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BRIEF REPORT

Urbanization and Knee Cartilage Growth Among Children and Adolescents in Western Kenya

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Objective. Previous studies have demonstrated that low physical activity levels during youth are associated with the development of thin knee cartilage, which may increase susceptibility to osteoarthritis later in life. Here, we propose and test the hypothesis that reductions in physical activity impair knee cartilage growth among people in developing countries experiencing urbanization and increased market integration.

Methods. Ultrasonography was used to measure knee cartilage thickness in 168 children and adolescents (aged 8-17 years) from two groups in western Kenya: a rural, physically active group from a small-scale farming community and an urban, less physically active group from the nearby city of Eldoret. We used general linear models to assess the relative effects of age on cartilage thickness in these two groups, controlling for sex and leg length.

Results. Both groups exhibited significant reductions in knee cartilage thickness with increasing age ($P < 0.0001$; 95% confidence interval [CI] 0.15-0.06 mm), yet the rate of reduction was significantly less in the rural than in the urban group ($P = 0.012$; 95% CI 0.01-0.10 mm).

Conclusion. The results support our hypothesis by showing that individuals from the more physically active rural group exhibited less knee cartilage loss during youth than the more sedentary urban group. Our findings suggest that reduced physical activity associated with urbanization in developing nations may affect adult knee cartilage thickness and thus could be a factor that increases susceptibility to osteoarthritis.

INTRODUCTION

In many developing countries, subsistence farming populations that have traditionally lived in remote rural areas are undergoing major lifestyle changes because of rapid urbanization and integration into market economies. These changes, which include declines in physical activity and greater consumption of highly processed foods, are expected to increase susceptibility to knee osteoarthritis (OA) (1). In particular, it has recently been proposed that individuals born under conditions of energetic scarcity who later encounter greater energy abundance are predisposed to accumulate abdominal adipose tissue, engendering chronic low-grade systemic inflammation, which plays a pathophysiological role in knee OA (2).

Here, we propose and test a related hypothesis: reductions in physical activity among populations transitioning from rural to market-integrated, urban lifestyles impair the growth of knee articular cartilage during childhood and adolescence, increasing the probability that individuals enter adulthood with biomechanically vulnerable cartilage structure. Evidence from developed countries indicates that low levels of physical activity during youth are associated with thinner knee cartilage both during the growing years (3) and in adulthood (4). Moreover, thin baseline knee cartilage has been shown to predispose to greater knee cartilage degeneration with aging (5). In contrast, elevated body mass index (BMI) during youth has not been found to have a strong association with knee cartilage growth (3), leading us to focus on the hypothesis that physical inactivity influences cartilage growth in the knee.

To test our hypothesis, we measured knee cartilage thickness in two groups of children and adolescents in western Kenya. The first group consisted of individuals living in a remote, rural region

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of Nandi County, where families continue to subsist almost entirely on small-scale farming and have little access to the market economy, running water, electricity, or mechanized farming equipment (6,7) (Figure 1A). The second group consisted of urban individuals living in Eldoret, the fifth largest and fastest growing city in Kenya (Figure 1B). Previous studies of children and adolescents from these two groups have demonstrated that compared with rural individuals, urban individuals engage in markedly lower levels of physical activity and have lower levels of physical fitness (6,7). Our prediction was that during childhood and adolescence, urban individuals would develop thinner knee cartilage than rural individuals.

METHODS

Participants. One hundred sixty-eight children and adolescents aged 8 to 17 years were recruited from rural and urban schools in western Kenya. The rural group consisted of 78 participants (40 girls, 38 boys) who attended the Pemja Primary School located in Nandi County, 50 km from the city of Eldoret. This school is remote and inaccessible by paved roads, requiring students to walk or run long distances (greater than 7 km, on average) over rugged terrain to get to and from school (6,7). Students in the rural group also frequently engage in strenuous subsistence activities after school, including farming and collecting firewood and water. The urban sample consisted of 88 participants (48 girls, 40 boys) who attended the Uasin Gishu Primary and Secondary Schools located in downtown Eldoret. Students travel to these schools primarily by motorized vehicle (6). The same sampling strategy was used in both schools: teachers invited their students to participate and described the measurements to be taken. Neither the teachers nor the students were made aware of our hypothesis. Although circumstances prevented us from collecting information on who declined to participate, there was no indication of selection bias within groups. Prior to any study procedure, data collection was described to participants and their guardians by researchers in Swahili. Participants then provided both verbal and written assent, and their guardians provided written consent. All study procedures complied with the Helsinki

Figure 1. **A**, Photograph from Pemja Village in Nandi County, Kenya. Participants from the rural, high physical activity group attended Pemja Primary School in this village. Photograph courtesy of Benjamin Sibson. **B**, Photograph of the city of Eldoret in Uasin Gishu County, Kenya. Participants from the urban, low physical activity group were residents of this city and attended Uasin Gishu Primary and Secondary Schools, located downtown. Photograph credit: Tuko News.

Declaration and were reviewed and approved by the Committee on the Use of Human Subjects at Harvard University and Moi University College of Health Sciences Institutional Research and Ethics Committee.

Procedures. Each participant's stature, body weight, waist circumference (at the level of the navel), and leg length (height of the greater trochanter while standing) were measured; age was self-reported. Some participants in the rural group did not know their exact birth date, so age in whole years was recorded for all participants and confirmed with school teachers. To measure knee cartilage thickness, a single experienced sonographer (NBH) conducted ultrasound imaging of each participant's right knee using an L12-4 broadband linear array ultrasound transducer (Philips Lumify; Philips) with the following settings: 14 MHz, 3.5-cm depth, 0.3-dB power, 0.5 mechanical index, and 0 thermal index. Following a validated protocol, participants sat upright in a chair with their right knee fully flexed and right foot planted on a chair in front of them; the transducer was then placed transversely to the flexed knee surface just above the upper pole of the patella (8). Three ultrasound images were captured of the distal femoral cartilage at the site of the intercondylar notch and saved for later analysis. After all data were collected and prior to any data analyses, all image files were duplicated and the duplicates were assigned random identification numbers to blind the sonographer to the participant identity and group associated with the image. Cartilage thickness was measured in all deidentified images using ImageJ software; then measurements were reassociated with the participant from whom they came. The three measurements from each participant were averaged to calculate a single cartilage thickness value.

Prior to this study, we conducted a repeatability analysis, in which cartilage thickness measurements were performed by the same sonographer (NBH) on five participants on three separate days. The intraclass correlation coefficient consistency score calculated from these measurements was 0.98, with a 95% confidence interval (CI) of 0.91 to 0.99, indicating high intrarater repeatability. The average coefficient of variation among participants was 4%.

Statistics. A general linear model (GLM) estimated using weighted least squares (WLS) was used to compare growth patterns of knee cartilage thickness between participants from the rural and urban settings. The model included average knee cartilage thickness as the response variable, and the focal explanatory variables were age and environment (rural or urban) as well as their interaction. To mitigate the confounding effects of body size variation, controls were included for leg length and sex. The WLS estimator allowed for separate residual variances for each environment and sex. To account for the possible effects of differences in developmental growth trajectories between urban and rural participants, an additional analysis was conducted, in which the two groups were matched for leg length within 2-year age strata by a nearest neighbor algorithm using propensity scores as a distance measure. This resulted in the removal of 26 participants who could not be matched. A second GLM was estimated using this matched sample, with the same terms as described for the first model but with the addition of sampling weights from the matching analysis. Model assumptions were checked by visualizing fitted values versus standardized residuals; model goodness of fit was assessed using likelihood ratio tests (LRTs) between target models and null, intercept-only models. The significance of individual estimates was determined through two-sided Wald tests with an α level of 0.05. All statistical procedures were performed using R software (v.3.6.1; R Core Team and the R Foundation for Statistical Computing).

RESULTS

Full sample characteristics for rural and urban participants are presented in Table 1, with participants divided into 2-year age strata to allow for comparisons at different ages. Across all age strata, rural participants had, on average, lower body masses, BMIs, and waist circumferences compared with urban participants. Average

Table 1. Mean (SD) sample characteristics across different ages in rural and urban children

Age, y	Group	n, male/female	Body mass, kg	Height, cm	BMI	Waist circumference, cm	Leg length, cm	Cartilage thickness, mm
8-9	Rural	5/5	23.3 (2.1)	125.4 (4.3)	14.8 (0.6)	56.9 (3.0)	65.8 (3.2)	2.94 (0.31)
	Urban	5/4	27.9 (6.5)	132.1 (4.2)	15.9 (2.9)	63.4 (7.8)	68.2 (3.3)	3.05 (0.62)
10-11	Rural	5/4	25.7 (2.0)	136.7 (13.2)	14.1 (2.5)	57.5 (3.1)	74.1 (6.6)	2.87 (0.30)
	Urban	9/12	31.8 (4.3)	139.9 (7.7)	16.2 (1.5)	63.6 (4.8)	75.8 (5.6)	3.01 (0.46)
12-13	Rural	8/14	33.6 (5.9)	145.2 (8.1)	15.9 (1.6)	64.0 (3.9)	79.0 (6.6)	2.71 (0.30)
	Urban	9/12	36.3 (6.9)	148.3 (8.3)	16.4 (1.8)	66.5 (5.9)	80.0 (4.5)	2.79 (0.35)
14-15	Rural	13/12	43.3 (6.6)	156.4 (6.7)	17.7 (2.1)	66.8 (3.9)	84.6 (4.1)	2.70 (0.38)
	Urban	7/10	47.9 (6.6)	156.1 (6.3)	19.7 (2.8)	70.9 (7.5)	85.4 (4.8)	2.57 (0.45)
16-17	Rural	7/5	49.8 (6.6)	165.8 (9.4)	18.1 (1.8)	69.7 (4.2)	90.4 (7.1)	2.67 (0.35)
	Urban	8/10	52.8 (6.2)	162.5 (6.1)	20.0 (2.6)	72.3 (5.6)	89.1 (3.6)	2.31 (0.36)
All ages	Rural	38/40	37.0 (10.5)	148.4 (14.9)	16.4 (2.3)	64.1 (5.7)	80.3 (9.2)	2.75 (0.35)
	Urban	40/48	40.0 (10.8)	149.0 (12.0)	17.7 (2.8)	67.6 (7.0)	80.7 (7.8)	2.73 (0.50)

Abbreviation: BMI, body mass index.

stature and leg length were lower in younger (less than 12 years old) rural versus urban participants, but across all ages, rural and urban participants had similar statures and leg lengths. In the leg length–matched sample (Supplementary Table 1), urban and rural participants had similar matched leg lengths at all ages, including in participants younger than age 12.

For the first GLM with the full sample, the goodness of fit test revealed that the target model performed better than the null model (LRT = 57.8, $P < 0.0001$). Among urban participants, knee cartilage thickness declined by 0.11 mm per year on average ($t = -4.7$, $P < 0.0001$; 95% CI 0.15-0.06 mm), whereas among rural participants, it declined by only 0.047 mm per year on average ($t = -2$, $P = 0.047$; 95% CI 0.093-0.0007). The age × area estimate reveals that this rate of decline was 0.06 mm greater per year on average among urban participants than rural participants ($t = 2.5$, $P = 0.012$; 95% CI 0.01-0.10 mm) (Figure 2). Because of this difference in rate, the average difference in cartilage thickness between environments changed depending on age. Urban participants tended to have thicker cartilage prior to age 13, but thereafter rural participants had increasingly thicker cartilage, with 16% thicker cartilage, on average, by ages 16 to 17 (Figure 2). Across ages and environments, boys had 7% greater adjusted mean cartilage thickness than girls ($t = 3.4$, $P = 0.0008$; 95% CI 3%-12%). Leg length was not significantly associated with cartilage thickness ($t = 0.3$, $P = 0.76$).

Results changed only slightly with the second GLM using the leg length–matched sample, which also performed better than a null model (LRT = 53.1, $P < 0.0001$). Knee cartilage thickness declined by 0.11 mm per year among urban participants ($t = -3.9$, $P = 0.0001$; 95% CI 0.17-0.06 mm) and by 0.06 mm per year among rural participants ($t = -2.3$, $P = 0.022$; 95% CI 0.1-0.007 mm). The age × area estimate still showed that the rate of decline was greater among urban participants than rural participants (average 0.05 mm/year difference, $t = 2.3$, $P = 0.025$; 95% CI 0.01-0.10 mm). Again, urban participants had thicker cartilage before age 13, and rural participants had thicker cartilage thereafter. In this model, boys had 8% greater adjusted mean cartilage thickness than girls ($t = 3.4$, $P = 0.0004$; 95% CI 4%-13%), and leg length was not significantly associated with cartilage thickness ($t = 0.4$, $P = 0.72$).

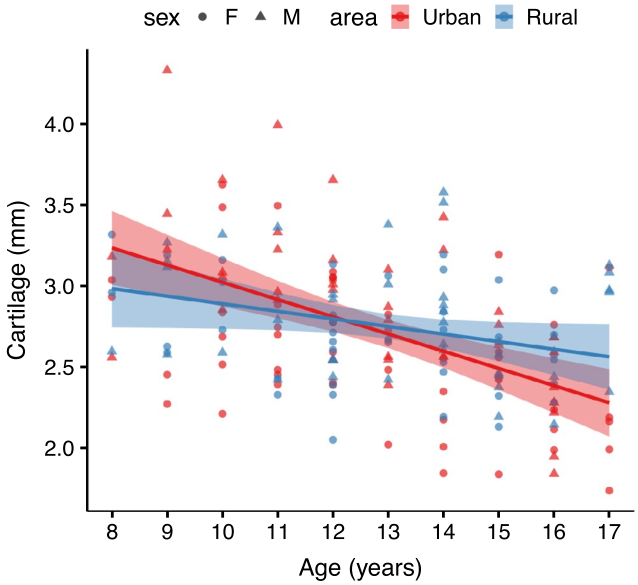

Figure 2. Cartilage thickness in urban and rural participants. Data points represent individual participants, and lines indicate associations between age and cartilage thickness within rural and urban groups, controlling for sex and leg length. Shading represents 95% confidence intervals. F, female; M, male.

DISCUSSION

This study investigated knee cartilage thickness over the course of childhood and adolescence in cross-sectional samples of rural and urban Kenyans from groups previously demonstrated to differ in physical activity levels. Our results indicate that among both rural and urban individuals, cartilage thickness declines with age, as has been found in ultrasound-based studies of youths in other countries (9,10). However, the degree of age-related cartilage thinning was greater in the less physically active, urban group than the more physically active, rural group. These results support the hypothesis that reduced physical activity associated with urbanization can impair knee cartilage development during youth and thus increase the probability that individuals enter adulthood with thinner cartilage that is biomechanically vulnerable. Following findings from developed countries (5), we expect that urban individuals entering adulthood with thinner baseline knee cartilage will have a greater risk of knee OA later in life than rural individuals with thicker knee cartilage. Because this cross-sectional study of children and adolescents cannot directly test this hypothesis, further research is necessary to determine whether cartilage growth differences like those documented here affect relative OA susceptibility in societies undergoing urbanization.

Although urbanization affects many aspects of lifestyle, several lines of evidence suggest that physical activity is the factor most likely to have driven the greater age-related cartilage thinning among the urban compared with rural Kenyan youths (6). First, experiments with animal models demonstrate the importance of physical activity for attaining optimal knee cartilage structure. For example, prolonged periods of limb immobilization have been shown to lead to thinner knee cartilage (11), and daily running by young animals has been shown to augment knee cartilage thickness (12). Second, two studies of people from a developed country (Australia) indicate that high levels of physical activity while young promote the growth of thicker knee articular cartilage: Antony et al (4) found that childhood physical performance measurements were correlated with knee cartilage volume 25 years later in adulthood, and Jones et al (3) found a positive association between intensity of athletic activity and knee articular cartilage volume accrual over the course of 1.6 years among adolescents.

Although the results of the latter study superficially appear to differ from those of this study in showing increases in knee cartilage during adolescence, this discrepancy is almost certainly because Jones et al could differentiate growing, uncalcified knee articular cartilage from underlying ossifying cartilage in magnetic resonance images (MRIs). The ultrasound protocol used in our study precluded us from distinguishing between these two types of cartilage, but the relatively slower rate of cartilage thinning exhibited by the rural Kenyan group in this study can be interpreted as indicating greater articular cartilage thickening during growth when compared with the urban group. Thus, the results of this study are generally concordant with these prior studies (3,4) and build on their findings by providing a natural test of the hypothesis that physical activity while young is related to knee articular cartilage growth among geographically close but behaviorally distinct groups. Additionally, our findings highlight the potential implications of this relationship for developing countries, where shifts from rural subsistence farming to urban, market-integrated economies are leading to reduced physical activity levels.

Although physical activity appears to be the most conspicuous candidate for the cause of differences in knee cartilage growth between the two groups in this study, in many developing countries the urbanization-related lifestyle change that has had the greatest health consequences is the shift toward obesogenic diets (13). Among adults, such dietary changes have been hypothesized to increase knee OA risk by promoting adiposity-induced chronic low-grade systemic inflammation (2). Among children and adolescents, however, it is unclear whether or how obesogenic diets might impair knee cartilage growth. In developed countries, obesity has been found to be a poor predictor of knee cartilage thickness during youth (3). In this study, obesity was nearly absent in both the rural and urban groups, although individuals in the urban group tended to have higher BMIs and larger waist circumferences.

Another consideration that requires future study is that youths in the rural group in this study are frequently barefoot, whereas individuals in the urban group regularly wear shoes (verified by observation and interviews with teachers at the schools). This difference is noteworthy because barefoot walking has been shown to generate more rapid ground reaction force spikes at foot contact in these groups than shod walking (14), and it is widely believed that activities that expose knees to repetitive impacts characterized by high rates of loading can be harmful to knee cartilage (15). For this reason, shoes with cushioned soles are commonly recommended to help reduce pain associated with OA and delay disease progression (16). However, our finding that regularly barefoot individuals seemed to exhibit more healthy cartilage growth indicates that additional work is needed to assess the relationship between footwear cushioning and knee cartilage health.

This study has several limitations. First, although our data indicate that urbanization can negatively influence knee cartilage development, this study lacked individual-level data on physical activity, diet, and other lifestyle variables, limiting our ability to tease apart pathways linking urbanization and cartilage thickness. Second, disparities in nutrition and energy availability may have affected cartilage growth rates in rural versus urban participants in a way similar to how they affect overall skeletal growth. However, our leg length–matched GLM statistically controlled for growth differences between groups and still found a significant difference in cartilage development between urban and rural participants. Third, to collect data from individuals in a remote region of Kenya, we used ultrasonography to measure knee cartilage thickness rather than MRI, thus limiting our ability to assess uncalcified articular cartilage and underlying calcified cartilage separately. We were also unable to examine features of cartilage composition, such as collagen networks and proteoglycan content, that are major determinants of the mechanical properties of cartilage. Even so, the data reported here merit attention by rheumatological researchers and health care providers because individuals in developing countries undergoing rapid lifestyle changes make up a large fraction of the global population and may have a heightened vulnerability to knee OA (2).

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Holowka had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Holowka, Wallace, Mathiessen, Lieberman.

Acquisition of data. Holowka, Mang'eni Ojiambo, Okutoyi, Lieberman.

Analysis and interpretation of data. Holowka, Wallace, Worthington, Lieberman.

REFERENCES

1. Berenbaum F, Wallace IJ, Lieberman DE, Felson DT. Modern-day environmental factors in the pathogenesis of osteoarthritis. Nat Rev Rheumatol 2018;14:674–81.
2. Wallace IJ, Felson DT, Worthington S, Duryea J, Clancy M, Aliabadi P, et al. Knee osteoarthritis risk in non-industrial societies undergoing an energy balance transition: evidence from the indigenous Tarahumara of Mexico [published erratum appears in Ann Rheum Dis. 2021;80:e27]. Ann Rheum Dis 2019;78:1693–8.
3. Jones G, Ding C, Glisson M, Hynes K, Ma D, Cicuttini F. Knee articular cartilage development in children: a longitudinal study of the effect of sex, growth, body composition, and physical activity. Pediatr Res 2003;54:230–6.
4. Antony B, Jones G, Venn A, Cicuttini F, March L, Blizzard L, et al. Childhood physical performance measures and adulthood knee cartilage volume and bone area: a 25-year cohort study. Arthritis Care Res (Hoboken) 2015;67:1263–71.
5. Dório M, Hunter DJ, Collins JE, Asher R, Eckstein F, Guermazi A, et al. Association of baseline and change in tibial and femoral cartilage thickness and development of widespread full-thickness

cartilage loss in knee osteoarthritis–data from the Osteoarthritis Initiative. Osteoarthritis Cartilage 2020;28:811–8.

6. Ojiambo RM, Easton C, Casajús JA, Konstabel K, Reilly JJ, Pitsiladis Y. Effect of urbanization on objectively measured physical activity levels, sedentary time, and indices of adiposity in Kenyan adolescents. J Phys Act Heal 2012;9:115–23.
7. Castillo ER, Sang MK, Sigei TK, Dingwall HL, Okutoyi P, Ojiambo R, et al. Physical fitness differences between rural and urban children from western Kenya. Am J Hum Biol 2016;28:514–23.
8. Naredo E, Acebes C, Möller I, Canillas F, de Agustín JJ, de Miguel E, et al. Ultrasound validity in the measurement of knee cartilage thickness. Ann Rheum Dis 2009;68:1322–7.
9. Spannow AH, Pfeiffer-Jensen M, Andersen NT, Herlin T, Stenbøg E. Ultrasonographic measurements of joint cartilage thickness in healthy children: age- and sex-related standard reference values. J Rheumatol 2010;37:2595–601.
10. Samanta M, Mitra S, Samui PP, Mondal RK, Hazra A, Sabui TK. Evaluation of joint cartilage thickness in healthy children by ultrasound: an experience from a developing nation. Int J Rheum Dis 2018;21:2089–94.
11. Nomura M, Sakitani N, Iwasawa H, Kohara Y, Takano S, Wakimoto Y, et al. Thinning of articular cartilage after joint unloading or immobilization. An experimental investigation of the pathogenesis in mice. Osteoarthritis Cartilage 2017;25:727–36.
12. Kiviranta I, Tammi M, Jurvelin J, Säämänen AM, Helminen HJ. Moderate running exercise augments glycosaminoglycans and thickness of articular cartilage in the knee joint of young beagle dogs. J Orthop Res 1988;6:188–95.
13. Popkin B. An overview on the nutrition transition and its health implications: the Bellagio meeting. Public Health Nutr 2002;5:93–103.
14. Holowka NB, Wynands B, Drechsel TJ, Yegian AK, Tobolsky VA, Okutoyi P, et al. Foot callus thickness does not trade off protection for tactile sensitivity during walking. Nature 2019;571:261–4.
15. Radin EL. Who gets osteoarthritis and why. J Rheumatol Suppl 2004;70:10–5.
16. McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage 2014;22:363–88.