EXTENDED REPORT

Development of radiological knee osteoarthritis in patients with knee complaints

B M de Klerk,[1] S Willemsen,[2] D Schiphof,[1] J B J van Meurs,[3 4] B W Koes,[1] A Hofman,[5] S M A Bierma-Zeinstra[1 6]

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[1]Department of General Practice, Erasmus University Medical Center, Rotterdam, The Netherlands
[2]Department of Biostatistics, Erasmus University Medical Center, Rotterdam, The Netherlands
[3]Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands
[4]Netherlands Genomics Initiative (NGI)-sponsored Netherlands Consortium for Healthy Aging (NCHA), Den Haag, The Netherlands
[5]Department of Epidemiology, Erasmus MC, Rotterdam, The Netherlands
[6]Department of Orthopaedics, Erasmus University Medical Center, Rotterdam, The Netherlands

Correspondence to
Bianca M de Klerk, Department of General Practice, Erasmus University Medical Center, P O Box 2040, 3000 CA Rotterdam, The Netherlands;
b.deklerk@erasmusmc.nl

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ABSTRACT

Objectives It is currently impossible to identify which patients with knee complaints presenting to the general practitioner will develop knee osteoarthritis (OA) pathology at a later stage. This study examines the determinants for developing OA pathology on x-ray in patients with knee complaints but no radiological OA at baseline in the painful knee.

Methods Data from the prospective Rotterdam cohort study (including subjects aged ≥55 years) were used. Analysis was performed on 623 subjects with knee complaints at baseline and their data at 6-year follow-up (T1; n=607) and at 11-year follow-up (T2; n=457). At baseline, none had radiological OA (rOA=Kellgren and Lawrence (KL) grade ≥2) in the painful joint. At follow-up, predictors for rOA were determined using multivariate ordinal logistic regression analysis.

Results At T1, 8.5% of the group had developed knee rOA and, by T2, this had increased to 23%. Determinants remaining significant in the multivariate analysis were female gender (OR 1.95, 95% CI 1.15 to 3.36), other joint complaints (OR 2.22, 95% CI 1.12 to 4.35) and KL grade 1 at baseline in the painful knee joint (OR 7.14, 95% CI 4.55 to 11.1). All outcomes are adjusted for all included determinants.

Conclusion The best predictors of development of knee rOA are a combination of female gender, other joint complaints and KL grade 1 in the painful joint. KL grade 1 in combination with knee pain should be considered as early OA in patient management.

INTRODUCTION

Many people consult their general practitioner (GP) with knee complaints.[1] In older patients this pain is often due to osteoarthritis (OA),[2] but not all these patients have radiological signs of OA in the painful joint. This discrepancy between the presence of pain and OA pathology on x-ray is well reported.[3–5] In daily GP practice, the absence of radiological established OA may lead to different patient management.

A consensus guideline (mainly for clinical diagnosis of knee OA) was published in 2010 by the European League Against Rheumatism (EULAR) OA Task Force.[6] It stated that the diagnosis should be based on three key symptoms (persistent knee pain, morning stiffness and functional impairment) and three typical clinical signs (crepitus, restricted movement and bony enlargement). However, several of these symptoms are features of advanced disease and may not be applicable to the early diagnosis of OA in a primary care setting. Also, the fact that radiological OA (rOA) is not often established in early disease leaves the GP with even less certainty about the diagnosis.

In general practice much information related to OA is available. Known risk factors such as age, comorbidities (eg, hypertension[7] and diabetes),[8] data on other joint diseases or complaints and OA in other joints[9] are registered in the GP's database. Other risk factors can be measured or determined, such as body mass index (BMI), history of heavy workload,[6 10 11] familial OA, presence of morning stiffness in the painful knee[12] and lower limb disability score[13] using the Health Assessment Questionnaire (HAQ). After referral, radiographic data are available on, for example, knee alignment (for which evidence of an association with the incidence of knee OA is not yet established)[14] and the presence or absence of rOA.[15]

Although many risk factors are known, a high-risk profile for early identification of knee OA is still lacking. Patients presenting with knee complaints might be in an early stage of OA development. Early recognition of knee OA will help the diagnostic process and the establishment of early intervention studies.

The EULAR Task Force also proposed a 'future research agenda'.[6] One of the agenda items was the 'development of diagnostic criteria for early symptomatic knee OA (eg, by prospective investigation of people with knee pain who fulfil the criteria of knee OA several years later)'. The present study aims to identify the best prognostic determinants for developing rOA (Kellgren and Lawrence grade (KL) ≥2) at follow-up in older people with knee complaints at baseline but no rOA (KL<2) in the painful joint at baseline.

METHODS

Setting and study population

The Rotterdam study is a population-based prospective cohort study on chronic and disabling diseases in older people which started in 1990. Follow-up takes place every 2–3 years. Participants were aged 55 years and older, living in Ommoord (Rotterdam, The Netherlands). There were 7983 participants (78% of 10 215 invited to participate).[16]

All participants were interviewed at home and were invited to the research centre for medical examinations and x-rays. A total of 6450 participants underwent baseline measurements.

For the present study, eligible subjects were those with knee x-rays and data on knee complaints (pain or stiffness) available at baseline and at least one of the two follow-up visits. Subjects were only included if they reported knee complaints (previous month and/or past 5 years) at baseline but had no rOA in either knee at baseline (KL grade <2).

OA assessment

Weight-bearing anterior-posterior (AP) x-rays of the knees were taken at the research centre. Knees were x-rayed in the extended weight-bearing position with the patella as the centre point. rOA of the tibiofemoral joint was assessed using the KL grading scale.[17] All x-rays were scored independently by three trained researchers. Inter-reader variability was moderate (0.55, 95% CI 0.50 to 0.59) for KL grades 0 versus 1 and good for KL grades ≥2 (0.68, 95% CI 0.61 to 0.75). In total, 5652 knee x-rays were scored at baseline, 3288 x-rays at first follow-up and 2503 radiographs at second follow-up. All researchers were blinded to the clinical and demographic data of the subjects. Knee rOA is defined as KL grade ≥2 of one or both joints or a total joint replacement (TJR). Hand OA is defined as KL grade ≥2 in two out of three hand joint groups (distal interphalangeal joints, proximal interphalangeal joints, CMC1/TS) of each or both hands. The incidence of knee OA is defined as KL grade <2 at baseline and KL grade ≥2 at follow-up/incident TJR at follow-up.

Pain assessment

Data were collected via a standardised interview at home in which participants were asked if they had suffered knee pain in the previous month (yes/no) and/or in the past 5 years (yes/no). Pain in the knees was defined as having pain in the left or right joint or both, either during the previous month or during the past 5 years. Pain was assessed at baseline and at follow-up.

Determinants

Potentially relevant baseline variables were selected based on the literature and availability in the clinical setting of the GP and in the Rotterdam study:

- General information: age, gender, BMI[18] and heavy workload[10] (having worked outdoors for ≥4 h/day during at least 25 years).
- Joint complaints: general joint complaints in the previous month (yes/no; positive score if pain reported in one or more of the arm, neck, shoulder, elbow, low back, hip, knee or foot; collected via standardised interview) and the duration of these general joint complaints (<1 year vs ≥1 year), the HAQ lower limb disability score[13] (functional impairment score: no trouble (score 0) vs any trouble (score 1,2 or 3)) and morning stiffness (<30 min).[12]
- Comorbidities: hypertension[7] (systolic blood pressure ≥160 mm Hg, diastolic blood pressure ≥100 mm Hg or use of antihypertensive medication), diabetes[8] (prevalent case if using antidiabetic medication and/or abnormal non-fasting or postload glucose level (11.1 mmol/l or over) and/or an abnormal oral glucose tolerance test), joint disease other than OA (Bechterev, gout or rheumatoid arthritis: all reported for the previous month or the past 5 years) and familial rheumatoid arthritis.
- OA variables: rOA in hip or hand[9] (prevalent cases at baseline KL grade ≥2).
- Imaging data: alignment in the painful joint and KL grade 1 at baseline in the painful joint.

Statistical analysis

Ordinal logistic regression analysis was used to investigate associations between the potentially relevant determinants and the development of knee rOA. All the abovementioned determinants were included in the model. The outcome was measured at two follow-up moments and was categorised as: (1) no rOA incidence on first (T1) or second follow-up (T2); (2) late rOA development: incident rOA at T2; and (3) fast rOA development: incident rOA at T1. For subjects with missing x-ray data at T1 who had no rOA at T2, we imputed that they also had no rOA at T1.

Analysis was performed using R 2.11.1 and OpenBugs 3.0.3 using the BRugs package. The model was run taking 20 000 samples (the first 10 000 were discarded) from each of three independent Markov chains. Convergence was checked both visually and using the Gelman-Rubin statistic.[19] Standard non-informative priors were used.

RESULTS

Study population

Subjects were only included if, at baseline, they reported knee pain in the previous month or the past 5 years but had no knee rOA in the painful joint. This resulted in 944 eligible subjects. The mean time from baseline to T1 was 6.5 years (range 5.5–8.8) and from baseline to T2 was 11.1 years (range 9.4–13.2).

Of these 944 subjects, 321 did not return for x-ray follow-up at T1 or T2, leaving 623 subjects available for analysis. Follow-up x-ray data were available for 607 subjects at T1 and for 457 subjects at T2 (figure 1) (see table S1 in the online supplement for reasons for non-participation at each stage).

Because a large number of patients had missing information for variables 'hand rOA' or 'deviant knee alignment in painful knee', these variables were excluded from the analysis.

Baseline GP consultation data for joint complaints were available for 159 subjects included in the analysis. Of these, 58.5% had visited their GP both in the previous month and in the past 5 years, 10% had consulted their GP in the previous month and 26.5% had done so in the past 5 years but not in the previous month. Only 5% had never visited their GP for joint complaints. These percentages for GP consultation relating to joint complaints are comparable to those in the total eligible population (n=944).

Table 1 shows the gender distribution of the subjects included in the ordinal regression analysis. The mean age was 64.5 years (range 55–85) and mean (SD) BMI was 26.2 (3.46) kg/m^2. At baseline, 211 subjects reported bilateral knee complaints during the previous month while 224 reported knee pain in the past 5 years but not in the previous month.

Determinants of knee rOA development

Table 2 presents the results of the ordinal logistic regression analysis. All determinants were tested in one multivariate model, adjusting all outcomes for all included determinants. Three determinants were significantly associated: female gender, having other joint complaints and KL grade 1 in the painful joint at baseline.

Risk of rOA development

In total, 23% of the subjects developed knee rOA at some point during follow-up. Of the 623 subjects who had no rOA at T1, 136 were lost to follow-up by T2. In the total population the risk of developing rOA (for an average person) at some point during follow-up was 16% (table 3). Comparison of various

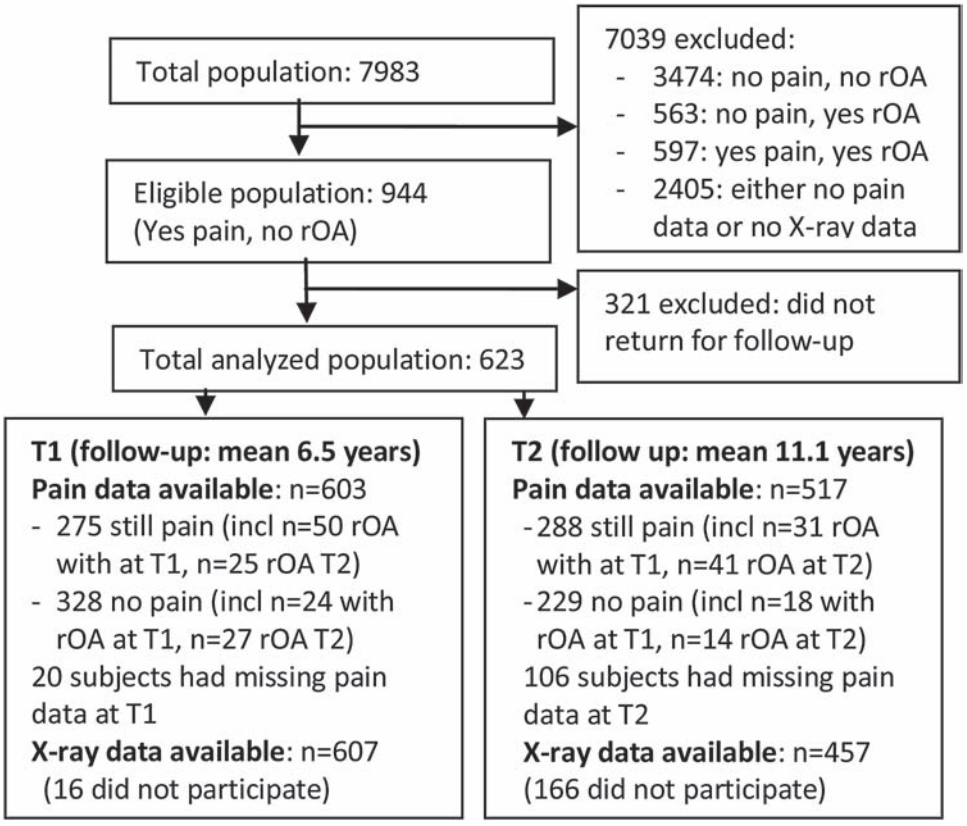

Figure 1 Flowchart.

Table 1 Distribution of women and men and complaint status at follow-up according to osteoarthritis (OA) development status

Osteoarthritis development status	Total	Women	Men
No OA development	344	217	127
Slow OA development (T2)	74	58	16
Fast OA development (T1)	53	36	17
No OA or slow OA development*	136	81	55
Fast or slow OA development†	16	11	5
Total in analysis	**623**	**403**	**220**
Lost to follow-up	321	216	105
Total eligible population	944	619	325

*Subjects without knee radiological OA at first follow-up visit (T1) and missing x-ray data at second follow-up visit (T2).
†Subjects with incident knee radiological OA at T2 but with missing x-ray data at T1.

subgroups shows that the risk of developing rOA in the total eligible population differed between subgroups (table 3). For example, in the group with KL grade 0, 13.5% developed knee rOA during follow-up (fast or slow) compared with 52.2% in the group with KL grade 1. For male versus female gender the risks were 11.1% and 19.5%, respectively, and for no general joint complaints versus having general joint complaints the risks were 11.9% and 18.3%, respectively.

DISCUSSION

The three determinants found to be the best predictors for developing knee rOA in this study were KL grade 1 at baseline in the painful knee, female gender and having general joint complaints during the previous month.

Female gender may be related to OA in the path of oestrogen deficiency and general joint complaints may possibly be an indication for generalised OA. We found that having KL grade 1 was the strongest predictor and we therefore focus on this in this discussion. Analysis of the data in two separate models (either fast or slow rOA development) gave similar results, although with less statistical power.

In this study population, those who reported knee complaints but had no established knee rOA (KL grades 0 or 1) had higher odds of developing knee rOA than those with no knee complaints. Of course, the reported knee complaints may have had different diagnoses such as widespread pain, soft tissue pain (tendinitis/bursitis) or referred pain from hip pathology. The population attributable risk for rOA development some time during follow-up (mean 11.1 years) in those with knee complaints and KL grade 0 was 11.5% and in those with knee complaints and KL grade 1 was 56.8%; in subjects without knee complaints these values were 8% and 41.2%, respectively.

Owing to lack of physical examination data, we were unable to test the key clinical signs as suggested by the EULAR Task Force.[6] However, the key symptoms 'morning stiffness' and 'functional impairment' proved to be non-significant. These symptoms may be more relevant in people with more advanced disease and may not be sensitive for early disease or predictive for rOA development.

Patients consulting the GP for knee complaints may be in an early stage of OA disease which is not yet visible on x-ray. In the Dutch guidelines for GPs (and in the UK guidelines), the use of x-ray as a diagnostic tool for knee OA in patients with knee complaints in primary care is considered inappropriate[20–22] because the absence of visible radiological abnormalities does not exclude knee OA. Nevertheless, in practice, x-ray is regularly used for diagnostic purposes. According to Bedson *et al*, the presence of OA changes on x-ray clearly influences the treatment and referral decisions of the GP. This was found to be the case for GPs who would not have chosen to x-ray the patient in the first place as well as for those who would have done so.[20]

Table 2 Results of the ordinal logistic regression analysis showing all the determinants included in the analysis

Characteristics	Mean (SD)/n (%)	OR	95% CI
Age in years	64.5 (6.5)*	1.22	0.97 to 1.52
BMI	26.2 (3.5)*	1.18	0.94 to 1.47
Female gender	**623 (64.7)**	**1.95**	**1.15 to 3.36**
Heavy workload†	623 (14.9)	1.61	0,83 to 3,11
Joint complaints			
HAQ lower limb disability‡	623 (10.0)	0.81	0.38 to 1.,69
General joint complaints in last month	**623 (80.7)**	**2.22**	**1.12 to 4.35**
Duration of general joint complaints§	503 (60.5)	0.64	0.37 to 1.08
Morning stiffness <30 min in legs	620 (10.3)	0.93	0.44 to 1.82
Comorbidities			
Hypertension	617 (28.5)	0.82	0.50 to 1.35
Diabetes	622 (8.8)	0.57	0.24 to 1.30
Other rheumatic diseases	623 (4.8)	1.54	0.67 to 3.57
Family rheumatoid arthritis	623 (18.1)	0.97	0.56 to 1.64
Osteoarthritis (OA) variables			
Hip rOA	617 (9.0)	0.83	0.39 to 2.08
Family OA	588 (27.1)	1.08	0.68 to 1.72
Imaging data			
KL grade 1 in painful joint	**623 (30.3)**	**7.14**	**4.55 to 11.1**

Significant outcomes are printed bold.
*Mean (SD) rest =n (%).
†Worked outdoors for 25 years 4 h/day.
‡No disability vs any disability.
§<1 year vs ≥1 year.
BMI, body mass index; HAQ, Health Assessment Questionnaire; KL, Kellgren and Lawrence; rOA, radiological osteoarthritis.

Table 3 Odds of developing rOA according to KL grade, gender and presence or absence of other joint complaints for an average subject with knee pain in the total eligible population

		Risk of rOA development			
Baseline variable	**n**	**rOA by T1, % (95% CI)**	**rOA by T2, % (95% CI)**	**rOA at T1 or T2, % (95% CI)**	**No rOA T1 and T2, % (95% CI)**
Risk total eligible population	944	6.1 (4.3 to 8.2)	9.9 (7.3 to 13.0)	16.0 (12.5 to 20.1)	84.0 (79.9 to 87.5)
KL grade 0	585	5.1 (3.5 to 7.0)	8.4 (6.1 to 11.3)	13.5 (10.2 to 17.4)	86.5 (82.6 to 89.8)
KL grade 1	**359**	**27.1 (20.9 to 33.8)**	**25.1 (19.5 to 31.0)**	**52.2 (44.3 to 60.0)**	**47.8 (40.0 to 55.7))**
Male gender	325	4.1 (2.3 to 6.4)	7.0 (4.3 to 10.4)	11.1 (6.9 to 16.3)	88.9 (83.7 to 93.1)
Female gender	**619**	**7.6 (5.3 to 10.5)**	**11.9 (8.6 to 15.6)**	**19.5 (14.9 to 24.6)**	**80.5 (75.4 to 85.1)**
No general joint complaints	176	4.4 (2.3 to 7.4)	7.5 (4.3 to 11.7)	11.9 (6.8 to 18.5)	88.1 (81.5 to 93.2)
General joint complaints*	**768**	**7.1 (5.0 to 9.6)**	**11.2 (8.2 to 14.7)**	**18.3 (14.2 to 22.9)**	**81.7 (77.1 to 85.8)**

Significant risk factors are printed in bold.
*Combined score of other joint complaints of pain in arm, neck, shoulder, elbow, low back, hip, knee and foot.
KL, Kellgren and Lawrence; rOA, radiological osteoarthritis.

Hart and Spector[15] suggested that, when using the KL scoring system in epidemiological studies, KL grade 1 should not be grouped with KL grade 0 but KL grade 1 should be considered as a 'predisease group' with KL grade 0 as a control group for comparison. Our study supports this finding and confirms that KL grade 1 predicts future development of radiological disease of the tibiofemoral joint in people with knee complaints. Thorstensson *et al* also tested the hypothesis that idiopathic chronic knee pain is an early sign of knee OA and concluded that this was the case.[23] In the present study we did not investigate chronic knee pain but only the duration of general joint complaints (eg, knee pain or stiffness). We found a significant association with the presence of general joint complaints in the previous month but not with the duration of these complaints (<1 year vs ≥1 year).

Peat *et al* investigated whether a false-positive clinical diagnosis of knee OA was equivalent to an early diagnosis of preradiographic disease over 3 years and their analysis suggested that this was not the case.[24] However, their follow-up period may have been too short to reveal similar results to ours since our study and that of Hart *et al*[15] and Thorstensson *et al*[23] had a longer follow-up period (11, 10 and 12 years, respectively).

Currently, the usefulness of x-rays is not aimed at confirmation of osteoarthritic disease but rather to rule out other diseases.[25] MRI potentially has additional value since it can visualise tissue damage at an earlier stage. The clinical value of the present study lies in highlighting the potential additional value of x-rays in the diagnostic process in patients who consult their GP for a knee complaint that has no clear cause. Radiologists do not generally report the actual KL grade to the GP, but simply whether (or not) a patient has an established rOA. In cases with no established rOA, a radiologist may report 'minimal degeneration complying with normal ageing' or 'mild degenerative signs', which might comply with KL grade 1. The chance that someone with KL grade 1 will develop knee rOA in the future is significantly greater than a person with KL grade 0.

Some limitations of the present study need to be addressed. First, because a relatively large number of patients had missing information for the variables 'hand rOA' and 'deviant knee

alignment in painful knee', these determinants were disregarded for analysis. Analysis including these two variables, considering only the complete cases for these variables, produced a model with observations for only 215 subjects. Because neither of these two variables was significant in that analysis, it was deemed appropriate to exclude them. Second, it is possible that subjects with knee complaints at baseline but no tibiofemoral OA had complaints related to a prevalent patellofemoral OA. Mazzuca *et al* reported a 41% presence of patellofemoral rOA in subjects with tibiofemoral KL grade 0–1.[26] Unfortunately, because only AP x-rays were available for the present study, we were unable to review the presence of patellofemoral OA and only considered radiographic tibiofemoral OA as knee rOA. Third, because no data on physical examination were available for this cohort, we were unable to test the applicability of the clinical signs for early OA diagnosis in primary care (as suggested by the EULAR Task Force)[6]. Perhaps restricted movement or crepitus in the knee (or even joint line tenderness) may predict future development of rOA better and should therefore be examined whenever possible. We plan to do this using the third cohort of the Rotterdam study in whom baseline data include crepitus, restricted movement and bony enlargement; follow-up measurements of this cohort will start in 2012. Fourth, we included patients who reported having knee complaints in the previous month and/or in the past 5 years. Since pain is episodic and activity-related[6 27] (especially in the early stages of disease), we included those with knee complaints in the past 5 years because complaints of, for example, 1.5 months ago would otherwise be missed. This led to the inclusion of 224 subjects who had not had knee complaints in the previous month, of which 48 developed OA during follow-up. Inclusion of these patients might have led to an underestimation of the estimates. We therefore believe that including patients without knee complaints in the previous month but with knee complaints in the past 5 years was appropriate. Fifth, selecting subjects on the basis of availability of x-ray data at baseline and follow-up introduced a type of selection bias called the 'healthy worker effect' since subjects in better health are more likely to revisit the research centre for follow-up measurements. On the other hand, the long follow-up period is a strength of the study.

Currently, it is not possible to prevent degeneration to established OA owing to the lack of disease-modifying interventions. Conservative treatments available for OA symptom relief are weight reduction in case of overweight/obesity, exercise, suitable footwear, pain medication, referral to a physiotherapist and insoles or braces. The GP generally starts by giving advice, followed by pain medication if a lifestyle change is insufficient. Generally, guided exercise therapy and insoles and braces are not the first choice, although exercise therapy should be according to the guidelines of the National Institute for Health and Clinical Excellence,[28] Osteoarthritis Research Society International[29] and EULAR.[6] The effect of these therapies on symptoms in patients with knee complaints but without established OA is not yet clear.

In summary, in this open population, being a woman, having general joint complaints besides knee complaints and having KL grade 1 in the painful knee are the most important variables predicting the development of knee rOA. Early recognition of those at high risk of developing rOA will help GPs in the diagnostic process.

Contributors All authors contributed to the final manuscript. In addition, BMdK and DS collected data. BMdK, SW and SMAB-Z performed statistical analysis and data interpretation. BMdK wrote the manuscript. BWK and SMAB-Z critically revised the article for important intellectual content. AH conceived the original Rotterdam Study. SMAB-Z conceived the study, and participated in its design and coordination, helped to draft the manuscript and supervised the whole study. BMdK had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

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Competing interests None.

Patient consent Obtained.

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REFERENCES

1. **Peat G**, McCarney R, Croft P. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. *Ann Rheum Dis* 2001;**60**:91–7.
2. **McCormick A**, Fleming D, Charlton J. *Morbidity statistics from general practices. Fourth national study 1991–1992. Office of Population Censuses and Surveys. Series MB5 No.3*. London: HMSO, 1995.
3. **Cobb S**, Merchant WR, Rubin T. The relation of symptoms to osteoarthritis. *J Chronic Dis* 1957;**5**:197–204.
4. **Kidd BL**. Osteoarthritis and joint pain. *Pain* 2006;**123**:6–9.
5. **Bedson J**, Croft PR. The discordance between clinical and radiographic knee osteoarthritis: a systematic search and summary of the literature. *BMC Musculoskelet Disord* 2008;**9**:116.
6. **Zhang W**, Doherty M, Peat G, *et al.* EULAR evidence-based recommendations for the diagnosis of knee osteoarthritis. *Ann Rheum Dis* 2010;**69**:483–9.
7. **Cimmino MA**, Sarzi-Puttini P, Scarpa R, *et al.* Clinical presentation of osteoarthritis in general practice: determinants of pain in Italian patients in the AMICA study. *Semin Arthritis Rheum* 2005;**35**(1 Suppl 1):17–23.
8. **Berenbaum F**. Diabetes-induced osteoarthritis: from a new paradigm to a new phenotype. *Ann Rheum Dis* 2011;**70**:1354–6.
9. **Dahaghin S**, Bierma-Zeinstra SM, Reijman M, *et al.* Does hand osteoarthritis predict future hip or knee osteoarthritis? *Arthritis Rheum* 2005;**52**:3520–7.
10. **Lievense A**, Bierma-Zeinstra S, Verhagen A, *et al.* Influence of work on the development of osteoarthritis of the hip: a systematic review. *J Rheumatol* 2001;**28**:2520–8.
11. **Bierma-Zeinstra SM**, Koes BW. Risk factors and prognostic factors of hip and knee osteoarthritis. *Nat Clin Pract Rheumatol* 2007;**3**:78–85.
12. **Altman R**, Asch E, Bloch D, *et al.* Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheum* 1986;**29**:1039–49.
13. **Bruce B**, Fries JF. The Stanford Health Assessment Questionnaire: a review of its history, issues, progress, and documentation. *J Rheumatol* 2003;**30**:167–78.
14. **Tanamas S**, Hanna FS, Cicuttini FM, *et al.* Does knee malalignment increase the risk of development and progression of knee osteoarthritis? A systematic review. *Arthritis Rheum* 2009;**61**:459–67.
15. **Hart DJ**, Spector TD. Kellgren & Lawrence grade 1 osteophytes in the knee–doubtful or definite? *Osteoarthr Cartil* 2003;**11**:149–50.
16. **Hofman A**, Breteler MM, van Duijn CM, *et al.* The Rotterdam Study: objectives and design update. *Eur J Epidemiol* 2007;**22**:819–29.
17. **Kellgren JH**, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis* 1957;**16**:494–502.
18. **Reijman M**, Pols HA, Bergink AP, *et al.* Body mass index associated with onset and progression of osteoarthritis of the knee but not of the hip: the Rotterdam Study. *Ann Rheum Dis* 2007;**66**:158–62.
19. **Gelman A**, Rubin DB. Inference from iterative simulation using multiple sequences. *Stat Sci* 1992;**7**:457–511.
20. **Bedson J**, Jordan K, Croft P. How do GPs use x rays to manage chronic knee pain in the elderly? A case study. *Ann Rheum Dis* 2003;**62**:450–4.
21. Royal College of Radiologists. *Making the best use of a Department of Clinical Radiology. Guidelines for doctors*. Fourth edition. London: Royal College of Radiologists, 1998.

22. Dutch Orthopaedic Society. Guideline diagnostics and management of hip and knee osteoarthritis [Richtlijn diagnostiek en behandeling van heup- en knieartrose. Nederlandse Orthopaedische Vereniging] 2007. http://www.inbalanspmc.hgn.uwpraktijkonline.nl/uploads/usersftp/130808/KNGF%20richtlijnen/Richtlijn%20Heup%20en%20Knie%20Arthrose.pdf (accessed 14 Jan 2011).
23. **Thorstensson CA**, Andersson ML, Jönsson H, *et al.* Natural course of knee osteoarthritis in middle-aged subjects with knee pain: 12-year follow-up using clinical and radiographic criteria. *Ann Rheum Dis* 2009;**68**:1890–3.
24. **Peat G**, Thomas E, Duncan R, *et al.* Is a "false-positive" clinical diagnosis of knee osteoarthritis just the early diagnosis of pre-radiographic disease? *Arthritis Care Res (Hoboken)* 2010;**62**:1502–6.
25. **Mazzuca SA**, Brandt KD, Katz BP, *et al.* Risk factors for progression of tibiofemoral osteoarthritis: an analysis based on fluoroscopically standardised knee radiography. *Ann Rheum Dis* 2006;**65**:515–19.
26. **Neogi T**, Zhang Y. Osteoarthritis prevention. *Curr Opin Rheumatol* 2011;**23**:185–91.
27. **Hunter DJ**, McDougall JJ, Keefe FJ. The symptoms of osteoarthritis and the genesis of pain. *Med Clin North Am* 2009;**93**:83–100, xi.
28. National Institute for Health and Clinical Excellence (NICE). Osteoarthritis: the care and management of osteoarthritis in adults. NICE Clinical Guideline 59. London: NICE, 2008.
29. **Zhang W**, Moskowitz RW, Nuki G, *et al.* OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthr Cartil* 2008;**16**:137–62.

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B M de Klerk, S Willemsen, D Schiphof, et al.

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