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Comparison of radiographic and MRI osteoarthritis definitions and their combination for prediction of tibial cartilage loss, knee symptoms and total knee replacement: a longitudinal study

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SUMMARY

Objective: To describe the value of radiographic- and magnetic resonance imaging (MRI)-defined tibiofemoral osteoarthritis (ROA and MRI-OA, respectively) and in combination for predicting tibial cartilage loss, knee pain and disability and total knee replacement (TKR) in a population-based cohort.
Design: A radiograph and 1.5T MRI of the right knee was performed. ROA and MRI-OA at baseline were defined according to the Osteoarthritis Research Society International atlas and a published Delphi exercise, respectively. Tibial cartilage volume was measured over 2.6 and 10.7 years. Knee pain and disability were assessed at baseline, 2.6, 5.1 and 10.7 years. Right-sided TKRs were assessed over 13.5 years.
Results: Of 574 participants (mean 62 years, 49% female), 8% had ROA alone, 15% had MRI-OA alone, 13% had both ROA and MRI-OA. Having ROA (vs. no ROA) and MRI-OA (vs. no MRI-OA) predicted greater tibial cartilage loss over 2.6 years (−75.9 and −86.4 mm^3/year) and higher risk of TKR over 13.5 years (Risk Ratio [RR]: 15.0 and 10.9). Only MRI-OA predicted tibial cartilage loss over 10.7 years (−7.1 mm^3/year) and only ROA predicted onset and progression of knee symptoms (RR: 1.32−1.88). In participants with both MRI-OA and ROA, tibial cartilage loss was the greatest (over 2.6 years: −116.1 mm^3/year; over 10.7 years: −11.2 mm^3/year), and the onset and progression of knee symptoms (RR: 1.75−2.89) and risk of TKR (RR: 50.9) were the highest.
Conclusions: The Delphi definition of MRI-OA is not superior to ROA for predicting structural or symptomatic OA progression but, combining MRI-OA and ROA has much stronger predictive validity.

Introduction

Knee osteoarthritis (OA) is a progressive joint disease characterised by knee pain, disability and articular cartilage loss. Identifying structural features that precede clinically diagnosable disease is crucial for implementing early interventions and therefore slowing disease trajectory[1]. Currently, plain radiography remains the 'gold standard' for morphological assessment of OA, and radiographic joint space narrowing (JSN) is used in many clinical trials for developing disease-modifying drugs. However, JSN is only a surrogate marker for cartilage thinning and has poor sensitivity[2]. Indeed, over 10% of cartilage is already lost when there is the first sign of JSN[3]. In contrast, magnetic resonance imaging (MRI) enables direct view of cartilage volume. More importantly, MRI provides further information on early structural changes not detectable on radiographs that may be important for assessing disease severity and monitoring disease progression[4,5].

Defining radiographic OA (ROA) using the Kellgren−Lawrence (K-L) classification criteria[6] or the Osteoarthritis Research Society International (OARSI) atlas[7] reuires assessment of two semi-quantitative measures including JSN and osteophytes. In contrast, defining structural OA using MRI is much more complicated given

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there are numerous MRI detected osteoarthritic changes. Commonly reported MRI changes, such as cartilage defects[8,9], effusion synovitis[10,11], meniscal lesions[12], bone marrow lesions (BMLs)[13,14] and MRI-detected osteophytes (MRI-OP)[15], predict OA progression, but which changes are most important in OA progression are unclear. In the absence of a clear definition of OA using MRI features, the OARSI OA Imaging Working Group developed a definition of MRI-defined structural OA (MRI-OA) by incorporating MRI changes using a Delphi approach[16], but this needs validation. A clear definition of MRI-OA would be of great importance in both clinical and research settings if it adds value for predicting structural and symptomatic progression of OA. To date, only a single study has compared the associations of MRI-OA and ROA with knee pain and body weight and found similar associations for both[17]. Whether the Delphi definition of MRI-OA is a better predictor of cartilage loss, worsening knee symptoms and OA-related total knee replacement (TKR) than ROA have not been evaluated. Moreover, it is clinically important to know whether the Delphi definition of MRI-OA adds value to ROA for predicting OA progression.

This study aimed to use a population-based older adult cohort to describe the value of ROA and the Delphi definition of MRI-OA and their combination for predicting tibial cartilage loss, the presence, onset and progression of knee pain and disability and the risk of TKR.

Methods

Participants

The Tasmania Older Adult Cohort (TASOAC) is a prospective, population-based older adult cohort. From March 2002 to September 2004, 1,099 out of 1904 older adults randomly selected from the electoral roll in Southern Tasmania (population 229,000) were included in this cohort (57% response rate). At baseline, 992 participants underwent an MRI scan on the right knee (Supplementary Fig. 1). Three follow-ups were conducted at 2.6, 5.1 and 10.7 years. In the current study, participants who had undergone any right-sided knee replacement surgery prior to baseline visits were excluded. For those who underwent a right-sided knee replacement during the study, follow-up data before the surgery were retained for analysis of cartilage loss and knee symptoms. Eventually, 574 participants who had adequate data to evaluate the status of MRI-OA and ROA at baseline were included in this study (Supplementary Fig. 1). Ethical approval was granted by the Southern Tasmanian Health and Medical Human Research Ethics Committee, and all participants provided written informed consent.

MRI

MRI scans of the right knee were performed in all participants ($n = 574$) with a 1.5T whole-body magnetic resonance unit (Picker, Cleveland, Ohio, USA) at baseline and in 60% (345/574) of participants at 2.6 years due to the decommissioning of the MRI machine halfway through the follow-up period. Another 1.5T whole-body MRI unit (Siemens, Espree, Pennsylvania, USA) was used for the 10.7-year follow-up in 66% (377/574) of participants due to loss to follow-up or other reasons (Supplementary Fig. 1). Both MRI units used a commercial transmit-receive extremity coil. Sagittal image sequences and technical parameters were: 1) a T1-weighted fat saturation 3-dimensional gradient-recalled acquisition in the steady state, flip angle 30°, repetition time 31 ms, echo time 6.71 ms, field of view 16 cm, 60 partitions, 512 × 512 pixel matrix, slice thickness of 1.5 mm without an interslice gap; and (2) a T2-weighted fat saturation 2-dimensional fast spin echo, flip angle 90°, repetition time 3,067 ms, echo time 112 ms, field of view 16 cm, 15 partitions, 228 × 256 pixel matrix, slice thickness of 4 mm with a interslice gap of 0.5–1.0 mm.[18]

MRI-defined tibiofemoral OA at baseline was defined as the presence of a definite osteophyte and full-thickness cartilage loss, or one of these two features plus at least two of the following[16]: a) subchondral BML or cyst not associated with meniscal or ligamentous attachments; b) meniscal subluxation, maceration or degenerative (horizontal) tear; and c) partial thickness cartilage loss. A fourth criterion[16] for bone attrition was not measured in this study. “Meniscal subluxation, maceration or degenerative (horizontal) tear” was considered present if any meniscal tear or extrusion was observed. The measurements of these MRI features including osteophyte, cartilage lesion, meniscal lesion and subchondral BML are detailed in Supplementary text.

Tibial cartilage volume (mm^3) was measured on T1-weighted MRI at baseline and 2.6 years by a trained observer (RW) with 1 year of experience and adjusted by a researcher (CD) with 5 years of experience in OA research, and both readers were blinded to chronological order and participants' identification[19]. The difference between these values was used to calculate change in cartilage volume over 2.6 years. Additionally, a completely new and paired reading of tibial cartilage volume at baseline and 10.7 years was conducted in participants with MRI data at both baseline and 10.7 years by a single reader (RW) with 12 years of experience reading tibial cartilage volume. Chronological order was known to the reader, and the difference between these readings was used to calculate change in cartilage volume over 10.7 years. The volumes of individual cartilage plates (medial tibia and lateral tibia) were isolated from the total volume by manually drawing disarticulation contours around the cartilage boundaries on a section by section basis. These data were then re-sampled by means of bilinear and cubic interpolation (area of 312 × 312 mm and 1.5 mm thickness, continuous sections) for the final 3-dimensional rendering. The coefficient of variation ranged from 2.1% to 2.2%[19]. Femoral cartilage volume was not measured as we have previously shown a strong correlation between longitudinal changes in femoral and tibial cartilage volume[20]. For each of the unpaired (baseline and 2.6 years) and paired (baseline and 10.7 years) measures, annual change in tibial cartilage volume (mm^3/year) was calculated as (follow-up volume - baseline volume)/time between two scans in years. Annual percentage change in tibial cartilage volume (%/year) was calculated as 100 × [(follow-up volume - baseline volume)/baseline volume]/time between two scans in years.

Radiography

A standing anteroposterior semi-flexed view of the right knee with 15° of fixed knee flexion was performed in all participants at baseline. JSN and femoral and tibial osteophytes of the medial and lateral compartments were assessed and scored 0–3 based on the OARSI atlas[7]. Each score was determined by consensus of a geriatrician with 6 years of experience (VS) and a rheumatologist with 5 years of experience (HC) who simultaneously evaluated the radiograph, and the intra-observer reliability assessed by ICC ranged from 0.65 to 0.85[21]. Tibiofemoral ROA was considered present if any of the following criteria were achieved in either the medial or lateral compartments: a) JSN of grade ≥2; b) the sum of osteophytes grades ≥2; or c) grade one JSN plus grade one osteophytes. This definition approximates grade two ROA according to the K-L criteria[22].

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Knee pain and disability

Knee pain and disability were evaluated using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and function subscales at baseline, 2.6, 5.1 and 10.7 years. The WOMAC has five items for knee pain and 17 for disability, with each item's score ranging from 0 to 9, giving a subscale score range of 0–45 for knee pain and 0–153 for disability, with higher scores indicating more severe pain/disability.

Participants were classified as presence or absence of knee pain (WOMAC pain $\geq$1) at baseline. Onset of knee pain was defined as presence of knee pain (WOMAC pain $\geq$1) at follow-up in those without knee pain at baseline. The minimal clinically important difference[23] was calculated to be 0.9 for this population[24], so we defined progression of knee pain as an increase in WOMAC pain of $\geq$1. The same strategy was also applied to define the presence/absence, onset and progression of disability using the WOMAC function subscale, for which progression of disability was defined if there is an increase in WOMAC function score of $\geq$3.

Other measures

Weight was measured to the nearest 0.1 kg (with shoes, socks and bulky clothing removed) using an electronic scale (Seca Delta Model 707). Height was measured to the nearest 0.1 cm (with shoes and headgear removed) using a stadiometer. Body mass index (BMI) was calculated (kg/m^2).

Data on the side, reason and date of TKR were extracted from the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR)[25] from 1 March 2002 to 21 September 2016, as previously described[26]. In this sample, all TKR procedures were performed due to OA.

Statistical analysis

OA and non-OA groups were defined firstly according to ROA status alone, secondly according to MRI-OA status alone and thirdly by ROA- and MRI-OA status in combination, yielding four categories (neither ROA nor MRI-OA, ROA alone, MRI-OA alone and both ROA and MRI-OA). Baseline characteristics of participants are described using mean ± standard deviation (SD) and n (%) by the four categories of ROA- and MRI-OA status in combination.

The sensitivity and specificity of MRI-OA to detect ROA was assessed. Linear regression models were used to compare tibial cartilage loss between OA and non-OA groups over 2.6 and 10.7 years. The analyses of tibial cartilage loss over 2.6 (unpaired readings) and 10.7 years (paired readings) were conducted separately as the two measurements were not comparable. Model one adjusted for age, sex, BMI and tibial cartilage volume at baseline, and Model two further adjusted for bone area at baseline and change in BMI over time[27,28]. Log-binomial regression models were used to compared the presence, onset and progression of knee symptoms between OA and non-OA groups. Specifically, the presence of knee symptoms was evaluated at baseline adjusting for age, sex and BMI; the onset and progression of knee symptoms were assessed at each follow-up (i.e., 2.6, 5.1 and 10.7 years) in asymptomatic and symptomatic participants at baseline, respectively, with adjustment for age, sex, BMI and corresponding values of knee pain or function scores at baseline and time of follow-up. Log-binomial regression models were also used to evaluate the value of OA definitions for predicting the risk of TKR, with and without adjustment for age, sex, BMI and knee pain at baseline.

Sensitivity analyses were performed using inverse probability weighting to assess the potential influence of participants not included in this study and missing follow-up data among included participants[29], and this was done for each outcome measure. The weights were estimated from logistic regression models, where the predictors were baseline complete variables (age, sex, BMI, knee pain and function scores, co-morbidity, use of pain medications, employment status and quality of life score). All analyses were performed using Stata version 15.1 (Stata/SE, College Station). A two-tailed *P*-value of 0.05 was considered statistically significant.

Results

Baseline characteristics

Of 574 participants included, 21% had ROA and 28% had MRI-OA. Among them, 8% had ROA only, 15% had MRI-OA only and 13% had them both. Sensitivity of MRI-OA for ROA was 62% and specificity 82%. Knee pain and disability were reported in 51% and 56% of participants at baseline, respectively. Almost all participants had meniscal tear/extrusion at baseline. Compared to participants with neither MRI-OA nor ROA, those with either MRI-OA or ROA were older, had more structural changes and higher prevalence of knee symptoms (Table I). In addition, participants with both MRI-OA and ROA were older, more likely to be males, had higher BMI, larger bone size and more structural changes and knee symptoms than those with neither. While tibial cartilage volume measured by unpaired readings were systematically higher than those measured by paired readings, the two measures at baseline were strongly correlated ($r = 0.89$).

Compared to participants who were included in this study ($n = 574$), those who were not included ($n = 525$) had similar baseline characteristics in terms of sex, BMI, knee symptoms and most structural changes measured on MRI and radiographs, although they were older and had a lower prevalence of osteophytes and cartilage defects (Supplementary Table 1). Among participants included in this study, those with missing follow-up data were older and had more structural abnormalities at baseline (Supplementary Table 2).

Value of ROA and MRI-OA for predicting OA progression

Compared to participants without ROA, those with ROA had higher tibial cartilage loss over 2.6 years but not over 10.7 years (Table II). Tibial cartilage loss over both 2.6 and 10.7 years was greater in participants with than without MRI-OA (Table II).

Having ROA or MRI-OA were both associated with a higher prevalence of knee pain and functional disability at baseline (Table III and Supplementary Table 3). However, participants with ROA were about twice as likely to experience onset of knee pain over 2.6 and 5.1 years and progression of knee pain and disability over 5.1 and 10.7 years, compared to those without. In contrast, differences in effect size for risk of onset and progression of knee pain and disability were smaller between people with and without MRI-OA, and did not reach statistical significance (Table III).

Twenty-seven (4.7%) primary TKR procedures were performed for the right knees. Having ROA or MRI-OA at baseline both strongly predicted the incidence of TKR, although the risk was higher in participants with ROA (RR: 15.0 vs 10.9) (Table IV).

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	Neither 64% ($n = 368$)	ROA only 8% ($n = 47$)	MRI-OA only 15% ($n = 83$)	Both 13% ($n = 76$)
Age, year	61.5 (7.1)	63.4 (6.3)	63.2 (7.3)	65.6 (7.8)
Females, %	51	62	41	39
Body mass index, kg/m^2	27.1 (4.0)	26.8 (4.0)	28.9 (4.7)	30.3 (5.5)
ROA, %				
Any osteophytes	0	36	5	62
Any joint space narrowing	50	100	55	97
MRI-OA, %				
MRI-defined osteophytes ($n = 572$)	10	15	100	100
Full thickness cartilage loss	0	0	5	25
Partial thickness cartilage loss	13	32	64	68
Meniscal tear or extrusion ($n = 548$)	99	100	100	100
Bone marrow lesions ($n = 537$)	32	40	89	90
Tibial cartilage volume, mm^3				
Unpaired measures ($n = 571$)*	5,104 (1,226)	4,582 (957)	5,297 (1,209)	5,029 (1,384)
Paired measures ($n = 377$)†	3,621 (979)	3,085 (837)	3,723 (1,004)	3,536 (967)
Bone size, mm^2, ($n = 528$)	3,266 (456)	3,157 (360)	3,493 (528)	3,618 (578)
Any knee pain, %	44	49	55	79
Any functional disability, %	48	60	65	86

Results are shown as mean (standard deviation) unless specified otherwise (%).
MRI, magnetic resonance imaging; OA, osteoarthritis; ROA, radiographic osteoarthritis; SD, standard deviation; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
* Unpaired measures were conducted at baseline and 2.6 years.
† Paired measures were conducted between baseline and 10.7 years.

Table I Baseline characteristics of study participants (***n*** = 574)

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Value of the combination of ROA and MRI-OA for predicting OA progression

Compared to participants with neither ROA nor MRI-OA at baseline, those with MRI-OA only (i.e., meeting MRI-OA but not ROA criteria) had greater annual tibial cartilage loss over 2.6 but not 10.7 years, while having ROA only (i.e., meeting ROA but not MRI-OA criteria) was not significantly associated with cartilage loss (Table V). In contrast, having both MRI-OA and ROA at baseline predicted the greatest cartilage loss over both 2.6 (−116.1 mm^3/year) and 10.7 years (−11.2 mm^3/year).

Compared to participants with neither ROA nor MRI-OA at baseline, those with MRI-OA only and with both ROA and MRI-OA, were more likely to have knee pain and disability at baseline with the prevalence being greatest in the latter group (Table VI and Supplementary Table 4). Participants with either MRI-OA or ROA only did not show an increased risk of onset or progression of knee symptoms over time, except that having ROA only was associated with an increased risk of progressive knee symptoms over 10.7 years (Table VI). However, having both MRI-OA and ROA predicted the onset and progression of knee symptoms over time.

Participants with either MRI-OA alone or ROA alone were more likely to undergo a TKR compared to those with neither (Table IV), and the incidence of TKR in participants with ROA only was higher than those with MRI-OA only (6.4% vs 3.6%). Those with both MRI-OA and ROA had the highest risk (25%) of undergoing a TKR.

	Tibial cartilage volume loss (mm^3/year), β (95% CI)		
	Univariable	Multivariable 1*	Multivariable 2†
Baseline to 2.6 years			
ROA vs non-ROA ($n = 345$)	**−75.7 (-133.6 to -17.9)**	**−81.1 (-137.3 to -24.9)**	**−75.9 (-134.9 to -17.0)**
MRI-OA vs non-MRI-OA ($n = 345$)	**−107.9 (-159.8 to -56.1)**	**−89.3 (-140.3 to -38.3)**	**−86.4 (-140.4 to -32.5)**
Baseline to 10.7 years			
ROA vs non-ROA ($n = 377$)	−2.6 (−8.3 to 3.1)	−4.3 (−9.7 to 1.2)	−3.0 (−9.0 to 2.9)
MRI-OA vs non-MRI-OA ($n = 377$)	**−10.2 (-15.3 to -5.2)**	**−7.9 (-12.8 to -3.1)**	**−7.1 (-12.4 to -1.9)**

CI, confidence interval; MRI-OA, magnetic resonance imaging-defined osteoarthritis; ROA, radiographic osteoarthritis. Bold values indicate statistical significance at the $p < 0.05$ level.
* Model 1: adjusted for age, sex, body mass index, tibial cartilage volume at baseline..
† Model 2: Model 1 + further adjusted for bone size at baseline and change in body mass index over time.Bold values indicate statistical significance ($p < 0.05$)

Table II The association of radiographic- and MRI-defined osteoarthritis with tibial cartilage volume loss over 2.6 and 10.7 years

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	Presence of symptoms, PR (95% CI)*		Onset of symptoms, RR (95% CI)†		Progression of symptoms, RR (95% CI)†	
	Pain	Function	Pain	Function	Pain	Function
ROA (With vs. without)						
Baseline ($n = 574$)	**1.44 (1.23 to 1.69)**	**1.36 (1.17 to 1.58)**	–	–	–	–
2.6 years ($n = 557$)	–	–	**1.85 (1.06 to 3.23)**	1.22 (0.63–2.38)	0.99 (0.63–1.55)	1.11 (0.69–1.78)
5.1 years ($n = 507$)	–	–	**1.90 (1.14 to 3.18)**	1.71 (0.94–3.12)	**2.38 (1.55 to 3.65)**	1.54 (0.92–2.60)
10.7 years ($n = 421$)	–	–	0.86 (0.43–1.72)	0.84 (0.37–1.92)	**1.85 (1.23 to 2.79)**	**1.51 (1.09 to 2.08)**
MRI-OA (With vs. without)						
Baseline ($n = 574$)	**1.48 (1.25 to 1.75)**	**1.44 (1.24 to 1.67)**	–	–	–	–
2.6 years ($n = 557$)	–	–	1.63 (0.95–2.81)	1.49 (0.81–2.74)	1.07 (0.70–1.65)	1.24 (0.78–1.96)
5.1 years ($n = 507$)	–	–	1.62 (0.94–2.78)	1.42 (0.77–2.59)	1.06 (0.66–1.69)	1.12 (0.71–1.79)
10.7 years ($n = 421$)	–	–	0.86 (0.48–1.53)	0.78 (0.39–1.57)	0.84 (0.51–1.38)	1.30 (0.89–1.88)

CI, confidence interval; MRI-OA, magnetic resonance imaging-defined osteoarthritis; PR, prevalence ratio; ROA, radiographic osteoarthritis; RR, risk ratio. Bold values indicate statistical significance at the $p < 0.05$ level.

* Adjusted for age, sex and body mass index.

† Adjusted for age, sex, body mass index and knee pain or function scores at baseline and time of follow-up.

Table III The association of radiographic- and MRI-defined osteoarthritis with the presence, onset and progression of knee symptoms

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Sensitivity analysis

Sensitivity analyses using inverse probability weighting did not change the associations of ROA and MRI-OA with tibial cartilage loss, knee symptoms or TKR (data not shown).

Discussion

This study is the first to describe the value of ROA and a published Delphi definition of MRI-OA for predicting tibial cartilage loss, knee symptoms and TKR in a population-based older adult cohort. Overall, the Delphi definition of MRI-OA had a minor benefit for predicting tibial cartilage loss but had lower value for predicting the onset and progression of knee symptoms and the risk of TKR compared to ROA. However, combining assessment of MRI-OA with ROA gave much better predictive validity for OA outcomes. These findings indicate that while the current MRI definition of OA is not superior to ROA, it may provide extra value when combined with ROA.

Compared to participants with neither MRI-OA nor ROA, knee structural abnormalities at baseline were more frequently observed in OA patients meeting either the MRI or radiographic definition and were most common in those who met both definitions. Given that MRI is more sensitive to structural changes than radiographs[2], the magnitude of difference (7%) in the prevalence of MRI-OA and ROA is perhaps less than we would expect, although it is similar to the differences seen in other studies of 4.7–8.3%[17,30]. Moreover, the sensitivity of MRI-OA for ROA in our study was only moderate (62%) and similar to that in other studies[30,31]. This and the fact it failed to identify a substantial number of participants with definite ROA (grade ≥ 2) could imply that the MRI definition has a limited diagnostic value for structural OA. However, the moderate sensitivity could also be due to the very high prevalence of meniscal lesions being misclassified as radiographic JSN[32], which led to some participants meeting criteria for ROA but probably not MRI-OA at the same time, since meniscal lesions only make a relatively small contribution to the MRI definition, which is rather based on a variety of structural changes.

While neither ROA nor the Delphi definition of MRI-OA was initially designed for predicting OA progression, it is likely that patients with OA on radiograph or MRI would have a greater risk of progression. This study indicated that both ROA and MRI-OA predicted a moderate increase in tibial cartilage loss over 2.6 years. Such an increase was only observed in participants with MRI-OA over 10.7 years, and the magnitude of the increased cartilage loss (MRI-OA vs non-MRI-OA) over 10.7 years was small. Of note, the current study evaluated tibial cartilage volume using unpaired reading of MRI scans over 2.6 years and paired reading over 10.7 years, so the magnitude of the change in cartilage volume at the different time points are not directly comparable, although each reading had excellent internal validity. Moreover, a 'floor effect' is unlikely to explain the findings that each of ROA and MRI-OA alone predicted tibial cartilage loss over 2.6 but not 10.7 years, as tibial cartilage loss continues to progress with increasing age in this cohort[33]. These findings suggest that the value of MRI-OA and ROA for predicting tibial cartilage loss is similar.

Both ROA and MRI-OA were associated with a higher prevalence of knee pain and functional disability at baseline, but ROA predicted the onset and progression of knee pain and disability over time while MRI-OA did not. A previous study also reported an increased odds of knee pain at baseline in participants with ROA and those with MRI-OA, but in that case neither was associated with the onset of knee pain over 2 years, possibly due to its limited power because of a low prevalence (4.4%) of ROA[17]. Furthermore, in a recent study conducted in young adults (mean age 23 years) who had knee injury within the past three–10 years, MRI-defined OA was not associated with the severity of knee symptoms, although it may influence the quality of life[34]. These studies together with our results suggest that the MRI-OA definition alone has little value for predicting the onset and progression of knee symptoms.

A higher risk of TKR was observed in participants with ROA and those with MRI-OA, compared to those without ROA or MRI-OA, respectively. Of note, ROA showed a stronger value for predicting TKR than did MRI-OA, and this may be that ROA *per se* is an important indicator of performing a TKR.[35]

While MRI is a more sensitive technique than radiographs for morphologic changes of OA[2], the current definition of MRI-OA shows no or limited value, compared to ROA, for prediction of tibial cartilage loss, onset and progression of knee symptoms and risk of TKR. There are several potential reasons for this. First, the Delphi definition of MRI-OA is subjective based on expert consensus which may not necessarily reflect the ideal definition, and the arbitrary

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	No. of TKR	Risk ratio (95% confidence interval)	
		Univariable	Multivariable*
ROA vs non-ROA ($n = 574$)	22 vs 5	**16.1 (6.2 to 41.7)**	**15.0 (5.8 to 39.2)**
MRI-OA vs non-MRI-OA ($n = 574$)	22 vs 5	**11.5 (4.4 to 29.8)**	**10.9 (4.1 to 29.1)**
No ROA or MRI-OA	2/368 (0.5%)	Ref.	Ref.
ROA only	3/47 (6.4%)	**11.7 (2.0 to 68.5)**	**11.5 (2.0 to 66.8)**
MRI-OA only	3/83 (3.6%)	**6.7 (1.1 to 39.2)**	**6.8 (1.2 to 39.8)**
Both ROA and MRI-OA	19/76 (25%)	**46.0 (10.9 to 193.4)**	**50.9 (11.8 to 218.7)**

MRI-OA, magnetic resonance imaging-defined osteoarthritis; ROA, radiographic osteoarthritis; TKR, total knee replacement. Bold values indicate statistical significance at the $p < 0.05$ level.

* Adjusted for age, sex, body mass index, knee pain scores at baseline.

Table IV The association of radiographic- and MRI-defined osteoarthritis with right-sided total knee replacement over 13.5 years

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nature of the definition may obscure associations. Second, associations of other MRI changes such as synovitis and infrapatellar fat pad pathology with both structural and symptomatic progression of OA have been reported since the definition was made[11,36,37]. The inclusion of these MRI features could improve prediction of disease progression. Third, disease progression is more likely to be seen in patients with advanced OA[38,39]. Therefore, although the Delphi definition of MRI-OA may have a role for identifying patients with milder disease, its value for predicting OA progression was diluted and not superior to ROA.

Another important finding of this study is that MRI-OA in combination with ROA strongly predicted structural and symptomatic progression of OA. Indeed, participants with both MRI-OA and ROA had greatest tibial cartilage loss over both 2.6 and 10.7 years, highest risk of onset and progression of knee symptoms, and the most substantial proportion (25%) subsequently had TKR. These findings suggest that having both MRI-OA and ROA represents a phenotype of patients with severe structural changes in both bony and surrounding soft tissues, such that the current definition of structural OA using MRI provides additional information to the existing ROA definition for prediction of OA progression. This agrees with previous indications that the combination of imaging techniques would provide a more comprehensive assessment of the OA joint.[40]

The strengths of our study include the long follow-up and the inclusion of cartilage volume loss and TKR as outcome measures. This study also has limitations. Firstly, we used 'any meniscal extrusion or tear' as a surrogate definition of 'meniscal subluxation, maceration or degenerative (horizontal) tear' as specified in the Delphi definition of MRI-OA. However, the adapted criteria for meniscal lesions did not lead to fewer participants meeting the definition of MRI-OA because almost all participants had meniscal extrusion or tear, although this may have led to more participants being misclassified as having MRI-OA. Secondly, we did not measure bone attrition, but there is a strong association between the presence of bone attrition and BMLs, with bone attrition being unlikely to be detected in BML absent regions[41], suggesting this would have a limited effect on our results as we have measured BMLs. Moreover, we defined full-thickness cartilage lesion as the presence of any denuded subchondral bone while the Delphi

	Tibial cartilage volume loss, mean %/year	Tibial cartilage volume loss (mm^3/year), β (95% CI)		
		Univariable	Multivariable*	Multivariable†
Baseline to 2.6 years ($n = 345$)				
No ROA or MRI-OA	−1.76	Ref.	Ref.	Ref.
ROA only	−3.03	−41.7 (−124.1 to 40.7)	−67.0 (−146.5 to 12.5)	−68.7 (−148.8 to 11.3)
MRI-OA only	−3.81	**−97.9 (-163.8 to -32.1)**	**−80.4 (-143.3 to -17.4)**	**−81.7 (-146.1 to -17.3)**
Both ROA and MRI-OA	−4.47	**−131.3 (-205.1 to -57.5)**	**−118.6 (-191.4 to -45.8)**	**−116.1 (-195.0 to -37.2)**
Baseline to 10.7 years ($n = 377$)				
No ROA or MRI-OA	−1.19	Ref.	Ref.	Ref.
ROA only	−1.27	4.6 (−2.8 to 11.9)	0.7 (−6.2 to 7.6)	0.8 (−6.7 to 8.2)
MRI-OA only	−1.38	**−7.4 (-13.4 to -1.4)**	−5.3 (−11.0 to 0.3)	−5.4 (−11.3 to 0.6)
Both ROA and MRI-OA	−1.65	**−14.1 (-22.1 to -6.1)**	**−13.1 (-20.9 to -5.3)**	**−11.2 (-20.0 to -2.5)**

CI, confidence interval; MRI-OA, magnetic resonance imaging-defined osteoarthritis; ROA, radiographic osteoarthritis. Bold values indicate statistical significance at the $p < 0.05$ level.

* Model 1: adjusted for age, sex, body mass index and tibial cartilage volume at baseline。.

† Model 2: Model 1 + further adjusted for bone size at baseline and change in body mass index over time.

Table V The association of radiographic- and MRI-defined osteoarthritis with tibial cartilage volume loss over 2.6 and 10.7 years

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	Presence of symptoms, PR (95% CI)*		Onset of symptoms, RR (95% CI)†		Progression of symptoms, RR (95% CI)†	
	Pain	Function	Pain	Function	Pain	Function
Baseline (n = 574)						
No ROA or MRI-OA	Ref.	Ref.	–	–	–	–
ROA only	1.13 (0.82–1.54)	1.22 (0.94–1.58)	–	–	–	–
MRI-OA only	**1.27 (1.01 to 1.60)**	**1.35 (1.12 to 1.64)**	–	–	–	–
Both ROA and MRI-OA	**1.80 (1.51 to 2.15)**	**1.66 (1.38 to 1.98)**	–	–	–	–
2.6 years (n = 557)						
No ROA or MRI-OA	–	–	Ref.	Ref.	Ref.	Ref.
ROA only	–	–	1.36 (0.59–3.13)	1.03 (0.41–2.61)	0.99 (0.47–2.08)	0.69 (0.27–1.79)
MRI-OA only	–	–	1.31 (0.67–2.54)	1.39 (0.67–2.92)	1.11 (0.65–1.88)	1.03 (0.56–1.89)
Both ROA and MRI-OA	–	–	**2.89 (1.41 to 5.91)**	1.69 (0.70–4.08)	1.03 (0.59–1.79)	1.36 (0.78–2.38)
5.1 years (n = 507)						
No ROA or MRI-OA	–	–	Ref.	Ref.	Ref.	Ref.
ROA only	–	–	1.69 (0.80–3.59)	1.74 (0.86–3.53)	1.75 (0.96–3.20)	1.12 (0.55–2.25)
MRI-OA only	–	–	1.42 (0.74–2.72)	1.38 (0.68–2.84)	0.38 (0.12–1.16)	0.76 (0.38–1.51)
Both ROA and MRI-OA	–	–	**2.54 (1.27 to 5.05)**	1.90 (0.70–5.15)	**2.24 (1.28 to 3.89)**	1.61 (0.95–2.72)
10.7 years (n = 421)						
No ROA or MRI-OA	–	–	Ref.	Ref.	Ref.	Ref.
ROA only	–	–	0.80 (0.33–1.95)	0.88 (0.31–2.44)	**1.88 (1.11 to 3.18)**	**1.32 (0.78 to 2.25)**
MRI-OA only	–	–	0.82 (0.42–1.60)	0.80 (0.37–1.71)	0.68 (0.33–1.39)	1.12 (0.70–1.79)
Both ROA and MRI-OA	–	–	0.89 (0.32–2.47)	0.71 (0.20–2.55)	1.48 (0.84–2.61)	**1.75 (1.16 to 2.64)**

CI, confidence interval; MRI-OA, magnetic resonance imaging-defined osteoarthritis; PR, prevalence ratio; ROA, radiographic osteoarthritis; RR, risk ratio. Bold values indicate statistical significance at the $p < 0.05$ level.

* Adjusted for age, sex and body mass index.

† Adjusted for age, sex, body mass index, time of follow-up and knee pain or function scores at baseline.

Table VI The association of radiographic- and MRI-defined osteoarthritis with the presence, onset and progression of knee symptoms

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definition of MRI-OA showed that denuded subchondral bone equals or greater than 10 mm^2 has a higher discriminatory power for cartilage lesion (c-statistics 0.73 vs 0.65)[16]. The definition of full-thickness more participants may have been identified as having MRI-OA in this study. Thirdly, self-reported WOMAC knee pain and function scores were not side-specific but structural changes were measured for the right knee only. This may have diluted the association between structural OA and knee symptoms. However, previous evidence has indicated substantial discordance between ROA and knee pain[42,43], and our findings were consistent with another study using the same definition of MRI-OA[17]. This suggests that our results are robust. In addition, the associations of ROA and MRI-OA with tibial cartilage loss may have been underestimated because participants with OA were more likely to undergo a TKR and were excluded from the analyses of tibial cartilage loss. Nonetheless, the results were unlikely to change materially since only a small number of participants underwent TKR ($n = 27$, 4.7%). Lastly, only half of the participants in TASOAC were included in the analysis. However, the characteristics between participants included and not included in this study were similar, suggesting that this has not biased the results. Moreover, the results were unchanged after sensitivity analyses using inverse probability weighting.

In conclusion, the Delphi definition of MRI-OA is not superior to ROA for predicting structural or symptomatic OA progression but, its combination with ROA has much stronger predictive validity.

Ethics approval

Southern Tasmanian Health and Medical Human Research Ethics Committee.

Contributions

GC had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study design: GC and GJ. Acquisition of data: DA, ZZ and GJ. Analysis and interpretation of data: All authors. Manuscript preparation and approval: All authors.

Conflict of interest

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.joca.2020.04.017.

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