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Knee Articular Cartilage Development in Children: A Longitudinal Study of the Effect of Sex, Growth, Body Composition, and Physical Activity

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ABSTRACT

The aim of this study was to describe the effect of sex, growth, Tanner stage, and physical activity on knee articular cartilage volume development. A total of 74 randomly selected male and female children aged 9–18 y were measured on two occasions at an average interval of 1.6 y (range 1.3–1.9). Articular cartilage volume was determined at the patella, medial tibial, and lateral tibial compartments by processing images acquired in the sagittal plane using T1-weighted fat saturation magnetic resonance. Height, weight, and BMI were measured while Tanner stage and physical activity were assessed by questionnaire. Articular cartilage volume increased at all sites peaking in Tanner stage two. Males gained articular cartilage faster than females at all sites (patella +233 μL/y, 95% CI −7, +473, medial tibial +350 μL/y, 95% CI +118, +582, lateral tibial +256 μL/y, 95% CI +22, +488). In both sexes, articular cartilage volume accrual at tibial but not patella sites correlated significantly with height change but not weight change. Overweight children did not differ significantly from normal children in articular cartilage volume either cross-sectionally or longitudinally. The most consistent physical activity association was with average intensity of sport with those above the median gaining approximately twice as much as those below the median at tibial ($p < 0.05$) but not patella sites. In conclusion, most children gain articular cartilage during growth, but there is wide variation in the amount of articular cartilage accrual. In particular, younger children, males, and those undertaking more vigorous sports have substantially higher accrual rates. These results provide novel data on articular cartilage development in humans. The long-term significance of these results with regard to osteoarthritis of the knee in later life remains hypothetical. **(*Pediatr Res* 54: 230–236, 2003)**

Abbreviations
BMI, body mass index
MRI, magnetic resonance imaging

Osteoarthritis (OA) is the major cause of disability in those over age 65 y (1). Risk factors such as genetic factors, sex, and body mass index have been identified for knee OA (2–4). However, much remains to be understood about this very common condition. There is convincing evidence that other diseases of later life such as ischemic heart disease, diabetes mellitus, and particularly osteoporosis are associated with childhood development (5, 6). Although there are no data in humans with regard to early life exposures and risk of osteoarthritis in later life, a study in senescent moose linked a higher incidence of osteoarthritis with a famine when the moose were weanlings (7). Defects in articular cartilage are widely considered to be the initial problem in osteoarthritis (8) although this viewpoint is not shared by all authors (9). However, articular cartilage development in humans is poorly understood. In part, this has been due to the lack of a noninvasive, accurate, *in vivo* assessment of articular cartilage. Recently, magnetic resonance imaging (MRI) has been shown to be a simple, safe, noninvasive, and reproducible technique for measuring knee articular cartilage thickness (10) and volume (10–12) *in vivo*. We recently reported sex and site differences in articular cartilage development in the knee, which are a possible explanation for the observed variations in knee OA in later life as well as beneficial physical activity associations (13). This study was cross-sectional in design and thus it is necessary to consider if these associations remain if a longitudinal design is used. In this study, therefore, we describe factors associated with knee articular cartilage volume accrual in healthy, asymptomatic male and female children.

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METHODS

The study was conducted in Hobart, Tasmania (latitude 42°S) at a single co-educational school. Subjects were a random selection of six male and six female students from each of 10 year groups (grades 3–12) by random numbers using school lists. Subjects were excluded on the basis of contraindication to MRI (including metal sutures, presence of shrapnel, iron filing in eye, and claustrophobia) or significant knee pain. Subjects who took part in the initial cross-sectional study were contacted in 2000 for repeat measurement. The study was approved by the Southern Tasmanian Health and Medical Human Research Ethics Committee and all subjects and/or their parents/guardians provided informed written consent.

Weight was measured to the nearest 0.1 kg (with shoes, socks, and bulky clothing removed) using a single pair of electronic scales (Seca Delta Model 707) that were calibrated using a known weight at the beginning of each clinic. Height was measured to the nearest 0.1 cm (with shoes and socks removed) using a stadiometer. Body Mass Index (BMI) (kg/m^2) was calculated. Overweight or obesity was defined according to recent guidelines in children (14). Lower limb muscle strength was measured to the nearest 1.0 kg by dynamometry (TTM Muscular Meter, Tokyo, Japan) on two occasions. The muscles measured with this technique are predominantly quadriceps and hip flexors. Subjects were instructed in technique before testing. Reproducibility in our hands is excellent (intraclass correlation 0.91 or CV 1.8%) (15). One observer (KH) performed all physical measurements at baseline and follow-up.

Tanner pubertal stage was assessed by questionnaire by using drawings made from Tanner's photographs illustrating the five stages of pubertal development. This approach has a high correlation with actual examination of 0.63 for males and 0.81 for females (16). Timing of menarche was also recorded for females. Physical activity was retrospectively assessed in the year before study entry on two occasions using a questionnaire validated in U.S. adolescents (17), which was modified after piloting to include popular Australian Sports. The test-retest Spearman correlation of overall leisure physical activity in hours/week over the last year was found to be 0.66 (16). This questionnaire has demonstrated predictive validity in our hands (13). Subjects were unaware of their MRI results at the time of questionnaire completion. This questionnaire has items on days of either vigorous activity or strenuous activity for greater than 20 min in the last 2 weeks (1, none; 2, 1–2 d; 3, 3–5 d; 4, 6–8 d; 5, 9 or more days); daily television watching in last week (1, none; 2, 1 or less hours; 3, 2–3 h; 4, 4–5 h; 5, 6 or more hours); number of competitive sports in the last 12 mo (1, none; 2, one; 3, two; 4, three; 5, 4 or more) and activities done at least 10 times in the last 12 mo. Average sport intensity in METs was calculated based on this list by averaging the intensity based on published tables (18).

Knee articular cartilage volume was determined by means of image processing on an independent work station using the software program Osiris as previously described (19). Knees were imaged in the sagittal plane on a 1.5-T whole body magnetic resonance unit (PICA) with use of a commercial transmit-receive extremity coil. The following image sequence was used: a T1-weighted fat saturation 3D gradient recall acquisition in the steady state; flip angle 55 degrees; repetition time 58 ms; echo time 12 ms; field of view 16 cm; 60 partitions; 512 × 512 matrix; acquisition time 11 min 56 s; one acquisition. Sagittal images were obtained at a partition thickness of 1.5 mm and an in-plane resolution of 0.31 × 0.31 (512 × 512 pixels). The image data were transferred to the workstation. The volume of individual articular cartilage plates (medial tibial, lateral tibial, and patella) were isolated from the

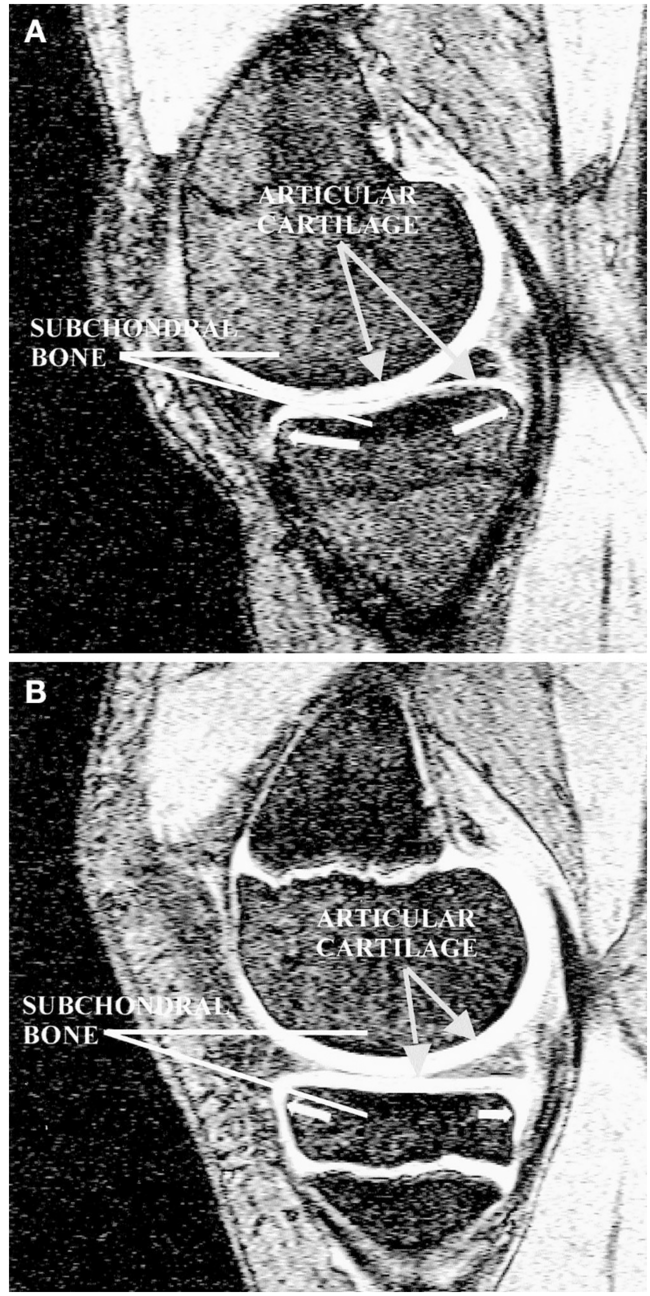

Figure 1. Distinguishing the anterior and posterior edges of joint articular cartilage where the growth plate is fused and nonfused. (*A*) Typical fused articular cartilage MR image. *Arrows* indicate extension of articular cartilage along anterior and posterior surfaces. (*B*) Typical nonfused articular cartilage MR image. *Arrows* indicate the position at which articulator articular cartilage is defined to translate to growth articular cartilage.

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Table 1. *Characteristics of participants*

	Boys ($n = 40$)	Girls ($n = 34$)	p-Value for difference
Age at baseline, years	13.2 (2.9)	13.2 (2.9)	0.99
Height change, cm/year	5.0 (2.9)	3.1 (3.0)	0.01
Weight change, kg/year	4.6 (3.2)	2.7 (3.1)	0.01
BMI at baseline, kg/m^2	20.5 (3.3)	20.5 (4.1)	0.99
Proportion overweight, %	27	31	0.62*
Sports participation, %	93	94	0.89*
Average sport intensity, METs	7.42 (0.39)	7.31 (0.36)	0.83
Articular cartilage variables			
Patella volume change, μl/year	286 (271)	210 (467)	0.38
Medial tibial volume change, μl/year	418 (400)	195 (291)	0.007
Lateral tibial volume change, μl/year	364 (460)	105 (266)	0.004
Patella volume change, %/year	7.1 (2.5)	6.2 (0.9)	0.73
Medial tibial volume change, %/year	14.8 (2.1)	10.0 (2.2)	0.11
Lateral tibial volume change, %/year	11.4 (1.8)	4.6 (2.1)	0.02
Bone size variables			
Medial tibial area change (mm^2/year)	153 (112)	92 (105)	0.02
Lateral tibial area change (mm^2/year)	151 (89)	102 (71)	0.01
Patella volume change (ml/year)	1.3 (1.1)	0.8 (0.9)	0.001

* Mann-Whitney U test, all others are unpaired t-tests and are presented as mean (standard deviation).

Table 2. *Sex differences in articular cartilage volume*

	Males versus females		
Articular cartilage site	*Unadjusted* Model R^2 Partial R^2 (sex) Difference (95% CI)	*Adjusted step 1** Model R^2 Partial R^2 (sex) Difference (95% CI)	*Adjusted step 2** Model R^2 Partial R^2 (sex) Difference (95% CI)
Patella, μl/year	**R^2 0%** Partial R^2 0% +77 (−103, +251)	**R^2 0%** Partial R^2 0% +54 (−128, +236)	**R^2 6%** Partial R^2 2% +233 (−7, +473)
Medial tibial, μl/year	**R^2 8%** Partial R^2 8% +223 (+58, +388)	**R^2 12%** Partial R^2 6% +183 (+15, +351)	**R^2 30%** Partial R^2 15% +350 (+118, +582)
Lateral tibial, μl/year	**R^2 9%** Partial R^2 9% +260 (+80, +440)	**R^2 12%** Partial R^2 7% +210 (+28, +392)	**R^2 18%** Partial R^2 8% +256 (+22, +488)

* Adjusted for sport intensity and BMI in step 1. In step 2, the adjustment is as for step 1 as well as Tanner stage, height change, bone area/volume change, and baseline articular cartilage volume at that site.

total volume by manually drawing disarticulation contours around the articular cartilage boundaries on a section by section basis. These data were then resampled by means of bilinear and cubic interpolation (area of 312 and 312 μm and 1.5 mm thickness, continuous sections) for the final 3D rendering. The volume of the particular cartilage plate was then determined by summing all the pertinent voxels within the resultant binary volume. In children with nonfused growth plates, the discrimination between articular cartilage and growth plate articular cartilage is less clear. MR articular cartilage imaging does not discriminate these articular cartilage forms so we have used an algorithm. In a mature knee (with fused growth plates), tibiofemoral articular cartilage can been seen to extend slightly down both the anterior and posterior surfaces of the tibia within the images (see Fig. 1*A*). For consistency of measurement, the articular cartilage boundary was placed at a point where the shape of the internal contour of the articular cartilage reached the vertical. In mature, fused subjects this generally incorporates most of the articular cartilage extensions seen. In the nonmature knee (Fig. 1*B*), which displays a nonfused and continuous "ring like" articular cartilage, the same rule was applied. The articular cartilage was held to extend to a point marked by the curvature on the inner surface reaching the vertical. Placement of this limiting boundary in both the fused and nonfused case results in a similar appearance. Using this method we had high intra-observer and inter-observer reproducibility. The coefficient of variation (CV) for articular cartilage volume measures was 2.1% for medial tibial, 2.2% for lateral tibial, and 2.6% for patella (13). Femoral articular cartilage volume was not assessed due to problems with edge detection in children. The medial and lateral tibial cartilage thickness was measured using callipers on all sections and the maximum thickness of any section was recorded independently. This paper concentrates on volume measures due to the problems with positioning when thickness is the main outcome measure especially longitudinally in children where positioning will be made more complicated by growth (12).

The following measures of bone size were determined on both occasions: total patella bone volume, medial and lateral tibial plateaux areas. Total patella bone volume was calculated by using the same method as for articular cartilage volume.

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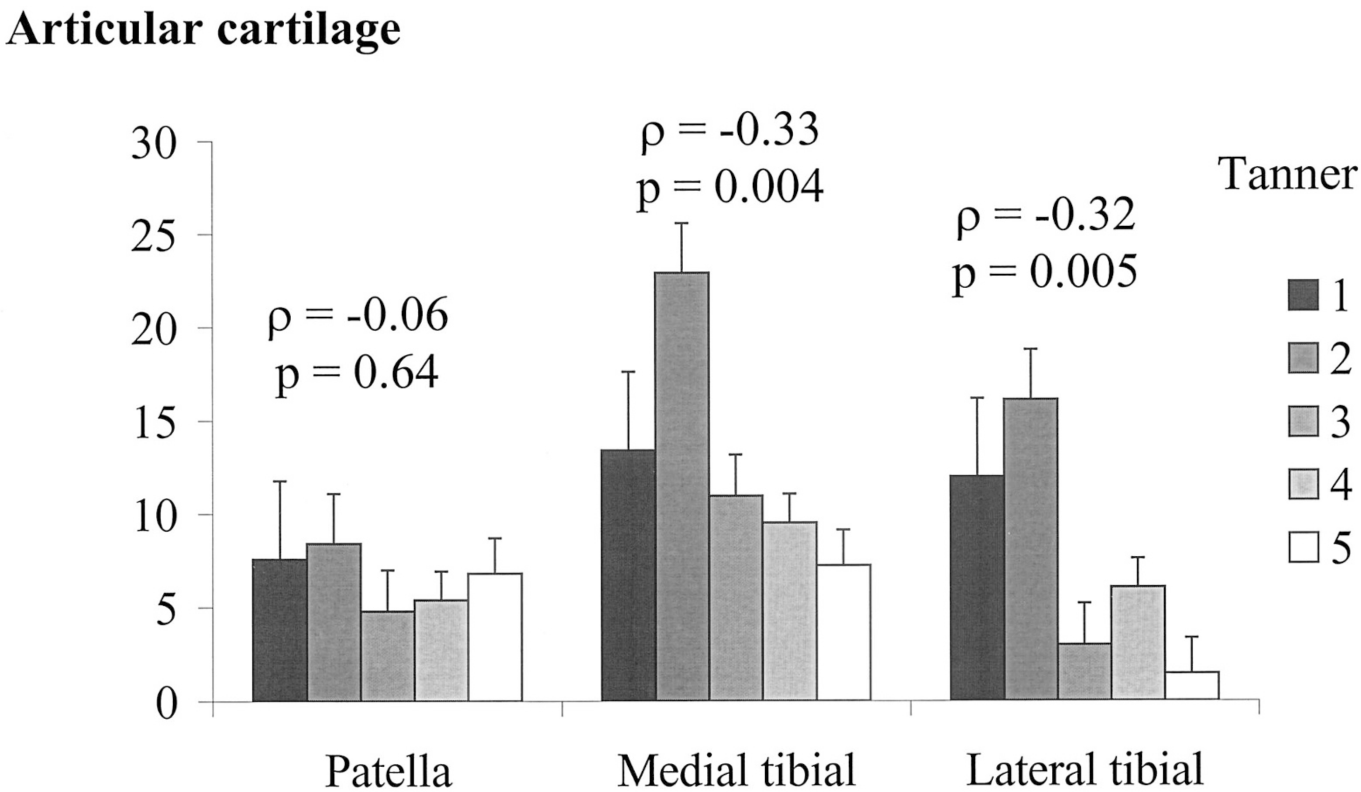

Figure 2. Tanner stage and articular cartilage volume accrual. Articular cartilage accrual at all sites (but particularly tibial) peaks at Tanner stage 2. The rate of accrual at tibial but not patella sites decreases with increasing Tanner stage. Data are presented as mean % per annum ± SEM. The correlation coefficient is Spearman's rho.

Contours were drawn around the patella in images 1.5 mm apart on sagittal views. Total volume was calculated for the patella due to its irregular shape, which made it difficult to identify a simpler, representative measure of patella size. Medial and lateral tibial plateau areas were determined by creating an isotropic volume from the input images. This was reformatted in the axial plane. The areas of the medial and lateral tibial plateaux were then directly measured from these images.

Statistics. Rates of change in articular cartilage volume were calculated in two ways (absolute change per annum and percentage change per annum). To account for measurement error regarding the significance of individual changes, the least significant criterion (LSC) was used. Due to the high within subject correlation for articular cartilage volume (all greater than 0.7) the most appropriate formula was as follows:

$$\text{LSC} = 1.96 \times \sigma_i \times \text{square root } (2(1\text{-}\rho_i)) \text{ (20).}$$

Where σ_i^2 is the within subject variance and ρ_i is the correlation between serial measurements.

t-Tests or Mann-Whitney Utests (where appropriate) were used for comparison of the mean rate of change. Mechanisms for sex differences in articular cartilage accrual were further examined by multivariate modeling. To assess whether these were mediated by differences in life style factors, a model was constructed containing BMI and sports intensity (above median*versus*below median). This model was then further adjusted for height change, Tanners tage at baseline and base line articular cartilage volume. For the analysis of physical activity, raw data were first plotted to look at patterns of association. Any variable with a *p*-value less than or equal to 0.10 at any site was then examined in a multivariate model containing only questionnaire based physical activity variables and bone area/volume change at all sites. Paired *t*-tests were used for comparison of lateral and medial articular cartilage compartment accrual. All R^2 values were adjusted for number of independent variables. A *p*-value less than 0.05 (two-tailed) or a 95% confidence interval not including the null point were regarded as statistically significant. All statistical analyses were performed on SPSS version 10.0 for Windows (Chicago, IL, U.S.A.).

RESULTS

A total of 74 children (males $n = 40$, females $n = 34$) competed the study (80% of those originally studied). The mean interval between measurements was 1.6 y (range 1.3–1.9). Demographic and study factors are presented in Table 1. Males had greater height and weight gain than females but other factors were similar. Most children had an increase in their articular cartilage volume during the study (patella, $n = 63$; medial tibial, $n = 64$; and lateral tibial, $n = 56$). When measurement error was taken into account, most children had a significant increase (patella, $n = 54$; medial tibia, $n = 62$; lateral tibia, $n = 50$) while a smaller number had a significant decrease (patella, $n = 8$; medial tibia, $n = 6$; lateral tibia, $n = 16$). In contrast, medial tibial thickness did not change (+0.01

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mm/y, $p = 0.85$) while lateral tibial thickness decreased (-0.59 mm/y, $p < 0.001$).

In unadjusted analysis, males had greater articular cartilage volume accrual than females at tibial but not patella sites. This was most obvious for absolute rather than percentage change. However, in multivariate analysis, males had higher articular cartilage volume accrual at all sites ($p = 0.06$ at patella), which persisted after adjustment for multiple confounders including bone area (Table 2). Adjustment for body mass index and sports intensity only had a modest effect on the parameter estimates for sex.

Cross-sectionally, cartilage volume was negatively associated with increasing Tanner stage (patella, $\rho = -0.27$, $p = 0.008$; medial tibial, $\rho = -0.39$, $p < 0.001$; lateral tibial, $\rho = -0.09$, $p = 0.41$). However, longitudinal data did not confirm this. Peak articular cartilage accrual was during Tanner stage two at all sites but especially tibial where the rate of increase decreased significantly with increasing Tanner stage (Fig. 2). Articular cartilage volume accrual at the three sites correlated significantly (medial tibial lateral tibial, r = 0.72; medial tibial patella, r = 0.53; lateral tibial patella, r = 0.49, all $p < 0.001$) but only modestly and inconsistently with change in bone area/volume (r = 0.01–0.41). Articular cartilage volume accrual correlated significantly with height change at tibial (medial, r = 0.38; lateral, r = 0.36; both $p = 0.001$) but not patella sites (r = −0.01, $p = 0.97$). Being overweight or obese was associated with a trend to lower cartilage volume and accrual rates at all sites but none achieved statistical significance either cross-sectionally (patella, −298 μL, 95% CI = −760,+184; medial tibial, −101 μL, 95% CI = −414,+211; lateral tibial, −149 μL, 95% CI = −493,+99) or longitudinally (patella, −108 μL/y, 95% CI = −314,+196; medial tibial, −64 μL/y, 95% CI = −268,+140, lateral tibial, −94 μL/y, 95% CI = −316,+129). Weight change did not correlate significantly with articular cartilage accrual (data not shown).

Physical activity associations were somewhat variable possibly due to sample size considerations. No vigorous activity within the last 2 weeks at baseline was associated with lower articular cartilage accrual at all sites but this only reached significance at the patella. Television watching for 3 or greater hours per day was associated with substantially lower articular cartilage accrual at all sites, which did not reach statistical significance while those above the median for average intensity of sports at baseline had significantly and substantially higher articular cartilage accrual at tibial sites (Fig. 3). When these three variables were forced into a multivariate model, they explained 0% to 10% of the variance in articular cartilage accrual with average sport intensity being the only significant predictor at tibial sites (Table 3). These associations became nonsignificant after adjustment for age or Tanner stage. If sport intensity was considered as a continuous variable, there were borderline associations at tibial (medial, r = 0.22, p, = 0.06; lateral, r = 0.23, $p = 0.05$) but not patella sites (r = 0.02, $p = 0.92$). Neither lower limb muscle strength at baseline (patella, r = 0.08, $p = 0.92$; medial tibial,r = −0.13, $p = 0.52$; lateral tibial, r = −0.07, $p = 0.71$) nor change in muscle strength (patella, r = −0.07, $p = 0.56$; medial tibial, r = 0.06, $p = 0.62$; lateral tibial, r = 0.05, $p = 0.70$) were significantly associated with articular cartilage accrual. This also applied to a quartile based analysis (data not shown). Numbers of sports or type of sport were not significantly associated with articular cartilage accrual (data not shown).

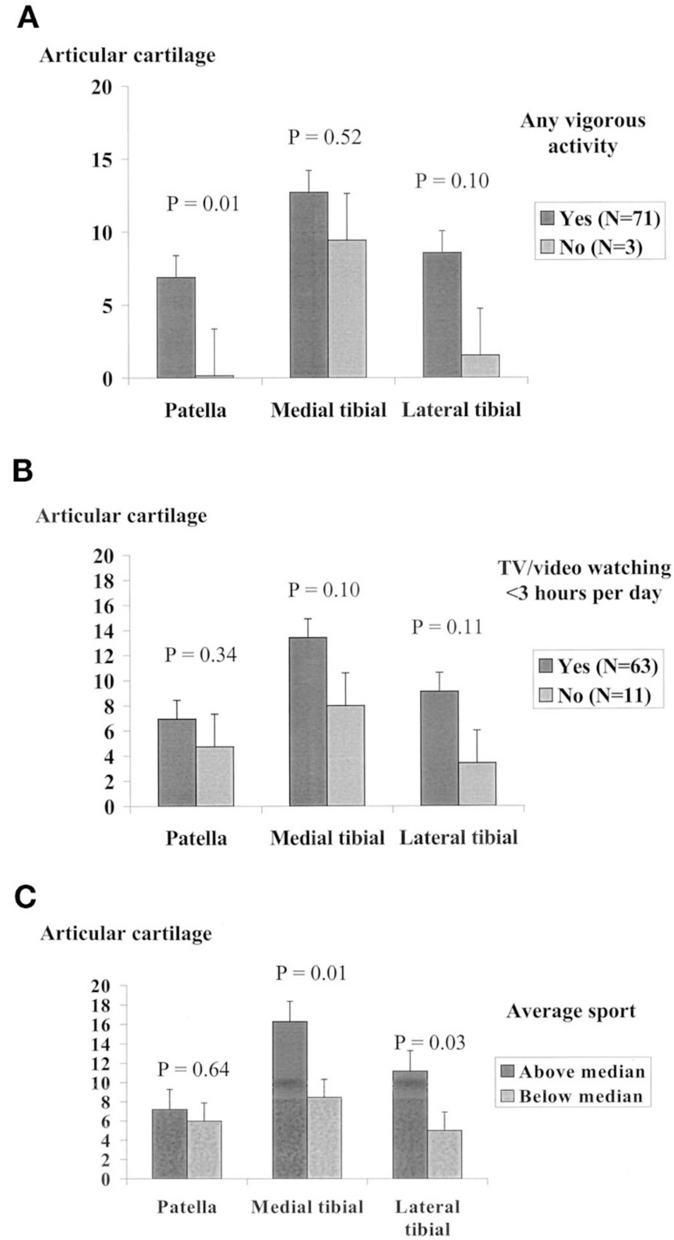

Figure 3. Selected physical activity variables and articular cartilage volume accrual. (*A*) Vigorous activity in the last 2 weeks (any *vs* none). (*B*) Television or video watching (≥ 3 h *vs* < 3 h). (*C*) Mean sport intensity (split at median which is 6.5 METs). Overall, the results suggest a substantial benefit with physical activity. The most consistent association is for sport intensity and tibial articular cartilage volume accrual. Data are presented as mean % per annum ± SEM.

Lastly, there was greater articular cartilage volume accrual in lateral compared with medial tibial compartments (difference 70 μL/y, 95% = CI 3,137), but this did not correlate with Tanner stage (r = 0.03, $p = 0.80$) indicating a consistently increasing difference during growth.

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Table 3. *Multivariate analysis of selected physical activity variables and articular cartilage accrual**

	Patella	Medial tibial	Lateral tibial
Goodness of fit	**R^2 0% (p = 0.68)**	**R^2 9% (p = 0.041)**	**R^2 10% (p = 0.029)**
Vigorous exercise in last 14 days, none *vs* any	−246 μl/year (95% CI = −700, +207)	−65 μl/year (95% CI = −493, +361)	−220 μl/year (95% CI = −659, +218)
Hours of daily television watching, 3 or greater *vs* less than 3	−58 μl/year (95% CI = −323, +207)	−95 μl/year (95% CI = −345, +155)	−79 μl/year (95% CI = −337, +179)
Intensity of all sports, ≥6.5 versus <6.5 METs	+66 μl/year (95% CI=−120, +252)	**+198 μl/year (95% CI = +20, +375)**	**+185 μl/year (95% CI = +3, +367)**

* Adjusted for other factors in Table and change in bone area/volume at that site. Bold denotes statistical significance.

DISCUSSION

This longitudinal study describes the crucial stages of articular cartilage volume development in children. There was wide individual variation in articular cartilage volume development with less mature children gaining more articular cartilage than older children while novel beneficial physical activity associations are documented. These results are consistent with the previous cross-sectional report for sex, site, and physical activity but not age.

Most children gained significant amounts of articular cartilage although a minority also decreased during the 1.6-y interval. In contrast, no change was seen in the medial tibial thickness and a significant decrease was observed in the lateral tibial compartment. This implies that articular cartilage spreads out to cover the growing bone surface area without any increase in thickness (or even a decrease). While there was significant correlation with change in height and less so with change in bone area, the wide variation in articular cartilage volume accrual suggests that articular cartilage volume in children may be very responsive to environmental manipulation. Indeed, the children who participated in more vigorous sports gained twice as much articular cartilage as those who participated in less active sports while the less active children (identified by the frequency of vigorous exercise or watching more than 3 h per day of television or video games) gained substantially less articular cartilage. However, not all of these results attained statistical significance. This was not mediated by body composition as overweight or obese children were not significantly different in terms of articular cartilage accrual. This suggests that vigorous physical activity, in the absence of knee pain and injury, is beneficial for articular cartilage volume accrual especially given the recent methodological findings that recent physical activity acutely decreases articular cartilage volume in adults through compression (21). Higher articular cartilage volume with activity suggests that articular cartilage in children can respond to increased loads unlike preliminary data in adult triathletes where no significant difference was reported in comparison to controls (22). This implies superior articular cartilage health, but it remains to be seen if articular cartilage development is a predictor of osteoarthritis in later life. Our cohort was relatively small in size, and there were high overall levels of physical activity indicating the need for further larger studies particularly including less active children. In addition, the physical activity associations became nonsignificant after adjusting for age or Tanner stage but not bone growth suggesting that the well-recognized decline in physical activity during childhood may be responsible or that this association may be confounded by decreasing growth with increasing age. Further studies will ideally follow children of a similar age.

Consistent with cross-sectional reports in adults (19, 23) and our earlier study in children (13), males gained more articular cartilage at all sites than females. This was only weakly explained by any of the factors we measured in this study (including bone area changes) indicating that the sex difference is due to other factors most likely genetic or hormonal. Similarly, the lateral tibial compartment consistently gained more than the medial tibial compartment suggesting our cross-sectional observation of an increasing difference with increasing Tanner stage is correct (13). This observation still remains largely unexplained. However, age and Tanner stage was negatively associated with articular cartilage volume at some sites cross-sectionally suggesting that the rate of articular cartilage accrual should be negative. This is in direct contrast to our longitudinal results where the majority of children gained articular cartilage and suggests that cohort effects apply to the relationship between age, Tanner stage, and articular cartilage volume in children.

This study has a number of potential limitations. The subjects are a valid random sample of healthy children with high response rates. Nevertheless, the high overall levels of physical activity in this sample do limit the generalisability of these results. Furthermore, measurement of physical activity is difficult in children. While our physical activity questionnaire has good test-retest reproducibility, there is still a considerable margin for measurement error to occur. The likely effect of this is to decrease the strength of the associations between physical activity and articular cartilage volume and lead to lower power to find moderate associations, and this may explain the lower goodness-of-fit estimates for the longitudinal data. Tanner stage was also assessed by self-report and this may lead to misclassification particularly at younger ages. However, the agreement between self-report and actual examination is good and very similar associations were observed with age suggesting this is not of major concern. There are few limitations in using MRI for articular cartilage volume estimates. The accurate delineation of articular cartilage depends on high contrast relative to adjacent tissues. Our method has been validated against cadavers (19) and has excellent reproducibility with CVs of 2% to 3%, which compares very favorably to the magnitude of the differences we have reported.

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CONCLUSIONS

Most children gain articular cartilage during growth, but there is wide variation in the amount of articular cartilage accrual. In particular, younger children, males and those undertaking more vigorous sports have substantially higher accrual rates. These results provide novel data on articular cartilage development in humans. The long-term significance of these results with regard to osteoarthritis of the knee in later life is speculative at this stage.

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