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Magnetic Resonance Imaging–Assessed Subchondral Cysts and Incident Knee Pain and Knee Osteoarthritis: Data From the Multicenter Osteoarthritis Study

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Objective. To examine whether knee subchondral cysts, measured on magnetic resonance imaging (MRI), are associated with incident knee osteoarthritis (OA) outcomes.

Methods. We used longitudinal data from the Multicenter Osteoarthritis Study, a community-based cohort of subjects with risk factors for knee OA. Participants without a history of knee surgery and/or inflammatory arthritis (i.e., rheumatoid arthritis and gout) were followed up for 84 months for the following incident outcomes: 1) radiographic knee OA (Kellgren/Lawrence grade ≥2), 2) symptomatic radiographic knee OA (radiographic knee OA and frequent knee pain), and 3) frequent knee pain (with or without radiographic knee OA). In a subset of participants, subchondral cysts were scored on baseline MRIs of 1 knee. Multiple logistic regression, with adjustment for participant characteristics and other baseline knee MRI findings, was used to assess whether subchondral cysts were predictive of incident outcomes.

Results. Among the participants with knees eligible for analyses of outcomes over 84 months, incident radiographic knee OA occurred in 22.8% of knees with no baseline radiographic knee OA, symptomatic radiographic knee OA occurred in 17.0% of knees with no baseline symptomatic radiographic knee OA, and frequent knee pain (with or without radiographic knee OA) occurred in 28.8% of knees with no baseline radiographic knee OA and 43.7% of knees with baseline radiographic knee OA. With adjustment for age, sex, and body mass index, the presence of subchondral cysts was not associated with incident radiographic knee OA but was associated with increased odds of incident symptomatic radiographic knee OA (odds ratio 1.92 [95% confidence interval 1.16–3.19]) and increased odds of incident frequent knee pain in those who had radiographic knee OA at baseline (odds ratio 2.11 [95% confidence interval 0.87–5.12]). Stronger and significant associations were observed for outcomes based on consistent reports of frequent knee pain within ~1 month of the study visit.

Conclusion. Subchondral cysts are likely to be a secondary phenomenon, rather than a primary trigger, of radiographic knee OA, and may predict symptoms in knees with existing disease.

INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis and is a leading cause of global disability, pain, and reduction in physical function (1). Knee pain is the hallmark feature of knee OA (2) and is the main reason health care is sought among older adults (3). While knee pain may be chronic, many patients experience fluctuations in the presence/

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absence of pain and in pain severity (4). Understanding which knee joint structures contribute to the development of structural OA, as radiographic knee OA, and nociceptive activation with radiographic knee pain will help to better clarify the etiology of the disease.

There are considerable magnetic resonance imaging (MRI) data in knee OA research, with a principle focus on the assessment of cartilage, synovitis, and bone marrow lesions (BMLs) (5), though recently there has been a growing interest in the contribution of subchondral cysts to the development of knee OA. Subchondral cysts, also referred to as cystic lesions or bone cysts (6), are defined as regions of markedly increased signal on fluid-sensitive MRI (7) and are typically spherical or ellipsoidal cavities (8). Subchondral cysts are common both in healthy knee joints, occurring in up to 25% of adults age >50 years who have no evidence of radiographic knee OA (9), and in up to 31% of patients with symptomatic knee OA (6). Moreover, using a subsample of subjects in the Multicenter Osteoarthritis Study (MOST), subchondral cysts were shown to occur in the absence of both MRI-assessed BMLs and cartilage loss in men and women with knee OA or at risk for knee OA (10). Despite this evidence, most epidemiologic studies concerning subchondral cysts are in the context of established knee OA. Thus, there is a need for the evaluation of the effect of subchondral cysts on incident knee OA outcomes.

The etiology of subchondral cyst development is unclear (6); however, subchondral cysts in the absence of established radiographic OA may provide a pathway to disease development and pain. Histologic assessment has shown that subchondral cysts contain necrotic bone fragments (11), which may stimulate nociceptive activation, and cystic lesions have shown positive responses to staining for substance P (12), an inflammation marker in pain signaling (13). Data from an in vivo study in a rodent model of posttraumatic knee OA induced by meniscectomy showed that subchondral cysts developed within just 12 weeks of injury (14). It is, therefore, possible that subchondral cysts precede the development of more conventional radiographic features including joint space narrowing, osteophytes, and subchondral sclerosis. Subchondral cysts have been shown to contain activated cells that express matrix metalloproteinase 1 (15), which has been linked to joint damage (16). In established knee OA, subchondral cysts typically present adjacent to abnormal joint tissue (11) and have been shown to colocalize with BMLs (12–14). Subchondral cysts have also been found to influence the biomechanical properties of the subchondral bone by affecting bone mineral density (8) and by creating increased intraosseous stress (17). Together, these mechanisms may thereby provide a potential path for the development of knee OA.

In the present study, we aimed to examine the association between MRI-assessed subchondral cysts and incident knee OA outcomes in participants who were at high risk for developing knee OA over 84 months of follow-up.

PATIENTS AND METHODS

Study design and participants. We used longitudinal data from the MOST study, a prospective, observational study of risk factors for the development and progression of knee OA (http://most.ucsf.edu/). Details of the MOST study and study population have been previously published (18). Briefly, 3,026 men and women ages 50–79 years were recruited from 2 US communities and were followed up for up to 84 months. Participants either had evidence of knee OA at baseline or were at high risk for developing the disease. At prespecified time points (baseline, 30 months, 60 months, and 84 months), clinical assessments were performed and knee radiographs and MRIs were obtained.

In the present study, we used data from the "V035WORMS" MRI data set, the largest of 4 MRI subsets which can be used for the analysis of multiple end points. This subsample comprises 1,182 participants who had a readable pair of MRIs of at least 1 knee at 60 months and 84 months. A single index knee MRI obtained from each participant was read for all Whole-Organ Magnetic Resonance Imaging Score (WORMS) features (7), described in more detail below. If a participant had a readable pair of MRIs of both knees at 60 months and 84 months, 1 knee was randomly selected for MRI reading.

All participants underwent weight-bearing posteroanterior fixed-flexion knee radiographs at baseline and follow-up clinic visits. Knee radiographs were graded on a 0–4 scale across the whole knee joint (including the patellofemoral and tibiofemoral regions) using the Kellgren/Lawrence (K/L) scoring criteria (19). Radiographic OA of the whole knee was defined as a K/L grade ≥2 in either, or both, the tibiofemoral or patellofemoral joints.

Knee-specific frequent pain was assessed at each clinic visit using a modified version of the National Health and Nutrition Examination Survey (NHANES) questions (20). In accordance with current guidelines, this was considered to be the most suitable measure of current knee pain (21). Participants also completed assessment of frequent knee pain by telephone interview ~30 days prior to each clinical visit. A stricter definition of persistent, frequent knee pain included positive responses to the NHANES questions during both the telephone interview and clinical visits (22–25).

Our goal was to determine the risk of incident radiographic knee OA, incident symptomatic radiographic knee OA, and incident frequent knee pain separately in participants with and without radiographic knee OA in the index knee at baseline. We included only the subset of participants who had a knee with available baseline data on subchondral cysts and other WORMS features (the index knee: 1 knee per participant). Outcomes in index knees were based on radiographic knee OA and knee symptom data from the 60-month and 84-month follow-up visits.

Participants with missing data on baseline radiographic knee OA, baseline frequent knee pain, missing outcomes in the index knee that could not be imputed (see below), and baseline covariate data were excluded. We also excluded participants with evidence of inflammatory arthritis (rheumatoid arthritis and/or gout) and/or a history of knee-related surgery (including knee replacement) at baseline in either knee. In addition, only knees with available baseline data on MRI structural features across all knee subregions were included.

Magnetic resonance imaging. Non–contrast-enhanced MRIs were acquired using a dedicated 1.0T extremity system (OrthOne; ONI Medical Systems) with a 160-mm–diameter circumferential transmit–receive extremity coil. Axial and sagittal proton density–weighted fat-suppressed fast spin-echo sequences were acquired (repetition time 4,800 msec, echo time 35 msec, slice thickness 3.0 mm, interslice gap 0.0 mm, number of slices 32, field of view 140 mm × 140 mm, matrix 288 × 192 pixels, number of excitations 2, echo train length 8 msec) (10).

MRI structural features, including subchondral cysts, BMLs, synovitis/effusions, and cartilage lesions, were semiquantitatively assessed using the WORMS criteria (7). Subchondral cysts were defined as areas of markedly increased signal intensity in the subarticular bone, with sharply defined, rounded margins and with no evidence of internal marrow tissue or trabecular bone on fluid-sensitive MRI. Subchondral cysts were scored from 0 to 3 across 15 joint subregions (whole knee joint), including the subspinous region of the tibia, with scores related to the extent of regional involvement: 0 = no involvement, 1 = <25% of the region, 2 = 25–50% of the region, and 3 = >50% of the region. BMLs were assessed across the same joint compartments using the same scoring criteria. Synovitis and effusion were scored collectively at the intercondylar and infrapatellar regions only and were not distinguished. Using a previously validated method of semiquantitative assessment for non–contrast-enhanced scans (26), synovitis and effusion were scored from 0 to 3, with 3 representing severe. Cartilage lesions were assessed across 14 subregions (not including the tibia subspinous region), and scored from 0 to 6 (0 = normal signal, 6 = diffuse [≥75% of the region] full-thickness loss).

MRI-assessed subchondral cyst exposure. We used 3 exposure variables to predict incident outcomes. Our first exposure was coded as a binary variable, with 0 representing the absence of subchondral cysts (i.e., no evidence of subchondral cysts across all joint subregions) and 1 representing the presence of subchondral cysts (i.e., evidence of subchondral cysts in at least a single subregion across the knee joint). Our second exposure variable was equal to the maximum subchondral cyst score across the 15 joint subregions (range 0–3), and our final exposure variable was equal to the number of subregions with subchondral cysts present (range 0–15).

Outcome measures. *Incident symptomatic radiographic knee OA.* Incident symptomatic radiographic knee OA was defined as the simultaneous occurrence of a combination of frequent knee symptoms and radiographic knee OA (K/L grade ≥2) at one or both of the 60-month or 84-month visits, in an index knee that did not have this combination at baseline.

Incident radiographic knee OA. Incident radiographic knee OA was defined as the occurrence of radiographic knee OA (K/L grade ≥2) during follow-up (60 months and 84 months), in an index knee without radiographic knee OA (K/L grade 0–1) at baseline.

Incident frequent pain in knees with or without radiographic knee OA at baseline. Due to a lack of data from other studies concerning the relationship between subchondral cysts and incident knee pain in the absence of radiographic knee OA, and the conflicting data regarding the association between subchondral cysts and knee pain in established knee OA (27–29), we conducted 2 separate incident knee pain analyses: 1) participants without radiographic knee OA (i.e., K/L grade 0–1) in the index knee at baseline and 2) participants with radiographic knee OA in the index knee at baseline. Incident knee pain was defined as the occurrence of frequent knee pain at one or both of the 60-month or 84-month visits, in an index knee that did not have frequent knee pain at baseline.

Covariates. Information on age, sex, and body mass index (BMI) was assessed at baseline. Baseline BML status, synovitis status, and cartilage lesion status were defined as the maximum severity score across the respective knee joint regions assessed. MRI findings were selected for inclusion as covariates in our model based on the available data. There are data to support the notion that subchondral cysts that colocalize with bone marrow lesions (10,30,31) are linked with histologically assessed synovitis (32), and while the exact etiology of subchondral cysts is unclear, it is thought that they may develop in response to cartilage loss with synovial infiltration (6,33).

Statistical analysis. Descriptive statistics were calculated for age, sex, BMI, and MRI findings. To examine the relationship between subchondral cyst exposures and incident outcomes, we performed logistic regression analyses in index knees. Results were presented as odds ratios (ORs) with 95% confidence intervals (95% CIs) for crude and adjusted models. We adjusted for baseline age, sex, and BMI. In additional analyses, we also adjusted for MRI-assessed synovitis (categorical), BML score (categorical), and cartilage lesion score (continuous).

We used imputation (last observation carried forward) to impute missing data on follow-up radiographic knee OA status at the 60-month and 84-month follow-up visits if radiographic knee OA was known to be present at the previous visit (imputed to be present at the visit with missing data) or was known to be absent at the previous visit and the subsequent visit (imputed to be absent at the visit with missing data). We included participants

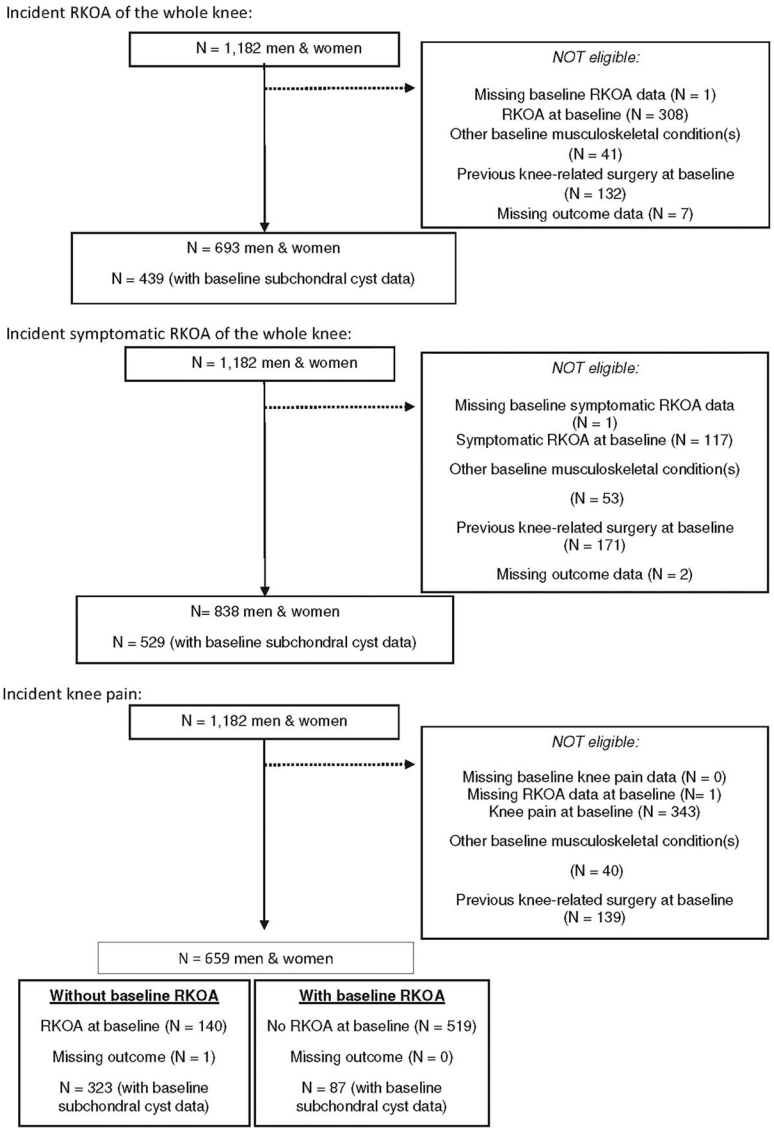

Figure 1. Flow chart of participants eligible for study investigation. RKOA = radiographic knee osteoarthritis.

with missing radiographic knee OA or knee symptom data in cases where it was still possible to determine symptomatic radiographic knee OA status (e.g., negative for radiographic knee OA, missing knee symptom data). For the second exposure variable, maximum subchondral cyst severity score, there were too few knees with a score of 3. Scores of 2 and 3 were combined into a single category of ≥2. Similarly, for the third exposure variable, the number of regions with subchondral cysts, there were too few knees with subchondral cyst involvement across ≥2 regions. Therefore, we categorized the data as 0 regions, 1 region, and ≥2 regions. We also performed sensitivity analyses using the stricter definition of persistent, frequent knee pain (i.e., positive responses for knee pain during the telephone interview and clinical visit) (22–25) for both incident symptomatic radiographic knee OA and incident knee pain outcomes.

Data availability. All data generated and analyzed in this study are available upon reasonable request. Access to data generated in this study is available upon request from the corresponding author, whereas requests for the MOST data should be submitted to the cohort principal investigators. Information regarding the MOST public use data sets is available at http://most.ucsf.edu/.

RESULTS

The distribution of participants with knees eligible for analyses for incident radiographic knee OA, incident symptomatic radiographic knee OA, and incident frequent knee pain (with or without radiographic knee OA at baseline) is presented in Figure 1. Characteristics of the study participants and baseline data on subchondral cysts in the eligible index knees are shown in Table 1. Incident

radiographic knee OA occurred in 22.8% of knees (n = 100) eligible for this outcome, and incident symptomatic radiographic knee OA occurred in 17.0% of knees (n = 90) eligible for this outcome. Incident frequent knee pain occurred in 28.8% of knees (n = 93) without radiographic knee OA at baseline and 43.7% of knees (n = 37) with radiographic knee OA at baseline.

Incident symptomatic radiographic knee OA. After adjustment for baseline age, BMI, and sex and using the presence of subchondral cysts (yes/no) as the exposure, knees with evidence of subchondral cysts at baseline had increased odds of incident symptomatic radiographic knee OA compared to knees with no evidence of subchondral cysts (OR 1.92 [95% CI 1.16–3.19]) (Table 2). Using the maximum subchondral cyst score as the exposure, compared to knees with no subchondral cyst involvement, knees with a maximum subchondral cyst score of 1 (<25% of the region) had a 2-fold increased risk of incident symptomatic radiographic knee OA (OR 1.96 [95% CI 1.15–3.33]); there was no statistically significant association between a maximum subchondral cyst score of ≥2 and incident symptomatic radiographic knee OA (OR 1.73 [95% CI 0.53–5.65]). Finally, we observed a statistically significant association between the presence of ≥2 regions with subchondral cysts and incident symptomatic radiographic knee OA. After further adjustment for BMLs, synovitis, and cartilage lesions at baseline, there was no longer a statistically significant association between subchondral cyst exposures and incident symptomatic radiographic knee OA.

Table 1. Baseline demographic and clinical characteristics of eligible participants in the MOST study*

	No radiographic knee OA (n = 439)	No symptomatic radiographic knee OA (n = 529)	No knee pain without radiographic knee OA (n = 323)	No knee pain with radiographic knee OA (n = 87)
Age, median (IQR) years	60 (11)	60 (12)	60 (11)	64 (13)
Female	268 (61.05)	334 (63.14)	184 (56.97)	64 (73.56)
BMI, median (IQR) kg/m^2	28.65 (6.19)	28.83 (6.11)	28.25 (5.96)	30.14 (5.79)
Right knee as index knee	218 (49.66)	271 (51.23)	159 (49.23)	52 (59.77)
Subchondral cysts				
No	354 (80.64)	409 (77.32)	262 (81.11)	52 (59.77)
Yes	85 (19.36)	120 (22.68)	61 (18.89)	35 (40.23)
Subchondral cyst severity				
0	354 (80.64)	409 (77.32)	262 (81.11)	52 (59.77)
1	76 (17.31)	104 (19.66)	56 (17.34)	28 (32.18)
≥2	9 (2.05)	16 (3.02)	5 (1.55)	7 (8.05)
No. of regions with subchondral cysts				
0	354 (80.64)	409 (77.32)	262 (81.11)	52 (59.77)
1	69 (15.72)	89 (16.82)	49 (15.17)	20 (22.99)
≥2	16 (3.64)	31 (5.86)	12 (3.72)	15 (17.24)
Bone marrow lesion score				
0	137 (31.21)	143 (27.03)	105 (32.51)	5 (5.75)
1	173 (39.41)	209 (39.51)	133 (41.18)	35 (40.23)
2	92 (20.96)	120 (22.68)	63 (19.50)	27 (31.05)
3	30 (6.83)	49 (9.26)	17 (5.26)	19 (21.84)
Missing†	7 (1.59)	8 (1.51)	5 (1.55)	1 (1.15)
Synovitis score				
0	192 (43.74)	219 (41.40)	137 (42.41)	27 (31.03)
1	196 (44.65)	245 (46.31)	152 (47.06)	46 (52.87)
2	43 (9.79)	54 (10.21)	28 (8.67)	11 (12.64)
3	8 (1.82)	11 (2.08)	6 (1.86)	3 (3.45)
Missing†	0 (0)	0 (0)	0 (0)	0 (0)
Cartilage thickness score‡				
0	57 (12.98)	58 (10.96)	41 (12.69)	1 (1.15)
2	54 (12.30)	58 (10.96)	45 (13.93)	3 (3.45)
2.5	6 (1.37)	7 (1.32)	4 (1.24)	1 (1.15)
3	179 (40.77)	196 (37.05)	134 (41.49)	17 (19.54)
4	6 (1.37)	8 (1.51)	5 (1.55)	2 (2.30)
5	111 (25.28)	144 (27.22)	76 (23.53)	31 (35.63)
6	6 (1.37)	31 (5.86)	3 (0.93)	25 (28.74)
Missing†	20 (4.56)	27 (5.10)	15 (4.64)	7 (8.05)

* Except where indicated otherwise, values are the number (%). Subgroups eligible for assessment of each outcome were not mutually exclusive but were overlapping. MOST = Multicenter Osteoarthritis Study; osteoarthritis = OA; IQR = interquartile range; BMI = body mass index.
† Data were missing for at least 1 region assessed for the given magnetic resonance imaging structure.
‡ Grade 1 on Whole-Organ Magnetic Resonance Imaging Score was not used when scoring cartilage thickness on magnetic resonance imaging.

Table 2. Association between subchondral cysts and incident symptomatic radiographic knee OA*

	Univariate model		Multivariate model 1†		Multivariate model 2‡	
	OR (95% CI) (n = 529)	*P*	OR (95% CI) (n = 529)	*P*	OR (95% CI) (n = 500)	*P*
Presence of subchondral cysts						
No (n = 409/59)	Referent	–	Referent	–	Referent	–
Yes (n = 120/31)	2.07 (1.26–3.38)	0.004	1.92 (1.16–3.19)	0.01	1.53 (0.85–2.75)	0.15
Subchondral cyst severity score						
0 (n = 409/59)	Referent	–	Referent	–	Referent	–
1 (n = 104/27)	2.08 (1.24–3.49)	0.006	1.96 (1.15–3.33)	0.01	1.60 (0.87–2.94)	0.13
≥2 (n = 16/4)	1.98 (0.62–6.34)	0.25	1.73 (0.53–5.65)	0.36	1.14 (0.32–4.10)	0.84
No. of regions with subchondral cysts						
0 (n = 409/59)	Referent	–	Referent	–	Referent	–
1 (n = 89/20)	1.72 (0.97–3.04)	0.06	1.69 (0.95–3.03)	0.08	1.46 (0.76–2.81)	0.25
≥2 (n = 31/11)	3.26 (1.49–7.16)	0.003	2.61 (1.17–5.84)	0.02	1.71 (0.69–4.21)	0.24

* N values represent the number of participants for the given category/number of incident cases of symptomatic radiographic knee osteoarthritis (OA). OR = odds ratio; 95% CI = 95% confidence interval.
† Adjusted for age, sex, and body mass index.
‡ Adjusted for age, sex, body mass index, bone marrow lesion severity, synovitis severity, and cartilage lesions.

In a sensitivity analysis using a stricter definition of persistent, frequent knee pain, in a fully adjusted model (adjusted for age, sex, BMI, and other MRI features), knees in which subchondral cysts were present (OR 2.16 [95% CI 1.18–3.96]), knees with a maximum subchondral cyst score of 1 (OR 2.29 [95% CI 1.23–4.26]), and knees with subchondral cyst involvement at 1 region (OR 2.24 [95% CI 1.16–4.32]) had an increased risk of symptomatic radiographic knee OA (Supplementary Table 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41917/abstract).

Incident radiographic knee OA. After adjustment for age, BMI, and sex, there was no statistically significant association between the presence of subchondral cysts and incident radiographic knee OA compared to knees with no evidence of subchondral cysts (OR 1.20 [95% CI 0.68–2.10]) (Table 3). Similarly, using the maximum subchondral cyst severity score as the exposure, knees with a maximum grade of 1 (OR 1.25 [95% CI 0.69–2.25]) and a grade of ≥2 (OR 0.81 [95% CI 0.15–4.27]) were not at increased risk for incident radiographic knee OA. Finally, using the number of regions with subchondral cysts as the exposure, there was no statistically significant association between having involvement at 1 region (OR 1.27 [95% CI 0.69–2.34]) or involvement at ≥2 regions (OR 0.93 [95% CI 0.28–3.12]) compared to participants with no evidence of knee subchondral cysts. After further adjustment for synovitis, BMLs, and cartilage lesions, there remained no statistically significant association between subchondral cyst exposures and incident radiographic knee OA.

Incident frequent knee pain. *Index knees without radiographic knee OA at baseline.* Among participants without radiographic knee OA in the index knee at baseline, in a fully adjusted model, there was no statistically significant association between the

Table 3. Association between subchondral cysts and incident radiographic knee OA*

	Univariate model, OR (95% CI) (n = 439)	Multivariate model 1, OR (95% CI) (n = 439)†	Multivariate model 2, OR (95% CI) (n = 417)‡
Presence of subchondral cysts			
No (n = 354/77)	Referent	Referent	Referent
Yes (n = 85/23)	1.34 (0.78–2.29)	1.20 (0.68–2.10)	0.98 (0.52–1.86)
Subchondral cyst severity score			
0 (n = 354/77)	Referent	Referent	Referent
1 (n = 76/21)	1.37 (0.78–2.41)	1.25 (0.69–2.25)	1.01 (0.52–1.95)
≥2 (n = 9/2)	1.03 (0.21–5.05)	0.81 (0.15–4.27)	0.73 (0.13–4.07)
No. of regions with subchondral cysts			
0 (n = 354/77)	Referent	Referent	Referent
1 (n = 69/19)	1.37 (0.76–2.46)	1.27 (0.69–2.34)	1.09 (0.55–2.17)
≥2 (n = 16/4)	1.20 (0.38–3.82)	0.93 (0.28–3.12)	0.64 (0.18–2.27)

* N values represent the number of participants in the given category/number of incident cases of radiographic knee osteoarthritis (OA). None of the odds ratios (ORs) shown were statistically significant. 95% CI = 95% confidence interval.
† Adjusted for age, sex, and body mass index.
‡ Adjusted for age, sex, body mass index, bone marrow lesion severity, synovitis severity, and cartilage lesions.

Table 4. Association between subchondral cysts and incident frequent knee pain without radiographic knee OA at baseline*

	Univariate model, OR (95% CI) (n = 323)	Multivariate model 1, OR (95% CI) (n = 323)†	Multivariate model 2, OR (95% CI) (n = 307)‡
Presence of subchondral cysts			
No (n = 262/76)	Referent	Referent	Referent
Yes (n = 61/17)	0.95 (0.51–1.76)	0.94 (0.50–1.77)	0.93 (0.45–1.91)
Subchondral cyst severity score			
0 (n = 262/76)	Referent	Referent	Referent
1 (n = 56/17)	1.07 (0.57–2.00)	1.08 (0.57–2.07)	1.02 (0.49–2.11)
≥2 (n = 5/0)	–	–	–
No. of regions with subchondral cysts			
0 (n = 262/76)	Referent	Referent	Referent
1 (n = 49/14)	0.98 (0.50–1.92)	1.01 (0.51–2.03)	1.03 (0.48–2.25)
≥2 (n = 12/3)	0.82 (0.22–3.10)	0.69 (0.18–2.67)	0.60 (0.14–2.56)

* N values represent the number of participants for the given category/number of incident cases of knee pain without radiographic knee osteoarthritis (OA). None of the odds ratios (ORs) shown were statistically significant. 95% CI = 95% confidence interval.
† Adjusted for age, sex, and body mass index.
‡ Adjusted for age, sex, body mass index, bone marrow lesion severity, synovitis severity, and cartilage lesions.

presence of subchondral cysts and incident knee pain compared to knees with no evidence of subchondral cysts (OR 0.93 [95% CI 0.45–1.91]) (Table 4). Similarly, using the maximum subchondral cyst severity score as the exposure, knees with a maximum score of 1 were not at increased risk for developing knee pain (OR 1.02 [95% CI 0.49–2.11]). There were no occurrences of incident knee pain in the grade ≥2 group. Finally, using the number of regions with subchondral cysts as the exposure, there was no statistically significant association between subchondral cyst involvement at 1 region (OR 1.03 [95% CI 0.48–2.25]) or at ≥2 regions (OR 0.60 [95% CI 0.14–2.56]) compared to participants with no evidence of subchondral cysts. In a sensitivity analysis using a stricter definition of persistent frequent knee pain, in a fully adjusted model, no statistically significant association was observed between any of the predictors and incident knee pain (Supplementary Table 2, http://onlinelibrary.wiley.com/doi/10.1002/art.41917/abstract).

Index knees with radiographic knee OA at baseline. Among participants with radiographic knee OA in the index knee at baseline, there were moderate, but not statistically significant, associations between subchondral cyst exposures and incident knee pain, both in models with adjustment for age, sex, and BMI and in fully adjusted models; e.g., for the association of incident frequent knee pain with presence of subchondral cysts in fully adjusted models, the OR was 2.47 (95% CI 0.87–7.03, $P = 0.091$) (Table 5). However, when we used the stricter definition of persistent, frequent knee pain, presence of subchondral cysts (OR 3.14 [95% CI 1.15–8.59]), subchondral cyst severity score of 1 (OR 3.80 [95% CI 1.33–10.89]), and knees with subchondral cyst involvement at 1 region (OR 4.46 [95% CI 1.39–14.36]) were each statistically significantly associated with increased odds of incident frequent knee pain (Supplementary Table 3, http://onlinelibrary.wiley.com/doi/10.1002/art.41917/abstract).

Table 5. Association between subchondral cysts and incident frequent knee pain in knees with radiographic knee OA at baseline*

	Univariate model, OR (95% CI) (n = 87)	Multivariate model 1, OR (95% CI) (n = 87)†	Multivariate model 2, OR (95% CI) (n = 80)‡
Presence of subchondral cysts			
No (n = 262/76)	Referent	Referent	Referent
Yes (n = 61/17)	2.06 (0.86–4.93)	2.11 (0.87–5.12)	2.47 (0.87–7.03)
Subchondral cyst severity score			
0 (n = 262/76)	Referent	Referent	Referent
1 (n = 56/17)	2.32 (0.91–5.91)	2.40 (0.93–6.23)	2.91 (0.96–8.82)
≥2 (n = 5/0)	1.30 (0.26–6.45)	1.26 (0.24–6.57)	1.19 (0.18–7.65)
No. of regions with subchondral cysts			
0 (n = 262/76)	Referent	Referent	Referent
1 (n = 49/14)	2.12 (0.75–6.04)	2.14 (0.75–6.13)	2.85 (0.84–9.63)
≥2 (n = 12/3)	1.99 (0.62–6.34)	2.08 (0.63–6.83)	2.00 (0.50–7.96)

* N values represent the number of participants for the given category/number of incident cases of knee pain with radiographic knee osteoarthritis (OA). None of the odds ratios (ORs) shown were statistically significant. 95% CI = 95% confidence interval.
† Adjusted for age, sex, and body mass index.
‡ Adjusted for age, sex, body mass index, bone marrow lesion severity, synovitis severity, and cartilage lesions.

DISCUSSION

To our knowledge, this study is the first to examine the relationship between subchondral cysts, measured on fluid-sensitive MRI, and incident knee pain (with or without radiographic knee OA of the index knee) and knee OA in a large, long-term study of participants at risk for developing knee OA. In the present study, after adjustment for age, BMI, and sex, we found no association between the presence of subchondral cysts at baseline and incident radiographic knee OA over 84 months of follow-up. Results were similar in analyses that also adjusted for other baseline MRI features (i.e., synovitis, BMLs, and cartilage lesions). In contrast, after adjustment for age, BMI, and sex, the presence of ≥1 subchondral cyst(s) and the presence of multiple subchondral cysts at baseline were significantly associated with 1.9–2.6-fold increased odds of incident symptomatic radiographic knee OA. After further adjustment for other baseline MRI features, there was no longer a statistically significant association between any of the exposures and incident symptomatic radiographic knee OA. In addition, we observed no association between subchondral cysts and incident frequent knee pain in knees without radiographic knee OA at baseline. In knees with radiographic knee OA at baseline, we observed a non–statistically significant increase in the odds of incident frequent knee pain over 84 months of follow-up (2.5-fold increase).

In sensitivity analyses, we also examined the incidence of knee pain and symptomatic radiographic knee OA using a stricter definition of persistent, frequent knee pain (22–25) (positive responses reported during both the telephone interview and the clinical visit within ~1 month versus the clinical visit only). The rationale for this was that knee OA pain is known to fluctuate in occurrence and severity over time. Using this outcome, after adjustment for age, sex, and BMI, there was a nearly 3-fold significantly increased odds of incident symptomatic OA in knees with subchondral cysts, with the association remaining statistically significant even after further adjustment for other MRI structures (Supplementary Table 1, http://onlinelibrary.wiley.com/doi/10.1002/art.41917/abstract). Although using this stricter definition of persistent, frequent knee pain strengthened the association between subchondral cysts and incident knee pain in knees without radiographic knee OA at baseline, the results remained non–statistically significant. In contrast, for incident knee pain in knees with subchondral cysts and radiographic knee OA at baseline, the less strict definition of persistent, frequent knee pain yielded modestly increased, but nonsignificant, odds of incident knee pain, whereas the stricter definition yielded 3–4-fold significantly increased odds of incident knee pain (Supplementary Table 4, http://onlinelibrary.wiley.com/doi/10.1002/art.41917/abstract). This finding is consistent with the findings from the symptomatic radiographic knee OA analysis. Since knees with frequent pain that did not have radiographic knee OA at baseline and knees without frequent pain that had radiographic knee OA at baseline were both eligible for analysis of the incident symptomatic radiographic knee OA outcome, the observed association of subchondral cysts with symptomatic radiographic knee OA may include an increased risk for developing frequent pain in knees with radiographic knee OA at baseline.

These data suggest that knee subchondral cysts may be linked with knee pain, but not with the development of radiographic knee OA. The data further suggest that it may not be useful to focus clinical efforts on identifying individuals with subchondral cysts without radiographic knee OA, as they are not at increased risk for developing knee pain or incident radiographic knee OA. We decided to use pain on most days of the previous month assessed at the clinical visit only as our primary, predefined definition of frequent knee pain, as it was consistent with the recommendations from a recent study that examined the best methods for harmonizing OA and pain among observational cohort studies (21). The stricter definition of persistent, frequent knee pain may represent a more advanced and severe stage of knee pain (22–25), and subchondral cysts may play a role in the development of this type of knee pain.

Our study has several strengths. To our knowledge, it had a longer duration of follow-up compared to earlier investigations of the association of subchondral cysts with incident knee symptoms and knee OA, as well as having a large, well-characterized study cohort. Additionally, the association between subchondral cysts and incident knee OA outcomes was examined using 3 exposures: 1) presence of subchondral cysts (yes/no), 2) maximum subchondral cyst severity score, and 3) number of regions with subchondral cyst involvement. This allowed us to evaluate which attributes of subchondral cysts, presence versus absence and severity, may increase the risk for developing knee OA. We examined the association between subchondral cysts and incident outcomes at a joint level, with 1 index knee assessed per participant. We hypothesized that subchondral cysts would carry an increased risk of incident knee OA only in the index knee, due to the focal damage attributed to the presence of subchondral cysts.

There are also several potential limitations to our study. First, the MOST study cohort is not a random sample of the population, and selection factors that affect both the occurrence of the exposure and the outcomes may be potential sources of bias in our analysis. This could include factors that affect both the availability of baseline MRI data on subchondral cysts and the knee OA and knee pain outcomes. For example, in the sample of knees with baseline MRI data that were available from the MOST study for the present investigation, it is not possible to examine incident total joint replacement as an outcome. This is because patients who underwent knee replacement would not receive MRIs at subsequent visits, and MRIs of knees were only read for changes between baseline and these later visits if they were available at 60 months and 84 months. Whether there is an association between subchondral cysts and subsequent joint replacement is

an important question that should be examined, but one that needs to be addressed using a different sample of knees with MRI readings than the sample from the MOST study used in the present investigation. The knees in this sample may have been more likely to have subchondral cysts at baseline and to develop OA and knee pain. We recognize this as a potential source of bias.

The number of knees with baseline MRI data on subchondral cysts was limited, since we analyzed the subset of knees that had available MRI data from the MOST data set of paired 60-month and 84-month MRI readings. While 4 MRI data sets were available, we used this data set because it was the largest, an important consideration since subchondral cysts and incident knee OA outcomes were both relatively uncommon, and this was the most generalizable sample. The long follow-up in the selected data set ensured an adequate number of radiographic and symptomatic OA outcomes. Thus, by using this MRI data set (baseline, 60 months, and 84 months), we were able to examine the effect of baseline subchondral cyst exposures on all incident outcomes using the same data set and with the same duration of follow-up. However, we recognize that as a result of our choice of data set, we could not investigate short-term outcomes of subchondral cysts.

Defining our pain outcome as incident frequent pain at either, or both, of the 60-month and 84-month time points increased our chances of capturing incident frequent knee pain that comes and goes. Nevertheless, even assessing knee pain every 1–2 years is an insufficient frequency to capture pain that fluctuates, and more frequent follow-up is needed to better understand risk factors for knee pain that fluctuates. The association of subchondral cysts and fluctuating pain, particularly over the short-term, also warrants further investigation.

Compared to the frequency observed in knees with OA (6,34), the low prevalence of subchondral cysts in knees without OA in this study, and the fact that they were not associated with incident radiographic knee OA, suggest that subchondral cysts may not be of clinical use to predict incident knee OA. In addition, we did not examine the effect of subchondral cyst location on the development of compartment-specific incident radiographic knee OA; the number of tibiofemoral-specific and/or patellofemoral-specific subchondral cysts and incident cases would likely be too few for robust statistical testing. Similarly, we were unable to perform further stratification (i.e., incident symptomatic radiographic knee OA stratified according to those with and those without radiographic knee OA at baseline) due to small numbers of participants in these subsets.

Finally, we adjusted for other MRI features, including BMLs, synovitis, and cartilage lesions. The association between subchondral cysts and such findings is still unclear, and it remains unknown where subchondral cysts fall on the causal pathway to disease and pain development. It is possible that adjustment for other baseline MRI features, which may be downstream effects of subchondral cysts, is an overadjustment, thereby limiting the interpretation of the adjusted data, and we acknowledge this as a potential limitation. In the present study, however, incident symptomatic OA was the only outcome in which adjustment for the other MRI features resulted in substantial changes in the ORs by attenuating the effect, although the association of subchondral cysts with this outcome using the strict definition of knee pain remained significant in the fully adjusted models. Adjusting for other MRI features strengthened the association between subchondral cysts and incident knee pain in those with baseline radiographic knee OA, though it was only of marginal statistical significance, and these findings were corroborated by the results using the more stringent definition.

These data suggest that subchondral cysts are likely to be a secondary phenomenon of knee OA, rather than a primary trigger of radiographic structural change. Subchondral cysts may be associated with the development of knee pain in knees with existing radiographic OA.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Perry had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Perry, O'Neill, Felson, Nevitt.

Acquisition of data. Perry, Nevitt.

Analysis and interpretation of data. Perry, O'Neill, Tolstykh, Lynch, Felson, Arden, Nevitt.

REFERENCES

1. Felson DT. Osteoarthritis of the knee [review]. N Engl J Med 2006; 354:841–8.
2. Neogi T. The epidemiology and impact of pain in osteoarthritis. Osteoarthritis Cartilage 2013;21:1145–53.
3. Dominick KL, Ahern FM, Gold CH, Heller DA. Health-related quality of life and health service use among older adults with osteoarthritis. Arthritis Rheum 2004;51:326–31.
4. Zhang Y, Nevitt M, Niu J, Lewis C, Torner J, Guermazi A, et al. Fluctuation of knee pain and changes in bone marrow lesions, effusions, and synovitis on magnetic resonance imaging. Arthritis Rheum 2011;63:691–9.
5. Kijowski R, Demehri S, Roemer F, Guermazi A. Osteoarthritis year in review 2019: imaging. Osteoarthritis Cartilage 2020;28:285–95.
6. Audrey HX, Abd Razak HR, Andrew TH. The truth behind subchondral cysts in osteoarthritis of the knee. Open Orthop J 2014;8: 7–10.
7. Peterfy CG, Guermazi A, Zaim S, Tirman PF, Miaux Y, White D, et al. Whole-organ magnetic resonance imaging score (WORMS) of the knee in osteoarthritis. Osteoarthritis Cartilage 2004;12:177–90.
8. Burnett WD, Kontulainen SA, McLennan CE, Hazel D, Talmo C, Wilson DR, et al. Knee osteoarthritis patients with more subchondral cysts have altered tibial subchondral bone mineral density. BMC Musculoskelet Disord 2019;20:14.
9. Guermazi A, Niu J, Hayashi D, Roemer FW, Englund M, Neogi T, et al. Prevalence of abnormalities in knees detected by MRI in adults

without knee osteoarthritis: population based observational study (Framingham Osteoarthritis Study). BMJ 2012;345:e5339.

10. Crema MD, Roemer FW, Marra MD, Niu J, Lynch JA, Felson DT, et al. Contrast-enhanced MRI of subchondral cysts in patients with or at risk for knee osteoarthritis: the MOST study. Eur J Radiol 2010;75:e92–6.
11. Pouders C, De Maeseneer M, Van Roy P, Gielen J, Goossens A, Shahabpour M. Prevalence and MRI-anatomic correlation of bone cysts in osteoarthritic knees. AJR Am J Roentgenol 2008;190: 17–21.
12. Ogino S, Sasho T, Nakagawa K, Suzuki M, Yamaguchi S, Higashi M, et al. Detection of pain-related molecules in the subchondral bone of osteoarthritic knees. Clin Rheumatol 2009;28:1395–402.
13. Fortier LA, Nixon AJ. Distributional changes in substance P nociceptive fiber patterns in naturally osteoarthritic articulations. J Rheumatol 1997;24:524–30.
14. McErlain DD, Ulici V, Darling M, Gati JS, Pitelka V, Beier F, et al. An in vivo investigation of the initiation and progression of subchondral cysts in a rodent model of secondary osteoarthritis. Arthritis Res Ther 2012;14:R26.
15. Kaspiris A, Khaldi L, Grivas TB, Vasiliadis E, Kouvaras I, Dagkas S, et al. Subchondral cyst development and MMP-1 expression during progression of osteoarthritis: an immunohistochemical study. Orthop Traumatol Surg Res 2013;99:523–9.
16. Tetlow LC, Adlam DJ, Woolley DE. Matrix metalloproteinase and proinflammatory cytokine production by chondrocytes of human osteoarthritic cartilage: associations with degenerative changes. Arthritis Rheum 2001;44:585–94.
17. McErlain DD, Milner JS, Ivanov TG, Jencikova-Celerin L, Pollmann SI, Holdsworth DW. Subchondral cysts create increased intra-osseous stress in early knee OA: a finite element analysis using simulated lesions. Bone 2011;48:639–46.
18. Segal NA, Nevitt MC, Gross KD, Gross KD, Hietpas J, Glass NA, et al. The Multicenter Osteoarthritis Study: opportunities for rehabilitation research. PM R 2013;5:647–54.
19. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494–502.
20. Felson DT, Naimark A, Anderson J, Kazis L, Castelli W, Meenan RF. The prevalence of knee osteoarthritis in the elderly: the Framingham Osteoarthritis Study. Arthritis Rheum 1987;30914–8.
21. Leyland KM, Gates LS, Nevitt M, Felson D, Bierma-Zeinstra SM, Conaghan PG, et al. Harmonising measures of knee and hip osteoarthritis in population-based cohort studies: an international study. Osteoarthritis Cartilage 2018;26:872–9.
22. Wise BL, Felson DT, Clancy M, Niu J, Neogi T, Lane NE, et al. Consistency of knee pain and risk of knee replacement: the Multicenter Osteoarthritis Study. J Rheumatol 2011;38:1390–5.
23. Neogi T, Nevitt MC, Yang M, Curtis JR, Torner J, Felson DT. Consistency of knee pain: correlates and association with function. Osteoarthritis Cartilage 2010;18:1250–5.
24. Carlesso LC, Niu J, Segal NA, Frey-Law LA, Lewis CE, Nevitt MC, et al. The effect of widespread pain on knee pain worsening, incident knee osteoarthritis (OA), and incident knee pain: the Multicenter OA (MOST) Study. J Rheumatol 2017;44:493–8.
25. Carlesso LC, Segal NA, Frey-Law L, Zhang Y, Na L, Nevitt M, et al. Pain susceptibility phenotypes in those free of knee pain with or at risk of knee osteoarthritis: the Multicenter Osteoarthritis Study. Arthritis Rheumatol 2019;71:542–9.
26. Roemer FW, Guermazi A, Zhang Y, Yang M, Hunter DJ, Crema MD, et al. Hoffa's fat pad: evaluation on unenhanced MR images as a measure of patellofemoral synovitis in osteoarthritis. AJR Am J Roentgenol 2009;192:1696–700.
27. Perry TA, Parkes MJ, Hodgson RJ, Felson DT, Arden NK, O'Neill TW. Association between bone marrow lesions & synovitis and symptoms in symptomatic knee osteoarthritis. Osteoarthritis Cartilage 2020;28: 316–23.
28. Torres L, Dunlop DD, Peterfy C, Guermazi A, Prasad P, Hayes KW, et al. The relationship between specific tissue lesions and pain severity in persons with knee osteoarthritis. Osteoarthritis Cartilage 2006;14: 1033–40.
29. Kornaat PR, Bloem JL, Ceulemans RY, Riyazi N, Rosendaal FR, Nelissen RG, et al. Osteoarthritis of the knee: association between clinical features and MR imaging findings. Radiology 2006;239:811–7.
30. Crema MD, Roemer FW, Zhu Y, Marra MD, Niu J, Zhang Y, et al. Subchondral cystlike lesions develop longitudinally in areas of bone marrow edema-like lesions in patients with or at risk for knee osteoarthritis: detection with MR imaging—the MOST study. Radiology 2010;256:855–62.
31. Carrino JA, Blum J, Parellada JA, Schweitzer ME, Morrison WB. MRI of bone marrow edema-like signal in the pathogenesis of subchondral cysts. Osteoarthritis Cartilage 2006;14:1081–5.
32. Yusup A, Kaneko H, Liu L, Ning L, Sadatsuki R, Hada S, et al. Bone marrow lesions, subchondral bone cysts and subchondral bone attrition are associated with histological synovitis in patients with end-stage knee osteoarthritis: a cross-sectional study. Osteoarthritis Cartilage 2015;23:1858–64.
33. Dürr HD, Martin H, Pellengahr C, Schlemmer M, Maier M, Jansson V. The cause of subchondral bone cysts in osteoarthrosis: a finite element analysis. Acta Orthop Scand 2004;75:554–8.
34. Tanamas SK, Wluka AE, Pelletier JP, Martel-Pelletier J, Abram F, Wang Y, et al. The association between subchondral bone cysts and tibial cartilage volume and risk of joint replacement in people with knee osteoarthritis: a longitudinal study. Arthritis Res Ther 2010;12:R58.