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Journal

Annals of the Rheumatic Diseases, 75(9)

ISSN

0003-4967

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Publication Date

2016-09-01

DOI

10.1136/annrheumdis-2015-208129

Peer reviewed

Published in final edited form as:

Ann Rheum Dis. 2016 September ; 75(9): 1630–1636. doi:10.1136/annrheumdis-2015-208129.

Clinical significance of worsening versus stable preradiographic MRI lesions in a cohort study of persons at higher risk for knee osteoarthritis

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Abstract

Background—Whether preradiographic lesions in knees at risk for osteoarthritis are incidental versus disease is unclear. We hypothesised, in persons without but at higher risk for knee

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Correction notice

This article has been corrected since it was published Online First. Changes have been made to the author affiliations and the shading in tables 1 and 2 has been corrected.

Contributors

All authors contributed to the planning, conduct, and reporting of the work described and fulfil the ICMJE recommendations for authorship credit: Substantial contributions to the conception or design of the work, or the acquisition, analysis or interpretation of data. Drafting the work or revising it critically for important intellectual content. Final approval of the version published. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests

None declared.

Provenance and peer review

Not commissioned; externally peer reviewed.

osteoarthritis, that: 12–48 month MRI lesion status worsening is associated with 12–48 month incident radiographic osteoarthritis (objective component of clinical definition of knee osteoarthritis) and 48–84 month persistent symptoms.

Methods—In 849 Osteoarthritis Initiative participants Kellgren/Lawrence (KL) 0 in both knees, we assessed cartilage damage, bone marrow lesions (BMLs), and menisci on 12 month (baseline) and 48 month MRIs. Multivariable logistic regression was used to evaluate associations between 12–48 month worsening versus stable status and outcome (12–48 month incident KL ≥ 1 and KL ≥ 2, and 48–84 month persistent symptoms defined as frequent symptoms or medication use most days of ≥1 month in past 12 month, at consecutive visits 48–84 months), adjusting for age, gender, body mass index (BMI), injury and surgery.

Results—Mean age was 59.6 (8.8), BMI 26.7 (4.2) and 55.9% were women. 12–48 month status worsening of cartilage damage, meniscal tear, meniscal extrusion, and BMLs was associated with 12–48 month incident radiographic outcomes, and worsening of cartilage damage and BMLs with 48–84 month persistent symptoms. There was a dose-response association for magnitude of worsening of cartilage damage, meniscal tear, meniscal extrusion, and BMLs and radiographic outcomes, and cartilage damage and BMLs and persistent symptoms.

Conclusions—In persons at higher risk, worsening MRI lesion status was associated with concurrent incident radiographic osteoarthritis and subsequent persistent symptoms. These findings suggest that such lesions represent early osteoarthritis, and add support for a paradigm shift towards investigation of intervention effectiveness at this stage.

INTRODUCTION

Knowledge concerning early knee osteoarthritis (OA) is limited. By the time osteophytes are present radiographically (Kellgren/Lawrence (KL) grade ≥2, the definition of knee OA[1–6]), it is likely that the disease process has been underway for years. MRI lesions have been identified at KL 0 (normal) or 1 (possible/small osteophytes);[7–21] however, few previous studies have evaluated their significance at these stages.[1718] Strongly associated with risk of incident KL ≥2,[22] KL 1 is increasingly viewed as an early stage of OA. The significance of MRI lesions is likely to differ at each stage of OA; findings from studies including KL1 knees may or may not persist in knees that are normal by X-ray. We undertook MRI readings in a cohort of Osteoarthritis Initiative (OAI) participants who were KL 0 in both knees (since risk of knee OA is increased by contra-lateral knee OA) in an effort to better understand the significance of MRI lesions in a large segment of the high-risk population, those with normal knee X-rays. We initially found baseline cartilage damage, bone marrow lesions (BMLs), and meniscal tears were associated with symptoms over 4 years; baseline BMLs with incident patellofemoral (PF) cartilage damage; and a dose-response association for severity of cartilage damage and BMLs with symptoms, and BMLs with cartilage damage.[21]

OA appears to have stable/compensated (anabolic balancing catabolic activity) and progressive/decompensated phases. White *et al*[23] illustrated that changing knee structure may be more consequential than stable structure: persons with incident (vs no incident) radiographic OA and worsening (vs stable) OA were at greater risk for incident severe

function limitation. If MRI lesions represent early OA, an association, within the bilateral KL 0 cohort, between worsening (vs stable) lesion status and important clinical outcomes would be expected.

Previous studies evaluating the impact of changing lesions in knees KL <2 have, with rare exception,[24] analysed the association between lesion change and other MRI change[8121525] but not radiographic outcome, and none have been limited to KL 0 knees. Whether, in knees with normal X-rays, changing lesion status is associated with incident radiographic OA (the objective component of the clinical definition of knee OA) or persistent symptoms in a subsequent period is not known. Understanding whether preradiographic MRI lesions represent early disease will aid prevention and disease-modifying strategy design. If such lesions constitute early OA, they could become targets; such treatment, given before the downward spiral of tissue interactions of established knee OA, may be able to alter disease course.[14] At present, there are no agents approved for the indication of OA disease modification.

We tested the hypotheses, in persons at higher risk of knee OA but KL 0 in both knees, that: 12–48-month MRI lesion status worsening is associated with greater risk of 12–48-month incident radiographic OA and 48–84-month persistent symptoms.

METHODS

The OAI is a prospective, observational cohort study of persons with or at higher risk (on the basis of knee symptoms, overweight by gender/age-specific cut points, knee injury, knee surgery, family history of total knee replacement for OA in a biological parent or sibling, Heberden's nodes, repetitive knee bending, and/or age 70–79 years) for symptomatic, radiographic knee OA.[26] Incidence subcohort eligibility required absent symptomatic, radiographic knee OA in either knee and present characteristics associated with increased risk of developing it[2728] Exclusion criteria were: inflammatory arthritis; severe bilateral joint space narrowing; total knee replacement and severe contralateral narrowing; bilateral total knee replacement or plan for it within 3 years; MRI or radiography contraindications; inability to provide blood sample; aides other than one straight cane for >50% of ambulation; severe comorbidity; double-blind trial participation.[27]

Current study inclusion additionally required KL 0 in both knees at the 12-month OAI visit, our ancillary study's baseline MRI assessment. The Institutional Review Board at each site approved the study.

Knee radiography

The posteroanterior fixed-flexion weight-bearing protocol[2729] with a SynaFlexer frame was used. Two experts, blinded to each other's reading, hypotheses and all other data, assessed KL grade.[1] Weighted κ, between-reader agreement, was 0.79 for KL. Prespecified discrepancies (KL 1 vs 2) were adjudicated by consensus with a third reader.[30]

Knee MRI

Image acquisition used 3.0 T Siemens Trio scanners installed at each OAI site.[31] Sequences included: coronal intermediate-weighted turbo spin echo, sagittal intermediate-weighted turbo spin echo with fat-suppression, and 3D Double Echo Steady State (DESS) water excitation (WE) sequence acquired in the sagittal plane with coronal and axial multiplanar reformat (MPR) reconstruction.[31]

We undertook 12-month and 48-month right (left, if right technically unacceptable) readings in persons determined by the coordinating centre to meet the KL criterion. Three experts who had not performed the X-ray readings (MC, AG and FWR) used modified MRI OA Knee Score (MOAKS),[32] blinded to hypotheses, KL criterion and all other data. Evidence of their reliability using MOAKS to assess OAI images has been published, with very good to excellent inter-rater reliability for nearly all features.[32] Paired images were read, with the chronology known.[33] Cartilage morphology was scored separately for 4 PF and 10 tibiofemoral (TF) subregions: 0, normal; 1.0, 1–10% area damaged, no full thickness; 1.1, 1–10% area, 1–10% full thickness; 2.0, 10–75% area, no full thickness; 2.1, 10–75% area, 1–10% full thickness; 2.2, 10–75% area, 10–75% full thickness; 3.0, >75% area, no full thickness; 3.1, >75% area, 1–10% full thickness; 3.2, >75% area, 10–75% full thickness; 3.3, >75% area, >75% full thickness. BMLs were scored in the same subregions: 0, none; 1, <25% of subregions; 2, 25–50%; 3, >50%. For each meniscus, three subregions were scored: 0, normal; 1, signal abnormality; 2, horizontal tear; 3, vertical tear; 4, complex tear; 5, root tear; 6, partial maceration; 7, complete maceration; 8, progressing maceration. Extrusion was scored in each meniscus[34]: 0, none; 1, <50% extruded; 2, ≥ 50% extruded.

Covariate measurement

Covariates included age, gender, body mass index (BMI, body weight by standard balance beam scale, height by wall mounted stadiometer), knee injury (ever injured (study knee) badly enough to limit walking ≥ 2 days) and knee surgery (any previous, study knee).

Statistical analysis

All analyses used one knee per person. Multivariable logistic regression was used to evaluate associations between worsening lesion status (12–48-month incident lesion or worsening of established lesion) versus stable lesion status and each outcome (12–48-month incident KL ≥1 and incident KL ≥2, and 48–84-month persistent symptoms defined as frequent knee symptoms or medication use for them more than half the days in at least one of the past 12 months, at two consecutive annual visits between 48 months and 84 months), adjusting for age, gender, BMI, knee injury and knee surgery. Results are summarised using adjusted ORs and 95% CIs.

For cartilage damage, BMLs and meniscal extrusion, incident lesion was defined by 48-month occurrence of a score >0 in ≥one subregion among knees with all 12-month subregions 0 for that lesion, and worsening of established lesion was defined by 12–48-month worsening in ≥one subregion among knees with a 12-month score >0 for that lesion in ≥one subregion. For meniscal tear, incident lesion was defined by 48-month occurrence of a score ≥2 in ≥one subregion among knees with all 12-month subregions <2, and worsening

of established lesion by 12–48 month worsening in ≥one subregion among knees with a 12-month score ≥2 in ≥one subregion.

We also defined an ordered categorical variable for number of lesion types with 12–48-month worsening status and used logistic regression to analyse associations of this variable (to assess trends across ordered categories) with each outcome. We explored a dose-response association between greater magnitude of worsening (using TF region with greatest worsening, for KL outcomes, and TF or PF region with greatest worsening, for persistent symptoms outcome) and each outcome. For 'dose' of worsening area of damage, we recoded cartilage damage severity: 0=normal; 1=1.0 or 1.1; 2=2.0, 2.1 or 2.2; and 3=3.0, 3.1, 3.2 or 3.3. For 'dose' of worsening full thickness involvement, we recoded cartilage damage severity: 0=normal; 1=1.0, 2.0 or 3.0; 2=1.1, 2.1 or 3.1; 3=2.2 or 3.2; and 4=3.3. For 'dose' of worsening meniscal lesions, we recoded meniscal lesions: 0=0 or 1; 1=2 or 3; 2=4 or 6; and 3=7 or 8. SAS software V.9.3 (SAS Institute, Cary, North Carolina, USA) was used.

RESULTS

Figure 1 delineates sample derivation. Among 1114 eligible, 77 missed the 48-month evaluation (withdrew (28), difficulty contacting/scheduling (32), died (14), health problems (2), caregiving responsibilities (1)), 176 attended without MRI, and 12 had inadequate images. We assessed right knee MRIs (left, if right inadequate) at 12 months and 48 months in the remaining 849 (mean age 59.6 years (SD 8.8), BMI 26.7 kg/m^2 (4.2), 475 (55.9%) women; 88.7% Caucasian, 9.0% African-American, 1.1% Asian, 1.2% other non-white; 8 (0.9%) Hispanic, including 2 Caucasian, 1 African-American, 5 other non-white). Persons KL 0 in both knees and not in the analysis sample were similar (age 58.7 years (9.3), BMI 27.0 (4.8), 63.0% women). An additional 57 were not included in radiographic analyses due to missing radiographic or covariable data; their characteristics were similar (mean age 58.3 years (7.8), BMI 26.9 (3.6), 63.2% women, 11.8% non-white). Of the 792 knees from 792 persons in the radiographic analysis sample, 50 developed incident KL ≥1 and 25 incident KL ≥2 by 48 months. Of the 841 knees from 841 persons, 200 had persistent symptoms in the 48–84-month period.

Tables 1 and 2 show outcome frequency by 12–48-month lesion status groups: none→none, none→incident lesion, lesion→no worsening and lesion→worse. As shown in table 1, status worsening (vs no worsening) in TF cartilage damage, PF cartilage damage, meniscal tear, meniscal extrusion and TF BMLs was associated with incident KL ≥1 and incident KL ≥2. In post hoc analyses further adjusting for TF cartilage damage worsening, PF cartilage damage worsening was associated with incident KL ≥1 (adjusted OR 2.28, 95% CI 1.18 to 4.39) but not incident KL ≥2 (adjusted OR 2.16, 95% CI 0.88 to 5.32); in these models, TF cartilage damage worsening was associated with both outcomes (adjusted OR 2.49, 95% CI 1.38 to 4.51, and adjusted OR 8.44, 95% CI 3.10 to 23.03, respectively). As shown in table 2, status worsening in TF cartilage damage, PF cartilage damage, TF BMLs and PF BMLs was associated with 48–84-month persistent symptoms (findings persisting after further adjustment for 12–48-month symptoms, not shown). In sensitivity analyses further adjusting for comorbidity (ie, having two or more comorbid conditions) as well as side of leg dominance, these covariables were not consistently associated with the outcomes and the

OR estimates for the associations between lesion worsening and outcomes were minimally affected.

Cartilage damage status worsened in TF and PF compartments in 49 knees; combined worsening (vs all other possibilities) was associated with persistent symptoms (adjusted OR 2.18, 95% CI 1.19 to 3.99). BML status worsened in both compartments in 21 knees; combined worsening was associated with persistent symptoms (adjusted OR 3.65, 95% CI 1.50 to 8.86). As shown in table 3, there was a significant linear increase (p for trend) in the odds of each outcome (on the logit scale) as number of lesion types with worsening increased.

As shown in table 4, greater 12–48-month worsening of TF cartilage damage (surface area and extent of full thickness involvement), meniscal tear, meniscal extrusion and TF BML scores was associated with 12–48-month incident radiographic KL ≥1 and KL ≥2; greater 12–48-month worsening of TF or PF cartilage damage (surface area and full thickness involvement) and TF or PF BMLs was associated with 48–84-month persistent symptoms.

In analyses using an alternative definition of worsening (subregion maximum score worse at 48 months than 12 months among knees with that lesion at 12 months), findings were similar. Twelve-month to 48-month radiographic medial and lateral TF joint space grade progression occurred in 10 knees and 5 knees, respectively, precluding examination of TF compartment-specific radiographic outcome.

DISCUSSION

In persons at higher risk of knee OA but KL 0 in both knees, 12–48-month status worsening in TF cartilage damage, meniscal tear, meniscal extrusion and TF BMLs by MRI was associated with 12–48-month incident radiographic KL ≥1 and incident KL ≥2. Twelve-month to 48-month status worsening in TF cartilage damage, PF cartilage damage, TF BMLs and PF BMLs was associated with 48–84-month persistent symptoms. More lesion types with worsening were associated with greater odds of each outcome. There was a dose-response association for magnitude of worsening of TF cartilage damage, meniscal tear, meniscal extrusion and TF BML score and each radiographic outcome, and for magnitude of worsening of TF or PF cartilage damage and TF or PF BMLs and the persistent symptom outcome.

Conceptually, the study of early OA is compelling. As stated by Ding, preradiographic MRI lesions “allow us to explore the very subtle, potentially reversible, early aberrations in joint morphology, prior to the onset of radiographic disease… we can identify reversible structural changes and risk factors for these, to enable us to turn the individual off the pathway to OA and avert progressive change”.[14] A recent symposium dealt with strategies to transform the approach to OA from palliation to prevention.[35] The need to better understand the ‘tilting point’ at which initial anabolic events shift to net catabolic activity in early OA was described.[36] McGonagle *et al*[37] proposed knee OA classification based on site(s) of earliest joint involvement, noting that treatment for early disease could theoretically target specific tissues to delay whole-organ involvement. Luyten *et al*[38] suggested patient

categories that fit and would aid work within regenerative medicine and tissue engineering: MRI tissue lesions in otherwise healthy joints; tissue lesions with early radiographic signs; established OA by American College of Rheumatology criteria. As stimulating as these ideas are, whether preradiographic lesions are important or incidental is unclear. Advancing this knowledge clarifies whether they can serve as targets or as parameters to define knees requiring early treatment.

MRI lesions were not infrequent in knees without radiographic OA in the Framingham study: TF cartilage damage in 69%, TF BMLs in 52%, meniscal tears in 25%.[1120] Rates in persons at higher risk to develop knee OA are not substantially higher: in the Multicenter Osteoarthritis Study, TF or PF cartilage damage in 67–81%, BMLs in 55–74%;[13] and, in our recent report regarding the current sample, cartilage damage in 76%, BMLs in 61%, meniscal tears in 21%, meniscal extrusion in 14%.[21] Different findings may reflect different MRI methods and inclusion of persons with contralateral knee OA.

To our knowledge, no prior study has examined the impact of worsening MRI lesions in persons with normal knee X-rays. In knees without OA by American College of Rheumatology clinical criteria or knee pain, incident BML development (but not change in prevalent BMLs) was associated with pain development.[12] In other cohorts largely without radiographic OA (KL <2), cartilage defect change was associated with cartilage volume change.[825] In persons without radiographic OA (KL <2), BML size change was associated with concurrent pain and function change.[15] In a case-control study involving OAI participants with KL 0 or 1 in at least one knee, Roemer *et al*[24] recently reported that the presence of specific MRI features 2 years prior to incident radiographic OA was associated with risk of incident OA, and incident lesions were associated with greater risk (than fluctuating or prevalent lesions).

We previously reported that, within the bilateral KL 0 sample at higher risk, lesions at 12 months were associated with 48-month incident MRI cartilage damage and persistent symptoms by 60 months.[21] The current study extends this work by showing that, within this sample, worsening (vs stable) lesion status is associated with incident radiographic OA over the same time interval and persistent symptoms in the subsequent 3 years. The pattern of findings was similar for KL ≥1 and KL ≥2 outcomes (although we had lower power for the latter), in keeping with a report that KL 1 is associated with future radiographic knee OA (KL ≥2).[22] As anticipated, TF lesion status change was associated with KL outcomes. The association between PF cartilage damage status worsening and KL outcomes was at least partially explained by TF status worsening. Notably, PF lesion status change was important for the persistent symptom outcome.

This study has limitations. The OAI focuses on persons at higher risk for knee OA, a group of public health importance that will grow with expansion of the aging and overweight populations. However, our findings may or may not apply in a population not at higher risk for knee OA. Our MRI readings did not include effusion/synovitis, another potentially important factor in early OA.[24] Improvement in lesion status is possible, particularly with BMLs. In our analyses, BML improvement was grouped with ‘no worse’. It would have been interesting to further subdivide knees to examine whether BML improvement was

associated with a reduced risk of outcomes, but we did not have sufficient power for this. MOAKS cartilage assessment ranges correspond to focal, extensive and diffuse involvement; the middle group has wide bounds (10–75%). However, MOAKS is an established, and among the most widely used, reading systems for knee OA, and affords the important opportunity to assess surface area of involvement and extent of full thickness involvement. It was not among our objectives to evaluate the clinical utility of MRI in this population; the role of MRI in the care of patients at this stage is, at present, uncertain.

That, within this sample worsening lesion status was associated with the concomitant new development of radiographic knee OA as well as persistent symptoms in the subsequent 3 years, along with robust dose-response findings, adds to the evidence that these lesions represent early OA and are clinically significant. Given the absence of disease-modifying therapy for OA, widespread clinical application of MRI is difficult to justify. Nevertheless, the findings have important implications. Prevention or delay of worsening of early-stage lesions should be considered as a target for emerging pharmacological and non-pharmacological treatments in an effort to prevent or delay full-blown disease. Candidate interventions should be studied at this stage, when they are more likely to be effective, potentially even in a shorter duration or intermittently applied. The findings support the recent call to no longer consider OA as a disorder of hyaline cartilage,[39] and additionally support a paradigm shift towards investigation of tissue-targeted intervention effects at this early stage.

In conclusion, in persons at higher risk but with normal knee X-rays at baseline, worsening MRI lesion status over a 3-year interval was associated with concurrent development of radiographic OA and persistent symptoms over a subsequent 3-year follow-up. These findings support the concept of compensated/stable and decompensated/progressive phases at very early stages of OA and suggest that such lesions represent early disease and illness.

Acknowledgments

The authors acknowledge the dedication and commitment of the OAI study participants.

Funding

NIH/NIAMS R01 AR52918, R01 AR065473, P60 AR064464, and the Osteoarthritis Initiative. The OAI is a public-private partnership comprised of five contracts (N01-AR-2-2258; N01-AR-2-2259; N01-AR-2-2260; N01-AR-2-2261; N01-AR-2-2262) funded by the NIH and conducted by the OAI Study Investigators. Private funding partners include Merck Research Laboratories, Novartis Pharmaceuticals Corporation, GlaxoSmithKline, and Pfizer, Private sector funding for the OAI is managed by the Foundation for the NIH. This manuscript was prepared using an OAI public use data set (in addition to data obtained within NIH/NIAMS funded ancillary grants) and does not necessarily reflect the opinions or views of the OAI investigators, the NIH, or the private funding partners. The study sponsor played no role in study design or the collection, analysis, and interpretation of data and the writing of the article or the decision to submit it for publication; researchers were independent from funders and sponsors; researchers had access to all the data.

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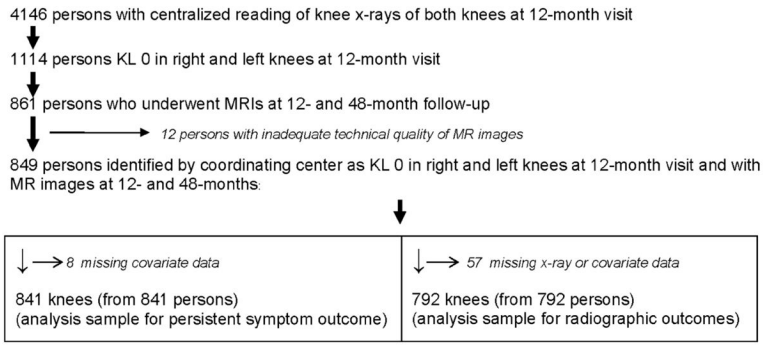

Figure 1.

Derivation of analysis samples. The figure shows the derivation of analysis samples. KL, Kellgren and Lawrence.

Table 1

12-month to 48-month MRI lesion status worsening and 12–48-month incident KL ≥1 and incident KL ≥2 radiographic outcomes

12–48-month lesion status	12–48-month Incident KL ≥1 Number (%) with outcome n=50/792 (6.3%)	Adjusted OR (95% CI), 12–48-month lesion status worsening (vs no worsening)	12–48-month Incident KL ≥2 Number (%) with outcome n=25/792 (3.2%)	Adjusted OR (95% CI), 12–48-month lesion status worsening (vs no worsening)
TF cartilage damage				
None → none	13/392 (3.3)	Reference	0/392 (0)	Reference
Damage → no worse	10/159 (6.3)		5/159 (3.1)	
None → incident damage	8/40 (20.0)	***2.69 (1.50 to 4.84)***	6/40 (15.0)	***9.03 (3.32 to 24.50)***
Damage → worse	19/201 (9.5)		14/201 (7.0)	
PF cartilage damage				
None → none	11/268 (4.1)	Reference	4/268 (1.5)	Reference
Damage → no worse	24/402 (6.0)		13/402 (3.2)	
None → incident damage	7/36 (19.4)	***2.57 (1.35 to 4.89)***	4/36 (11.1)	***2.74 (1.14 to 6.55)***
Damage → worse	8/86 (9.3)		4/86 (4.7)	
Meniscal tear				
None → none	18/592 (3.0)	Reference	5/592 (0.8)	Reference
Tear → no worse	16/125 (12.8)		9/125 (7.2)	
None → incident tear	11/40 (27.5)	***5.73 (2.94 to 11.16)***	7/40 (17.5)	***9.05 (3.86 to 21.23)***
Tear → worse	5/35 (14.3)		4/35 (11.4)	
Meniscal extrusion				
None → none	27/664 (4.1)	reference	9/664 (1.4)	Reference
Extrusion → no worse	14/103 (13.6)		9/103 (8.7)	
None → incident extrusion	6/19 (31.6)	***10.68 (4.35 to 26.18)***	5/19 (26.3)	***19.07 (6.73 to 54.01)***
Extrusion → worse	3/6 (50.0)		2/6 (33.3)	
TF BMLs				
None → none	23/521 (4.4)	Reference	6/521 (1.2)	Reference
BML → no worse	8/162 (4.9)		4/162 (2.5)	
None → incident BML	11/63 (17.5)	***4.93 (2.62 to 9.27)***	9/63 (14.3)	***11.83 (5.01to 27.97)***
BML → worse	8/46 (17.4)		6/46 (13.0)	
PF BMLs				
None → none	16/320 (5.0)	Reference	6/320 (1.9)	Reference
BML → no worse	18/299 (6.0)		10/299 (3.3)	
None → incident BML	5/63 (7.9)	1.74 (0.92 to 3.28)	2/63 (3.2)	2.17 (0.92to 5.13)
BML → worse	11/110 (10.0)		7/110 (6.4)	

The table shows the frequency of knees (one knee per person) with 12–48 month incident radiographic KL ≥1 (second column) and incident KL ≥2 (fourth column) among knees without that lesion at 12 months and 48 months, knees with that lesion at baseline and no worsening by 48 months, knees without that lesion at baseline and newly developed lesion by 48 months, and knees with that lesion at baseline and worsening by 48 months. Adjusted OR shown is the odds of the outcome for knees with 12–48 month lesion status worsening, compared with the odds for knees with no lesions or stable lesion status (reference group) over the same 3-year interval, adjusted for age, gender, body mass index (BMI), knee injury and knee surgery. Significant results are shown in bold italics.

BML, bone marrow lesion; KL, Kellgren and Lawrence; PF, patellofemoral; TF, tibiofemoral.

Table 2

12-month to 48-month MRI lesion status worsening and 48–84-month persistent knee symptoms

12–48-month lesion status	48–84-month Persistent knee symptoms Number (%) with outcome n = 200/841 (23.8%)	Adjusted OR (95% CI), 12–48 months lesion status worsening (vs no worsening)
TF cartilage damage		
None → none	85/417 (20.4)	Reference
Damage → no worse	38/164 (23.2)	
None → incident damage	15/45 (33.3)	***1.50 (1.07 to 2.11)***
Damage → worse	62/215 (28.8)	
PF cartilage damage		
None → none	47/286 (16.4)	Reference
Damage → no worse	110/426 (25.8)	
None → incident damage	13/38 (23.1)	***1.76 (1.16 to 2.65)***
Damage → worse	30/91 (33.0)	
Meniscal tear		
None → none	136/623 (21.8)	Reference
Tear → no worse	38/138 (27.5)	
None → incident tear	11/41 (26.8)	1.61 (0.97to 2.67)
Tear → worse	15/39 (38.5)	
Meniscal extrusion		
None → none	158/707 (22.3)	Reference
Extrusion → no worse	36/108 (33.3)	
None → incident extrusion	3/19 (15.8)	0.96 (0.38 to 2.44)
Extrusion → worse	3/7 (42.9)	
TF BMLs		
None → none	123/553 (22.2)	Reference
BML → no worse	40/171 (23.4)	
None → incident BML	14/66 (21.2)	***1.62 (1.05 to 2.50)***
BML → worse	23/51 (45.1)	
PF BMLs		
None → none	60/345 (17.4)	Reference
BML → no worse	82/315 (26.0)	
None → incident BML	19/65 (29.2)	***1.67 (1.15 to 2.41)***
BML → worse	39/116 (33.6)	

The table shows the frequency of knees with 48–84 month persistent knee symptoms among knees without that lesion at 12 months and 48 months, knees with that lesion at baseline and no worsening by 48 months, knees without that lesion at baseline and newly developed lesion by 48 months, and knees with that lesion at baseline and worsening by 48 months. Adjusted OR is the odds of the outcome over 48–84 month follow-up for knees

with 12–48 month lesion status worsening, compared with the odds for knees with no lesions or stable lesion status (reference group) over 12–48 months, adjusted for age, gender, body mass index (BMI), knee injury and knee surgery. Significant results are shown in bold italics.

BML, bone marrow lesion; KL, Kellgren and Lawrence; PF, patellofemoral; TF, tibiofemoral;

Table 3

Number of lesion types with 12–48-month status worsening and 12–48-month incident KL ≥1, 12–48-month incident KL ≥2, and 48–84-month persistent knee symptoms

Outcome variable	Number of lesion types with 12–48 m status worsening (predictor)	Number (%) with outcome	Adjusted OR (95% CI)	p for trend
12–48 m incident KL ≥ 1 (n = 792 knees from 792 persons)				
	0	27/641 (4.2%)	Reference	
	1 (vs 0)	9/112 (8.0%)	1.82 (0.82 to 4.05)	<0.0001
	2–4 (vs 0)	14/39 (35.9%)	***15.08 (6.73 to 33.79)***	
12–48 m incident KL ≥ 2 (n = 792 knees from 792 persons)				
	0	9/641 (1.4%)	Reference	
	1 (vs 0)	5/112 (4.5%)	3.06 (0.99, 9.50)	<0.0001
	2–4 (vs 0)	11/39 (28.2%)	***29.83 (10.93 to 81.41)***	
48–84 m persistent knee symptoms (n=841 knees from 841 persons)				
	0	109/525 (20.8%)	Reference	
	1 (vs 0)	58/230 (25.2%)	1.25 (0.87 to 1.81)	0.0007
	2 (vs 0)	20/56 (35.7%)	***1.98 (1.09to 3.60)***	
	3 (vs 0)	6/16 (37.5%)	2.20 (0.77 to 6.24)	
	4–6 (vs 0)	7/14 (50.0%)	***3.85 (1.31 to 11.35)***	

For each of the outcome variables listed in the first column of the table, the adjusted ORs and 95% CIs are shown for the predictor variables, that is, number of lesion types with 12–48 month status worsening versus the reference category of 0 lesion types with 12–48 month status worsening. The predictor variable was defined as an ordered categorical variable with values: 0 (reference category), 1, and 2, 3 and 4 combined for the first two (KL) outcomes (lesion types including TF cartilage damage, TF bone marrow lesion, meniscal tear, meniscal extrusion); and as 0, 1, 2, 3, and 4, 5, and 6 combined for the last (persistent knee symptoms) outcome (lesion types including TF or PF cartilage damage, TF or PF bone marrow lesion, meniscal tear, meniscal extrusion). Higher numbers of lesion types with change (for the KL ≥1 and KL ≥2 outcomes, 2, 3, and 4; for the persistent symptom outcome, 4, 5, and 6) were combined into a single category due to an insufficient number of knees in each category separately. Each model was adjusted for age, gender, body mass index (BMI), knee injury and knee surgery. Significant results are shown in bold italics. Also shown is the p value for a test for linear trend in the odds (on the logit scale) across all the levels of the ordered categorical predictor variable.

KL, Kellgren and Lawrence; PF, patellofemoral; TF=tibiofemoral.

Table 4

Greater magnitude of 12–48-month worsening of each lesion type: association with 12–48-month incident KL ≥1, 12–48-month incident KL ≥2 and 48–84-month persistent knee symptoms

12–48-month magnitude of worsening	12–48-month Incident KL ≥1 Adjusted OR (95% CI)	12–48-month Incident KL ≥2 Adjusted OR (95% CI)	48–84-month Persistent knee symptoms Adjusted OR (95% CI)
TF cartilage damage, surface area	***2.28 (1.60 to 3.24)***	***4.47 (2.66 to 7.53)***	–
TF cartilage damage, extent of full thickness	***1.93 (1.31 to 2.86)***	***3.30 (2.04 to 5.34)***	–
TF or PF cartilage damage, surface area	—	–	***1.36 (1.10 to 1.68)***
TF or PF cartilage damage, extent of full thickness	–	–	***1.48 (1.17 to 1.89)***
Meniscal tear	***3.94 (2.41 to 6.43)***	***5.74 (3.09 to 9.69)***	1.46 (0.97 to 2.18)
Meniscal extrusion	***8.97 (3.87 to 20.80)***	***14.51 (5.46 to 38.52)***	1.14 (0.54 to 2.42)
TF BMLs	***3.16 (1.89 to 5.28)***	***5.38 (2.87 to 10.09)***	–
TF or PF BMLs	–	–	***1.50 (1.11 to 2.01)***

The table shows findings for dose-response analyses, based on logistic regression models for the association between greater magnitude of worsening (using the data from the TF region with greatest worsening, for the KL outcomes, and the data from the TF or PF region with greatest worsening, for the persistent symptoms outcome) and each outcome. Each cell in the table represents results from a different model. Since MOAKS scoring is not conducive to examining the magnitude of worsening of cartilage damage, to explore 'dose' of worsening *area* of cartilage damage, we recoded cartilage damage severity using an ordered categorical variable, where: 0=normal; 1=MOAKS 1.0 or 1.1; 2=2.0, 2.1 or 2.2; and 3=MOAKS 3.0, 3.1, 3.2 or 3.3. These findings are shown in the first and third results rows of the table. To explore 'dose' of worsening *extent of full thickness involvement*, we recoded cartilage damage severity using an ordered categorical variable, where: 0=normal; 1=1.0, 2.0 or 3.0; 2=1.1, 2.1 or 3.1; 3=2.2 or 3.2; and 4=3.3. These findings are shown in the second and fourth results rows of the table. High correlation between worsening area of cartilage damage and worsening extent of full thickness involvement (Spearman's correlation coefficient 0.86) precluded entry into the same model. To explore 'dose' of worsening meniscal lesions, we recoded meniscal lesions using an ordered categorical variable, where: 0=0 or 1; 1=2 or 3; 2=4 or 6; and 3=7 or 8. Adjusted ORs and 95% CIs are the odds of the outcome per unit of 12–48 month worsening of the lesion type, adjusted for age, gender, body mass index (BMI), knee injury and knee surgery. Significant results are shown in bold italics.

BML, bone marrow lesion; KL, Kellgren and Lawrence; MOAKS, MRI OA Knee Score; PF, patellofemoral; TF, tibiofemoral.