ORIGINAL RESEARCH

Predicting Knee Pain and Knee Osteoarthritis Among Overweight Women

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Background: **There is a need for prediction of knee osteoarthritis (KOA) in general practice to motivate subjects for preventive therapies and optimize preventive trials.**

Aim: **To develop a prediction model, with questionnaire and physical examination variables, for incident frequent knee pain (FKP) and symptomatic KOA after 2.5 and/or 6.5 years among overweight and obese middle-aged women.**

Design and Setting: **Models were developed in the Prevention of Knee Osteoarthritis in Overweight Females study (age 50 to 60 years, body mass index [BMI] ≥ 27 kg/m^2) (ISRCTN 42823086). FKP was defined as knee pain during most days in the past month. Symptomatic KOA was defined according to the combined (clinical and radiographic) American College of Rheumatology criteria.**

Method: **Multivariable analysis by backward stepwise deletion was performed for questionnaire and physical examination variables. The prediction model was externally validated in Rotterdam Study (RS)–III. Area under the curves (AUCs) of receiver operating characteristic were calculated.**

Results: **32% of 237 women (mean age 55.7 ± 3.2 years; mean BMI, 31.9 ± 3.8 kg/m^2) developed FKP and 30% developed symptomatic KOA. AUC of age and BMI was 0.63 (0.55 to 0.71) for incident FKP. The final model included age, BMI, mild knee symptoms, knee problems climbing stairs, morning stiffness, postmenopausal status, and heavy work. AUC was 0.71 (0.63 to 0.78). Results were similar for incident KOA. Applying external validation, similar results were observed in the RS-III.**

Conclusion: **In this study, easy-obtainable variables modestly improved the prediction of FKP and symptomatic KOA above age and BMI. To improve the identification of high-risk individuals, development of valid tests for other known risk factors, like meniscal damage, that are applicable in primary care, are urgently needed. (J Am Board Fam Med 2019;32:575–584.)**

Keywords: **Body Mass Index, Chronic Disease, Netherlands, Obesity, Osteoarthritis of Knee, Pain, Primary Health Care, Rheumatology**

Frequent knee pain (FKP) and knee osteoarthritis (KOA) are common complaints in general practice and constitute a substantial workload.[1,2] Knee pain affects ± 25% in those over 55 years of age; more women than men.[1] KOA is the most frequent diagnosis associated with FKP in older people.[3]

In primary care, attention for prevention of diseases is common. Due to the large individual and

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socioeconomic burden of KOA and FKP, there is growing interest in early detection and prevention.[1,4] Although overweight is one of the most important risk factors, other factors might also predict FKP or symptomatic KOA.[5] Identification of high-risk subjects is necessary for 2 reasons. First, to offer and motivate them for preventive strategies such as changes in lifestyle and in occupational habits. Heightening risk appraisals might change people's intentions and behavior, as shown in literature,[6] without leading to unintended adverse effects.[7,8] Second, identification is necessary to optimize preventive trials in osteoarthritis (OA) research in a most cost-effective manner by including subjects in a study who are at highest risk of developing FKP/KOA on a short term.

Several studies have investigated prediction of KOA.[9–11] Zhang et al[10] developed a model with conventional and modifiable risk factors for the prediction of symptomatic radiographic KOA in a general population aged 40 to 70 years. This model, incorporating age, gender, body mass index (BMI), occupational kneeling/lifting, family history, and knee injury, resulted in an area under the curve (AUC) of 0.70.[10] Kerkhof et al[9] developed a model for the prediction of radiographic KOA in a general population aged 55 years and over, incorporating age, gender, BMI, questionnaire variables, genetic score, a urinary biomarker, and radiographic signs of possible osteophytes (Kellgren and Lawrence [KL]) grade 1[12]). Questionnaire variables, genetic score or a urinary biomarker did not improve prediction versus age, gender, and BMI (AUC, 0.66). The AUC increased to 0.79 by adding baseline KL 1.[9] Sharma et al[11] developed a model for prediction of radiographic KOA among persons at higher risk for KOA but with KL 0 in both knees (no radiographic KOA). They found that Magnetic Resonance Imaging (MRI) lesions in tissues known to be involved in KOA improved prediction when added to models including age, gender, BMI, hand OA, injury, surgery, occupational activity, and knee symptoms or function (AUC, 0.84).[11]

For a general practitioner (GP) however, the use of easily obtainable variables without the need for additional laboratory or radiologic assessments is highly preferable. It is known that the most important risk factors for incident knee pain/symptomatic KOA are older age, female gender, and overweight/obesity. However, even in such a high-risk population, not all women develop KOA, as shown by the preventive trial of Runhaar et al.[13] Therefore, it would be interesting to investigate predictors within such a high-risk group.[14] In addition, up to now, no studies have evaluated prediction of FKP, while this symptom is more important for patients than the underlying pathology (structural KOA).[15,16]

Therefore, the objective of this study was to develop a risk prediction model for the development of FKP and symptomatic KOA in general practice among overweight middle-aged women incorporating questionnaire and physical examination variables.

Method

Study Design and Population

We used data from the Prevention of Knee Osteoarthritis in Overweight Females (PROOF) study,[13] a randomized controlled trial in general practices in the Rotterdam area, the Netherlands. PROOF evaluated the preventive effects of a tailor-made diet and exercise program and of oral glucosamine sulfate versus placebo on the development of KOA over 2.5 years in 407 overweight and obese women of 50 to 60 years (ISRCTN 42823086).[13] Post-hoc long-term outcome evaluation was performed over 6.5 years' followup (mean, 6.7 ± 0.7 years). The Institutional Review Board of Erasmus University Medical Center approved the study and participants gave written informed consent. Participants were recruited by their GP by sending study information and a reply card to all registered women between 50 and 60 years. They had to be free of KOA according to the clinical American College of Rheumatology (ACR) criteria.[17] Further inclusion criteria were BMI $\geq$ 27 kg/m^2, no inflammatory rheumatic diseases, no severely disabling comorbidities, not under treatment of a physical therapist or GP for knee complaints, not using walking aids, not using oral glucosamine for the past 6 months, and mastering of the Dutch language. At baseline, participants filled in a questionnaire and underwent standardized physical examination at the research institute. Baseline posterior-anterior radiographs of both knees were taken using the semiflexed metatarsophalangeal protocol.[18] Measurements were repeated after 2.5 and 6.5 years. Only women participating at 2.5 years were asked to participate at 6.5 years.

Risk Factor Assessment

Candidate predictors were selected on literature[14,19–21] and expert recommendation. They had to be easily obtainable through history taking or physical examination. We identified 16 relevant variables for the prediction of FKP (pain in or around 1 or both knees during most days in the past month[22]) and symptomatic KOA.

Questionnaire Variables

Age, assessed by questionnaire. Postmenopausal status was defined after 12 consecutive months of amenorrhoea. Depression was defined when diagnosed with depression or having depressive complaints during the previous 3 months. Family history of OA (self reported) was present when at least 1 first-degree relative had OA. Injury was defined when the women had ever visited a doctor for knee injury (no/yes). Physically demanding work was defined as doing heavy physical work "quite often" or "(almost) always." Mild knee symptoms were assessed using the question, "Did you experience any pain in or around your knee within the past 12 months?" (no/yes). Instability of the knee was assessed with the question, "Did you experience a sensation of the knee giving way within the past 12 months?"(no/yes). "Knee problems while climbing stairs" and "knee problems while standing up from a chair," defined with the Knee Injury and Osteoarthritis Outcome Score (KOOS) subscale on "Function, daily living,"[23] were present when the women had any (seldom/sometimes/often/always) physical limitation due to her knee while climbing stairs or standing up from a chair, respectively. Morning stiffness, evaluated with KOOS subscale on "Stiffness,"[23] was present when the women had moderate/much/very much knee joint stiffness after sleeping (vs no/little). Swelling of the knee, assessed with KOOS subscale on "Symptoms," was present when the women had any swelling of the knee during the last week. The cutoff points for the KOOS variables were based on their distribution, with 10% as lower limit.

Physical Examination Variables

Body height in standing position without shoes and weight were measured at baseline examination; BMI was calculated (kg/m^2). Both hands were examined for Heberden's nodes (no/yes). Both knees were examined for pain at palpation of the medial and lateral joint line (no/yes) and tested for crepitus[21] during active flexion and extension of the knee (no/yes).

Outcome Measure Assessment

Outcome measures were incident FKP and incident symptomatic KOA after 2.5 and/or 6.5 years. FKP was assessed by questionnaire ("Did you experience pain in or around 1 or both knees during most days in the past month?" [no/yes]). Incident FKP after 2.5 and/or 6.5 years was defined when present at 2.5 and/or 6.5 years and not present at baseline. Symptomatic KOA was defined according to the combined (clinical and radiographic) ACR criteria[17]: FKP and a definite tibiofemoral osteophyte in the same knee and one of the following: age >50 years, morning stiffness <30 minutes, crepitus on active knee motion. Incident symptomatic KOA after 2.5 and/or 6.5 years was defined when present at 2.5 and/or 6.5 years and not present at baseline.

Statistical Analysis

Analyses were done using the subject as unit of analysis. Descriptive data were presented as mean ± standard deviation (SD) or as counts (percentages). Age and BMI were kept continuous, other predictors were dichotomous. Preliminary analyses were conducted to ensure no violation of the multicollinearity assumption. Tolerance values were >0.6 for all predictors. For each outcome a binary logistic regression model was created with age and BMI (basic model). Next, all potential predictors were analyzed in a multivariable logistic regression model for each outcome. Backward stepwise deletion based on the Wald test was applied using a P value of .20, to reduce the number of predictors in the final model. Since study participants were part of a randomized trial, analyses were additionally run with adjustments for the original randomization groups and their interaction.[13] The Hosmer-Lemeshow χ^2 statistics for goodness-of-fit were used to compare observed and predicted risks. The explained variance was assessed by the Nagelkerke R^2. Discriminative ability was assessed with the AUC of the receiver operating characteristic. Analyses were performed with SPSS 21.0 (Chicago, IL). $P < .05$ were considered statistically significant.

External Validation

For external validation of the final model, data from the Rotterdam Study (RS) were used. The RS

is a population-based cohort study in the Netherlands that investigates determinants, incidence, and progression of chronic disabling diseases in the elderly.[24] We used data of the RS-III-1 subcohort. Apart from "physically demanding work," risk factor assessment was identical in the RS and in PROOF. In the RS, "physically demanding work" was defined as doing intense work (regularly lifting heavy objects at work) (no/yes) obtained with the Short Questionnaire to Assess Health-Enhancing Physical Activity (SQUASH[25]). Women aged 50 to 60 years with BMI $\geq$ 27 kg/m^2 were included for validation. Mean follow-up of RS-III-1 was 4.62 $\pm$ 0.56 years.[21] The medical ethics committee of Erasmus University Medical Center approved the study and participants provided written consent.

Results

Study Population

Thirty-six of 407 women (9%) with baseline FKP were excluded for analyses, and 134 of 371 women (36%) had missing data for baseline, 2.5, or 6.5 years FKP questions. Reasons were not completing the FKP questions (n = 7), unattainability (n = 8), no further time available or interest in the study (n = 114). Five women died (not related to the study outcomes). For the prediction of symptomatic KOA, 24 women (6%) were excluded due to baseline symptomatic KOA, and 148 of 383 women (39%) had missing data for FKP (n = 134) or for radiography data (n = 14).

Table 1 describes the baseline characteristics of both study populations. There were only 0.8% missing values of predictor variables. Dropouts based on missing outcome had a lower presence of "family history of OA" compared with those with complete outcome (35% vs 48% for FKP, 38% vs 49% for symptomatic KOA).

Seventy-five of 237 women (32%) developed FKP and 70 of 235 (30%) symptomatic KOA. Within those with incident FKP (n = 75), 93% (n = 70) had a tibiofemoral osteophyte ipsilateral, hence also fulfilled the combined ACR criteria. Given the large overlap between the 2 cohorts, the results of the incident symptomatic KOA cohort are presented in Appendix Table 1.

Risk Prediction Models

In the final model for incident FKP, the following predictors were selected based on our selection criteria: age, BMI, mild knee symptoms, knee problems while climbing stairs, morning stiffness, postmenopausal status, and physically demanding work (Table 2). When the analysis was additionally corrected for the original trial interventions and their interaction, minor nonrelevant changes were found (data not shown).

Internal Validation

Internal validation showed good calibration for the basic and final prediction model for incident FKP (Table 2). The basic model showed an AUC of 0.63 (0.55 to 0.71). Prediction improved in the final model to an AUC of 0.71 (0.63 to 0.78).

External Validation

In RS-III-1, 346 women were 50 to 60 years with BMI $\geq$ 27 kg/ m^2. Two hundred thirty-six of 346 women (68%) had data available for the prediction of FKP and 264 (76%) for the prediction of symptomatic KOA. In the FKP cohort (mean age, 55.4 $\pm$ 3.2 years; mean BMI, 30.8 $\pm$ 3.5 kg/m^2), 41 (17%) developed FKP. In the symptomatic KOA cohort (mean age, 55.5 $\pm$ 3.3 years; mean BMI, 30.9 $\pm$ 3.6 kg/m^2), 19 (7%) developed symptomatic KOA. The AUC for the prediction of FKP was 0.71 (0.62 to 0.79) (Table 3). For the prediction of symptomatic KOA, the AUC was 0.81 (0.72 to 0.90) (Appendix Table 2).

Discussion

Summary

We aimed to develop a risk prediction model for GPs with easily obtainable predictors for incident FKP and incident symptomatic KOA among overweight and obese middle-aged women. A basic model, with only age and BMI had little discriminative power. With the variables age, BMI, mild knee symptoms, knee problems while climbing stairs, morning stiffness, postmenopausal status, and physically demanding work, the AUC of the prediction model for incident FKP increased to 0.71 (0.63 to 0.78). Similar results were found for the prediction model of incident symptomatic KOA.

Comparison with Existing Literature

Besides age and BMI, several variables were selected in the final prediction model for FKP, among which mild knee symptoms, problems while

Table 1. Baseline Characteristics

Baseline Characteristics	Study Population for Incident Frequent Knee Pain[§§] (n = 237)	Study Population for Incident Symptomatic Knee OA[¶¶] (n = 235)
Questionnaire variables		
Age (years), mean (SD)	55.7 ± 3.2	55.8 ± 3.2
BMI (kg/m^2), mean (SD)	31.9 ± 3.8	31.9 ± 3.8
Postmenopausal status, n (%)	159 (67)	159 (68)
Comorbidity of depression*, n (%)	16 (7)	16 (7)
Family history of OA[†], n (%)	113 (48)	112 (48)
History of knee injury[‡], n (%)	46 (19)	47 (20)
Physically demanding work[§], n (%)	24 (10)	24 (10)
Mild knee symptoms[¶], n (%)	98 (41)	100 (43)
Feeling of giving way[‖], n (%)	35 (15)	37 (16)
Knee problems while climbing stairs**, n (%)	20 (8)	20 (9)
Knee problems standing up from chair**, n (%)	56 (24)	58 (25)
Morning stiffness[††], n (%)	29 (12)	29 (12)
Swollen knee[‡‡], n (%)	27 (11)	27 (11)
Physical examination variables		
Heberden's nodes (in ≥1 finger), n (%)	65 (27)	64 (27)
Joint line tenderness (medial and/or lateral), n (%)	26 (11)	25 (11)
Crepitus during active motion, n (%)	134 (57)	135 (57)

BMI, body mass index; N, number of women; OA, Osteoarthritis; SD, standard deviation.
*Comorbidity of depression was defined as being diagnosed with depression and/or currently under treatment.
[†]Present when at least one first-degree relative had OA.
[‡]Present when visited a doctor for a knee injury.
[§]Doing heavy physical work "quite often" or "(almost) always".
[¶]Pain in or around the knee within the last 12 months.
[‖]The sensation of the knee giving way within the last 12 months.
**Defined with the Knee Injury and Osteoarthritis Outcome Score (KOOS) on physical functioning.
[††]Defined with the KOOS on stiffness.
[‡‡]Defined with the KOOS on symptoms.
[§§]Incident frequent knee pain after 2.5 and/or 6.5 years was defined when frequent knee pain was present at 2.5 and/or 6.5 years and when no knee pain was reported at baseline. Frequent knee pain was defined as self-reported pain in or around one or both knees during most days in the past month.
[¶¶]Incident symptomatic knee OA after 2.5 and/or 6.5 years was defined when incident symptomatic knee OA was present at 2.5 and/or 6.5 years and not present at baseline. Symptomatic knee OA was defined according to the clinical and radiographic ACR criteria: self-reported frequent knee pain and a definite osteophyte in the tibiofemoral joint of the same knee and one of the following: age >50 years, morning stiffness <30 minutes, crepitus on active motion of the knee.

climbing stairs, morning stiffness, and physically demanding work. These factors are also found in other studies: the Osteoarthritis Initiative showed that pain during weight-bearing, knee-bending activities like climbing stairs, could be used to identify early OA.[26] In addition, studies showed that increased risk of chronic knee pain was found among occupations that involve knee bending and heavy lifting.[27,28] Recently, a proposal for classification criteria for early knee OA has been published, including stiffness as a symptom of early knee OA.[29] The incidence of developing FKP in the present study was 32%. This increases to 47% ("post-test") when knee problems while climbing stairs are present and to 52% when morning stiffness is present. None of the physical examination variables, except BMI, were selected in the final model. The only one study that evaluated physical examination variables for the prediction of KOA was the study by Sharma et al.[11] In their study, "Heberden's nodes" was selected in their final prediction model by selection of univariable significance ($P < .1$). Joint line tenderness and crepitus were not examined in their study.[11] Although our final model improved the basic model, the overall explained variance is still low and suggests that prediction of FKP (and symptomatic KOA) with easily obtainable risk factors seems not yet clinically applicable.

Table 2. Multivariable Models in Prediction of Incident Frequent Knee Pain and Internal Validation (Calibration and Discrimination) of the Risk Prediction Models

	Basic Model		Backward Model	
Selected Predictors	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age (years)	1.07 (0.98–1.16)	.16	**1.15 (1.03–1.28)**	**.02**
BMI (kg/m^2)	**1.09 (1.01–1.17)**	**.02**	**1.13 (1.04–1.23)**	**.004**
Mild knee symptoms*			1.74 (0.88–3.44)	.12
Knee problems while climbing stairs†			**2.06 (1.03–4.12)**	**.04**
Morning stiffness‡			**3.03 (1.17–7.81)**	**.02**
Postmenopausal status			0.57 (0.28–1.18)	.13
Physically demanding work§			2.05 (0.72–5.83)	.18
AUC of the model	0.63 (0.55–0.71)		0.71 (0.63–0.78)	
Calibration: Hosmer-Lemeshow *P* value	.72		.93	
Variance explained (Nagelkerke), %	4.6		21.0	

AUC, area under the curve of the receiver operating characteristic; BMI, body mass index; CI, confidential interval; OR, odds ratio. Bold indicates $P < .05$.
*Pain in or around the knee within the last 12 months.
†Defined with the Knee Injury and Osteoarthritis Outcome Score (KOOS) on physical functioning.
‡Defined with the KOOS on stiffness.
§Doing heavy physical work "quite often" or "(almost) always".

Incidence rates in the present study are higher than in population-based cohorts,[9,30] but comparable to rates found among overweight subjects.[31,32] In RS-III-1, incidence of FKP (17%) and symptomatic KOA (7%) was lower than in PROOF. This might be explained by lower baseline BMI and prevalence of mild knee symptoms in RS-III-1. In addition, no X-rays were performed during an intermediate assessment, as done in PROOF after 2.5 years. Hence, incidence was based on the outcome after ± 5 years. As seen in Appendix Table 2, we found a higher AUC in RS-III-1 (0.81 [0.72 to 0.90]) than in the PROOF study (0.72 [0.64 to 0.80]) for prediction of symptomatic KOA, due to the strong association between "knee problems while climbing stairs" and incident symptomatic KOA (OR, 4.47 [1.31 to 15.23]) in RS-III-1. In addition, the baseline prevalence of "knee problems while climbing stairs" was higher in RS-III-1 (30%) than in PROOF (9%). This both resulted in better prediction within RS-III-1.

Table 3. External Validation for the Prediction of Incident Frequent Knee Pain in Rotterdam Study-III-1

	Study Population (n = 236)	
Candidate Predictor	OR (95% CI)	*P* Value
Age (years)	1.01 (0.89–1.15)	.88
BMI (kg/m^2)	1.08 (0.98–1.18)	.13
Mild knee symptoms*	1.80 (0.84–3.87)	.13
Knee problems while climbing stairs†	2.14 (0.95–4.82)	.07
Morning stiffness‡	1.65 (0.66–4.16)	.29
Postmenopausal status	0.98 (0.36–2.69)	.96
Physically demanding work§	1.14 (0.49–2.66)	.76
AUC of the model	0.71 (0.62–0.79)	
Calibration: Hosmer-Lemeshow *P* value	.57	
Variance explained (Nagelkerke), %	12.2	

AUC, area under the curve of the receiver operating characteristic; BMI, body mass index; CI, confidential interval; OR, odds ratio.
*Pain in or around the knee within the last 12 months.
†Defined with the Knee Injury and Osteoarthritis Outcome Score (KOOS) on physical functioning.
‡Defined with the KOOS on stiffness.
§Defined as doing intense work (regularly lifting heavy objects at work).

Strengths and Limitations

With the PROOF study, the first preventive randomized controlled trial in KOA, the first steps in preventive research within a high-risk population for KOA, have been made.[13] The present study is directly applicable to GPs, since only easily obtainable variables were used for the prediction models and also a symptom-only definition was used. Moreover, models were externally validated, which confirmed our results.

There are also some limitations. High numbers lost to followup might have introduced selection bias. There were no significant differences in baseline variables compared with complete cases, except for a lower frequency of "family history of OA" in dropouts due to missing data (38% vs 49%). One could debate whether this difference is clinical relevant. An association between development of KOA and family history of OA has been described;[33] however, others could not confirm this.[34] Overall, we estimated the possibility of selection bias as minimal. As a solution for the missing data, multiple imputation was considered. However, as described in a article by Von Hippel et al,[35] multiple imputation is only the solution when the independent variables are missing at random. When the outcome is missing and the independent variables are complete, as in our study, the incomplete cases contribute no information to the outcome estimate and would only add noise to these estimates.[35] Second, a possible disadvantage of using an randomized controlled trial for prediction modeling is that there are set points for follow-up measurements, in the present study after 2.5 and 6.5 years. In this way, no difference can be made between participants who develop knee pain after a short or after a longer follow-up time. Ultimately, there might have been more use from a model that took "time to development of FKP/KOA" as the outcome of interest, but these data were not available. Further, the overlap between the prediction of both outcomes is large, since age >50 years and FKP are part of the definition of the combined ACR criteria.[17] To make prediction applicable to a GP's daily practice, we presented the symptom-only definition in the main text and the official definition for symptomatic KOA in the Appendix. By analyzing data on subject level, with the aim to predict for a person and not for a knee, details on knee level are lost. As a consequence, it might be possible that presented symptoms were in the other knee than the outcome. Significant associations might be noncausal. Since proving causality is not the aim in prediction analysis,[36] this seems not to affect results.

Implications for Research and/or Practice

Although incidence rates were relatively high after 6.5 years, the majority of women were free of FKP and symptomatic KOA. It might be worthwhile to obtain other variables that can discriminate in high-risk subjects. We did not include, for instance known risk factors for incident knee OA like malalignment, meniscal damage or effusion synovitis.[37–39] Those measures are obtained by radiologic assessments and not directly applicable in a GP's office. Surprisingly, no literature is available about the diagnostic accuracy of the clinical diagnosis of malalignment by a GP or the validity of knee specific questions for the diagnosis of synovitis. Diagnostic accuracy of the McMurray or Apley test for meniscal damage is small and not advised in general practice.[40] It seems necessary to improve the clinical diagnosis of the above risk factors in general practice or search for others.

This study showed that in middle-aged overweight women in general practice, the use of easily obtainable risk factors contributed moderately to prediction of FKP and symptomatic KOA. Since the discriminative ability of the prediction models was moderate, the prediction of FKP and symptomatic KOA seems not yet clinically applicable.

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Appendix Table 1. Multivariable Models in Prediction of Incident Symptomatic Knee Osteoarthritis (OA) and Internal Validation (Calibration and Discrimination) of the Risk Prediction Models

	Basic Model		Backward Model	
Selected Predictors	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age (years)	1.07 (0.98–1.17)	.15	**1.14 (1.02–1.28)**	**.02**
BMI (kg/m^2)	**1.12 (1.04–1.20)**	**<.01**	**1.16 (1.06–1.26)**	**.001**
Mild knee symptoms*			1.73 (0.85–3.49)	.13
Knee problems while climbing stairs†			**2.08 (1.03–4.23)**	**.04**
Morning stiffness‡			2.46 (0.97–6.25)	.06
Postmenopausal status			0.54 (0.26–1.12)	.10
Physically demanding work§			2.38 (0.83–6.83)	.11
AUC of the model	0.63 (0.54–0.71)		0.72 (0.64–0.80)	
Calibration: Hosmer-Lemeshow *P* value	.96		.20	
Variance explained (Nagelkerke), %	6.5		21.9	

AUC, area under the curve of the receiver operating characteristic; BMI, body mass index; CI, confidential interval; OR, odds ratio. Bold indicates $P < .05$.
*Pain in or around the knee within the last 12 months.
†Defined with the Knee Injury and Osteoarthritis Outcome Score (KOOS) on physical functioning.
‡Defined with the KOOS on stiffness.
§Defined as doing intense work (regularly lifting heavy objects at work).

Appendix Table 2. External validation for the prediction of incident symptomatic knee Osteoarthritis (OA) in Rotterdam Study-III-1

	Study Population (n = 264)	
Selected Predictors	OR (95% CI)	*P* Value
Age (years)	1.13 (0.93–1.37)	.22
BMI (kg/m^2)	1.09 (0.97–1.22)	.15
Mild knee symptoms*	1.53 (0.49–5.08)	.44
Knee problems while climbing stairs†	**4.47 (1.31–15.23)**	**.02**
Morning stiffness‡	2.14 (0.68–6.73)	.19
Postmenopausal status	1.33 (0.22–7.98)	.76
Physically demanding work§	1.50 (0.50–4.53)	.48
AUC of the model	0.81 (0.71–0.90)	
Calibration: Hosmer-Lemeshow *P* value	.17	
Variance explained (Nagelkerke), %	21.9	

AUC, area under the curve of the receiver operating characteristic; BMI, body mass index; CI, confidential interval; OR, odds ratio. Bold indicates $P < .05$.
*Pain in or around the knee within the last 12 months.
†Defined with the Knee Injury and Osteoarthritis Outcome Score (KOOS) on physical functioning.
‡Defined with the KOOS on stiffness.
§Defined as doing intense work (regularly lifting heavy objects at work).