**Title**

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Peer reviewed

# Significance of Pre-Radiographic MRI Lesions in Persons at Higher Risk for Knee Osteoarthritis

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## Abstract

**Objective**—Little is known about early knee osteoarthritis (OA). The significance of MRI lesions in older persons without radiographic OA is unclear. Our objectives were to determine extent of tissue pathology by MRI and evaluate its significance by testing the hypotheses: cartilage damage, bone marrow lesions (BMLs), and meniscal damage are associated with prevalent frequent knee symptoms and incident persistent symptoms; BMLs and meniscal damage are associated with incident tibiofemoral cartilage damage; BMLs are associated with incident patellofemoral cartilage damage.

**Methods**—In a cohort study of 849 OAI (Osteoarthritis Initiative) participants who had bilateral K/L 0, we assessed cartilage, BMLs, and meniscal damage using MOAKS, as well as prevalent frequent knee symptoms, incident persistent symptoms, and incident cartilage damage. Multiple logistic regression (one knee/person) was used to evaluate associations between MRI lesions and each of these outcomes.

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**Results—**76% had cartilage damage, 61% BMLs, 21% meniscal tears, and 14% meniscal extrusion. Cartilage damage (any; tibiofemoral and patellofemoral), BMLs (any; tibiofemoral and patellofemoral), meniscal extrusion, and BMI were associated with prevalent frequent symptoms. Cartilage damage (isolated patellofemoral; tibiofemoral and patellofemoral), BMLs (any; isolated patellofemoral; tibiofemoral and patellofemoral), meniscal tears, and BMI were associated with incident persistent symptoms. Hand OA but no individual lesion type was associated with incident tibiofemoral cartilage damage, and BMLs (any; any patellofemoral) with incident patellofemoral damage. Having more lesion types was associated with a greater risk of outcomes.

**Conclusions—**MRI-detected lesions are not incidental and may represent early disease in persons at higher risk for knee OA.

## INTRODUCTION

Little is known about the early stages of knee osteoarthritis (OA). It is widely agreed that OA is established by the time osteophytes are present on a knee x-ray [Kellgren/Lawrence (K/L) grade 2, the definition of knee OA (1-7)]. While it is not possible to capture the point of OA onset, MRI is better able than radiography to capture the interval during which onset occurs. MRI lesions have been identified in K/L 0 or 1 knees, including cartilage damage, bone marrow lesions, and meniscal damage (8-22), but their significance is unclear. Studies evaluating the significance of MRI lesions have predominantly dealt with knees with prevalent radiographic OA (K/L ≥ 2) (18,19).

It is important to investigate if pre-radiographic lesions are incidental findings vs. harbingers of OA, to improve understanding of how the disease begins. If, ultimately, it is determined that such lesions constitute early OA, in theory they could become targets of emerging pharmacologic and non-pharmacologic disease-modifying treatment which, if given before the downward spiral of tissue interactions that characterizes established knee OA, may be more likely to alter the course of disease. At present, there are no disease-modifying interventions for knee OA.

The Osteoarthritis Research Society International (OARSI)-FDA Disease State Working Group distinguished structural changes, the *disease* of OA, from symptoms, the *illness* of OA (23). Efforts to understand the significance of pre-radiographic lesions should include both outcomes. Whether preradiographic cartilage damage, bone marrow lesions, and meniscal damage are associated with *incident* persistent knee symptoms has not been reported previously. Bone marrow lesions and meniscal damage may be a consequence of OA. Whether they are associated with greater risk of initial cartilage damage in a knee not already damaged and vulnerable is not clear. As a longitudinal study including persons without but at higher risk to develop knee OA, the Osteoarthritis Initiative (OAI) (24) is an outstanding setting to evaluate frequency and significance of pre-radiographic joint pathology.

We identified OAI participants with both knees K/L 0 on x-ray in order to A) determine the extent of tissue pathology by MRI, and B) evaluate its significance by testing the following hypotheses: 1) cartilage damage, bone marrow lesions, and meniscal damage are associated with a) prevalent frequent knee symptoms and b) incident persistent knee symptoms; 2)

bone marrow lesions and meniscal damage are associated with incident tibiofemoral (TF) cartilage damage; and 3) bone marrow lesions are associated with incident patellofemoral (PF) cartilage damage.

## METHODS

The OAI is a prospective, observational cohort study of men and women, ages 45-79 years, all with or at increased risk to develop symptomatic, radiographic knee OA, enrolled in: Baltimore, MD; Columbus, OH; Pittsburgh, PA; or Pawtucket, RI (24). Incidence subcohort eligibility required absence of symptomatic, radiographic knee OA in either knee and characteristics associated with increased risk of developing it (25,26). 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 in the next 3 years; MRI and joint radiography contraindications; inability to provide a blood sample; aides other than 1 straight cane for >50% of ambulation; comorbid conditions precluding participation; current double-blind trial participation (25).

Inclusion in the current study additionally required K/L 0 in both knees (by coordinating center organized centralized readings) at the 12-month OAI visit, our ancillary study's baseline MRI assessment. Because risk of knee OA is increased by contralateral knee OA, we required K/L 0 in both knees to maximize the likelihood of disease absence. In the 849 participants who met this criterion, percentage with each OAI incidence subcohort eligibility criterion were: above cut-off for overweight (21.3%); 1 frequent knee bending activity (71.0%); on most days, climb 10 flights (54.1%), kneel 30 minutes (11.1%), squat or deep knee bend 30 minutes (13.0%), lift or move objects 25 pounds, (34.5%); immediate family had knee replacement (16.8%); hard bumps on joints closest to fingertips (32.2%); and, in either knee, any symptoms past year (82.6%), medication use for knee symptoms past year (41.2%), knee injury (35.1%), and knee surgery (11.0%). IRB at each site approved the study.

### Knee X-Ray Acquisition and Assessment

The OAI used the PA fixed-flexion weight-bearing protocol (27,28) with a plexiglass positioning frame (SynaFlexer[TM]). Two experts assessed each film, blinded to each other's reading and all other data. The weighted kappa for between-reader agreement was 0.79 for K/L grade. Pre-specified discrepancies were adjudicated in a consensus session with a third reader (29).

### MR Image Acquisition and Assessment

MR image acquisition utilized 3.0T Siemens Trio scanners installed for the OAI at each site (30). Sequences included: coronal intermediate-weighted (IW) turbo spin echo (TSE), sagittal IW TSE with fat-suppression (FS), 3D DESS WE sequence acquired in the sagittal plane with coronal and axial MPR reconstruction, and a coronal T1-weighted 3D FLASH WE sequence (30).

As a component of our ancillary study, we undertook 12- and 48-month right (left, if right technically unacceptable) knee image readings in persons determined by the coordinating

center to meet the K/L criterion. Three experts (MC, AG, FWR) used the MRI OA Knee Score (MOAKS) system (31), blinded to hypotheses, K/L criterion, and all other data. Evidence of their reliability using MOAKS has been published (31). Paired images were read, chronology known (32). Cartilage morphology was scored separately for 4 PF and 10 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 (31). Bone marrow lesions were scored in the same subregions using WORMS (33) categories (to be consistent with other OAI studies in defining large lesions, not relevant to the current report): *0*, none; *1*, <25% of subregion; *2*, 25-50%; *3*, >50%. Tear was scored in 3 subregions for each meniscus: *0*, normal; *1*, signal abnormality; *2*, horizontal tear; *3*, vertical tear; *4*, complex tear; *5*, partial maceration; *6*, complete maceration. Extrusion was scored in each meniscus: *0*, none; *1*, <50% extruded; *2*, 50%.

### Covariate Measurement

Body weight (standard balance beam scale) and height (wall mounted stadiometer) measurement (34,35) enabled body mass index (BMI) calculation. In the study knee, injury was defined as "ever injured badly enough to limit walking 2 days" and surgery as "any previous surgery". Hand OA was defined as 2 distal interphalangeal joint bony enlargements in either hand by trained examiner (36). Physical activity was assessed using the Physical Activity Scale for the Elderly (PASE) (37,38).

### Statistical Analysis

All analyses used 1 knee per person. For objective A, BMI was categorized as normal (<25 $kg/m^2$), overweight ( 25 to <30), or obese ( 30), and age as <60, 60 to <70, or 70 years. We calculated percentages of knees with cartilage damage, bone marrow lesions, meniscal tear, and meniscal extrusion, overall, and for each gender, BMI, and age stratum at the 12-month visit (baseline for our study); chi-square tests compared percentages across strata.

We used separate logistic regression models to evaluate each hypothesis. For hypothesis 1a, we used the full sample to evaluate associations with prevalent frequent knee symptoms [knee symptoms (pain, aching, or stiffness) or medication use for knee symptoms most days of 1 in the past 12 months], the outcome variable, ascertained at the 12-month visit, of lesions assessed on 12-month MR images (independent variables). Specifically, for cartilage damage (defined as subregion score >0), we separately analyzed: knees with each pattern [any (TF or PF or both), TF only, PF only, TF and PF (in order to evaluate the significance of a lesion in the knee as a whole, in a specific compartment, or in both compartments combined)] vs. knees with no damage in either compartment (reference); bone marrow lesions (subregion score >0) in the same patterns vs. no bone marrow lesions in either compartment (reference); meniscal tear (any subregion score >1, extending to the meniscal surface) vs. no tear (reference); and meniscal extrusion (any score >0) vs. no extrusion (reference). For hypothesis 1b, we analyzed the subsample of knees without frequent knee symptoms (defined above) at OAI enrollment to evaluate associations with incident persistent knee symptoms (reported at 2 consecutive annual OAI visits by the 60-month

visit), the outcome variable, of cartilage damage, bone marrow lesions, meniscal tear, and meniscal extrusion defined as for hypothesis 1a. For each hypothesis, we also explored a potential dose-response association, by analyzing in logistic regression models the association between cartilage damage severity (using an ordered categorical variable, defined as the score category for the most severely damaged cartilage across all subregions in a knee at 12-months, where: 0 = normal; 1 = MOAKS 1.0 or 1.1; 2 = MOAKS 2.0, 2.1, or 2.2; and 3 = MOAKS 3.0, 3.1, 3.2, or 3.3) and worst bone marrow lesion score (across all subregions in a knee at 12-months) and each symptom outcome.

For hypothesis 2, we analyzed the subsample of knees without any TF cartilage damage on 12-month images to evaluate associations with incident TF cartilage damage by 48 months, the outcome variable, of: any bone marrow lesions (TF or PF or both) vs. no bone marrow lesions (reference); TF bone marrow lesions vs. no TF bone marrow lesions (reference); meniscal tear vs. no tear (reference); and meniscal extrusion vs. no extrusion (reference). For hypothesis 3, we analyzed the subsample of knees without any PF cartilage damage on 12-month images to evaluate the association with incident PF cartilage damage by 48 months of: any bone marrow lesions (TF or PF or both) vs. no bone marrow lesions (reference); and PF bone marrow lesions vs. no PF bone marrow lesions (reference). We explored a potential dose-response by evaluating the associations between the worst bone marrow lesion score across all subregions in a knee and each incident cartilage damage outcome.

Hypotheses 1a and 1b models were adjusted for age (continuous), gender, BMI (continuous), and previous knee injury and surgery. Hypotheses 2 and 3 models were adjusted for these covariates, hand OA, and physical activity (continuous). Results are reported as adjusted odds ratios (ORs) and 95% confidence intervals (CIs).

Finally, to summarize overall lesion presence, we created an ordered categorical variable for number of lesion types present (0 to 4, or 0 to 3 as appropriate), and used similar methods to examine the associations of this variable (a linear predictor, to assess trends across ordered categories) with prevalent frequent knee symptoms, incident persistent knee symptoms, and incident TF cartilage damage.

### Role of Funding Source

Funding sources played no role in the study's design, conduct, or reporting.

## RESULTS

Figure 1 shows sample derivation for each objective and hypothesis. Among the 1114 persons who were K/L 0 in both knees at the 12-month visit, 77 did not attend the 48-month evaluation (28 persons withdrew from study, 32 could not be contacted or scheduled, 14 had died, 2 had health problems, 1 had caregiving responsibilities), 176 attended but did not have a 48-month MRI, and 12 had inadequate technical quality of MR images. We assessed right knee MR images (left, if right was technically inadequate) at 12- and 48-months in the remaining 849 persons [mean age 59.6 years (SD 8.8), BMI 26.7 kg/m$^2$ (4.2), 475 (55.9%) women]. Persons who were K/L 0 in both knees and were not included in the analysis

sample did not differ in these characteristics [mean age 58.7 years (9.3), BMI 27.0 (4.8), 63% women].

Table 1 (corresponding with Objective A) shows lesion frequencies on the 12-month MRI in the sample overall and gender, BMI, and age strata. As shown in Table 2 (hypothesis 1a), cartilage damage (any; TF and PF), bone marrow lesions (any; TF and PF), meniscal extrusion, and BMI were each significantly associated with prevalent frequent knee symptoms. Also associated with this outcome in the dose-response model were more severe cartilage damage (adjusted OR per unit increase 1.41, 95% CI: 1.15-1.73) and worse bone marrow lesions (adjusted OR per unit increase 1.76, 95% CI: 1.42-2.17). Table 3 (hypothesis 1b) shows that, among the 573 knees [573 participants, mean age 59.3 years (9.0), BMI 26.6 kg/m$^2$ (4.3), 324 (56.1%) women] without frequent knee symptoms at baseline, cartilage damage (isolated PF; TF and PF), bone marrow lesions (any; isolated PF; TF and PF), meniscal tears, and BMI were each significantly associated with incident persistent symptoms. Also associated with this outcome were more severe cartilage damage (adjusted OR per unit increase 1.37, 95% CI: 1.04-1.81) and worse bone marrow lesions (adjusted OR per unit increase 1.82, 95% CI: 1.35-2.45). As shown in Table 4, among the 457 knees [457 participants, mean age 58.6 years (8.8), BMI 26.6 kg/m$^2$ (4.2), 277 (60.6%) women] without TF cartilage damage, only hand OA was significantly associated with incident TF cartilage damage (top part of table 4). However, worse bone marrow lesions were significantly associated with incident TF cartilage damage (adjusted OR per unit increase 1.52, 95% CI: 1.05-2.19). Among the 322 knees [322 participants, mean age 58.3 years (8.8), BMI 26.6 kg/m$^2$ (4.2), 169 (52.5%) women] without PF damage, bone marrow lesions (any; any PF) were significantly associated with incident PF cartilage damage (bottom part of table 4). Also associated with this outcome were worse bone marrow lesions (adjusted OR per unit increase 2.86, 95% CI: 1.58-5.20).

As shown in Table 5, for each outcome, there was evidence of a significant linear increase in the odds of the outcome (on the logit scale) as the number of lesion types increased. Further adjustment using a quadratic term did not suggest a departure from linearity for this variable (data not shown).

## DISCUSSION

In persons at higher risk for knee OA but with K/L 0 in both knees, 76% had cartilage damage, 61% bone marrow lesions, 21% meniscal tears, and 14% meniscal extrusion. Cartilage damage (any; TF and PF), bone marrow lesions (any; TF and PF), meniscal extrusion, and BMI were associated with prevalent frequent knee symptoms. Cartilage damage (isolated PF; TF and PF), bone marrow lesions (any; isolated PF; TF and PF), meniscal tears, and BMI were associated with incident persistent symptoms. Hand OA, but no single type of MRI lesion, was associated with incident TF cartilage damage; bone marrow lesions (any; any PF) were associated with incident PF cartilage damage. There was evidence of a dose-response association for severity of cartilage damage and bone marrow lesions and each of the symptom outcomes, and for bone marrow lesions and each of the incident cartilage damage outcomes. More concomitant lesion types were associated with a

greater risk of symptom outcomes and incident TF cartilage damage. These findings suggest that, in persons at higher risk, these lesions are not incidental.

Lesion frequencies are consistent with prior studies of knees without radiographic OA: in the Framingham study (12,21), TF cartilage damage in 69%, TF bone marrow lesions in 52%, meniscal tears in 25%; in MOST, TF or PF cartilage damage in 67-81%, bone marrow lesions in 55-75% (14); in studies of Ding et al, cartilage damage in 28-70%, bone marrow lesions in 13-39%, meniscal tear in 45% (15); in the Southeast Michigan OA cohort, large TF or PF cartilage defects in 35%, large bone marrow lesions in 9% (8). Our rates are not substantially higher than those for persons not explicitly at higher risk for knee OA. However, the Framingham sample may have been at somewhat elevated risk given their age (mean 62.3 years) and BMI (mean 27.9 kg/m$^2$) (21). Different findings may reflect different MRI methods and whether the PF compartment was also evaluated. Another possible explanation for the frequencies in previous studies is inclusion of persons with contralateral knee OA, which may reflect a more advanced disease process.

To evaluate the significance of these lesions, we analyzed their relationship with illness and disease outcomes. Cartilage damage, bone marrow lesions, meniscal extrusion, and BMI were associated with prevalent frequent symptoms. In the Framingham study, TF bone marrow lesions were not associated with prevalent knee pain (21); prevalence of meniscal tear was 32% and 23% in those with and without knee symptoms, respectively (12).

We found that cartilage damage, bone marrow lesions, and meniscal tears were each associated with incident persistent symptoms, an outcome that has not previously been evaluated in this context. Reviews of the MRI lesion/symptom relationship reveal few longitudinal studies, mostly of knees *with* radiographic knee OA (18,19). Among the few previous studies of knees *without* OA, baseline bone marrow lesions were associated with frequent symptoms at 15-month follow-up (14), bone marrow lesion change was associated with pain and function score change (17), and incident bone marrow lesions were associated with incident pain (13).

Hand OA (included as a putative marker of cartilage vulnerability) but no single type of lesion was associated with incident TF cartilage damage; bone marrow lesions were associated with incident PF cartilage damage. Risk of incident TF damage was increased by the presence of 2-3 lesion types vs. no lesions. These findings have not previously been reported. Included in a recent review (19), longitudinal studies evaluated the relationship between a baseline lesion and other MRI features 2-3 years later [cartilage defect score (9-11) and bone marrow lesions (16) predicted cartilage volume loss and defect progression]. Subsequent studies, having goals differing from ours, included persons with OA (39,40). We were able to identify only 2 previous longitudinal reports specifically evaluating the initial development of cartilage damage in knees without damage by MRI at baseline, our MOST report in which varus alignment was associated with incident medial damage (22), and another in which effusion/synovitis was associated with cartilage loss (20).

This study has limitations. The OAI focuses on persons at higher risk for knee OA, a group of particular public health importance that will grow with expansion of the aging and overweight populations; the US population is increasingly acquiring the attributes of a high risk population. 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. Our numbers were insufficient to evaluate specific meniscal tear patterns; certain patterns may be associated with incident cartilage damage. It was not among our objectives to evaluate the clinical utility of MRI in persons at higher risk but without radiographic knee OA; the role of MRI in patients at this stage is uncertain, particularly given the paucity of treatments for such lesions.

Our findings suggest an important role for PF lesions. The subsample for incident PF cartilage damage analyses included only knees initially without any PF cartilage damage. Because symptom outcome analyses did not exclude knees with cartilage damage, we looked at severity of TF and PF damage. While diffuse damage was rare in both compartments, more knees had grade 2.0 (10-75% involved) or greater score in a PF than in a TF subregion (47% of 837 knees vs. 18%). The extent of PF involvement coupled with the significance of lesions there compels us to ask the question: does the *illness* of knee OA begin in the PF compartment? Further, these findings illustrate what may be missed at this early stage by relying on K/L scoring. PF changes are common and significant from the outset; the common TF targeting by trials may be misguided. In theory, both preventive and therapeutic strategies may be more efficacious targeting the whole knee.

How best to define disease presence and absence in knee OA is unclear. The established definition, K/L 2, is supported by an historic literature demonstrating an osteophyte/pain association. However, considering K/L 2 as the *beginning* of knee OA constrains what can be learned about early disease, as illustrated by our findings in K/L 0 knees [the significance of pre-radiographic lesions, and that 271 of 849 knees had frequent knee symptoms at baseline (Figure 1)]. Referent or control group identification hinges upon ability to accurately phenotype no vs. early disease. Knowledge of the knee OA onset transition is also vital to preventive and therapeutic strategy development. As the current definition is not conducive to advancing knowledge of early knee OA, further work to establish an MRI-based definition of early OA should occur. Hunter et al proposed an elegant MRI definition of knee OA but stated that it is not intended to identify early disease (41). Our findings also imply that the optimal window for cohort studies to capture knee OA onset by MRI may fall earlier in the lifetime of individuals than is being evaluated in many studies.

In conclusion, in persons at higher risk for knee OA but with K/L 0 in both knees, 76% had cartilage damage, 61% bone marrow lesions, 21% meniscal tears, and 14% meniscal extrusion. Cartilage damage (any; TF and PF), bone marrow lesions (any; TF and PF), meniscal extrusion, and BMI were associated with prevalent frequent symptoms. Cartilage damage (isolated PF; TF and PF), bone marrow lesions (any; isolated PF; TF and PF), meniscal tears, and BMI were associated with incident persistent symptoms. Hand OA but no single lesion type was associated with incident TF cartilage damage; bone marrow lesions (any; any PF) were associated with incident PF damage. There was evidence of a dose-response association for severity of cartilage damage and bone marrow lesions and

each of the symptom outcomes, and for bone marrow lesions and each of the incident cartilage damage outcomes. Having more lesion types present together was associated with a greater risk of each outcome. These findings suggest that these lesions are not incidental in persons at higher risk and may represent early disease and illness.
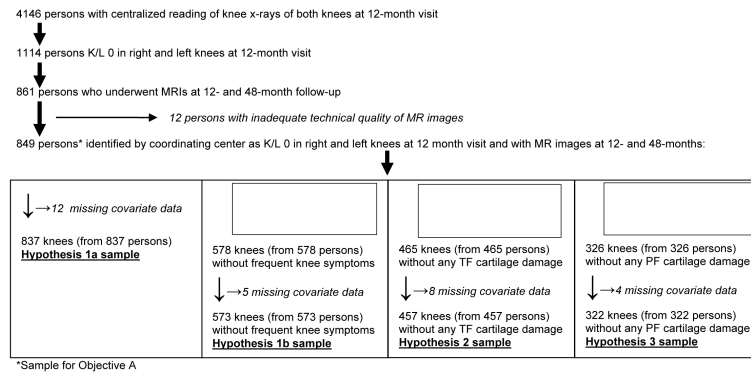
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4146 persons with centralized reading of knee x-rays of both knees at 12-month visit

1114 persons K/L 0 in right and left knees at 12-month visit

861 persons who underwent MRIs at 12- and 48-month follow-up

*12 persons with inadequate technical quality of MR images*

849 persons* identified by coordinating center as K/L 0 in right and left knees at 12 month visit and with MR images at 12- and 48-months:

→*12 missing covariate data*

837 knees (from 837 persons)
**Hypothesis 1a sample**

578 knees (from 578 persons) without frequent knee symptoms

465 knees (from 465 persons) without any TF cartilage damage

326 knees (from 326 persons) without any PF cartilage damage

→*5 missing covariate data*

→*8 missing covariate data*

→*4 missing covariate data*

573 knees (from 573 persons) without frequent knee symptoms
**Hypothesis 1b sample**

457 knees (from 457 persons) without any TF cartilage damage
**Hypothesis 2 sample**

322 knees (from 322 persons) without any PF cartilage damage
**Hypothesis 3 sample**

*Sample for Objective A

**Figure 1. Derivation of Analysis Samples**
The figure shows the derivation of analysis samples for each hypothesis.

**TABLE 1**

Frequencies of Pre-Radiographic Lesionson MR Images Acquired at the 12-Month OAI Visit (n = 849 knees from 849 persons with both knees K/L 0). Cells show number of knees (column %). Significant differences between groups are shown in bold italics.

(TF = tibiofemoral; PF = patellofemoral)

| Lesion present[*] | Overall (n = 849) | Gender, n (%) | | BMI, n (%) | | | Age, n (%) | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Women (n = 474) | Men (n = 375) | Normal weight (n = 316) | Over-weight (n = 345) | Obese (n = 188) | <60 yrs (n = 474) | 60 to <70 yrs (n = 227) | 70 yrs (n = 148) |
| Cartilage damage, TF or PF or both[†] | 641 (75.5%) | 356 (75.1%) | 285 (76.0%) | 226 (71.5%) | 265 (76.8%) | 150 (79.8%) | *341 (71.9%)* | *180 (79.3%)* | *120 (81.1%)* |
| Cartilage damage, TF only[‡] | 118 (13.9%) | *52 (11.0%)* | *66 (17.6%)* | 41 (13.0%) | 44 (12.8%) | 33 (17.6%) | 69 (14.6%) | 28 (12.3%) | 21 (14.1%) |
| Cartilage damage, PF only[‡] | 257 (30.3%) | *162 (34.2%)* | *95 (25.3%)* | 91 (28.8%) | 102 (29.6%) | 64 (34.0%) | 149 (31.4%) | 65 (28.6%) | 43 (29.1%) |
| Cartilage damage, both TF and PF[§] | 266 (31.3%) | 142 (30.0%) | 124 (33.1%) | 94 (29.8%) | 119 (34.4%) | 53 (28.2%) | *123 (26.0%)* | *87 (38.3%)* | *56 (37.8%)* |
| Bone marrow lesion, TF or PF or both[†(BMI),] [†(age)] | 514 (60.5%) | 287 (60.6%) | 227 (60.5%) | *173 (54.8%)* | *214 (62.0%)* | *127 (67.6%)* | *269 (56.8%)* | *147 (64.8%)* | *98 (66.2%)* |
| Bone marrow lesion, TF only | 79 (9.3%) | 42 (8.9%) | 37 (9.9%) | 27 (8.5%) | 39 (11.3%) | 13 (6.9%) | 47 (9.9%) | 15 (6.6%) | 17 (11.5%) |
| Bone marrow lesion, PF only[†] | 288 (33.9%) | 165 (34.8%) | 123 (32.8%) | *96 (30.4%)* | *111 (32.2%)* | *81 (43.1%)* | 154 (32.5%) | 75 (33.0%) | 59 (39.9%) |
| Bone marrow lesion, both TF and PF[‡] | 147 (17.3%) | 80 (16.9%) | 67 (17.9%) | 50 (15.8%) | 64 (18.6%) | 33 (17.6%) | *68 (14.4%)* | *57 (25.1%)* | *22 (14.9%)* |
| Meniscal tear[§(gender),] [‡(age)] | 180 (21.2%) | *70 (14.8%)* | *110 (29.3%)* | 65 (20.6%) | 76 (22.0%) | 39 (20.7%) | *85 (17.9%)* | *51 (22.5%)* | *44 (29.7%)* |
| Meniscal extrusion[§] | 117 (13.9%) | 64 (13.5%) | 53 (14.1%) | 37 (11.7%) | 58 (16.8%) | 22 (11.7%) | *46 (9.7%)* | *38 (16.7%)* | *33 (22.13%)* |

[*] Overall comparisons of lesion prevalences between groups that differed statistically (Gender: 2 groups; BMI, Age: 3 groups) based on chi-square tests are shown in bold italics;

[†] significance levels for bolded results are indicated as: $p < 0.05$;

[‡] $p < 0.01$;

[§] $p < 0.001$.

**TABLE 2**

Pre-radiographic MRI Lesionsand Risk of Prevalent Frequent Knee Symptoms at the 12-Month Visit (n = 837 knees from 837 persons with both knees K/L 0). The table shows the frequency of knees with prevalent frequent knee symptoms among knees without and with each lesion and the lesion present vs. absent adjusted odds ratio (OR) and associated 95% confidence interval (CI) for prevalent frequent knee symptoms. Significant results (95% CI excluding 1) are shown in bold italics. (TF = tibiofemoral; PF = patellofemoral)

| | Number of knees (1 knee per person) | Number of knees (row%) with prevalent frequent knee symptoms | OR (95% CI) Adjusted for age, gender, BMI, previous knee injury, previous knee surgery |
|---|---|---|---|
| Cartilage damage, TF or PF or both[*] | 633 | 174 (27.5%) | *1.75 (1.16, 2.63)* [‡] |
| Cartilage damage, TF only[*] | 117 | 26 (22.2%) | 0.78 (0.48, 1.25)[‡] |
| Cartilage damage, PF only[*] | 254 | 63 (24.8%) | 0.95 (0.67, 1.34)[‡] |
| Cartilage damage, both TF and PF[*] | 262 | 85 (32.4%) | *1.84 (1.31, 2.58)* [‡] |
| *No cartilage damage (TF or PF)* | 204 | 36 (17.6%) | *reference* |
| Bone marrow lesion, TF or PF or both[†] | 507 | 151 (29.8%) | *1.96 (1.38, 2.77)* [‡] |
| Bone marrow lesion, TF only[†] | 77 | 20 (26.0%) | 1.04 (0.60, 1.79)[‡] |
| Bone marrow lesion, PF only[†] | 285 | 83 (29.1%) | 1.38 (0.99, 1.93)[‡] |
| Bone marrow lesion, both TF and PF[†] | 145 | 48 (33.1%) | *1.62 (1.09, 2.40)* [‡] |
| *No bone marrow lesion (TF or PF)* | 330 | 59 (17.9%) | *reference* |
| Meniscal tear[§,‖] | 177 | 49 (27.7%) | 1.04 (0.68, 1.60)[‡] |
| *No meniscal tear* | 660 | 161 (24.4%) | *reference* |
| Meniscal extrusion[‖] | 115 | 38 (33.0%) | *1.64 (1.02, 2.62)* [‡] |
| *No meniscal extrusion* | 722 | 172 (23.8%) | *reference* |

[*]Each cartilage damage pattern was evaluated in a separate model in which no cartilage damage in either TF or PF compartmentwas the reference group

[†]Each bone marrow lesion pattern was evaluated in a separate model in which no bone marrow lesion in either TF or PF compartment was the reference group

[‡]BMI also significant

[§]Of the 177 meniscal tears, 125 were horizontal tears, 14 were vertical, 8 were complex, and 30 menisci were partially macerated

[‖]To adjust for the presence of the other meniscal lesion, meniscal tear and meniscal extrusion were included in the same model

**TABLE 3**

Pre-radiographic MRI Lesionsat the 12-Month Visit and Risk of Incident Persistent Knee Symptoms by the 60-Month Visit (n = 573 knees without frequent knee symptoms at baseline from 573 persons with both knees K/L 0). The table shows the frequency of knees with incident persistent knee symptoms among knees without and with each lesion and the lesion present vs. absentad justed odds ratio (OR) and associated 95% confidence interval (CI) for incident persistent knee symptoms. Significant results (95% CI excluding 1) are shown in bold italics. (TF = tibiofemoral; PF = patellofemoral)

| | Number of knees (1 knee per person) | Number of knees (row%) with incident persistent knee symptoms | OR (95% CI) Adjusted for age, gender, BMI, previous knee injury, previous knee surgery |
|---|---|---|---|
| Cartilage damage, TF or PF or both[*] | 419 | 84 (20.1%) | 1.73 (0.98, 3.03)[‡] |
| Cartilage damage, TF only[*] | 83 | 12 (14.5%) | 1.18 (0.51, 2.74)[‡] |
| Cartilage damage, PF only[*] | 176 | 37 (21.0%) | *1.98 (1.05, 3.76)* [‡] |
| Cartilage damage, both TF and PF[*] | 160 | 35 (21.9%) | *2.00 (1.04, 3.85)* |
| *No cartilage damage (TF or PF)* | 154 | 18 (11.7%) | **reference** |
| Bone marrow lesion, TF or PF or both[†] | 334 | 73 (21.9%) | *1.90 (1.18, 3.06)* [‡] |
| Bone marrow lesion, TF only[†] | 47 | 8 (17.0%) | 1.42 (0.59, 3.45)[§] |
| Bone marrow lesion, PF only[†] | 195 | 42 (21.5%) | *1.82 (1.07, 3.09)* |
| Bone marrow lesion, both TF and PF[†] | 92 | 23 (25.0%) | *2.31 (1.24, 4.32)* |
| *No bone marrow lesion (TF or PF)* | 239 | 29 (12.1%) | *reference* |
| Meniscal tear[‖,¶] | 108 | 29 (26.9%) | *1.83 (1.05, 3.19)* [‡] |
| *No meniscal tear* | 465 | 73 (15.7%) | *reference* |
| Meniscal extrusion[¶] | 60 | 17 (28.3%) | 1.34 (0.68, 2.62)[‡] |
| *No meniscal extrusion* | 513 | 85 (16.6%) | *reference* |

[*] Each cartilage damage pattern was evaluated in a separate model in which no cartilage damage in either TF or PF compartmentwas the reference group

[†] Each bone marrow lesion pattern was evaluated in a separate model in which no bone marrow lesion in either TF or PF compartmentwas the reference group

[‡] BMI also significant

[§] Previous surgery also significant

[‖] Of the 108 meniscal tears, 80 were horizontal tears, 11 were vertical, 4 were complex, and 13 menisci were partially macerated

[¶] To adjust for the presence of the other meniscal lesion, meniscal tear and meniscal extrusion were included in the same model

**TABLE 4**

**Pre-Radiographic Lesions at the 12-Month Visit and 12-to-48 Month <u>Incident TF Cartilage Damage</u> (upper portion of table) and 12-to-48 Month <u>Incident PF Cartilage Damage</u> (lower portion of table)**

The table shows the frequency of knees with incident cartilage damage among knees without and with each lesion and the lesion present vs. absentadjusted odds ratio (OR) and associated 95% confidence interval (CI) for incident TF cartilage damage. Significant results (95% CI excluding 1) are shown in bold italics. (TF = tibiofemoral; PF = patellofemoral)

| | Number of knees *without TF cartilage damage* at the 12-month visit (457 knees from 457 persons with both knees K/L 0) | Number of knees (row%) with *incident TF cartilage damage* | OR (95% CI) adjusted for age, gender, BMI, previous knee injury, previous knee surgery, hand OA, physical activity |
|---|---|---|---|
| Bone marrow lesion, TF or PF or both | 234 | 30 (12.8%) | 1.83 (0.94, 3.57)[*] |
| *No bone marrow lesion (TF or PF)* | 223 | 15 (6.7%) | *reference* |
| Bone marrow lesion, any TF | 64 | 8 (12.5%) | 1.38 (0.60, 3.17)[†] |
| *No TF bone marrow lesion* | 393 | 37 (9.4%) | *reference* |
| Meniscal tear[§,‖] | 56 | 6 (10.7%) | 1.05 (0.39, 2.82)[‡] |
| *No meniscal tear* | 401 | 39 (9.7%) | *reference* |
| Meniscal extrusion[§] | 37 | 6 (16.2%) | 1.72 (0.63, 4.71)[‡] |
| *No meniscal extrusion* | 420 | 39 (9.3%) | *reference* |
| | Number of knees *without PF cartilage damage* at the 12-month visit (322 knees from 322 persons with both knees K/L 0) | Number of knees (row%) with *incident PF cartilage damage* | OR (95% CI) adjusted for age, gender, BMI, previous knee injury, previous knee surgery, hand OA, physical activity |
| Bone marrow lesion, TF or PF or both | 94 | 18 (19.2%) | ***2.68 (1.32, 5.43)*** |
| *No bone marrow lesion (TF or PF)* | 228 | 19 (8.3%) | *reference* |
| Bone marrow lesion, any PF | 52 | 14 (26.9%) | ***4.26 (1.97, 9.22)*** |
| *No PF bone marrow lesion* | 270 | 23 (8.5%) | *reference* |

[*] hand OA also significant in this model, adjusted OR ***2.07 (1.02, 4.19)***

[†] hand OA also significant in this model, adjusted OR ***2.09 (1.04, 4.20)***

[‡] hand OA also significant in this model, adjusted OR ***2.03 (1.004, 4.10)***

[§] To adjust for the presence of the other meniscal lesion, meniscal tear and meniscal extrusion were included in the same model

[‖] Of the 56 meniscal tears, 43 were horizontal tears, 8 were vertical, 1 was complex, and 4 menisci were partially macerated

**TABLE 5**

**Association between Number of Lesion Types Present and Prevalent Frequent Knee Symptoms, Incident Persistent Knee Symptoms, and Incident TF Cartilage Damage**

For each of the outcome variables listed in the left column of the table, the adjusted odds ratios (ORs) and associated 95% confidence intervals (CIs) are shown for the predictor variables: number of lesion types present [defined as an ordered categorical variable with values 0 (reference category), 1, 2, 3, or 4 for the first two outcomes (lesion types including any cartilage damage, any bone marrow lesion, meniscal tear, or meniscal extrusion), and as 0, 1, and 2 and 3 combined for the last outcome (lesion types including any bone marrow lesion, meniscal tear, or meniscal extrusion)]vs. the reference category of 0 lesion types present. For incident TF cartilage damage, the highest numbers of lesion types (2 and 3) were combined into a single category due to insufficient knees in each category separately. Other variables in the models include age, gender, BMI, previous knee injury, and previous knee surgery; the third outcome models are further adjusted for hand OA and physical activity. 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.

| Outcome variable | Number of lesion types present (predictor) | Adjusted OR (95%CI) | p for trend |
|---|---|---|---|
| Prevalent frequent knee symptoms (n = 837 knees from 837 persons) | | | |
| | 1 type of lesion (vs. 0, reference) | 0.90 (0.49, 1.64) | < 0.0001 |
| | 2 | *1.87 (1.13, 3.10)* | |
| | 3 | *2.02 (1.09, 3.74)* | |
| | 4 | *3.23 (1.50, 6.96)* | |
| Incident persistent knee symptoms (n = 573 knees from 573 persons) | | | |
| | 1 type of lesion (vs. 0, reference) | 1.32 (0.57, 3.07) | 0.0004 |
| | 2 types (vs. 0) | 2.06 (0.99, 4.30) | |
| | 3 types (vs. 0) | *3.72 (1.57, 8.82)* | |
| | 4 types | *4.07 (1.32, 12.53)* | |
| Incident TF cartilage damage (n = 457 knees from 457 persons) | | | |
| | 1 type of lesion (vs. 0, reference) | 1.43 (0.69, 2.94) | 0.046 |
| | 2-3 types (vs. 0) | *2.76 (1.07, 7.14)* | |