A longitudinal study of the effect of sex and age on rate of change in knee cartilage volume in adults

Changhai Ding, Flavia Cicuttini¹, Leigh Blizzard, Fiona Scott and Graeme Jones

Objective. To describe the association between sex, age and rate of change in knee cartilage volume in adults.

Methods. A total of 325 subjects (mean age 45 yrs, range 26–61) was measured at baseline and ∼2 yrs later. Knee cartilage volume and bone size were determined using T1-weighted fat saturation magnetic resonance imaging (MRI). Height, weight, body mass index and radiographic osteoarthritis (ROA) were measured by standard protocols.

Results. Knee cartilage volume decreased by 1.5–4.2% per annum. In multivariable analysis, females had higher rates of change per annum in knee cartilage volume than males (medial tibia: −3.5%, P < 0.001; lateral tibia: −2.6%, P < 0.001 and patella: −0.8%, P = 0.053). The sex difference first appeared at age 40 and became more marked with increasing age at the medial tibial site only (P = 0.039). Age was significantly associated with annual change in knee cartilage volume at all three sites (β = −0.06 to −0.12%/yr, all P < 0.05), and these associations were stronger in females. With the exception of the medial site (β = −0.05/yr, P = 0.117 for ROA exclusion, and β = −0.06%/yr, P = 0.056 for ROA adjustment), the association with age did not change when subjects with ROA were excluded from analyses or after further adjustment for ROA.

Conclusions. Within the age range we studied, knee cartilage volume declines at a faster rate with increasing age. This is partly mediated by ROA at the medial tibial site only. Furthermore, women have substantially higher knee cartilage loss than men, and these sex differences first appear at age 40 and become more marked with increasing age, which has implications for prevention of cartilage loss from middle age.

KEY WORDS: Knee, Cartilage volume, Sex, Age, Osteoarthritis.

Introduction

Osteoarthritis (OA) is a slowly progressive disease characterized by gradual loss of articular cartilage. It is well-established that female sex and age are strong risk factors for knee OA [1, 2]. Before the age of 50 yrs, the incidence of this disease is low and men have a slightly higher prevalence than women, but after age 50, the disease becomes frequent and women have a higher prevalence [1, 2]. The underlying mechanism remains obscure, but sex- and age-related alteration in knee cartilage structure is one possible explanation. Cross-sectional studies have shown that males have consistently higher knee cartilage volume than females, predominantly due to greater body size [3–6], but age is inconsistently associated with knee cartilage volume [7–9] possibly due to the inability of cartilage volume assessment to differentiate swollen from normal cartilage. Recently, we reported an interaction between age and sex cross-sectionally, where the sex differences in knee cartilage volume became more marked for subjects >50 yrs of age, implying higher rates of loss in older females [4]. The limited longitudinal data reveal inconsistent associations between sex, age and change in knee cartilage volume [10–14], which may reflect study design issues and/or small sample sizes. Large longitudinal studies are the only way to resolve these issues. Furthermore, rate of loss in cartilage volume is important because it is substantial in subjects with established OA [10] and is predictive of knee arthroplasty [15], and thus appears to be a key measure of OA progression.

Magnetic resonance imaging (MRI) can visualize joint structure and is recognized as a valid, accurate and reproducible tool to measure articular cartilage volume [3–6] and its rate of change [10–14]. The aim of this longitudinal MRI-based study, therefore, was to describe the association between sex, age and rate of change in knee cartilage volume in a large convenience sample of adults aged 25–61 yrs.

Materials and methods

Subjects

The study was carried out in southern Tasmania, and primarily in the capital city of Hobart, from June 2000 to December 2001. The follow-up study was conducted ∼2 yrs later. Subjects were selected from two sources. Half of the subjects were the adult children (offspring) of subjects who had a knee replacement performed for primary knee OA at any Hobart hospital from 1996 to 2000. This diagnosis was confirmed by the reference to the medical records of the orthopaedic surgeon and the original radiograph where possible. The other half were controls selected at random from the state Electoral Roll, a comprehensive listing of the population. Subjects from either group were excluded on the basis of contraindication to MRI (including metal sutures, presence of shrapnel, iron filings in the eye and claustrophobia). No women were on hormone replacement therapy at the time of the study. This study was approved by the Southern Tasmanian Health and Medical Human Research Ethics Committee and all subjects provided informed written consent.

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Anthropometrics

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) 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/m²) was calculated.

X-ray

A standing anteroposterior semiflexed view of the right knee was performed in all subjects at baseline and scored individually for osteophytes and joint space narrowing as previously described [16].

Knee cartilage volume measurement

MRI scans of the right knees of the subjects were performed at baseline and follow-up. Knees were imaged in the sagittal plane on a 1.5-T whole body magnetic resonance unit (Picker, Cleveland, OH, USA) 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°; 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). Knee cartilage volume was determined (Fig. 1) by means of image processing on an independent workstation using Osiris (University of Geneva) by a single observer (C.D.) as previously described [3–6]. The volumes of individual cartilage plates (medial tibial, lateral tibial and patella) were isolated from the total volume by manually drawing disarticulation contours around the 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 continuous sections) for the final 3D rendering. Femoral cartilage volume was not assessed because it is correlated strongly with cartilage volume at two tibial sites and patellar site [17]. Measurements made using this method have high intra- and inter-observer reproducibility [3]. The coefficient of variation (CV) for cartilage volume measures was 2.1% for medial tibial, 2.2% for lateral tibial and 2.6% for patella [3].

Knee bone size measurement

Knee tibial plateau bone area and patellar bone volume were determined by means of image processing on an independent workstation using Osiris as previously described [3–5]. To transform the images to the axial plane, the Analyse Software package developed by the Mayo Clinic was employed. The CVs for these measures in our hands are 2.2–2.6% [3].

Data analysis

Rates of change in cartilage volume were calculated as: percentage change per annum = [(follow-up cartilage volume – baseline cartilage volume)/baseline cartilage volume]×time between two scans in years.

Linear regression analysis was used to examine the associations between annual percentage change and age or sex before and after adjustment for the factors such as offspring-control status, BMI, baseline cartilage volume, bone size and/or radiographic OA (ROA). Standard diagnostic checks of model fit and residuals were routinely made, and data points with large residuals and/or high influence were investigated for data errors. Interactions between age and sex were investigated by regressing the change in cartilage volume on a binary (0/1) term for sex within age strata (<40, 40–44, 45–49 and ≥50 yrs), and assessed by testing the statistical significance of the coefficient of a (sex × age score) product term where the age score assigned were <40 yrs = 1, 40–44 yrs = 2, 45–49 yrs = 3 and ≥50 yrs = 4.

Results

A total of 325 subjects (males n = 135, females n = 190) completed the study (87% of those originally studied). The reasons for loss to follow-up were: two deceased, five moved interstate, three claustrophobic, four due to illness and others no reason. This was a young sample with an average age of 45 yrs at baseline (range 26–61 yrs). The average time between visits was 2.3 yrs (range 1.8–2.6 yrs). Characteristics of the subjects are presented in Table 1. Males and females were similar in terms of baseline age, BMI and ROA, but males had greater baseline height and weight. Over 2.3 yrs, knee cartilage volume decreased on average by 0.04–0.15 ml/year or 1.5–4.2%/yr in individual sites (all P < 0.001) (Table 1). Offspring had greater knee cartilage loss (1.7–4.8%) than controls (1.0–4.3%), and subjects with ROA (n = 56) trended have greater knee cartilage loss than subjects without ROA in total sample (differences: <0.1% at medial tibia; −0.6% at lateral tibia; −0.8% at patellar and −0.6% for total cartilage volume), and in males or females (Table 2), but this did not reach statistical significance.

In unadjusted analyses, annual percentage knee cartilage volume change at medial tibial, lateral tibial and patellar sites did not differ between males and females (Table 1). These results remained unchanged after adjustment for age, BMI and offspring-control status (data not shown); however, after further adjustment for baseline cartilage volume and bone size, females had a significantly higher rate of change in medial and lateral tibial cartilage volume in the whole sample (Table 3), in offspring (sex differences: −2.01% and −1.87% at medial and lateral tibial sites, respectively, both P < 0.01), in controls (sex differences: −4.77 to −3.05% at medial and lateral tibial sites, respectively, both P < 0.001) and in subjects without ROA (sex differences: −3.47 to −2.57% at medial and lateral tibial sites, respectively, both P < 0.001). There were no significant sex differences in
Knee cartilage loss, sex and age

Table 1. Characteristic of participants

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 325)</th>
<th>Male (n = 135)</th>
<th>Female (n = 190)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>45.2 (6.4)</td>
<td>45.0 (6.5)</td>
<td>45.3 (6.4)</td>
<td>0.668</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169.0 (8.4)</td>
<td>176.0 (6.5)</td>
<td>164.1 (5.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77.4 (15.4)</td>
<td>84.6 (12.7)</td>
<td>72.4 (15.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.0 (4.8)</td>
<td>27.3 (3.7)</td>
<td>26.9 (5.4)</td>
<td>0.447</td>
</tr>
<tr>
<td>Radiographic OA (%)</td>
<td>17</td>
<td>16</td>
<td>19</td>
<td>0.493**</td>
</tr>
<tr>
<td>Change in patellar cartilage volume p.a. (%)</td>
<td>-0.26 (0.27)</td>
<td>-0.31 (0.30)</td>
<td>-0.22 (0.23)</td>
<td>0.004</td>
</tr>
<tr>
<td>Change in medial tibial cartilage volume p.a. (%)</td>
<td>-0.06 (0.10)</td>
<td>-0.06 (0.11)</td>
<td>-0.06 (0.09)</td>
<td>0.785</td>
</tr>
<tr>
<td>Change in lateral tibial cartilage volume p.a. (%)</td>
<td>0.04 (0.09)</td>
<td>-0.05 (0.10)</td>
<td>-0.04 (0.09)</td>
<td>0.482</td>
</tr>
<tr>
<td>Change in total cartilage volume p.a. (%)</td>
<td>-0.15 (0.15)</td>
<td>-0.20 (0.17)</td>
<td>-0.12 (0.12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in patellar cartilage volume p.a. (%)</td>
<td>-3.0 (2.9)</td>
<td>-2.9 (2.9)</td>
<td>-3.0 (2.9)</td>
<td>0.875</td>
</tr>
<tr>
<td>Change in medial tibial cartilage volume p.a. (%)</td>
<td>-2.5 (4.1)</td>
<td>-2.1 (4.2)</td>
<td>-2.8 (4.0)</td>
<td>0.124</td>
</tr>
<tr>
<td>Change in lateral tibial cartilage volume p.a. (%)</td>
<td>-1.5 (3.4)</td>
<td>-1.4 (3.3)</td>
<td>-1.6 (3.5)</td>
<td>0.549</td>
</tr>
<tr>
<td>Change in total cartilage volume p.a. (%)</td>
<td>-4.2 (3.8)</td>
<td>-4.6 (4.0)</td>
<td>-4.0 (3.7)</td>
<td>0.163</td>
</tr>
</tbody>
</table>

Mean (s.d.) except for percentage for radiographic osteoarthritis.

**Chi-square, all others *t-test between males and females.

Table 2. Sex difference in knee cartilage volume in offspring and controls and subjects with and without ROA

<table>
<thead>
<tr>
<th></th>
<th>Male (n = 67)</th>
<th>Female (n = 95)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offspring</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in total cartilage volume p.a. (%)</td>
<td>-3.4 (2.6)</td>
<td>-3.5 (2.8)</td>
<td>0.822</td>
</tr>
<tr>
<td>Change in medial tibial cartilage volume p.a. (%)</td>
<td>-3.2 (3.6)</td>
<td>-3.0 (3.6)</td>
<td>0.814</td>
</tr>
<tr>
<td>Change in lateral tibial cartilage volume p.a. (%)</td>
<td>-1.7 (2.9)</td>
<td>-2.1 (3.3)</td>
<td>0.510</td>
</tr>
<tr>
<td>Change in patellar cartilage volume p.a. (%)</td>
<td>-4.8 (3.7)</td>
<td>-4.7 (3.7)</td>
<td>0.824</td>
</tr>
<tr>
<td>Controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in total cartilage volume p.a. (%)</td>
<td>-2.5 (3.2)</td>
<td>-2.5 (3.0)</td>
<td>0.990</td>
</tr>
<tr>
<td>Change in medial tibial cartilage volume p.a. (%)</td>
<td>-1.1 (4.5)</td>
<td>-2.7 (4.3)</td>
<td>0.030</td>
</tr>
<tr>
<td>Change in lateral tibial cartilage volume p.a. (%)</td>
<td>-1.0 (3.6)</td>
<td>-1.1 (3.7)</td>
<td>0.835</td>
</tr>
<tr>
<td>Change in patellar cartilage volume p.a. (%)</td>
<td>-4.3 (4.2)</td>
<td>-3.3 (3.5)</td>
<td>0.080</td>
</tr>
<tr>
<td>Subjects without ROA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in total cartilage volume p.a. (%)</td>
<td>-2.8 (3.0)</td>
<td>-2.9 (2.9)</td>
<td>0.786</td>
</tr>
<tr>
<td>Change in medial tibial cartilage volume p.a. (%)</td>
<td>-2.1 (4.2)</td>
<td>-2.9 (4.0)</td>
<td>0.123</td>
</tr>
<tr>
<td>Change in lateral tibial cartilage volume p.a. (%)</td>
<td>-1.3 (3.2)</td>
<td>-1.5 (3.4)</td>
<td>0.538</td>
</tr>
<tr>
<td>Change in patellar cartilage volume p.a. (%)</td>
<td>-4.4 (3.9)</td>
<td>-3.9 (3.6)</td>
<td>0.262</td>
</tr>
<tr>
<td>Subjects with ROA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in total cartilage volume p.a. (%)</td>
<td>-3.6 (2.8)</td>
<td>-3.4 (3.0)</td>
<td>0.746</td>
</tr>
<tr>
<td>Change in medial tibial cartilage volume p.a. (%)</td>
<td>-2.3 (4.7)</td>
<td>-2.8 (4.1)</td>
<td>0.652</td>
</tr>
<tr>
<td>Change in lateral tibial cartilage volume p.a. (%)</td>
<td>-1.9 (3.7)</td>
<td>-2.0 (4.0)</td>
<td>0.939</td>
</tr>
<tr>
<td>Change in patellar cartilage volume p.a. (%)</td>
<td>-5.7 (3.9)</td>
<td>-4.4 (4.3)</td>
<td>0.265</td>
</tr>
</tbody>
</table>

Mean (s.d.). *t-test between males and females.

Annual change in tibial cartilage volume among subjects younger than 40 yrs of age; however, females had significantly higher loss in cartilage volume among older subjects and these differences became more marked after 50 yrs old at the medial tibial site and total compartment (Table 4).

Age was significantly associated with annual rate of change in knee cartilage volume at all sites in univariable and multivariable analyses (Table 3) and these remained unchanged when subjects with ROA were excluded for analyses except for that at medial tibial site ($\beta = -0.05%/yr, P = 0.12$). Among females, annual rates of change in knee cartilage volume at all sites were significantly associated with age (Fig. 2), and the age difference in total cartilage volume loss became more marked after 50 yrs old ($\geq 50$ yrs vs $<50$ yrs: $\beta = -1.50%/yr, P = 0.001$). There were no significant associations between age and knee cartilage loss for males (Fig. 2), but annual patellar cartilage loss was significantly higher in males over 40 yrs of age than in those younger than 40 yrs of age (difference: $-1.92%/yr, P = 0.02$). The associations between age and knee cartilage loss were statistically significant among offspring ($\beta = -0.17$ to $-0.07%/yr$, all $P < 0.01$), but were generally weaker for controls ($\beta = -0.09$ to $-0.05%/yr$, $P = 0.04$ to $0.33$).

The results remained largely unchanged after further adjustment for ROA (data not shown) except that the association between age and change in medial tibial cartilage volume in the whole sample became of borderline significance ($\beta = -0.06%/yr, P = 0.056$). There were no statistically significant differences in the magnitude of the gender or age effect between the offspring and control group (all $P > 0.05$ for the interactions, data not shown), and these groups were combined for the sex–age analyses. There was no difference in results if absolute rather than percentage rate of change was examined (data not shown).

Discussion

This longitudinal study documents associations of rate of change in knee cartilage with sex and age in a large convenience sample of subjects. Advancing age was significantly associated with an increasing rate of tibial and patellar cartilage loss, and females had substantially higher tibial cartilage loss than males. Moreover, the sex differences in the rate of knee cartilage loss increased with age.
Knee cartilage volume at all three compartments decreased significantly over 2 yrs. The magnitude of cartilage loss was higher in offspring than controls [18] and the rate of change in controls was similar to previous reports in healthy subjects [13, 14] but lower than that in subjects with established symptomatic knee OA [10, 12]. In this sample, we found also that knee cartilage loss was higher in subjects with ROA, but this did not reach statistical significance possibly due to the small number affected. The annual cartilage loss at tibial sites for subjects with ROA was generally lower than that found (≈5%) in a sample of subjects with established symptomatic knee OA [10], which is most likely due to the predominantly mild ROA in this sample. With increasing age, the cartilage loss is both diffuse as described in this study and focal, as we recently reported that tibiofemoral and patellar cartilage focal defects also had an age gradient [19]. However, change in cartilage defects cannot completely account for the much larger change in cartilage volume [20].

We found consistent associations between age and rate of change in knee cartilage volume in all three compartments, especially in women. This implies that cartilage volume declines at an increasing rate with age and has implications for prevention of cartilage loss and possibly knee replacement. This finding is consistent with our recent report about association between age and change in knee cartilage defects [19], but is markedly different to the findings from cross-sectional studies, including from this sample [8], suggesting cartilage volume is subject to cohort effects in cross-sectional studies. We would hypothesize that cartilage volume measured cross-sectionally will be at different stages of change in different individuals. A higher cartilage volume may represent healthy cartilage or diseased cartilage that is swollen due to loss of aggrecan and increased water content [21]. In contrast, follow-up over time will be more reliable as it compares rates of change in the individual rather than regressing on age across the whole sample. Similar results have been observed for bone density, which also declines at an increasing rate with increasing age [22]. Radiographic studies have suggested a significant negative linear correlation between increasing age and joint space size in normal males and females [23], whereas inconsistent associations have been reported between joint space narrowing and age in subjects with knee OA [24, 25]. Similarly, MRI studies have shown that knee cartilage thickness [8, 9] or cartilage volume [7, 8] at some sites decreases with age, but age is not associated with tibial cartilage loss in healthy men and women [13, 14]. In subjects with knee OA, age has been found to be associated with lateral tibial cartilage loss, but not with medial tibial and patellar cartilage loss [10, 11]. The underlying reasons are unclear but they may reflect variations in sex hormones, growth factors, genetics and other factors. These may also reflect early disease status, because the association between age and medial tibial cartilage loss was reduced after adjustment for ROA or when subjects with ROA were excluded from analyses.

Females had substantially higher tibial cartilage loss than males. Patellar cartilage loss was also higher in females but this did not reach statistical significance. This is broadly consistent with our previous cross-sectional studies that show females have lower knee cartilage volume than males [3–5], and with the finding from a recent longitudinal study of subjects with knee OA that there were more women in the group with faster knee cartilage loss than in the group with slower knee cartilage loss over 2 yrs [12]. This is also consistent with our recent report that increases in tibiofemoral cartilage defect were 3.1–3.6-fold higher in females than males [19]. In contrast, studies from our group in other samples [10, 11] found no sex difference in tibial cartilage loss but the rate of patellar cartilage loss was greater in women than men over 2 yrs in subjects with knee OA. Our cross-sectional study in this sample showed that men had substantially higher knee cartilage volumes than women and these differences became larger after age 50 implying higher rates of cartilage loss in post-menopausal women [4]. This was confirmed by the current study. However, the sex difference in rate of change in medial tibial cartilage volume first appeared at age 40, which is a decade earlier than sex differences in the incidence of symptomatic knee OA [26] and would be consistent with...
knee cartilage loss preceding knee ROA. This study is the first to provide evidence that women have significant knee cartilage loss in their forties and this has implications for prevention of cartilage loss and possibly knee replacement from middle age.

The reasons for sex differences in knee cartilage loss are unclear. In the present sample, ROA was uncommon, and sex differences in knee cartilage loss did not change after adjustment for ROA, suggesting sex difference in knee cartilage loss is unlikely to be due to pre-existing OA, but may reflect early disease. It may also reflect sex differences in the effect of aging on knee cartilage, because we found that the sex differences in knee cartilage loss increased with age and were most marked after age 50, suggesting that women may have rapid cartilage loss around the time of menopause when they have a marked decrease in sex hormones. Indeed, oestrogens, progesterone and testosterone receptors are present in human fetal cartilaginous tissue [27], and 17\beta-estradiol stimulates human articular chondrocytes from female, but not from male, donors to increase DNA synthesis, sulphate incorporation and alkaline phosphatase activity [28]. Androgens can also stimulate human chondrocytes proliferation as well as collagen and proteoglycan synthesis [29]. Cross-sectional data have suggested that hormone replacement therapy is associated with high tibial cartilage volume in post-menopausal women [30], and serum testosterone can explain up to 8% of variation in medial tibial cartilage volume in men [7].

However, there are little data at present to document the effects of sex hormones on knee cartilage in men. Therefore, further research is needed to understand the mechanisms underlying sex differences in knee cartilage loss and to develop sex-specific strategies for prevention and treatment of knee OA.
of sex hormones on knee cartilage loss, and thus the variations in sex hormones that may underlie the sex differences in knee cartilage loss need to be further explored.

There were no statistically significant differences in the magnitude of the gender or age effect between the offspring and controls. However, the sex difference in rate of change in medial tibial cartilage volume was −4.8% in controls compared with −2.0% in offspring, and the associations between age and knee cartilage loss were significant at all sites in offspring but not at all significant in controls. This may reflect an age–gene interaction on knee cartilage loss and expands our reports that in sib pairs the rate of knee cartilage loss had high heritability especially at the medial tibial site [31], and that offspring of those with severe knee OA in later life had higher rates of knee cartilage loss in all compartments than controls without this history [18].

The loss to follow-up in this study was small, suggesting that non-participation is not a source of major concern, but the study has a number of potential limitations. The study was primarily designed to look at genetic mechanisms of knee OA and utilized a matched design of siblings and controls. The matching was broken for the current study but, as outlined above, adjustment for family history did not substantially alter the main results. The sample is a convenience sample, which limits the relevance of prevalence estimates; however, as an analytical study, Miettinen [32] states that for associations to be generalizable to other populations three key criteria need to be met regarding selection, sample size and adequate distribution of study factors, all of which are met by this study. Secondly, we used tibial cartilage as the measure of joint cartilage at the tibiofemoral joint rather than femoral cartilage and it is possible that changes in femoral cartilage are different to tibial sites. However, we have previously shown a strong correlation between the tibial and femoral cartilage in the medial and lateral tibiofemoral compartments both in cross-sectional [17] and longitudinal studies [33]. Since the femoral cartilage articulates with three joints (the medial and lateral tibiofemoral joints and the patellofemoral joints), it is more difficult to clearly identify the relevant component of the femoral joint when assessing the medial and lateral tibiofemoral joints since this requires arbitrary definitions. In contrast, each of the tibial cartilage plates that we examined in this study only forms part of one joint (either the medial or the lateral tibiofemoral joint). Lastly, measurement error may influence results, but our measurements of knee cartilage volume, bone size and ROA measurement were highly reproducible [3, 16], suggesting this is unlikely.

Conclusion
This longitudinal study suggests that, within the age range we studied, knee cartilage volume declines at a faster rate with increasing age. This is partly mediated by ROA at the medial tibial site only. Furthermore, women have substantially higher knee cartilage loss than men and these sex differences first appear at age 40 and become more marked with increasing age, which has implications for prevention of cartilage loss and possibly knee replacement from middle age.

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The authors have declared no conflicts of interest.

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