Association between MRI-detected osteophytes and changes in knee structures and pain in older adults: a cohort study

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ABSTRACT

Objective: To describe cross-sectional and longitudinal associations between magnetic resonance imaging (MRI)-detected osteophytes (OPs) and knee structural abnormalities and knee pain in older adults.

Method: A prospective population-based cohort study of 895 participants aged 50-80 years (mean age 62 years, 50% female) was performed. T1- or T2-weighted fat suppressed MRI was used to assess knee OPs, cartilage volume, cartilage defects and bone marrow lesions (BMLs) at baseline and after 2.6 years. Radiographically-detected OPs were scored according to the Osteoarthritis Research Society International atlas. Knee pain was assessed using a self-administered questionnaire at baseline, 2.6 and 5 years later.

Results: 85% of participants had MRI-detected OPs at baseline, while 10% of participants had radiographically-detected OPs. Cross-sectionally, higher gardes of MRI-detected OPs in all compartments were significantly, independently and site-specifically associated with higher prevalences of cartilage defects and BMLs, lower cartilage volume and higher prevalence of knee pain. Longitudinally, higher gardes of baseline MRI-detected OPs site-specifically predicted greater risks of any increase in cartilage defects or BMLs, and loss of cartilage volume in medial and lateral tibiofemoral and total compartments over 2.6 years in multivariable analyses. These significant associations were similar in those without radiographically-detected OPs. Medial tibiofemoral and total OP scores were significantly associated with change in total knee pain over 2.6 and 5 years but these became non-significant after adjustment for cartilage defects and BMLs.

Conclusion: MRI-detected knee OPs are common and appear to be clinically relevant to knee structural changes in older adults.

Keywords

Knee Osteoarthritis; Magnetic Resonance Imaging; Osteophytes; Knee Pain; Knee Structures Abnormalities

INTRODUCTION

Osteoarthritis (OA) is the most common type of arthritis, with prevalence estimates expected to increase dramatically worldwide due to aging and increasingly obese populations [1, 2]. There is a pressing need for biomarkers that can identify or predict the potential structural abnormalities and subsequent symptoms of disease, which would aid decision-making at both individual and community levels. Osteophyte formation is one of the common features of OA[3-5]. However, there are only modest correlations between knee OPs and clinical features [6, 7]. Additionally, change in knee symptoms is poorly predicted by OPs on baseline radiographs [8].

Magnetic resonance imaging (MRI) is a non-invasive multiplanar tomographic tool that has been introduced to evaluate knee osteoarthritic changes such as bone marrow lesions (BMLs) [9], cartilage defects [10] and cartilage volume [11]. Although MRI can assess OPs in locations that are not easily visualised by conventional radiography [12, 13], and at greater sensitivity than radiographs for detection of early formation of OP [14], few data are available to compare the prevalence of OPs detected by MRI and radiography in population-based samples. It has been shown that greater size of MRI-detected OPs correlated with higher Kellgren-Lawrence score [15] and increased knee pain [16], and cross-sectional studies have suggested that increasing size and presence of MRI-defined OPs was associated with severity of knee OA [15, 17, 18] as well as presence of pain. However, longitudinal studies are rare [16, 19]. Thus, the purposes of current study are to describe cross-sectional and longitudinal associations between MRI-

detected OPs and knee structural abnormalities over 2.6 years as well as knee pain during 5 years in older adults.

MATERIALS AND METHODS

Subjects. This study used data from the Tasmania Older Adult Cohort (TASOAC) study, which is an ongoing, prospective, population-based study that aimed to identify the environmental, genetic, and biochemical factors associated with the development and progression of OA. Participants between 50 and 80 years old were randomly selected from the electoral roll in Southern Tasmania (population 229, 000) using sex-stratified random sampling (response rate 57%). Participants were excluded if they were institutionalised or had contraindications to MRI. The Southern Tasmania Health and Medical Human Research Ethics Committee approved the study, and written informed consent was obtained from all participants. Baseline examinations were taken between February 2002 and September 2004, and follow-up measures were taken at approximately 2.6 and 5.1 years later.

Anthropometrics. Height was measured to the nearest 0.1 cm (with shoes, and headgear removed) using a stadiometer. Weight was measured to the nearest 0.1 kg (with shoes, socks, and bulky clothing removed) by using a single pair of electronic scales (Delta Model 707, Seca, Hamburg, Germany) that were calibrated using a known weight at the beginning of each clinic. Body mass index (BMI, weight (kg)/height^2 (m^2)) was also calculated.

WOMAC pain assessment. Knee pain was assessed using the Western Ontario McMaster Osteoarthritis Index (WOMAC) [20] at baseline, 2.6 and 5 years later using a 10-point scale from 0 (no pain) to 9 (most severe pain). The 5 subscales (walking on flat surface, going up/down stairs, at night, sitting/lying and standing upright) were assessed separately and summed to create a total pain score (0 to

45). Change in knee pain score was calculated as follow-up value - baseline value. An increase in total WOMAC pain was defined as a change in WOMAC pain score of ≥1.

X-ray assessment. A standing anteroposterior semiflexed view of the right knee with 15° of fixed knee flexion was performed in all subject at baseline [21]. Joint space narrowing (JSN) and radiographic osteophytes (OPs) were scored at the medial tibia, medial femur, lateral tibia and lateral femur on a scale of 0-3 (0=normal, 3= severe) according to the Osteoarthritis Research Society International (OARSI) atlas developed by Altman et al [22]. OP score in the whole knee was the highest score of all compartments of the knee. The presence of radiographically- detected OP was defined as the OP score ≥ 1 on X-ray. The presence of radiographic OA (ROA) was defined as any JSN or OP score of ≥1. Each score was determined by two readers (VS & HC) who simultaneously assessed the radiograph with immediate reference to the atlas. Intraobserver repeatability was tested in 40 subjects one month apart with intraclass correlation coefficients (ICCs) of 0.65-0.85 [23].

Magnetic Resonance Imaging. MRI scans of the right knees were performed on two occasions (baseline and 2.6 years later) and imaged in the sagittal plane on a 1.5-T whole body magnetic resonance unit (Picker, Cleveland, OH) using a commercial transmit-receive extremity coil. The image sequences were used as follows: (1) a T1-weighted fat saturation 3D gradient recall acquisition in the steady state; flip angle 30°; repetition time 31 ms; echo time 6.71 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). (2) a T2-weighted fat saturation 3-D fast spin echo, flip angle 90, repetition time 3067 ms, echo time 112 ms, field of view 16 cm, 15 partitions, 228x256-pixel matrix; sagittal images were obtained at a partition thickness of 4 mm with a between-slices gap of 0.5

to 1.0 mm. The image database was transferred to an independent computer workstation using the software program Osirix (University of Geneva, Geneva, Switzerland) as previously described [24, 25].

MRI-detected OP assessment. MRI-detected OPs were measured (Supplementary Figure 1) by ZZ according to the Knee Osteoarthritis Scoring System [26] where OPs are defined as focal bony excrescences, seen on sagittal, axial or coronal images, extending from a cortical surface. OPs were measured using the following scale: grade 0, absent; grade 1, minimal (<3 mm); grade 2, moderate (3-5 mm); grade 3, severe (>5 mm). Size was measured from the base (distinguished from that of adjacent articular cartilage with a normal MRI appearance) to the tip of the OP [13] at each of the following 14 sites: the anterior (a), central weight- bearing (c) and posterior (p) margins of the femoral condyles and tibial plateaus, and the medial (M) and lateral (L) margins of the patella [27]. The highest score of each individual site in the relevant compartment (or whole knee) was regarded as the OP score in that compartment (or whole knee). MRI-detected OP was considered as present if OP score of ≥1. Intra-observer reliability (expressed as ICC) was 0.94-0.97 and inter-observer reliability was 0.90-0.96.

Cartilage defects. Cartilage defects were assessed on T1-weighted MRI and graded at medial tibial, lateral tibial, medial femoral, lateral femoral and patellar regions as previously described [28, 29] as follows: grade 0, normal cartilage; grade 1, focal blistering and low-signal intensity change with an intact surface and bottom; grade 2, irregularities on the surface or bottom and loss of thickness of less than 50%; grade 3, deep ulceration with loss of thickness of more than 50%; grade 4, full thickness cartilage loss with exposure of subchondral bone [28]. The highest score of each individual site in the relevant compartment (or whole knee) was regarded as the cartilage defect score in that compartment (or whole knee). The presence of cartilage defects was defined as a cartilage defect score of ≥2 at any site. An increase in cartilage defects was defined as a change

in cartilage defects of ≥1. Intra-observer reliability (expressed as ICC) was 0.89-0.94 and inter-observer reliability was 0.85-0.93 [28].

Cartilage volume. Knee cartilage volume was measured on T1-weighted images by a single trained observer as previously described [30, 31]. The volumes of individual cartilage plates (medial tibial, lateral tibial) were isolated from the total volume by manually drawing disarticulation contours around the cartilage boundaries on a section by section basis. These data were resampled by means of bilinear and cubic interpolation (area of 312×312) um and 1.5 mm thickness, continuous sections) for the final 3-dimensional rendering. Changes in cartilage volume were calculated as: percentage change per annum= [(follow-up volume – baseline volume)/baseline cartilage volume]/time between 2 scans in years × 100. The coefficient of variation (CV) for cartilage volume measures was 2.1% to 2.6% [30, 31].

Bone marrow lesions. Subchondral BMLs were defined as discrete areas of increased signal adjacent to the subcortical bone on T2-weighted MRI and scored at medial tibial, lateral tibial, medial femoral, lateral femoral, medial patellar and lateral patellar regions using a modified version of Whole-Organ Magnetic Resonance Imaging Score (WORMS): grade 0, absence of BML; grade 1, area smaller than 25% of the region; grade 2, area between 25% to 50% of the region; grade 3, area larger than 50% of the region [27]. The highest score of each individual site in the relevant compartment (or whole knee) was regarded as the BML score in that compartment (or whole knee). An increase in BMLs was defined as a change in BMLs of ≥1. The inter-reader reliability of this BML scoring system has been shown to be excellent [32, 33].

Statistical analysis. Student t or χ^2 tests were used to compare means or proportions between those with and without baseline MRI-detected total knee OP. Site-specific associations were defined as the associations within the same site or

compartment. Multivariable linear regression analyses were used to examine the site-specific associations between baseline MRI-detected OPs (independent variables) and knee cartilage volume or change in cartilage volume (dependent variables), after adjustment for age, sex, BMI, cartilage defects and BMLs. Multivariable log binominal regression analyses were used to assess the site-specific associations between baseline MRI-detected OPs (independent variable) and presences of knee cartilage defect/BMLs as well as increases in cartilage defects/BMLs (dependent variables) over 2.6 years, before and after adjustment for age, sex, BMI, cartilage volume (if cartilage defects or BMLs), cartilage defect (if cartilage volume or BMLs) and BMLs (if cartilage defects or cartilage volume). Sensitivity analyses were performed by repeating the analyses in those without radiographically-detected OPs. Standard diagnostic checks of model fit and residuals were made and showed that the residuals of baseline and absolute changes of WOMAC knee pain scores were not normally distributed. Therefore, multivariable log binominal regression analyses were also used to evaluate cross-sectional and longitudinal associations between baseline MRI-detected osteophytes and WOMAC knee pain over 2.6 and 5 years (yes vs no at baseline, increase vs no increase over years), both after adjustment for age, sex, BMI, cartilage defects and BMLs. All statistical analyses were performed on Stata version 12.0 for Windows (StataCorp, College Station, TX, USA).

A p-value < 0.05 (2-tailed) or a 95% confidence interval (CI) not including the null point (for linear regression) or 1 (for log binominal regression) was considered statistically significant.

RESULTS

At baseline, 895 subjects were included for MRI assessments of OP. Mean age was 62.4 years, mean BMI was 27.7 and 50% were females. 406 subjects

completed MRI measures at 2.6 years' follow-up but the rest discontinued MRI measures due to decommissioning of the MRI scanner in the local hospital. WOMAC knee pain data were available at baseline, 2.6 (n=874) and 5 years' follow-up (n=751). There were no significant differences in demographic factors, cartilage defects, BMLs, cartilage volume and radiographic OA (ROA) at baseline between participants who completed and did not complete MRI measures [34].

A total of 837 participants had readable x-ray and MRI images out of 895 baseline participants. The frequencies of OP grades detected by radiography and MRI are presented in Supplementary Table 1/Table 2. 85% of participants had MRI-detected OPs at baseline, while only 10% of participants had radiographically-detected OPs. 439 of 755 (58%) participants without radiographically-detected OPs exhibited modest MRI-detected OPs (grade 1), and 189 of 755 (25%) participants without radiographically-detected OPs showed larger MRI-detected OPs (grade 2 and 3). In contrast, only 2 out of 129 participants without MRI-detected OPs showed radiographically-detected OPs.

The baseline characteristics of the participants are shown in Table 1. Compared with those without baseline MRI-detected OPs, those with baseline MRI-detected OPs were older, and had more proportion of males, higher weight and BMI, and larger lateral tibial bone area. Additionally, participants with baseline MRI-detected OPs had significant less patellar cartilage volume, and higher prevalence of cartilage defects, BMLs and knee pain. The differences in prevalence of joint space narrowing and ROA between those with and without baseline MRI-detected OPs were of borderline significance (Table 1).

Cross-sectionally, higher grades of baseline MRI-detected OPs in medial tibiofemoral, lateral tibiofemoral and patellar compartments were significantly and site-specifically associated with higher prevalences of cartilage defects, after

adjustment for age, sex, BMI, baseline BMLs and cartilage volume (Table 2). Longitudinally, higher grades of baseline MRI-detected OPs were site-specifically associated with greater risks of any increase in cartilage defects in all compartments except for patellar site, after adjusted for covariates (Table 2, Figure 1a).

In cross-sectional analyses, higher grades of baseline MRI-detected OPs were significantly associated with lower baseline cartilage volume in all compartments, after adjustment for age, sex, BMI, baseline cartilage defects and BMLs (Table 3). In longitudinal analyses, higher grades of baseline MRI-detected OPs were significantly associated with more loss of cartilage volume in total knee, medial and lateral tibiofemoral compartments, after adjustments for covariates (Table 3, Figure 1b).

Similarly, higher grades of baseline MRI-detected OPs were significantly and site-specifically associated with greater prevelances of baseline BMLs at all compartments, after adjustment for age, sex, baseline cartilage volume and cartilage defects (Table 4). The longitudinal associations between baseline grades of MRI-detected OPs and any increase in BMLs at total knee, medial and lateral tibiofemoral compartments were also significant in multivariable analyses (Table 4, Figure 1c). Sensitivity analyses showed that these significant associations between MRI-detected OPs and structural abnormalities were similar in those without X-ray OPs (data not shown).

Table 5 described the associations between baseline MRI-detected OPs and the presence of or any increase inWOMAC knee pain. Participants who had higher grades of baseline MRI-detected OPs, particularly in grade 2 and 3, had higher prevalence of WOMAC pain and greater risks of worsening WOMAC pain scores over 2.6 and 5 years, before and after adjustments for age, sex, BMI (Table 5). Figure 1d shows significant associations between baseline MRI-detected OPs in

different compartments and worsening total WOMAC knee pain over 5 years. The cross-sectional associations remained significant after further adjustment for baseline cartilage defects and BMLs; however, longitudinal associations were no longer statistically significant after further adjustments (Table 5).

DISCUSSION

In our study, OPs detected on MRI were much more common than OPs visible on conventional radiographs, as expected. MRI-detected OPs were associated with knee structural abnormalities both cross-sectionally and longitudinally. Significant associations between MRI-detected OPs and WOMAC knee pain were also found but these were largely dependent of knee structural abnormalities. These results suggest that MRI-detected OPs may be an early marker of the disease process in knee OA.

Conventional radiographs are known to be relatively insensitive to the structural changes of OA [35], in part because of their inability to detect three-dimensional (3D) joint structures [35], and inadequate visualization of early and central OPs. One study reported that prevalence of MRI-defined OPs was 72% among middle-aged women [16]. Another study looked at the prevalence of MRI-depicted abnormalities in knees without radiographic evidence of OA and found that OPs were the most common abnormality, being present in 74% of 710 participants [35]. Our data also showed a much higher prevalence of MRI-detected OPs in older adults than the prevalence of radiographically-detected OPs (85% vs 10%). MRI-detected OPs also had high reliabilities than radiographically-detected OPs. These findings suggest that MRI is far more sensitive and reliable than X-ray to detect osteophytes and our data suggest these OPs have clinical relevance.

Structural changes

Significant cross-sectional associations between MRI-identified OPs and radiographic severity of knee OA were reported among middle-aged women [15]. Another cross-sectional study revealed that MRI-detected OPs was only weakly associated with synovitis or joint effusion [36]. There are only two longitudinal studies so far, which reported inconsistent results [16, 37]. The first did not reveal any significant associations between MRI- defined OPs and knee structural progression [16]. The second was a nested case-control study reporting that subjects with 6 or more locations affected by OPs had 4.4-fold the odds of being both radiographic and pain progression compared with 0-2 locations affected [37]. Our current study reported positive, consistent and independent associations between MRI-detected OPs and changes in knee cartilage and bone abnormalities both cross-sectionally and longitudinally in a community-based older population. These associations remained unchanged after those with X-ray detected OPs were excluded. Although the underlying mechanisms are unable to be determined in this study, our findings imply that MRI-detected osteophytes could be a precursor of cartilage degradation and BMLs.

Pain

The association between OPs and knee pain is still controversial. One cohort study reported that increasing baseline OP size was associated with increasing WOMAC pain severity score [16] in a middle-aged female population (n=363). Another cross-sectional study reported a significant association between presence of OPs and knee pain among symptomatic OA patients (n=368) only when OPs were located in the patellofemoral compartment or when more than four OPs (any grade) were present anywhere in the knee [38]. In contrast, Link et al [18] reported that MRI-defined OPs were not associated with clinical findings as assessed with the WOMAC scores in patients with varying degrees of OA (n=50). A recent systematic review concluded that there was limited level of evidence for associations between MRI-detected OPs and knee pain [39]. Compared to these

previous studies, our study was performed in a general population with a large sample size (n=837) and revealed that there was a significant associations between MRI-detected OPs and total WOMAC knee pain cross-sectionally, independent of knee structural abnormalities. MRI-detected OPs were also significantly associated with changes in knee pain over 2.6 years and 5 years, but these associations became non-significant after adjustment for cartilage defects and BMLs, indicating MRI-detected OPs may cause OA symptoms through other structural changes.

Strengths of this study included the random selection of participants for the cohort from the community, with a large sample size and both structural and symptomatic measurements. Our results have good external validity, as they can be generalizable to all white older adults in the population. Study limitations included the unavailability of follow-up MRI scans in 489 participants due to decommissioning of MRI scanner. However, the current study sample is similar to the remainder of the cohort in terms of demographic factors, ROA, baseline cartilage volume, defects and BMLs. Second, we did not perform MRI scan at year 5 so were not able to assess the associations with changes in knee structures over 5 years. Last, different semi-quantitative scoring systems were used for OPs, cartilage defects and BMLs which may influence results; however, given all measures were highly reproducible, this is considered unlikely.

In conclusion, MRI-detected OPs are common and appear to be clinically relevant to knee structural changes in older adults.

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research nurses Boon C and Boon P. Warren R assessed MRIs and Dr Srikanth V and Dr Cooley H assessed radiographs.

AUTHOR CONTRIBUTIONS

ZZ had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study design: CD, FC and GJ. Acquisition of data: ZZ, CD, XJ and ML. Analysis and interpretation of data: ZZ, LL, XJ, WH, XW, BA, GJ, and CD. Manuscript preparation and approval: ZZ, LL, XJ, WH, BA, XW, ML, FC, GJ and CD.

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Patient consent Obtained.

Ethics approval This study was approved by the Southern Tasmania Health and Medical Human Research Ethics Committee, and written informed consent was obtained from all participants.

Competing interest. The authors declare that they have no competing interests.

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Table 1. Characteristics of participants at baseline

	Any MRI osteophytes in total knee		p-value
	Absent	Present	
	N=129	N=708	
Age (year)	**60.3±6.4**	**62.7±7.5**	**<0.01**
Female sex (%)	**58**	**49**	**0.05**
Weight (kg)	**72.4 ± 12.5**	**78.6 ± 14.8**	**<0.01**
BMI (kg/m²)	**26.3 ± 3.8**	**27.9 ± 4.7**	**<0.01**
Patella cartilage volume (ml)	**3.4±0.9**	**3.2±0.9**	**0.02**
Total tibial cartilage volume (ml)	5.0 ± 1.2	5.1 ± 1.2	0.66
Medial tibial bone area (cm²)	21.8±16.4	21.0±3.1	0.23
Lateral tibial bone area (cm²)	**11.8±2.0**	**12.2 ±2.2**	**0.03**
Any joint space narrowing (%)	52	61	0.07
Any cartilage defects (%)	**17**	**59**	**<0.01**
Baseline cartilage defects score, n (%)			
1	105 (81)	294 (41)	
2	18 (14)	215 (30)	
3	4 (3)	145 (21)	
4	2 (2)	54 (8)	

Any BMLs (%)	**21**	**37**	**<0.01**
Baseline BML score, n (%)			
0	101 (78)	446 (63)	
1	27 (21)	183 (26)	
2	1 (1)	67 (9)	
3	0 (0)	12 (2)	
Knee pain present (%)	**43**	**53**	**0.03**
Radiographic OA (%)	**52%**	**61%**	**0.05**

Two-tailed t tests were used for differences between means, and $\chi 2$ tests were used for proportions (percentages). Significant differences are shown in bold. Mean ± SD except for percentages. Radiographic OA was defined using Osteoarthritis Research Society International definition with a total score of >=1. BMI: body mass index; OA: osteoarthritis; BML: bone marrow lesions; MTF: medial tibiofemoral; LTF: lateral tibiofemoral

Table 2. Site-specific associations between baseline MRI-detected osteophytes and baseline/increases in knee cartilage defects

	Multivariable* PR (95% CI)	p	Multivariable** PR (95% CI)	p
Presence of cartilage defects at baseline N=895				
Medial tibiofemoral				
Grade 0	*Ref.*		*Ref.*	
Grade 1	**2.70 (1.98, 3.69)**	**<0.01**	**2.61 (1.91, 3.56)**	**<0.01**
Grade 2	**4.51 (3.26, 6.25)**	**<0.01**	**4.11 (2.95, 5.74)**	**<0.01**
Grade 3	**7.06 (5.45, 9.13)**	**<0.01**	**6.01 (4.50, 8.02)**	**<0.01**
P for trend				**<0.01**
Lateral tibiofemoral				
Grade 0	*Ref.*		*Ref.*	
Grade 1	**2.60 (1.73, 3.90)**	**<0.01**	**2.41 (1.61, 3.60)**	**<0.01**
Grade 2	**6.29 (4.11, 9.65)**	**<0.01**	**4.80 (3.09, 7.45)**	**<0.01**
Grade 3	**10.5 (7.18, 15.3)**	**<0.01**	**7.46 (5.00, 11.1)**	**<0.01**
P for trend				**<0.01**
Patellar				
Grade 0	*Ref.*		*Ref.*	
Grade 1	**2.46 (1.72, 3.50)**	**<0.01**	**2.39 (1.68, 3.42)**	**<0.01**

Grade 2	**4.89 (3.44, 6.95)**	**<0.01**	**4.52 (3.17, 6.44)**	**<0.01**
Grade 3	**5.78 (4.04, 8.28)**	**<0.01**	**5.22 (3.63, 7.50)**	**<0.01**
P for trend				**<0.01**
Total				
Grade 0	*Ref.*		*Ref.*	
Grade 1	**2.52 (1.73, 3.67)**	**<0.01**	**2.46 (1.68, 3.58)**	**<0.01**
Grade 2	**4.20 (2.89, 6.11)**	**<0.01**	**3.89 (2.67, 5.67)**	**<0.01**
Grade 3	**4.98 (3.44, 7.21)**	**<0.01**	**4.31 (2.96, 6.27)**	**<0.01**
P for trend				**<0.01**
Any increase in cartilage defects	RR		RR	
N=402				
Medial tibiofemoral				
Grade 0	*Ref.*		*Ref.*	
Grade 1	1.15 (0.81, 1.61)	0.44	1.12 (0.79, 1.57)	0.53
Grade 2	**1.72 (1.14, 2.59)**	**<0.01**	**1.60 (1.07, 2.40)**	**0.02**
Grade 3	**1.70 (1.14, 2.51)**	**<0.01**	**1.54 (1.01, 2.34)**	**0.04**
P for trend				**0.01**
Lateral tibiofemoral				
Grade 0	*Ref.*		*Ref.*	
Grade 1	**1.82 (1.12, 2.94)**	**0.02**	**1.81 (1.08, 3.04)**	**0.02**
Grade 2	**2.40 (1.22, 4.69)**	**0.01**	1.91 (0.90, 4.09)	0.09
Grade 3	**2.51 (1.11, 5.67)**	**0.03**	**2.61 (1.20, 5.69)**	**0.02**
P for trend				**0.03**
Patellar				
Grade 0	*Ref.*		*Ref.*	
Grade 1	0.84 (0.55, 1.29)	0.42	0.83 (0.54, 1.27)	0.39
Grade 2	1.20 (0.71, 2.02)	0.50	1.16 (0.68, 1.97)	0.59
Grade 3	1.50 (0.79, 2.85)	0.22	1.59 (0.84, 3.03)	0.15
P for trend				0.20
Total				
Grade 0	*Ref.*		*Ref.*	
Grade 1	1.09 (0.84, 1.42)	0.52	1.08 (0.83, 1.41)	0.57
Grade 2	**1.38 (1.04, 1.84)**	**0.03**	**1.33 (1.00, 1.77)**	**0.05**
Grade 3	**1.57 (1.20, 2.07)**	**<0.01**	**1.45 (1.09, 1.91)**	**0.01**
P for trend				**<0.01**

Dependent variable: baseline presence of (yes vs no) or any increase (yes vs no) in cartilage defects. Independent variable: MRI-detect osteophytes (per grade). OP: osteophytes; PR: prevalence ratio; RR: relative risks; Ref: reference group; *****adjusted for age, sex and BMI; ** further adjusted for BMLs, cartilage volume; Significant differences are shown in bold.

Table 3. Site-specific associations between baseline MRI osteophytes and baseline/changes in cartilage volume

	Multivariable* β (95% CI)	p	Multivariable** β (95% CI)	p
Baseline cartilage volume (mm^3)				
N=895				
Medial tibiofemoral				
Grade 0	*Ref.*		*Ref.*	
Grade 1	64.7 (-19.9, 149)	0.13	80.8 (-5.75, 167)	0.07
Grade 2	99.2 (-31.7, 230.1)	0.14	131 (-4.42, 267)	0.06
Grade 3	**-229 (-362, -96.5)**	**<0.01**	**-178 (-323, -33.1)**	**0.02**
P for trend				0.60
Lateral tibiofemoral				
Grade 0	*Ref.*		*Ref.*	
Grade 1	6.20 (-72.1, 84.5)	0.88	14.6 (-65.6, 94.8)	0.72
Grade 2	-42.3 (-182, 97.6)	0.55	-24.2 (-171, 123)	0.75
Grade 3	**-326 (-481, -171)**	**<0.01**	**-296 (-466, -126)**	**<0.01**
P for trend				**0.03**
Patellar				
Grade 0	*Ref.*		*Ref.*	
Grade 1	**-153 (-276, -30.5)**	**0.01**	**-129 (-251, -7.19)**	**0.04**
Grade 2	**-373 (-531, -214)**	**<0.01**	**-288 (-451, -125)**	**<0.01**
Grade 3	**-737 (-962, -512)**	**<0.01**	**-623 (-854, -392)**	**<0.01**
P for trend				**<0.01**
Total				
Grade 0	*Ref.*		*Ref.*	
Grade 1	-259 (-523, 5.62)	0.06	-217 (-481, 46.4)	0.11
Grade 2	-172 (-498, 153)	0.30	-43.3 (-374, 287)	0.80
Grade 3	**-813 (-1168, -457)**	**<0.01**	**-555 (-940, -171)**	**<0.01**
P for trend				**0.01**
Change in cartilage volume (% pa)	β		β	
N=402				
Medial tibiofemoral				
Grade 0	*Ref.*		*Ref.*	
Grade 1	0.61 (-0.98, 2.20)	0.45	0.66 (-0.95, 2.27)	0.42
Grade 2	**-4.88 (-7.57, -2.19)**	**<0.01**	**-5.0 (-7.79, -2.21)**	**<0.01**
Grade 3	**-3.13 (-6.10, -0.17)**	**0.04**	**-3.25 (-6.43, -0.06)**	**0.05**
P for trend				**0.01**
Lateral tibiofemoral				
Grade 0	*Ref.*		*Ref.*	
Grade 1	0.93 (-0.16, 2.03)	0.09	0.98 (-0.13, 2.09)	0.08
Grade 2	-1.17 (-3.34, 1.00)	0.29	-1.07 (-3.30, 1.17)	0.35
Grade 3	**-5.96 (-8.36, -3.55)**	**<0.01**	**-5.95 (-8.53, -3.37)**	**<0.01**

P for trend				**<0.01**
Patellar				
Grade 0	*Ref.*		*Ref.*	
Grade 1	-0.21 (-1.51, 1.08)	0.75	-0.16 (-1.47, 1.14)	0.81
Grade 2	-0.49 (-2.16, 1.19)	0.57	-0.25 (-1.98, 1.48)	0.78
Grade 3	-0.90 (-3.12, 1.33)	0.43	-0.49 (-2.85, 1.87)	0.68
P for trend				0.68
Total				
Grade 0	*Ref.*		*Ref.*	
Grade 1	-0.03 (-0.72, 0.66)	0.93	-0.01 (-0.69, 0.70)	0.98
Grade 2	**-1.17 (-2.01, -0.33)**	**<0.01**	**-1.10 (-1.94, -0.25)**	**0.01**
Grade 3	**-0.90 (-1.80, -0.01)**	**0.05**	-0.78 (-1.75, 0.20)	0.12
P for trend				**<0.01**

Dependent variable: baseline or change in cartilage volume. Independent variable: MRI-detect osteophytes (per grade). OP: osteophytes; PR: prevalence ratio; RR: relative risks; Ref: reference group; *****adjusted for age, sex and BMI; ** further adjusted for BMLs and cartilage defects; Significant differences are shown in bold.

Table 4. Site-specific associations between baseline MRI osteophytes and baseline/increases in BMLs

	Multivariable* PR (95% CI)	p	Multivariable** PR (95% CI)	p
Presence of BMLs at baseline N=895				
Medial tibiofemoral				
Grade 0	*Ref.*		*Ref.*	
Grade 1	**1.51 (1.08, 2.12)**	**0.02**	1.37 (0.97, 1.93)	0.08
Grade 2	**2.07 (1.35, 3.18)**	**<0.01**	**1.72 (1.11, 2.68)**	**0.02**
Grade 3	**3.85 (2.89, 5.13)**	**<0.01**	**2.74 (1.96, 3.84)**	**<0.01**
P for trend				**<0.01**
Lateral tibiofemoral				
Grade 0	*Ref.*		*Ref.*	
Grade 1	1.31 (0.93, 1.84)	0.12	1.09 (0.75, 1.57)	0.57
Grade 2	**2.29 (1.44, 3.63)**	**<0.01**	**1.89 (1.11, 3.21)**	**0.02**
Grade 3	**3.62 (2.39, 5.49)**	**<0.01**	**2.10 (1.32, 3.35)**	**<0.01**
P for trend				**<0.01**
Patellar				
Grade 0	*Ref.*		*Ref.*	
Grade 1	**1.66 (1.08, 2.56)**	**0.02**	**1.72 (1.08, 2.74)**	**0.02**
Grade 2	**2.87 (1.81, 4.57)**	**<0.01**	**2.87 (1.75, 4.70)**	**<0.01**

Grade 3	**2.42 (1.31, 4.47)**	**<0.01**	**2.02 (1.01, 4.05)**	**0.05**
P for trend				**<0.01**
Total				
Grade 0	*Ref.*		*Ref.*	
Grade 1	**1.34 (1.05, 1.70)**	**0.02**	1.21 (0.95, 1.54)	0.13
Grade 2	**2.06 (1.42, 2.99)**	**<0.01**	**1.78 (1.18, 2.69)**	**<0.01**
Grade 3	**2.93 (2.04, 4.23)**	**<0.01**	**1.88 (1.24, 2.84)**	**<0.01**
P for trend				**<0.01**
Any increase in BMLs	RR		RR	
N=402				
Medial tibiofemoral				
Grade 0	*Ref.*		*Ref.*	
Grade 1	1.27 (0.70, 2.30)	0.43	1.14 (0.62, 2.10)	0.67
Grade 2	**2.79 (1.42, 5.48)**	**<0.01**	1.92 (0.96, 3.84)	0.07
Grade 3	**3.64 (2.00, 6.60)**	**<0.01**	**2.08 (1.12, 3.86)**	**0.02**
P for trend				**<0.01**
Lateral tibiofemoral				
Grade 0	*Ref.*		*Ref.*	
Grade 1	0.97 (0.61, 1.54)	0.88	0.86 (0.54, 1.37)	0.52
Grade 2	1.57 (0.81, 3.07)	0.18	1.02 (0.50, 2.09)	0.95
Grade 3	**3.19 (1.98, 5.14)**	**<0.01**	**2.04 (1.14, 3.65)**	**0.02**
P for trend				**<0.01**
Patellar				
Grade 0	*Ref.*		*Ref.*	
Grade 1	1.16 (0.64, 2.12)	0.62	1.11 (0.59, 2.08)	0.39
Grade 2	1.19 (0.58, 2.42)	0.64	1.32 (0.60, 2.91)	0.50
Grade 3	1.71 (0.74, 3.93)	0.21	2.22 (0.90, 5.49)	0.08
P for trend				0.35
Total				
Grade 0	*Ref.*		*Ref.*	
Grade 1	0.91 (0.62, 1.33)	0.63	0.88 (0.59, 1.30)	0.57
Grade 2	1.48 (0.93, 2.36)	0.10	1.11 (0.64, 1.92)	0.71
Grade 3	**2.53 (1.78, 3.61)**	**<0.01**	**1.56 (1.03, 2.40)**	**0.04**
P for trend				**<0.01**

Dependent variable: baseline presence (yes vs no) of or any increase (yes vs no) in BMLs. Independent variable: MRI-detect osteophytes (per grade). BMLs: bone marrow lesions; OP: osteophytes; PR: prevalence ratio; RR: relative risks; Ref: reference group; *****adjusted for age, sex and BMI; ** further adjusted for cartilage defects and cartilage volume. Significant differences are shown in bold.

Table 5. Cross-sectional and longitudinal associations between baseline MRI-detected osteophytes and baseline and increases in WOMAC knee pain

	Multivariable* PR (95% CI)	p	Multivariable** PR (95% CI)	p
Presence of knee pain at baseline				
N=892				
Total MRI-detected OPs				
Grade 0	*Ref.*		*Ref.*	
Grade 1	1.05 (0.84, 1.30)	0.68	1.05 (0.84, 1.31)	0.64
Grade 2	**1.30 (1.03, 1.66)**	**0.03**	**1.31 (1.03, 1.66)**	**0.03**
Grade 3	**1.80 (1.44, 2.26)**	**<0.01**	**1.79 (1.41, 2.27)**	**<0.01**
P for trend				**<0.01**
Increase in WOMAC knee pain over 2.6 years				
N=787	RR (95% CI)	p	RR (95% CI)	p
Total MRI-detected OPs				
Grade 0	*Ref.*		*Ref.*	
Grade 1	1.20 (0.78, 1.85)	0.40	1.16 (0.75, 1.80)	0.50
Grade 2	1.07 (0.63, 1.83)	0.80	0.95 (0.55, 1.66)	0.87
Grade 3	**1.67 (1.00, 2.78)**	**0.05**	1.35 (0.77, 2.37)	0.30
P for trend				**0.03**
Increase in WOMAC knee pain over 5 years				
N=690				
Total MRI-detected OPs				
Grade 0	*Ref.*		*Ref.*	
Grade 1	0.90 (0.65, 1.26)	0.55	0.85 (0.61, 1.20)	0.37
Grade 2	1.20 (0.77, 1.88)	0.41	1.01 (0.63, 1.60)	0.98
Grade 3	**1.63 (1.08, 2.45)**	**0.02**	1.24 (0.78, 1.97)	0.37
P for trend				**0.04**

Dependent variable: baseline and increases in WOMAC knee pain (yes or no). Independent variable: MRI-detect total knee osteophytes. OP: osteophytes; PR: prevalence ratio; *****adjusted for age, sex and BMI. ** further adjustment for baseline cartilage defects and BMLs. Significant differences are shown in bold.

Figure legends:

Figure 1. Association of baseline MRI-detected OPs with increases in total knee cartilage defects (a), changes in cartilage volume per annum (%) (b), increases in total knee BMLs (c), and increases in total WOMAC knee pain over 5 years (d). MTF: medial tibiofemoral; LTF: lateral tibiofemoral. p values were for trends at different compartments after adjustment for baseline age, sex and body mass index.

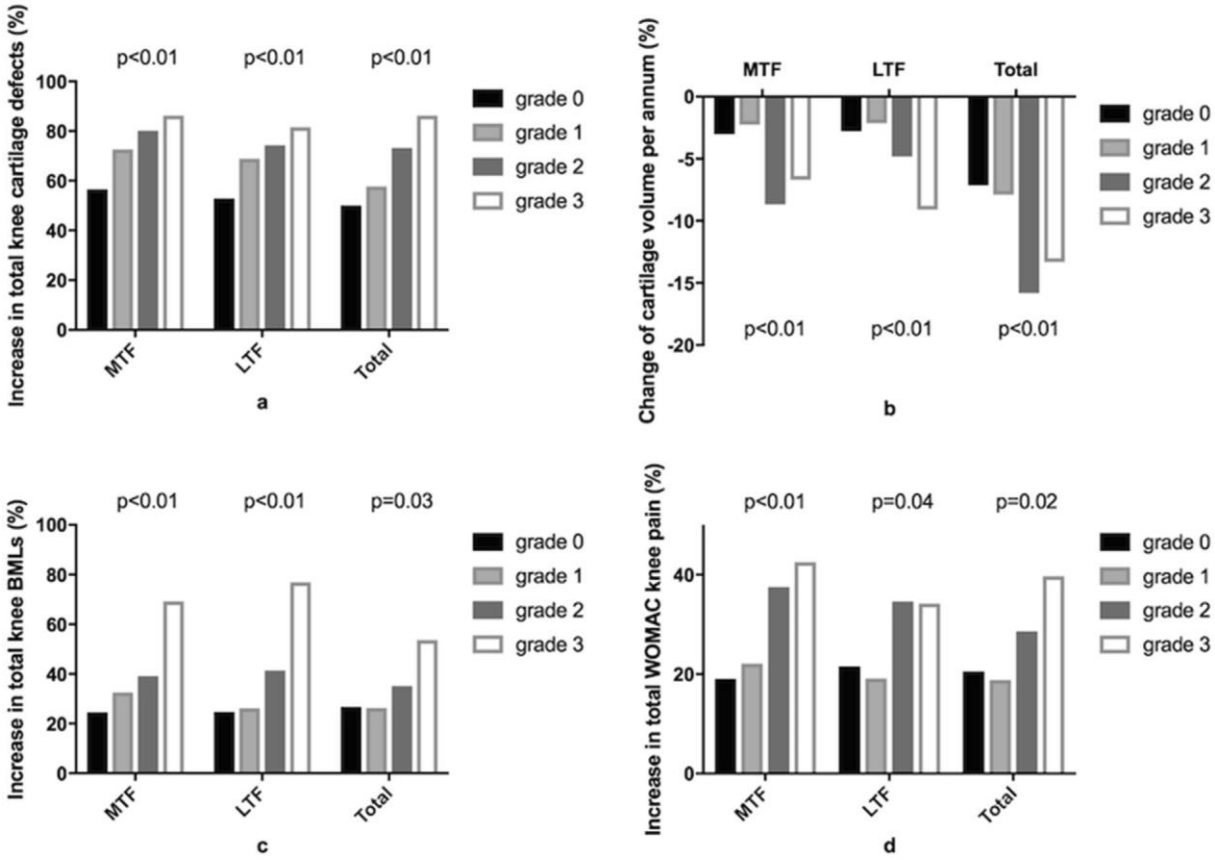

Figure 1