Published in final edited form as:
Ann Rheum Dis. 2008 November ; 67(11): 1545–1549. doi:10.1136/ard.2007.076810.

Premorbid knee osteoarthritis is not characterised by diffuse thinness: the Framingham Osteoarthritis Study

D J Hunter[1,2], **J B Niu**[1], **Y Zhang**[1], **M LaValley**[1], **C E McLennan**[1,2], **M Hudelmaier**[3], **F Eckstein**[3], and **D T Felson**[1]

[1]Boston University School of Medicine, Massachusetts, USA

[2]Division of Research, New England Baptist Hospital, Boston, Massachusetts, USA

[3]Institute of Anatomy and Musculoskeletal Research, Paracelsus Private Medical University, Salzburg, Austria

Abstract

Objective—It is hypothesised that, like low bone density and fracture, thin cartilage predisposes to osteoarthritis (OA). Inferences about the effects of cartilage thickness on the development of OA can be made by evaluating the status of an unaffected non-diseased contralateral knee, in persons with unilateral OA, which we shall label the “premorbid knee”. The primary objective of this analysis was to compare cartilage thickness in premorbid knees with non-OA knees drawn from persons without any knee OA to determine if cartilage in the premorbid knee was thinner than in the knee drawn from someone without OA in either knee.

Methods—From 2002 to 2005, The Framingham Osteoarthritis Study recruited subjects without respect to OA from the community. We obtained posteroanterior, semiflexed and lateral films of both knees and knee magnetic resonance imaging to quantify cartilage volume in one knee. The cartilage plates of the patella, medial and lateral femur, medial and lateral tibia were quantified, using a 3D FLASH-water excitation sequence (in plane resolution 0.3×0.3 mm, 512 matrix, slice thickness 1.5 mm) and digital post-processing, involving three-dimensional reconstruction. Radiographs were used to define the OA status of knees with disease defined as Kellgren and Lawrence grade ≥2 and or patellofemoral OA on the lateral film. Of 1020 participants included in this analysis, 720 had no OA in either knee (no-knee OA sample), and 55 subjects had no OA in the knee that was examined using magnetic resonance imaging and OA in the contralateral knee (premorbid knee OA sample). We compared cartilage thickness and percentage of cartilage coverage (total bone interface covered with cartilage) between these groups. After initial plate-specific univariate comparisons we performed a multiple regression to assess the association between OA status (premorbid versus no OA knee) and cartilage thickness adjusting for age, sex and body mass index. We used the Generalised Estimating Equation to account for correlation between plates. To further determine if the cartilage was diffusely thinned or had only increased areas of denuded cartilage, we removed plates with denuded areas (less than 95% cartilage coverage) from the analysis.

Results—55% of subjects were women. There was no difference in cartilage thickness between the premorbid knees and the no-knee OA sample. After adjusting for age, sex and body mass index and removing plates with less than 95% coverage from the analysis, we found the same or even thicker cartilage in premorbid knees compared with the knee OA sample.

Correspondence to: Dr Hunter at Division of Research, New England Baptist Hospital, Boston, MA 02120, USA; djhunter@caregroup.harvard.edu.

Competing interests: None.

Conclusions—Premorbid knees do not have diffuse cartilage thinness. Rather the cartilage is normal or thicker with denuded areas suggesting that this may be the initial pathology rather than diffuse thinning.

Knee osteoarthritis (OA) tends to be a highly symmetrical condition where involvement in one knee is highly associated with contralateral involvement.[12] Cartilage thickness in persons unaffected by OA is highly symmetrical.[3] It is hypothesised that, like low bone density and fracture,[4] thin cartilage predisposes to OA. An important question is whether the relative thinness of cartilage in one person compared with another constitutes a risk factor for the development of OA.

Several pieces of indirect evidence suggest that cartilage thinning makes the knee joint vulnerable to disease. First, in almost all studies, cartilage thins with age, and the central predisposing risk factor for OA in humans is advancing age.[56] Second, cartilage is considerably thinner in women than in men, and obviously, women are much more predisposed to OA.[78] Further, in natural history studies of knee[910] and hip OA,[11] joints with narrower joint spaces (implying greater cartilage thinness at baseline) experience a higher rate of joint space loss than osteoarthritic joints with wider joint spaces. Thus, there are cogent reasons to support the notion that thinner cartilage may predispose the knee to the development of OA and in the presence of OA facilitate more rapid progression.

Not all evidence suggests that thin cartilage poses a risk for OA. In fact, early osteoarthritic cartilage may not be thin but rather thicker and swollen with water, which is imbibed by cartilage when the collagen network is disrupted and the role of proteoglycans is altered.[12–15] The documentation that cartilage gets increasingly thin with increasing stages of OA suggests that this swelling phenomenon is an early one and is not an important contributor to thickness in manifest OA. None the less, in the pre-morbid state, it is possible that thinness represents a normal state and thickness an early disease state. Also, thickness may reflect simply a healthy trophic response to focal loading and for normal cartilage, thicker cartilage may be cartilage that experiences greater loads (eg, patellar cartilage is thick and sustains great loads).

If cartilage thinness turns out to be a risk factor for disease, does this matter? First, thinness of cartilage may be a mediator by which a number of risk factors affect disease occurrence. One prime example might be sedentary levels of physical activity. In a study of children, Jones *et al*[8] reported that increased physical activity in the last 2 weeks was strongly correlated with greater cartilage thickness. Quadriceps strength showed a similar relationship to increased cartilage thickness. Thus, we may gain a better understanding of how potentially modifiable risk factors act on knees by understanding their relationship to cartilage thickness. Genetic predispositions may affect cartilage thickness and explain inherited resistance or susceptibility to disease.[16] Lastly, if thickness is protective, a variety of ways to manipulate cartilage matrix synthesis or degradation such as the administration of growth factors or inhibition of cytokine-mediated cartilage degradation may actually work by making cartilage thicker and therefore less likely to later break down. If cartilage thickness is important in this way, then tracking cartilage thickness over time may serve as a way to monitor therapeutic efficacy as in OA cartilage thickness diminishes as the severity of disease increases.[17] Thus, identifying any relationship of cartilage thickness to OA may help us understand better how risk factors work to cause or protect against disease and how we may treat disease.

Inferences about the effects of cartilage thickness on the development of OA can be made by evaluating the status of an unaffected non-diseased contralateral knee, in persons with unilateral OA, which we shall label the “premorbid knee”. The primary objective of this

analysis was to assess if cartilage in the premorbid still non-OA knees was thinner or a percentage of denuded bone (focal defects) was greater than that in the knees without OA. Thinness could be a function of diffuse thinning, which could make cartilage more vulnerable, or alternatively, early focal cartilage erosions, suggesting the beginning of OA.

MATERIALS AND METHODS

Study sample

The Framingham Heart Study is a longitudinal population-based cohort study established in 1948 to examine risk factors for heart disease.[18] A study of the offspring of the original cohort was initiated in 1971, and members of this cohort participated in a study on the inheritance of OA, between 1992 and 1994. The details of this cohort have been previously described.[19] All active (surviving and those not lost to follow-up) members of this group received an invitation letter and a follow-up phone call to recruit them into the current study.

We also recruited a community cohort drawn from a random sample from the town of Framingham using random digit dialling and Framingham census tract data. To enhance recruitment efforts, community leaders and senior centres were informed about the study described as a study of health sponsored by Boston University, and flyers were hung in public areas to increase the public's familiarity with the study. Eligibility criteria included: men and women aged 50–80 years; ambulatory (use of assistive devices such as canes and walkers was allowed); and willing to participate in a follow-up study in the near future. Exclusion criteria were: the presence of bilateral total knee replacements, and the presence of rheumatoid arthritis. In neither group was participant selection based on the presence or absence of knee OA.

The Framingham Osteoarthritis Study protocol involved multiple components one of which was a radiographic exam, including posteroanterior fixed flexion[20] and lateral radiographs[21] of both knees. In addition all members of the newly derived community cohort were eligible for a bilateral knee magnetic resonance imaging (MRI) exam, including the 3D FLASH sequence performed of their right knee only, although 44 participants refused or were unable to complete the MRI exam, which resulted in 953 with complete MRI exams. In an attempt to minimise the respondent burden on the frequently studied Offspring Cohort, only those with knee pain in either knee underwent the bilateral MRI exam (n = 356) and only those with positive Kellgren and Lawrence scores from the previous exam (n = 92 of the 356) were eligible for the additional 3D FLASH sequences on the knee with the lesser degree of disease.

Subjects included in the current analysis consisted of 1305 members of the Offspring Cohort of Framingham Heart Study and 997 new recruits (none of whom were members of the Framingham Heart Study) from Framingham, Massachusetts, USA. Participants in this combined group, designated the Framingham Osteoarthritis Study cohort, were examined in 2002–05.[22]

Radiographs and magnetic resonance imaging

Using the posteroanterior, fixed flexion radiographs of both knees, we defined knees with tibiofemoral radiographic OA (TF ROA), as those with evidence of Kellgren and Lawrence grade ≥2 on posteroanterior view.[23] Using the lateral radiograph we defined patellofemoral radiographic OA (PF ROA) as any osteophyte grade≥2 or and osteophyte grade = 1 with joint space narrowing ≥2.[24] For this study, we focus on knees without radiographic OA, selecting knees both from persons who had no *x*-ray OA (in both TF and PF) in either knee and those who had *x*-ray OA in one knee (in either the PF or TF compartment; we focused on the contralateral knee in these subjects).

The MRI was acquired with coronal and axial 3D FLASH-water excitation sequences (slice thickness 1.5 mm, in-plane resolution 0.3×0.3 mm ×1.5 mm).

The cartilage plates of the patella (P), central medial femur (cMF), central lateral femur (cLF), medial tibia (MT) and the lateral tibia (LT) were quantified as described previously using a 3D digital post-processing using dedicated Chondrometrics Works software (Chondrometrics, Ainring, Germany).[25] Segmentation was performed by technicians who had all received formal training in cartilage segmentation prior to the study, and all segmentations in all segmented slices of all data sets were quality controlled by an expert reader (FE). If necessary, corrections were made to the segmentations. In a previous study test–retest coefficient of variations (with joint repositioning) ranged from 2.0% to 3.6%.

Using this technique we computed the following measures:

1. Total mean cartilage thickness (ThCtAB)(including denuded cartilage areas as 0 mm cartilage thickness).
2. Percentage denuded area (dAB = total cartilage bone interface area denuded of cartilage where 0% represents completely denuded and 100% represents complete coverage).
3. Mean cartilage volume (mm^3).

First, to define the non-diseased knees to be used in this analysis, we used *x*-ray knee OA, defining OA knees as having either Kellgren & Lawrence grade ≥2 in the TF joint or PF OA on the lateral radiograph; and non-OA as Kellgren & Lawrence grade <2 and no PF OA on the lateral radiograph.

Using this radiograph definition, 720 subjects had no OA in the MRI knee and no OA in the contralateral knee (no OA sample), and 55 subjects had no OA in the MRI knee and OA in the contralateral knee (premorbid OA sample). We compared the ThCtAB, and dAB between these groups.

Statistical analysis

We compared the cartilage thickness (ThCtAb), percentage denuded area (dAB) and cartilage volume between the premorbid OA sample and the OA sample. Initially the results were compared using t-tests done on the five individual cartilage plates. To further refine the differences in thickness the central region of the medial tibia and central medial femur was also assessed. We then performed a multiple regression to assess the association between OA status (premorbid versus no OA knee) and cartilage thickness adjusting for age, sex and body mass index. We used Generalised Estimating Equations to account for correlation within plates in a knee. To further determine if the cartilage was diffusely thinned or had increased areas of denuded cartilage, we removed plates with denuded areas (of bone surface generally covered with hyaline cartilage, less than 95% of the bone was covered by cartilage) from the analysis.

RESULTS

Of the 1079 knees read for cartilage volume and thickness, 1020 had radiographic knee OA information for both knees within the subject. Of these 1020 knees, 720 subjects had no OA in the MRI knee and no OA in the contralateral knee (no OA sample); 55 subjects had no OA in the MRI knee and OA in the contralateral knee (premorbid OA sample) (table 1). For our study question, we compared the ThCtAB and dAB between these two groups.

Mean cartilage thickness was greater in the no-knee OA sample than in the premorbid knee in the patella (see table 2). For the remainder of the plates there was no significant difference in cartilage thickness between these two groups. Similarly, there was no more denuded cartilage (lower percentage cartilage coverage) in the premorbid knee OA group than in the no OA group. Consistent with the results for thickness there is no suggestion of a meaningful difference between the two groups of knees for volume.

The Generalised Estimating Equations linear regression model for the outcome of ThCtAB with the five plates giving repeated measures was fit to the data with plate, group (no OA, premorbid knee OA), and a group by plate interaction (table 3). The interaction was significant with a p-value of 0.001 suggesting that the effect of group (no OA versus premorbid knee OA) on cartilage thickness may differ by plate. Inspection of the interaction effects at the plate level indicated that premorbid knees had thinner cartilage in the patella; however, for the medial tibia (0.04 mm thicker in premorbid knees), like other plates, there was no suggestion that the cartilage was thinner in premorbid knees than no OA knees.

To consider the effect of percentage of coverage on these results, knees with coverage less than 95% were excluded from the analysis and the previous model was fit again. The 95% level was chosen by looking at the plots of cartilage thickness against coverage. We did this to ensure that persons with grossly denuded areas (pre-radiographic OA) were not included and rather the contrast was between knees with less evidence of OA. As a result 58 knees were excluded in the data presented in table 3.

There was no evidence of thinner cartilage in the tibiofemoral joint among premorbid knees. The interaction was still significant ($p<0.001$) suggesting that the effect of group (no OA versus premorbid knee OA) differed by plate. The results suggest some diminution of the difference for the patella to those obtained with the denuded cartilage knees included in the analysis. Inspection of the interaction effects at the plate level indicated that premorbid knees had slightly thicker cartilage in medial tibia (0.03 mm (standard error = 0.03)) and central lateral femur (0.04 mm (standard error = 0.04)) than no OA knees (although these differences were not significant).

DISCUSSION

Premorbid knees have thinner patella cartilage than knees from persons without OA. The differences in cartilage thickness are a result of denuded cartilage areas. For other plates there was no evidence of thinner cartilage in premorbid knees. Similarly premorbid knees did not have more denuded areas than the no-knee OA group. After adjusting for age, body mass index and gender, premorbid knees had slightly increased thickness compared with those with no-knee OA in the medial tibia. Given the symmetrical nature of OA this provides insights as to the type of pathology (full thickness cartilage loss with normal or increased thickness elsewhere in the plate) in the premorbid OA knee. It also provides indications that the earliest location of this pathology may be in the patella cartilage.

Knee OA tends to be a highly symmetrical condition where involvement in one knee is highly associated with contralateral involvement.[12] Cartilage thickness in persons unaffected by OA is highly symmetrical.[3] It was hypothesised that, like low bone density and fracture,[4] thin cartilage predisposes to OA. In fact, some authors have reported t scores of cartilage thickness (as a parallel to t scores for bone density) with the idea that low t scores (or thin cartilage) are likely to be a precursor to cartilage loss.[5] In addition, a smaller cartilage volume relative to bone surface area may predispose to OA because load is distributed over a smaller area and pressure is thus higher and shear stress in cartilage increases with

thinness, suggesting that thin cartilage is more vulnerable to shear injury than thicker cartilage.

Our findings suggest that the initial pathology of OA does not involve diffuse thinning. Rather they suggest that focal areas of denuded cartilage and potentially increased thickness could be part of the initial evolution of this disease. Previous studies have suggested that the initial pathology includes cartilage thickening, and it is not clearly understood if it represents an initial reversible phenomenon, permanent tissue damage or if it is the expression of a reparative process.[26] This is consistent with suggestions that cartilage defects measured semi-quantitatively may occur in early knee OA and precede cartilage volume loss.[27]

It has been suggested that an alteration in the role of proteoglycans in the hydration of cartilage (by facilitating expression and imbibition of extracellular water associated with disruption of the collagen microarchitectural network) may facilitate oedema of the extracellular matrix. Therefore, it is possible that the cartilage can swell because of alterations in the proteoglycans and water content.[1528] This will alter the mechanical properties of cartilage and the way load support and stresses are handled.[29] These micro-architectural changes could alter the frictional coefficient of the joint that would impose detrimental higher shear stresses on the already damaged extracellular matrix of cartilage, continuing the accelerated deterioration of its mechanical properties. Pathologically increased water imbibition may also cause a reduced swelling pressure in the matrix and therefore more deformable cartilage and higher strains and stresses. Morphometric measurement of volume and thickness in clinical studies is unlikely to detect this phenomenon on its own, and would be greatly enhanced by combining with techniques that assess the constituents of cartilage such as dGEMRIC (delayed gadolinium enhanced MRI of cartilage) or other compositional MRI techniques.

Radiographic abnormalities are a relatively late feature of OA,[30] and MRI is more likely to detect early changes of OA than radiographs.[31] Our definition of disease relied upon the radiograph to delineate a population with and without disease. A substantial proportion of subjects in the premorbid OA group had denuded cartilage with ostensibly normal radiographs. This finding needs to be considered when a person with unilateral radiographic OA presents with symptoms in their contralateral knee but their radiograph does not confirm their disease. What lead time MRI provides in making this diagnosis is uncertain, which is an issue this study was not designed to address.

This study also speaks to the way we should quantify cartilage morphometry in early disease. If cartilage initially swells and with this cartilage volume and thickness increase these measures may provide directions of change that investigators do not expect. Efforts to further investigate combining measures of morphometry with measures of composition could be helpful in this regard.

There are a number of important limitations of this study. First, and most importantly, we are assuming in our cross-sectional study that the premorbid knee will follow the same path as the contralateral knee and develop knee OA. This may not be the case (as in knees that have previously sustained an injury), although most disease is symmetric. The number of premorbid disease subjects was small raising the potential that the lack of difference found in cartilage thickness may be Type II error. However, we did not find results even in the right direction—for tibiofemoral cartilage, cartilage in premorbid knees was, if anything thicker, not thinner than in the no-knee OA cartilage. Further, no attempt was made to account for or adjust for diurnal variation in cartilage thickness. Because of the small number of knees with premorbid knee OA potentially we have limited power to detect differences. With 720 knees without OA and 55 knees with premorbid OA, we have 80%

power to detect the difference between the two groups in thickness as small as 0.40 SD of thickness. Take lateral tibia cartilage thickness as an example, SD = 0.30 mm, the smallest difference to be detected with this sample size is 0.12 = 0.30×0.40 mm.

Premorbid knees do not have diffuse cartilage thinness but rather normal or potentially increased thickness with areas of denuded cartilage. Given the symmetrical nature of OA this provides insights as to the initial type of pathology (cartilage thickening with full thickness cartilage loss) in the premorbid OA knee.

Acknowledgments

We would like to thank the participants and staff of the Framingham Osteoarthritis Study.

Funding: The study sponsor was not involved in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or the decision to submit the paper for publication. Supported by NIH AR47785.

References

1. Spector TD, Hart DJ, Doyle DV. Incidence and progression of osteoarthritis in women with unilateral knee disease in the general population: the effect of obesity. Ann Rheum Dis. 1994; 53:565–8. [PubMed: 7979593]
2. Mazzuca SA, Brandt KD, German NC, Buckwalter KA, Lane KA, Katz BP, et al. Development of radiographic changes of osteoarthritis in the “Chingford knee” reflects progression of disease or non-standardised positioning of the joint rather than incident disease [see comment]. Ann Rheum Dis. 2003; 62:1061–5. [PubMed: 14583568]
3. Eckstein F, Muller S, Faber SC, Englmeier KH, Reiser M, Putz R, et al. Side differences of knee joint cartilage volume, thickness, and surface area, and correlation with lower limb dominance—an MRI-based study. Osteoarthritis Cartilage. 2002; 10:914–21. [PubMed: 12464551]
4. Taylor BC, Schreiner PJ, Stone KL, Fink HA, Cummings SR, Nevitt MC, et al. Long-term prediction of incident hip fracture risk in elderly white women: study of osteoporotic fractures. J Am Geriatr Soc. 2004; 52:1479–86. [PubMed: 15341549]
5. Burgkart R, Glaser C, Hinterwimmer S, Hudelmaier M, Englmeier KH, Reiser M, et al. Feasibility of T and Z scores from magnetic resonance imaging data for quantification of cartilage loss in osteoarthritis. Arthritis Rheum. 2003; 48:2829–35. [PubMed: 14558088]
6. Felson DT, Zhang Y. An update on the epidemiology of knee and hip osteoarthritis with a view to prevention [Review] [116 refs]. Arthritis Rheum. 1998; 41:1343–55. [PubMed: 9704632]
7. Cicuttini F, Forbes A, Morris K, Darling S, Bailey M, Stuckey S. Gender differences in knee cartilage volume as measured by magnetic resonance imaging. Osteoarthritis Cartilage. 1999; 7:265–71. [PubMed: 10329301]
8. Jones G, Glisson M, Hynes K, Cicuttini F. Sex and site differences in cartilage development: a possible explanation for variations in knee osteoarthritis in later life. Arthritis Rheum. 2000; 43:2543–9. [PubMed: 11083279]
9. Dougados M, Gueguen A, Nguyen M, Thiesce A, Listrat V, Jacob L, et al. Longitudinal radiologic evaluation of osteoarthritis of the knee. J Rheumatol. 1992; 19:378–84. [PubMed: 1578451]
10. Buckland-Wright JC, MacFarlane DG, Lynch JA, Jasani MK. Quantitative microfocal radiography detects changes in OA knee joint space width in patients in placebo controlled trial of NSAID therapy [see comments]. J Rheumatol. 1995; 22:937–43. [PubMed: 8587086]
11. Dougados M, Gueguen A, Nguyen M, Berdah L, Lequesne M, Mazieres B, et al. Radiological progression of hip osteoarthritis: definition, risk factors and correlations with clinical status. Ann Rheum Dis. 1996; 55:356–62. [PubMed: 8694574]
12. Maroudas A, Bullough P. Permeability of articular cartilage. Nature. 1968; 219:1260–1. [PubMed: 5677422]
13. Maroudas A. Physical chemistry and the structure of cartilage. J Physiol. 1972; 223:21–2P. [PubMed: 5046150]

14. Mow, V.; Setton, L. Mechanical properties of normal and osteoarthritis articular cartilage. In: Brandt, K.; Doherty, M.; Lohmander, LS., editors. Osteoarthritis. New York: Oxford Medical Publications; 1998. p. 108-22.
15. Maroudas A, Venn M, Maroudas A, Venn M. Chemical composition and swelling of normal and osteoarthritic femoral head cartilage. II. Swelling. Ann Rheum Dis. 1977; 36:399–406. [PubMed: 200188]
16. Hunter DJ, Snieder H, March L, Sambrook PN. Genetic contribution to cartilage volume in women: a classical twin study. Rheumatology. 2003; 42:1495–500. [PubMed: 12832711]
17. Eckstein F, Glaser C. Measuring cartilage morphology with quantitative magnetic resonance imaging [Review] [150 refs]. Semin Musculoskeletal Radiol. 2004; 8:329–53.
18. Dawber TR, Meadors GF, Moore FE Jr. Epidemiological approaches to heart disease: the Framingham Study. Am J Public Health. 1951; 41:279–81.
19. Felson DT, Couropmitree NN, Chaisson CE, Hannan MT, Zhang Y, McAlindon TE, et al. Evidence for a Mendelian gene in a segregation analysis of generalized radiographic osteoarthritis: the Framingham Study [see comments]. Arthritis Rheum. 1998; 41:1064–71. [PubMed: 9627016]
20. Peterfy C, Li J, Zaim S, Duryea J, Lynch J, Miaux Y, et al. Comparison of fixed-flexion positioning with fluoroscopic semi-flexed positioning for quantifying radiographic joint-space width in the knee: test-retest reproducibility. Skeletal Radiol. 2003; 32:128–32. [PubMed: 12605275]
21. LaValley MP, McLaughlin S, Goggins J, Gale D, Nevitt MC, Felson DT, et al. The lateral view radiograph for assessment of the tibiofemoral joint space in knee osteoarthritis: its reliability, sensitivity to change, and longitudinal validity. Arthritis Rheum. 2005; 52:3542–7. [PubMed: 16255043]
22. Lo GH, Hunter DJ, Zhang Y, McLennan CE, LaValley MP, Kiel DP, et al. Bone marrow lesions in the knee are associated with increased local bone density. Arthritis Rheum. 2005; 52:2814–21. [PubMed: 16145676]
23. Kellgren, JH.; Lawrence, JS. Atlas of standard radiographs. Oxford: Blackwell Scientific; 1963.
24. Felson DT, McAlindon TE, Anderson JJ, Naimark A, Weissman BW, Aliabadi P, et al. Defining radiographic osteoarthritis for the whole knee. Osteoarthritis Cartilage. 1997; 5:241–50. [PubMed: 9404469]
25. Eckstein F, Hudelmaier M, Wirth W, Kiefer B, Jackson R, Yu J, et al. Double echo steady state magnetic resonance imaging of knee articular cartilage at 3 Tesla: a pilot study for the Osteoarthritis Initiative. Ann Rheum Dis. 2006; 65:433–41. [PubMed: 16126797]
26. Calvo E, Palacios I, Delgado E, Sanchez-Pernaute O, Largo R, Egido J, et al. Histopathological correlation of cartilage swelling detected by magnetic resonance imaging in early experimental osteoarthritis. Osteoarthritis Cartilage. 2004; 12:878–86. [PubMed: 15501403]
27. Ding C, Garnero P, Cicuttini F, Scott F, Cooley H, Jones G, et al. Knee cartilage defects: association with early radiographic osteoarthritis, decreased cartilage volume, increased joint surface area and type II collagen breakdown. Osteoarthritis Cartilage. 2005; 13:198–205. [PubMed: 15727885]
28. Armstrong CG, Mow VC, Armstrong CG, Mow VC. Variations in the intrinsic mechanical properties of human articular cartilage with age, degeneration, and water content. J Bone Joint Surg. 1982; 64:88–94. [PubMed: 7054208]
29. Mow VC, Guo XE, Mow VC, Guo XE. Mechano-electrochemical properties of articular cartilage: their inhomogeneities and anisotropies [Review] [136 refs]. Annu Rev Biomed Eng. 2002; 4:175–209. [PubMed: 12117756]
30. Stammberger T, Eckstein F, Michaelis M, Englmeier KH, Reiser M. Interobserver reproducibility of quantitative cartilage measurements: comparison of B-spline snakes and manual segmentation. Magn Reson Imaging. 1999; 17:1033–42. [PubMed: 10463654]
31. Chan WP, Lang P, Stevens MP, Sack K, Majumdar S, Stoller DW, et al. Osteoarthritis of the knee: comparison of radiography, CT, and MR imaging to assess extent and severity. AJR Am J Roentgenol. 1991; 157:799–806. [PubMed: 1892040]

Table 1

Description of no OA and premorbid OA sample

	No OA n = 720	Premorbid OA n = 55
Male (%)	44.2	47.3
Mean age in years (SD)	62.1 (8.3)	66.7 (8.4)
Body mass index, mean (SD)	27.7 (5.1)	29.4 (6.2)
Knee pain on most days (in one or more knees) (%)	21.4	57.4
History of knee injury * in the MRI knee (%)	8.1	7.4
History of knee injury * in contralateral knee (%)	9.3	38.9

MRI, magnetic resonance imaging; OA, osteoarthritis.

* Knee injury history was determined by a positive response to the question: Have you ever had an injury to your knee that required the use of a cane or crutches?

Table 2

Comparison of cartilage thickness, denuded cartilage % (expressed as percentage cartilage coverage of cartilage bone interface area) and cartilage volume between no-knee OA and premorbid knee OA samples

	No-knee OA (n = 720)	Premorbid knee OA (n = 55)	
Plate	**Mean cartilage thickness (mm) (SD)**	**Mean cartilage thickness (mm) (SD)**	**p Value**
Lateral tibia	2.08 (0.30)	2.04 (0.33)	0.32
Medial tibia	1.73 (0.23)	1.76 (0.25)	0.36
Central medial tibia	2.32 (0.39)	2.37 (0.47)	0.38
Central lateral femur	1.72 (0.27)	1.75 (0.35)	0.58
Central medial femur	1.81 (0.31)	1.81 (0.37)	0.94
Central part of central medial femur	2.24 (0.46)	2.23 (0.54)	0.89
Patella	2.10 (0.43)	1.96 (0.48)	0.02
	% Cartilage coverage	**% Cartilage coverage**	**p Value**
Lateral tibia	99.1	98.0	0.43
Medial tibia	98.5	96.0	0.17
Central lateral femur	99.2	100.0	0.56
Central medial femur	99.4	97.6	0.20
Patella	87.7	80.4	0.13
	Mean cartilage volume (mm^3) (SD)	**Mean cartilage volume (mm^3) (SD)**	**p Value**
Lateral tibia	2198.83 (619.47)	2228.80 (721.75)	0.32
Medial tibia	2077.19 (566.02)	2182.30 (652.33)	0.36
Central lateral femur	1099.59 (343.19)	1151.58 (418.75)	0.38
Central medial femur	1057.58 (340.05)	1106.01 (391.40)	0.58
Patella	2780.40 (861.36)	2618.47 (965.31)	0.94

Table 3

Results of group×plate interaction before and after excluding knees with coverage <95% (patella was referent plate), adjusted for age, sex and body mass index

	Difference in cartilage thickness of no OA plates compared with premorbid OA plates		Excluding knees with coverage <95%	
	Point estimate (SE)	p Value	Point estimate (SE)	p Value
Lateral tibia	0.03 (0.04)	0.36	0.03 (0.04)	0.39
Medial tibia	−0.04 (0.03)	0.20	−0.03 (0.03)	0.27
Central lateral femur	−0.04 (0.04)	0.28	−0.04 (0.04)	0.33
Central medial femur	0.00 (0.04)	0.96	0.00 (0.04)	0.94
Patella	0.14 (0.06)	0.03	0.08 (0.05)	0.11

OA, osteoarthritis; SE, standard error.