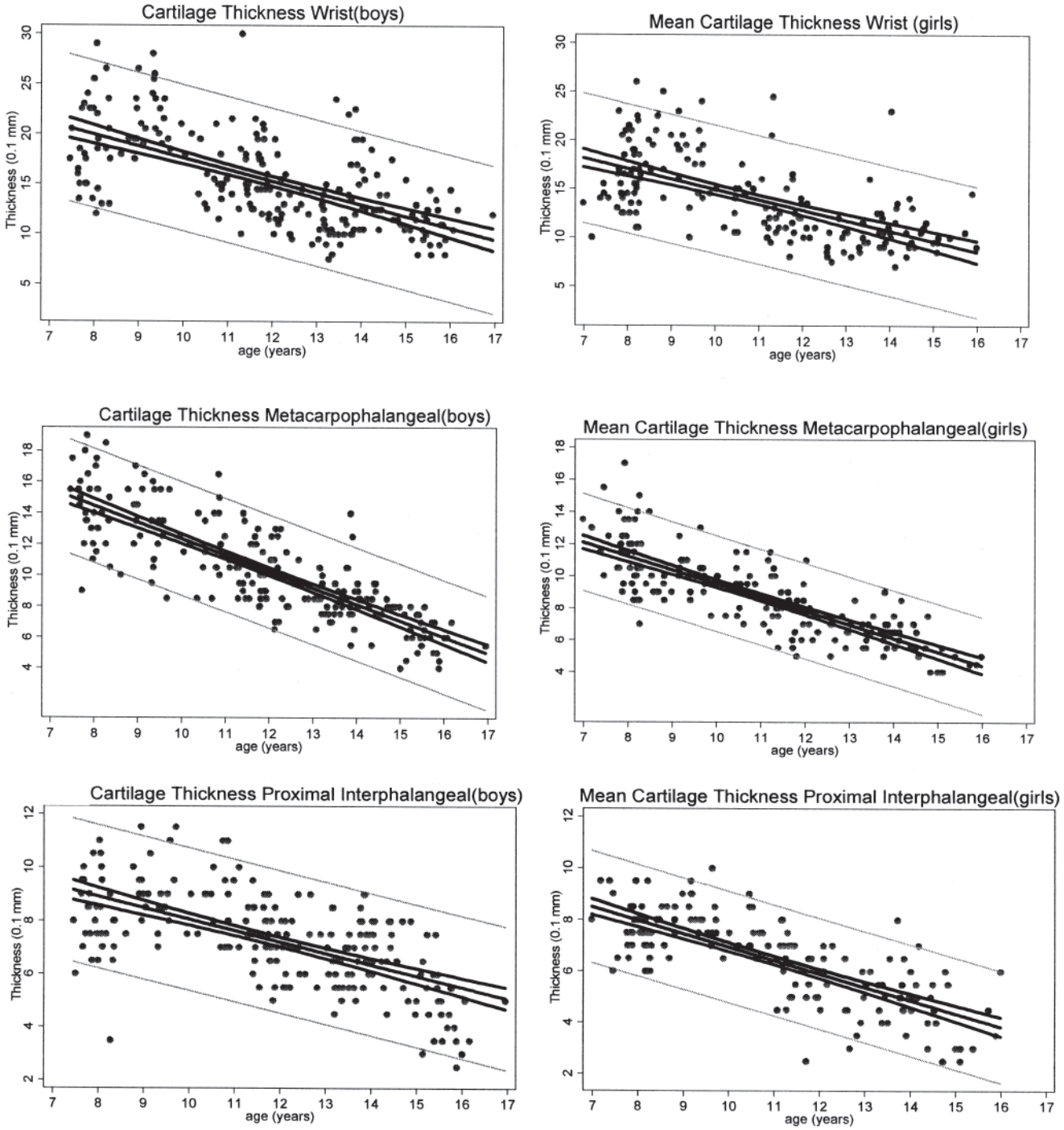

Figure 2. Cartilage thickness measures in the wrists, MCP joints, and PIP joints of healthy boys and girls. Mean cartilage thickness along with 95% confidence interval (3 solid black lines, mean is the solid center line) and predicted 95% confidence interval (grey lines).

mated thickness for an 8-year-old boy y_8, the common slope ß, the estimated difference between girls and boys, and the common standard deviation of the residual SD_{line} are given (Table 3B). From this the estimated thickness for an x-year-old boy can be calculated using the above formula and the estimated thickness for an x-year-old girl can be calculated by adding the estimated difference between girls and boys.

DISCUSSION

Growing use of US for diagnosing and monitoring joint diseases in children raises the need for age- and sex-related standard reference values for cartilage thickness from healthy individuals. In our study, we found statistically significant age- and sex-related differences in cartilage thickness for all bilaterally examined joints in 8- to 15-year-old

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Table 2. Difference in cartilage thickness between boys and girls aged 7-16 years.

	Difference Boys vs Girls*	
	mm	955 CI
Knee	0.47	0.38 to 0.56
Ankle	0.12	0.08 to 0.16
Wrist	0.26	0.19 to 0.33
MCP	0.26	0.22 to 0.29
PIP	0.12	0.10 to 0.15

* $p < 0.001$ for all joints. MCP: metacarpophalangeal joint; PIP: proximal interphalangeal joint.

healthy children, with boys having a higher absolute cartilage thickness than girls of the same age. These data on cartilage thickness in clinically dominant joints could be of interest to the pediatric rheumatologist or radiologist performing musculoskeletal US of affected joints to determine whether the measured cartilage thickness of a child with JIA lies within the reference interval of a healthy, age-matched child. Only 2 other pediatric studies[13,18,19] and one adult study[20] have suggested standard reference values for cartilage thickness in selected anatomical regions. These previous pediatric studies have been limited by the small number of subjects examined and by the fact that they neither evaluated cartilage thickness in multiple joints relevant to JIA nor correlated these results with the age of the subjects examined.

Studying sex and site differences in knee cartilage thickness and volume with MRI in healthy children, Jones and co-workers[6,21,22] found that knee cartilage was thicker and its volume larger in the lateral than in the medial tibiofemoral compartment in boys versus girls. These findings are consistent with our findings of sex differences in cartilage thickness.

Some authors have suggested that sex hormones may play a role[21,23,24], but solid explanations for these sex differences have not yet been offered. Estrogen receptors have been found on articular chondrocytes, and as estrogen may act on subchondral bone and cartilage receptors via second messengers like regulatory polypeptides (transforming growth factor-ß or cartilage inducing factor-A), it is possible that estrogen interferes with cartilage turnover[21,23,25]. Two adult studies[24,26,27] of cartilage volume and sex differences speculated whether the sex differences could be ascribed to testosterone hormone receptors, which are also present in cartilage[24], and that this could explain why males in general have a larger cartilage volume and bone surface area than females.

However, our results indicate that the difference between sexes is present even in prepubertal age groups, so the effect of sex hormones is probably not the only factor at play, but genetic factors also play a pivotal role. Our findings are in agreement with observations made by Jones and co-workers: that cartilage volume did not increase with age or with Tanner stage. This suggests that sex differences develop before 9 years of age and that environmental factors and physical activity may explain the observed sex differences.

In contradiction to Jones and co-workers' results[6,21], we found a decreasing articular cartilage thickness throughout childhood that was significant for almost every examined joint (except the ankle and wrist). Collado and co-workers[13] found that the mean dorsal thickness of the radial cartilage was greater among children younger than 5 years than among children above this age threshold, but the observed

Table 3A. Decrease in cartilage thickness in 0.1/year for boys and girls age 7 to 16 years.

	Boys Estimated Slopes*	95% CI	Girls Estimated Slopes*	95% CI	Equal Slopes, p
Knee	–0.07	–0.09 to 0.05	–0.11	–0.13 to 0.08	0.057
Ankle	–0.04	–0.05 to 0.03	–0.03	–0.04 to 0.02	0.39
Wrist	–0.12	–0.14 to 0.10	–0.11	–0.13 to 0.09	0.52
MCP	–0.11	–0.12 to 0.10	–0.09	–0.10 to 0.08	0.004
PIP	–0.04	–0.05 to 0.04	–0.05	–0.06 to 0.05	0.072

* Changes, mm/year. MCP: metacarpophalangeal joint; PIP: proximal interphalangeal joint.

Table 3B. Estimates assuming equal slope/changes.

	Boys 8 yrs, mm*		Difference Boys vs Girls, mm*		Common Slope, mm*	
	Mean*	95% CI	Mean*	95% CI	Mean*	95% CI
Knee	3.96	3.86 to 4.10	0.47	0.38 to 0.56	–0.089	–0.10 to –0.07
Ankle	1.14	1.10 to 1.18	0.12	0.08 to 0.16	–0.03	–0.04 to –0.03
Wrist	1.99	1.91 to 2.08	0.26	0.19 to 0.33	–0.11	–0.13 to –0.09
MCP	1.45	1.41 to 1.49	0.26	0.22 to 0.29	–0.09	–0.10 to –0.090
PIP	0.89	0.86 to 0.92	0.12	0.09 to 0.15	–0.05	–0.05 to –0.04

* Changes mm/year. MCP: metacarpophalangeal joint; PIP: proximal interphalangeal joint.

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Table 4. Variation around mean cartilage thickness shown as the standard deviations (mm) and the difference between right and left extremity.

	Boys	Girls
Knee		
SD_{within}	0.196	0.191
SD_{line}	0.417	0.457
Ankle		
SD_{within}	0.133	0.113
SD_{line}	0.198	0.165
Wrist		
SD_{within}	0.271	0.266
SD_{line}	0.370	0.335
MCP		
SD_{within}	0.102	0.090
SD_{line}	0.185	0.151
PIP		
SD_{within}	0.086	0.074
SD_{line}	0.135	0.109

SD_{within}: standard deviation within child (right/left extremity); SD_{line}: standard deviation of mean. MCP: metacarpophalangeal joint; PIP: proximal interphalangeal joint.

difference was not significant. This is in accord with our findings, even though we measured cartilage thickness of the wrist joint using a longitudinal scan corresponding to the articulating surface of the radial and scaphoid bones[11].

In a previous study of inter- and intraobserver variation of cartilage thickness measurements with US in 74 healthy children, we found no difference in joint cartilage thickness between the left and right extremity in any of the examined joints of the healthy children[10]. These observations were confirmed in this larger cross-sectional study (Table 4). Our findings are of particular interest when US measurement of cartilage thickness is implemented in a JIA patient group, because it indicates that it may be possible to use the subject's non-affected extremity as a reference value along with the standard age- and gender-matched reference value reported here. Data on joint cartilage thickness were not investigated in children under 6 years, and future studies are needed in this age group.

In conclusion, we established age- and sex-related reference intervals for cartilage thickness obtained by US in 394 healthy children (3940 joints). Cartilage thickness decreases with age throughout this 7- to 16-year-old age group (see the age- and sex-related regression curves for cartilage thickness). Boys have thicker hyaline cartilage thickness than girls. No variation in hyaline cartilage thickness between the right and left extremity was observed for any of the investigated joints. We established a formula for calculating hyaline cartilage thickness in the clinically dominant joints for all ages. If the cartilage thickness differs from this value in JIA patients, the clinicians should be aware that this may herald disease progression and they should consider a change in treatment strategy.

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