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MRI-Assessed Subchondral Cysts and Incident Knee Pain and Knee Osteoarthritis: data from the Multicentre Osteoarthritis Study

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Abstract

Objective: Our aim was to examine whether knee subchondral cysts, measured on magnetic resonance imaging (MRI), were associated with incident knee OA outcomes.

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Patient and Public Involvement (PPI):

We did not include PPI in this study.

Conflict of Interest Disclosures:

TAP, MN, TON, DF, IT and JL declare no conflicts of interest. NKA has received honorariums from Novartis, Alliance for Better Health, and Lilly; held advisory board positions (which involved receipt of fees) at Merck, Merck Sharp and Dohme, Roche, Novartis, Smith and Nephew, Q-MED, Nicox, Servier, GlaxoSmithKline, Schering-Plough, Pfizer, and Rottapharm; and received consortium research grants from Alliance for Better Bone Health, Amgen, Novartis, Merck Sharp and Dohme, Servier, Eli Lilly, and GlaxoSmithKline; he has no other relationships or activities that could appear to have influenced the submitted work. All fees did not exceed more than $10,000 for each item listed under consulting fees, speaking fees, or honoraria.

Methods: We used longitudinal data from the Multicentre Osteoarthritis Study (MOST), a community-based cohort of risk factors for knee OA. Participants without a history of knee surgery and/or inflammatory arthritis (i.e., rheumatoid arthritis and gout) were followed for 84-months for incident outcomes; i) radiographic knee OA (RKOA) (Kellgren-Lawrence (KL) ≥2), ii) symptomatic RKOA (RKOA and frequent knee pain) and iii) frequent knee pain (in participants with/without RKOA). Subchondral cysts were scored on baseline MRIs of one knee in a subset of participants. 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: Incident RKOA, symptomatic RKOA and frequent knee pain occurred in 22.8%, 17.0% and 28.8% (no RKOA) / 43.7% (with RKOA) of participants eligible for each outcome, respectively. Adjusting for age, sex and BMI, the presence of subchondral cysts was not associated with incident RKOA, but was associated with increased odds of incident symptomatic RKOA (OR: 1.92 (95% CI: 1.16 to 3.19) and knee pain in those with baseline RKOA (2.11 (0.87 to 5.12). Stronger and significant associations were observed for outcomes based on consistent reports of frequent pain within approximately one month.

Conclusions: Subchondral cysts are likely to be a secondary phenomenon, rather than a primary trigger, of RKOA, and may predict symptoms in knees with existing disease.

Keywords

Subchondral cysts; Osteoarthritis (OA); Incident knee OA

Introduction

Osteoarthritis is the most common form of arthritis and is a leading cause of global disability, painful symptoms and a reduction in physical function[1]. Knee pain is the hallmark feature of knee OA[2] and is the main reason for seeking healthcare among older adults[3]. Whilst knee pain may be chronic, many patients experience fluctuations in the presence/absence of pain and in severity[4]. Understanding which knee joint structures contribute to the development of structural OA, as radiographic knee OA (RKOA), and nociceptive activation with RKOA will help to better understand the aetiology of the disease.

There are considerable MRI-data[5] in knee OA research with a principle focus on the assessment of cartilage, synovitis and BMLs, 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’ and ‘bone cysts’[6], are defined as regions of markedly increased signal on fluid sensitive MRI[7] and are typically spherical and/or ellipsoidal cavities[8]. Subchondral cysts are common in both healthy knee joints, occurring in up to 25% of adults aged >50 who have no evidence of RKOA[9], and in up to 31% of patients with symptomatic knee OA[6]. Moreover, using a subsample of MOST, subchondral cysts were shown to occur in the absence of both MRI-assessed BMLs and cartilage loss in men and women with/at risk of knee OA[10]. Despite this evidence, most epidemiology 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 aetiology for subchondral cyst development is unclear[6] however, subchondral cysts, in the absence of established radiographic OA, may provide a pathway to disease development and painful symptoms. Histological 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 inflammatory marker in pain signalling[13]. Data from an *in vivo* study has shown that in a rodent model of post-traumatic knee OA, by meniscectomy, 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 which express matrix metalloproteinase-1 (MMP-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 co-localise with BMLs[12–14]. Subchondral cysts have been shown to influence the biomechanical properties of the subchondral bone by affecting bone mineral density[8] and by creating increased intra-osseous stress[17]. Together, these mechanisms may thereby provide a potential path for the development of knee OA.

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

Methods

Study Design and Participants

We used longitudinal data from MOST; 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 published previously[18]. In brief, 3,026 men and women aged 50 to 79 years were recruited from 2 communities in the United States and were followed for up to 84-months. Study participants either had evidence of knee OA at baseline or were at high risk of developing the disease. At each time point (baseline, 30, 60 and 84 months), clinical assessments were conducted, and knee radiographs and MRIs collected.

For the current study, we utilised data from the 'V035WORMS' MRI dataset; the largest of four MRI sub-sets which can be used for the analysis of multiple endpoints. This subsample comprises 1,182 study participants who had a readable pair of 60-month and 84-month MRIs in at least one knee. A single index knee of each participant was read for all WORMS features, described in more detail in the subsequent sections. If a participant had a readable pair of 60- and 84-month MRIs in both knees, one knee was randomly selected for MRI reading.

All participants underwent weight-bearing postero-anterior fixed flexion view knee radiographs at baseline and follow-up clinic visits. Knee radiographs were graded on a 0–4

scale, across the whole knee joint (including patellofemoral and tibiofemoral regions), using Kellgren & Lawrence (KL) criteria[19]. Radiographic OA of the whole knee was defined as a KL score of ≥2 (in either, or both, the tibiofemoral and patellofemoral joints).

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

Our aim was to determine the risk of: i) incident RKOA, ii) incident symptomatic RKOA and iii) incident frequent knee pain, separately in participants with, and without, RKOA in the index knee at baseline. For the current study we included only the subset of participants with a knee that had baseline data on subchondral cysts and other WORMS features (the index knee, one knee per participant). Outcomes in index knees were based on RKOA and knee symptom data from the 60- and 84-month follow-up visits.

We excluded participants with missing data on baseline RKOA, baseline frequent knee pain, missing outcomes in the index knee that could not be imputed (see below) and baseline covariate data. 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 baseline data on MRI structural features across all knee subregions were included.

Magnetic Resonance Imaging (MRI)

Non-CE MRIs were acquired using a dedicated 1.0 T extremity system (OrthOne™, ONI Medical Systems, Wilmington, MA) with a 160 mm diameter circumferential send-receive extremity coil. Axial and sagittal proton density-weighted fat-suppressed fast spin-echo sequences (PD-FS) (TR=4800 ms, TE=35 ms, 3.0 mm slice thickness, 0.0 mm interslice gap, 32 slices, 140 mm × 140 mm field of view (FOV), matrix=288 × 192, number of excitations=2, echo train length=8)[10] were acquired.

MRI-structural features, including subchondral cysts, bone marrow lesions (BMLs), synovitis/effusions and cartilage lesions were semi-quantitatively assessed using the Whole Organ MRI Scoring (WORMS) criteria[7]. Subchondral cysts were defined as areas of markedly increased signal intensity in the subarticular bone with sharply defined rounded margins with no evidence of internal marrow tissue or trabecular bone on fluid sensitive MRI. Subchondral cysts were scored from 0–3 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% to 50% of the region and 3 = >50% of the region. Bone marrow lesions 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; and were scored from 0 to 3 (3 = severe) using a previously validated method of semi-

quantitative assessment for non-enhanced scans[26]. Cartilage lesions were assessed across 14 sub regions (not including the tibia subspinous region), and scored from 0 to 6 (0 = normal signal, 6 = diffuse (≥75% of the region) full-thickness loss).

Exposure: MRI-assessed Subchondral Cysts

We used three exposure variables to predict incident outcomes. Our first exposure was coded as a binary variable with 0 equal to the absence of subchondral cysts (i.e., no evidence of subchondral cysts across all joint subregions) and 1 equal to 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) whilst our final exposure variable was equal to the number of subregions with subchondral cysts present (range: 0–15).

Outcomes

i. Incident Symptomatic RKOA

Incident symptomatic RKOA was defined as the simultaneous occurrence of a combination of frequent knee symptoms and RKOA (KL score ≥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.

ii. Incident RKOA

Incident RKOA was defined as the occurrence of RKOA (KL score of ≥2) during follow-up (60- and 84-months) in an index knee without RKOA (KL 0–1) at baseline.

iii. Incident Frequent Pain (in knees with and without baseline RKOA)

Due to a lack of data from other studies concerning the relationship between subchondral cysts and incident knee pain in the absence of RKOA and, the conflicting data regarding the association between subchondral cysts and knee pain in established knee OA[27–29], we conducted two separate incident knee pain analyses; 1) in participants without RKOA (i.e. KL 0–1) in the index knee at baseline and ii) in participants with RKOA 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-months visits in an index knee that did not have frequent knee pain at baseline.

Covariates

Information on age, sex and body mass index (BMI) were 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 upon the available data. There are data to support that subchondral cysts co-localise with BMLs[10, 30, 31], are linked with histologically assessed synovitis[32] and, whilst the exact aetiology of subchondral cysts is

unclear, it is thought that subchondral cysts may develop in response to cartilage loss with synovial infiltration[6, 33].

Statistics

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 (OR) with 95% confidence intervals (CIs) for crude and adjusted models. We adjusted for baseline age, sex and BMI. In additional analyses, we also adjusted for MRI-assessed synovitis (categoric), BML score (categoric) and cartilage lesion score (continuous).

We used imputation (last observation carried forward) to impute missing follow-up RKOA status at 60- and 84-months follow-up visits where RKOA status was known either at the previous visit (i.e., RKOA positive) or at both the adjacent visits (i.e., RKOA negative). We included participants with missing RKOA or knee symptom data in cases where it was still possible to determine symptomatic RKOA status (e.g., RKOA negative, missing knee symptom data). For our second exposure variable, maximum subchondral cyst severity score, there were too few knees belonging to grade 3 and so grades 2 and 3 were combined into a single category of ≥2. Similarly, for our third exposure variable of the number of regions with subchondral cysts, there were too few knees with subchondral cyst involvement across 2 or more regions and so we categorised the data as; i) 0 regions, 1 region and ≥2 regions.

We also conducted sensitivity analyses using the stricter definition of persistent, frequent knee pain (i.e., positive responses for knee pain at the telephone and clinical visit)[22–25] for both incident symptomatic RKOA and incident knee pain outcomes.

Results

Participants eligible for incident RKOA, incident symptomatic RKOA and incident knee pain (with, and without, RKOA at baseline) analyses are described in Figure 1.

Characteristics of participants and index knees with baseline data on subchondral cysts eligible for each outcome are shown in Table 1. Incident RKOA occurred in 22.8% (N = 100) and incident symptomatic RKOA in 17.0% (N = 90) of knees eligible for each outcome. Incident knee pain occurred in in 28.8% (N = 93) of knees without RKOA and in 43.7% (N = 37) of knees with baseline RKOA.

Incident Symptomatic RKOA

After adjusting for baseline age, BMI and sex, and using presence of subchondral cysts (yes/no) as our exposure, knees with evidence of subchondral cysts at baseline had increased odds of incident symptomatic RKOA compared to knees with no evidence of subchondral cysts (1.92, 95% CI 1.16 to 3.19); see Table 2. Using maximum subchondral cysts score as our exposure, compared to knees with no subchondral cyst involvement, knees with a maximum subchondral cyst grade of 1 (<25% of the region) had a 2-fold increased risk of incident symptomatic RKOA (1.96, 95% CI 1.15 to 3.33); there was no statistically

significant association between a maximum subchondral cyst score of ≥2 and incident symptomatic RKOA (1.73, 95% CI 0.53 to 5.65). Lastly, we observed a statistically significant association between the 2 or more regions with subchondral cysts and incident symptomatic RKOA. After further adjustment for baseline BMLs, synovitis and cartilage lesions, there was no longer a statistically significant association between subchondral cysts exposures and incident symptomatic RKOA.

In a sensitivity analysis, using a stricter definition of persistent, frequent knee pain, in a fully adjusted model (age, sex, BMI and other MRI features), the presence of subchondral cysts (2.16, 95% CI 1.18 to 3.96), knees with a maximum subchondral cyst grade of 1 (2.29, 95% CI 1.23 to 4.26) and knees with subchondral cyst involvement at 1 region (2.24, 95% CI 1.16 to 4.32) had an increased risk of symptomatic RKOA respectively; see Appendix 1.

Incident RKOA

After adjustment for age, BMI and sex, there was no statistically significant relationship between the presence of subchondral cysts and incident RKOA compared to knees with no evidence of subchondral cysts (odds ratio (OR): 1.20, 95% CI 0.68 to 2.10) see Table 3. Similarly, using maximum subchondral cyst severity score as our exposure, knees with a maximum grade of 1 (1.25, 95% CI 0.69 to 2.25) and grade ≥2 (0.81, 95% CI 0.15 to 4.27) were not at increased risk of incident RKOA. Lastly, using count of regions with subchondral cysts as our exposure, there was no statistically significant relationship between having involvement at 1 region (1.27, 95% CI 0.69 to 2.34) and at ≥2 regions (0.93, 95% CI 0.28 to 3.12) compared to participants with no evidence of subchondral cysts. Upon further adjustment for synovitis, BMLs and cartilage lesions, there remained no statistically significant association between subchondral cyst exposures and incident RKOA.

Incident Frequent Knee Pain

i) In index knees without baseline RKOA—In participants without RKOA in the index knee at baseline, in a fully adjusted model there was no statistically significant relationship between the presence of subchondral cysts and incident knee pain compared to knees with no evidence of subchondral cysts (0.93, 95% CI 0.45 to 1.91); see Table 4. Similarly, using maximum subchondral cyst severity score as our exposure, knees with a maximum grade of 1 (1.02, 95% CI 0.49 to 2.11) were not at increased risk of developing knee pain. There were no occurrences of incident knee pain in the grade ≥2 group. Lastly, using count of regions with subchondral cysts as our exposure, there was no statistically significant relationship between having involvement at 1 region (1.03, 95% CI 0.48 to 2.25) and at ≥2 regions (0.60, 95% CI 0.14 to 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 there was no statistically significant association observed between any of our predictors and incident knee pain (see Appendix 2).

ii) In index knees with baseline RKOA—Among participants with RKOA 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 adjusting for age, sex and BMI and in fully adjusted models, e.g. for presence of subchondral cysts in fully adjusted

models, OR: 2.47 (95% CI: 0.87 to 7.03), p = 0.091; see Table 5. However, when using the stricter definition of persistent, frequent knee pain, presence of subchondral cysts (3.14, 95% CI 1.15 to 8.59), subchondral cyst severity grade 1 (3.80, 95% CI 1.33 to 10.89) and knees with subchondral cyst involvement at 1 region (4.46, 95% CI 1.39 to 14.36) were statistically significantly associated with increased odds of incident knee pain respectively (Appendix 3).

Discussion

This study is the first to examine the relationship between subchondral cysts, measured on fluid sensitive MRI, and incident knee pain (with/without RKOA of the index knee) and knee OA in a large, long-term study of participants at risk of developing knee OA.

In the current study, after adjustment for age, BMI and sex, we found no association between baseline subchondral cysts and incident RKOA. Results were similar in analyses also adjusting for other baseline MRI features (synovitis, BMLs and cartilage lesions). In contrast, after adjustment for age, BMI and sex the presence of one or more, and the presence of multiple, subchondral cysts at baseline were significantly associated with a 1.9 to 2.6-fold increased odds of incident symptomatic RKOA. After further adjustment for other baseline MRI features, there was no longer a statistically significant association between any of our exposures and incident symptomatic RKOA. Further, we observed no association between subchondral cysts and incident frequent knee pain in knees without baseline RKOA, and a 2.5-fold, but not statistically significant, increase odds of incident pain in knees with RKOA at baseline.

In sensitivity analyses, we also examined the incidence of knee pain and symptomatic RKOA using a stricter definition of persistent, frequent knee pain[22–25] (positive responses at both telephone interview and clinical visit within about one month vs. 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 relationship remaining statistically significant even after further adjustment for other MRI structures (see Appendix 1). While using this more strict definition strengthened the relationship between subchondral cysts and incident knee pain in knees without baseline RKOA, the results remained non-statistically significant. In contrast, for incident knee pain in knees with subchondral cysts and RKOA at baseline, which had nonsignificant but modestly increased odds of incident knee pain using the less strict definition, using the strict definition we found a 3- to 4-fold significantly increased odds of incident pain (see Appendix 4). This finding is consistent with the symptomatic RKOA analysis. Since knees at baseline with frequent pain without RKOA, and knees with RKOA without frequent pain, were both eligible for the incident symptomatic RKOA outcome, the observed association of subchondral cysts with symptomatic RKOA may include an increased risk of developing frequent pain in knees with RKOA at baseline.

These data suggest that knee subchondral cysts may be linked with knee pain, but not with the development of RKOA. More so, these data suggest that it may not be useful to focus

clinical efforts on identifying those with subchondral cysts without RKOA as these people are not at increased risk for developing knee pain or incident RKOA. We decided to use pain on most days of the previous month assessed at the clinical visit only as our primary, pre-defined definition of frequent knee pain as it was in line with the recommendations of a recent study which examined the best methods for harmonising 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 development of this type of knee pain.

There are several strengths to this study. To our knowledge, this is the longest study to examine the relationship between subchondral cysts and incident knee symptoms and knee OA using a large, well-characterised cohort. More so, we examined the relationship between subchondral cysts and incident outcomes using three exposures: i) presence (yes/no), ii) maximum subchondral cyst severity score and iii) number of regions with subchondral cyst involvement. This allowed us to evaluate which attributes of subchondral cysts, presence vs. absence and severity, may increase risk of knee OA. We examined the relationship between subchondral cysts and incident outcomes at a joint level with one index knee assessed per participant. We hypothesised 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 several potential limitations to our study. Firstly, MOST 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 pain outcomes. For instance, in the sample of knees with baseline MRI reading data that was available from MOST for the present study, it is not possible to examine incident total joint replacement as an outcome. This is because replaced knees would not have MRIs at subsequent visits and knees were only read for change between baseline and these later visits if they had 60- and 84-month MRIs available. Examination of the association of subchondral cysts with subsequent joint replacement is an important question but one that needs to be addressed in a different sample of knees with MRI readings than the one available from MOST for the present study. These knees may have been more likely to have both 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 analysed the subset of knees that had available MRI data from the MOST dataset of paired 60- and 84-month MRI readings. Whilst four MRI datasets were available, we used this dataset because it was the largest, an important consideration since subchondral cysts and incident knee OA outcomes were both relatively uncommon, and was the most generalizable sample. The long follow-up in the selected dataset ensured an adequate number of radiographic and symptomatic OA outcomes. Thus, by using this MRI dataset (baseline, 60- and 84-months) it allowed us to examine the effect of baseline subchondral cysts exposures on all incident outcomes using the same dataset and with the same duration

of follow-up. We, however, recognize that as a result of our choice of dataset, 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 and 84 month time points increased our chances of capturing incident frequent knee pain that comes and goes. Nevertheless, even assessing knee pain every one to two 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 relationship of subchondral cysts with 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 RKOA suggests that subchondral cysts may not be of clinical use to predict incident knee OA. Further, we did not examine the effect of subchondral cyst location on the development of compartment-specific incident RKOA; 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 RKOA by those with/without baseline RKOA) due to small numbers in these subsets.

Lastly, we adjusted for other MRI features including BMLs, synovitis and cartilage lesions. The relationship 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 adjusting for other baseline MRI features, which may be downstream effects of subchondral cysts, is an over adjustment thereby limiting the interpretation of the adjusted data, and we acknowledge this as a potential limitation. In the current study however, incident symptomatic OA is the only outcome in which adjustment for the other MRI features results in substantial changes in the odds ratios by attenuating the effect, although the association of subchondral cysts with this outcome using the strict definition of knee pain remains significant in the fully adjusted models. Adjusting for other MRI features strengthens the association between subchondral cysts and incident knee pain in those with baseline RKOA, though it is only of marginal statistical significance, and these findings are corroborated by the results using the more stringent definition.

Conclusions

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 RKOA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Availability of data and materials:

All data generated and analysed in this study are available upon reasonable request. Access to data generated in this report should be sent to the corresponding author at 23homas.perry@ndorms.ox.ac.uk whilst requests for MOST data should be submitted to the cohort principal investigators. Information about MOST public use data sets is available at http://most.ucsf.edu/.

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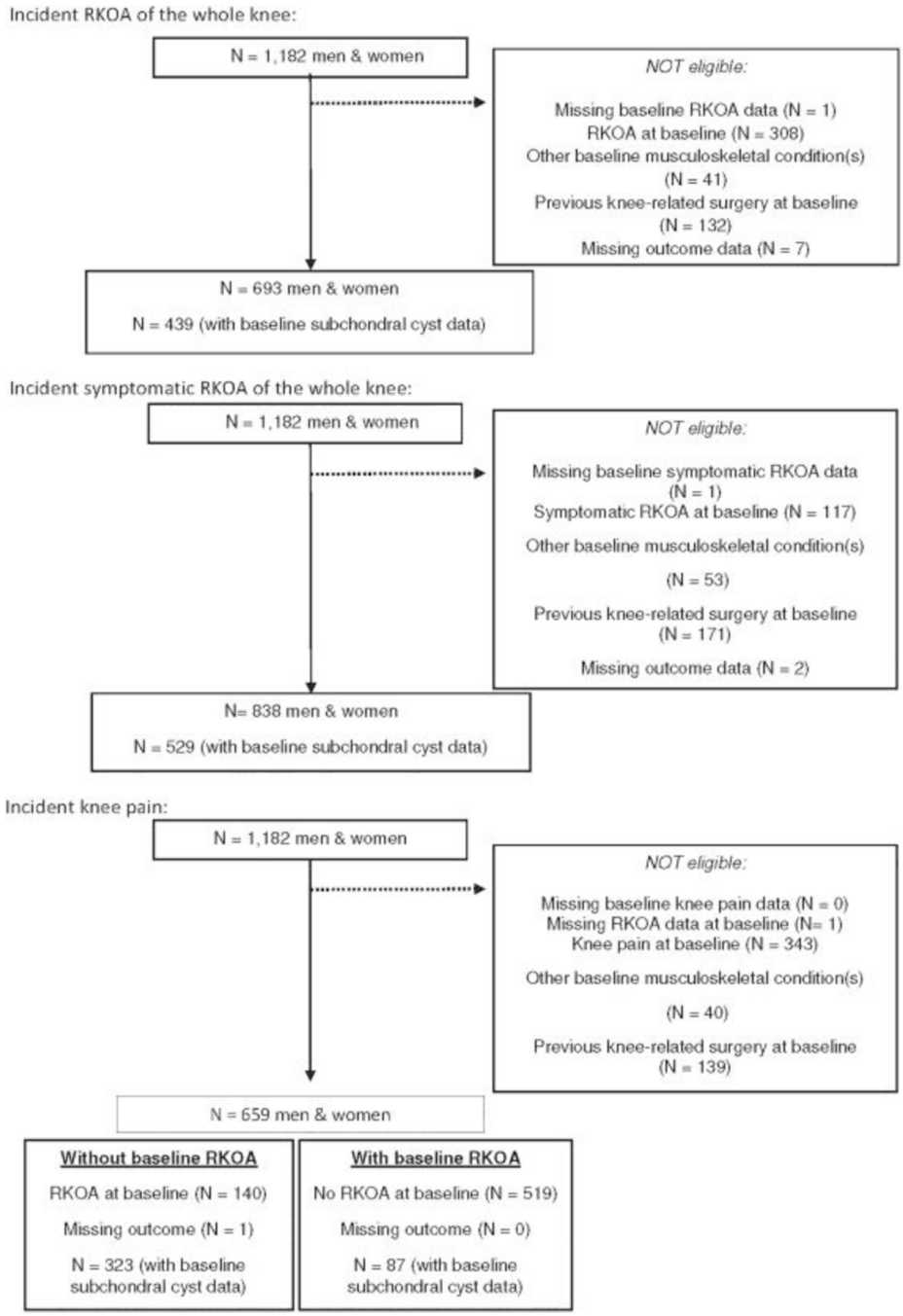

Figure 1:

Flow chart of participants eligible for study investigation.

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

Table 1:

Baseline demographics of eligible study participants.

Variable	MOST			
	No RKOA (N = 439)	**No Symptomatic RKOA (N = 529)**	**No Knee Pain and no RKOA (N = 323)**	**No Knee Pain and RKOA (N = 87)**
Age (years) (median, IQR)	60 (11)	60 (12)	60 (11)	64 (13)
Sex, n (% female)	268 (61.05)	334 (63.14)	184 (56.97)	64 (73.56)
BMI (kg/m^2) (median, IQR)	28.65 (6.19)	28.83 (6.11)	28.25 (5.96)	30.14 (5.79)
Index knee, right n(%)	218 (49.66)	271 (51.23)	159 (49.23)	52 (59.77)
Subchondral Cysts, n (%)				
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, n (%)				
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)
Count 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)
BML score[¥], n (%)				
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)

Variable	MOST			
	No RKOA (N = 439)	No Symptomatic RKOA (N = 529)	No Knee Pain and no RKOA (N = 323)	No Knee Pain and RKOA (N = 87)
Synovitis score[¥], n (%)				
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[¥,≠], n (%)				
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)

Abbreviations: MOST, Multicentre Osteoarthritis Study; BMI, body mass index; SD, standard deviation; IQR, inter-quartile range; BML, bone marrow lesion; MRI, magnetic resonance imaging; RKOA, radiographic knee osteoarthritis (OA).

Subgroups eligible for each outcome were not mutually exclusive, but were overlapping.

[¥]Missingness was based on missing data for at least one region assessed for the given MRI structure.

[≠]Grade 1 on WORMS was not used when scoring cartilage thickness on MRIs.

Table 2:

Association Between Subchondral Cysts and Incident Symptomatic RKOA.

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

All results presented as odds ratios with 95% confidence intervals and P-values.

N-values are presented as the number of participants for the given category with the number of incident cases.

Abbreviations: RKOA, radiographic knee osteoarthritis; BMI, body mass index; BML, bone marrow lesion.

Results shown in bold were statistically significant at the ≤0.05 level.

[1]Adjusted for age, sex and BMI.

[2]Adjusted for sex, age, BMI, BML severity, synovitis severity and cartilage lesions.

Table 3:

Association Between Subchondral Cysts and Incident RKOA.

Outcome	Univariate (N = 439)	Multivariate[1] (N = 439)	Multivariate[2] (N = 417)
Subchondral Cysts, present			
No (n = 354, 77)	reference	reference	reference
Yes (n = 85, 23)	1.34 (0.78 to 2.29), 0.30	1.20 (0.68 to 2.10), 0.54	0.98 (0.52 to 1.86), 0.95
Subchondral cyst severity score			
0 (n = 354, 77)	reference	reference	reference
1 (n = 76, 21)	1.37 (0.78 to 2.41), 0.27	1.25 (0.69 to 2.25), 0.46	1.01 (0.52 to 1.95), 0.98
≥2 (n = 9, 2)	1.03 (0.21 to 5.05), 0.97	0.81 (0.15 to 4.27), 0.81	0.73 (0.13 to 4.07), 0.72
Count of regions with subchondral cysts			
0 (n = 354, 77)	reference	reference	reference
1 (n = 69, 19)	1.37 (0.76 to 2.46), 0.30	1.27 (0.69 to 2.34), 0.45	1.09 (0.55 to 2.17), 0.81
≥2 (n = 16, 4)	1.20 (0.38 to 3.82), 0.76	0.93 (0.28 to 3.12), 0.91	0.64 (0.18 to 2.27), 0.49

All results presented as odds ratios with 95% confidence intervals and P-values.

N-values are presented as the number of participants for the given category with the number of incident cases.

Abbreviations: RKOA, radiographic knee osteoarthritis; BMI, body mass index; BML, bone marrow lesion.

[1]Adjusted for age, sex and BMI.

[2]Adjusted for sex, age, BMI, BML severity, synovitis severity and cartilage lesions.

Table 4:

Association Between Subchondral Cysts and Incident Knee Pain in knees without RKOA at baseline.

Outcome	Univariate (N = 323)	Multivariate[1] (N = 323)	Multivariate[2] (N = 307)
Subchondral Cysts, present			
No (n = 262, 76)	reference	reference	reference
Yes (n = 61, 17)	0.95 (0.51 to 1.76), 0.86	0.94 (0.50 to 1.77), 0.84	0.93 (0.45 to 1.91), 0.84
Subchondral cyst severity score			
0 (n =262, 76)	reference	reference	reference
1 (n = 56, 17)	1.07 (0.57 to 2.00), 0.84	1.08 (0.57 to 2.07), 0.82	1.02 (0.49 to 2.11), 0.97
≥2 (n = 5, 0)	-	-	-
Count of regions with subchondral cysts			
0 (n = 262, 76)	reference	reference	reference
1 (n = 49, 14)	0.98 (0.50 to 1.92), 0.95	1.01 (0.51 to 2.03), 0.97	1.03 (0.48 to 2.25), 0.93
≥2 (n = 12, 3)	0.82 (0.22 to 3.10), 0.77	0.69 (0.18 to 2.67), 0.59	0.60 (0.14 to 2.56), 0.49

All results presented as odds ratios with 95% confidence intervals and P-values.

N-values are presented as the number of participants for the given category with the number of incident cases.

Abbreviations: RKOA, radiographic knee osteoarthritis; BMI, body mass index; BML, bone marrow lesion.

[1]Adjusted for age, sex and BMI.

[2]Adjusted for sex, age, BMI, BML severity, synovitis severity and cartilage lesions.

Table 5:

Association Between Subchondral Cysts and Incident Knee Pain in knees with baseline RKOA.

Outcome	Univariate (N = 87)	Multivariate[1] (N = 87)	Multivariate[2] (N = 80)
Subchondral Cysts, present			
No (n = 52, 19)	reference	reference	reference
Yes (n = 35, 19)	2.06 (0.86 to 4.93), 0.10	2.11 (0.87 to 5.12), 0.097	2.47 (0.87 to 7.03), 0.091
Subchondral cyst severity score			
0 (n =52, 19)	reference	reference	reference
1 (n = 28, 16)	2.32 (0.91 to 5.91), 0.079	2.40 (0.93 to 6.23), 0.071	2.91 (0.96 to 8.82), 0.059
≥2 (n = 7, 3)	1.30 (0.26 to 6.45), 0.75	1.26 (0.24 to 6.57), 0.78	1.19 (0.18 to 7.65), 0.86
Count of regions with subchondral cysts			
0 (n = 52, 19)	reference	reference	reference
1 (n = 20, 11)	2.12 (0.75 to 6.04), 0.16	2.14 (0.75 to 6.13), 0.16	2.85 (0.84 to 9.63), 0.092
≥2 (n = 15, 8)	1.99 (0.62 to 6.34), 0.25	2.08 (0.63 to 6.83), 0.23	2.00 (0.50 to 7.96), 0.33

All results presented as odds ratios with 95% confidence intervals and P-values.

N-values are presented as the number of participants for the given category with the number of incident cases.

Abbreviations: RKOA, radiographic knee osteoarthritis; BMI, body mass index; BML, bone marrow lesion.

[1]Adjusted for age, sex and BMI.

[2]Adjusted for sex, age, BMI, BML severity, synovitis severity and cartilage lesions.