Outcomes	Hazard ratio (95%CI), P
KOA radiographic incidence	1.5 (1.05-2.15), P:0.026
NASS symptomatic incidence	1.34 (0.67-2.69), P:0.41

Table 2 Osteoarthritis and Cartilage

Assessment of the risk of KOA incidence according to the presence of treated hypothyroidism

		Estimate (95% CI), P		
	Muscle mediatory variables	Total effect of treated hypothyroidism on KOA radiographic incidence	Direct effect of treated hypothyroidism on KOA radiographic incidence	Mediation effect of treated hypothyroidism on KOA radiographic incidence through muscle changes
	4-year changes in:			
KOA radiographic incidence	**Quadriceps CSA (mm2)**	-3.185 (-5.814 - -0.755), P:0.008	-2.908 (-5.555 - -0.472), P:0.022	**-0.277 (-0.633 - -0.051), P:0.008**
	Total thigh muscles CSA	-3.307 (-5.746 - -0.616), P:0.020	-3.216 (-5.667 - -0.475), P:0.026	-0.091 (-0.332 - 0.091), P:0.362

Table 3 Osteoarthritis and Cartilage

Mediation analysis

hypothyroidism and NASS incidence, treated hypothyroidism was significantly associated with increased 8-year risk for radiographic KOA incidence (hazard ratio, 95% confidence interval (95%CI): 1.5, 1.05-2.15). (Table 2)Mediation analysis showed that a decrease in quadriceps CSA partially mediated increased KOA incidence risk in patients with treated hypothyroidism. (Table 3)Moreover, results were not sensitive to the use of PS-matching or changing selection criteria of hypothyroid patients.
Conclusions: Levothyroxine users, as a proxy indicator of clinically overt hypothyroidism, are at risk of increased quadriceps atrophy, but not adiposity. In addition, these participants may also have an increased risk of radiographic KOA incidence risk, which is partially mediated through increased quadriceps atrophy associated with treated hypothyroidism.

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DEVELOPMENT AND VALIDATION OF PREDICTION MODELS FOR THE RISK OF TOTAL KNEE REPLACEMENT USING DATA FROM MULTI-CENTER COHORT STUDIES

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Purpose: There is a paucity of prognostic prediction models for total knee replacement (TKR) and the role of radiographic findings in predicting TKR remains unclear. We aimed to develop and validate predictive models for TKR and assess whether adding radiographic findings improves predictive performance using data from the Multicenter Osteoarthritis Study (MOST) and the Osteoarthritis Initiative (OAI)
Methods: We included participants who reported knee pain in the past 3 months at their baseline visit and followed them up until 60 months so that participants of MOST and OAI had the same length of follow-up time. We selected only one knee from each participant based on the severity of knee pain measured by either WOMAC pain questionnaire or other instruments. TKRs that occurred during the 60 month follow-up period in both cohorts were identified and adjudicated by medical records and/or post-operative radiographs. The date of TKR was obtained from medical records or self-report by participants when medical records were unavailable. We identified 26 potential predictors, collected and assessed at baseline visit, based on an expert review of the current studies on the risk factors of TKR by a census group of orthopedic surgeons led by the chief investigator (Table 1). We developed two predictive models for the risk of TKR within 60 months by fitting Cox proportional hazard models among participants in the MOST. The first model included socio-demographic and anthropometric factors, medical history and clinical measures (i.e., clinical model). The second model added radiographic findings into predictive model (i.e., radiographic model). A significance level of 0·20 was chosen so that important predictors relevant to TKR would not be missed and to avoid deleting less significant ones that may have practical and clinical implication. We performed a 10-fold cross-validation to minimize overfitting. We evaluated each model's discrimination and calibration performance and assessed the incremental value of radiographic findings using both category-free net reclassification improvement (NRI) and integrated discrimination improvement (IDI). We tuned the models and externally validated among participants in the OAI.
Results: We included 2658 participants of the MOST (mean age=62·4 years (SD=8·1), 1646 (61·9%) women) and 4060 participants of the OAI (mean age=60·9 years (SD=9·1), 2379 (58·6%) women). The C statistic was 0·79 (95% CI: 0·76-0·81) for the clinical model and 0·87 (95% CI: 0·85-0·99) for the radiographic model. The calibration slope was 0·95 (95% CI: 0·86-1·05) and 0·96 (0·87-1·04), respectively. Adding radiograph findings significantly improved predictive performance with an NRI of 0·42 (95% CI: 0·34-0·48) and IDI of 0·13 (95% CI: 0·09-0·16). The clinical model and radiographic model were tuned with an adjustment size of 0·839 and 0·941, respectively, using the validation dataset. C statistics of tuned clinical model and radiographic model were 0·78 (95% CI: 0·71-0·85) and 0·88 (95% CI: 0·84-0·92), respectively (Table 2). The calibration slopes of clinical model and radiographic model were 1·004 (95% CI: 0·81-1·19) and 1·03 (95% CI: 0·95-1·10), with a corresponding intercept of -0·004 (95% CI: -0·18-0·18) and -0·02 (95% CI: -0·09-0·04), respectively. Adding radiographic findings significantly improved in predictive performance with NRI of 0·51 (95% CI: 0·39-0·59) and an IDI of 0·09 (95% CI: 0·06-0·11) (Table 2). Free access to the tuned models was provided through http://116.62.145.8:8899/predictTKR.html. We also derived nomograms to graphically present the predictive models (Figure 1).
Conclusions: While the risk of TKR can be predicted based on common risk factors with good discrimination and calibration , adding radiographic findings of knee OA into the predictive model substantially improves the predictive performance. This study adds empirical evidence that radiographs, a commonly collected information in routine clinical care, significantly improved performance of predicting future TKR. Patients and clinicians should be informed by these findings that the risk of TKR can be

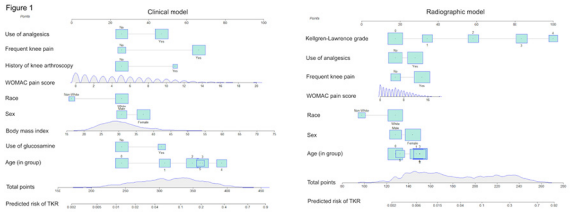
Table 1. Characteristics of study populations for the knee replacement model in training and validation cohort.

Predictor	Number (%) of Participants MOST (Training dataset) n=2658	OAI (Validation dataset) n=4060
Outcome, n (%)		
Knee replacement	290 (10.9)	174 (4.30)
Age, mean (SD), years	62.4 (8.1)	60.9 (9.1)
<55	602 (22.7)	1233 (30.37)
55-59	436 (16.4)	684 (16.8)
60-64	542 (20.4)	651 (16.0)
65-69	487 (18.3)	600 (14.8)
70-74	361 (13.6)	559 (13.8)
≥75	230 (8.6)	333 (8.2)
Sex, n (%)		
Male	1012 (38.1)	1681 (41.4)
Female	1646 (61.9)	2379 (58.6)
Race, n (%)		
White	2191 (82.4)	3179 (78.3)
Non-White	467 (17.6)	881 (21.7)
Education, n (%)		
High school and below	793 (29.8)	654 (16.3)
College	1228 (46.2)	1843 (45.8)
Graduate and above	637 (24.0)	1526 (37.9)
Married, n (%)	1917 (72.5)	2672 (66.4)
Living alone, n (%)	523 (19.7)	933 (23.0)
Smoker, n (%)	1177 (44.3)	806 (20.1)
History of knee injury, n (%)	900 (34.0)	1441 (35.9)
History of knee arthroscopy, n (%)	348 (13.1)	573 (14.1)
History of hip fracture, n (%)	33 (1.2)	40 (1.0)
History of spine/vertebrae fracture, n(%)	131 (4.9)	117 (2.9)
Frequent knee pain, n (%)	1906 (71.7)	1806 (44.5)
Use of medication, n (%)		
Analgesics	1419 (53.4)	862 (21.2)
Glucosamine	701 (26.4)	9 (0.2)
Chondroitin	513 (19.3)	8 (0.2)
Hyaluronic acid	21 (0.8)	1 (0.0)
Steroids	251 (9.4)	2 (0.1)
Kellgren-Lawrence grade, n (%)		
0	960 (36.1)	1306 (32.2)
1	409 (15.4)	677 (16.7)
2	441 (16.6)	1117 (27.5)
3	534 (20.1)	693 (17.1)
4	314 (11.8)	267 (6.6)
Body mass index, mean (SD), kg/m^2	30.9 (6.1)	28.8 (4.9)
WOMAC pain score, median (IQR)	5.0 (6.0)	3.0 (5.0)
WOMAC disability score, mean (SD)	16.7 (12.9)	9.2 (11.6)
WOMAC stiffness score, mean (SD)	2.6 (1.8)	2.1 (1.7)
CES-D, median (IQR)	6.0 (9.0)	5.0 (8.0)
Charlson comorbidity index, median (IQR)	0.0 (1.0)	0.0 (1.0)
PASE score, mean (SD)	173.5 (88.0)	160.8 (82.4)
Number of other sites with frequent pain, median (IQR)	3.0 (4.0)	1.0 (2.0)

* MOST = the Multicenter Osteoarthritis Study, OAI = The Osteoarthritis Initiative, WOMAC = The Western Ontarioand McMaster Universities Osteoarthritis Index, CES-D = Center for Epidemiologic Studies Depression Scale, PASE = Physical Activity Scale for the Elderly, SD = Standard deviation, IQR = Interquartile range.

accurately estimated using several common risk factor, but radiographs, if available, should be included and provide added value.

Figure 1



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A COMPARISON OF ULTRASOUND-DETECTED PATHOLOGIES IN PERSONS WITH AND WITHOUT KNEE OSTEOARTHRITIS AND THE ASSOCIATIONS WITH PAIN

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Purpose: Ultrasound can be performed to evaluate the degree of osteophytes and synovitis in persons with knee OA bedside to patients, without any side effects or contraindications. Few studies have looked at the associations between ultrasound findings and pain, and there is limited knowledge regarding ultrasound as a valid examination to assess OA pathology of the knee. Hence, we aimed to compare the degree of OA changes by ultrasound among people with and without knee OA according to established classification criteria and study the associations between ultrasound findings and pain.

Methods: The Nor-Hand study is an observational cohort in which 300 patients with hand OA (89% women, median (IQR) 61 (57-66) years old) were recruited. The current analyses include cross-sectional data from the baseline examination. We included 286 participants in the present analyses after excluding participants with knee prostheses or arthrodesis. The participants reported the levels of knee/hip pain using the Western/Ontario McMaster University index (WOMAC) and marked their painful joints (including the bilateral knees) during the last 24 hours and last 6 weeks on two separate homunculi. An experienced rheumatologist (BSC) examined whether the participants fulfilled the clinical ACR criteria for knee OA or not (n=7 missing). A trained medical student performed the ultrasound examination of the knees using a General Electric (GE) Logic E9 ultrasound machine with a 6-15Mz probe. Both knees were scored for 1) the severity of osteophytes in the medial and lateral tibia and femur on 0-3 semi-quantitative scales (0=no, 1=small, 2=medium, and 3=large; sum range = 0-12 per knee), and 2) grey-scale synovitis on 0-3 semi-quantitative scales (0=no, 1=mild, 2=moderate, and 3=severe pathology). The highest score of osteophytes and grey-scale synovitis (range: 0-3) and the sum scores of both knees together (range: 0-24 for osteophytes and 0-6 for synovitis) were calculated.
We compared the degree of ultrasound pathologies in persons with vs. without clinical knee OA according to the ACR criteria using Chi-square tests for categorical data and Mann-Whitney U test or T-test for continuous data as appropriate. The associations between ultrasound pathologies and pain scores were explored by linear and logistic regression analyses, adjusted for age, sex, and body mass index. Generalized Estimating Equations were applied to account for two knees belonging to the same person.

Results: Knee osteophytes on ultrasound, but not grey-scale synovitis, were significantly more common in persons with knee OA compared with persons without knee OA (p<0.001) (Table 1). Osteophytes were associated with higher levels of WOMAC pain, while no association was found between grey-scale synovitis and WOMAC pain (Table 2). However, in analyses on joint level, both osteophytes (OR=1.8-8.2) and grey-scale synovitis (OR=1.2-8.2) were associated with pain in the same joint in both a short (24 hours) and long term (6 weeks) and with a stronger association for more severe ultrasound scores (Table 3).

Conclusions: People with knee OA had significantly more osteophytes by ultrasound than people without knee OA, while they had no

	MOST (Training dataset), n=2658		OAI (Validation dataset), n=2932	
	Clinical model	Radiographic model	Clinical model	Radiographic model
C-statistic	0·79 (0·76-0·81)	0·87(0·85-0·89)	0·78 (0·71-0·85)	0·88 (0·84-0·92)
Calibration slope	0·95 (0·86-1·05)	0·96 (0·87-1·04)	1·004 (0·81-1·19)	1·03 (0·95-1·10)
Calibration intercept	0·01 (-0·08-0·11)	0·01 (-0·04-0·05)	-0·004 (-0·18-0·18)	-0·02 (-0·09-0·04)
NRI	Reference	0·43 (0·38-0·50)	Reference	0·51 (0·39-0·59)
IDI	Reference	0·14 (0·10-0·18)	Reference	0·09 (0·06-0·11)

Table 2

Performance in discrimination and calibration and measures of improvement of the radiograp