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Nottingham knee osteoarthritis risk prediction models

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ABSTRACT

Objectives (1) To develop risk prediction models for knee osteoarthritis (OA) and (2) to estimate the risk reduction that results from modification of potential risk factors.

Method This was a 12-year retrospective cohort study undertaken in the general population in Nottingham, UK. Baseline risk factors were collected by questionnaire. Incident radiographic knee OA was defined by Kellgren and Lawrence (KL) score ≥ 2 . Incident symptomatic knee OA was defined by KL ≥ 2 plus knee pain. Progression of knee OA was defined by KL ≥ 1 grade increase from baseline. A logistic regression model was used for prediction. Calibration and discrimination of the models were tested in the Osteoarthritis Initiative (OAI) population and Genetics of Osteoarthritis and Lifestyle (GOAL) population. ORs of the models were compared with those obtained from meta-analysis of existing literature.

Results From a community sample of 424 people aged over 40, 3 risk prediction models were developed. These included incidence of radiographic knee OA, incidence of symptomatic knee OA and progression of knee OA. All models had good calibration and moderate discrimination power in OAI and GOAL. The ORs lied within the 95% CIs of the published studies. The risk reduction due to modifying obesity at the individual and the population levels were demonstrated.

Conclusions Risk prediction of knee OA based on the well established, common modifiable risk factors has been established. The models may be used to predict the risk of knee OA, and risk reduction due to preventing a specific risk factor.

Knee osteoarthritis (OA) is the most common form of chronic joint disease and the leading cause of lower limb disability in older patients.¹ Although there are more than 50 treatments for symptomatic relief, the benefits of these treatments are only marginal over placebo,^{2–4} and often outweighed by their side effects.^{2–4} Currently there is no effective treatment for structure modification. The majority of patients have to cope with the disease for most of their lives, and even of those who undergo total joint replacement, 6% to 30% still have persistent knee pain after the surgery.^{5–8} At present, established symptomatic OA is a chronic, disabling and incurable condition.

In contrast, research in the past two decades into the epidemiology of knee OA has identified opportunities for primary and secondary disease prevention.⁹ A number of risk factors for development of knee OA have been confirmed.¹⁰ For the purpose of prevention, they may be classified into non-modifiable (eg, age, gender, genetic susceptibility/family history) and potentially modifiable risk

factors (eg, body mass index (BMI), occupational risk, joint injury, quadriceps weakness, nutrients, bone mineral density and oestrogen deficiency).⁹ Some new risk factors have been recently identified such as the longer ring finger (2D:4D ratio),^{11–12} varus/valgus mal-alignment^{13–14} and genetic pre-disposition^{15–16} but many of these have yet to be ratified.

This project aimed to develop conventional risk prediction models for knee OA. The objectives were to: (1) establish (development and validation) risk prediction models for the development and progression of knee OA focusing on the conventional and modifiable risk factors and (2) estimate the risk reduction consequent upon successful modification of a single or multiple risk factors at the individual and population levels. To the best of our knowledge, such conventional risk prediction models, although well established in cardiovascular and cancer research,^{17–18} have not been developed for OA.

METHODS

Development

Study design and setting

A 12-year retrospective cohort study was undertaken involving four general practices in North Nottinghamshire. The study was approved by the Nottinghamshire County Primary Care Trust, Nottingham University Hospitals NHS Trust and the Nottingham Research Ethics Committee 1.

Participants

Individuals were recruited from two baseline community postal questionnaire studies for knee pain.^{19–20} Baseline data were collected between 1996 and 1999 from 9429 adults aged 40–79 on the general practice registers. A follow-up survey was undertaken during 2007–2008 in 5479 individuals who are still registered with the general practices and eligible for the study. People with terminal illness, psychiatric illness and severe dementia were excluded. Radiographs of both knees at baseline and follow-up were obtained from 424 participants according to availability and willingness to participate through informed, written consent.

Definitions of incident knee OA and progression

Baseline and follow-up tibiofemoral and patellofemoral radiographs were taken using the same protocol (standing posteroanterior and skyline views) and scored by a single, experienced observer (SAD) as a single batch. Those with a Kellgren and Lawrence (KL) score²¹ < 2 for the tibiofemoral compartment and equivalent categories (ie, completely normal, possible osteophyte or doubtful narrowing) for the patellofemoral compartment of both

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knees at baseline and follow-up were defined as non-OA. Those that satisfied the definition of KL score ≥ 2 or equivalent for any compartment of any knee were defined as knee OA. Participants with no knee OA at baseline, who had knee OA at follow-up were defined as incident knee OA. Also, those with incident knee OA and concurrent knee pain were defined as symptomatic knee OA. Those with knee OA at baseline and an increase of 1 or more in KL score or equivalent at follow-up in any of their knee compartments were defined as knee OA progression.

Risk prediction model

Logistic regression was used for each prediction.²²

$$\text{Logit} = \ln(p/1-p) = \alpha + \beta_1 X_1 + \dots + \beta_i X_i \quad (1)$$

where p is the probability of the disease, α is the constant and β is the logarithm value of OR for a specific predictor X_i . For convenient prediction, we kept age and BMI as continuous variables and others as dichotomous or categorical variables. The logit operator maintains the linearity of the model and allows the calculation of a probability of disease given the different sets of predictors, according to²²:

$$p = \frac{e^{\text{logit}}}{e^{\text{logit}} + 1} \quad (2)$$

Selection of the predictors

For the purpose of the risk prediction and modification, we focused on well established conventional predictors age (years), gender (0=male, 1=female) and modifiable predictors, such as, BMI (kg/m^2), occupational risks (0–4), previous knee injury (0=no, 1=yes) and familial OA (0=no, 1=yes). Occupational risk was scored retrospectively from work performed during the last 12 years. We were particularly interested in occupational kneeling and lifting; each of these was scored as 0=never, 1=seldom, 2=sometimes, 3=often, 4=always and the highest value was taken. Familial OA was determined at follow-up and scored as positive if participants reported parents, siblings or grandparents having a diagnosis of OA, having undergone arthroplasty of the knee or hip, or if they were reported to have Heberden's nodes (0=no, 1=yes). Knee injuries up to follow-up were included (0=no, 1=yes). Sport activity during the last 12 years was defined as regular leisure activity such as golf, tennis, cricket, ballroom dancing, aerobics, hiking and walking, etc. Knee pain during the last 12 years was defined as pain in or around a knee on most days for at least a month. Knee pain was not used as a predictor, but part of outcome measures for knee OA.

Validation

Calibration and discrimination

Calibration and discrimination abilities¹⁷ of the models were examined in three populations: (1) the Nottingham knee OA retrospective cohort study population ($n=424$); (2) the Nottingham Genetics of Osteoarthritis and Lifestyle (GOAL) case-control study population ($n=3174$)¹¹ and (3) the Osteoarthritis Initiative (OAI) cohort study population ($n=4796$).²³

Calibration assesses how closely the predicted probabilities reflect actual risk. A risk score was calculated for each individual using equation (1). The higher the risk score the greater the risk of disease. The individuals were classified into different groups (deciles) according to the risk scores. Observed and predicted frequencies of the disease in subgroups were calculated. The Hosmer–Lemeshow χ^2 statistics for goodness-of-fit were used for calibration to compare observed and predicted risk deciles; and small values indicate good calibration.²⁴

Discrimination examines the ability to correctly classify subjects into different groups. To assess this parameter, the area under the receiver operating characteristic (ROC) curve was used. ROC presents a curve of sensitivity (y axis) against 1–specificity (x axis) at different cut-off points of the risk score. Larger values of the ROC indicate better discriminative power.²⁵

Systematic review

Systematic literature reviews and meta-analyses were undertaken for three major modifiable risk factors: BMI,²⁶ occupational risk²⁷ and knee injury. Data were extracted by at least two investigators and disagreements were discussed and ratified. The purposes of these reviews were: (1) to further validate the model estimate in the context of the general relative risk and 95% CI pooled from the literature and (2) to calculate risk reduction at the population level using pooled relative risk estimates. Pooled ORs from cohort studies were used for the comparison and the risk reduction estimation.

Risk reduction

The risk reduction was estimated for individuals using the models; and the populations using population attributable risk percentage (PAR%). PAR% is the proportion of people with knee OA that would have been avoided, should the risk factor(s) be modified.⁹ It is calculated by $\text{PAR}\% = P_e(\text{OR}-1)/(P_e(\text{OR}-1)+1) \times 100\%$, where P_e is the prevalence of risk factor (eg, obesity), and OR is the odds ratio or relative risk of the disease associated with the risk factor. We used pooled OR from the systematic review of cohort studies to calculate the PAR%.

RESULTS

Population characteristics

Development

In total, 424 people participated in radiographic examinations at baseline and follow-up. The sample had mean age of 56.8 years (SD 7.9), 64% women, mean BMI of 25.5 (SD 3.5) and 56% people with knee pain. The sample was slightly younger and lighter, had more women and people with knee pain than the source population.²⁸ The median (IQR) time period of follow-up was 12 years (7–12 years). Incident knee OA was seen in 55% (99/179) of patients and progression was found in 67% (75/112).

Validation

In addition to the internal population, two external populations were used for the model validation: OAI and GOAL. The characteristics are compared in table 1.

Table 1 Comparison between internal and external groups

| | Internal | OAI | GOAL |
|--------------------------------|----------------------|----------------|--------------------|
| Study design | Retrospective cohort | Cohort | Case-control study |
| N | 424 | 4796 | 3170 |
| Age, mean \pm SD | 56.8 \pm 7.9 | 61 \pm 9 | 66.6 \pm 7.9 |
| BMI, mean \pm SD | 25.5 \pm 3.5 | 28.6 \pm 4.8 | 29.3 \pm 5.3 |
| Women, n | 64% | 42% | 48% |
| Occupational risk median (IQR) | 3 (2–4) | 2 (1–3) | 1 (1–3) |
| Percentage injury | 12% | 41% | 22% |
| Percentage familial OA | 32% | 20% | Not known |

Age and BMI presented as mean and SD. Occupational risk presented as median and IQR and others presented as percentage prevalence. Knee injury was defined in OAI as an injury that limited walking for at least 7 days. BMI, body mass index; GOAL, Genetics of Osteoarthritis and Lifestyle; OA, osteoarthritis; OAI, Osteoarthritis Initiative.

The OAI study is a community-based cohort study for knee OA in higher risk population.²³ For incident knee OA in OAI, doctor-diagnosed knee OA was used as the end point as radiographic assessment had not yet been performed at follow-up. The OAI population we used for analyses contained 1489 people, and 162 were diagnosed as having knee OA during 36 months of follow-up. Kneeling, squatting and lifting at work were used to estimate occupational risk factors; and familial knee OA was estimated by relatives undergoing arthroplasty. The GOAL study was a hospital-based case-control study of low limb large joint OA. Participants had clinically severe knee OA sufficient to warrant consideration of total knee replacement (TKR)¹¹; GOAL had 1385 with knee OA (from the index knee OA and hip OA groups) and 1125 without knee OA (from the control and index hip OA groups). The assessment of risk factors in GOAL was broadly similar to the internal population.

Risk prediction models

Three risk prediction models have been developed, two for the incidence and one for the progression of knee OA:

1. Incidence of radiographic OA (KL \geq 2)

$$\text{Logit} = -7.542 + 0.055 \text{ age} + 0.2 \text{ female} + 0.105 \text{ BMI} + 0.3 \text{ occupational risk} + 0.42 \text{ family history} + 0.673 \text{ knee injury} \quad (\text{model 1})$$

2. Incidence of symptomatic knee OA (KL \geq 2 and current pain in the same knee)

$$\text{Logit} = -7.733 + 0.056 \text{ age} + 0.029 \text{ female} + 0.089 \text{ BMI} + 0.245 \text{ occupational risks} + 0.543 \text{ family history} + 0.870 \text{ knee injury} \quad (\text{model 2})$$

3. Progression of knee OA (KL increased \geq 1 grade)

$$\text{Logit} = 2.804 - 0.061 \text{ age} - 0.066 \text{ female} + 0.818 \text{ knee injury} + 0.877 \text{ sports} + 0.435 \text{ OA compartments} \quad (\text{model 3})$$

Definitions of the predictors are illustrated in table 2.

Validation

Calibration

The Hosmer–Lemeshow χ^2 statistics for goodness-of-fit showed good calibration internally and externally for all three models (table 3).

Discrimination

The area under the ROC curve for internal cohort showed a moderate discriminative ability of model 1 (ROC 0.69, 95%

CI 0.62 to 0.76). Similar but slightly better discriminative ability was seen for models 2 and 3 (table 3). In the external populations, the models demonstrated moderate discriminative power to predict the incidence and progression of knee OA in the OAI population and stronger discriminative power to separate knee OA in the GOAL population (figure 1).

Comparison between the models and meta-analysis of other cohort studies

ORs for BMI, occupation risk and knee injury estimated from the model were compared with those obtained from the literature. The OR estimated from the model tended to be smaller than that from the published cohort studies, but the 95% CIs were overlapping (table 4).

Risk reduction

Individual risk reduction

The risk reduction varied depending on the risk factor(s) to be modified. For example, a woman aged 50 with BMI 30, seldom kneeling/lifting, no family history of OA and no knee injury had a risk of 24% to develop knee OA in 12 years. By reducing BMI to 25, the risk would reduce to 16%. These may be calculated using equation (2).

Population risk reduction

Our systematic review showed that for obese individuals pooled OR for radiographic and symptomatic knee OA were 3.36 (95% CI 2.74 to 4.13) and 3.98 (95% CI 2.77 to 5.71), respectively.²⁶ These pooled estimates and country-specific obesity

Table 2 Definition of predictors

| Predictor | Definition | Model application |
|--|---|---------------------------|
| Age | Age in years | Incidence and progression |
| Gender | Female=1, male=0 | Incidence and progression |
| Body mass index | kg/m ² | Incidence |
| Occupational risks | Kneeling/lifting at work: 0=never, 1=seldom, 2=sometimes, 3=often, 4=always | Incidence |
| Family osteoarthritis | First-degree relative with osteoarthritis, joint replacement, or finger nodes=1. None=0 | Incidence |
| Knee injury | Previous serious knee injury=1. No injury=0 | Incidence and progression |
| Knee pain | Pain in or around a knee on most days for at least a month=1, no knee pain=0 | Progression |
| Sports | Regular physical activity (eg, golf, tennis, cricket)=1, none=0 | Progression |
| Number of knee compartments with osteoarthritis (OA) | Knee compartments with radiographic OA (1–4) | Progression |

Table 3 Validation of the risk prediction models

| | Calibration: Hosmer–Lemeshow χ^2 (p value) | | | Discrimination: ROC (95% CI) | | |
|-------------------------------|---|---------------|---------------|------------------------------|---------------------|---------------------|
| | Internal | OAI | GOAL | Internal | OAI | GOAL |
| Incidence | | | | | | |
| Model 1: radiographic knee OA | 2.29 (0.971) | 7.59 (0.576) | 9.87 (0.362) | 0.69 (0.62 to 0.76) | 0.60 (0.55 to 0.64) | 0.74 (0.72 to 0.76) |
| Model 2: symptomatic knee OA | 11.76 (0.162) | 16.86 (0.051) | 8.231 (0.511) | 0.70 (0.61 to 0.79) | 0.60 (0.58 to 0.63) | 0.79 (0.77 to 0.81) |
| Progression | | | | | | |
| Model 3: radiographic knee OA | 12.01 (0.151) | 11.66 (0.233) | NA | 0.71 (0.61 to 0.82) | 0.52 (0.45 to 0.58) | NA |

NA: models for knee OA progression could not be tested in the GOAL study due to its cross-sectional nature.

GOAL, Genetics of Osteoarthritis and Lifestyle; OA, osteoarthritis; OAI, Osteoarthritis Initiative; ROC, receiver operating characteristic.

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Table 4 Comparison of OR and 95% CI for knee osteoarthritis (OA) between the model and the meta-analyses of cohort studies from literature

| | OR (95% CI) | |
|--------------------------|---------------------|---------------------|
| | Model 1 | Literature* |
| BMI (kg/m ²) | | |
| Normal (<25) | 1 | 1 |
| Overweight (25–29.9) | 1.29 (0.71 to 2.33) | 1.94 (1.63 to 2.31) |
| Obese (≥30) | 1.88 (1.20 to 2.96) | 3.17 (2.40 to 4.19) |
| Occupational risk | 1.35 (1.05 to 1.73) | 1.45 (1.16 to 1.81) |
| Knee injury | 1.96 (0.98 to 3.92) | 3.15 (1.52 to 6.52) |

*Three independent meta-analyses for body mass index (BMI), occupational risk and knee injury were undertaken and the details will be reported elsewhere.

Table 5 Population attributable risks for knee osteoarthritis (OA) associated with obesity (BMI >30 kg/m²)

| Country | Prevalence of obesity* | Radiographic KOA PAR% (95% CI) | Symptomatic KOA PAR% (95% CI) |
|-------------|------------------------|--------------------------------|-------------------------------|
| USA | 33.8 | 44.4 (37.0 to 51.4) | 50.2 (37.4 to 61.4) |
| Australia | 24.8 | 36.9 (30.1 to 43.7) | 42.5 (30.5 to 53.9) |
| UK: England | 24.5 [†] | 36.6 (29.9 to 43.4) | 42.2 (30.2 to 53.6) |
| Germany | 20.8 | 32.9 (26.6 to 39.4) | 38.3 (26.9 to 49.5) |
| Norway | 18.3 | 30.1 (24.1 to 36.4) | 35.2 (24.4 to 46.2) |
| Morocco | 15.0 | 26.1 (20.6 to 31.9) | 30.8 (20.9 to 41.3) |
| Spain | 14.6 | 25.6 (20.3 to 31.4) | 30.3 (20.5 to 40.7) |
| Finland | 14.2 | 25.1 (19.8 to 30.8) | 29.7 (20.1 to 40.1) |
| Sweden | 12.9 | 23.3 (18.3 to 28.8) | 27.8 (18.6 to 37.8) |
| Netherlands | 10.3 | 19.5 (15.1 to 24.3) | 23.4 (15.4 to 32.6) |
| Thailand | 6.9 | 14.0 (10.7 to 17.8) | 17.1 (10.9 to 24.5) |
| China | 2.9 | 6.4 (4.8 to 8.3) | 8.0 (4.9 to 12.0) |

*Prevalence estimates obtained from International Obesity Task Force.²⁹

[†]Average obesity prevalence from England.

BMI, body mass index; KOA, knee osteoarthritis, PAR%, population attributable risk percentage.

prevalence²⁹ were used to calculate PAR% (table 5), in the USA where the prevalence of obesity in the population is estimated at 34%, PAR% for radiographic and symptomatic knee OA was 44% and 50%, respectively.

DISCUSSION

Several studies have claimed risk prediction models in OA^{30–32} but, apart from one examining blood levels of vascular cell adhesion molecule 1 as a predictor at baseline for total hip/knee replacement in 15 years,³⁰ all others in fact are not prediction but classification models of the disease.^{31–32} This is the first study to develop risk prediction models in knee OA using conventional risk factors such as age, gender, family history, BMI, occupational risk and joint injury. The models were developed from a 12-year retrospective community cohort study, and therefore they are suitable for the general population. Two models for the incidence of radiographic and symptomatic knee OA, and one model for the progression of radiographic knee OA were developed. Knee pain was treated as part of the disease outcome, not a predictor to keep the models simple and easy to use. Further development may be made in the future for the prediction model for the progression of symptomatic knee OA taking into account of knee pain and radiographic change at baseline. The models have been validated in three different populations with reasonable calibration and discriminative abilities. Better discrimination in the GOAL population, a hospital-based case-control study, suggests that the models have good discrimination power between established hospital cases and controls. However, these are not

classification models, and therefore should not be used for the purpose of the clinical diagnosis or classification of the disease. The latter should follow the established diagnostic algorithm³³ or classification criteria³⁴ as appropriate.

The generalisability of the models has been further examined by comparing relative risk estimates with those obtained by meta-analysis of published literature. The smaller relative risk estimates derived from the models may be caused by adjustments for multiple covariates and also population variations.

There are some differences between the incidence models (model 1 and 2) and the progression model (model 3). While age, gender, BMI, occupational exposure, family history and knee injury are the major positive predictors for the incidence of knee OA, number of compartments affected, knee injury and sport activities predict the progression. OA in older age and female gender is less likely to progress. BMI is not predictive for the progression (model 3). These suggest the aetiological differences between the development and the progression of knee OA.

Several differences between populations may affect the results of the validation. OAI is a rheumatology cohort study, which measured most of the predictors in a compatible way to the Nottingham cohort. The data from OAI are currently most suitable for validation of radiographic OA progression models, as baseline and follow-up radiographs for these patients have been assessed by the same research team as part of a single project. The follow-up radiographs in OAI for those without knee OA at baseline have not yet been assessed, and so we used self-reported doctor diagnosis of incident knee OA as our end point for validation purposes. OAI will assess them at a later time point and further validation will be undertaken once the data become available. In addition, OAI used a study population at high risk of knee OA and only measured tibiofemoral OA, whereas Nottingham measured tibiofemoral and patellofemoral OA. GOAL is only suitable for classification, not prediction of the disease as it is a case-control study and the population was selected from hospital lists with clinically severe knee OA sufficient to warrant consideration of TKR. Population differences are always a potential problem for the risk prediction. It is therefore suggested that a validation/modification should be undertaken before applying any risk prediction model.³⁵

There are several limitations to this study. First, the internal cohort was small (424) and it was not a random sample of the general population. Participants were slightly younger and lighter, had more smokers and people with knee pain than the source population. Therefore this may limit the model's generalisability. Although we have undertaken multiple validations in different populations, further validation is required prior to the use of the Nottingham models. Second, only conventional predictors (such as age, gender, family history, BMI, occupational risk and knee injury) have been included. Many others such as quadriceps weakness, oestrogen deficiency, genetics or biomarkers may be added. Third, several of the predictors from the internal cohort were measured retrospectively, by asking about the last 12 years of life. Occupation was assessed only during the last 12 years, whereas knee injury included all previous time. Family history of OA was self-reported and so open to recall or measurement bias. Fourth, the risk factors for tibiofemoral and patellofemoral OA are likely to differ. However, the size of this study was insufficient to discriminate between the two major sites of knee OA, without losing statistical power. Furthermore, BMI is the only risk factor that may be directly modified, others (occupational risk and injury) are theoretically modifiable but practically difficult to change. Prevention or indirect modification

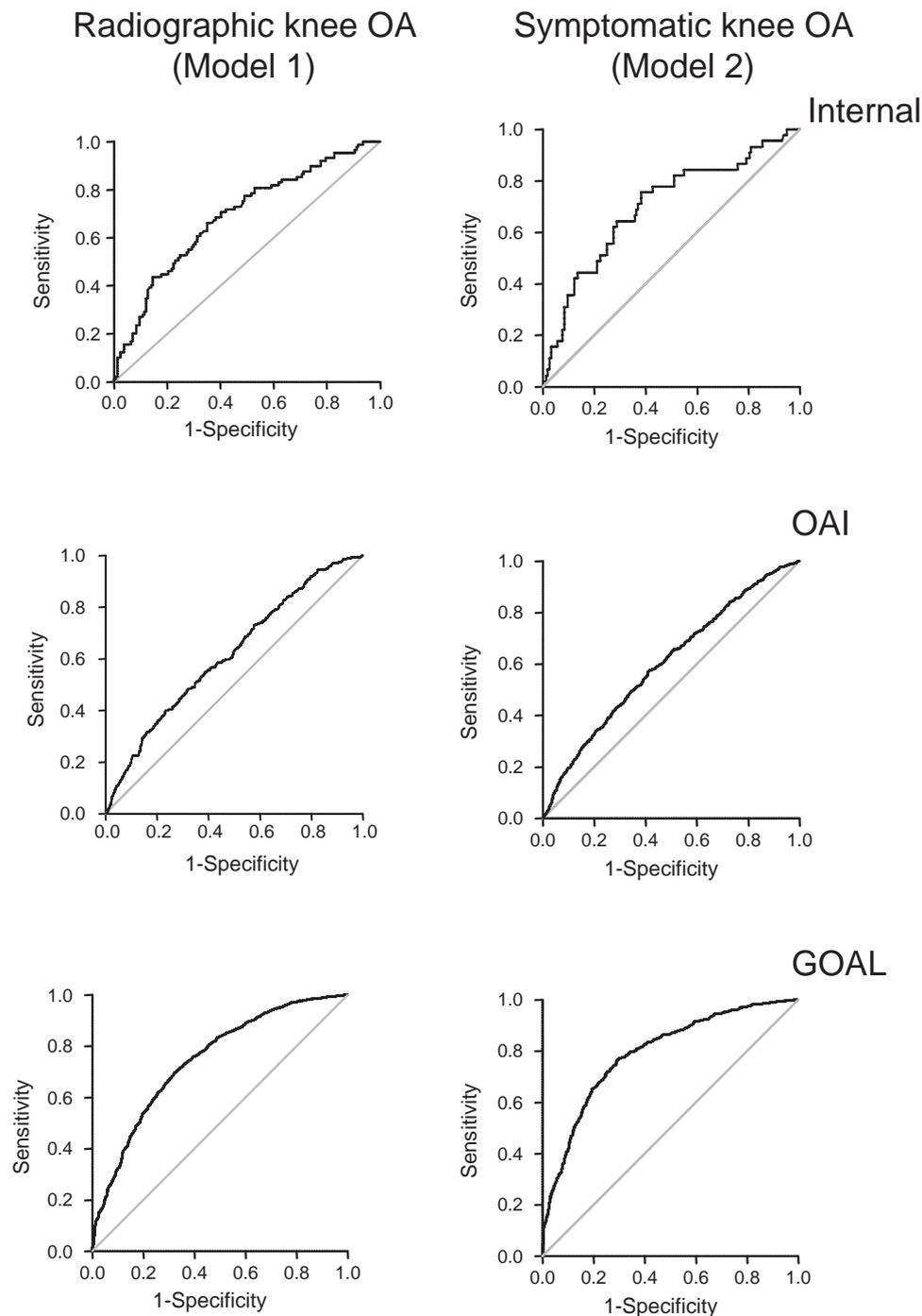


Figure 1 Receiver operating characteristic (ROC) curves for radiographic (model 1) and symptomatic (model 2) knee osteoarthritis (OA). Areas under the ROC curve and 95% CIs were 0.69 (0.62 to 0.76) and 0.70 (0.61 to 0.79) in the Nottingham knee OA retrospective cohort (internal), 0.60 (0.55 to 0.64) and 0.60 (0.58 to 0.63) in the Osteoarthritis Initiative (OAI) population, and 0.74 (0.72 to 0.76) and 0.79 (0.77 to 0.81) in the Genetics of Osteoarthritis and Lifestyle (GOAL) study. The grey line indicates level of prediction by chance alone.

of these risk factors, for example, via protection of knees from the exposures, is a challenge in practice.

In conclusion, we have developed and validated three conventional risk prediction models for the development and progression of knee OA based on a 12-year retrospective cohort study. It is our hope that these models are not to be used as gold standards for knee OA prediction, but as pilots to lead further research in this area. The models may be applied at the individual level to predict the risk, and to encourage risk reduction. They may also be used at the population level,

with reference to other relative risks from published studies, to estimate the potential population risk reduction that may be gained by primary prevention of the major risk factors of knee OA.

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Competing interests None.

Ethics approval This study was conducted with the approval of the Nottingham University Hospitals NHS Trust and the Nottingham Research Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

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