Seminars in Arthritis and Rheumatism 59 (2023) 152170

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Association between baseline meniscal extrusion and long-term incident knee osteoarthritis in two different cohorts

Jan A. van der Voet [a,b,*], Dieuwke Schiphof [c], Dammis Vroegindeweij [d], Edwin H. Oei [a], Sita M.A. Bierma-Zeinstra [c,e], Jos Runhaar [c]

[a] Dept. of Radiology & Nuclear Medicine, Erasmus MC University Medical Center, Rotterdam, the Netherlands
[b] Dept. of Radiology, Alrijne Hospital, Leiderdorp, the Netherlands
[c] Dept. of General Practice, Erasmus MC University Medical Center Rotterdam, the Netherlands
[d] Dept. of Radiology, Maasstad Hospital, Rotterdam, the Netherlands
[e] Dept. of Orthopedics, Erasmus MC University Medical Center, Rotterdam, the Netherlands

ARTICLE INFO

Keywords:
Meniscus
Knee joint
Osteoarthritis
Overweight
Obesity

ABSTRACT

Objective: Previously, we identified a significant association between meniscal extrusion and short-term incident knee osteoarthritis (KOA). To validate these findings, we evaluated long-term incident KOA in knees with meniscus extrusion, using two different cohorts.
Methods: We used data from the PROOF study, which evaluated a high-risk population of overweight women, and a female subcohort of the population-based Rotterdam Study (RS). Meniscal extrusion was defined as $\geq$ 3 mm on MRI. Outcomes were incident radiographic (KL $\geq$ 2) or clinical KOA according to the ACR criteria, assessed at 6.6 years (PROOF) and 5.1 years (RS). With generalized estimating equations, we determined the association of knees with and without baseline meniscal extrusion and incident KOA, adjusting for confounders. Furthermore, we computed the population attributable risk percentage (PAR%) of meniscal extrusion.
Results: PROOF: of 421 available knees 23% had baseline meniscal extrusion. Incident radiographic KOA was significantly higher in knees with meniscal extrusion compared to those without (adjusted OR 2.54, 95% CI 1.34, 4.80; $p = 0.004$; PAR 21%). Incident clinical KOA was also significantly higher (adjusted OR 2.44, 95% CI 1.29, 4.60; $p = 0.006$; PAR 19%).
RS: 46% of 872 available knees had meniscal extrusion. Incident radiographic KOA was significantly higher (adjusted OR 9.86, 95% CI 2.13, 45.67; $p = 0.002$; PAR 77%). Incident clinical KOA was borderline significantly higher (adjusted OR 2.65, 95% CI 0.96, 7.30; $p = 0.06$; PAR 44%).
Conclusion: Meniscal extrusion is significantly associated with long-term incident KOA. A high number of incident cases were attributable to extrusion.

Introduction

In recent years, the role of the meniscus in the development and progression of knee osteoarthritis (OA) has become more acknowledged, with meniscal pathology, including extrusion, being a common finding in knees with established OA. Extrusion is where the outer margin of the meniscus is displaced beyond the borders of the femoral and tibial joint surfaces[1]. It is thought that an extruded meniscus alters the load distribution within the knee joint, increasing the pressure on cartilage, thereby initiating the development of knee OA associated with the loss of articular cartilage and other structural features of the disease[2-5]. However, to date it is not completely clarified whether extrusion precedes OA development or whether it is a consequence of the degenerative process. Previously, we found a statistically significant association between baseline meniscus extrusion and the 2.5 years incidence of knee OA in a high-risk population, free of OA at baseline[6]. This provided further support for the assumption that extrusion is prior to knee OA, especially since this study was conducted in a cohort without established OA, in contrast to most other studies[1,2,4,5]. Yet, 2.5 years is a relatively short follow-up period. To validate these findings, the objective of the

* Corresponding author at: Department of Radiology & Nuclear Medicine, Erasmus MC, University Medical Center, Rotterdam, The Netherlands, Department of Radiology, Alrijne Hospital, Leiderdorp, The Netherlands, PO box 2040, 3000, CA, Rotterdam, the Netherlands.
E-mail address: j.vandervoet@erasmusmc.nl (J.A. van der Voet).

https://doi.org/10.1016/j.semarthrit.2023.152170

Available online 29 January 2023

present study was to assess the long-term incidence of knee OA in knees with baseline meniscal extrusion, using two different cohorts. Outcome measures were radiographic as well as clinical knee OA, whereas most other papers focused on structural knee changes only. We hypothesized that in both cohorts meniscus extrusion is significantly related to incident knee OA. To provide more insight in the clinical impact of our results, we additionally calculated the population attributable risk percentage (PAR%).

Material and methods

Study design

We conducted a cohort study using data from the PROOF study (PRevention of knee Osteoarthritis in Overweight Females, ISRCTN 42,823,086), approved by the Medical Research Ethics Committee (MREC) of Erasmus University Medical Center, and the Rotterdam Study, approved by the MREC and by the review board of The Netherlands Ministry of Health, Welfare and Sports[7,8]. For both studies, all participants provided written consent.

Data collection/participants

The PROOF study

PROOF is a large prospective intervention study in a high-risk population of 407 middle-aged overweight and obese women with a body mass index (BMI) of $\geq$ 27 kg/m^2, free of clinical knee OA at baseline. This study has been described in detail previously[7]. The aim was to assess the preventive effect of a lifestyle intervention (diet and exercise) and of oral glucosamine sulfate (double-blind placebo controlled) on the development of knee OA. At baseline, subjects filled in a questionnaire to assess physical activity and were asked for menopausal status and history of knee injury. Body weight, height, knee alignment and maximum strength of the quadriceps muscle were measured, presence of Heberden's nodes (as an indication for generalized OA) were documented, and, to assess the Kellgren & Lawrence (K&L) grade, a standardized semi-flexed weight-bearing posteroanterior (PA) radiograph of both knees was taken according to the MTP protocol[9].

Radiographs were scored by a trained researcher, blinded to clinical data. A second researcher blinded to clinical data and the reading results of the first researcher determined the interobserver variability, scoring a subset of 20% of the radiographs. The differences in baseline characteristics between knees with and without meniscal extrusion as well as in- and excluded knees were compared and tested for significance, including OA features scored on MRI (see *2.3 MRI technique and scoring*). Participants had mean follow-up visits after 2.5 and 6.6 years.

The Rotterdam study

The Rotterdam Study is a prospective, population-based cohort study. It aims to investigate risk factors for chronic diseases in elderly people, including musculoskeletal disorders. The design and objectives of the Rotterdam Study have been described previously[8]. Up to 2008, 14,926 inhabitants aged $\geq$ 45 years had been recruited from Ommoord, a city district of Rotterdam, The Netherlands. In 2006 subjects aged $\geq$ 45 years not yet included in the original study were invited to participate (RS-III-1). Of this cohort, 1116 women aged 45–60 years were asked to participate in a sub-study investigating early signs of knee OA. Participating women underwent an MRI of both knees at baseline and physical and radiographic examination at baseline and at follow-up.

As in the PROOF study, body weight, height, knee alignment and maximum quadriceps muscle strength were measured and the presence of Heberden's nodes was documented. Knee radiographs were taken in an anteroposterior (AP) direction, weight-bearing and in full extension (70 kV, focus 1.8 mm^2, focus-to-film distance 120 cm). Two extensively trained researchers scored the radiographs, blinded for clinical and MRI data. Subjects were asked for clinical symptoms, postmenopausal status, and history of knee injury. The groups with and without extrusion as well as in- and excluded knees were compared regarding baseline characteristics, including MRI OA features. After +/- 2 years, participants were asked the same knee-specific questions by a mailed questionnaire. Follow-up examination was performed after a mean follow-up period of 5.1 years.

MRI technique and scoring

The PROOF study

A 1.5 Tesla MRI of both knees was made at baseline. The MRI protocol included the following sequences: coronal and sagittal proton density (PD) weighted with 3.0 mm slice thickness and a slice gap of 0.3 mm, coronal T2 weighted Spectral Presaturation by Inversion Recovery (SPIR) (slice thickness 5 mm / slice gap 0.5 mm), axial dual spin-echo (slice thickness 4.5 mm / slice gap 0.5 mm) and fat saturated sagittal 3D water selective (WATS) (slice thickness 1.5 mm). MRIs were scored by two readers (JR, PvdP) who were trained by a highly experienced musculoskeletal radiologist (EO; 10 years of experience with musculoskeletal MRI in clinical and research settings), using the MRI Osteoarthritis Knee Score (MOAKS), a semi-quantitative MRI OA scoring method introduced by a group of experienced researchers in OA[10]. This method encompasses - besides meniscal extrusion - other meniscal pathologies (i.e. tear, maceration, hypertrophy, cyst), BMLs with or without cysts, cartilage defects and osteophytes.

The Rotterdam study

At baseline, knees were scanned with a 1.5 Tesla MRI system, using an eight-channel cardiac coil to enable scanning of two knees in one session to reduce scanning time. The multi-sequence protocol included a sagittal fast spin echo (FSE) PD and T2 weighted sequence (slice thickness 3.2 mm), sagittal FSE fat suppressed T2 weighted sequence (slice thickness 3.2 mm), sagittal spoiled fat suppressed gradient echo (slice thickness 3.2 (1.6) mm) and a sagittal FIESTA (fast-imaging employing steady-state acquisition) sequence (slice thickness 1.6 mm), which was later reformatted in the coronal and transverse plane. MRIs were scored according to the MOAKS criteria by two readers (DS, DvE) who were extensively trained by the same experienced musculoskeletal radiologist as in the PROOF Study (EO).

Definitions

Meniscal extrusion was defined as grade 2 (3–4.9 mm) or grade 3 ($\geq$ 5 mm) extrusion according to MOAKS. Grade 0 or 1 extrusion ($<$ 2 mm, 2 - 2.9 mm) was considered as no extrusion[11,12].

Outcome measures were either incident radiographic or incident clinical knee OA, defined at knee level. Incident radiographic knee OA was defined as a K&L score $\geq$ 2, with baseline K&*L* $<$ 2, meaning that knees with a K&L score $\geq$ 2 at baseline were excluded from the analysis. Incident clinical OA was defined using the American College of Rheumatology (ACR) criteria, which include knee pain and osteophytes in combination with either age $>$ 50 years, morning stiffness or crepitus[13].

To assess the impact of our results on the population, we computed the population attributable risk percentage (PAR%), defined as PAR% = [($\text{Rate}_{\text{total population}}$ – $\text{Rate}_{\text{unexposed}}$) / ($\text{Rate}_{\text{total population}}$)] x 100% [14]. An equivalent expression in terms of rate ratio (RR) and prevalence of exposure ($\text{P}_{\text{exposed}}$) is PAR% = $\text{P}_{\text{exposed}}$ (RR – 1) / [1 + $\text{P}_{\text{exposed}}$ (RR – 1)] [14]. Here, PAR% represents the percentage of new cases of knee OA that can be attributed to meniscal extrusion.

Statistical methods

In both cohorts, knees with and without meniscal extrusion were compared for the outcome measures using generalized estimating equations (GEE), with which we corrected for both the correlation between two knees within subjects as well as for confounding covariates.

Confounding was defined by the three criteria as formulated by Jager et al.; the variable must be associated with both the disease (1) and the exposure (irrespective of *P* value) (2) but may not be a factor in the causal pathway (3)[15]. Based upon these criteria, we considered age, BMI, a history of knee injury, postmenopausal status, varus alignment, meniscal pathologies, and quadriceps strength as confounders and, consequently, we incorporated them in the main analysis model. In the PROOF cohort, a sensitivity analysis was performed to correct for the potential effects of the interventions of the original trial, their interaction, and their interaction with baseline meniscal extrusion on the outcomes. In the Rotterdam Study cohort, the interaction of BMI with baseline meniscal extrusion was assessed. In both cohorts the effect of additional adjustment for baseline presence of K&L grade 1 was evaluated. Finally, a sensitivity analysis for incident radiographic knee OA was conducted, with K&L grade 0 at baseline and incident OA defined as K&$L > 0$.

The outcomes are presented in percentages, odds ratios and confidence intervals and *P* values. A two-sided *P* value of < 0.05 was considered statistically significant. Secondary, for each cohort the PAR% was computed using the above stated definition. All analyses were performed with the SPSS-software, version 25.0.0.0 (2017, IBM, NY, USA).

Results

Baseline characteristics

Baseline characteristics for the groups with and without meniscal extrusion in both cohorts are shown in Tables 1 and 2.

The PROOF study

407 women were enrolled in the original trial of which 160 were lost to follow-up, primarily due to lack of interest or time (Fig. 1). Furthermore, knees with K&$L \geq 2$ (51) and lack or insufficient quality of MRI (20) at baseline were excluded from the analysis. Thus, 421 knees were eligible for statistical analysis. Ninety-seven of the 421 knees had baseline meniscal extrusion on MRI (23%). The participants had a mean age of 56.2 +/- 2.8 years and a mean BMI of 31.9 +/- 3.8 kg/m^2.

Analysis of missing and non-missing knees showed a significantly higher prevalence of meniscal extrusion ($p = 0.004$), meniscal pathologies ($p = 0.004$) and osteophytes in the tibiofemoral joint (TFJ) at baseline in excluded knees, as well as a higher BMI ($p < 0.001$). Quadriceps strength was lower in the excluded group ($p < 0.001$).

Table 1
Baseline characteristics PROOF study.

	All ($n = 421$)	Meniscal extrusion ($n = 97$)	No meniscal extrusion ($n = 324$)
Age (yr)	55.7 +/- 3.1	56.2 +/- 2.8	55.6 +/- 3.2
BMI (kg/m2)	31.7 +/- 3.7	31.9 +/- 3.8	31.7 +/- 3.6
K&L grade 1 (%)	47	59	42
Mild pain/symptoms (%)	27	37	24
History of knee injury (%)	11	20	8
Varus alignment (%)	41	52	38
Postmenopausal (%)	71	71	71
Heberden's nodes (%)	28	36	25
Osteophytes in TFJ (%)	12	29	7
Full-thickness cartilage defects in TFJ (%)	8	12	7
Bone marrow lesions in TFJ (%)	32	40	29
Meniscal pathologies (%)[a]	60	81	54
Quadriceps strenght (Nm)[b]	3.2 +/- 0.7	3.1 +/- 0.7	3.2 +/- 0.7

Table 1. Baseline characteristics PROOF cohort.
[a] Meniscal pathologies: tears, maceration, hypertrophy, cysts and (degenerative) signal abnormalities.
[b] Mean of two measurements with hand-held dynamometer. BMI: Body Mass Index. K&L: Kellgren and Lawrence. TFJ: tibiofemoral joint.

Table 2
Baseline characteristics Rotterdam Study cohort.

	All ($n = 872$)	Meniscal extrusion ($n = 399$)	No meniscal extrusion ($n = 473$)
Age (yr)	55.2 +/- 3.7	55.4 +/- 3.8	55.1 +/- 3.7
BMI (kg/m2)	26.6 +/- 4.2	26.9 +/- 4.3	26.3 +/- 4.1
K&L grade 1 (%)	12	14	12
Mild pain/symptoms (%)	7	7	6
History of knee injury (%)	6	6	5
Varus alignment (%)	20	19	20
Postmenopausal (%)	68	72	66
Heberden's nodes (%)	25	25	25
Osteophytes in TFJ (%)	8	14	4
Full-thickness cartilage defects in TFJ (%)	4	4	5
Bone marrow lesions in TFJ (%)	35	39	32
Meniscal pathologies (%)[a]	17	20	15
Quadriceps strenght (Nm)[b]	224 +/- 46	226 +/- 47	222 +/- 46

[a] Meniscal pathologies: tears, maceration, hypertrophy, cysts and (degenerative) signal abnormalities.
[b] Mean of two measurements with hand-held dynamometer. BMI: Body Mass Index. K&L: Kellgren and Lawrence. TFJ: tibiofemoral joint.

The Rotterdam study

225 of the 1116 invited women were not included. Main reasons for exclusion were lack of time or interest, claustrophobia, sickness, moving out of the region and linguistic barrier (see Fig. 2 for the selection process). Furthermore, knees or subjects with radiographic and/or clinical signs of OA at baseline or with incomplete follow-up data were excluded from the analysis. As a result, 872 knees in 438 women were available for statistical analysis. Of these 872 knees, 399 (46%) had baseline meniscal extrusion on MRI. Mean age was 55.4 +/- 3.8 years and mean BMI was 26.9 +/- 4.3 kg/m^2.

Missing knees showed a statistically significantly higher baseline prevalence of meniscal pathologies ($p = 0.008$) and osteophytes ($p < 0.001$) and full thickness cartilage defects ($p = 0.002$) in the TFJ. Furthermore, subjects linked to excluded knees had a higher age ($p < 0.001$), a higher BMI ($p < 0.001$), less quadriceps strength ($p = 0.003$) and less Heberden's nodes ($p = 0.027$).

Association between meniscal extrusion and incident knee OA

The PROOF study

The association between baseline meniscal extrusion and the outcome measures are presented in Table 3. After 6.6 years, 29 of the 97 knees (30%) with baseline meniscal extrusion developed radiographic knee OA, compared to 10% in knees without extrusion (adjusted OR 2.54, 95% CI 1.34, 4.80). Furthermore, significantly more subjects met the criteria for clinical knee OA at follow-up in the subjects with extrusion (25% versus 12%) (adjusted OR 2.44, 95% CI 1.29, 4.60). Adjusted and unadjusted ORs were not significantly different (see Table 3). The sensitivity analyses showed neither a significant interaction between baseline meniscal extrusion and either of the original interventions, nor did the original interventions significantly affect the outcomes (data not shown). Additional adjustment for K&L grade 1 did not significantly influence the ORs for either incident radiographic or clinical knee OA (data not shown). Sensitivity analysis with baseline

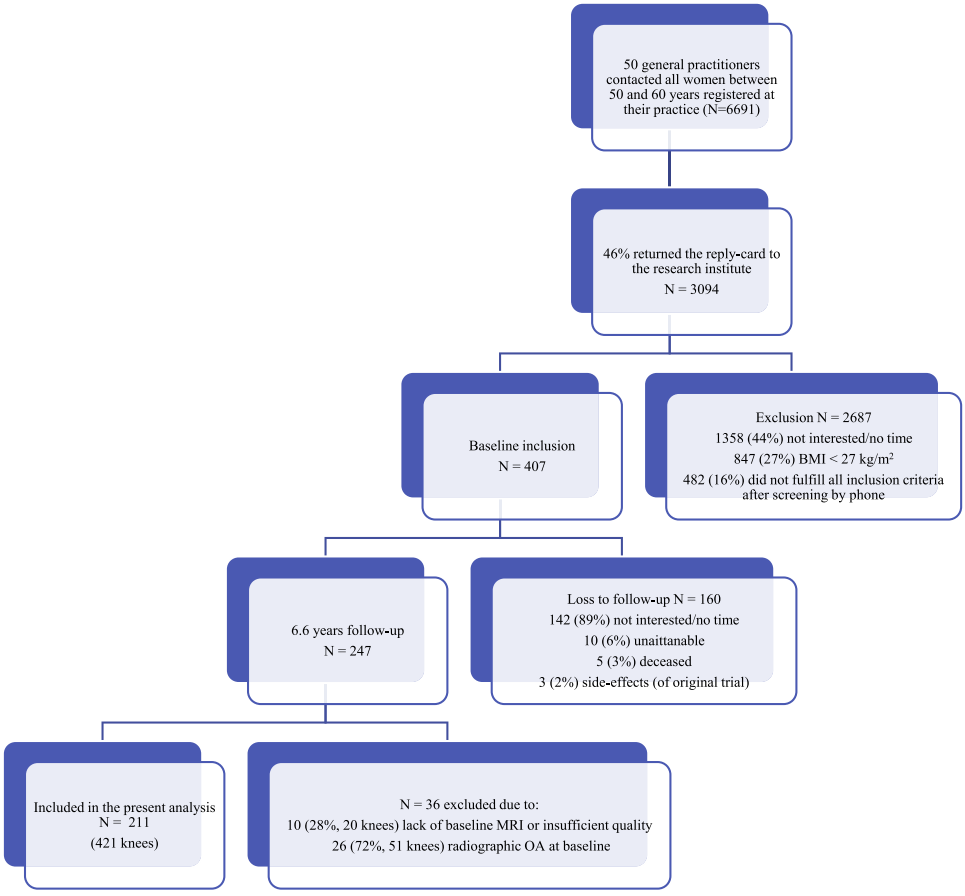

Fig. 1. Flowchart of selection process for the PROOF cohort.

K&L grade 0 and incidence defined as K&$L > 0$ resulted in non-significant associations; OR 0.7, 95% CI 0.41, 1.21.

The Rotterdam study

The outcomes are presented in Table 4. After 5.1 years, radiographic knee OA was seen in 30 of the 399 knees (8%) with baseline meniscal extrusion, versus 2% in knees without extrusion (adjusted OR 9.86, 95% CI 2.13, 45.67). Incident clinical knee OA was 6% (23/399) in knees with extrusion and 2% in knees without extrusion (adjusted OR 2.65, 95% CI 0.96, 7.30). Adjusted and unadjusted ORs were not significantly different, although the adjusted OR for radiographic knee OA was almost three times higher (3.59 vs. 9.86, see Table 4). Additional adjustment for K&L grade 1 did not significantly influence the ORs for either incident radiographic or clinical knee OA (data not shown). Sensitivity analysis with baseline K&L grade 0 and incidence defined as K&$L > 0$ resulted in non-significant associations; OR 0.63, 95% CI 0.64, 1.51. Overweight or obesity (BMI of $\geq$ 27 kg/m^2) did not show a statistically significant interaction with baseline meniscal extrusion for either incident clinical knee OA ($p = 0.160$) or incident radiographic OA ($p = 0.828$).

Population attributable risk percentage

Within PROOF, the PAR% was 21% for radiographic knee OA and 19% for clinical knee OA. Within the Rotterdam Study cohort, the PAR% was 77% and 44%, respectively.

Discussion

In the present study, we aimed to validate the previously identified association between baseline meniscal extrusion and the short-term incidence of radiographic and clinical knee OA. Therefore, we assessed the long-term incidence of knee OA in the same cohort with 6.6 years follow-up and executed an identical analysis in a different cohort with 5.1 years follow-up. Within middle-aged overweight and obese women (the PROOF cohort), the long-term incidences of radiographic and clinical knee OA were three and two times higher in knees with meniscal extrusion compared to knees without extrusion, respectively. Within an unselected population of middle-aged women (the Rotterdam Study cohort), the absolute incidences of both radiographic and clinical knee OA were lower, but the ratios between knees with and without extrusion were roughly equal, with a four and three times higher incidence, respectively. In all cases, the associations were statistically (borderline) significant. The results are in line with the previous study with short-term follow-up, as well as the few other studies conducted in OA free cohorts, providing further support for a largely independent association and a causal pathway between meniscal extrusion and incident knee OA[16,17]. Emmanuel et al. was the first evaluating quantitative measures of meniscal position predicting incident knee OA (K&$L \geq 2$) and found a significant association between medial and lateral meniscal extrusion with incident medial and lateral knee OA, respectively[5]. Sharma et al. reported a modest association of meniscus extrusion with incident cartilage damage although the OR was not significant, possibly because of the relative low baseline prevalence of meniscus extrusion of 14%[16]. These studies only focused on structural signs of OA, whereas the present study also evaluated the association with clinical symptoms. Radiography is the most widely used outcome measure in clinical trials to detect OA related joint changes but might be insufficient to completely define the clinical syndrome. Especially in the earlier stages, discrepancies between pain and the degree of radiographic disease may exist with up to 40% of patients with radiographic signs of OA being asymptomatic[18]. This phenomenon was also observed in the

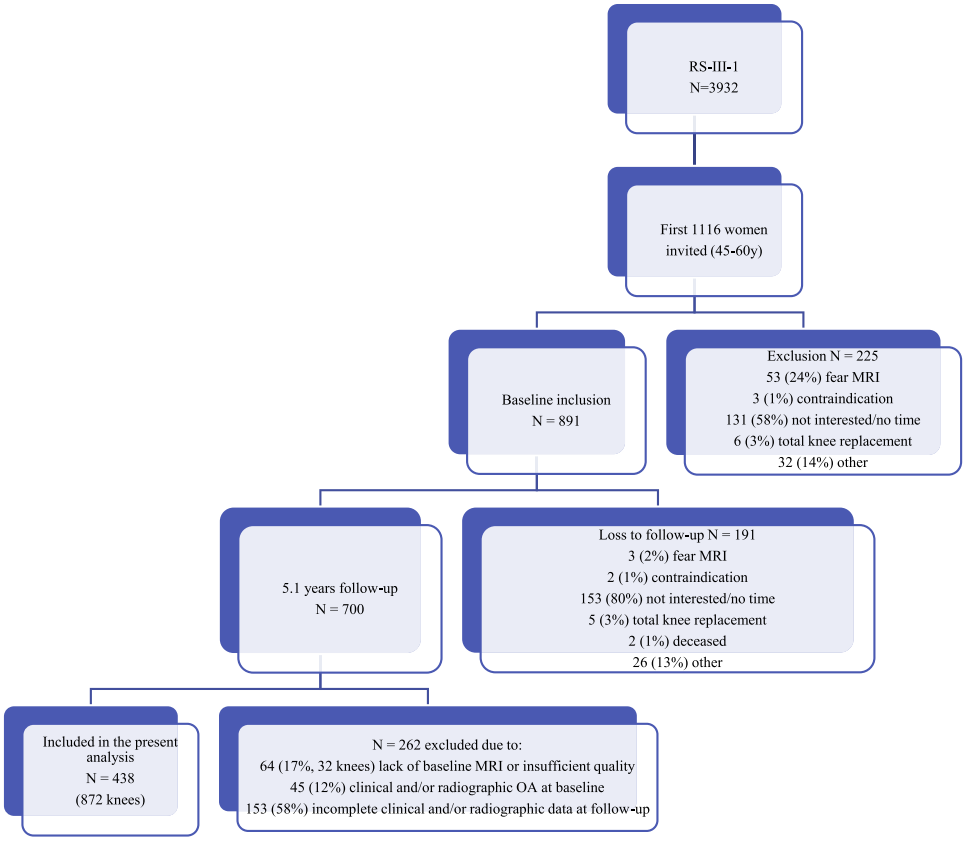

Fig. 2. Flowchart of selection process for the Rotterdam Study cohort.

Table 3
Associations between meniscal extrusion and incident knee OA after 6.6 years in the PROOF cohort (*n* total = 421 knees, *n* meniscal extrusion = 97, *n* no meniscal extrusion = 324).

	Radiographic knee OA[a] Incidence,%	Unadjusted OR (95% CI)	Adjusted OR[c] (95% CI)	Clinical knee OA[b] Incidence,%	Unadjusted OR (95% CI)	Adjusted OR[c] (95% CI)
Total	14 (60/421)			15 (63/421)		
Meniscal extrusion	30 (29/97)	3.30 (1.83, 5.93)	2.54 (1.34, 4.80)	25 (24/97)	2.33 (1.26, 4.29)	2.44 (1.29, 4.60)
No meniscal extrusion	10 (31/324)	1 (reference)	1 (reference)	12 (39/324)	1 (reference)	1 (reference)

[a] Knee OA, defined as Kellgren & Lawrance ≥ 2.
[b] Knee OA according to the ACR criteria.
[c] Generalized estimating equations adjusted for correlation of knees within subjects and confounding baseline variables: age, body mass index, history of knee injury, varus alignment, postmenopausal status, meniscal pathologies (other than extrusion) and quadriceps strength. OR: odds ratio. CI: confidence interval.

Table 4
Associations between meniscal extrusion and incident knee OA after 5.1 years in the Rotterdam Study cohort (*n* total = 872 knees, *n* meniscal extrusion = 399, *n* no meniscal extrusion = 473).

	Radiographic knee OA[a] Incidence,%	Unadjusted OR (95% CI)	Adjusted OR[c] (95% CI)	Clinical knee OA[b] Incidence,%	Unadjusted OR (95% CI)	Adjusted OR[c] (95% CI)
Total	4.5 (39/872)			3.7 (32/872)		
Meniscal extrusion	7.5 (30/399)	3.59 (1.77, 7.31)	9.86 (2.13, 45.67)	5.8 (23/399)	2.77 (1.28, 6.00)	2.65 (0.96, 7.30)
No meniscal extrusion	1.9 (9/473)	1 (reference)	1 (reference)	1.9 (9/473)	1 (reference)	1 (reference)

[a] Knee OA, defined as Kellgren & Lawrance ≥ 2.
[b] Knee OA according to the ACR criteria.
[c] Generalized estimating equations adjusted for correlation of knees within subjects and confounding baseline variables: age, body mass index, history of knee injury, varus alignment, postmenopausal status, meniscal pathologies (other than extrusion) and quadriceps strength. OR: odds ratio. CI: confidence interval.

previous study with short-term follow-up, with a clearly lower incidence of clinical knee OA[6]. Therefore, it is of added value to have knee OA based on clinical criteria as an extra outcome measure, alongside the K&L grade.

Another strength of the current study is that we found similar results within two different cohorts. The PROOF cohort is a selection of high-risk subjects, whereas the Rotterdam Study is an open population study, which explains the difference regarding the absolute incidences of both radiographic and clinical knee OA, which were much higher in PROOF. Noteworthy is the difference in baseline prevalence of meniscal extrusion between the two cohorts, with 23% in the PROOF cohort and 46% in the Rotterdam Study cohort. We know that meniscal extrusion is relatively common in asymptomatic individuals, with Gale et al. reporting up to 64% of OA free controls having $\geq$ 3 mm meniscal extrusion[1,19,20]. Within the PROOF cohort (BMI $\geq$ 27 kg/m^2) subjects with severe complaints at baseline (indicative for the presence of knee OA) were excluded. If there is a strong interaction between BMI and meniscal extrusion on the development of knee OA[21,22], this means many potential subjects would already suffer from knee OA at the age of inclusion into the PROOF study and were therefore excluded from the analysis. This might explain why the prevalence of baseline meniscal extrusion is lower in the PROOF Study.

Remarkable was the high PAR% within the open population of the Rotterdam Study cohort, suggesting that up to 77% of new cases of radiographic knee OA were attributable to meniscal extrusion. This is an unexpected high percentage, largely explained by a combination of the aforementioned high baseline prevalence of meniscal extrusion, a relatively low incidence (2% in knees without extrusion) and a large odds ratio. Nonetheless, it clearly indicates the possible impact on public health and the potential benefit of prevention or reduction of meniscal extrusion. Several factors are associated with meniscal extrusion, of which some might be possible targets for non-surgical interventions to reduce or reverse extrusion, thus decelerating or preventing the development of OA[22-28]. A randomized controlled trial of Landsmeer et al. evaluated the effect of a diet and exercise program to reduce weight on progression of MRI features of knee OA, which significantly diminished the progression of meniscal extrusion[23]. Englund et al. described the independent association between a higher BMI and meniscal extrusion, suggesting that losing weight might reduce or reverse extrusion[24]. Malalignment is another modifiable risk factor associated with meniscal extrusion and knee OA[25-27], which may be corrected using wedged insoles or knee braces, although long-term effectiveness is questioned[29-31].

Finally, surgical reduction of meniscal extrusion might be an interesting option to decelerate the degenerative course with, according to recent studies, promising short- and long-term results, although outcomes are contradictory and surgery in general has its limitations and complication risks[32–36].

There are several limitations to our study. The first and most important regards the relative high percentage of loss to follow-up, especially within the PROOF cohort (+/- 50%), which might have induced selection bias. In both cohorts, missing knees and subjects had significantly more meniscal pathologies, a higher BMI, and less quadriceps strength, suggesting an association between these variables and loss to follow-up. Since meniscus tears and a higher BMI both are related to meniscus extrusion as well as knee OA, the results of our analysis might be an underestimation due to these higher drop-out rates[21,22]. Furthermore, it is known that drop-out rates in weight-loss studies such as PROOF are relatively high, which, according to Elobeid et al., should be coped with multiple imputation[37]. In a recent paper from De Vos et al. using the same study sample from PROOF, the authors adopted this recommendation and conducted multiple imputation, but concluded that the results were unreliable[38]. Based hereupon, we did not perform multiple imputation.

Second, radiography with the K&L grading system was used to define incident structural knee OA. MRI might be more sensitive and reliable for assessing the relationship between meniscal extrusion and the initiation of knee OA, for example in quantifying cartilage damage or subchondral bone marrow lesions. However, the clinical relevance of these features remains unclear and there is no defined cut-off point for OA based on MRI[16,39]. Therefore, the K&L grading system assessed with radiography remains a central outcome measure in clinical trials in knee OA. Third, we included knees with K&L grade 1 at baseline in the analysis since they were considered not having knee OA according to the definition. There is an ongoing debate how to define incident radiographic knee OA based on the K&L scoring system, given the relatively high inter- and intra-observer variability[40,41]. Felson et al. therefore proposed only knees with grade 0 to be included in clinical studies, and only classify knees with JSN as incident OA[42]. This would have possibly resulted in more reliable outcomes, although the sensitivity analyses with additional adjustment for K&L grade 1 did not significantly affected the outcomes in neither of the cohorts. Fourth, in the Rotterdam Study cohort, knee radiographs were taken in full extension, which might have underestimated the JSN and thereby incident radiographic knee OA, compared to fixed-flexion radiographs in PROOF[43]. However, these effects are probably limited since JSN is less relevant than osteophytes for the definition of K&L grade 2 and thus incident knee OA ('definite osteophytes and possible joint space narrowing'). Fifth, MRIs were without load bearing, possibly underestimating the grade of meniscus extrusion[44]. However, according to Boxheimer et al., variation in meniscus position is minimal under loading and non-loading conditions[45]. Sixth, in the Rotterdam Study cohort, two knees were scanned in one session to reduce scanning time, resulting in a substantial lower spatial resolution. This might have had a negative effect on the detection and grading of meniscus extrusion. Last, in both cohorts only women were analyzed. The change in postmenopausal status during follow-up might have influenced the results, although the effects are probably limited since the majority in both cohorts was already postmenopausal at baseline.

Conclusions

With the present study we provided further evidence that meniscus extrusion also in the long term is largely independently associated with the development of radiographic and clinical knee OA, with clearly higher incidences of knee OA in both cohorts. The high population attributable risk percentage reflects the relevance of these results and indicates the possible impact on public health. MRI could be used for early detection of meniscus extrusion in an attempt to prevent the onset or progression of knee OA by engaging preventive non-surgical measures.

Author contributions

JvdV contributed to the analysis and interpretation of data, writing of the manuscript and final approval of the article. DS contributed to the collection and assembly of data and the semi-quantitative scoring of the MRIs, analysis and interpretation of data, critical revision of the article for important intellectual content and final approval of the article. DV and EO contributed to the conception and design of the study, critical revision of the article for important intellectual content and final approval of the article. SBZ contributed to the conception and design of the study (including obtaining of funding for the PROOF Study), critical revision of the article for important intellectual content and final approval of the article. JR contributed to the conception and design of the study, including collection and assembly of data, scoring of the MRIs, analysis and interpretation of data, critical revision of the article for important intellectual content and final approval of the article.

All authors approved the final version of the manuscript.

Role of the funding source

The PROOF Study is supported by the Netherlands Organisation for

Health Research and Development (ZonMw, grant number 120520001); European Union's Seventh Framework Programme for research, technological development and demonstration (D-BOARD, grant number 305815); and the Dutch Arthritis Foundation (grant numbers LLP19 and 12-1-304). The knee OA cohort of The Rotterdam Study is supported by the Netherlands Organisation for Scientific Research (NWO) (project no. 917.66.350); and the Dutch Arthritis Foundation (project no. 12-1-304). The Rotterdam Study is supported by the Netherlands organization of Scientific Research NWO Investments (no. 175.010.2005.011, 911.03.012); the Research Institute for Diseases in the Elderly (014-93-015; RIDE2); the Netherlands Genomics Initiative (NGI)/ Netherlands Organisation for Scientific Research (NWO) (project no. 050-060-810); Netherlands Consortium of Healthy Aging; and the Erasmus Medical Center and Erasmus University Rotterdam. The study sponsors had no further involvement than funding the study.

Declaration of Competing Interest

All authors declare no conflict of interest.

Acknowlegdments

The authors would like to thank Diana van Emmerik and Peter van der Plas for their efforts in scoring the baseline MRIs of the Rotterdam Study cohort (DvE) and the PROOF cohort (PvdP).

References

[1] Gale DR, Chaisson CE, Totterman SM, Schwartz RK, Gale ME, Felson D. Meniscal subluxation: association with osteoarthritis and joint space narrowing. Osteoarthr Cartil 1999;7:526–32.
[2] Wang Y, Wluka AE, Pelletier JP, Martel-Pelletier J, Abram F, Ding C, et al. Meniscal extrusion predicts increases in subchondral bone marrow lesions and bone cysts and expansion of subchondral bone in osteoarthritic knees. Rheumatology 2010;49:997–1004.
[3] Ghouri A, Muzumdar S, Barr AJ, Robinson E, Murdoch C, Kingsbury SR, et al. The relationship between meniscal pathologies, cartilage loss, joint replacement and pain in knee osteoarthritis: a systematic review. Osteoarthr Cartil 2022;30:1287–327.
[4] Wenger A, Wirth W, Hudelmaier M, Noebauer-Huhmann I, Trattnig S, Bloecker K, et al. Meniscus body position, size, and shape in persons with and persons without radiographic knee osteoarthritis: quantitative analyses of knee magnetic resonance images from the osteoarthritis initiative. Arthritis Rheumatism 2013;65:1804–11.
[5] Emmanuel K, Quinn E, Niu J, Guermazi A, Roemer F, Wirth W, et al. Quantitative measures of meniscus extrusion predict incident radiographic knee osteoarthritis - data from the Osteoarthritis Initiative. Osteoarthr Cartil 2016;24:262–9.
[6] van der Voet JA, Runhaar J, van der Plas P, Vroegindeweij D, Oei EH, Bierma-Zeinstra SMA. Baseline meniscal extrusion associated with incident knee osteoarthritis after 30 months in overweight and obese women. Osteoarthr Cartil 2017;8:1299–303.
[7] Runhaar J, Middelkoop van M, Reijman M, Willemsen S, Oei EH, Vroegindeweij D, et al. Prevention of knee osteoarthritis in overweight females: the first preventive randomized controlled trial in osteoarthritis. Am J Med 2015;128:888–95.
[8] Ikram MA, Brussele G, Ghanbari M, Goedegebure A, Ikram MK, Kavousi M, et al. Objectives, design and main findings until 2020 from the Rotterdam Study. Eur J Epidemiol 2020;35(5):483–517.
[9] Buckland-Wright JC, Wolfe F, Ward RJ, Flowers N, Hayne C. Substantial superiority of semiflexed (MTP) views in knee osteoarthritis: a comparative radiographic study, without fluoroscopy, of standing extended, semiflexed (MTP), and schuss views. J Rheumatol 1999;26:2664–74.
[10] Hunter DJ, Guermazi A, Lo GH, Grainger AJ, Conaghan PG, Boudreau RM, et al. Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score). Osteoarthr Cartil 2011;19:990–1002.
[11] Costa CR, William BM, Carrino JA. Medial meniscus extrusion on knee MRI: is extent associated with severity of degeneration or type of tear? Am J Roentgenol 2004;183(1):17–23. Jul.
[12] Lerer DB, Umans HR, Hu MX, Jones MH. The role of meniscal root pathology and radial meniscal tear in medial meniscal extrusion. Skeletal Radiol 2004;33(10):569–74. Oct.
[13] Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, 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.
[14] Kelsey JL, Thompson WD, Evans AS. Methods in observational epidemiology. New York, NY: Oxford University Press, Inc; 1986.
[15] Jager KJ, Zoccali C, MacLeod A, Dekker FW. Confounding: what is it and how to deal with it. Kidney Int 2008;73:256–60.
[16] Sharma L, Chmiel JS, Almagor O, Dunlop D, Guermazi A, Bathon JM, et al. Significance of preradiographic magnetic resonance imaging lesions in persons at increased risk of knee osteoarthritis. Arthritis Rheumatol 2014;66:1811–9.
[17] Teichtal AJ, Cicuttini FM, Abram F, Wang Y, Pelletier JP, Dodin P, et al. Meniscal extrusion and bone marrow lesions are associated with incident and progressive knee osteoarthritis. Osteoarthr Cartil 2017;25:1076–83.
[18] Vital Health Statistics. Prevalence of osteoarthritis in adults by age, sex, race, and geographic area, United States 1960-1962. US Department of Health, Education, and Welfare publication No. 15, Series 11. Government Printing Office; 1966. June.
[19] Bruns K, Svensson F, Turkiewicz A, Wirth W, Guermazi A, Eckstein F, et al. Meniscus body position and its change over four years in asymptomatic adults: a cohort study using data from the Osteoarthritis Initiative (OAI). BMC Musculoskelet Disord 2014;5:5–32.
[20] Bloecker K, Englund M, Wirth W, Hudelmaier M, Burgkart R, Frobell RB, et al. Revision 1 size and position of the healthy meniscus, and its correlation with sex, height, weight, and bone area – a cross-sectional study. BMC Musculoskelet Disord 2011;12:248.
[21] Van der Voet JA, Wesselius D, Zhang F, Vroegindeweij D, Oei EH, Bierma-Zeinstra SMA, et al. Factors associated with longitudinal change of meniscal extrusion in overweight women without clinical signs of osteoarthritis. Rheumatology 2021;11(60):5175–84. Nov 3.
[22] Zhang F, Bierma-Zeinstra SM, Oei EHG, Turkiewicz A, Englund M, Runhaar J. Factors associated with meniscal body extrusion on knee MRI in overweight and obese women. Osteoarthr Cartil 2017;25:694–9.
[23] Landsmeer ML, Runhaar J, van der Plas P, Middelkoop van M, Vroegindeweij D, Koes B, et al. Reducing progression of knee OA features assessed by MRI in overweight and obese women: secondary outcomes of a preventive RCT. Osteoarthr Cartil 2016;24:982–90.
[24] Englund M, Felson DT, Guermazi A, Roemer FW, Wang K, Crema MD, et al. Risk factors for medial meniscal pathology on knee MRI in older US adults: a multicentre prospective cohort study. Ann Rheum Dis 2011;70:1733–9.
[25] Hunter DJ, Sharma L, Skaife T. Alignment and osteoarthritis of the knee. J Bone Joint Surg Am 2009;91:85–9.
[26] Runhaar J, van Middelkoop M, Reijman M, Vroegindeweij D, Oei EHG, Bierma-Zeinstra SMA. Malalignment: a possible target for prevention of incident knee osteoarthritis in overweight and obese women. Rheumatology 2014;53:1618–24.
[27] Achtnich A, Petersen W, Willinger L, Sauter A, Rasper M, Wörtler K, et al. Medial meniscus extrusion increases with age and BMI and is depending on different loading conditions. Knee Surg Sports Traumatol Arthrosc 2018;26:2282–8.
[28] Crema MD, Roemer FW, Felson DT, Englund M, Wang K, Jarraya M, et al. Factors Associated with Meniscal Extrusion in Knees with or at Risk for Osteoarthritis: the Multicenter Osteoarthritis Study. Radiology 2012;264:494–503.
[29] van Raaij TM, Reijman M, Brouwer RW, Bierma-Zeinstra SMA, Verhaar JAN. Medial knee osteoarthritis treated by insoles or braces: a randomized trial. Clin Orthop Relat Res 2010;468:1926–32.
[30] Duivenvoorden T, van Raaij TM, Horemans HLD, Brouwer RW, Bos K, Bierma-Zeinstra SMA, et al. Do laterally wedged insoles or valgus braces unload the medial compartment of the knee in patients with osteoarthritis? Clin Orthop Relat Res 2015;473:265–74.
[31] Bennell KL, Bowles KA, Payne C, Cicuttini F, Williamson E, Forbes A, et al. Lateral wedge insoles for medial knee osteoarthritis: 12 month randomised controlled trial. BMJ 2011;342:d2912.
[32] Chernchujit B, Prasetia R. Arhtroscopic direct meniscal extrusion reduction: surgical tips to reduce persistent meniscal extrusion in meniscal root repair. Eur J Orthop Surg Traumatol 2018;28:727–34.
[33] Ozeki N, Muneta T, Kawabata K, Koga H, Nakagawa Y, Saito R, et al. Centralization of extruded medial meniscus delays cartilage degeneration in rats. J Orthop Sci 2017;22:542–8.
[34] Faucett SC, Geisler BP, Chahla J, Krych AJ, Kurzweil PR, Garner AM, et al. Meniscus root repair vs meniscectomy of nonoperative management to prevent knee osteoarthritis after medial meniscus root tears: clinical and economic effectiveness. Am J Sports Med 2019;47:762–9.
[35] Feucht MJ, Kühle J, Bode G, Mehl J, Schmal H, Südkamp NP, et al. Arthroscopic transtibial pullout repair for posterior medial meniscus root tears: a systematic review of clinical, radiographic, and second-look arthroscopic results. Arthroscopy 2015;31:1808–16.
[36] Moon HK, Koh YG, Kim YC, Park YS, Jo SB, Kwon SK. Prognostic factors of arthroscopic pull-out repair for a posterior root tear of the medial meniscus. Am J Sports Med 2012;40:1138–43.
[37] Elobeid MA, Padilla MA, McVie T, et al. Missing data in randomized clinical trials for weight loss: scope of the problem, state of the field, and performance of statistical methods. PLoS ONE 2009;4:e6624.
[38] De Vos BC, Landsmeer MLA, Van Middelkoop M, Oei EHG, Krul M, Bierma-Zeinstra SMA, et al. Long-term effects of a lifestyle intervention and oral glucosamine sulphate in primary care on incident knee OA in overweight women. Rheumatology 2017;56:1326–34.
[39] Yusuf E, Kortekaas MC, Watt I, Huizinga TW, Kloppenburg M. Do knee abnormalities visualized on MRI explain knee pain in knee osteoarthritis? A systematic review. Ann Rheum Dis 2011;70:60–7.
[40] Schiphof D, Boers M, Bierma-Zeinstra SM. Differences in descriptions of Kellgren and Lawrence grades of knee osteoarthritis. Ann Rheum Dis 2008;67:1034–6.
[41] Schiphof D, de Klerk B, Kerkhof H, et al. Impact of different descriptions of the Kellgren and Lawrence classification criteria on the diagnosis of knee osteoarthritis. Ann Rheum Dis 2011;70:1422–7.

[42] Felson DT, Niu J, Guermazi A, Sack B, Aliabadi P. Defining radiographic incidence and progression of knee osteoarthritis: suggested modifications of the Kellgren and Lawrence scale. Ann Rheum Dis 2011;70(11):1884–6. Nov.
[43] Niinimäki T, Ojala R, Niinimäki J, Leppilahti J. The standing fixed flexion view detects narrowing of the joint space better than the standing extended view in patients with moderate osteoarthritis of the knee. Acta Orthop 2010;81(3):344–6.
[44] Stehling C, Souza RB, Hellio Le Graverand MP, Wyman BT, Li X, Majumdar S, et al. Loading of the knee during 3.0T MRI is associated with significantly increased medial meniscus extrusion in mild and moderate osteoarthritis. Eur J Radiol 2012; 81:1839–45.
[45] Boxheimer L, Lutz AM, Treiber K, Goepfert K, Crook DW, Marincek B, et al. MR imaging of the knee: position related changes of the menisci in asymptomatic volunteers. Invest Radiol 2004;39:254–63.