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TITLE PAGE

Manuscript title**:** Predicting incident radiographic knee osteoarthritis in middle-aged women within 4 years: the importance of knee-level prognostic factors.

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ABSTRACT

Objective

Develop and internally validate risk models and a clinical risk score tool to predict incident radiographic knee osteoarthritis (RKOA) in middle-aged women.

Methods

We analysed 649 women in the Chingford 1000 Women study. The outcome was incident RKOA, defined as Kellgren/Lawrence grade 0-1 at baseline and ≥2 at year 5. We estimated predictors' effects on the outcome using logistic regression models. Two models were generated. The clinical model considered patient characteristics, medication, biomarkers, and knee symptoms. The radiographic model considered the same factors, plus radiographic factors (e.g., angle between the acetabular roof and ilium's vertical cortex (hip α-angle)). The models were internally validated. Model performance was assessed using calibration and discrimination (area under the receiver characteristic curve, AUC).

Results

The clinical model contained age, quadriceps circumference, and a cartilage degradation marker (CTX-II) as predictors (AUC = 0.692). The radiographic model contained older age, greater quadriceps circumference, knee pain, knee baseline Kellgren/Lawrence 1 (versus 0), greater hip α-angle, greater spinal bone mineral density, and contralateral RKOA at baseline as predictors (AUC = 0.797). Calibration tests showed good agreement between the observed and predicted incident RKOA. A clinical risk score tool was developed from the clinical model.

Conclusion

Two models predicting incident RKOA within 4 years were developed; including radiographic variables improved model performance. First-time predictor hip α-angle and contralateral RKOA suggest osteoarthritis origins beyond the knee. The clinical tool has the potential to help

physicians identify patients at risk of RKOA in routine practice, but should be externally validated.

SIGNIFICANCE AND INNOVATIONS

- Identifying women with knees at high risk of developing radiographic knee osteoarthritis (RKOA) will enable preventive measures to be tested. To do so, we have developed clinical and radiological predictive models for short-term incidence of RKOA.

- We have generated a risk score tool to help clinicians use the clinical model and inform their patients about their risk of developing osteoarthritis.

- Both models and the risk score tool could be useful in identifying participants at risk of developing osteoarthritis in the short-term for clinical trials.

- The radiographic model selected hip α-angle, bone mineral density at the spine lumbar, and contralateral knee osteoarthritis as predictors of RKOA, suggesting osteoarthritis origins beyond the knee area.

Knee osteoarthritis is one of the greatest contributors to global disability and a major global public health burden (1). It was the indication for surgery in 96% of the 98,147 primary knee joint replacements conducted in the United Kingdom in 2016 (2). The current treatment for knee osteoarthritis pain is limited to symptom relief with analgesics and/or physiotherapy. Preventing knee osteoarthritis is thus an increased focus of public health.

Previous studies have identified risk factors for the incidence and progression of radiographic knee osteoarthritis (RKOA), such as older age, female gender, and higher body mass index (BMI) (3-6). However, only three prognostic models have been developed for incident RKOA (7-9). Two of these models were developed using 9 and 12 years of participant follow-up data (7, 9). The most recent study followed participants for 5 years to identify rapid progression and considered radiographic tibiofemoral osteoarthritis as the outcome (8).

As the rate at which knee osteoarthritis progresses varies considerably between patients (10), a model for short-term incident RKOA is needed to identify homogeneous phenotypes of patients, to facilitate forecasting and target potential treatments (11). Many of the known risk factors for RKOA have only been studied in isolation (12, 13). Their combined effects and any other risk factors for the onset of short-term RKOA are needed to better identify those at risk.

This is the first study to asses a wide range of potential predictors that includes physical assessment, sociodemographic characteristics, medication, biomarkers, medical history (family history, knee pain, activity associated with a painful knee, and occupation), spine and hip radiographs and densitometries, and lifestyle. Incorporating new predictors in clinical prediction models adds value, improving the information available to clinicians and patients when deciding on preventive strategies to reduce rapid disease incidence. A description of

patients at risk of rapid progression to RKOA will also help in selecting participants for randomised controlled trials of new interventions.

We aimed to develop and internally validate a prognostic model for short-term incidence of RKOA in a population-based cohort of women, focusing on knee-level risk factors. We also aimed to develop a clinical risk prediction tool to help clinicians to identify women who are most likely to develop RKOA within 4 years.

MATERIALS AND METHODS

Data source and sample size

This study was carried out retrospectively using data from the Chingford 1000 Women study. This is a well-described prospective population-based cohort of 1003 women seen annually for osteoporosis and osteoarthritis over 23 years (3). Women were selected from the age/sex register of a large general practice in Chingford, North London, UK. They lived in a middle-class area and were mostly white (98%) and middle-aged (44-67 years). For the purpose of this analysis, women were recruited at baseline between 1988 and 1989, and seen again 4 years later.

Participants

The unit of analysis was the knee. Each woman participated with one or both knees, which were radiographed at baseline (year 1) and follow-up (year 5). Exclusion criteria for participants were any indication of inflammatory arthritis (rheumatoid arthritis or lupus) or a neurological medical condition (poliomyelitis, Parkinson's disease, stroke, multiple sclerosis, or cerebral palsy) at baseline or year 10, as this information was not available for year 5. Fifty participants were excluded using these criteria. Individual knees were also excluded if they had

a Kellgren and Lawrence (K/L) grade of 2 or more (14), an osteophyte (lateral or medial), or joint space narrowing (JSN) of grade 1 or more at baseline (10).

The ethics committee approved the Chingford study (reference number: LREC R & WF 96), and written informed consent was obtained from each participant.

Outcome

The outcome was incident RKOA, defined as a knee with a K/L grade of 0 or 1 at baseline and of grade 2 or more at year 5. The K/L classification progresses from grade 0 to 4, based on X-rays, where 0 = normal; 1 = no JSN and possible osteophyte; 2 = possible JSN and definite osteophyte; 3 = definite JSN and multiple osteophytes, sclerosis, and possible bony deformity; and 4 = marked JSN, large osteophytes, severe sclerosis, and definite bony deformity (15, 16). The Chingford study collected weight-bearing anteroposterior-view radiographs of the knee for all participants at baseline and follow-up. These X-rays were used to assign each knee a K/L grade, using previously described protocols (3, 17).

Predictor variables

The Chingford investigators collected around 700 variables at baseline. A panel of experts in osteoarthritis research selected candidate predictors for RKOA from these variables in a three-round Delphi process. Categorical variables with under five values in at least one category and variables with a poor association with the outcome (P-value > 0.2) were excluded. The remaining potential predictors were used to develop the model. Supplementary Tables S1-S6 list the potential predictors and Supplementary Text S1 describes how the predictors were assessed.

Statistics

We developed the prediction model as follows (18, 19):

Step 1: To address the issue of missing data, we generated 50 imputed datasets (20). The linearity of continuous variables with incident RKOA was assessed using fractional polynomials.

Step 2: We evaluated the independent associations between the potential predictor variables and RKOA incidence with logistic regression, using clustered standard errors at the person-level. Two hundred bootstrap samples with replacement were combined with the 50 imputed datasets. Within each bootstrap sample, automatic backward selection was applied using a significance level of 0.157 (21), corresponding to the Akaike information criterion.

Step 3: Variables that appeared in at least 70% of the bootstrap samples were retained in the final models (22). We developed two models. The first only considered variables that clinicians routinely have access to: patient characteristics, medications, biomarker risk factors, and knee symptoms (clinical model). The second also considered radiographic variables (radiographic model).

Internal validation

We used 200 bootstrap samples with replacement combined with multiple imputations to assess bias-corrected estimates of predictive ability.

Further details of the multiple imputation, bootstrapping, and internal validation methods are described in Supplementary Text S1.

Model performance

We assessed the models' predictive performance using calibration and discrimination measures (21). The area under the receiver characteristic curve (AUC) was used to assess discrimination. Calibration – how closely predicted risk corresponds with observed risk – was assessed visually using calibration plots.

Clinical scoring tool

We created a points-based risk-scoring tool from the clinical model for easy clinical use, using previously described methods (23, 24). The tool estimates the short-term risk of incident RKOA.

All analyses were conducted using Stata version 13.1. We followed the TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) guideline to properly report this study (25).

RESULTS

Study characteristics

We analysed 1184 knees from 649 women for whom radiographic data were available at baseline (year 1) and year 5. The participants' mean age (±standard deviation) was 54 (±6) years. Figure 1 shows the selection criteria for the included knees and that 109 knees (9.2%, 95 women) had developed RKOA by year 5.

We excluded 20 categorical variables for having less than 5 observations in at least 1 category. Following univariable analysis, we excluded 53 of the possible variables (see Supplementary

Tables S1-S6 for univariable analysis results). Missing data for the variables included in this study are shown in Supplementary Table S7.

The remaining 30 potential predictors were used to develop the model, of which 24 are routinely available to clinicians and 6 are radiographic variables. Table 1 compare the 30 candidate risk factors between knees that developed RKOA within 4 years (by year 5) and those that did not. Supplementary Table S8 describes the 30 potential risk factors in greater detail.

Almost half of the 30 potential factors have been described previously (9, 11, 18-20). Sixteen were evaluated for the first time in the development of a model of RKOA incidence: age at menopause, waist-to-circumference ratio, weight at 20 years old, knee-level quadriceps circumference, painkiller use, duration of knee symptoms in months, stiffness during joint examination, pain during joint examination, swelling during joint examination, knees injured enough to rest them for a week, unstable knees (knees that give way), weather affecting knees, loss of height or a stoop or hump, number of thoracic and lumbar vertebrae with osteophytes or discs with narrowing space (26), and hip α-angle (the angle between the acetabular roof and ilium's vertical cortex).

Multivariable models predicting RKOA

The 24 of the 30 candidate predictors that are routinely available to clinicians (excluding the radiographic variables) were used to build the clinical multivariable model. Three candidates were identified as predictors ($P<0.157$): older age, greater quadriceps circumference, and

higher urine concentration of C-terminal telopeptide of type II collagen (CTX-II) corrected for creatinine at baseline (Table 2).

The model is described by:

Predicted probability of incident RKOA at year 5 = 1/(1+exp(-(-10.54 + 0.06 x age + 0.11 x quadriceps circumference + 0.63 x CTX-II (≥229.9 ng/mL category))).

All 30 candidate predictors, including the radiographic variables, were used to build the radiographic multivariable model. Seven candidate variables were identified as predictors (*P*<0.157): older age, greater quadriceps circumference, presence of knee pain, K/L grade 1, contralateral RKOA at baseline, greater hip α-angle (28), and greater bone mineral density (BMD) Z-score at the spine (Table 2).

The model is described by:

Predicted probability of incident RKOA at year 5 = 1/(1+exp(-11.64 + 0.07 x age + 0.09 x quadriceps circumference + 0.53 x knee pain (same side) + 1.88 x knee K/L grade 1 + 1.09 x contralateral knee with K/L grade≥2 + 0.02 x hip α-angle + 0.28 x BMD Z-score at the spine L1-L4)).

Model performance

The upper panels of Figure 2 show the models' discrimination. The radiographic model (right upper panel) showed better discrimination (AUC = 0.809, optimism = 0.012, bias-corrected AUC = 0.797) than the more limited clinical model (left upper panel, AUC = 0.699, optimism = 0.007, bias-corrected AUC = 0.692).

The agreement between the predicted and observed values of incident RKOA at year 5 is shown in the lower panels of Figure 2 and was assessed visually. Both models showed good calibration: all of the 95% confidence interval (CI) bars and some of the mean values (data points) intersect with the 45° line that indicates perfect agreement between the predicted and observed RKOA at year 5. However, both models slightly overestimated some of the lowest values. Our models therefore estimated that fewer patients would develop RKOA than was observed in our sample for those patients that had a low probability of developing RKOA.

Clinical scoring tool

The clinical model with routinely available variables (age, quadriceps circumference, and urine CTX-II) was developed into a clinical scoring tool (Table 3). The tool gives scores from 0 (lowest risk) to 17 (greatest risk). A woman will reach the highest score if she is 52-66 years old, has a quadriceps with a circumference of 44-63 cm, and has a concentration of urine CTX-II of 0.23-1.34 mcg/mL.

We also generated a tool that adds the four radiographic variables to the three routinely available variables, for those physicians with access to radiographs (Supplementary Table S9).

DISCUSSION

We developed and internally validated two prediction models for incident RKOA in middle-aged women, one using information readily available to clinicians (clinical model) and the other supplementing this information with radiographic features (radiographic model). Both models showed good predictive validity, with bias-corrected AUCs of 0.692 (clinical model)

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and 0.797 (radiographic model). Calibration tests showed good agreement between the observed and predicted incident RKOA.

We also developed a clinical risk score tool to identify women at short-term risk of RKOA, using the predictors identified in the clinical model so that it can easily be used in clinical practice. A participant with a score of 5 would have a 30% ((5/17) x 100 = 29.4) probability of developing RKOA within 4 years. Higher risk is driven by the urine CTX-II marker. Patients with no risk from age (44–48 years) or quadriceps circumference (32–39 cm) but with high urine CTX-II (0.2–1.3 µg/mL) would have a 77% ((13/17) x 100 = 76.5) probability of developing RKOA within 4 years.

Older age, bigger quadriceps circumference, and elevated urine CTX-II were predictors of incident RKOA in the clinical model. When radiographic features, hip α-angle, and bone density were added to form the radiographic model, the predictive ability improved considerably, increasing from 69% to 80%. The radiographic model selected age and quadriceps circumference like the clinical model, but did not select urine CTX-II. The radiographic model also selected knee pain, baseline K/L grade, contralateral knee with RKOA at baseline, hip α-angle, and Z score BMD at the spine L1-L4. The principal predictors (those with the highest odds ratios and strongest predictive ability) in the radiographic model were RKOA in the contralateral knee (3 times more associated with incidence RKOA than a contralateral knee free of RKOA, Table 2) and K/L grade 1 in the index knee (6.5 times more related to incidence RKOA than the index knee with K/L grade 0, Table 2), at baseline.

Within the National Institute for Health and Care Excellence (NICE) recommendations (29), patients with no pain or symptoms of knee osteoarthritis who are 45 years old or older and have an activity associated with knee pain could be assessed using our clinical predictive tool to predict their risk of developing RKOA in the next 4 years. The radiographic predictive tool that includes radiographic variables could be useful in clinical practice if further investigation is undertaken when diagnosis is in doubt or in preparation for referral to a rheumatologist.

Age (selected in both models) and knee pain (selected in the radiographic model) are both well-known risk factors for the incidence of RKOA (4, 10, 30-32).

Our models showed that a greater quadriceps circumference was associated with incidence RKOA. A larger circumference may reflect more subcutaneous fat around the knee. Individuals who are overweight may have added issues with load and muscle imbalance, which can lead to quadriceps inflammation (33, 34). It is easy to measure the quadriceps circumference in clinical practice, making this a useful predictor (35).

As urine CTX-II is a by-product of the degradation of knee components such as matrix and cartilage, its presence has been associated with osteoarthritis and osteoporosis (36). A meta-analysis that included the Chingford cohort used here found that a higher likelihood of incident knee osteoarthritis was associated with higher levels of urine CTX-II (37). Although urine CTX-II was a significant predictor in our clinical model, it was not selected in our radiographic model. Urine CTX-II may therefore be a surrogate for radiographic factors, which could be useful in clinical practice when X-rays are unavailable.

A K/L grade of 1 and contralateral RKOA were strong predictors of RKOA in our radiographic model. These associations are already well-known (7, 8) and an existing person-level prediction model also includes K/L grade of 1 as a predictor (7).

This is the first time that hip α-angle has been identified as a predictor of incident RKOA. The α-angle is a radiological measure used to diagnose femoroacetabular impingement at the hip, which causes hip pain and dysfunction (38). The most common threshold for diagnosis is an angle greater than 50° (28). The mean of α-angles in the group with RKOA at year 5 exceeded this threshold in our study. A larger hip α-angle may thus reflect serious biomechanical changes and point to an osteoarthritis origin beyond the knee that leads to an increased risk of knee RKOA. For example, a greater hip α-angle might indicate abnormal rotation of the tibia with respect to the femur, leading to knee osteoarthritis (39). It may also be related to hip osteoarthritis. Hip osteoarthritis flexes, externally rotates, and adducts the hip. These changes may lead to apparent limb shortening.

We found higher BMD at the spine in women with short-term incident RKOA than in those without RKOA. A lumbar spine with a higher BMD has previously been associated with knee osteoarthritis (40, 41). A recent population-based study found a correlation between the spine BMD and knee osteophyte score, and a negative correlation between the spine BMD and JSN (42). High systemic BMD has also been associated with incident RKOA (43, 44), and an estimated 45% of the association between high bone mass and knee osteoarthritis may be mediated by BMI (45). However, this is the first time that higher spine BMD has been shown to be useful in a predictive model of RKOA.

Clinical practice needs predictive tools for identifying those at risk of developing RKOA in the short term (6, 46). Identifying those at short-term risk will allow new interventions targeting this population to be developed. However, two of the three previously developed models for incidence of RKOA followed people for 9 (7) and 12 (9) years. They therefore selected prognostic factors that could predict RKOA in the medium- to long-term. Riddle et al. investigated short-term risk by following participants for 5 years, but focused on older people with a higher BMI who were at high risk for developing osteoarthritis, and only considered those with radiographic tibiofemoral osteoarthritis (8). Our model bridges this gap by predicting the short-term incidence of all RKOA.

Unlike our study, none of the three previous studies (7-9) included any form of internal validation to account for optimism in the predictive performance of the developed models (25, 47). The AUC values presented in these published studies would have been lower if internal validation were used.

Kerkhof et al. also produced a clinical model that excluded radiographic variables but included age, CTX-II, and BMI (7). This model had reasonable discriminatory power (AUC = 0.66). Our clinical model used knee-level quadriceps circumference instead of BMI and had better slightly discriminatory power (AUC = 0.69) than Kerkhof's clinical model. Both clinical models included urine CTX-II. It added little to the predictive value of their model, whereas higher urine CTX-II levels doubled the probability of short-term RKOA in our clinical model (48). Our clinical model was also better at predicting incidence RKOA than alternative models assessed by Kerkhof et al. that considered ambulation, disability, and genetic risk factors.

Our clinical model performed similarly (AUC = 0.69) to the model of Zhang et al. (9) when developed on the Nottingham knee osteoarthritis retrospective cohort (AUC = 0.70). However, our clinical model is simpler to implement because it only considers three predictors (age, knee-level quadriceps circumference, and urine CTX-II), in comparison with their six-predictor model (age, sex, BMI, occupational risk, family history of osteoarthritis, and previous serious knee injury).

None of the existing models used calibration plots to check agreement between predicted and observed probabilities (7-9). Instead, they used the Hosmer-Lemeshow test. The TRIPOD guideline discourages its use because it has limited statistical power when assessing poor calibration and tends to give a significant result if a large enough sample is used (25). We presented calibration plots showing that the CIs for most of our models' predictions overlapped with the 45° line, showing agreement with the observed RKOA incidence. The probability of developing incident RKOA in the next 4 years in our general population of middle-aged women varied between 3 out of 100 women and 20 out of 100 women. As this model was developed using data from a healthy, urban population of white middle-aged women, it cannot be assumed that the model will make accurate predictions in other populations. We suggest testing and validation before use in, for example, hospital inpatient, rural, younger female, older female, and male populations.

Strengths and limitations

This study has several strengths. Our knee-level approach allows to identify risk factors whose effects are connected to which side of the body they are in, in relation to the knee that developed RKOA: quadriceps circumference, knee pain evaluated by the physician, specific knee K/L grade, contralateral knee with RKOA, and ipsilateral hip α-angle.

The reproducibility of the model was ensured by using multiple imputation and bootstrapping (49), so that only significant predictors were selected. We grouped the risk factors together into those that clinicians readily have access to and those that require radiography. The resulting two risk models support clinical decision-making between the physician and patient in two common scenarios, before and after radiography. We created a risk prediction tool to assess the short-term risk of incident RKOA, which will help physicians to inform their patients about their risk for incident RKOA and support the physician in addressing preventive measures to avoid the outcome.

The study also has potential limitations. As uncontrolled parameters such as lifestyle factors may have changed since this study started in 1988-1989, the results may not be generalisable to individuals in 2018. However, our findings are consistent with recent studies (4, 12, 13, 37), which support that these potential differences may not have any impact on the relationship between the selected predictors and RKOA.

External validation was beyond the scope of this study, as an existing cohort of sufficient sample size containing the required predictors could not be found. Before the models are used in clinical practice, they should be externally validated using participant data from other than the Chingford study to test whether the model performance is overly optimistic. The models' generalisability in men, mixed-gender, and non-white populations should also be tested. It is possible that the predictive capacity identified here only applies to individuals with existing radiographic changes, which could limit the clinical utility of the tool. This requires further investigation.

K/L grade≥2 does not account for knee symptoms. However, K/L ≥2 is strongly associated with knee pain and closely linked to knee replacement (32). We instead tested knee pain as a potential predictor, which was selected in the radiographic model.

Conclusions

We developed two predictive models for short-term incidence of RKOA in middle-aged, predominantly white women, a simple clinical model and a more complete radiographic model. The clinical model uses three variables that clinicians can easily measure and use to identify and inform women who have knees at higher risk of RKOA in the clinical setting: age, quadriceps circumference, and urine CTX-II level. The radiographic predictive model uses seven variables and includes radiographic factors such as hip α-angle to increase the predictive capacity of the clinical model of short-term incidence of RKOA.

This is the first time that ipsilateral hip α-angle has been identified as a predictor of RKOA. The selection of hip α-angle, BMD at the lumbar spine, and contralateral knee osteoarthritis as predictors of RKOA suggest osteoarthritis origins beyond the knee area, although further research is needed before a mechanism for how these cause RKOA can be suggested. We also developed a risk score tool to help clinicians use the clinical model. Identifying women with knees at high risk of developing RKOA will enable preventive measures to be tested. Once externally validated, both models and the risk score tool could be useful in identifying participants for clinical trials.

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TABLES

Table 1. Baseline features of knees that do and do not develop radiographic knee osteoarthritis in 4 years.

Patient features	No RKOA (1075)	RKOA (109)	P-value
Age, years	53 (48, 58)	56 (51, 60)	<0.001[a]
Age at menopause			0.024
No menopause	278 (25.9)	21 (19.3)	
<48 years old	401 (37.3)	32 (29.4)	
49-51 years old	258 (24.0)	34 (31.2)	
>51 years old	138 (12.8)	22 (20.2)	
BMI (kg/m^2)	24.2 (22.5, 27.0)	26.4 (23.7, 28.9)	<0.001
Waist-hip ratio	0.76 (0.73, 0.80)	0.78 (0.75, 0.81)	0.005
Weight at 20 years old (kg)	54 (50, 60)	57 (53, 63)	0.002
Quadriceps circumference (cm)*	42 (39, 45)	44 (41, 47)	<0.001
Medication			
Oral contraceptive pill	363 (33.8)	29 (26.6)	0.130
Pain killers	79 (7.4)	13(11.9)	0.089
Biomarkers			
CTX-II tertiles (corrected for creatinine)			<0.001
52.7 – 133.1 ng/mL	294 (34.5)	14 (18.9)	
133.2 – 229.8 ng/mL	290 (34.0)	19 (25.7)	
≥229.9 ng/mL	268 (31.5)	41 (55.4)	
Oestradiol (E2) (picomol/L)	21 (20, 239)	20 (20, 153)	0.134[b]

Knee symptoms and height loss, stoop, or hump			
Duration (months)*	0 (0-1)	0 (0-12)	0.051[c]
Presence of stiffness*	247 (23.0)	34 (31.2)	0.055
Presence of pain*	238 (22.1)	37 (33.9)	0.005
Presence of swelling*	93 (8.6)	14 (12.8)	0.146
Injured knees for a week	81 (8.7)	19 (19.2)	0.001
Pain while walking	177 (19.1)	27 (27.3)	0.051
Pain while descending stairs	188 (20.2)	30 (30.3)	0.020
Pain while bending	188 (20.4)	28 (28.9)	0.051
Pain while sitting	112 (12.1)	19 (19.2)	0.043
Unstable knees	165 (17.8)	32 (33.0)	<0.001
Morning stiffness	233 (25.1)	33 (33.3)	0.077
Weather affects knees	157 (16.9)	28 (28.0)	0.006
Job/daily activities involved knee bending 10 years ago‡			0.020
None/little/moderate	699 (71.8)	58 (60.4)	
A lot/always	275 (28.2)	38 (39.6)	
Loss of height, stoop, or hump	119 (11.1)	17 (15.6)	0.160
Radiology factors			
Baseline knee K/L grade*			<0.001
0 grade	1029 (95.7)	75 (68.8)	
1 grade	46 (4.3)	34 (31.2)	
Contralateral knee with RKOA at baseline*	83 (7.7)	31 (28.4)	<0.001

Hip α-angle (degrees)*	55.4 (±18.3)	61.8 (±22.7)	0.004[d]
Spine – osteophytes (n)			0.080
0-3	676 (66.3)	57 (57.6)	
>3	343 (33.7)	42 (42.4)	
Spine discs - narrowing space (n)			0.027
0	900 (87.6)	79 (79.8)	
>3	127 (12.4)	20 (20.2)	
BMD Z-score at the spine L1-L4	0.32 (±1.25)	0.86 (±1.41)	0.002

These factors were considered potential prognostic factors in both the clinical and radiographic models. The data were collected in London, 1989/91. * Side level. ‡ collected at year 3. [a] Significant F-statistic. [b] Analysis of variance. Variances between groups were not equal. [c] Significant F-statistics (0.53) when there were no symptoms on the knee (values=0) were excluded. [d] Analysis of variance. Bartlett's test for equal variances ($P = 0.006$). Median and interquartile range (IQR) were used for continuous variables. Number and percentage (%) were used for categorical variables. Body mass index, BMI; crosslinked C-telopeptide of type II collagen, CTX-II; radiographic knee osteoarthritis (Kellgren/Lawrence grade≥2), RKOA. Bone mineral density, BMD.

Table 2. Multivariable logistic regression models identifying the predictors of RKOA in women after 4 years of follow-up.

Intercept and predictors (reference category)	Clinical model — % retained; OR (95% CI)	Radiographic model — % retained; OR (95% CI)
Intercept	2.64×10^{-5}	8.79×10^{-6}
Age, years	91%; 1.06 (1.02, 1.10)	78%; 1.07 (1.02, 1.12)
Quadriceps circumference, cm*	94%; 1.11 (1.06, 1.17)	91%; 1.09 (1.03, 1.15)
CTX-II tertiles‡, ng/mL (52.7–133.1)		
≥229.9 ng/mL	85%; 1.89 (1.13, 3.14)	—
Presence of pain* (No)		
Yes	—	73%; 1.70 (0.99, 2.90)
Baseline knee K/L grade* (grade 0)		
Grade 1	—	100%; 6.54 (3.62, 11.83)
Contralateral knee with RKOA at baseline* (No)		
Yes	—	95%; 2.97 (1.65, 5.33)
Hip α-angle, degrees*	—	95%; 1.02 (1.01, 1.03)
Z score BMD at the spine L1-L4	—	93%; 1.32 (1.06, 1.64)
AUC	**0.699**	**0.809**
Optimism	**0.7**	**1.2**
Bias-corrected AUC	**0.692**	**0.797**

"Retained" indicates how often, as a percentage, a variable was retained in the final model after 200 bootstrapping attempts. * Side level. ‡*133.2 – 229.8 ng/mL* of urine CTX-II was

retained only 3% of the time and was not considered for prediction. Body mass index, BMI; crosslinked C-telopeptide of type II collagen, CTX-II; odds ratio, OR; confidence interval, CI; Kellgren/Lawrence, K/L; radiographic knee osteoarthritis (K/L grade≥2), RKOA; bone mineral density, BMD; area under the receiver characteristic curve, AUC.

Table 3. Risk score points system for identifying women at risk of developing RKOA in the next 4 years, created using predictor variables identified in the clinical model.

Baseline risk factor	Regression coefficient	Reference value	Risk score	Final risk score
Age, years	1.06			
44 to 48		46	4	0
49 to 51		50	5	1
52 to 66		59	6	2
Quadriceps circumference, cm*	1.11			
32 to 39		35.5	3	0
40 to 43		41.5	4	1
44 to 63		53.5	5	2
CTX-II tertiles (mcg/mL)ǂ	1.9			
0.0527 to 0.1331		0.09	1	0
0.1332 to 0.2298		0.18	3	2
0.2299 to 1.3381		0.78	14	13

Score of 0 indicates lowest risk and score of 17 indicates greatest risk (column "final risk score"). To work out your patient's risk 1. Find their measurement for each characteristic. 2. Circle the appropriate final risk score for each characteristic. 3. Add up the scores to give a total risk score. 4. Convert the risk score to a % probability by dividing the score by the maximum possible (17) and multiplying by 100. * Side level. ǂ Original values in nanograms/mL transformed to micrograms/mL, i.e. divided by 1000. CTX-II, crosslinked C-telopeptide of type II collagen; Radiographic knee osteoarthritis (K/L grade≥2), RKOA.

FIGURE LEGENDS

Figure 1. Flowchart showing selection criteria and numbers excluded at each stage of knees from women who developed knee osteoarthritis within 4 years.

Figure 2. Discrimination and calibration plots with bias-corrected AUC.

The upper panels show discrimination when using age, quadriceps circumference, and CTX-II as predictors of incident RKOA (clinical model; left panel), and when using age, quadriceps, painful knee, and radiologic factors as predictors (radiographic model; right panel). The area under the solid line and above the dotted line (line of no-discrimination) indicates the ability of the model to predict whether patients will develop RKOA within 4 years. The lower panels show the calibration of the imputed development dataset for the clinical (left) and radiographic model (right) models. The sample used for validation was divided into ten equal parts, according to their predicted risk. For each decile, the mean predicted risk is shown on the x-axis and the mean observed cases on the y-axis. The bars indicate 95% Agresti–Coull confidence intervals. The red straight line indicates perfect agreement between the observed and predicted values.

Area under the receiver characteristic curve, AUC; urine crosslinked C-telopeptide of type II collagen, CTX-II; radiographic knee osteoarthritis (Kellgren/Lawrence grade≥2), RKOA.