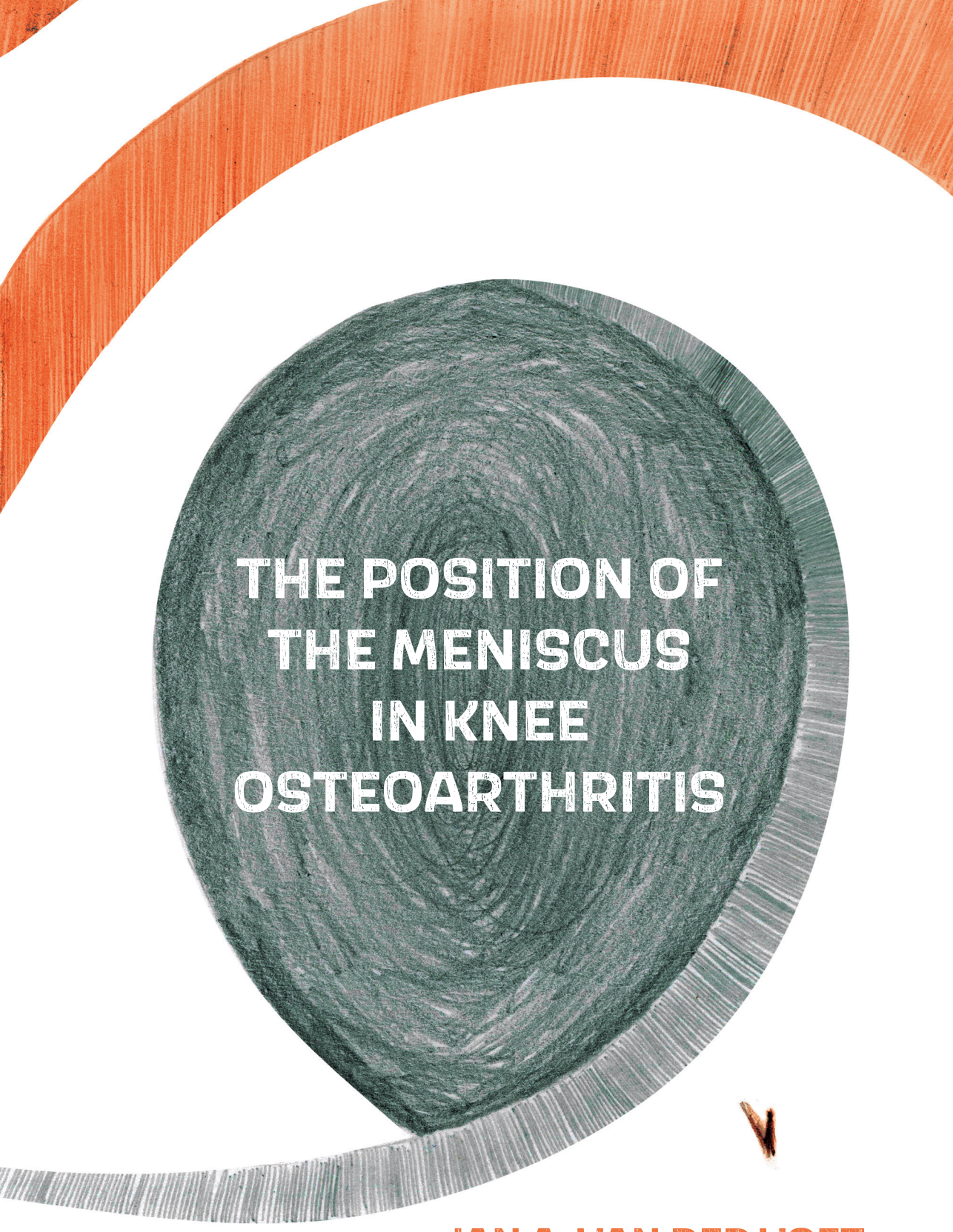

THE POSITION OF THE MENISCUS IN KNEE OSTEOARTHRITIS

JAN A. VAN DER VOET

The Position of the Meniscus in Knee Osteoarthritis

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The Position of the Meniscus in Knee Osteoarthritis

De positie van de meniscus in gonartrose

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op gezag van de rector magnificus

Prof. dr. A.L. Bredenoord

en volgens het besluit van het College voor Promoties.

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Co-promotoren:	Dr. J. Runhaar Dr. D. Vroegindeweij

Voor Mats

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General introduction

OSTEOARTHRITIS

With a worldwide growing population and increasing life expectancy, osteoarthritis (OA) prevalence and incidence increases, causing a major burden at individual and society level, with rising disability and medical and socioeconomic costs.[1-3] In 2017, OA accounted for 303.1 million prevalent cases, 14.9 million incident cases and 9.6 million years lived with disease (YLD) worldwide, based on age-standardized estimates of the Global Burden of Disease Study.[1] In the Netherlands, the prevalence of OA was 1.2 million in 2015, numbers which are likely to increase in the nearby future.[4,5] Women aged 60 years or older are almost twice as much affected as men (18% vs. 9.6%, respectively). In industrialized countries, the direct (e.g., joint replacement, medical treatment) and indirect (e.g., loss in productivity, premature retirement) costs of OA are 1 to 2.5% of the gross domestic product.[2,6]

Although the knee is the second most common involved joint (after the interphalangeal joints), knee OA is responsible for most of the disease burden.[7,8] A knee with established OA is characterized by loss of cartilage, osteophyte formation, subchondral bone sclerosis and cysts formation, synovial inflammation, and meniscal damage (Figure 1). This leads to progressive pain, stiffness, and functional impairment, often exerting a significant reduction in quality of life (QOL).[9,10] The clinical diagnosis is based on corresponding symptoms, radiographic changes, or both. OA is a slowly progressive degenerative disease with mainly symptomatic therapies. Therefore, prevention or delaying the degenerative process is important and can have a major beneficial impact both on patient and on society level. To date, several risk factors associated with incident knee OA have been identified, including age, obesity, gender, genetics, meniscal tears, and a history of knee injury, of which some are modifiable and therefore potential targets for preventative measures.[11,12] Meniscus extrusion is a common finding in knees with established OA, raising the question whether a displaced meniscus precedes the onset of OA and hence can be considered a risk factor, or if it is a consequence of the degenerative process. This chicken or egg dilemma persisted for quite a long time. The primary aim of this thesis is to clarify this problem.

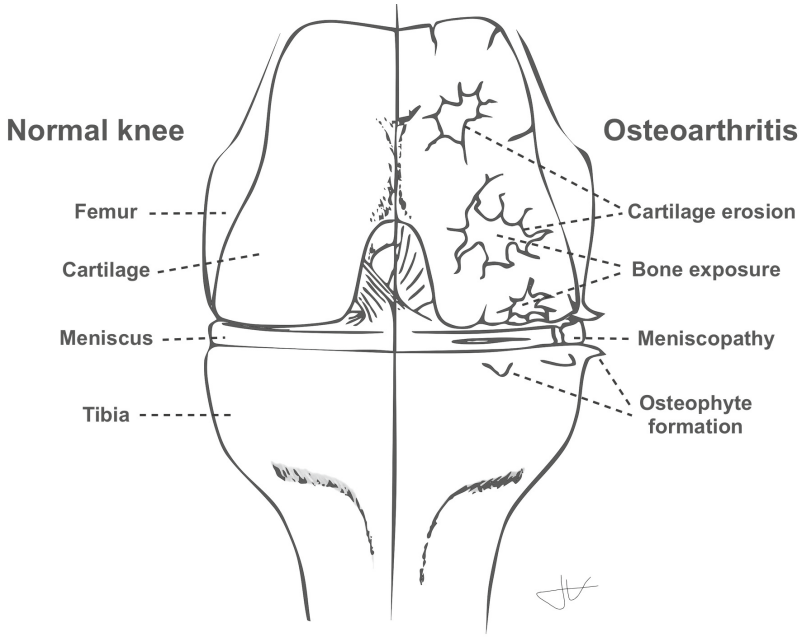

Figure 1. Normal knee vs. knee with osteoarthritis.

MENISCUS

Meniscus is derived from the Greek word *meniskos* meaning crescent moon.[13] The menisci are wedge-shaped fibrocartilaginous structures within the femorotibial joint, one medial and one lateral. They are connected to the bones and joint capsule by several ligaments and anteriorly to each other by the transverse ligament. The medial meniscus is larger and less mobile because of a firm attachment to the tibia plateau via the coronary ligament, making it more vulnerable to tears.[14] The lateral meniscus is connected to the articular capsule and tibia and posteriorly to the medial femoral condyle via the ligament of Humphrey or Wrisberg. It is more mobile because posterolaterally it is separated from the capsule by the popliteus tendon, and it has a more circular shape and covers more articular cartilage compared to the medial meniscus. The menisci are predominantly built up out of chondrocytes and fibroblasts, with a strong extracellular matrix of mostly type I collagen fibers (90-95%).[14] These predominantly circumferential oriented fibers result in great tensile stiffness and are thereby able to resist radial displacement during axial loading, also known as hoop strain.[15] The menisci are largely avascular except for the outer rim or red zone, supplied by the parameniscal capillary plexus originating from the superior and inferior medial and lateral geniculate arteries (Figure 2).

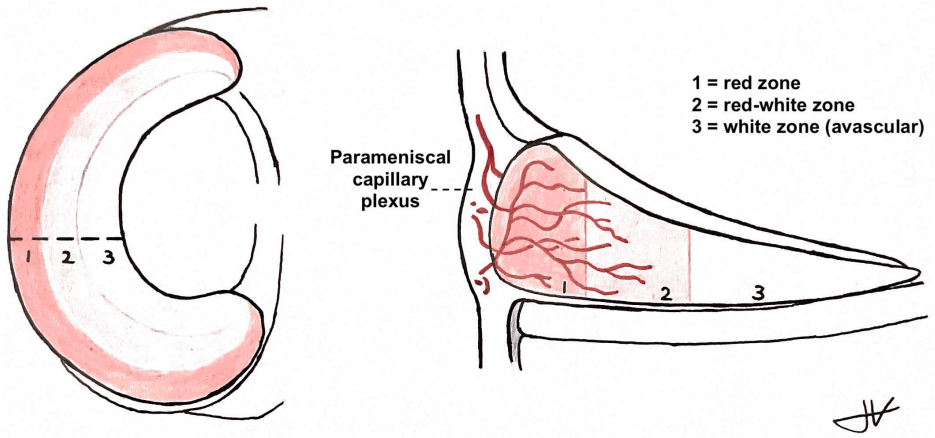

Figure 2. Axial and cross-sectional anatomy of the meniscus with its vascular supply.

In 1897, Bland-Sutton considered the menisci as 'functionless vestigial remnants of intra-articular leg muscles'.[16] This assumption led to total meniscectomy being the standard treatment for injured menisci until well in the 20th century, with excellent short-term results.[17] During the past century however, several papers were published describing potential negative long-term effects of a removed meniscus due to the altered biomechanics of the knee. King in 1936 and Fairbank in 1948 were one of the first to report that meniscectomy could predispose degenerative changes in the knee, which increased the awareness among surgeons of the true importance of the menisci.[18,19] In 1976, Krause *et al.* described that a decrease in the contact area after (partial) meniscectomy resulted in an up to three times increase in stress in the knee joint, causing overload of articular cartilage which leads to proteoglycan loss and disaggregation and increase in hydration.[20,21] In early OA stages, loss of proteoglycans and loosening of the collagen network occur in the superficial parts of the cartilage and may still be reversible at that point. Gradually, these changes extend into the deeper cartilage zones, diminishing the cartilage elasticity and making a return to homeostasis – the balanced interactions between the synthesis and breakdown of the extracellular matrix (ECM) – increasingly difficult and eventually impossible, resulting in irreparable damage.[22-25]

Many papers have described the prevalence of radiological changes after meniscectomy. One of the most comprehensive studies with a follow-up time of 21 years found a relative risk for definite tibiofemoral OA with advanced radiological changes of 14 (95% confidence interval (CI) 3.5 to 121.2).[26] Based on these new insights, there has been a slow shift towards partial meniscectomy in the second half of the 20th century, with

better long-term results, especially when the outer rim of the meniscus is preserved, which is to a great extent responsible for the biomechanical function of the knee.[27] The short-term outcomes further improved after the introduction of arthroscopic partial meniscectomy in the 1960s by Ikeuchi.[28,29] Nonetheless, also after partial meniscectomy subjects have a greater risk of knee OA development. In a randomized prospective trial with a median follow-up period of 7.8 years comparing partial and total meniscectomy, the function of the knee was inversely related to the amount of tissue removed.[27] In 1980, Goodfellow stated in an editorial in the *Journal of Bone and Joint Surgery* that "meniscectomy is only justifiable if a meniscus is causing more trouble than it is worth".[30] Therefore, the aim has shifted to avoid meniscectomy if possible and meniscal repair gained increased interest. Several techniques have been developed with promising results.[31] However, a large number of meniscal tears encountered during arthroscopy remain irreparable, especially when located in the avascularized inner white or red-white zone, and partial or (sub)total meniscectomy is frequently inevitable.[32]

Nowadays, the key role of the menisci in load bearing, load distribution and stabilization during knee movement is widely recognized.[33-36] Other functions include proprioception, joint lubrication, and cartilage nutrition.[37-39] They extend the contact area between femur and tibia, thereby increasing joint congruency and decreasing stress on the articular cartilage, which is illustrated with Figure 3. These biomechanical

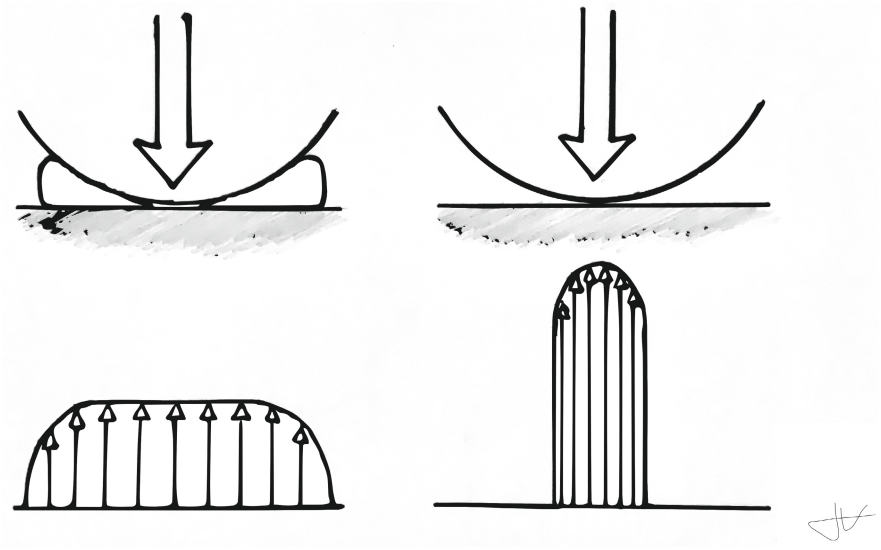

Figure 3. Illustration of the load distributing capacities of the meniscus resulting in less stress on the articular cartilage.

functions are declined in case of meniscal pathology, including extrusion, which might initiate the onset of OA. The definition of meniscus extrusion is displacement of the outer border of the meniscus beyond the femorotibial joint line (Figure 4). Often, extrusion is encountered simultaneously with an increased volume of the meniscus. The exact etiology behind this observation is unclear. Wenger *et al.* suggested that an extruded meniscus has the opportunity to expand because it is not being compressed between the bones of the femur and tibia.[40] Alternatively, an increase in meniscus volume and thickness results in limited joint space, squeezing the meniscus outside the joint margin.[41] Either way, these hypotheses of a cause-effect relationship suggest an interaction between meniscus extrusion, meniscus volume, their change over time and, possibly, knee OA development. To unveil the association between baseline meniscus volume and incident knee OA, as well as the mediation effect between change in meniscus volume, change in meniscus extrusion and incident knee OA is the secondary aim of this thesis.

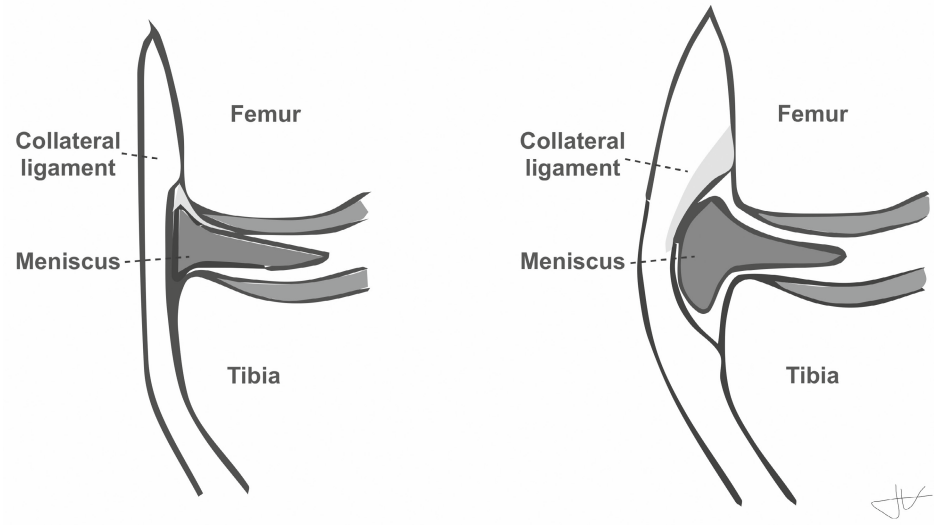

Figure 4. Normal meniscus versus meniscus extrusion.

MRI

To non-invasively visualize the meniscus and related pathology, Magnetic Resonance Imaging (MRI) is the preferred modality. MRI is widely used in radiology for diagnosing and staging diseases. It provides three-dimensional information about both the anatomy and physiology of the soft tissues, with excellent contrast and spatial resolution. The underlying physics are based on hydrogen atoms within water nuclei of which roughly two-thirds of the human body is composed.[42] Hydrogen atoms contain

a nucleus with a single proton, which is very sensitive for (changes in) magnetic fields, like a compass needle. The MRI produces such strong magnetic fields, in which the protons all line up in the same plane, either in the positive or negative direction of the magnetic field ('equilibrium state'). With a radiofrequency (RF) pulse the protons are excited, producing a signal which is measured by a receiving coil. The rate at which excited protons return to their equilibrium state (thereby emitting RF energy) depends on the type of tissue and therewith determines the contrast between these tissues. The time between the delivery of the RF pulse and the receipt of the echo signal is called Time to Echo (TE). The time between consecutive pulse sequences applied to the same slice is called the Repetition Time (TR). This information is used to generate the diagnostic images. The amount of detail or resolution of the images depends on the field strength of the scanner, expressed in tesla (T). A higher field strength also reduces the scanning time. In knee imaging, a major advantage of MRI compared to other modalities is that it depicts not only the meniscus but also the other tissues in the knee (e.g., articular cartilage, ligaments, bone marrow, synovium), making it a powerful tool in clinical practice and research settings (Figure 5). However, given the cost and availability of MRI, selecting a target population for the primary prevention of knee OA would rather be done using radiographic and clinical criteria.

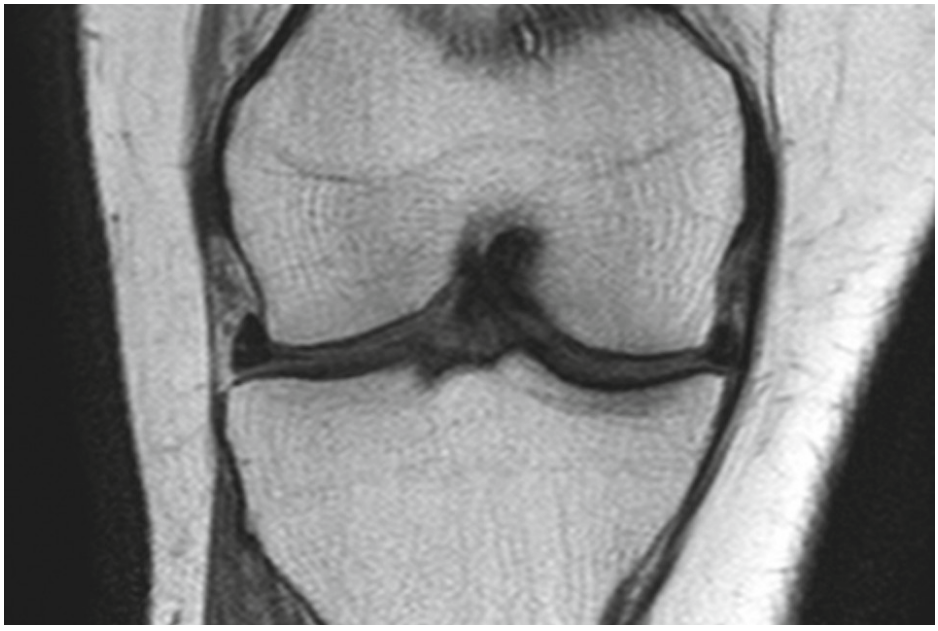

Figure 5. Example of a 1.5 T mid-coronal proton density weighted magnetic resonance image, showing normal aspect and position of both the medial (left) and lateral (right) meniscus.

THE PROOF AND ROTTERDAM STUDY

Most of the data used for this thesis are provided by the PROOF Study (PRevention of knee Osteoarthritis in Overweight Females), the first prospective intervention study aimed to assess the preventive effect of an oral glucosamine sulphate and a lifestyle intervention (diet and exercise) on incident radiographic and clinical knee OA.[43] The study population consisted of 407 middle-aged overweight and obese women at risk for the development of knee OA, but free of clinical knee OA at baseline according to the American College of Rheumatology (ACR) criteria.[44] Because the risk for incident knee OA increases significantly with a Body Mass Index (BMI) ≥ 27 kg/m^2, this was used as a cut-off point for inclusion.[45] Extensive clinical, radiographic, and magnetic resonance imaging (MRI) data were collected at baseline, after a short-term follow-up of +/- 2.5 years and a long-term follow-up of +/- 6.6 years. Sensitivity analyses were performed to correct for the potential effects of the interventions, their interaction, and their interaction with meniscus extrusion.

Another important data source was a nested cohort of the Rotterdam Study. The Rotterdam Study is a large prospective and ongoing population-based cohort study conducted in Ommoord, a city district of Rotterdam, the Netherlands, investigating the incidences and related risk factors of multiple chronic diseases of various organ systems in elderly people, including the musculoskeletal apparatus.[46] In 2006 subjects aged ≥ 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 pre-clinical knee OA, aiming to identify subjects at high-risk of knee OA development. At baseline and after a mean follow-up of 5.1 years, participating subjects filled in comprehensive questionnaires, underwent physical and radiographic examination and an MRI of both knees was performed.

AIMS AND OUTLINE OF THE THESIS

The primary aim of this thesis is to determine the relationship between meniscus extrusion and the onset of knee OA. Second, the association of meniscus volume with knee OA is assessed, as well as the interplay between change in volume and extrusion and OA development. Third, we try to identify potential risk factors associated with meniscus extrusion.

The focus of **Part I** lies on meniscus extrusion and volume and their relationship with incident knee OA. **Chapter 2** focusses on the short-term incidence of knee OA in a high-risk population of overweight and obese women, without clinical and radiographic signs of OA at baseline (PROOF study). The outcome measures were either radiographic knee OA (Kellgren & Lawrence (K&L) grade 2 or higher), clinical OA according to the ACR criteria, or medial or lateral joint space narrowing (JSN) of ≥ 1.0 mm. In **Chapter 3**, we aim to validate the findings of Chapter 2 by assessing the long-term association of meniscus extrusion with incident knee OA in two different cohorts (PROOF and the Rotterdam Study). In **Chapter 4** we evaluate the possible association between baseline and change in meniscal volume (delta volume) with knee OA development. **Chapter 5** focusses on the change in meniscal volume and extrusion, their interplay, and the association with incident knee OA. For both Chapter 4 and Chapter 5, data of the PROOF study were used.

In **Part II**, multiple variables are analyzed for their potential relationship with meniscus extrusion, which might act as potential targets for prevention or delaying knee OA development. In **Chapter 6,** we conducted a longitudinal analysis with data from the PROOF study to identify variables associated with change in meniscus extrusion over time. **Chapter 7** has a special focus on postmenopausal status and meniscus extrusion, using data from the Rotterdam Study.

In the general discussion of **Chapter 8** we summarize and critically evaluate the findings, try to draw connections and conclusions, and propose practical implications.

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1

PART I

The role of meniscus extrusion and meniscus volume in the development of knee osteoarthritis

2

Baseline meniscal extrusion associated with incident knee osteoarthritis after 30 months in overweight and obese women

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ABSTRACT

Objective

To investigate the association between baseline meniscal extrusion and the incidence of knee osteoarthritis (KOA) after 30 months in a high-risk population of overweight and obese women, free of clinical and radiological KOA at baseline.

Methods

407 middle-aged overweight women (body mass index – BMI ≥ 27 kg/m^2) were evaluated at baseline and after 30 months of follow-up. Meniscal extrusion was defined as grade ≥ 2 on MRI according to MRI Osteoarthritis Knee Score (MOAKS). The primary outcome measure was KOA after 30 months follow-up, defined using the following criteria: either incidence of radiographic KOA (Kellgren & Lawrence grade 2 or higher), or clinical osteoarthritis (OA) according to the American College of Radiology (ACR) criteria, or medial or lateral joint space narrowing (JSN) of ≥ 1.0 mm. Using generalized estimating equations (GEE), we determined the association between knees with and without meniscal extrusion and both outcomes, corrected for the baseline differences.

Results

640 knees were available at baseline of which 24% (153) had meniscal extrusion. There was a significantly higher incidence of KOA according to the primary outcome measure in women with meniscal extrusion compared to those without extrusion (28.8%, odds ratio – OR 2.39, 95% CI 1.53, 3.73). A significantly higher incidence was found for the development of radiographic KOA (12.4%, OR 2.61, 95% CI 1.11, 6.13) and medial JSN (11.8%, OR 3.19, 95% CI 1.59, 6.41). Meniscal extrusion was not significantly associated with clinical KOA and lateral JSN.

Conclusion

Meniscal extrusion was associated with a significantly higher incidence of KOA, providing an interesting target for early detection of individuals at risk for developing KOA.

INTRODUCTION

Meniscal pathology, including tears, destruction and extrusion, is a common finding in knees with osteoarthritis (OA). Since knee osteoarthritis (KOA) is a largely irreversible condition, identifying risk factors before onset or in an early stage of the disease is of great importance. Meniscal extrusion might be such an interesting target for early detection. Extrusion is where the meniscus is partially or totally displaced from the tibial cartilage surface.[1] It can occur secondary to meniscal tears, but multiple other factors are related to extrusion, including higher age, obesity, history of knee trauma, malalignment and generalized OA.[2-5] The generally accepted idea is that a displaced meniscus affects the weight-bearing and load distribution capacities within the knee joint, which leads to loss of cartilage and increase in bone marrow lesions, ultimately resulting in KOA.[6-8] Multiple studies affirm this relationship between meniscal extrusion and the development of KOA or features thereof.[6-10] However, most of these studies were carried out in cohorts of subjects with established OA. In order to confirm that meniscal extrusion is largely independently related to incident KOA, evaluation should take place in a large high-risk population, free of KOA at baseline. Therefore, the objective of the present study was to evaluate the association between baseline meniscal extrusion and the incidence of KOA in a high-risk population, free of clinical and radiographic KOA at baseline.

METHODS

Data collection/study population

Data were derived from the PROOF study, 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 ≥ 27 kg/m^2, free of clinical and radiographic KOA at baseline. This study has been described in detail previously (ISRCTN 42823086).[11] Aim of this study was to assess the preventative effect of a lifestyle intervention (diet and exercise) and of oral glucosamine sulphate (double-blind placebo controlled) on the development of KOA. At baseline, subjects filled in a questionnaire to assess physical activity and were asked for menopausal status and history of knee injury. Bodyweight, height, Heberden's nodes (as an indication for generalized OA), knee alignment and maximum strength of the quadriceps muscle were measured and, to assess the K&L grade, a standardized semi-flexed posteroanterior (PA) radiograph of both knees was taken according to the metatarsophalangeal (MTP) protocol.[12] The duration of follow-up was 30 months.

MRI technique and scoring

At baseline a multisequence 1.5 T Magnetic Resonance Imaging (MRI) of both knees was made, including a coronal and sagittal proton density (PD) weighted sequence with 3.0 mm slice thickness and a slice gap of 0.3 mm, which we used for our study. MRIs were scored by trained readers (Jos Runhaar, Peter van der Plas) as well as an experienced musculoskeletal radiologist (Edwin Oei) using the MRI Osteoarthritis Knee Score (MOAKS).[13]

Definitions

Meniscal extrusion was defined as grade 2 or grade 3 extrusion according to the MOAKS criteria, which corresponds to an extrusion of 3 mm or more. Grade 0 or 1 extrusion (< 2 mm, 2–2.9 mm) was considered as no extrusion. The primary outcome measure was the incidence of KOA, defined using the following criteria: either radiographic KOA (Kellgren & Lawrence (K&L) grade 2 or higher), clinical OA according to the ACR criteria, or medial or lateral joint space narrowing (JSN) of ≥ 1.0 mm. Subsequently we evaluated the exact location of extrusion by subdividing both the medial and lateral meniscus into the body and anterior horn (resulting in four subregions).

Statistical analysis

Knees with and without meniscal extrusion were compared for the primary outcome measure and its separate items using generalized estimating equations (GEE), with which we corrected for both the correlation between two knees within subjects as well as the baseline differences between the two groups. To correct for the potential effects of the interventions of the original trial, their mutual interactions and their interactions with baseline meniscal extrusion on the outcomes, a sensitivity analysis in which all these factors were added to the analyses was performed. Furthermore, the effect of additional adjustment for baseline K&L grade was evaluated. The outcomes are being presented in percentages, odds ratios (ORs) and confidence intervals. A two-sided p-value of < 0.05 was considered statistically significant. All analyses were performed with the SPSS-software, version 22.0.0.0 (2013, IBM, NY, USA).

RESULTS

Patient characteristics

Initially, 407 women were enrolled in the study, of which 330 women and 640 knees were eligible for statistical analysis; 77 women and 174 knees did not have an MRI

at baseline, or had incomplete data regarding the primary outcome measure, or had K&L ≥ 2 at baseline and were therefore excluded from the analysis. Of these 640 knees, 153 showed meniscal extrusion on MRI (23.7%). The majority of the extrusions were located in the medial meniscus; primarily in the body (71%), followed by anterior extrusion (35%). Only a few knees had extrusion in the lateral meniscus (8%). The subjects had a mean age of 56.2 ± 3.0 years and a mean BMI of 32.5 ± 4.26 kg/m^2. More than one-third (69%) of the women were postmenopausal (*n* = 102). At baseline, there were significant differences between knees with and without meniscal extrusion regarding age, history of knee injury, varus alignment, Heberden's nodes, maximum strength of the quadriceps muscle, osteophytes in the tibiofemoral joint, bone marrow lesions in the tibiofemoral joint and meniscal pathologies (of which the latter three were scored on MRI). Consequently, the main model was adjusted for all these variables.

Association between meniscal extrusion and primary and secondary outcome measures

Associations between baseline meniscal extrusion, the primary outcome measure and its separate criteria are shown in Table 1. 28.8% of the 153 knees with meniscal extrusion at baseline had developed KOA (adjusted OR 2.39, 95% CI 1.53, 3.73), which is significantly more compared to the group without extrusion (14.2%). Incidence of radiographic KOA was seen in 12.4% of the knees with extrusion, which is also significantly higher compared to the control knees (adjusted OR 2.61, 95% CI 1.11, 6.13). Furthermore, medial JSN was seen significantly more often in knees with meniscal extrusion (11.8%, adjusted OR 3.19, 95% CI 1.59, 6.41). The incidence rates of both clinical KOA and lateral JSN were also higher for patients with extrusion, but these differences did not reach statistical significance. Of the four separate locations, only extrusion of the medial meniscus body was significantly associated with the incidence of KOA (Table 2). Since the numbers of lateral extrusion were too low for reliable statistical analysis, only the percentages and OR's of medial extrusion are shown in the table. The sensitivity analyses showed a non-significant interaction between either of the original interventions and baseline meniscal extrusion. The interaction between the original interventions was statistically significant but did not influence the outcomes significantly (data not shown). Additional adjustment for baseline K&L grade did not essentially affect the results from the main model (data not shown).

Table 1. Associations between meniscal extrusion and incident knee OA after 30 months (*n* total = 640 knees, *n* meniscal extrusion = 153, *n* no meniscal extrusion = 487).

	Knee OA*		Radiographic knee OA		Clinical knee OA		Medial JSN		Lateral JSN	
	Incidence, %	**OR (95% CI)**	**Incidence, %**	**OR (95% CI)**	**Incidence, %**	**OR (95% CI)**	**Incidence, %**	**OR (95% CI)**	**Incidence, %**	**OR (95% CI)**
Total	17.8 (113/640)		5.5 (35/640)		5.2 (33/640)		5.5 (35/640)		6.4 (41/640)	
Meniscal extrusion	28.8 (44/153)	2.39 (1.53, 3.73)	12.4 (19/153)	2.61 (1.11, 6.13)	6.5 (10/153)	1.62 (0.7, 3.74)	11.8 (18/153)	3.19 (1.59, 6.41)	8.5 (13/153)	1.5 (0.84, 2.66)
No meniscal extrusion	14.2 (69/487)	1 (reference)	3.3 (16/487)	1 (reference)	4.7 (23/487)	1 (reference)	3.5 (17/487)	1 (reference)	5.7 (28/487)	1 (reference)

*Defined as the incidence of radiographic knee OA (K&L grade ≥ 2), clinical knee OA (ACR criteria) or medial or lateral joint space narrowing (≥ 1.0 mm) at follow-up. JSN = joint space narrowing, OR = odds ratio. All analyses were adjusted for age, history of knee injury, varus alignment, Heberden's nodes, maximum strength of the quadriceps muscle, osteophytes in the tibiofemoral joint, bone marrow lesions in the tibiofemoral joint and meniscal pathologies.

Table 2. Associations between central and anterior medial meniscal extrusion and incident knee OA after 30 months.

	Meniscal extrusion (*n* =153)	Knee OA*		Radio-graphic knee OA		Radio-graphic knee OA		Medial JSN		Lateral JSN	
		Incidence (%)	Adjusted OR (95% CI)	Incidence (%)	Adjusted OR (95% CI)	Incidence (%)	Adjusted OR (95% CI)	Incidence (%)	Adjusted OR (95% CI)	Incidence (%)	Adjusted OR (95% CI)
Central medial meniscal extrusion	71% (108/153	34 (37/108)	2.75 (1.72, 4.4)	15 (16/108)	2.6 (1.15, 5.89)	7 (8/108)	1.9 (0.88, 4.07)	16 (17/108)	4.5 (2.16, 9.36)	11 (12/108)	2.33 (1.21, 4.49)
No central medial meniscal extrusion		14 (76/532)	1 (reference)	4 (19/532)	1 (reference)	5 (25/532)	1 (reference)	3 (18/532)	1 (reference)	5 (29/532)	1 (reference)
Anterior medial meniscal extrusion	35% (53/153)	23 (12/53)	1.08 (0.52, 2.23)	13 (7/53)	1.7 (0.68, 4.25)	4 (2/53)	0.73 (0.13, 4.12)	6 (3/53)	0.61 (0.17, 2.21)	4 (2/53)	0.48 (0.17, 1.37)
No anterior medial meniscal extrusion		17 (101/587)	1 (reference)	5 (28/587)	1 (reference)	5 (31/587)	1 (reference)	5 (32/587)	1 (reference)	7 (39/587)	1 (reference)

*Defined as the incidence of radiographic knee OA (K&L grade ≥ 2), clinical knee OA (ACR criteria) or medial or lateral joint space narrowing (≥ 1.0 mm) at follow-up. JSN = joint space narrowing, OR = odds ratio. Analysis for central medial meniscal extrusion were adjusted for the following baseline differences: varus alignment, maximum strength of the quadriceps muscle, osteophytes in the tibiofemoral joint, meniscal pathologies and anterior medial meniscal extrusion. Analysis for anterior medial meniscal extrusion were adjusted for the following baseline differences: Heberden's nodes, osteophytes in the tibiofemoral joint, meniscal pathologies and central medial meniscal extrusion.

DISCUSSION

We assessed the association between baseline meniscal extrusion with the incidence of KOA in a high-risk population, free of clinical and radiographic KOA at baseline. We found that almost 30% of our population developed KOA, which is a remarkably high percentage considered the relatively short follow-up time of 30 months. Since this study was performed in a large high-risk population without OA at baseline, this result provides strong evidence that extrusion is related to incident KOA.

The results further indicate a discrepancy between radiographic and clinical signs of KOA, since knees with meniscal extrusion did not show a statistically significant association with clinical KOA, despite a higher incidence of almost 40% compared to those without. Particularly for mild KOA, the most likely cause for this phenomenon is the variability in pain perception between individuals.

One of the strengths of our study is that we evaluated four meniscal subregions, while most studies in the field focused on medial body extrusion only. Still, our data confirm that medial body extrusion is more strongly associated with incident KOA than any other location, which, to save time and costs, supports the choice for one sole measurement location in previous and future studies. The vast majority of the meniscal extrusions were located in the medial meniscus, especially in the body (71%), which corresponds to previous findings.[6,9] The difference seen in our study however is slightly more pronounced, with only 12 knees (8%) showing lateral extrusion.

Since we demonstrated that meniscal extrusion is largely independently related to the development of KOA, it is important to know what causes meniscal extrusion. Crema *et al*. performed a large observational study among 1527 patients and 2131 knees and described several extrusion related factors.[2] Independent of the type and location (e.g., radial, longitudinal, vertical, complex, root and non-root), tears of the meniscus are associated with extrusion in both compartments, which was confirmed by Zhang *et al*. in a recent study using longitudinal data.[3] Crema *et al*. further demonstrated an independent association of tibiofemoral cartilage damage with meniscal extrusion, most likely due to the altered weight bearing and load distribution capacities in knees with a displaced meniscus.[6-10] Their hypothesis is that the cascade begins with loss of cartilage, narrowing the tibiofemoral space, squeezing the meniscus and leading to extrusion. Still, there is limited evidence which supports this theory that cartilage damage is predictive for meniscal extrusion.

Meniscal tears and cartilage damage however are both largely non-modifiable risk factors. To prevent development or progression of meniscal extrusion and thus KOA, knowledge about modifiable factors is important. Malalignment might be an interesting modifiable factor related to both meniscal extrusion and KOA, where varus alignment is associated with medial extrusion and valgus alignment with lateral extrusion.[14] Nevertheless, it is not clear whether malalignment on its own precedes extrusion or is just secondary to progressive meniscal extrusion and KOA. Englund *et al*. showed that a higher BMI is related to meniscal extrusion, although this was not confirmed in another study sample.[3,4] Since obesity is modifiable, one can hypothesize that losing weight might reduce or reverse extrusion, thus preventing development or progression of KOA. The results of the study of Landsmeer *et al*. could be interpreted as an extension of these findings.[15] They found that the diet and exercise program resulted in significantly less progression of meniscal extrusion in the same population used in the present study.

The definition for meniscal extrusion used for the present study was grade 2 or grade 3 according to the MOAKS criteria, which corresponds to an extrusion of 3 mm or more. MOAKS is an evolution of older methods such as Knee Osteoarthritis Scoring System (KOSS), Whole-Organ Magnetic Resonance Imaging Score (WORMS) and Boston Leeds Osteoarthritis Knee Score (BLOKS) and has proven itself as a valid tool for the evaluation of MRI OA features.[13] However, a semi-quantitative scoring method for the meniscus does not take into account the proportion of the tibial cartilage surface covered by the meniscus. It does not consider the absolute sizes of both meniscus and tibial plateau which obviously varies between individuals. Several recent studies described a new approach for quantitative MRI analysis of meniscal extrusion using 3D imaging techniques, which might be a more reliable way to assess volumetric morphometry and extrusion of the meniscus and a more truthful representation of the *in vivo* situation.[9,10]

Conclusion and implications

With this prospective study among middle-aged overweight and obese women without KOA at baseline we provided solid evidence that meniscal extrusion is a largely independent predictor for the development of KOA, which gives further insight in the pathogenesis of the disease. Meniscal extrusion might be used for early detection of patients at risk for developing KOA and could potentially be used for future preventative therapies, especially in the young to middle-aged patient, which the field currently lacks. However, what these preventative therapies should look like, is still unknown.

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3

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

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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 ≥ 3 mm on MRI. Outcomes were incident radiographic (KL ≥ 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 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%).

MATERIALS AND METHODS

Study design

We conducted a cohort study using data from the PROOF study (PRevention of knee Osteoarthritis in Overweight Females, ISRCTN 42823086), 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 Dutch 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 ≥ 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 sulphate (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 *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 ≥ 45 years had been recruited from Ommoord, a city district of Rotterdam, the Netherlands. In 2006 subjects aged ≥ 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 (Jos Runhaar, Peter van der Plas) who were trained by a highly experienced musculoskeletal radiologist (Edwin Oei; 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 (Dieuwke Schiphof, Diana van Emmerik) who were extensively trained by the same experienced musculoskeletal radiologist as in the PROOF Study (Edwin Oei).

Definitions

Meniscal extrusion was defined as grade 2 (3-4.9 mm) or grade 3 (≥ 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 ≥ 2, with baseline K&L < 2, meaning that knees with a K&L score ≥ 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% = $[(Rate_{total\ population} - Rate_{unexposed}) / (Rate_{total\ population})] \times 100\%$.[14] An equivalent expression in terms of rate ratio (RR) and prevalence of exposure ($P_{exposed}$) is PAR% = $P_{exposed}\ (RR - 1) / [1 + P_{exposed}\ (RR - 1)]$. [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 Table 1 and Table 2.

Table 1. Baseline characteristics of the PROOF cohort.

	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

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

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 (Figure 1). Furthermore, knees with K&L ≥ 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/m².

Table 2. Baseline characteristics of the 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.

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 ($p < 0.001$).

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 Figure 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.

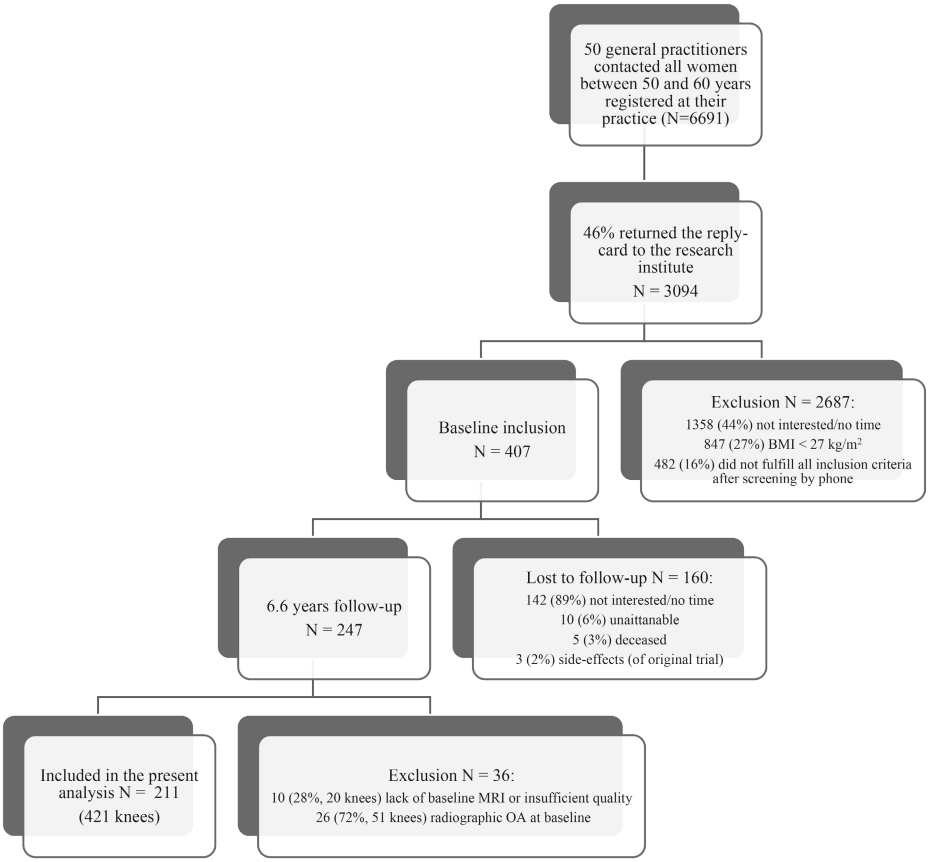

Figure 1. Flowchart of the selection process of the PROOF cohort.

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 ($p = 0.027$).

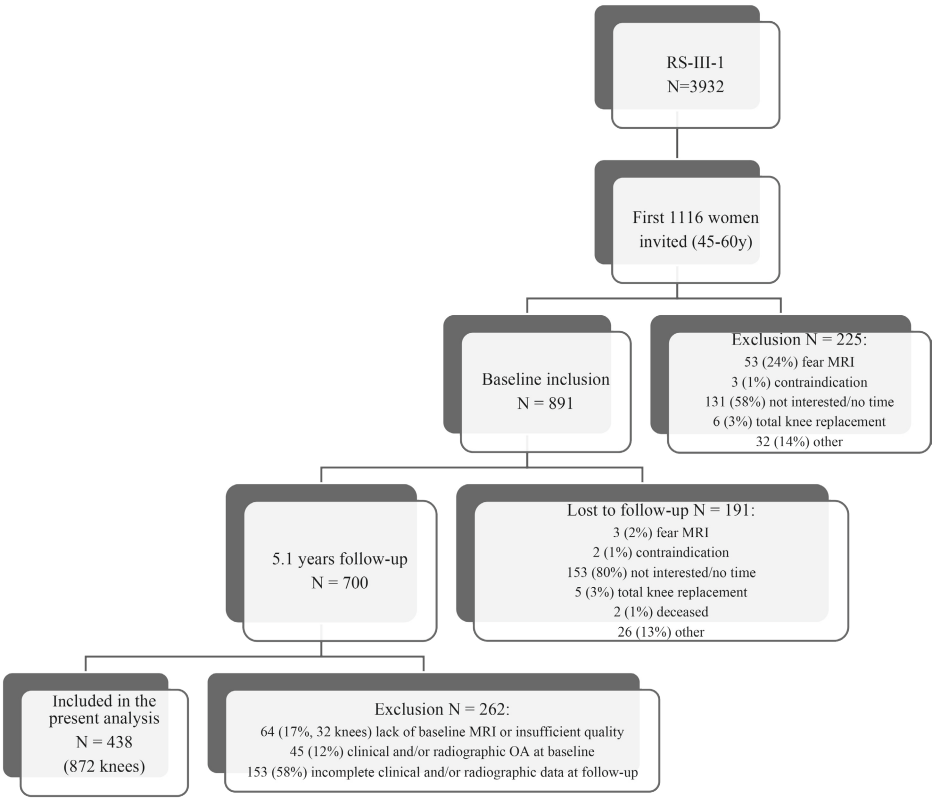

Figure 2. Flowchart of the selection process of the Rotterdam Study cohort.

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 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.

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]			Clinical knee OA[b]		
	Incidence, %	**Unadjusted OR (95% CI)**	**Adjusted OR[c] (95% CI)**	**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.

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 ≥ 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.

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]			Clinical knee OA[b]		
	Incidence, %	**Unadjusted OR (95% CI)**	**Adjusted OR[c] (95% CI)**	**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.

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 ≥ 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 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 ≥ 3 mm meniscal extrusion.[1,19,20] Within the PROOF cohort (BMI ≥ 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 affect 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.

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4

Association between meniscal volume and development of knee osteoarthritis

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ABSTRACT

Objective

To assess the association between meniscal volume, its change over time and the development of knee osteoarthritis (OA) after 30 months in overweight/obese women.

Methods

Data from the Prevention of knee Osteoarthritis in Overweight Females study were used. This cohort included 407 women with a BMI ≥ 27 kg/m^2, free of OA related symptoms. The primary outcome measure was incident knee OA after 30 months, defined by one out of the following criteria: 1) medial or lateral joint space narrowing (JSN) ≥ 1.0 mm, 2) incident radiographic knee OA (Kellgren and Lawrence (K&L) ≥ 2), or 3) incident clinical knee OA. The secondary outcomes were either of these items separately. Both menisci at both baseline and follow-up were automatically segmented to obtain meniscal volume and delta-volumes. Generalized estimating equations were used to evaluate associations between the volume measures and the outcomes.

Results

Medial and lateral baseline and delta-volumes were not significantly associated to the primary outcome. Lateral meniscal baseline volume was significantly associated to lateral JSN (OR= 0.87; 95%CI: 0.75-0.99), while other measures were not. Medial and lateral baseline volume were positively associated to K&L incidence (OR=1.32 and 1.22; 95%CI: 1.15-1.50 and 1.03-1.45 respectively), while medial and lateral delta-volume were negatively associated to K&L incidence (OR=0.998 and 0.997; 95%CI: 0.997-1.000 and 0.996-0.999 respectively). None of the meniscal measures were significantly associated to incident clinical knee OA.

Conclusion

Larger baseline meniscal volume and the decrease of meniscal volume over time were associated to the development of structural knee OA after 30 months in overweight and obese women.

INTRODUCTION

The diagnosis of osteoarthritis (OA) is mainly based on symptoms and radiographic features. Since 1986, criteria of the American College of Rheumatology (ACR) have been used to classify knee OA.[1] More recently, magnetic resonance imaging (MRI) was shown to have a higher sensitivity in detecting structural knee OA, especially when compared to Kellgren and Lawrence (K&L) grading on weight-bearing posterior-anterior flexed knee radiographs.[2] Several studies indicated that MRI is able to detect early OA features in asymptomatic persons without radiographic knee OA.[3,4] Radiographic abnormalities in OA have been described extensively, including joint space narrowing (JSN), sclerosis of subchondral bone and the presence of osteophytes. Compared to the surrogate measurement of JSN on radiographic images, MRI enables direct evaluation of the cartilage, which is the main abnormality in OA. Therefore, the MRI holds promise as an alternative to radiography in the evaluation of joint structure[5], although, until now, there has been no consensus or a standardized scoring system for knee OA, especially in quantitative MRI based measurement.

It is widely accepted that a strong causal relationship between meniscal damage and structural progression of OA exists.[6] A 'meniscal pathway' to knee OA was implicated by a loss of meniscal function due to damage or extrusion, leading to increased biomechanical stress in the knee joint. This stress results in damage such as cartilage loss, subchondral bone changes, bone marrow lesions and synovitis, eventually resulting in symptomatic OA.[7] In view of this significant pathway in the pathogenesis of OA, it is important to assess the presence of meniscal pathologies, especially when studying early-stage knee OA.

To better understand the meniscal changes, previous studies described meniscal constructs such as volume, extrusion, thickness (height) and tibial coverage.[8-10] In a recent study, we confirmed an independent association between meniscal extrusion and the development of knee OA in overweight and obese women.[11] However, extrusion was scored semi-quantitatively using MRI Osteoarthritis Knee Score (MOAKS)[12], which does not consider the absolute sizes of both tibial plateau and meniscus and the percentage of tibial cartilage covered by the meniscus.

The quantification of meniscal volume has been explored by segmentation of MRI images to obtain 3D volumetric morphometry. However, until now, there are still conflicting results on the association between meniscal volume and incident knee OA.[13-15] In this study, we therefore evaluated the association between both baseline

meniscal volume and its longitudinal change and incident knee OA among middle-aged, overweight and obese women. By quantitatively analyzing meniscal volume for those who are at high risk for OA development, we tried to determine whether meniscal volume could be a biomarker for incident knee OA.

METHODS

For this study, data from the Prevention of knee Osteoarthritis in Overweight Females (PROOF) study were used. Details regarding this study have been described previously (ISRCTN 42823086).[16] In short, the original study was a randomized controlled trial in which the intervention groups received a weight loss program and/or glucosamine sulfate or placebo, to determine whether these interventions prevent the onset of knee OA. As both interventions proved to have no significant effects on OA development, data is here treated as a cohort, with additional adjustments for the randomized intervention groups.

Subjects

This cohort consisted of 407 overweight and obese women between 50 and 60 years old with a Body Mass Index (BMI) ≥ 27 kg/m^2. At baseline they were free of symptoms of knee OA according to the clinical criteria of the American College of Radiology (ACR)[17] or other rheumatic diseases, were not treated for knee complaints, not using walking aids, had no contraindications for MRI, mastered the Dutch language, and did not use glucosamine.[16,18] The participating women were recruited through their general practitioner. At both baseline and 30 months follow-up (FU) time, all subjects filled in a questionnaire on knee pain, physical activity level, quality of life, previous knee injuries, menopausal status, and comorbidities. They also underwent physical examination for Heberden's nodes and measurement of body weight and height to calculate the BMI at baseline and FU.

MRI and radiography

MRI (1.5 T) was performed using the Philips Medical Systems (Model Intera), SIEMENS (Model Symphony and Model Magnetom Essenza) with a dedicated rigid knee coil for all knees at baseline and after 30 months FU. The protocol included coronal and sagittal non-fat suppressed proton density (PD) weighted sequences (slice thickness 3.0 mm/ slice gap 0.3 mm) and a sagittal 3D water selective sequence (WATS) with fat saturation (slice thickness 1.5 mm) with a coronal planar reconstruction, amongst other

sequences.[18] Meniscal pathology, including extrusion and tears, was scored on the MR images by two trained readers and an experienced musculoskeletal radiologist, using the MOAKS scoring system.[12,19] As previously published, the reliability of the scoring of the change in MOAKS features, determined by prevalence-adjusted bias-adjusted kappa (PABAK) statistics, showed 'substantial' to 'nearly perfect agreement (range 0.77-0.88, observed agreement 89-94%).[19,20]

Weight-bearing semi-flexed posterior-anterior knee radiographs of both knees were acquired with the metatarsophalangeal protocol at baseline and after 30 months and scored according to the K&L criteria.[21,22] Joint space width and the medial knee alignment angle were measured on the radiographs for all knees. As previously described, reproducibility tests showed moderate agreement for KL grade (κ = 0.6) and good agreement for alignment (κ = 0.7) and minimal joint space width (κ = 0.7).[16]

Meniscus segmentation and volume quantification

The medial and lateral menisci from all knees at baseline and FU were segmented fully automatically in the coronal, proton-density weighted MRI scan, using in-house developed software that combines multi-atlas segmentation-by-registration with a high-dimensional voxel-based appearance model.[23-25] In this approach, the atlas was formed by 25 MRI scans from the PROOF data which were manually segmented by using open source ITK-SNAP software.[26] Manual segmentation of the menisci was performed on the coronal PD sequence and was checked on the sagittal PD and sagittal WATS images. Segmentation was done from anterior to posterior and performed on all slices where the meniscus was identifiable.

After the baseline and FU meniscal volumes were acquired from the segmentation, volume change over time (delta-volume) and relative volume change (relative delta-volume) were calculated. Delta-volumes were calculated by subtracting the baseline volume from the FU volume. The relative delta-volume was obtained by expressing the delta-volume as a percentage of the baseline volume, positive changes of volume over time signifying growth of meniscus, while negative changes signify shrinkage.

Outcome measures

The primary outcome measure was the incidence of knee OA after 30 months, which was defined for each knee as at least one out of the following three criteria: 1) joint space narrowing (JSN) in the medial or lateral compartment ≥ 1.0 mm; 2) incident radiographic knee OA, defined by K&L ≥ 2 at FU, with baseline K&L < 2; or 3) incident

clinical knee OA according to the combined clinical and radiographic ACR criteria. The secondary outcomes were either of these items separately.

Statistics

Descriptive statistics were used for the baseline characteristics. To verify the reliability of the automated meniscus segmentation on MRI, we performed a 10-fold cross-validation experiment on the atlas set of 25 MRI scans, comparing the automatic segmentations with the manual segmentations using the Dice Similarity Coefficient (DSC).[27,28] The value of DSC ranges from 0, indicating no spatial overlap between the two segmentations, to 1, indicating perfect agreement.[28] The association between independent variables (baseline and (relative) delta-volumes) and both primary and secondary outcomes were analyzed separately. These analyses were done by performing generalized estimating equations (GEE) in SPSS 25, which treated two knees within subjects as repeat measurement. The GEEs were adjusted for baseline meniscal volume of medial or lateral side (when using baseline volume as independent factor, using 100 mm^3 as a unit), medial or lateral delta-volume (when using delta-volume as independent factor, using 100 mm^3 as a unit), BMI, age, knee injury, knee alignment, postmenopausal status, Heberden's nodes, meniscal pathologies, meniscal extrusion, osteophytes and cartilage defects at baseline. Also, to further understand the relationship between meniscal volume and meniscal extrusion, we analyzed whether meniscal volume was a confounder for the previously published association between meniscal extrusion and OA development in the same cohort.[11] A p-value < 0.05 was used to indicate statistical significance in all tests.

RESULTS

Baseline and FU characteristics

407 women were eligible to participate in the PROOF study. Firstly, 97 knees without MRI data at baseline were removed. In addition, knees with missing data for the primary outcome (N = 91) were excluded leaving 626 knees (338 subjects) for the final analysis. There were no statistically significant differences in baseline characteristics between included and excluded knees (data not shown). All baseline characteristics of the eligible sample are presented in Table 1. One hundred eleven knees (17.7%) developed knee OA according to the primary outcome after 30 months. Thirty-three knees (5.3%) developed medial JSN, 36 knees (5.8%) developed lateral JSN, 72 knees (11.6%) developed incident radiographic knee OA, and 49 knees (7.8%) developed incident clinical knee OA.

Table 1. Characteristics and features of the knee joint at baseline.

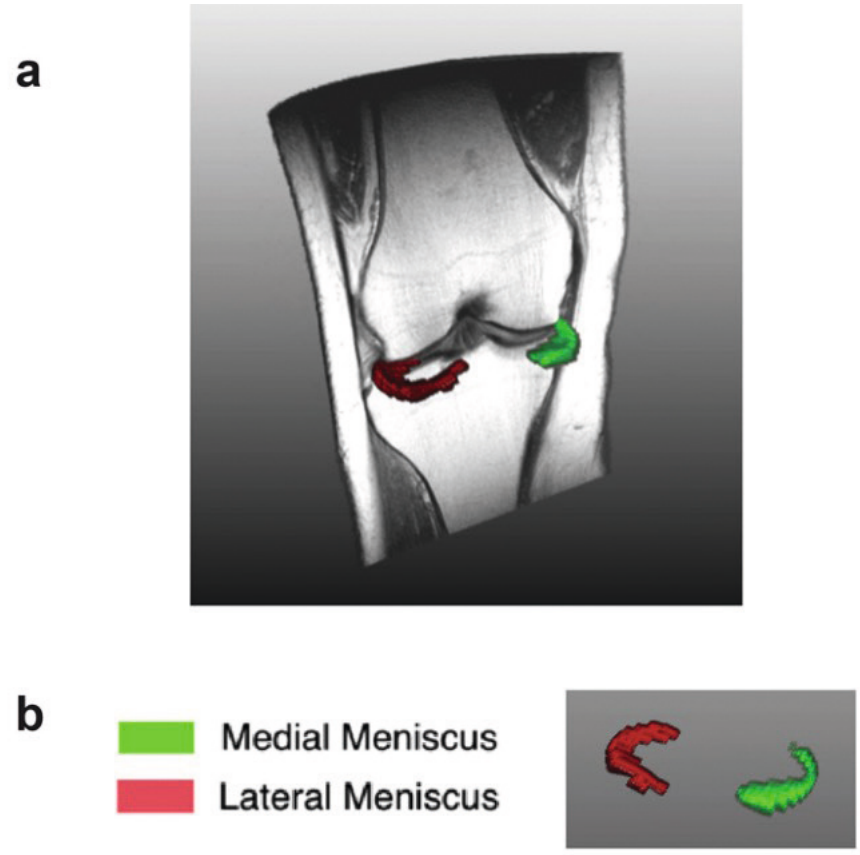
Characteristic variables	N (%)	Mean (SD)
Age at baseline (yr)	814 (100)	55.7 (3.2)
Baseline BMI (kg/m^2)	814 (100)	32.4 (4.3)
Baseline self-report knee injury	101 (12.4)	
Baseline cartilage defect	411 (50.5)	
Baseline osteophyte	474 (58.2)	
Heberden's nodes	216 (26.5)	
Knee varus alignment	323 (39.7)	
Baseline postmenopausal	550 (67.6)	
Meniscus pathologies without extrusion	504 (61.9)	
Baseline medial volume (mm^3)	723 (88.8)	1343.21 (320.50)
Baseline lateral volume (mm^3)	721 (88.6)	1129.99 (263.17)
Baseline medial meniscal extrusion	203 (24.9)	
Baseline lateral meniscal extrusion	18 (2.2)	
K&L scores	810 (100)	
K&L= 0	412 (50.9)	
K&L= 1	344 (42.5)	
K&L= 2	49 (6.0)	
K&L= 3	5 (0.6)	
Clinical knee OA	32 (4.0)	

Baseline meniscal extrusion was defined as MOAKS ≥ 2, Heberden's nodes was defined as a Heberden's node in at least one hand. K&L = Kellgren and Lawrence.

Meniscus segmentation

An example of meniscus segmentation was shown in Figure 1. The cross-validation experiment on the atlas resulted in an average DSC of 0.75, which is in line with results reported in literature for automated meniscus segmentation on 1.5T MRI.[29,30]

Figure 1. Example of meniscus segmentation.

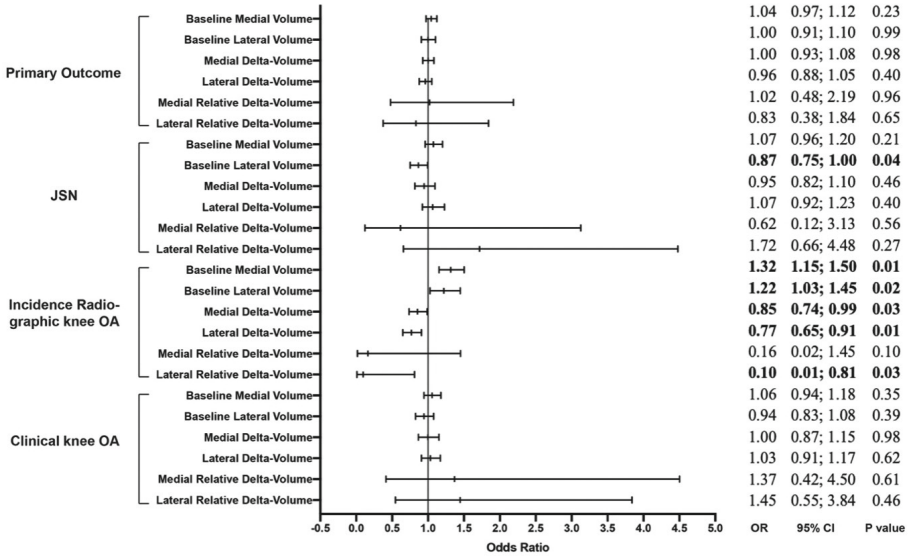


a: 3D overview of one left knee and coronal view of meniscus segmentation. b: 3D view of meniscus from segmentation (green = medial meniscus; red = lateral meniscus).

Baseline meniscal volume and knee OA development

Baseline medial and lateral volume were not significantly associated to the primary outcome (odds ratio (OR) 1.04, 95% confidence interval (CI) 0.97-1.12 and OR 1.000, 95% CI 0.91-1.10). Lateral meniscal volume (not medial) was significantly associated to lateral JSN (OR 0.87, 95% CI 0.75-1.00). Baseline medial and lateral volume were both significantly associated with incident radiographic knee OA (OR 1.32, 95% CI 1.15-1.50 and OR 1.22, 95% CI 1.03-1.45). Additional adjustments for intervention groups did not result in significant changes of the results (data no shown). The associations between all baseline meniscal volumes and incident clinical knee OA were not statistically significant (see Figure 2).

Figure 2. Association between baseline and delta meniscal volume and primary and secondary outcomes (baseline and 30 months)



All odds ratios are adjusted for meniscal volume, BMI, age, knee injury and knee alignment, postmenopausal status, Heberden's nodes, meniscal pathologies, extrusion, osteophytes and cartilage defects at baseline. OR=odds ratio, 95% CI = 95% confidence interval, JSN medial (lateral) = medial (lateral) joint space narrowing. OR > 1 signify larger volume at baseline or growth of volume during follow-up. OR < 1 signify lower volume at baseline or shrinkage of volume during follow-up.

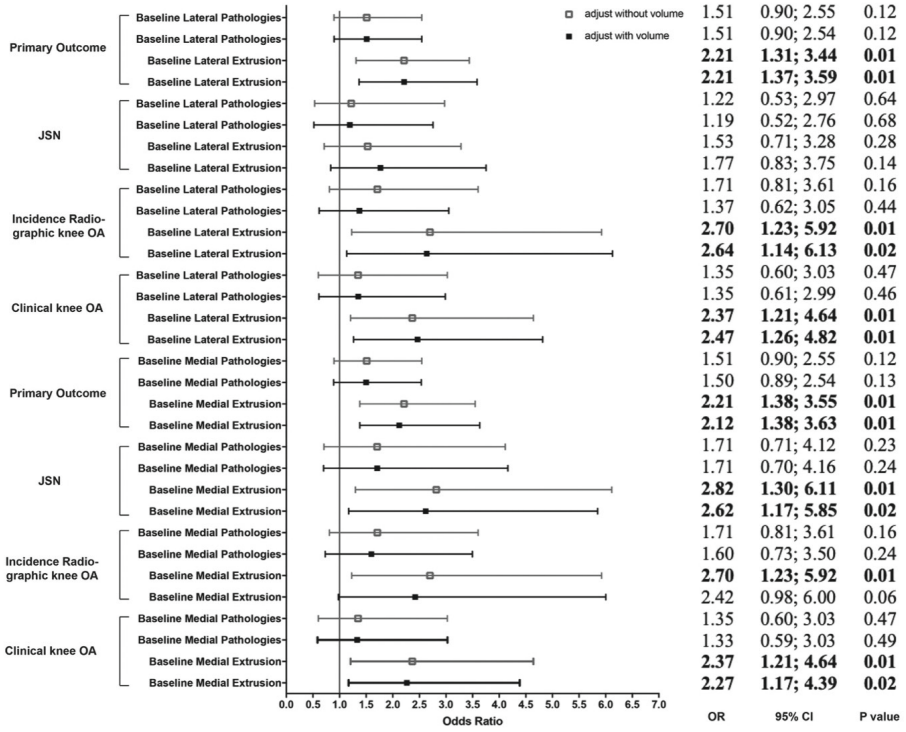
Longitudinal meniscal volume changes and knee OA development

All associations between meniscal delta-volume, relative delta-volume and the primary and secondary outcome measures are presented in Figure 2. Neither medial nor lateral delta-volume were significantly associated with the primary outcome or medial/lateral JSN. Both medial and lateral delta-volume showed significant associations with incident radiographic knee OA (OR 0.85, 95% CI 0.74-0.99 and OR 0.77, 95% CI 0.65-0.91). Lateral relative delta-volume was significantly associated to incident radiographic knee OA (OR 0.10, 95% CI 0.01-0.81). The associations between all meniscal changes and incident clinical knee OA were not significant. Additional adjustments for intervention groups did not result in significant changes of the results (data no shown).

Meniscal extrusion

By comparing the association between meniscal extrusion and all outcomes with and without adjusting for baseline meniscal volume, we found the odds for OA development in knees with meniscal extrusion only changed marginally after additional adjustment for baseline meniscal volume (Figure 3).

Figure 3. Association between baseline meniscal extrusion and primary and secondary outcomes, with and without adjustment for meniscal volume (baseline and 30 months).



All odds ratios are adjusted for meniscal volume, BMI, age, knee injury and knee alignment, postmenopausal status, Heberden's nodes, meniscal pathologies, extrusion, osteophytes and cartilage defects at baseline. OR = odds ratio, CI = confidence interval, JSN = joint space narrowing. Hollow square: adjusted without meniscal volume; solid square: adjusted with meniscal volume.

DISCUSSION

In the present study we evaluated the association between the volume of the meniscus and its change over time and the development of knee OA in a high-risk group of overweight and obese women. We found that subjects with larger baseline volume (potentially suggestive for meniscus swelling) and a decrease of meniscal volume over time had a higher risk for incident radiographic knee OA. Only baseline lateral meniscal volume was associated with lateral JSN, while neither medial nor lateral meniscal volume were significantly related to incident clinical knee OA.

The meniscus is considered a protective structure by providing biomechanical support in a healthy knee joint. However, as our results indicate, both larger meniscal volume at baseline and the decrease of volume during FU may act as risk factors for the

development of knee OA in overweight/obese women. Previously, Wenger *et al.* reported larger meniscal volume in the lateral meniscus body in knee OA subjects and Wirth *et al.* found that menisci were thicker in OA knees and had a larger meniscal volume when compared to non-OA knees.[8,13] As individuals in the current study were free of clinical knee OA at baseline, the results suggest that swelling of the menisci may take place prior to the shrinkage of the menisci, along with the development of structural knee OA; similar to cartilage swelling that is reported to occur prior to cartilage degeneration.[31,32]

We found that meniscal volume was not significantly related to the incidence of clinical knee OA. This may be because the FU period was only 30 months, when clinical complaints like pain may not be observed yet in people free of symptoms and disease at baseline.[17] Other studies also concluded that structural features of OA (e.g., osteophytes) were more reliable than clinical symptoms as an early indication of knee OA, as pain is more commonly seen in higher grades of OA.[33,34] As individuals with more severe radiographic OA features show an increased risk for the presence of knee pain[35], it is important to identify individuals at increased risk for radiographic knee OA, for example using meniscal volume as a predictive biomarker.

As greater baseline meniscal volume and decrease of volume during FU were associated to the incidence of K&L ≥ 2, which is defined by the combination of definite osteophytes and possible JSN, but not to JSN alone, we could further hypothesize that meniscal volume is related to osteophyte formation. As a consequence of meniscal volume change, mechanical stresses or soluble growth factors like insulin-like growth factor-1, fibroblast growth factor and bone morphogenetic protein or transforming growth factor-β may activate compensatory cartilage repairment, which then induce the osteophyte formation.[36-38]

According to previous studies and our current results, meniscal volume and meniscal extrusion are both independently associated to incidence of radiographic knee OA.[11,39] There are several theories suggesting that meniscal volume and extrusion are interrelated. Wenger *et al.* suggested that meniscal extrusion could coexist with change in meniscal volume, possibly because the extruded part of the meniscus potentially swells as it becomes unloaded outside the joint margin.[13] Another hypothesis is that a swollen meniscus at baseline might be more vulnerable to become extruded, owning to its larger size. The displacement of the meniscus caused by both meniscal extrusion and swelling might alter the knee load distribution capacities, which could further lead

to osteophyte formation and cartilage loss. However, further research is needed to test these hypotheses.

There are some strengths and limitations to our study. By using MRI, we confirmed a quantitative biomarker of meniscal volume to be associated with the incidence of radiographic knee OA. This measurement potentially provides a tool to detect knee OA in overweight women, especially in the early phase of the disease. Early detection may help intervention since pre-osteoarthritis is suggested to be a modifiable disease process.[40] Also, the change in meniscal volume during FU has the potential to become a surrogate endpoint. Moreover, our analyses make use of automatic segmentations of the meniscus, instead of manual segmentations, as it means the segmentations are objective and repeatable, which would make it more suitable for future clinical use. One limitation is that three different scanners were used throughout the cohort. However, the scanner type was only associated to meniscal volume which was the exposure in the GEE models. The adjustment for scanner type should therefore be unnecessary.[41] Although there were different treatment groups in this cohort, additional adjustment for the treatment groups did not significantly affect the results (data no shown). Another limitation was the FU time of only 30 months, which might be relatively short for evaluating a degenerative disease, especially in subjects without symptoms at baseline. In this study, we did not indicate a cut-off value for meniscal volume in subjects with high risk of knee OA. Once meniscal volume is indisputably proven as biomarker for knee OA development, new initiatives on valuable cut-off scores should be undertaken.

CONCLUSION

As is known for cartilage volume, knees with higher baseline meniscal volume and a stronger decrease in meniscal volume over time are at increased risk for developing radiographic knee OA. Given the lack for a (reversed) association between meniscal measures and medial/lateral JSN, this suggests a relation with osteophyte growth, but this relation needs to be confirmed in future studies. Meniscal volume might function as a prognostic biomarker for future structural knee OA in overweight and obese women.

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5

Are changes in meniscus volume and extrusion associated to knee osteoarthritis development? A structural equation model

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ABSTRACT

Objective

To explore the interplay between (changes in) medial meniscus volume, meniscus extrusion and radiographic knee osteoarthritis (OA) development over 30 months follow-up (FU).

Methods

Data from the PRevention of knee Osteoarthritis in Overweight Females study were used. This cohort included 407 middle-aged women with a body mass index ≥ 27 kg/m^2, who were free of knee OA at baseline. Demographics were collected by questionnaires at baseline. All menisci at both baseline and FU were automatically segmented from MRI scans to obtain the meniscus volume and the change over time (delta volume). Baseline and FU meniscus body extrusion was quantitatively measured on mid-coronal proton density MR images. A structural equation model was created to assess the interplay between both medial meniscus volume and central extrusion at baseline, delta volume, delta extrusion, and incident radiographic knee OA at FU.

Results

The structural equation modeling yielded a fair to good fit of the data. The direct effects of both medial meniscus volume and extrusion at baseline on incident OA were statistically significant (Estimate = 0.124, p = 0.029, and Estimate = 0.194, p < 0.001, respectively). Additional indirect effects on incident radiographic OA through delta meniscus volume or delta meniscus extrusion were not statistically significant.

Conclusion

Baseline medial meniscus volume and extrusion were associated to incidence of radiographic knee OA at FU in middle-aged overweight and obese women, while their changes were not involved in these effects. To prevent knee OA, interventions might need to target the onset of meniscal pathologies rather than their progression.

INTRODUCTION

The knee menisci play a critical role in distributing mechanical loads on articular cartilage.[1] Meniscus pathologies, including morphologic deformity (extrusion) and meniscus incompleteness (tears), have been reported to be strongly associated to both incidence and progression of knee osteoarthritis (OA).[2,3] Although there are still some conflicting results on the association between meniscus size and incident knee OA, an increasing number of studies using quantitative measurements of knee menisci indicated that swelling of the menisci may be a risk factor for OA development.[4,5]

According to previous findings from the PRevention of knee Osteoarthritis in Overweight Females (PROOF) study,[6] both meniscus volume and meniscus extrusion are independently associated to incident radiographic knee OA.[7,8] Specifically, higher medial meniscus volume at baseline and a decrease of meniscus volume during follow-up (FU) were associated to incident knee OA, and greater meniscus extrusion, especially of the medial meniscus, was observed in knees with subsequent incident OA compared to non-incident OA knees.

There are two major theories on the co-existence of medial meniscus extrusion and greater meniscus volume during OA development. Previous studies hypothesized that the extruded part of the meniscus swells as it becomes unloaded outside the joint margin, which may alter knee load distribution capacities and might result in osteophyte formation and cartilage loss.[9] However, most observations were based on cross-sectional data which could not evaluate the causal inference in this hypothesis.[10] An alternative hypothesis is that increased meniscal volume precedes meniscal extrusion, since greater volume might lead to greater meniscus width and thickness, resulting in extrusion.[11]

As described, these hypothetical causal effect-chains suggest that meniscus pathologies, like extrusion, volume, and their changes over time, interact with each other and lead to the development of OA. The current study aimed to explore the mediation effect of the change in meniscus volume and meniscus extrusion in the previously established relationships between baseline meniscus volume/meniscus extrusion and incident radiographic knee OA, using structural equation modeling. Owing to the low number of subjects with baseline lateral meniscus extrusion and the weak association between lateral meniscus extrusion and incident knee OA in the PROOF study, only the medial meniscus was evaluated in the current study.[7]

METHODS

Data from the PRevention of knee Osteoarthritis in Overweight Females (PROOF) study were used, details of which were described previously (ISRCTN42823086).[6] This randomized controlled trial was originally designed for a lifestyle intervention and/or glucosamine sulfate to prevent the onset of knee OA. As both intervention groups proved to have no significant effects on OA development, data were treated as a cohort (data not shown).

Subjects

Four hundred seven middle-aged women with a body mass index (BMI) ≥ 27 kg/m^2, who were free of knee OA according to the clinical American College of Rheumatology (ACR) at baseline, were included in the cohort.[12] Demographics were collected by questionnaires containing knee pain, physical activity level, quality of life, previous knee injuries, menopausal status and comorbidities. All women also underwent physical examination for Heberden's nodes and measurement of body weight and height to calculate the BMI at both baseline and 30 months FU.

MRI and radiography data

MRI scanners (1.5T) used in this study included 3 types; Philips Medical Systems (Model Intera), Siemens (Model Symphony and Model Magnetom Essenza). The protocol included coronal and sagittal non-fat suppressed proton density (PD) weighted sequences (slice thickness 3.0 mm, slice gap 0.3 mm) and a sagittal 3D water selective (WATS) sequence with fat saturation (slice thickness 1.5 mm) with a coronal planar reconstruction, amongst other sequences.[13] Semi-flexed posterior-anterior knee radiographs of both knees were acquired with the metatarsophalangeal protocol at baseline and after 30 months and scored according to the Kellgren and Lawrence (K&L) criteria.[14,15] Incident radiographic knee OA was defined as K&L ≥ 2 at FU, with baseline K&L < 2. Medial knee alignment angle was also measured on radiographs for all knees.[16]

Meniscus volume and extrusion determination

We quantified meniscus volume as described previously.[8] In brief, medial menisci from all knees at baseline and FU were segmented fully automatically on the coronal, PD weighted MRI scan, using in-house developed software that combines multi-atlas segmentation-by-registration with a high-dimensional voxel-based appearance model.[17-19] All available medial meniscus volumes at baseline and 30 months FU were

calculated. Delta meniscus volume was calculated by subtracting baseline volume from FU volume.

We used a two-dimensional quantitative measurement method for meniscus extrusion, which was published previously.[20] Baseline and FU meniscus body extrusion was quantitatively measured on mid-coronal PD weighted MR images. Extrusion was defined as the horizontal distance between the outer edge of the meniscal body and the edge of the tibial plateau, excluding any possible osteophytes. Sante DICOM Editor (64-bit) software was used to measure medial meniscus coronal width and meniscal body extrusion for all medial menisci (measured in mm, at one decimal). A sample of thirty knees was randomly selected for reassessment. Delta-extrusion was calculated by subtracting the baseline value from the FU value.

Assessment of meniscus pathologies and progression of meniscus tear
Meniscus tears were scored by two trained readers (Jos Runhaar, Peter van der Plas) and one musculoskeletal radiologist (Edwin Oei) using MOAKS.[21] Extensive training was held to reach a high to nearly perfect inter-observer reliability.[22] Horizontal, complex and root tears were recorded for the anterior, body and posterior part of the medial meniscus. The progression of meniscus tears was defined as any change at FU in pre-existing tears at baseline, or newly present meniscus tears. In this study, meniscus pathologies scored included partial maceration, progressive partial maceration, complete maceration, meniscus cyst, and meniscus hypertrophy.

Statistics and structural equation modeling

Descriptive statistics were used for both baseline and FU characteristics. To verify the reliability of the automated meniscus segmentation on MRI, we performed a 10-fold cross-validation experiment on the atlas set of 25 MRI scans, comparing the automatic segmentations with the manual segmentations using the Dice Similarity Coefficient (DSC).[23,24] The value of DSC ranges from 0, indicating no spatial overlap between the two segmentations, to 1, indicating perfect agreement.[24] The baseline and FU volume were using 100 mm^3 as unit in the analyses. Central meniscus extrusion at baseline and delta extrusion were treated as continuous variables in the analyses.

In the structural equation model, baseline medial meniscus volume and baseline medial central meniscus extrusion were treated as covariant variables. The delta-medial meniscus volume and delta-extrusion over time were hypothesized as mediator from baseline meniscus volume and baseline meniscus extrusion to incident radiographic

OA. Confounders, including age, BMI at baseline and its change over time, baseline medial meniscus body width, meniscus pathologies, cartilage defects, self-reported knee injury, and knee varus alignment were also selected and included in the model, based on literature and expertise. Type of scanner was encoded as a categorical variable and as confounder between volume/extrusion and their change over time. Change in BMI and progression of medial meniscus tears were only modelled as confounders for estimates between delta-meniscus volume, delta-extrusion and incident radiographic OA. Since sensitivity analyses in previous studies regarding the possible interaction between the original intervention groups with either meniscal extrusion/volume or incident radiographic OA showed no significant effect, we did not consider the interventions as confounders in the model.[16] All variables in the model were hypothesized as observed variable. Error variables were added to represent the random measurement errors. The full model was tested by IBM SPSS AMOS (23.0) and is shown in the supplementary materials. As AMOS features maximum likelihood estimation in the presence of missing data, the modeling made use of all available data points.[25]

RESULTS

Baseline demographic and clinical characteristics are presented in Table 1. In the 407 women, the average (SD) age and BMI were 55.7 (3.2) years and 32.4 (4.3) kg/m^2, respectively. MRIs of 784 knees were obtained at baseline. The average baseline medial meniscus volume was 1343 ± 321 mm^3. The average baseline medial meniscus extrusion was 2.3 ± 1.2 mm (Table 1). After 30 months, MRIs of 691 knees were obtained. Thirty-six (5.4 %) knees had a progressive meniscus tear. The average FU medial meniscus volume was 1350 ± 265 mm^3. The average FU medial meniscus extrusion was 2.6 ± 1.4 mm (Table 2).

Repeatability

As previously described, reproducibility tests showed moderate agreement for KL grade (κ = 0.6) and good agreement for alignment (κ = 0.7) and minimal joint space width (κ = 0.7) [10]. The cross-validation experiment on the atlas resulted in an average DSC of 0.75, which is in line with results reported in literature for automated meniscus segmentation on 1.5T MRI.[26,27] Intra-observer reliability (intra-class correlation coefficient) and inter-observer reliability for meniscus width and meniscus extrusion ranged from 0.69 to 0.98 and 0.62 to 0.96, respectively.[12]

Table 1. Demographic characteristics.

Characteristic variables	N (%)	Mean (SD)
Age at baseline (yr)	814	55.7 (3.2)
Baseline BMI	814	32.4 (4.3)
Baseline self-reported history of knee injury	101 (12.7)	
Baseline meniscus pathologies	462 (56.8)	
Baseline cartilage defect	411 (52.6)	
Baseline medial meniscus width (mm)	784	11.1 (3.4)
Baseline knee varus alignment	323 (40.1)	

N = numbers of observation. % = valid percentage. SD= standard deviation. BMI = Body mass index.

Table 2. Baseline and follow-up characteristics.

Characteristics variables	N (%)	Mean (SD)
Baseline medial meniscus volume (mm^3)	723	1343 (321)
Baseline medial meniscus extrusion (mm)	784	2.3 (1.2)
Baseline KL	810 (100)	
KL = 0	412 (50.9)	
KL = 1	344 (42.5)	
KL ≥ 2	54 (6.6)	
FU medial meniscus volume (mm^3)	631	1350 (265)
FU medial meniscus extrusion (mm)	680	2.6 (1.4)
FU KL	712 (100)	
KL = 0	333 (46.8)	
KL = 1	300 (42.1)	
KL ≥ 2	79 (11.1)	

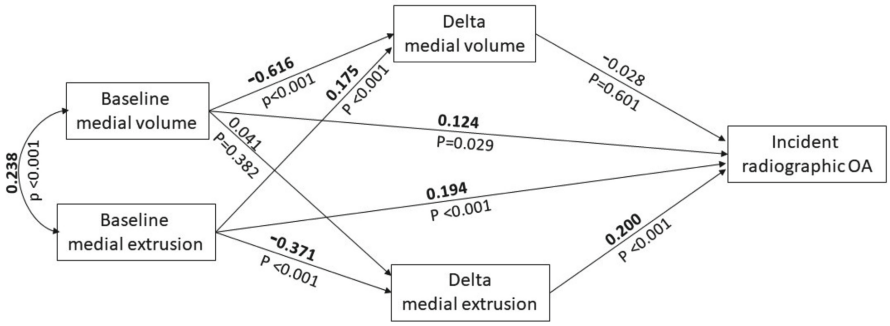
N = numbers of observation. SD = standard deviation. KL = Kellgren & Lawrence.

SEM model

The SEM model showed fair to good indices of fit. Minimum discrepancy/degrees of freedom (CMIN/DF) = 4.66 (CMIN/DF < 5: reasonable fit) and the Root Mean Square Error of Approximation (RMSEA) = 0.067 (RMSEA < 0.08: acceptable fit).[28,29] For clarity reason, a simplified directed acyclic graph (DAG) was shown in Figure 1 (see full DAG in Supplementary Figure 1). All standardized adjusted regression estimates

and corresponding p-values of the model are presented in the Figure 2 (full output presented in Supplementary Table 1).

Figure 1. Simplified Structural Equation Model to assess the interplay between baseline medial meniscus volume and extrusion, delta medial meniscus volume, and delta medial meniscus extrusion, and their associations with incident radiographic knee OA.



All estimates were adjusted for confounders (not provided in the figure for clarity reasons), which included baseline (BL) BMI, BL medial meniscus body width, age, meniscus pathologies (excluding extrusion), cartilage defects, self-reported knee injury, and knee varus alignment. Delta BMI and incident medial meniscus tear were only modelled as confounder for estimates between delta meniscus volume, delta meniscus extrusion and incident radiographic OA.

Effect of baseline medial meniscus volume on incident radiographic OA

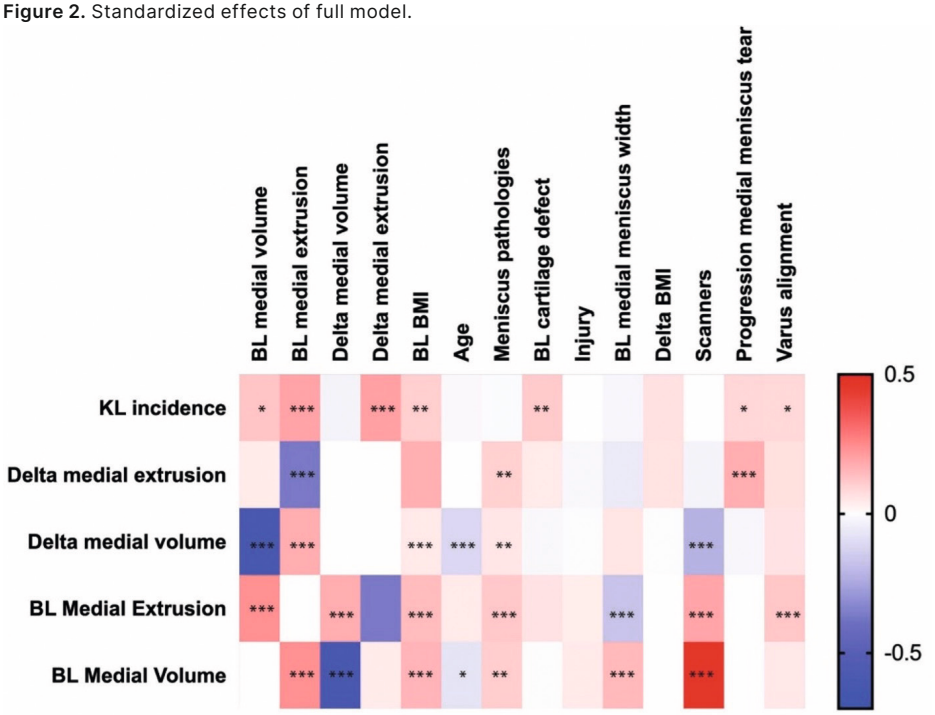
The direct effect of larger baseline medial meniscus volume on the incidence of radiographic knee OA was positive and with statistically significance [Estimate = 0.124, p = 0.029]. There was no statistically significant indirect effect of baseline medial meniscus volume on incident OA through delta medial meniscus volume (the effect of larger baseline medial meniscus volume on larger reduction in meniscus volume was significant [Estimate = -0.616, p < 0.001]; however, the effect of delta meniscus volume on incidence of radiographic OA was negative but not significant [Estimate = -0.028, p = 0.601]). The indirect effect through delta meniscus extrusion was also not statistically significant [Estimate = 0.041, p = 0.382].

Effect of baseline meniscus central extrusion on incident radiographic OA

The direct effect of greater baseline meniscus extrusion on increased incident radiographic OA was positive and statistically significant [Estimate = 0.194, p < 0.001]. There were no statistically significant indirect effects of baseline medial extrusion on incident radiographic OA through delta medial meniscus volume or delta meniscus extrusion. Greater baseline meniscus extrusion had a positive effect on increased meniscus volume [Estimate = 0.175, p < 0.001], but the effect on incident radiographic

OA was not significant (shown in paragraph 3.2.1). Greater baseline meniscus extrusion had a significant negative effect on decreased meniscus extrusion [Estimate = -0.371, p < 0.001]. However, delta meniscus extrusion had a statistically significant, but opposite effect on the incidence of radiographic knee OA [Estimate = 0.200, p < 0.001].

Figure 2. Standardized effects of full model.



All estimates were adjusted for confounders (not provided in the figure for clarity reasons), which included BL BMI at baseline, baseline medial meniscus body width, age, BL meniscus pathologies (excluding extrusion), BL cartilage defects, self-reported knee injury and knee varus alignment. Delta BMI and progression medial meniscus tear were only modelled as confounder for estimates between delta-meniscus volume, delta-extrusion and incident radiographic OA. Red color means positive association, blue color means negative association. Darker color stands for stronger association. *p<0.05, *** p<0.001.

DISCUSSION

In this cohort of overweight and obese women at high risk for incident knee OA, we analyzed the interplay of meniscus pathologies in the development of knee OA, using a structural equation model. We found greater baseline medial meniscus volume and extrusion to be independently associated to the increased incidence of radiographic knee OA after 30 months. However, these main effects on incident OA had no additional

mediation path through the changes of medial meniscus volume or medial meniscus extrusion during FU.

One previous study using Osteoarthritis Initiative (OAI) data reported that in asymptomatic subjects, knee medial meniscus body extrusion slightly increased over four years.[30] Also, in OAI data, Collins *et al*. found meniscus extrusion worsening was associated to radiographic progression of OA.[31] However, to our knowledge, the association between current level of meniscal extrusion and its change over time has rarely been described in the literature. In the current model, we observed that meniscus extrusion at baseline was negatively associated with progression of extrusion during FU. This indicated that knees with (more) extrusion undergo less progression over time than those with milder or without extrusion, suggesting a ceiling effect.

Meniscus extrusion was associated with larger medial meniscus volume at baseline and both factors were significantly associated with incident radiographic knee OA. Our two hypotheses could explain the causal interplay between meniscus extrusion, meniscus volume and incident radiographic knee OA. First and intuitively, greater meniscus volume may lead to greater meniscus width and thickness.[11] Limited femorotibial joint space could squeeze the meniscus outside of the tibial margin, which is measured as extrusion. However, greater baseline meniscus volume was not associated to progression of meniscus extrusion in our results, which makes this theory less likely plausible. In the alternative hypothesis, the extruded meniscus outside the joint margin is not compressed by the bones forming the joint which provides the opportunity for the meniscus to expand.[9] Recently published studies indicated that the delta-meniscus volume in vitro and in vivo could be initiated by load alteration on the meniscus.[32,33] The results in our study were consistent with this hypothesis, with baseline meniscus extrusion being positively associated with change in meniscus volume. However, delta meniscus volume was not significantly associated to incident radiographic knee OA, which contradicts our previous finding. Therefore, the effect of baseline meniscus extrusion on incident radiographic OA was not mediated through delta meniscus volume. It is still possible that a pre-existing meniscus extrusion (present well before the start of this cohort) led to greater meniscus volume at baseline, which then led to radiographic knee OA. However, this hypothesis needs to be tested in cohorts including subjects at a younger age.

There were some limitations to this study. First, there were three types of scanners used, but we accounted for this in the set of confounders. Second, the delta meniscus extrusion and delta volume were both recorded cross-sectionally with incident

radiographic OA, which made the causal effect less solid. Thirdly, the follow-up period was 30 months, which might be relatively short for evaluating a slowly progressing degenerative disease. But for many subjects, both medial meniscus volume and medial meniscus extrusion had substantial changes during the 30 months follow-up (Supplementary Figure 4a and 4b). In addition, the model did not measure the correlation between both sides of knees within subjects. However, the sensitivity analyses showed no difference for the main results (Supplementary materials Figure 2a and 2b). Finally, there were also some knees without MRI data at follow-up. According to the missing pattern (Supplementary material Figure 3), 26 observations of knees did not contribute to any association in the model. However, there were no significant differences in baseline characteristics (Supplementary material Table 2).

CONCLUSION

High baseline medial meniscus volume and high degree of meniscal body extrusion were associated with the incidence of radiographic knee OA after 30 months in middle-aged overweight and obese women. There was no additional mediating effect through the change in meniscus volume, nor the change in meniscus extrusion during FU. Thus, to prevent the incidence of radiographic knee OA, interventions such as BMI control which could be potentially targeting meniscus volume and extrusion should be applied at a younger age, rather than at the stage when these meniscus pathologies are already prevalent.

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Supplementary Table 1. Regression weights between structural variables.

			Estimate	Standard weight	SE	CR	P
BL medial volume	⟵	BL cartilage defect	-0.051	-0.008	0.214	-0.237	0.812
BL medial volume	⟵	BL BMI	0.120	0.159	0.025	4.836	***
BL medial volume	⟵	Age	-0.078	-0.077	0.033	-2.341	0.019
BL medial volume	⟵	Meniscus pathologies	0.706	0.105	0.224	3.151	0.002
BL medial volume	⟵	Injury	0.410	0.042	0.322	1.274	0.203
BL medial volume	⟵	BL medial meniscus width	0.139	0.148	0.031	4.474	***
BL medial volume	⟵	Scanners	1.533	0.470	0.124	12.345	***
BL medial volume	⟵	Varus alignment	0.317	0.048	0.217	1.456	0.145
BL medial extrusion	⟵	BL cartilage defect	0.142	0.060	0.080	1.772	0.076
BL medial extrusion	⟵	BL BMI	0.038	0.140	0.009	4.143	***
BL medial extrusion	⟵	Age	0.016	0.043	0.013	1.264	0.206
BL medial extrusion	⟵	Meniscus pathologies	0.283	0.115	0.084	3.373	***
BL medial extrusion	⟵	Injury	0.131	0.037	0.121	1.085	0.278
BL medial extrusion	⟵	BL medial meniscus width	-0.061	-0.176	0.012	-5.224	***
BL medial extrusion	⟵	Scanners	0.230	0.193	0.052	4.456	***
BL medial extrusion	⟵	Varus alignment	0.288	0.120	0.081	3.537	***
Delta medial volume	⟵	BL medial volume	-0.560	-0.616	0.035	-16.218	***
Delta medial volume	⟵	BL medial extrusion	0.434	0.175	0.082	5.270	***
Delta medial volume	⟵	BL BMI	0.030	0.044	0.021	1.425	0.154
Delta medial volume	⟵	Age	-0.109	-0.118	0.028	-3.916	***
Delta medial volume	⟵	Meniscus pathologies	0.316	0.052	0.187	1.690	0.091
Delta medial volume	⟵	BL cartilage defect	-0.08	-0.014	0.177	-0.452	0.651
Delta medial volume	⟵	Injury	0.016	0.002	0.267	0.060	0.952
Delta medial volume	⟵	BL medial meniscus width	0.047	0.055	0.027	1.758	0.079
Delta medial volume	⟵	Delta BMI	-0.008	-0.006	0.038	-0.215	0.830
Delta medial volume	⟵	Scanners	-0.653	-0.220	0.117	-5.573	***
Delta medial volume	⟵	Progression medial meniscus tear	-0.248	-0.019	0.394	-0.63	0.529
Delta medial volume	⟵	Varus alignment	0.345	0.058	0.182	1.898	0.058

Supplementary Table 1. *(continued)*

			Estimate	Standard weight	SE	CR	P
Delta medial extrusion	⟵	BL medial volume	0.015	0.041	0.017	0.874	0.382
Delta medial extrusion	⟵	BL medial extrusion	-0.372	-0.371	0.039	-9.629	***
Delta medial extrusion	⟵	BL BMI	0.047	0.170	0.010	4.763	***
Delta medial extrusion	⟵	Age	0.000	0.000	0.013	0.013	0.989
Delta medial extrusion	⟵	Meniscus pathologies	0.247	0.100	0.088	2.812	0.005
Delta medial extrusion	⟵	BL cartilage defect	0.100	0.043	0.083	1.213	0.225
Delta medial extrusion	⟵	Injury	-0.057	-0.016	0.125	-0.455	0.649
Delta medial extrusion	⟵	BL medial meniscus width	-0.020	-0.057	0.013	-1.573	0.116
Delta medial extrusion	⟵	Delta BMI	0.031	0.059	0.018	1.697	0.090
Delta medial extrusion	⟵	Scanners	-0.034	-0.028	0.061	-0.552	0.581
Delta medial extrusion	⟵	Progression medial meniscus tear	0.906	0.173	0.185	4.899	***
Delta medial extrusion	⟵	Varus alignment	0.161	0.067	0.085	1.888	0.059
KL incidence	⟵	BL medial volume	0.009	0.124	0.004	2.187	0.029
KL incidence	⟵	BL medial extrusion	0.038	0.194	0.008	4.469	***
KL incidence	⟵	Delta medial volume	-0.002	-0.028	0.004	-0.523	0.601
KL incidence	⟵	Delta medial extrusion	0.039	0.200	0.008	4.930	***
KL incidence	⟵	BL BMI	0.005	0.101	0.002	2.704	0.007
KL incidence	⟵	Age	0.001	0.008	0.003	0.214	0.830
KL incidence	⟵	Meniscus pathologies	-0.005	-0.011	0.018	-0.289	0.773
KL incidence	⟵	BL cartilage defect	0.050	0.109	0.017	3.007	0.003
KL incidence	⟵	Injury	0.000	0.000	0.025	-0.003	0.997
KL incidence	⟵	BL medial meniscus width	-0.001	-0.017	0.003	-0.437	0.662
KL incidence	⟵	Delta BMI	0.006	0.064	0.004	1.791	0.073
KL incidence	⟵	Progression medial meniscus tear	0.087	0.086	0.038	2.289	0.022
KL incidence	⟵	Varus alignment	0.039	0.084	0.017	2.318	0.020
Covariance							
BL medial volume	⟵	BL medial extrusion	0.713	0.238	0.125	5.684	***

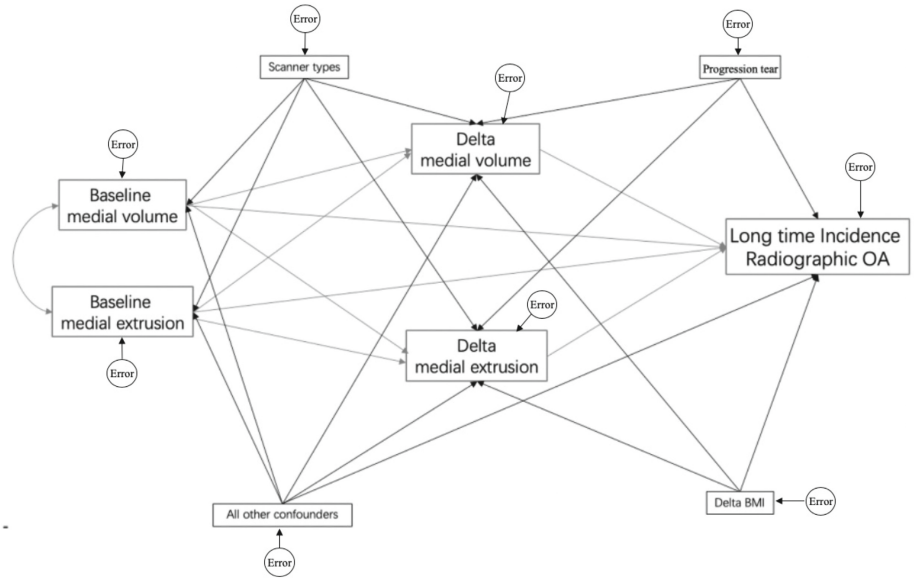
SE = standard error. CR= critical ratio. *** = P< 0.001

Supplementary Table 2. Baseline characteristics between complete and missing data.

Participants	Complete data(n=788)	Missing data(n=26)
Age(years)	55.72 (3.18)	55.34 (3.26)
BMI(kg/m^2)	32.35 (4.31)	33.01 (3.40)
Postmenopausal status(yes)	69.9%	70.8%
Varus alignment	69.9%	46.2%
Baseline KL		
KL 0	49.9 %	73.1%
KL 1	42.8 %	26.9%
KL 2	6.2 %	0
KL 3	0.6 %	0

Age and BMI were presented by mean value (standard deviation). KL = Kellgren & Lawrence.

Supplementary Figure 1. Full SEM model.



BL medial extrusion and BL medial volume were exposure, while delta medial volume and delta extrusion were mediators. Radiographic knee OA incidence was the outcome in the model. All estimates were adjusted for confounders, which included BMI at baseline, baseline medial meniscus body width, age, meniscus pathologies (excluding extrusion), cartilage defects, self-reported knee injury, and knee varus alignment. Delta BMI and Progression medial meniscus tear were only modelled as confounder for estimates between delta-meniscus volume, delta-extrusion and incident radiographic OA. SEM = Structural Equation Model.

Supplementary Figure 2. Main model results based on different sub-data.

Figure 2a. Full data analysis.

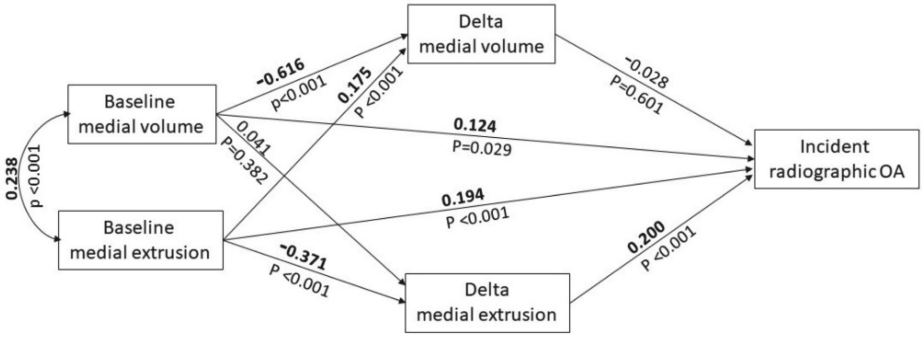
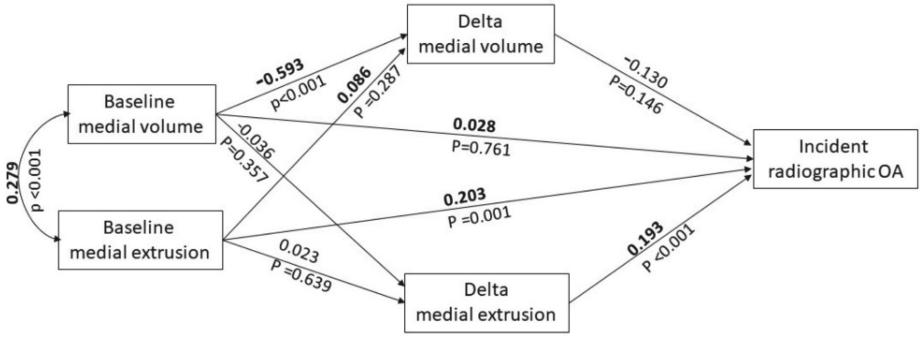
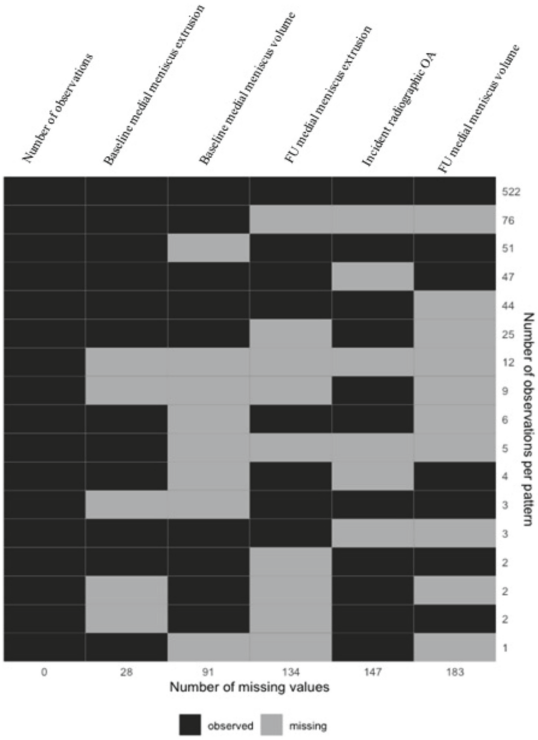


Figure 2b. Right knee sub-data.



The full data analysis and right knee sub-data analysis generate similar results overall. The major difference for the right knee sub-data, we observe baseline medial extrusion had opposite direct effect on delta medial extrusion. Because, this effect was without significance, the indirect effect of baseline medial volume on incident OA through delta extrusion was still not exist. Therefore, we assume the correlation within subjects did not change the final results when combining both sides of knees.

Supplementary Figure 3. Missing data pattern of the main model variables from full dataset.



There were only 26 observations that did not contribute to any association in the main model. (Black square per row less than 2, except for first column reference. So, in total: 12+9+5=26).

Supplementary Figure 4. Scatterplot of meniscus volume and extrusion.

Figure 4a. Scatter of follow-up volume medial meniscus versus baseline volume medial meniscus.

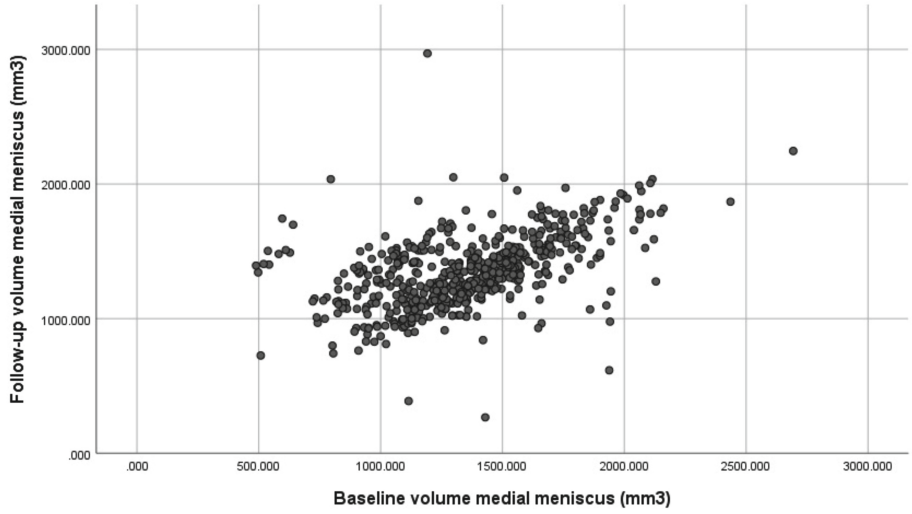
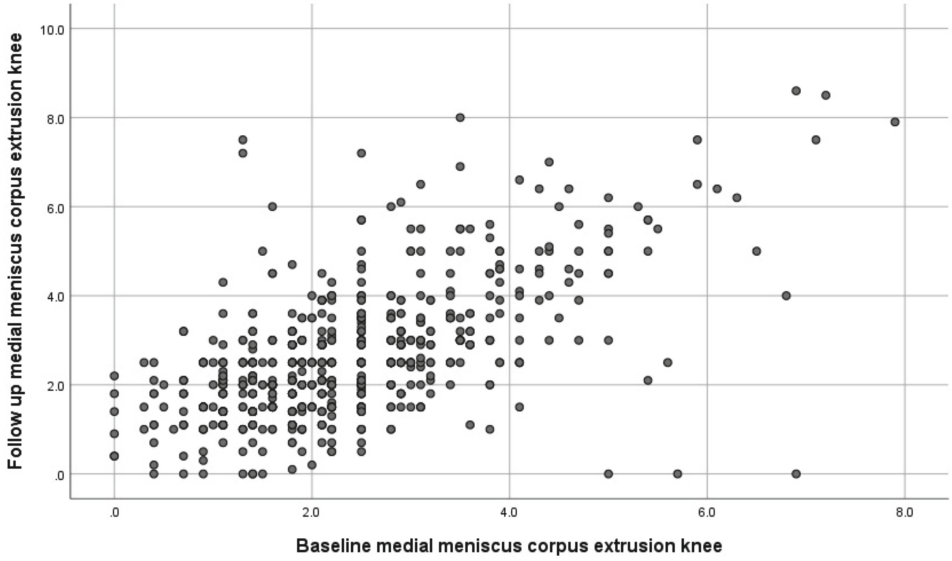


Figure 4b. Scatter of follow-up medial meniscus extrusion versus baseline medial meniscus extrusion.



Both medial meniscus volume and medial meniscus extrusion had substantial changes during 30 months follow-up.

Part II

Factors related with meniscus extrusion

6

Factors associated with longitudinal change of meniscal extrusion in overweight women without clinical signs of osteoarthritis

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Rheumatology (Oxford). 2021 Nov 3;60(11):5175-5184.

ABSTRACT

Objectives

To identify variables associated with longitudinal change in meniscal extrusion, which might be used as possible targets for knee osteoarthritis (KOA) prevention.

Methods

In a high-risk population of middle-aged overweight women, meniscal extrusion was assessed with magnetic resonance imaging (1.5T, coronal proton density, in-plane resolution 0.5 mm^2, Sante DICOM Editor) at baseline and after 30 months. Outcomes were the absolute change in medial and lateral extrusion (mm) and relative change in extrusion (%). Based upon literature, eleven factors were hypothesized to be associated with longitudinal change. Generalized estimating equations were used to model the effect on meniscal change ($p < 0.05$).

Results

677 knees of 343 women were available for analysis, with a mean age of 55.7 years (+/- 3.2) and a mean body mass index (BMI) of 32.3 kg/m^2 (+/- 4.2). The greatest change in meniscal extrusion appeared medially with incident meniscal tear (4.4%; absolute 0.9 mm (95% CI: 0.3, 1.5; p = 0.004); relative 14.5% (4.4, 24.7; 0.005)). Varus malalignment was associated with an increase of medial extrusion of 0.6 mm (37.6%; 0.1, 1.0; 0.009)). A 5 kg/m^2 higher baseline BMI was associated with absolute and relative increase of medial extrusion of 0.2 mm and 2.96% (0.1, 0.3; < 0.001 and 1.3, 4.8; 0.002). Less explicit but significant changes in extrusion appeared with longitudinal change in BMI.

Conclusion

Meniscal tears, varus malalignment and BMI were significantly associated with change in meniscal extrusion in middle-aged overweight women, providing viable therapeutic targets to prevent or reduce extrusion and thereby decelerate KOA development.

INTRODUCTION

The menisci are important wedge-shaped fibrocartilaginous structures within the tibiofemoral joint primarily acting as load bearers, load distributors and stabilizers during movement.[1-3] They increase the congruency of the knee joint by extending the contact area and thereby decreasing stress on the articular cartilage. In case of meniscal pathology (e.g., extrusion, tear, maceration) these biomechanical functions are compromised, leading to increased stress in the knee joint which may influence the cartilage matrix and the onset of knee osteoarthritis (OA).[4-6] In a recent study, we reported a largely independent association between baseline meniscal extrusion and incident knee OA in a high-risk population, supporting this theory.[7] Others found similar associations between meniscal extrusion and the development of knee OA or features thereof, although most studies were conducted in cohorts with established OA.[8-13] Two studies reported that meniscal extrusion can be seen in asymptomatic individuals as well, whether slowly increasing over time or not.[14,15] Given the apparently significant role of meniscal extrusion in the development of knee OA, evaluating its (modifiable) risk factors could be of high importance. Several cross-sectional studies identified multiple variables associated with the presence of meniscal extrusion, including meniscal degeneration and tears, age, sex, malalignment, obesity and knee trauma.[16-18] However, longitudinal data regarding risk factors for meniscal extrusion are scarce.[19-21] Of these prior studies, only Zhang *et al.* executed a multivariate analysis in an OA free cohort comparable to the present paper.[21] Extrusion is generally considered a risk factor for OA at a displacement of ≥ 3 millimeter[22], whereby slowly progressive meniscal extrusion beyond this border might be of greater clinical relevance than a limited static extruded meniscus. Therefore, it is important to evaluate change in meniscal position over time and identify demographic and knee-specific variables associated with this change. In the present study, we aimed to identify these variables in a population without clinical or radiographic knee OA at baseline. We hypothesized that a higher age, a higher BMI, prevalence of meniscal tears and knee malalignment would be significantly related to change in meniscal extrusion.

MATERIALS AND METHODS

Study population

Data from the PROOF trial (PRevention of knee Osteoarthritis in Overweight Females) were studied.[23] This trial investigated the effect of glucosamine and the effect of a

diet-and-exercise program on the incidence of knee OA. General practitioners in the Rotterdam area in the Netherlands were asked to invite all women between 50 and 60 years of age to participate in the study. To be eligible for participating, the women had to have a BMI ≥ 27 kg/m^2. Participants could not be included in the study when they had knee OA according to the clinical American College of Rheumatology (ACR) criteria.[24] Neither could they have any MRI contra-indications, have a medical history of rheumatic diseases or being under treatment for knee complaints. Furthermore, patients could not participate in the study when they relied on using walking aids, did not speak the Dutch language or used glucosamine in the past six months. Approval was given for the original PROOF trial by the ethics committee at the Erasmus University Medical Center Rotterdam, the Netherlands in 2005 (ISRCTN 42823086).

Data collection

All baseline data were collected between July 2006 and May 2009 and follow-up data between February 2009 and November 2011. All participating women signed the informed consent according to the Declaration of Helsinki. A questionnaire was filled out, containing questions about their age, postmenopausal status and medical history. Furthermore, their physical activity was assessed using SQUASH (Short QUestionnaire to ASsess Health-enhancing physical activity), measuring frequency, duration and intensity of four different physical activities.[25] A physical examination was performed to measure body weight and height and document the presence of Heberden's nodes in both hands, which might be an expression of generalized OA. With a hand-held dynamometer, quadriceps muscle strength was measured as a maximal isometric contraction in a supine position by a well-trained research assistant.

MRI and radiographic data

At baseline and after 30 months 1.5 T MRI scans of both knees were performed, using scanners from Philips Medical Systems (model Intera) and Siemens (model Symphony and Magnetom Essenza). The scans were made in a general hospital (Maasstad Hospital Rotterdam) and two specialized diagnostic centers. The MRI protocol included coronal and sagittal non-fat-suppressed proton density (PD) weighted sequences (slice thickness 3.0 mm/slice gap 0.3 mm echo time (TE) 27 ms/repetition time (TR) 2700 ms/matrix size (M) 320×320/field of view (FOV) 160×160 mm/ in-plane resolution (IPR) 0.5×0.5mm), a coronal T2 weighted Spectral Presaturation by Inversion Recovery (SPIR) sequence (slice thickness 5.0 mm/slice gap 0.5 mm/TE 79 ms/TR 2550ms/M 448×358/FOV 480×144/IPR 1.07×0.3mm), an axial dual spin-echo sequence (slice

thickness 4.5 mm/slice gap 0.5 mm/TE 14/100 ms/TR 3000 ms/M 512×512/FOV 160×160/IPR 0.31×0.31mm) and a sagittal 3D water selective cartilage sequence (WATS) with fat saturation (slice thickness 1.5 mm/TE 6 ms/TR 19.5 ms/M 384×384/FOV 160×160/IPR 0.42×0.42mm).

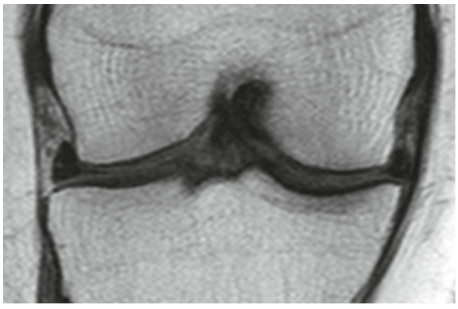
Standardized semi-flexed weightbearing posterior-anterior knee radiographs were obtained to grade the extent of radiographic tibiofemoral knee OA by a well-trained investigator with ~ 12 years of experience (Max Reijman), using the Kellgren and Lawrence (K&L) classification system.[26] The same knee radiographs were used to assess femorotibial alignment by estimating the anatomical axes of the femur and tibia.[27,28] A random sample of 20% of the radiographs were independently scored by a second blinded researcher (Jos Runhaar or Max Reijman), to assess the reproducibility of K&L grading (kappa 0.6) and knee alignment (kappa 0.7).

MRI measures

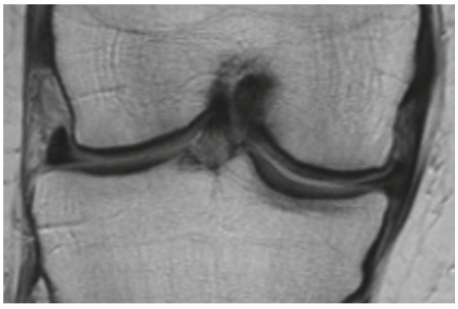
A two-dimensional quantitative measurement method was used to quantify the meniscal extrusion, originally described by Hunter *et al.* and Costa *et al.*[11,17] The measurements were performed at the mid-coronal slice of the PD weighted sequence, which was defined as the slice with the largest area of the medial tibial spine (Figure 1). When this area was similar on two slices, the slice with the largest width of the tibial plateau was used. Tibial plateau width was measured excluding osteophytes. The medial and lateral meniscus coronal width was measured, as well as meniscal body extrusion, to the closest 0.1 mm using Sante DICOM Editor (64-bit) software.[18] Measurements were performed by one observer (FZ), an orthopedic surgeon with prior experience in scientific readings for meniscal body extrusion on MR images, who was well-trained by another orthopedic surgeon (Fredrik Svensson), also with experience in study readings for meniscal extrusion on different datasets. FZ was blinded to clinical data and subject characteristics but had knowledge of the time sequence of the paired read MR images. At baseline, thirty randomly selected knees were reassessed by FZ and a second reader (Fredrik Svensson). The correlation coefficients for intra-reader and inter-reader reliability for meniscus width, meniscus extrusion and tibial plateau width ranged from 0.69 to 0.98 and 0.62 to 0.96, respectively (Supplementary Table S1). Test-retest reliability for meniscus extrusion was assessed using the healthy reference cohort of the OAI with MRI measurements similar to our study, showing a high level of reliability ($p < 0.001$, Pearson correlation coefficient 0.943). Meniscal tears were scored by two trained readers (Jos Runhaar, a human movement scientist and OA researcher with 7 years of research experience at the time of scoring, and Peter van der Plas, a resident in radiology), using the MOAKS scoring system.[29] MRIs were read unpaired, but the observers were

aware of the time sequence. A musculoskeletal radiologist with ~ 10 years of experience in clinical and research settings (EO) provided an extensive training for the two readers. Every tenth MRI was discussed by the readers and radiologist to learn from each other and keep the inter-observer variability as low as possible, resulting in a high to nearly perfect inter-observer agreement (range 0.77 - 0.88, observed agreement 89 - 94%).

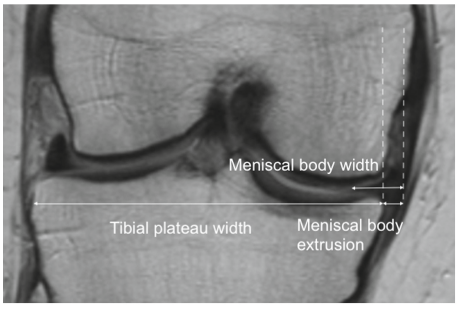
Figure 1. 1.5 T mid-coronal proton density weighted knee magnetic resonance images showing an example of medial meniscal body extrusion at follow-up (B), which has increased compared to baseline (A). C illustrates the measurements of meniscal coronal width, meniscal body extrusion and tibia plateau width using Sante DICOM Editor software (the two dashed vertical lines perpendicular to the tibial plateau indicate the peripheral border of the meniscus body and the outer edge of the tibial plateau, respectively).



A.



B.



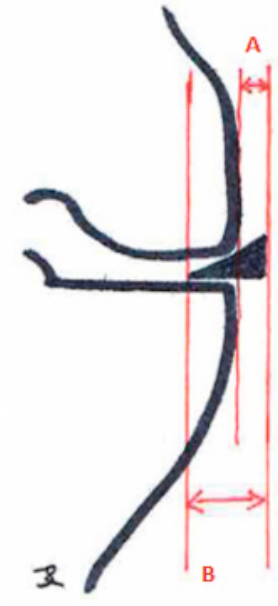
C.

Outcome measures

Primary outcomes of this study were the absolute change in meniscal extrusion and the absolute change in relative extrusion. Relative extrusion was calculated by dividing the extruded part by the total width of the meniscus (Figure 2). From this point on, we will refer to the absolute change in relative extrusion as change in relative extrusion. Factors that were hypothesized to be associated with a change in these measures of extrusion were based on prior studies and included age, BMI, postmenopausal status, malalignment,

quadriceps strength, physical activity, meniscal tears, having a past of knee injury and the presence of Heberden's nodes.[14-21,30] Furthermore, longitudinal variables including change in BMI in 30 months and incident meniscal tear (i.e., a tear occurring during follow-up) were incorporated in the model. Malalignment was defined as varus alignment (< 178 degrees) for medial meniscal extrusion and as valgus alignment (> 182 degrees) for lateral meniscal extrusion (with 178-182 degrees being considered as normal alignment).

Figure 2. Picture illustrating the measurements of meniscal extrusion (A) and meniscal width (B). Relative meniscal extrusion (%) is calculated by A/B * 100.



Statistical analysis

All participants with an MRI-scan at baseline and follow-up were included in the statistical analyses, which were performed by DW. Baseline characteristics of the participants were calculated. Age, BMI, postmenopausal status and physical activity were documented at participant level. Data regarding malalignment, quadriceps strength, meniscal tears and K&L grade were analyzed at knee level. Differences in baseline characteristics between in- and excluded knees were tested for their significance using a univariate linear regression model, with generalized estimating equations (GEE) to adjust for the correlation between knees within the same subject.

Univariate analysis (linear regression model with GEE) was executed to model the effect of aforementioned covariates on the absolute change in extrusion. Separate

models were used for the change in medial and lateral extrusion. These models used the side of the knee as within-subject repeated measure as well. An unstructured covariance matrix was used in all models. Secondly, models were made for the change in relative meniscal extrusion following the same procedure. Furthermore, the models for the change in extrusion were adjusted for tibial width, to take the difference in knee size into account. Lastly, a sensitivity analysis was performed to rule out the potential effects on the outcomes of the interventions of the original trial and their interactions with change in meniscal extrusion, where side of the knee was used as a within-subject repeated measure with an unstructured covariance matrix. Results are rounded off to one decimal digit given the restricted IPR of 0.5 mm^2 and are presented with 95% CIs. A two-sided p-value of < 0.05 was considered statistically significant. All analyses were performed with the SPSS software, version 25.0.0.0 (2017, IBM, NY, USA).

RESULTS

MRI data at baseline were available for 395 subjects (Table 1). Twelve participants did not have any MRI data available and for four patients, MRI data of only one knee were available at baseline. No statistically significant differences in baseline characteristics were found between knees with and without extrusion data.

Fifty-two participants did not undergo an MRI scan after 30 months and were therefore excluded from the analysis. These participants were not statistically significantly different in age, BMI, physical activity, and postmenopausal status compared to subjects with complete follow-up data (Supplementary Table S2).

The average meniscus extrusion at baseline across the entire cohort was 2.4 mm (+/- 1.2) for the medial meniscus and 0.9 mm (+/- 1.2) for the lateral meniscus. This was not statistically different compared to knees without follow-up data (Supplementary Table S3). The average change in medial and lateral meniscal extrusion was +0.3 mm (+/- 1.2) and -0.0 mm (+/- 1.1), respectively, meaning that there was no significant groupwise change in absolute extrusion.

The results of the multivariate linear GEE model for change in medial and lateral extrusion are shown in Table 2. A higher baseline BMI (kg/m^2) was associated with a statistically significant longitudinal increase in medial meniscal extrusion; per 5-points BMI, medial extrusion increased with 0.2 mm (95% CI: 0.1, 0.3; p < 0.001). Change in BMI within 30 months significantly increased both medial and lateral extrusion over time with 0.1 mm

and 0.1 mm per 1-point BMI (kg/m^2), respectively. A lateral meniscal tear at baseline was associated with a longitudinal increase in lateral meniscal extrusion (0.7 mm, 95% CI: 0.1, 1.2; p = 0.013). Incident medial meniscal tears were associated with significantly increased extrusion of the medial meniscus (n= 30 (4.4%); 0.9 mm, 95% CI: 0.3, 1.5; p = 0.004) (examples shown in Figure 3). On the contrary, extrusion in the lateral meniscus decreased by 0.5 mm in case of a new medial meniscal tear during follow-up (95% CI: -0.8, -0.3; p < 0.001). Varus malalignment was associated with an increase in medial meniscal extrusion of 0.6 mm (n= 255 (37.6%); 95%: 0.1, 1.0; p = 0.009). The other factors included in the model were not statistically significantly associated with a change in medial or lateral extrusion after 30 months. When adjusting these models for tibial width, no significant differences in the outcomes were observed (Supplementary Table S4 and S5).

Table 1. Characteristics of the study subjects (SD).

Participants		**N = 343**
Age (Years)		55.71 (3.18)
BMI (kg/m^2)		32.31 (4.17)
SQUASH		6976 (3703)
Postmenopausal status		69.9 %
Knees		**N = 677**
Medial knee angle (degrees)		181.93 (2.35)
Max quadriceps muscle strength[a] (Nm)		3.06 (0.68)
KL-Grade	0	333 (49.5%)
	1	300 (44.6%)
	2	37 (5.5%)
	3	3 (0.4%)
Meniscal tear at baseline		96 (14.2%)
	Medial	66 (9.7%)
	Lateral	32 (4.7%)
Incident meniscal tear after 30 months		45 (6.6%)
	Medial	30 (4.4%)
	Lateral	19 (2.8%)

Includes all participants with extrusion data at baseline. BMI = Body Mass Index. SQUASH = Short QUestionnaire to ASsess Health-enhancing physical activity. [a] Adjusted for body weight.

Figure 3. 1.5 T coronal and sagittal proton density weighted magnetic resonance images at baseline (A and B) and follow-up (C and D) from two different participants showing examples of an incident horizontal tear of the posterior horn of the medial meniscus.

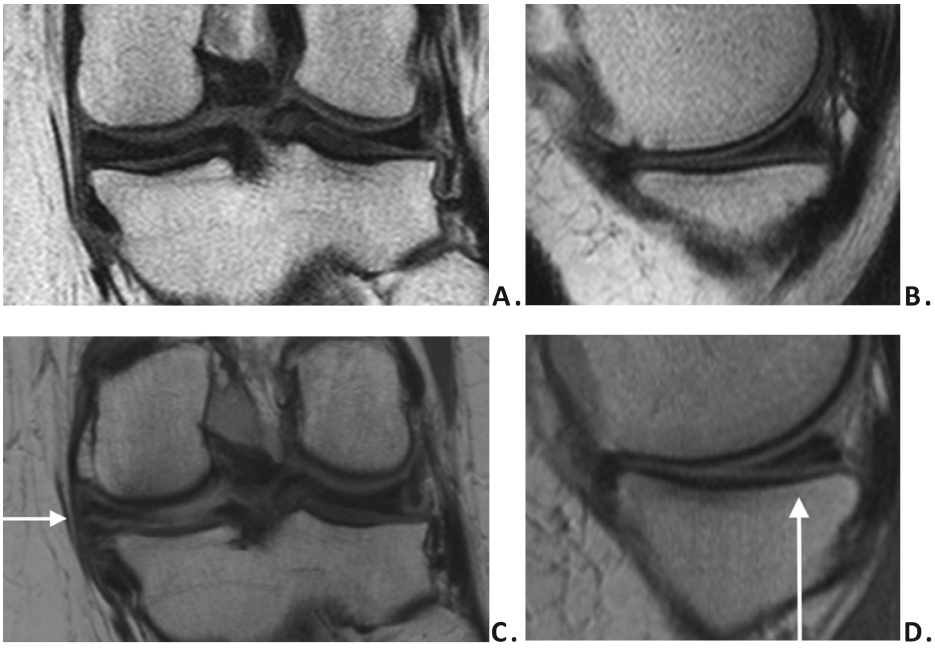


Table 2. Factors associated with the absolute change in meniscal extrusion after 30 months.

	Change in medial extrusion in mm (95% CI; p-value)	Change in lateral extrusion in mm (95% CI; p-value)
Age	0.0 (0.0, 0.0; 0.582)	0.0 (0.0, 0.0; 0.177)
BMI at baseline (per 5 points)	**0.2 (0.1, 0.3; < 0.001)**	0.1 (0.0, 0.2; 0.327)
Change in BMI in 30 months (per 1 point)	**0.1 (0.0, 0.1; 0.001)**	**0.1 (0.0, 0.1; 0.002)**
SQUASH (per 1000 points)	0.0 (0.0, 0.0; 0.388)	0.0 (0.0, 0.0; 0.893)
Postmenopausal status	-0.1 (-0.3, 0.1; 0.240)	-0.1 (-0.2, 0.1; 0.621)
Malalignment [a]	**0.6 (0.1, 1.0; 0.009)**	-0.0 (-0.2, 0.1; 0.647)
Medial meniscal tear at baseline	0.3 (-0.1, 0.6; 0.134)	-0.1 (-0.4, 0.1; 0.322)
Lateral meniscal tear at baseline	-0.2 (-0.6, 0.3; 0.530)	**0.7 (0.1, 1.2; 0.013)**
Incident medial meniscal tear after 30 months	**0.9 (0.3, 1.5; 0.004)**	**-0.5 (-0.8, -0.3; < 0.001)**
Incident lateral meniscal tear after 30 months	0.3 (-0.2, 0.8; 0.175)	0.1 (-0.4, 0.6; 0.690)
Past of knee injury	0.0 (-0.2, 0.2; 0.890)	-0.1 (-0.3, 0.2; 0.474)
Heberden's nodes	0.0 (-0.2, 0.2; 0.831)	-0.1 (-0.3, 0.1; 0.545)
Quadriceps strength [b]	-0.1 (-0.2, 0.0; 0.106)	-0.1 (-0.2, 0.0; 0.090)

BMI = Body Mass Index. SQUASH = Short QUestionnaire to ASsess Health-enhancing physical activity. [a] Defined as varus vs. the rest in medial extrusion and valgus vs. the rest in lateral extrusion. [b] Adjusted for body weight. Changes written in bold are statistically significant compared to baseline. All the variables were simultaneously included in the regression model.

The multivariate linear GEE model for change in relative meniscal extrusion showed roughly similar results, except the changes in relative extrusion in case of higher value of baseline medial extrusion, varus malalignment and baseline lateral tears were now non-significant (Table 3). Incident meniscal tears showed the strongest association with increase in relative medial extrusion on one hand (14.5%, 95%: 4.4, 24.7; p = 0.005) and decrease in relative lateral extrusion on the other hand (-5.8%, 95%: -8.6, -2.9; p < 0.001).

Neither of the interventions from the original PROOF trial showed a significant interaction with change in meniscal extrusion, nor did the interventions significantly influence the outcomes (Supplementary Table S6 and S7).

Table 3. Factors associated with the change in relative meniscal extrusion (= extrusion/total meniscal width) after 30 months.

	Absolute change in relative medial extrusion (%) (95% CI; p-value)	**Absolute change in relative lateral extrusion (%) (95% CI; p-value)**
Age	0.0 (-0.4, 0.4; 0.878)	0.0 (-0.3, 0.3; 0.907)
BMI at baseline (per 5 points)	**3.0 (1.3, 4.8; 0.002)**	-0.1 (-1.3, 1.1; 0.878)
Change in BMI in 30 months (per 1 point)	**0.6 (0.1, 1.2; 0.031)**	**0.4 (0.1, 0.8; 0.008)**
SQUASH (per 1000 points)	0.0 (-0.4, 0.4; 0.969)	0.1 (-0.2, 0.3; 0.556)
Postmenopausal status	-1.5 (-4.1, 1.1; 0.265)	-0.4 (-2.4, 1.6; 0.685)
Malalignment [a]	5.7 (-1.1, 12.5; 0.100)	-0.7 (-2.4, 1.1; 0.467)
Medial meniscal tear at baseline	4.9 (-0.8, 10.6; 0.094)	-1.1 (-3.5, 1.3; 0.373)
Lateral meniscal tear at baseline	-0.5 (-5.6, 4.7; 0.860)	5.1 (-0.1, 10.2; 0.052)
Incident medial meniscal tear after 30 months	**14.5 (4.4, 24.7; 0.005)**	**-5.8 (-8.6, -2.9; <0.001)**
Incident lateral meniscal tear after 30 months	4.0 (-3.2, 11.3; 0.272)	0.8 (-4.5, 6.0; 0.774)
Past of knee injury	2.9 (-1.7, 7.4; 0.220)	-0.1 (-3.1, 2.9; 0.954)
Heberden's nodes	-0.3 (-3.5, 2.8; 0.847)	-0.9 (-2.9, 1.1; 0.355)
Quadriceps strength [b]	-0.6 (-2.6, 1.4; 0.556)	-1.1 (-2.4, 0.2; 0.107)

BMI = Body Mass Index. SQUASH = Short QUestionnaire to ASsess Health-enhancing physical activity. [a] Defined as varus vs. the rest in medial extrusion and valgus vs. the rest in lateral extrusion. [b] Adjusted for body weight. Changes written in bold are statistically significant compared to baseline. All the variables were simultaneously included in the regression model.

DISCUSSION

The most important finding of the present study is the strong association of incident meniscal tears with change in meniscal extrusion, with an increase in relative medial meniscal extrusion of more than 14% (Table 3). The meniscus is composed of a strong matrix of circumferential and radial oriented type 1 collagen fibers resulting in great tensile stiffness.[31] Together with a strong meniscal root attachment, these fibers resist radial displacement during axial loading, also known as hoop strain. In case of a tear, the integrity of the meniscal matrix is compromised, thereby affecting the capability of the meniscus to resist the hoop strain, ultimately resulting in meniscal displacement. Complex, root and radial tears are mostly associated with meniscal displacement.[16,17,22,32] In keeping with this, an incident medial meniscal tear has an opposite effect on the lateral meniscus, with decreasing relative lateral extrusion by +/- 6%. Failure of medial meniscal hoop strain probably results in widening of the lateral compartment and keeps the lateral meniscus from extruding by ligamentotaxis in these non-weight bearing knees.

These findings might justify a tear to be surgically corrected to reduce extrusion and thereby decelerate the development of knee OA, especially in case of a medial meniscal root tear.[33-36] Chernchujit *et al.* elaborately described several techniques for arthroscopic direct meniscal extrusion reduction in case of a medial meniscus posterior root tear, with improved short-term clinical outcome.[37] In a recent meta-analysis, Faucett *et al.* compared meniscus root repair (to reduce extrusion), meniscectomy and nonoperative treatment and concluded that over 10 years meniscal repair leads to less OA and is cost-effective.[34] This meta-analysis however studied traumatic meniscal tears, whereas the tears of the present study were degenerative in nature. On the contrary, there are studies showing less clear results and (arthroscopic) surgery has several limitations, including higher costs, potential failure of the repair procedure and an (albeit low) complication risk.[35-37] Still, meniscal repair or replacement can be considered as an interesting option to potentially reduce the risk of OA development.[38]

Varus malalignment was associated with increased medial meniscal extrusion. This is most likely caused by increased load in the medial compartment in varus knees, as recently described by Schad *et al.* using MRI under mechanical loading.[39] To correct malalignment to reduce or reverse meniscal extrusion several interventions have been described, including laterally wedged insoles, valgus knee braces or, in severe cases, a high tibial wedge osteotomy.[40,41] All these interventions have never been tested in a preventive setting though.

BMI showed significant associations with longitudinal change in meniscal extrusion; for the medial meniscus, a higher baseline BMI resulted in progressive meniscal extrusion of 0.2 mm per 5 points. Increase in BMI over time was associated with a significant increase in both medial and lateral extrusion. Similar results were seen for change in relative extrusion. This might be explained by increased hoop stress on the meniscus, gradually leading to hoop stabilizing failure. These findings are in line with Englund *et al.* and Zhang *et al.*, proposing that a higher baseline BMI increases the risk for incident meniscal extrusion.[19,20] However, the finding that change in BMI over time results in change in extrusion is relatively novel and suggests that losing weight reverses extrusion, a theory supported by Landsmeer *et al.* and a recent paper from Munugoda *et al*.[21,42]

All the other variables incorporated in the analysis model (i.e., age, activity level, postmenopausal status, a history of knee injury, presence of Heberden's nodes and quadriceps strength) did not appear to be statistically significantly associated with change in meniscal extrusion, although several previous studies reported a relationship between either of these variables with knee OA or extrusion.[15-19] Furthermore, contrary to our hypothesis, adjustment for tibial width did not have a statistically significant effect on the outcomes.

For our study, a 2D quantitative and semi-quantitative measurement method was used to assess and analyze meniscal extrusion. With 3D quantitative imaging techniques, including T1 and T2 mapping, several recent studies focused on the composition and ultrastructural features of the meniscus in loaded and unloaded conditions, potentially indicating load transmission failure in degenerate menisci.[43-45] Although the papers describe variable results in the ability to detect compositional variations, these techniques provide further insight in the pathologic morphologic and functional changes occurring in degenerate menisci and may play a role in the future MRI-based quantification.

A remark should be made regarding the fact that most of the studied variables are related to chondropathy as well. However, based on our prior study and other papers, we believe that in most cases meniscal extrusion occurs before the initiation of chondral damage.[7-12] Therefore, in general, we think that these risk factors primarily act on the meniscus and secondary affect the cartilage.

Potential limitations of our study should be mentioned. First, we used data from an interventional trial, which could have influenced the outcomes. For example, the weight reduction program might have underestimated the effect of BMI on extrusion.

Also, glucosamine therapy could have had an effect on glycosaminoglycans content and thereby on meniscal behavior.[46] However, a sensitivity analysis did not show a significant effect of the original interventions on the results. Second, the 2D quantitative measurement method used to assess meniscal extrusion and meniscal width might not be representative for the entire meniscus and could potentially result in a relatively large test-retest error. We used anatomical lines and landmarks as a reference for reliable repeated measurements, but slight rotation in the coronal plane could not be ruled out, which could have had a minor influence on the measurements. Nonetheless, test-retest reliability was high in the healthy reference cohort of the OAI. Third, we only measured meniscal body extrusion on MRI in the coronal plane, extrusion in the anterior or posterior horn was not assessed. Fourth, the follow-up time of 30 months is relatively short for a degenerative condition with slow progression, although we managed to collect follow-up MRI data of many participants. Hypothetically, the non-significant associations of studied variables with changes in meniscal extrusion might become significant if the studied time period is longer. Fifth, we were unable to assess to possible effect of sex since the study sample consisted only of women. There are multiple indications that knee OA is more prevalent and might evolve faster in women than men[47], but evidence regarding the association with meniscal extrusion is scarce.[20] Sixth, given the low numbers of meniscal tears, we did not analyze the change in extrusion for each subtype (i.e., root, radial, vertical, horizontal, complex). Seventh, as mentioned, meniscal extrusion was assessed in supine position with a non-load bearing MRI, which might give an underestimation of the actual grade of meniscal extrusion.[48, 49] However, according to a study of Boxheimer *et al.*, variation in meniscal position under non-loading and loading conditions in asymptomatic individuals is relatively little.[50] Finally, femorotibial alignment was assessed using semi-flexed knee radiographs. Ideally, knee alignment is measured on a full-limb radiograph, which is considered the golden standard. However, a knee radiograph is a reliable cost-effective and time-saving alternative with a good correlation with the more cumbersome full-limb radiograph and with significant less radiation exposure.[29,30]

We found baseline BMI, change in BMI over time, varus malalignment, baseline lateral meniscal tears and incident medial meniscal tears to be statistically significantly associated with increase in meniscal extrusion in middle-aged overweight women. Since meniscal extrusion is related to the development of knee OA, they provide viable targets to prevent or decelerate the degenerative course.

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Supplementary Table S1. Intra-reader and inter-reader reliability coefficients for the measurements of tibial width, medial and lateral meniscus width, and medial and lateral meniscus extrusion.

	ICC intra-reader reliability (95% CI)	ICC inter-reader reliability (95% CI)
Tibial width	0.98 (0.96 – 0.99)	0.96 (0.93 – 0.98)
Medial meniscal width	0.69 (0.50 – 0.81)	0.78 (0.59 – 0.89)
Medial meniscal extrusion	0.81 (0.69 – 0.89)	0.62 (0.34 – 0.80)
Lateral meniscal width	0.70 (0.52 – 0.87)	0.84 (0.71 – 0.93)
Lateral meniscal extrusion	0.77 (0.63 – 0.86)	0.67 (0.53 – 0.77)

ICC = Intraclass Correlation Coefficient.

Supplementary Table S2. Baseline characteristics of the group with complete MRI-data vs. lost to follow-up (SD).

Participants		Complete follow-up N = 343	Lost to follow-up N = 52
Age (years)		55.71 (3.18)	55.91 (3.23)
BMI (kg/m^2)		32.31 (4.17)	32.79 (5.18)
SQUASH		6976 (3703)	5920 (3691)
Postmenopausal status		69.9%	72.7%
Knees		**N = 677**	**N = 109**
Medial knee angle (degrees)		181.93 (2.35)	182.13 (2.54)
Max quadriceps muscle strength[a] (Nm*s)		3.06 (0.68)	3.07 (0.72)
KL-Grade	0	333 (49.5%)	56 (51.4%)
	1	300 (44.6%)	42 (38.5%)
	2	37 (5.5%)	9 (8.3%)
	3	3 (0.4%)	2 (1.8%)
Meniscal tears		96 (14.3%)	10 (9.7%)

BMI = Body Mass Index; SQUASH = Short Questionnaire to assess health-enhancing physical activity.
[a] Adjusted for body weight.

Supplementary Table S3. Comparison of baseline meniscus extrusion between knees with complete follow-up data vs. knees lost to follow-up.

	Complete follow-up N = 677 knees	Lost to follow-up N = 109 knees	p-value
Medial meniscus extrusion in mm (SD)	2.4 (1.2)	2.2 (1.1)	0.325
Lateral meniscus extrusion in mm (SD)	0.9 (1.2)	1 (1.0)	0.576

Supplementary Table S4. Factors associated with the absolute change in meniscal extrusion after 30 months, adjusted for tibial width.

	Change in medial extrusion in mm (95% CI; p-value)	Change in lateral extrusion in mm (95% CI; p-value)
Age	0.0 (0.0, 0.0; 0.620)	0.0 (0.0, 0.0; 0.722)
BMI at baseline (per 5 points)	**0.2 (0.1, 0.3; 0.001)**	0.0 (-0.1, 0.1; 0.544)
Change in BMI in 30 months (per 1 point)	**0.1 (0.0, 0.1; 0.002)**	**0.1 (0.0, 0.1; 0.003)**
SQUASH (per 1000 points)	0.0 (0.0, 0.0; 0.378)	0.0 (0.0, 0.0; 0.891)
Postmenopausal status	-0.1 (-0.3, 0.1; 0.2)	-0.1 (-0.2, 0.1; 0.554)
Malalignment [a]	**0.6 (0.1, 1.0; 0.014)**	-0.6 (-0.2, 0.1; 0.560)
Medial meniscal tear at baseline	0.2 (-0.1, 0.6; 0.216)	-0.2 (-0.4, 0.1; 0.146)
Lateral meniscal tear at baseline	-0.2 (-0.7, 0.3; 0.414)	**0.6 (0.1, 1.1; 0.031)**
Incident medial meniscal tear after 30 months	**0.8 (0.3, 1.4; 0.006)**	**-0.6 (-0.9, -0.3; < 0.001)**
Incident lateral meniscal tear after 30 months	0.3 (-0.2, 0.8; 0.186)	0.1 (-0.4, 0.6; 0.789)
Past of knee injury	0.00 (-0.2, 0.3; 0.977)	-0.1 (-0.4, 0.1; 0.383)
Heberden's nodes	0.0 (-0.2, 0.2; 0.883)	-0.1 (-0.3, 0.2; 0.610)
Quadriceps strength [b]	-0.1 (-0.2, 0.0; 0.144)	-0.1 (-0.2, 0.0; 0.110)
Tibial width	**0.0 (0.00, 0.01; 0.028)**	**0.1 (0.0, 0.1; 0.003)**

BMI = Body Mass Index. SQUASH = Short QUestionnaire to ASsess Health-enhancing physical activity. [a] Defined as varus vs. the rest in medial extrusion and valgus vs. the rest in lateral extrusion. [b] Adjusted for body weight. Changes written in bold are statistically significant compared to baseline. All the variables were simultaneously included in the regression model.

Supplementary Table S5. Factors associated with the absolute change in relative meniscal extrusion (= extrusion/total meniscal width) after 30 months, adjusted for tibial width.

	Absolute change in relative medial extrusion (%) (95% CI)	Absolute change in relative lateral extrusion (%) (95% CI)
Age	0.0 (-0.4 – 0.4)	0.0 (-0.3 – 0.3)
BMI at baseline (per 5 points)	**2.9 (1.0 – 4.7)**	-0.3 (-1.5 – 0.9)
Change in BMI in 30 months (per 1 point)	**0.6 (0.1 – 1.2)**	**0.4 (0.1 – 0.7)**
SQUASH (per 1000 points)	0.0 (-0.4 – 0.4)	0.1 (-0.2 – 0.3)
Postmenopausal status	-1.5 (-4.1 – 1.1)	-0.5 (-2.5 – 1.5)
Malalignment [a]	5.6 (-1.3 – 12.7)	-0.8 (-2.5 – 1.0)
Medial Meniscal Tear at Baseline	4.6 (-1.1 – 10.2)	-1.6 (-4.1 – 0.8)
Lateral Meniscal Tear at Baseline	-0.8 (-5.9 – 4.3)	4.4 (-0.9 – 9.6)
Incident Medial Meniscal Tear after 30 months	**14.3 (4.0 – 24.5)**	**-6.3 (-9.1 – -3.4)**
Incident Lateral Meniscal Tear after 30 months	3.9 (-3.4 – 11.1)	0.4 (-4.7 – 5.6)
Past of knee injury	2.8 (-1.8 – 7.3)	-0.3 (-3.2 – 2.6)
Heberden's Nodes	-0.3 (-3.4 – 2.9)	-0.8 (-2.8 – 1.1)
Quadriceps Strength [b]	-0.5 (-2.6 – 1.5)	-1.0 (-2.2 – 0.3)
Tibial Width	0.2 (-0.2 – 0.7)	**0.5 (0.1 – 0.8)**

BMI = Body Mass Index. SQUASH = Short QUestionnaire to ASsess Health-enhancing physical activity. [a] Defined as varus vs. the rest in medial extrusion and valgus vs. the rest in lateral extrusion. [b] Adjusted for body weight. Changes written in bold are statistically significant compared to baseline. All the variables were simultaneously included in the regression model.

Supplementary Table S6. Factors associated with the absolute change in meniscal extrusion after 30 months, adjusted for the intervention groups of the original trial (sensitivity analysis).

	Change in medial extrusion in mm (95% CI; p-value)	Change in lateral extrusion in mm (95% CI; p-value)
Age	0.0 (0.0 – 0.0; 0.580)	0.0 (0.0 – 0.0; 0.702)
BMI at baseline (per 5 points)	**0.2 (0.1 – 0.3; <0.001)**	0.1 (-0.1 – 0.2; 0.371)
Change in BMI in 30 months (per 1 point)	**0.1 (0.0 – 0.1; 0.002)**	**0.1 (0.0 – 0.1; 0.002)**
SQUASH (per 1000 points)	0.0 (0.0 – 0.0; 0.339)	0.0 (0.0 – 0.0; 0.913)
Postmenopausal status	-0.1 (-0.3 – 0.1; 0.228)	-0.1 (-0.2 – 0.2; 0.636)
Malalignment [a]	**0.6 (0.1 – 1.0; 0.013)**	0.0 (0.2 – 0.1; 0.672)
Medial meniscal tear at baseline	0.3 (-0.1 – 0.6; 0.138)	-0.1 (-0.4 – 0.1; 0.377)
Lateral meniscal tear at baseline	-0.2 (-0.6 – 0.3; 0.506)	**0.7 (0.1 – 1.2; 0.012)**
Incident medial meniscal tear after 30 months	**0.9 (0.3 – 1.5; 0.004)**	**-0.5 (-0.8 – -0.3; <0.001)**
Incident lateral meniscal tear after 30 months	0.3 (-0.2 – 0.8; 0.186)	0.1 (-0.4 – 0.6; 0.749)
Past of knee injury	0.0 (-0.2 – 0.3; 0.970)	-0.1 (-0.3 – 0.2; 0.468)
Heberden's nodes	0.0 (-0.2 – 0.2; 0.906)	-0.1 (-0.3 – 0.1; 0.530)
Quadriceps strength [b]	-0.1 (-0.2 – 0.0; 0.123)	-0.1 (-0.3 – 0.0; 0.077)

Supplementary Table S6. *(continued)*

		Change in medial extrusion in mm (95% CI; p-value)	Change in lateral extrusion in mm (95% CI; p-value)
Intervention group	C & P	C	C
	WR & P	-0.2 (-0.4 – 0.0; 0.095)	0.0 (-0.3 – 0.2; 0.884)
	C & G	0.0 (-0.3 – 0.2; 0.973)	-0.1 (-0.4 – 0.2; 0.448)
	WR & G	-0.1 (-0.3 – 0.2; 0.637)	0.0 (-0.3 – 0.2; 0.850)

BMI = Body Mass Index. SQUASH = Short QUestionnaire to ASsess Health-enhancing physical activity. WR = weight reduction, P = placebo (vs glucosamine), C = control (vs weight reduction), G = Glucosamine. [a] Defined as varus vs. the rest in medial extrusion and valgus vs. the rest in lateral extrusion. [b] Adjusted for body weight. Changes written in bold are statistically significant compared to baseline. All the variables were simultaneously included in the regression model.

Supplementary Table S7. Factors associated with the change in relative meniscal extrusion after 30 months, adjusted for the intervention groups of the original trial (sensitivity analysis).

		Absolute change in relative medial extrusion (%) (95% CI; p-value)	Absolute change in relative lateral extrusion (%) (95% CI; p-value)
Age		0.0 (-0.4 – 0.4; 0.881)	0.0 (-0.3 – 0.3; 0.973)
BMI at baseline (per 5 points)		**3.0 (1.2 – 4.8; 0.001)**	-0.2 (-1.4 – 1.1; 0.759)
Change in BMI in 30 months (per 1 point)		**0.6 (0.1 – 1.2; 0.033)**	**0.5 (0.2 – 0.9; 0.004)**
SQUASH (per 1000 points)		0.0 (-0.4 – 0.4; 0.978)	0.1 (-0.2 – 0.3; 0.565)
Postmenopausal status		-1.5 (-4.0 – 1.1; 0.272)	-0.4 (-2.4 – 1.6; 0.680)
Malalignment [a]		5.6 (-1.3 – 12.4; 0.109)	-0.5 (-2.3 – 1.2; 0.545)
Medial meniscal tear at baseline		4.8 (-0.9 – 10.4; 0.101)	-0.8 (-3.2 – 1.6; 0.506)
Lateral meniscal tear at baseline		-0.5 (-5.6 – 4.7; 0.860)	**5.3 (0.3 – 10.4; 0.040)**
Incident medial meniscal tear after 30 months		**14.6 (4.5 – 24.7; 0.005)**	**-5.8 (-8.6 – -3.0; <0.001)**
Incident lateral meniscal tear after 30 months		3.9 (-3.3 – 11.2; 0.288)	0.4 (-4.8 – 5.6; 0.882)
Past of knee injury		2.8 (-1.8 – 7.3; 0.231)	-0.2 (-3.0 – 2.7; 0.914)
Heberden's nodes		-0.2 (-3.4 – 3.0; 0.907)	-1.0 (-3.0 – 1.0; 0.328)
Quadriceps strength [b]		-0.6 (-2.5 – 1.4; 0.589)	-1.2 (-2.6 – 0.2; 0.084)
Intervention group	C & P	C	C
	WR & P	-0.9 (-4.3 – 2.5; 0.598)	-1.2 (-3.7 – 1.4; 0.364)
	C & G	0.1 (-3.6 – 3.8; 0.959)	-2.2 (-5.2 – 0.9; 0.158)
	WR & G	0.8 (-2.6 – 4.2; 0.634)	-1.5 (-4.3 – 1.3; 0.288)

BMI = Body Mass Index. SQUASH = Short QUestionnaire to ASsess Health-enhancing physical activity. WR = weight reduction, P = placebo (vs glucosamine), C = control (vs weight reduction), G = Glucosamine. [a] Defined as varus vs. the rest in medial extrusion and valgus vs. the rest in lateral extrusion. [b] Adjusted for body weight. Changes written in bold are statistically significant compared to baseline. All the variables were simultaneously included in the regression model.

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Is postmenopausal status associated with increased risk for meniscus extrusion?

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ABSTRACT

Objectives

To evaluate the association between postmenopausal status and meniscus extrusion, a strong risk factor for OA development, in an open population of women aged 45-60 years.

Methods

We used data from a female subcohort of the Rotterdam Study. Outcome measures were the presence of medial meniscal extrusion, defined as ≥ 3 mm on MRI, at baseline and after a mean 5.1 year follow-up. Using generalized estimating equations, the association between postmenopausal status and the presence of meniscus extrusion was determined with a stepwise approach, unadjusted and adjusted for covariables and adjusted for the correlation between knees within subjects.

Results

At baseline, 1305 knees in 672 women were available for analysis. 65.1% were postmenopausal of which 48.7% had medial meniscus extrusion. In the unadjusted analysis, knees of postmenopausal women showed a borderline significant higher prevalence of meniscus extrusion at baseline (OR 1.29; 95% CI 0.98, 1.71) and follow-up (1.3; 0.99, 1.72). After adjustments, these associations became non-significant, with ORs 1.12 (0.8, 1.58) and 1.07 (0.66, 1.71), respectively.

Conclusion

No evidence was found that postmenopausal women have an increased risk for meniscal extrusion. Likely, the higher prevalence of meniscal extrusion among postmenopausal women is explained by mediating factors such as meniscus tears and a higher BMI.

INTRODUCTION

In recent years, the role of meniscal extrusion in the pathogenesis of knee osteoarthritis (KOA) has gained increased attention, with rising evidence for extrusion being a key element in a pathway leading to joint degeneration.[1-6] To obtain potential targets for the prevention or delay of the degenerative process, several studies aimed to identify variables associated with meniscal extrusion.[7-14] To date, there is limited information regarding the possible effect of the menopause, with corresponding decreased estrogen levels, on meniscal extrusion.

Estrogen has a metabolic effect on all musculoskeletal tissue, including bones, cartilage, muscles, tendons and ligaments.[15] Among others, it directly acts on the formation of collagen, which is an important component of the fibrocartilaginous menisci.[16] Hence, decreased estrogen levels in postmenopausal women might alter the integrity of the menisci, leading to weakening of the meniscal matrix, followed by extrusion. On the other hand, estrogen increases ligament laxity[15-19], implying that ligaments in estrogen deficient postmenopausal women are likely to become stiffer. Since multiple ligaments attach to the menisci, this might influence the position of the meniscus. Theoretically, more rigid ligaments should keep the menisci in place and prevent them from extrusion. The objective of the present study was to assess the possible relationship between postmenopausal status and meniscal extrusion among middle-aged women. We hypothesized that there is an independent and statistically significant positive association between menopausal status and the presence and development of meniscal extrusion.

METHODS

We conducted a cross-sectional and longitudinal analysis using data from the Rotterdam Study. Previously, the design of the Rotterdam Study has been described in detail.[20] In short, the Rotterdam Study is a large ongoing prospective, population-based cohort study among inhabitants of a specific city district in Rotterdam, the Netherlands, aged ≥ 45 years, aiming to identify risk factors for chronic diseases in elderly people, including musculoskeletal pathology. In a subcohort, 1116 women aged 45-60 years were asked to participate in a sub-study to investigate early signs of knee OA. At baseline, participating women underwent physical, radiographic and MRI examination.

Clinical and physical data

Subjects filled in questionnaires regarding menopausal status and clinical symptoms. Participants were considered postmenopausal if their last menstruation was more than three years ago. All other subjects were considered premenopausal. To calculate the Body Mass Index (BMI), body height and weight were obtained. The quadriceps muscle strength was assessed using the mean outcome of two measurements with a hand-held dynamometer. Knee alignment was measured on the knee radiographs (weightbearing in full extension), defining varus alignment as a medial knee joint angle < 179 degrees. Also, the presence of Heberden's nodes was documented.

MRI and radiographic data

A 1.5 Tesla MRI scan of both knees was performed at baseline and follow-up. Expected follow-up time was ≈ 5 years. To reduce scanning time, an eight-channel cardiac coil was used enabling scanning of two knees during one session. The MRI protocol included a sagittal FIESTA (fast-imaging employing steady-state acquisition) sequence (slice thickness 1.6 mm), which was later reformatted in the transverse and coronal plane. Other sequences included a sagittal spoiled fat suppressed gradient echo (slice thickness 3.2 (1.6) mm), sagittal fast spin echo (FSE) fat suppressed T2 weighted sequence (slice thickness 3.2 mm) and a sagittal FSE PD and T2 weighted sequence (slice thickness 3.2 mm). Two readers, extensively trained by an experienced musculoskeletal radiologist (EO), scored the MRI scans according to the MRI Osteoarthritis Knee Score (MOAKS).[21,22] Meniscus extrusion was measured in the coronal plane for the meniscal body and in the sagittal plane for the anterior horn. Radiographic examination was conducted to obtain the Kellgren and Lawrence (K&L) grade, a widely accepted KOA classification system.[23] The standardized weight-bearing knee radiographs of both knees were taken in an anteroposterior (AP) direction in full extension (70 kV, focus 1.8 mm^2, focus-to-film distance 120 cm). Radiographic KOA was defined as K&L grade ≥ 2. Two extensively trained researchers scored the radiographs, blinded for MRI and clinical data.

Outcome measures

Outcome measures were medial meniscal extrusion (y/n) at baseline and follow-up. Since medial meniscal extrusion was much more prevalent than lateral extrusion, we chose to limit the analysis to the medial meniscus. Meniscus extrusion was defined as MOAKS grade 2 (3 - 4.9 mm) or 3 (≥ 5 mm). Grade 0 or 1 extrusion (< 2 mm, 2 - 2.9 mm) was considered as no extrusion.

Statistical analysis

We conducted a cross-sectional analysis for the association between baseline postmenopausal status and baseline meniscus extrusion and a longitudinal analysis between baseline postmenopausal status and meniscus extrusion at follow-up. Knees of pre- and postmenopausal participants were compared for the outcome measures using a stepwise approach. First, the association between postmenopausal status and medial meniscus extrusion was assessed without adjusting for other factors. Second, we adjusted the model for the two confounders considered the most important, i.e., age and BMI. Third, based upon literature, other OA and extrusion related covariables were added to the model, i.e., K&L ≥ 2, medial meniscal tears at baseline, varus alignment, quadriceps muscle strength and the presence of Heberden's nodes.[7-13, 24,25] At follow-up, the adjusted models were additionally corrected for the prevalence of baseline meniscus extrusion. All analyses were performed using generalized estimating equations (GEE), which corrects for the correlation between knees within subjects.

The outcomes are presented in percentages, odds ratios, confidence intervals and p-values. A two-sided p-value of < 0.05 was considered statistically significant. All analyses were performed with the SPSS-software, version 28.0.1.0 (2021, IBM, NY, USA).

RESULTS

Baseline characteristics

Baseline characteristics of the pre- and postmenopausal women are shown in Table 1. Of the 1116 invited women, 225 were not included in the analysis. The main reasons for not participating the study were claustrophobia, lack of time or interest, illness, language barrier and moving out of the region. Furthermore, 477 knees with lack or insufficient quality of baseline MRI and incomplete clinical and radiographic data were excluded. As a result, 1305 knees in 672 women were available for statistical analysis at baseline. Of these 672 women, 65.1% were postmenopausal. Mean age of the participants was 56.2 +/- 3.1 years and mean BMI was 27 +/- 4.8 kg/m^2.

Table 1. Baseline characteristics.

	Postmenopausal at baseline (65.1%)	Premenopausal at baseline (34.9%)	p-value
Age (yr)	56.2 +/- 3.1	51.8 +/- 2.9	< 0.001
BMI (kg/m²)	27 +/- 4.8	26.6 +/- 4.2	0.016
K&L grade ≥ 2 (%)	5.8	1.9	< 0.001
Meniscal tear at baseline (%)	6.5	4.3	0.099
History of knee injury (%)	8.9	7.2	0.336
Varus alignment[a] (%)	16.1	23.8	< 0.001
Heberden's nodes (%)	28.8	17.5	< 0.001
Quadriceps muscle strength[b] (Nm)	226 +/- 47	219 +/- 46	0.007

BMI = Body Mass Index. K&L = Kellgren & Lawrence. a Defined as medial knee joint angle < 179 degrees. b Mean of two measurements with hand-held dynamometer.

Outcomes

Of the postmenopausal women, 48.8% had medial meniscal extrusion at baseline, compared to 42.3% of the premenopausal women. Unadjusted, a statistically borderline significant association was seen between postmenopausal status and baseline medial meniscal extrusion; OR 1.29 (95% CI 0.98, 1.71). After adjusting for age and BMI, the association became non-significant, with an OR of 1.14 (95% CI 0.82, 1.6). Also in the fully adjusted model, the association between postmenopausal status and meniscus extrusion was non-significant, with an OR of 1.12 (95% CI 0.8, 1.58) (Table 2).

For the fully adjusted model at follow-up, additional 42 knees were excluded because of incomplete clinical and radiographic data. The mean follow-up time was 5.1 years. At follow-up, the prevalence of medial meniscal extrusion had increased up to 57.1% for the postmenopausal women at baseline, compared to 50.5% for the women who were premenopausal at baseline. Unadjusted, meniscal extrusion at follow-up was significantly more often encountered in postmenopausal women at baseline (OR 1.3; 95% CI 0.99, 1.72). After adjustment for BMI and age, the OR became non-significant (1.09; 95% CI 0.68, 1.74). In the fully adjusted model, the OR remained non-significant (1.07; 95% CI 0.66, 1.71) (Table 3).

Table 2. Unadjusted and adjusted association between postmenopausal status and medial meniscal extrusion at baseline.

	Baseline medial meniscus extrusion - unadjusted		Baseline medial meniscus extrusion - adjusted	Baseline medial meniscus extrusion - adjusted
	Prevalence	OR (95% CI)	OR (95% CI)	OR (95% CI)
Postmenopausal at baseline	48.8%	1.29 (0.98, 1.71)	1.14 (0.82, 1.6)	(0.8, 1.58)
Premenopausal at baseline	42.3%	1 (reference)	1 (reference)	1 (reference)
Age			1.02 (0.98, 1.07)	1.03 (0.98, 1.07)
BMI			1.05 (1.02, 1.08)	1.05 (1.02, 1.08)
K&L grade ≥ 2				1.28 (0.67, 2.46)
Meniscal tear at baseline				2.31 (1.39, 3.85
Varus alignment[a]				1.16 (0.87, 1.56)
Heberden's nodes				1.03 (0.79, 1.34)
Quadriceps muscle strength[b]				1 (1, 1)

OR = Odds Ratio. CI = Confidence Interval. BMI = Body Mass Index. K&L = Kellgren & Lawrence. a Defined as medial knee joint angle < 179 degrees. b Mean of two measurements with hand-held dynamometer.

Table 3. Unadjusted and adjusted association between postmenopausal status at baseline and medial meniscal extrusion after mean 5.1 years follow up.

	Medial meniscus extrusion at FU - unadjusted		Medial meniscus extrusion at FU - adjusted[c]	Medial meniscus extrusion at FU- adjusted[c]
	Prevalence	OR (95% CI)	OR (95% CI)	OR (95% CI)
Postmenopausal at baseline	57.1%	1.3 (0.99, 1.72)	1.09 (0.68, 1.74)	1.07 (0.66, 1.71)
Premenopausal at baseline	50.5%	1 (reference)	1 (reference)	1 (reference)
Age			1.02 (0.96, 1.08)	1.01 (0.95, 1.07)
BMI			0.97 (0.96, 1.04)	0.98 (0.95, 1.04)
K&L grade ≥ 2				0.98 (0.33, 2.93)
Meniscal tear at baseline				1.41 (0.58, 3.44)
Varus alignment[a]				0.83 (0.51, 1.34)
Heberden's nodes				1.43 (0.91, 2.25)
Quadriceps muscle strength[b]				1 (0.99, 1)

FU = Follow up. OR = Odds Ratio. CI = Confidence Interval. BMI = Body Mass Index. K&L = Kellgren & Lawrence.
a Defined as medial knee joint angle < 179 degrees. b Mean of two measurements with hand-held dynamometer. c Additionally adjusted for meniscus extrusion at baseline.

DISCUSSION

For the present study, we hypothesized a positive association between postmenopausal status and the presence of medial meniscal extrusion. Both at baseline and after 5 years of follow-up, however, no significant association was found after adjusting for covariables.

Estrogen directly acts on the formation of collagen, an important component of the fibrocartilaginous menisci.[15] The rationale behind the assumed correlation was that the lower estrogen levels after menopause weakens the meniscal matrix, resulting in bulging of the meniscus beyond the outer margin of the tibia. In the unadjusted analysis a borderline significant correlation was seen between postmenopausal status

and meniscus extrusion. Nonetheless, after adjusting for confounding variables no significant correlation was found. Besides the assumed direct effect on the menisci, estrogen also acts on ligaments. Higher estrogen levels increase ligament laxity, implying that ligaments likely become stiffer in postmenopausal women. Theoretically, rigid parameniscal ligaments prevents the menisci from extrusion. This process might counteract the weakening of the meniscus, resulting in a net zero effect. With the unadjusted analysis at follow-up, there was a borderline significant positive association between postmenopausal status and meniscus extrusion, which dissolved after adjustments. This suggests a mediating effect of (one of) the covariables. Davies-Tuck *et al*. demonstrated that many postmenopausal women have asymptomatic meniscal tears.[26] In our study, the prevalence of meniscal tears was also higher in the postmenopausal group. Maybe, the estrogen related weakening of the meniscal matrix was related to meniscus extrusion through the formation of tears, which by themselves are one of the most important risk factors for extrusion.[8,9,14] Furthermore, it is known that postmenopausal status alters the body composition and fat distribution, which might result in weight gain.[27] In our model and according to the available literature, a higher BMI is significantly associated with meniscal extrusion at baseline and can be seen as an additional explanation for the unadjusted increased incidence of meniscal extrusion in postmenopausal women.[10,11,13,14]

Other factors might also have a mediation effect, although not supported by our findings. For example, decreased estrogen levels after menopause decreases muscle mass and strength.[28] A higher baseline quadriceps muscle strength theoretically has a stabilizing effect on the menisci (and vice versa), although evidence is limited.[29] A higher age is a known risk factor for extrusion, although in our cohort, there was no significant correlation between age and meniscal extrusion.

Potential limitations of the study should be mentioned. First, we had no data regarding hormone levels, which obviously would have been useful when comparing pre- and postmenopausal women. Second, at baseline and especially at follow-up, most women were postmenopausal. It is plausible that the inequal group sizes have affected the outcomes, possibly resulting in an overestimation, although nevertheless no significant correlation was found. Third, we used a semiquantitative measurement method (MOAKS) for meniscus extrusion. Quantitative measurements might have resulted in more reliable outcomes, although the cut-off point for what is generally considered significant meniscal extrusion (> 3 mm) is not different for continuous or categorical measurements. Fourth, the actual grade of meniscal extrusion might

be underestimated, since we assessed meniscal extrusion with a non-load bearing MRI in supine position, although variation in meniscal position is relatively small comparing non-loading and loading conditions in asymptomatic subjects, according to Boxheimer *et al.*[30] Fifth, femorotibial alignment was assessed using weightbearing knee radiographs in full extension. Although a full-limb radiograph is considered the golden standard for measuring knee alignment, a knee radiograph is a reliable cost-effective alternative with significant less radiation exposure.[31,32]

CONCLUSION

No evidence was found that postmenopausal women have an increased risk for meniscal extrusion. Likely, the higher prevalence of meniscal extrusion is explained by mediating factors such as meniscus tears and a higher BMI.

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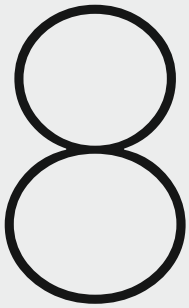

General discussion

To potentially provide new preventive options, this thesis addressed the fundamental role of the meniscus in the pathogenesis of knee OA, with a special focus on meniscus extrusion. We aimed to complement and improve the available knowledge related to this topic, using data from two high-quality prospective studies. In Part I, the relationship of meniscus extrusion and meniscus volume with incident knee OA was analyzed, as well as the interplay between (change in) meniscus volume, meniscus extrusion and incident knee OA. In Part II, we aimed to identify variables associated with (change in) meniscus extrusion, which might be potential targets for the prevention of extrusion and hence the onset or progression of knee OA.

STUDY POPULATIONS

The cornerstone of this thesis was the PROOF Study (PRevention of knee Osteoarthritis in Overweight Females), the first prospective intervention study assessing the preventive effect of a lifestyle intervention and oral glucosamine sulphate on incident radiographic and clinical knee OA.[1] Four hundred seven overweight and obese middle-aged women, at risk for knee OA development but free of clinical signs of the disease according to the American College of Rheumatology (ACR) criteria were included at baseline.[2] These data were used for **Chapter 2**, **3**, **4**, **5**, **and 6**. The second important data source was a subcohort of the Rotterdam Study, a large prospective cohort study in the general population investigating multiple chronic diseases in the elderly.[3] In 2006, 1116 of age 45 years and over women not yet included in the cohort study were asked to participate in a sub-study (RS-III-1) to investigate early signs of knee OA. (**Chapter 3** and **Chapter 7**.) Both studies are prospective in design but are fundamentally different regarding the participating subjects (a selected high-risk population vs. a general population) and are therefore complementary to each other, potentially providing more support for our hypotheses if obtained results are similar.

MAIN FINDINGS

PART I

We found that both meniscus extrusion and a higher meniscus volume at baseline were independently associated with the onset of radiographic knee OA (**Chapter 2**, **3** and **4**). Furthermore, meniscus extrusion was independently associated with incident clinical

knee OA, although this occurred at a later stage than the development of structural knee changes (**Chapter 3**). We found a high population attributable risk percentage (PAR%) of up to 77% for radiographic knee OA (RS), suggesting that 77% of new cases were attributable to or at least preceded by meniscus extrusion (**Chapter 3**). There was also an indication that a decrease in meniscus volume over time is a risk factor for knee OA (**Chapter 4**), which, however, could not be confirmed in another study investigating the interplay between meniscus extrusion, meniscus volume and OA incidence (**Chapter 5**), where no mediation effect of change in meniscus extrusion nor volume could be extracted.

PART II

In the second part of this thesis, we analyzed multiple factors with a potentially significant effect on changes in absolute and relative medial and lateral meniscus extrusion (**Chapter 6**). In a multivariate longitudinal analysis, we found baseline BMI, increase in BMI over time, varus malalignment, baseline lateral meniscal tears and incident medial meniscal tears to be significantly associated with increase in meniscus extrusion. Postmenopausal status however was not related to (change in) meniscus extrusion, neither in the PROOF nor the Rotterdam Study cohort, despite a plausible hypothesis, suggesting that the higher prevalence of meniscus extrusion in postmenopausal women might be explained by mediating factors such as a higher BMI and meniscal tears (**Chapter 7**). Estrogen levels therefore seem not to have a direct effect on the (position of) the meniscus.

Overall, our results are a valuable addition to the existing literature and provides a strong support for the 'meniscal pathway' to knee OA, especially regarding extrusion.

THEORETICAL AND METHODOLOGICAL CONSIDERATIONS

Meniscus extrusion

Semiquantitative measurements

For assessing meniscus extrusion, we used the validated semiquantitative MOAKS scoring system measuring extrusion on the mid-coronal MRI slice.[4] In the past two decades, 3D segmentation models of the meniscus have been developed, providing more comprehensive extrusion measurements of the complete meniscus with a

potential advantage of expressing the surface of the extruded part of the meniscus relative to its total surface.[5,6] However, especially manually conducted segmentations are labor intensive and therefore not suitable for large cohorts. Two studies compared these methods and concluded that measurements on the mid-coronal MRI slice closely correlate with the true perpendicular extrusion measurements, provided that a bony landmark like the apex of the medial tibial spine is used (as in our studies).[7,8] These findings suggest that our 2D measurements are non-inferior to the 3D segmented models and may be even more sensitive to between-group differences. The cut-off point to define significant meniscus extrusion was MOAKS grade ≥ 2, corresponding to 3 mm or more. Although generally accepted in the field[9], this is arbitrarily. Muzaffar *et al.* found in a retrospective study that most of the meniscal tears requiring surgical repair had extrusion ranging from 2 to 4 mm and therefore advocated to consider extrusion of more than 2 mm as clinically significant.[10] Others are more conservative and plead for a 4 mm cut-off, thereby maximizing the sensitivity and specificity with respect to cartilage damage, bone marrow lesions and radiographic OA.[11,12] Diermeier *et al.* also proposed to reconsider the 3 mm cut-of value based on the relative new insight that meniscus extrusion can be reversible over time when observed under extreme loads (in this study generated by a mountain ultramarathon), suggesting that menisci show short-term and temporary adaptations to high loads due to viscoelastic capacities.[13] Nonetheless, these absolute values do not consider the knee size variability between individuals and hence the proportionate displacement of the meniscus. Meniscus extrusion as a percentage of its total width (relative extrusion) might be more reliable (as used in **Chapter 6**), although the cut-off value to define significant relative extrusion has not been determined yet.

Medial versus lateral meniscus extrusion and meniscal subsegments

In **Chapter 2**, we analyzed the medial as well as the lateral meniscus and conducted a subanalysis subdividing medial meniscus extrusion in central and anterior subsegments. Generally, research involving meniscus extrusion focusses on the medial meniscus body as assessed on the coronal plane in MRI. The lateral meniscus as well as the anterior and posterior horns of the menisci are far less studied. For the lateral meniscus, this is likely due to the known relative low numbers of lateral extrusion compared to medial extrusion[14,15], which is in good agreement with our findings with only 8% of the encountered extrusions located laterally. Because of this lower prevalence the potential impact of lateral meniscus extrusion on incident knee OA in general is considered minimal and the numbers are often so low that statistical

analyses are less reliable. To our opinion, this justifies the choice to focus on the medial meniscus. Nonetheless, the menisci have different kinematics, with the lateral meniscus being more mobile, and therefore lateral extrusion might differ from medial extrusion.[16,17] The subanalysis did not show a significant association of medial anterior horn extrusion with incident knee OA. However, the relevance of assessing separate subsegments is questionable. Some suggest that extrusion of the anterior horn should be considered a physiological phenomenon, demonstrating a highly variable mobility which is maximal in the anterior-posterior direction in extended knees.[17] Therefore, in **Chapter 3** and **6** we limited the analyses to central meniscal extrusion and in **Chapter 7** to central medial meniscal extrusion.

Non-loading versus loading

Both in the PROOF and RS cohort, meniscus extrusion was assessed in supine non-loading conditions, possibly underestimating the true grade of meniscal displacement. Several papers describe a significant increase in meniscus extrusion during loading with either weight-bearing MRI or ultrasound, which is seen in normal subjects but might be more prominent in knees with OA features[13,18-22], although others found limited variation in meniscus position under different loading conditions.[23] In addition, knee flexion and internal and external rotation has a major effect on meniscal movement in normal knees as well, with significant differences in extent and direction between the medial and lateral meniscus.[24,25] However, the difference between physiologic and pathologic meniscal behavior under various loading and rotational conditions has not been elucidated yet. Anyhow, a supine non-weightbearing MRI does not represent the normal physiological setting of the menisci. Ultrasound might be an alternative to assess meniscus extrusion, with the advantage of a dynamic assessment in supine and upright position.[12,26] According to Nogueira-Barbosa *et al.*, ultrasound is a reliable method to evaluate meniscus position and movement with an excellent diagnostic performance, compared with MRI as the reference standard. Two studies evaluating meniscus extrusion dynamically with ultrasonography showed that meniscus extrusion was not only more frequent in knees with osteoarthritis compared to normal knees, but also worsened when changing from supine to upright examination.[20,27] A recent validation study confirmed the reliability of ultrasound in detecting lateral meniscus extrusion with good to excellent inter- and intrareader reliability, despite the known examiner-dependency of ultrasound, although in their study the agreement with MRI was poor.[28] They concluded that ultrasound is an easily accessible, reliable, and

cost-effective modality for lateral meniscus extrusion assessment, provided that a standardized measurement protocol is used.

Meniscus extrusion and joint space narrowing

Progression of joint space narrowing (JSN) (isolated or as part of the K&L scoring system) is the most widely used criterion for structural OA progression since it is considered an indication of cartilage loss.[29-31] In **Chapter 2**, we used it as a separate outcome measure. It is questionable however if narrowing of the joint space reliable indicates cartilage thinning, because it is not always clear whether the narrowing is caused by cartilage loss, meniscal pathology, or a combination of both.[32] Some authors state that in most cases JSN is secondary to meniscal extrusion rather than cartilage thinning, especially in early stages.[33,34] The strong association between central medial meniscal extrusion and medial JSN as seen in **Chapter 2** is also suggestive for extrusion to be at least partially responsible for the narrowing of the joint space on plain radiographs. Recently, Golsheini *et al.* reported on the utility to detect meniscus extrusion on plain knee radiographs with adjusted window settings, with a high specificity and a substantial to high inter-reader agreement and correlation, compared to MRI.[35] This might be an accessible and affordable tool not only to differentiate between cartilage loss or extrusion in case of JSN, but also to select a target population at risk for knee OA development, determining the need for additional clinical and MRI examination and to initiate preventive measures.

Clinical knee OA as a separate outcome measure

For the association between meniscus extrusion and knee OA, we additionally assessed incident clinical knee OA according to the ACR criteria[2], whereas other studies only focused on structural signs of the disease or radiographically confirmed symptomatic knee OA. There are known discordances between symptoms and the degree of radiographic disease, with up to 40% of patients with significant structural knee changes being asymptomatic.[36] According to Neogi *et al.,* structural changes are generally ahead of clinical symptoms, corresponding to our findings in **Chapter 2** and **Chapter 3**.[37] On the contrary, a significant percentage of the early painful patients with knee OA do not demonstrate radiographic changes yet.[38] Nevertheless, this indicates that radiography alone is insufficient to define the clinical syndrome. Possibly, structural changes on knee radiography may not have nociceptive innervation and therefore result in less pain than expected. Furthermore, pain experience varies between individuals and depends on several factors such as susceptibility and

tolerance. In general, either clinical or radiographic knee OA likely occur at an earlier stage than radiographically confirmed symptomatic knee OA and might provide a window of opportunity for disease prevention. For example, symptomatic therapies like insoles or exercise and disease-modifying osteoarthritis drugs (DMOADS) are likely to be more effective at an earlier stage of the disease. This emphasizes the value of clinical knee OA as an additional outcome measure in OA research.

Meniscus volume

Meniscus volume has long been a relatively underexposed phenomenon in OA research, with conflicting results regarding the possible association with incident radiographic knee OA.[39-43] The main challenge has been to define normal versus pathologic values of meniscus volume, since naturally large variations exists between individuals. MOAKS defines meniscus hypertrophy as an increase in meniscal volume in a certain sub-region when compared to normal but does not define what that 'normal' is.[4] Others postulated that we could speak of hypertrophy when the height of the medial meniscus is 2 mm greater than lateral, based on reference values of normal meniscus size, but did not actually provide a true meniscus hypertrophy definition.[44] This is even more troublesome and impractical if both menisci are affected. Also, the molecular background of meniscal hypertrophy has not been crystallized. It is known that loading temporarily increases the production of glycosaminoglycans (GAGs), an important component of the meniscal matrix, which could increase the osmotic and hydrostatic pressures and therewith increase the water content of the menisci, resulting in hypertrophy.[45,46]

We found that a higher baseline meniscal volume is associated with incident radiographic knee OA (**Chapter 4** and **Chapter 5**). Since there was no correlation between meniscus volume and medial or lateral JSN, the association with knee OA might be due to the induction of osteophyte formation (as radiographic knee OA is based on JSN, osteophytes, or both). The underlying molecular mechanism however is not certain. Theoretically, meniscal volume changes might stimulate the production of cytokines and growth factors like insulin-like growth factor-I, fibroblast growth factor or transforming growth factor- β to activate compensatory cartilage repairment, which might be followed by osteophyte formation, although not proven yet.[47-49] Although it is known that in the early phase of OA changes in both the menisci and cartilage can be observed,[50,51] no association was found between greater meniscal volume and cartilage defects (**Chapter 5**), probably due to the cross-sectional design of the study.

To extract a possible causal relationship between pre-existing meniscus hypertrophy and cartilage changes, longitudinal evaluation is required.

Greater meniscus volume and greater loss of volume over time are both associated with a higher OA risk (**Chapter 4)** and greater meniscus volume was associated with greater meniscus volume loss over time (**Chapter 5**). The exact underlying molecular mechanisms to these findings are unknown. Although the menisci are histologically not completely similar to articular cartilage, for example regarding the amount of type I collagen which is more abundant in menisci than cartilage, it is known that changes in cartilage volume show similarities with meniscus volume changes.[52] Increased cartilage volume, or swelling, correlates with the degradation of the proteoglycan matrix and volume loss, already present at a very early stage of OA.[53-56] Degraded collagen molecules remain integrated in the fibrils by certain crosslinks (pyridinoline), which levels remain normal but are no longer functional since they have lost their contact with the damaged collagen molecules on both ends of the crosslinks. During tensile loading, this results in degraded collagen molecules sliding along each other, explaining why the fibrils swell more easily at a certain osmotic pressure.[53] Furthermore, in early OA-stages, GAG content increases as a reaction to abnormal biomechanical stresses and collagen degeneration, especially in the middle and deep cartilage regions, resulting in increased cartilage volume. This mechanism is known in the literature as hypertrophic remodeling or repair and can be visualized by MRI.[57-59] However, if these biomechanical alterations also apply to the menisci remains unclear.

In **Chapter 5**, meniscus extrusion was associated with larger meniscus volume at baseline. The underlying physiology of the interplay between meniscus volume and extrusion is not certain. A plausible theory is that of a hypertrophic meniscus being squeezed out of the tibial margin because of the limited articular joint space, leading to extrusion. This could also be an explanation for the aforementioned temporarily increase in meniscus extrusion after a period of extreme loading, initiated by a temporarily increase in GAGs. Alternatively, an extruded meniscus might have the opportunity to expand when not being compressed between the bones of the femur and tibia, resulting in meniscal hypertrophy. Both baseline meniscus extrusion and larger medial meniscus volume were associated with incident knee OA. However, a mediation pathway through a change in meniscus volume or a change in meniscus extrusion could not be extracted, suggesting that prevention of the onset of meniscus hypertrophy and extrusion at a younger age is more important than the prevention of change/progression, in order to prevent knee OA development.

Meniscus hypertrophy and knee OA

Meniscus hypertrophy more likely should be considered an early sign of knee OA rather than a risk factor, since meniscus volume and volume loss over time may be secondary to other OA risk factors such as varus alignment, a higher BMI and quadriceps muscle strength.[60] As mentioned, to use meniscus hypertrophy as an early sign of OA, it is warranted to define a reference value for normal and pathologic meniscus volume, which is challenging.

PART II

In **Chapter 6** we tried to identify variables associated with the longitudinal change of meniscus extrusion. Most known risk factors for meniscus extrusion are based on cross-sectional studies in cohorts with established OA.[61,62] To develop potential preventive measures, it is of additional value to extract factors that influence the longitudinal change in meniscus extrusion, either positively or negatively. We were one of the first to execute such a longitudinal analysis and only the second in a cohort free of OA at baseline.[63]

Meniscus tears

Incident medial meniscal tears showed the greatest association with absolute and relative increase in meniscus extrusion. Since a meniscal tear at baseline is far less related to change in extrusion, our findings suggest extrusion follows relatively shortly after an incident tear, after which a new stable meniscal position is attained. As previously elaborated on, this is likely due to the compromised structural integrity of the meniscus in case of a tear, thereby unable to resist the hoop strain resulting in displacement of the meniscus.[64] As meniscus extrusion, a meniscal tear on its own is also a recognized risk factor for knee OA development. Although total meniscectomy since long has been replaced by partial meniscectomy or repair as a treatment for meniscal tears, the benefit of surgery is questionable. Several studies showed that partial meniscectomy did not prevent knee OA progression, especially when recorded with significant meniscus extrusion, as it generates meniscus insufficiency resulting in significant functional impairment with high rates of arthroplasty.[65-67] In a recent study in young patients with isolated traumatic meniscus tears, clinical outcomes after early arthroscopic partial meniscectomy were equal to a treatment strategy of physical therapy with an optional delayed arthroscopic partial meniscectomy.[68] In case of degenerative meniscal tears, a conservative treatment is also non-inferior to surgery according to a recent randomized clinical trial.[69] Antony *et al.* compared

several meniscal pathologies based on MRI and found that extrusion and maceration rather than tears were associated with OA severity and progression.[70] These findings suggests that tears might be clinically more relevant when co-existing with extrusion and warrant a restrained approach in case of isolated tears without extrusion. On the contrary, early meniscal repair might be justified to prevent extrusion, since extrusion likely occurs relatively short after an incident tear based on our findings, although not every tear leads to extrusion. Nonetheless, if surgery is opted as a treatment, current consensus is that meniscal repair is preferred over partial meniscal meniscectomy, since it restores the biomechanical properties of the meniscus and decelerates knee OA progression.[71,72] Partial meniscectomy should be limited to symptomatic cases with irreparable tears due to poor quality of the meniscal tissue.[73,74] When concurrent, repair of a meniscal tear might be performed simultaneously with reduction of meniscus extrusion, since in many cases no adequate reduction in meniscus extrusion is achieved after isolated meniscus repair.[75,76] Several techniques have been described, including suture anchors or direct arthroscopic meniscal extrusion reduction (ADMER) with transtibial pullout centralization as shown in Figure 1, with promising short-term clinical outcomes and significant reduction in meniscus extrusion.[77-79] However, to date there is no consensus for the indication of this procedure nor the cut-off value for extrusion distance, and more data regarding long-term effects are needed.[80,81]

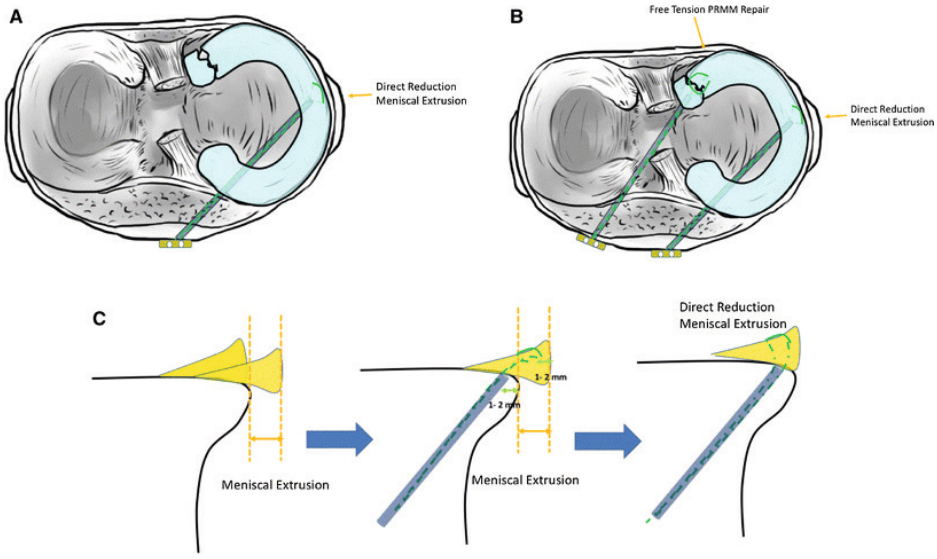

Figure 1. A Direct reduction meniscal extrusion with arthroscopic transtibial pullout extrusion reduction stitch on right knee. B Free tension posterior root medial meniscus tear repair. C Coronal view of arthroscopic direct meniscal extrusion reduction. [76]

Malalignment

Knee malalignment resulted in a significant absolute increase in medial meniscus extrusion. A greater varus angle in the knee joint increases the load on the medial compartment, which might result in the medial meniscus being squeezed out of the joint margin.[82-84] In the opposite compartment a contrary phenomenon might occur, with diminished loading resulting in diminished meniscus extrusion.[85] Albeit minor and non-significant, our results are supportive for this theory, with less meniscus extrusion in the lateral compartment at follow-up compared to baseline. Goto *et al.* described a linear correlation; the greater varus alignment, the greater medial meniscus extrusion, the more severe the osteoarthritis.[83] Although isolated knee malalignment is a known risk factor for knee OA development and progression[86], the combination with meniscus extrusion probably imposes a greater risk.[84] Xu *et al.* found both medial meniscus extrusion and varus alignment to be poor prognostic factors of arthroscopic partial meniscectomy in cases of degenerative meniscal tears.[87] A few non-invasive therapies have been described of which lateral wedged insoles show the best combination of a safe and easy application and low costs, although functional outcomes vary and whether they adequately correct malalignment and meniscus extrusion and delay the development of knee OA remains controversial.[88-91] A high tibial osteotomy (HTO) has been proposed in knees with mild to moderate OA, with significant reduction of malalignment and meniscus extrusion and satisfying short- and medium-term clinical outcomes.[91-94] Greater preoperative extrusion however is associated with inferior intermediate-term clinical outcomes.[95,96] HTO has never been tested in a preventive setting though. To date HTO is being utilized only in knees with already established unicompartmental OA features to alleviate symptoms and postpone knee arthroplasty.

BMI

A higher BMI at baseline was strongly associated with increase in medial meniscus extrusion and an increase in BMI during follow-up was significantly associated with increase in meniscus extrusion both for the medial and lateral meniscus. These relatively new insights indicate that losing weight could reverse extrusion, which is confirmed by a trial by Landsmeer *et al.*, showing significantly diminished progression of meniscal extrusion with a diet and exercise program.[97] Munogoda *et al.* described a similar phenomenon with less progression and even an actual decrease in mean and maximum extrusion in overweight men and women with weight loss over 18 months.[98] The results of an RCT of Messier *et al.* tie in with this, with greater reductions in knee compressive force in a diet group with significant weight loss.[99] This suggest that the

known association of overweight with incident and progression of radiographic and clinical knee OA may be at least partly mediated by meniscus extrusion. Vice versa, it is plausible that the clinical benefits of weight loss are explained by reduced meniscus extrusion, given the correlation between pain and meniscus extrusion[100], which might be explained by mechanical stress on the outer aspect of the meniscus and/or bulging and mechanical stretching of the joint capsule, which are both richly innervated with pain fibers.[101,102] During movement, most activities produce greater load on the medial compartment, reflected in greater medial to lateral ratios at peak compressive load, which, taken together with the low prevalence and incidence of lateral extrusion, likely underly the greater association of a higher BMI with medial meniscus extrusion compared to lateral meniscus extrusion.[103]

Postmenopausal status

In **Chapter 7** we evaluated the influence of postmenopausal status on meniscus extrusion. Beforehand it could have gone either way, with different hypotheses supporting a positive or negative association. Intuitively, since estrogen has a metabolic effect on the formation of collagen (an important component of the menisci)[104], postmenopausal status weakens the meniscal matrix due to the lower estrogen levels, resulting in extrusion. On the contrary, estrogen increases ligament laxity, implying that ligaments are stiffer in estrogen deficient postmenopausal women.[104-108] Since several ligaments attach to the menisci, i.e., tibial collateral, meniscotibial (or coronary), meniscofemoral, meniscocapsular and transverse ligaments, these might keep the menisci in place when becoming stiffer and prevent them from displacement. Since no significant correlation between menopause and meniscus extrusion was found, the latter theory is more likely than the first. Alternatively, these processes both exist but counteract each other, resulting in a net zero effect. In **Chapter 6**, no association was found between postmenopausal status and change in meniscus extrusion, therefore maybe the outcome of **Chapter 7** could have been predicted based hereupon. However, the study populations are fundamentally different (PROOF versus the Rotterdam Study) and given the plausible hypothesis for a positive correlation between menopause and meniscus extrusion, this study is an important addition to the literature, although the results indicate the absence of a direct correlation. The known association between postmenopausal status and OA might therefore not be mediated by meniscus extrusion but act via an alternative pathway.[109,110] Based on ovariectomized animal models, estrogen deprivation appears to have a main direct effect on articular cartilage and a minor indirect effect on subchondral bone.[110] Alternatively, postmenopausal status might be indirectly related

with meniscus extrusion through an increase in weight or the formation of meniscal tears, since many postmenopausal women appear to have asymptomatic tears.[111,112] Moreover, postmenopausal status might be a too rough measure in a population already close to menopause with insufficient discriminatory power.

STRENGHTS AND LIMITATIONS

We would like to highlight several strengths of the studies and results. We performed longitudinal analyses in knees without established OA at baseline, in contrast to previously published papers with mostly a cross-sectional design[41,113,114], providing a stronger indication that meniscus extrusion precedes the development of OA. In **Chapter 2** and **3**, outcomes were eighter incident radiographic or clinical knee OA according to the ACR criteria[2], a relatively uncommon combination in OA research which covers more of the clinical syndrome than radiography alone. Regarding radiographic knee OA, similar results were found both after a short and long-term follow up, with already a statistically significant positive association between meniscus extrusion and incident radiographic OA after just 30 months. Furthermore, a significant correlation between meniscus extrusion and incident knee OA was found in two very different populations (**Chapter 3**), reducing the ever-existing uncertainties with statistical analyses and diminishing the influence of potential flaws and biases. In **Chapter 4** and **5**, we used automated segmentations of the menisci, which are objective and repeatable and thereby more reliable and suitable for future use in clinical practice. **Chapter 6** was one of the first studies evaluating factors associated with longitudinal change of meniscus extrusion.

There are also a number of limitations deserving specific attention. Originally, the PROOF Study was an interventional trial possibly influencing our results. For example, the GAG content and thereby the behavior of the menisci could have been affected by the glucosamine therapy.[115] Also, when examining the association between baseline BMI and change in meniscus extrusion, the weight reduction program could have influenced the outcomes. Nonetheless, in every chapter the sensitivity analyses did not show significant effects of the interventions on the results. Furthermore, in **Chapter 3** we encountered a relatively high drop-out rate at long-term follow-up in the PROOF cohort of +/- 50%, a known phenomenon in weight-loss studies which lowers the power of a study.[116] Particularly for long-term preventive studies without directly perceived benefit for the participants, adherence is a large problem. Although this might have

elicited selection bias, the results of our analyses are more likely an underestimation rather an overestimation, since missing knees and subjects had significantly more meniscal pathologies and a higher BMI which are both related to meniscus extrusion and knee OA. The main drawback of **Chapter 7** was the lack of hormonal data, which obviously would have been of interest when examining the effect of menopausal status on meniscus extrusion.

IMPLICATIONS FOR CLINICAL PRACTICE AND FUTURE RESEARCH

With this thesis, we confirmed the pivotal role of meniscus extrusion in the pathogenesis of knee OA. It emphasizes the importance of increasing awareness amongst, for example, general practitioners (GPs), radiologists, and orthopedic surgeons, to prevent or delay knee OA development. Generally, knee radiography is the first of additional imaging research requested by GPs for patients with knee complaints. Especially when these patients are known with overweight, malalignment or a history of a meniscal tear, they might request radiographs with adjusted window settings or a targeted ultrasound to assess the presence or absence of meniscus extrusion, thereby selecting patients with increased OA risk in an accessible and affordable way. The task of radiologists is to facilitate this option by gaining topic-related knowledge, creating protocols and training of musculoskeletal radiologists with standardized ultrasound examinations. When reporting a routine knee MRI, radiologists should mention and emphasize the presence of meniscus extrusion, especially in relatively young patients without established OA features, to make clinicians aware of the advanced OA risk. When significant meniscus extrusion has been detected, conservative or surgical preventive measures can be considered, e.g., a weight reduction program, wedged insoles, or surgical centralization either isolated or in combination with a meniscal tear repair. However, to date there is no consensus regarding the best preventive strategy.

Meniscus extrusion exhibits a high degree of variation between the medial and lateral meniscus, between different physiological conditions and between different subregions and might even be reversible after a temporal increase in loading. Therefore, the currently used absolute value of 3 mm needs to be reconsidered. Future research needs to provide more insight in the normal physiologic behavior of the menisci under different circumstances. Ultimately, we think relative meniscus extrusion (extrusion as a percentage of the total meniscal width) is more reliable than an absolute value,

as it reckons with the size differences between individuals. With future studies a widely supported cut-off percentage for significant relative meniscus extrusion needs to be determined. Furthermore, histological changes in menisci with extrusion and/or increased volume are a black box and need to be examined to better understand the fundamental mechanisms. Hypotheses are mainly based on research regarding cartilage volume changes because of the histological similarities between cartilage and menisci, but this knowledge is not one-to-one applicable on the meniscus. Delayed gadolinium enhanced magnetic resonance imaging of cartilage (dGEMRIC) is an imaging technique used to identify pre-radiographic degenerative changes in articular cartilage which increasingly is being applied to the meniscus (dGEMRIM).[117-120] It is based on the distribution of contrast medium in the meniscus, which indicates the GAG content and might correlate with the degree of meniscal degeneration, but results are conflicting concerning the amount of GAG in pathologic menisci and suitability of the technique for clinical applications.[121-123] When applied specifically for meniscus extrusion and hypertrophy, dGEMRIM might provide further understanding of the underlying histological processes, but this needs to be tested in future studies. Alternative upcoming and promising techniques are T2 and T2* mapping, potential biomarkers for early OA based on the strong correlation between T2 relaxation time and histological degeneration of the meniscus, allowing detection and quantifying compositional changes without the need for contrast medium.[124,125] Future studies with greater sample sizes are needed to validate these techniques.

The benefits of early conservative and surgical treatment of meniscal extrusion to prevent or delay knee OA development needs to be further explored, aiming to provide a widely supported treatment algorithm, particularly in the absence of meniscal pathologies but also with associated comorbidities like meniscal tears, malalignment, and a higher BMI. The optimal surgical centralization technique needs to be selected based on fundamental biomechanical studies and resultant short- and long-term improvement in clinical outcomes.[126] Furthermore, isolated root repairs and root repairs with meniscus extrusion correction need to be compared in randomized controlled trials with long-term follow-up.

An interesting new insight has been provided by Hart *et al.*, reporting an association between baseline meniscal extrusion and tears and (progression of) OA in the patellofemoral joint (PFJ).[127] It is the first and, to date, only study describing this association, of which the causality however could not be inferred due to the cross-sectional nature of the study. Hypothetically, synovitis caused by meniscal pathology

may contribute to the onset and progression of cartilage damage in the PFJ. Alternatively, altered rotational tibial motion due to meniscal pathology might affect the stress distribution of the PFJ, leading to chondral damage.[128-130] Possibly, since the analyses were unadjusted, the association is noncausative and based on independent systemic risk factors influencing both the menisci and PFJ cartilage. Further research is needed to test these hypotheses and longitudinal studies are required to determine the exact causal pathway.

Lastly, this thesis provided insight in the role of meniscus volume changes and hypertrophy in the early phase of knee OA development, although the fundamental mechanisms remain hypothetical and need to be further explored and a clear and widely supported definition for meniscus hypertrophy needs to be established. Furthermore, research in other populations is necessary to test generalizability, since the results in this thesis are mainly based on Caucasian female subjects. Thereupon, meniscus hypertrophy cannot be utilized for clinical practice yet.

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Summary
Samenvatting

SUMMARY

Meniscus extrusion is often encountered in knees with established OA, but for long it has been unclear whether the onset of knee OA is preceded by meniscal disposition and hence might be considered a risk factor, or if meniscal disposition occurs in a later stage of the degenerative process. Clarifying this dilemma was the primary aim of this thesis. In Part I, we further assessed the relationship between baseline meniscus volume, meniscus volume changes and the interplay between meniscus volume and extrusion with incident knee OA. In Part II, we aimed to identify variables associated with (change in) meniscus extrusion, which might be used for the prevention of extrusion and, secondarily, knee OA incidence or progression.

Part I

In **Chapter 2**, we assessed the association between baseline meniscus extrusion with incident radiographic and clinical knee OA after 30 months follow-up in a high-risk cohort from the PRevention of knee Osteoarthritis in Overweight Females (PROOF) study, with 330 (640 knees) middle-aged overweight and obese women, without radiographic and clinical signs of knee OA at baseline. Meniscal extrusion was defined as ≥ 3 mm on MRI, with a baseline prevalence of 24%. The primary outcome measure was incident knee OA, defined as either incident radiographic OA (Kellgren and Lawrence (K&L) grade ≥ 2), incident clinical knee OA based on the ACR (American College of Radiology) criteria, or incident medial or lateral joint space narrowing (JSN) of ≥ 1.0 mm. The secondary outcome measure was either of these items separately. After adjusting for confounders, we found a significant association between baseline meniscus extrusion and incident knee OA with an odds ratio (OR) of 2.39 (95% CI 1.53, 3.73), although primarily based on radiographic knee OA and medial JSN. After 30 months, clinical knee OA was not (yet) more prevalent in knees with baseline meniscal extrusion compared to knees without extrusion.

In **Chapter 3**, we aimed to validate the findings of the first chapter by assessing the long-term incidence of knee OA in knees with baseline meniscal extrusion, using the same high-risk cohort as well as a subcohort of 438 women (872 knees) of the Rotterdam study (RS), a large prospective cohort study in the general population. In the PROOF cohort, 211 women (421 knees) were eligible for statistical analysis. The baseline prevalence of meniscus extrusion in the RS cohort was 46%. Mean follow-up time in the PROOF cohort was 6.6 years, in the RS cohort 5.1 years. In both cohorts we found a significant and independent association of baseline meniscal extrusion with incident

radiographic knee OA. In the PROOF cohort the association with incident clinical knee OA was statistically significant, in the RS cohort borderline significant. To extract the potential clinical impact of these findings, we additionally calculated the population attributable risk percentage (PAR%), ranging from 19% (incident clinical knee OA PROOF) up to 77% (incident radiographic knee OA RS), indicating that a high number of incident cases were attributable to or at least preceded by meniscus extrusion.

In **Chapter 4**, we assessed the relationship between baseline meniscal volume and meniscal volume changes with incident knee OA for both the medial and lateral meniscus after 30 months, in the same high-risk cohort from the PROOF study. The outcome measures were equal to those in Chapter 2. To obtain meniscus volume and delta-volume, both menisci were automatically segmented at baseline and follow-up. Both medially and laterally, neither baseline nor delta meniscus volume was significantly associated with the primary outcome measure. Baseline medial and lateral meniscus volume showed a significant association with incident radiographic knee OA. Only laterally, meniscus baseline volume was borderline significantly associated with incident JSN. Medial and lateral delta-volume was significantly associated with incident radiographic knee OA. Lateral relative delta-volume was significantly associated to incident radiographic knee OA. The associations between all baseline meniscal volumes and meniscal volume changes with incident clinical knee OA were not statistically significant. Based on this study, knees with a higher baseline meniscal volume and a stronger decrease in meniscal volume over time appear to be at increased risk for developing structural knee OA, possibly by inducing osteophyte formation given the lack of a (reversed) association between meniscal measures and medial/lateral JSN.

Based on the findings of the previous chapters and the available literature, we hypothesized an interplay between meniscal volume, meniscal extrusion, their changes over time and knee OA development, of which the analyses and results are described in **Chapter 5**. The same data from the PROOF study were used with a follow-up of 30 months. In accordance with previous results, we found that both medial meniscus volume and meniscus extrusion at baseline were statistically significant associated with incident knee OA. However, the indirect effects on incident knee OA through delta meniscus volume or delta meniscus extrusion were not statistically significant, which is (partially) contradictory with the results of Chapter 4. These findings suggest that the onset of meniscal pathologies is more relevant than their change over time and that potential measures should focus on the prevention of onset rather than their progression.

Part II

In **Chapter 6**, we aimed to identify variables related with longitudinal change in meniscal extrusion, using the same PROOF cohort with a follow-up time of 30 months. The outcome measures were the absolute and relative change in medial and lateral extrusion. Absolute change was measured in millimeters, relative change was defined as the amount of extruded meniscus related to its total width, expressed in percentages. The eleven factors we incorporated in our multivariate analyses were based upon the available literature. The greatest absolute and relative change in meniscal extrusion was measured medially with an incident medial meniscal tear. Other statistically significant associations were seen between baseline varus malalignment and increase of absolute medial extrusion and between a higher baseline BMI and absolute and relative increase of medial extrusion. Longitudinal change in BMI was less explicit but also significantly associated with change in meniscal extrusion, both medial and lateral and absolute and relative. Incident meniscal tears, varus malalignment and BMI therefore might be interesting targets to initiate measures to prevent the onset or progression of meniscus extrusion and thereby decelerate knee OA development.

In **Chapter 7**, we evaluated the influence of postmenopausal status on medial meniscus extrusion at baseline and follow-up in the same RS subcohort as in Chapter 3. At baseline, 672 women (1305 knees) were available for analysis, of which 65.1% was postmenopausal with medial meniscus extrusion in 48.7% of cases. We conducted a stepwise approach, with a borderline statistically significant higher prevalence of meniscus extrusion at baseline and FU in knees of postmenopausal women in the unadjusted analysis. After adjustments however, these associations became non-significant. Therefore, we concluded that there is no evidence for a direct effect of the menopause on meniscus extrusion. Hypothetically, the menopause might be indirectly related with meniscus extrusion through the formation of tears or an increase in weight, or the known association between postmenopausal status and OA might not be mediated by meniscus extrusion at all but act via an alternative pathway. Moreover, postmenopausal status might be a too rough measure in a population already close to menopause with insufficient discriminatory power.

In **Chapter 8**, we critically evaluate the findings, try to interconnect the results, elaborate on theoretical and methodological considerations, and propose practical implications and directions for future research.

SAMENVATTING

Meniscus extrusie wordt vaak gezien in knieën met artrose, maar lange tijd was het niet duidelijk of het ontstaan van artrose vooraf wordt gegaan door verplaatsing van de meniscus en derhalve als een risicofactor kan worden beschouwd, of dat de extrusie een gevolg is van het degeneratieve proces. Opheldering van dit dilemma was het primaire doel van dit proefschrift. In Deel I werd verder de relatie onderzocht tussen baseline meniscus volume, veranderingen in meniscus volume en het samenspel tussen meniscus volume en extrusie met de incidentie van gonartrose. In Deel II werd gepoogd factoren te identificeren die geassocieerd zijn met meniscus extrusie, welke mogelijkerwijs gebruikt kunnen worden voor de preventie van extrusie en daarmee de ontwikkeling en progressie van artrose.

Deel I

In **Hoofdstuk 2** onderzochten we de associatie tussen baseline meniscus extrusie en de incidentie van radiologische en klinische gonartrose na een follow-up van 30 maanden in een hoog-risico cohort van de 'PRevention of knee Osteoarthritis in Overweight Females' (PROOF) studie, met 330 vrouwen (640 knieën) van middelbare leeftijd met overgewicht en obesitas, zonder radiografische of klinische tekenen van artrose op baseline. Meniscus extrusie was gedefinieerd als ≥ 3 mm op MRI, met een baseline prevalentie van 24%. De primaire uitkomstmaat was de incidentie van gonartrose, gedefinieerd als óf radiologische gonartrose incidentie (Kellgren and Lawrence (K&L) graad ≥ 2), óf klinische gonartrose incidentie volgens de criteria van de ACR (American College of Radiology), óf de incidentie van mediale of laterale gewrichtsspleetversmalling van ≥ 1 mm. De secundaire uitkomstmaat was een van deze maten onafhankelijk. Na te adjusteren voor confounders vonden we een significante associatie tussen baseline meniscus extrusie en incidentie gonartrose met een odds ratio van 2.39 (95% CI 1.53, 3.73), hoewel voornamelijk gebaseerd op radiologische gonartrose en mediale gewrichtsspleetversmalling. Na 30 maanden was de prevalentie van klinische gonartrose (nog) niet significant hoger in knieën met baseline meniscus extrusie in vergelijking met knieën zonder meniscus extrusie.

In **Hoofdstuk 3** probeerden we de bevindingen van het tweede hoofdstuk te valideren door de lange termijn incidentie van gonartrose in knieën met baseline meniscus extrusie te onderzoeken, gebruikmakend van hetzelfde hoog-risico cohort van hoofdstuk 2 en een subcohort van 438 vrouwen (872 knieën) van de Rotterdam Study (RS), een grote prospectieve cohortstudie binnen de algemene populatie. In

het PROOF-cohort waren 211 vrouwen (421 knieën) beschikbaar voor de statistische analyse. De baseline prevalentie van meniscus extrusie in het RS-cohort was 46%. De gemiddelde follow-up tijd in het PROOF-cohort was 6.6 jaar, in het RS-cohort 5.1 jaar. In beide cohorten vonden we een significante en onafhankelijke associatie tussen baseline meniscus extrusie en incidentie radiologische gonartrose. In het PROOF-cohort was de associatie met incidentie klinische gonartrose statistisch significant, in het RS-cohort bordeline significant. Om de potentiële klinische impact van deze resultaten te kunnen extraheren berekenden we aanvullend het populatie attributieve risico percentage (PAR%), varierend van 19% (incidentie klinische gonartrose in PROOF) tot 77% (incidentie radiologische gonartrose RS), hetgeen erop wijst dat een groot aantal nieuwe gevallen van gonartrose zijn toe te schrijven aan of tenminste vooraf worden gegaan door meniscus extrusie.

In **Hoofdstuk 4** hebben we de relatie onderzocht tussen baseline meniscus volume en meniscus volumeveranderingen (delta-volume) van zowel de mediale als laterale meniscus en de incidentie van gonartrose na 30 maanden, in hetzelfde hoog-risico cohort van de PROOF-studie. De uitkomstmaten waren hetzelfde als in Hoofdstuk 2. Voor het verkrijgen van meniscus volume en delta-volume werden beide menisci automatisch gesegmenteerd op baseline en follow-up. Zowel mediaal als lateraal was noch baseline meniscus volume, noch delta meniscus volume significant geassocieerd met de primaire uitkomstmaat. Baseline meniscusvolume was zowel mediaal als lateraal significant positief geassocieerd met incidentie radiologische gonartrose. De verandering in mediaal en lateraal volume was echter negatief geassocieerd met incidentie radiologische gonartrose. Alleen lateraal was baseline meniscus volume borderline significant geassocieerd met de incidentie van gewrichtsspleetversmalling. Geen van de meniscusvolume maten was significant geassocieerd met de incidentie van klinische gonartrose. Op basis van deze studie concludeerden we dat knieën met een groter meniscus volume op baseline en een grotere afname van volume over de tijd een groter risico hebben op het ontwikkelen van structurele artrose, mogelijk door het induceren van de vorming van osteophyten gegeven het gebrek aan een (omgekeerde) associatie tussen meniscus volume en gewrichtsspleetversmalling.

Gebaseerd op de bevindingen van de vorige hoofdstukken en de beschikbare literatuur hypothethiseerden we een interactie tussen meniscus volume, meniscus extrusie, hun veranderingen over de tijd en de ontwikkeling van gonartrose, waarvan de analyses en resultaten zijn beschreven in **Hoofdstuk 5**. Dezelfde data van de PROOF-studie werden gebruikt met een follow-up van 30 maanden. In overeenstemming met de eerdere

resultaten vonden we dat zowel mediaal meniscus volume als mediale meniscus extrusie op baseline significant geassocieerd waren met de incidentie van gonartrose. De indirecte effecten echter op incidentie gonartrose via delta meniscus volume of delta meniscus extrusie waren niet statistisch significant, hetgeen (gedeeltelijk) in tegenstelling is tot de resultaten van Hoofdstuk 4. Deze bevindingen suggereren dat het ontstaan van meniscuspathologie van groter belang is dan hun veranderingen over de tijd, en dat potentiële maatregelen meer toegespitst moeten zijn op preventie van ontstaan dan op preventie van progressie.

Deel II

In **Hoofdstuk 6** probeerden we variabelen te identificeren die gerelateerd zijn aan veranderingen in meniscus extrusie, waarbij opnieuw gebruik werd gemaakt van hetzelfde PROOF-cohort met een follow-up van 30 maanden. De uitkomstmaten waren de absolute en relatieve verandering in mediale en laterale extrusie. Absolute verandering werd uitgedrukt in millimeters, relatieve verandering werd gedefinieerd als het geëxtrudeerde deel van de meniscus ten opzichte van de totale breedte, uitgedrukt in percentages. De elf variabelen die in de multivariate analyse werden opgenomen waren gebaseerd op de beschikbare literatuur. De grootste absolute en relatieve verandering in meniscus extrusie werd mediaal gemeten bij een tijdens follow-up nieuw ontstane mediale meniscusscheur. Andere statistisch significante associaties werden gezien tussen baseline genu varum en een toename in absolute mediale extrusie, en tussen een hogere baseline BMI en een absolute en relatieve toename in mediale extrusie. Longitudinale verandering van de BMI was minder uitgesproken maar ook significant geassocieerd met absolute en relatieve verandering in meniscus extrusie, zowel mediaal als lateraal. Incidentie meniscusscheuren, genu varum en BMI zijn derhalve potentiele aangrijpingspunten om maatregelen te ontwikkelen om het ontstaan of de progressie van meniscus extrusie te voorkomen en daarmee de ontwikkeling van gonartrose te vertragen.

In **Hoofdstuk 7** evalueerden we de invloed van de menopauze op mediale meniscus extrusie op baseline en follow-up in hetzelfde RS subcohort als in Hoofdstuk 3. Op baseline waren 672 vrouwen (1305 knieën) beschikbaar voor analyse, waarvan 65.1% postmenopauzaal was met meniscusextrusie in 48.7% van de knieën. We voerden een stapsgewijze statistische benadering uit, met een borderline significant hogere prevalentie van meniscus extrusie op baseline en follow-up in knieën van postmenopauzale vrouwen in de ongeadjusteerde analyse. Echter, na adjusteren werden deze associaties non-significant. We concludeerden derhalve dat er geen

bewijs is voor een direct effect van de menopauze op meniscus extrusie. Hypothetisch is de menopauze indirect gerelateerd aan meniscus extrusie door de vorming van scheuren of een toename in lichaamsgewicht, of wordt de bekende associatie tussen de menopauze en artrose niet gemedieerd door meniscus extrusie maar via een ander mechanisme. Daarnaast is postmenopauzale status misschien een te grove maat in een populatie die al dicht tegen de menopauze aanzit, met een te beperkt onderscheidingsvermogen.

In **Hoofdstuk 8** worden de belangrijkste bevindingen van het proefschrift kritisch geëvalueerd, resultaten onderling verbonden, theoretische en methodologische overwegingen besproken en doen we voorstellen voor praktische toepassingen en richtingen voor toekomstig onderzoek.

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PhD portfolio
List of publications
Dankwoord
About the author

PhD PORTFOLIO

Name PhD student: J.A. van der Voet
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PhD period: 1-9-2014 – 1-9-2022
Promotor: Prof. dr. S.M.A. Bierma-Zeinstra and prof. dr. E.H.G. Oei
Daily supervisors: Dr. J. Runhaar and dr. D. Vroegindeweij

GENERAL COURSES AND WORKSHOPS	YEAR	WORKLOAD (ECTS)
Regionaal cursorisch radiologie onderwijs	2014-2017	3
Regionale refereeravond (every trimester)	2014-2019	2.3
Radiation hygiene 3M Boerhaave	2014	2
CC02AB - Biostatistical Methods 1: basic principles (NIHES)	2016	5.7
ADMIRE research meetings	2016-2017	1
Integrity in Science	2017	0.3
ESP09 - Regression Analysis Summer Programme	2017	1.9
Biomedial English Writing and Communication	2017	2
Imaging techniques	2017	2

(INTER)NATIONAL ORAL PRESENTATIONS	YEAR	WORKLOAD (ECTS)
Radiological Society of North America (RSNA) annual meeting, Chicago (USA)	2016	3
Radiologendagen Netherlands Society of Radiology (NVvR), Rotterdam (the Netherlands)	2017	1.5
European Society of Musculoskeletal Radiology (ESSR) annual meeting, Amsterdam (the Netherlands)	2018	2
European Congress of Radiology (ECR) annual meeting, Vienna (Austria)	2019	2
Radiologendagen Netherlands Society of Radiology (NVvR), Hilversum (the Netherlands)	2019	1.5
International Workshop on Osteoarthritis Imaging annual conference (IWOAI), Tokyo (Japan)	2022	2

(INTER)NATIONAL POSTER PRESENTATIONS	YEAR	WORKLOAD (ECTS)

Osteoarthritis Research Society International (OARSI) annual meeting, Amsterdam (the Netherlands)	2016	2
International Workshop on Osteoarthritis Imaging annual conference (IWOAI), Oulu (Finland)	2016	2
International Workshop on Osteoarthritis Imaging annual conference (IWOAI), Sydney (Australia)	2017	2
Radiological Society of North America (RSNA) annual meeting, Chicago (USA)	2017	3
Osteoarthritis Research Society International (OARSI) annual meeting, Toronto (Canada)	2019	2

OTHER (INTER)NATIONAL CONFERENCES	YEAR	WORKLOAD (ECTS)
Radiological Society of North America (RSNA) annual meeting, Chicago (USA)	2020	2

TEACHING ACTIVITIES	YEAR	WORKLOAD (ECTS)
Lecturing medical students	2016-2017	1
Teach the teacher course	2019	0.3
Supervising radiology residents	2019-present	2
Ultrasound workshop medical students	2019	0.5
TOTAL ECTS		49

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LIST OF PUBLICATIONS

This thesis:

Baseline meniscal extrusion associated with incident knee osteoarthritis after 30 months in overweight and obese women
Van der Voet JA, Runhaar J, van der Plas P, Vroegindeweij D, Oei EH, Bierma-Zeinstra SMA
Osteoarthritis Cartilage. 2017 Aug;25(8)1299-1303

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Semin Arthritis Rheum. 2023 Apr;59:152-70.

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Van der Voet JA, Wesselius D, Zhang F, Vroegindeweij D, Oei EH, Bierma-Zeinstra SMA, Englund M, Runhaar J
Rheumatology (Oxford). 2021 Nov 3;60(11):5175-5184.

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Rheumatology (Oxford). 2021 Mar 2;60(3):1392-1399.

Are changes in meniscus volume and extrusion associated to knee osteoarthritis development? A structural equation model
Xu D, Van der Voet JA, Waarsing JH, Oei EH, Klein S, Englund M, Zhang F, Bierma-Zeinstra SMA, Runhaar J
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Is postmenopausal status associated with increased risk for meniscus extrusion?
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Under review.

Other:

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Under review

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World J Surg. 2020 Oct;44(10):3199-3206.

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ABOUT THE AUTHOR

Jannus Albert van der Voet was born on October 26th, 1983, in Vlaardingen, the Netherlands. He studied medicine at the Erasmus University in Rotterdam (EUR) and graduated in 2010. His last internship was at the department of orthopedics in Banjul, The Gambia. After medical school, he worked as a resident at the department of surgery in the former Sint Franciscus Gasthuis in Rotterdam and at the department of orthopedics and traumatology in the Evangelisches Krankenhaus in Wesel, Germany. In 2013, he started his radiology training in the Maasstad Hospital in Rotterdam, with an academic exchange with the Erasmus Medical Center (EMC) in 2016 and 2017. In 2019, he started as a radiologist in the Alrijne Hospital in Leiderdorp, the Netherlands, where he works up until today.

In 2014, during his radiology training, he was approached by his mentor at the Maasstad Hospital, dr. Dammis Vroegindeweij, and a research team at the EMC including prof. dr. Sita Bierma-Zeinstra, prof. dr. Edwin Oei and postdoc (now assistant professor) dr. Jos Runhaar, to start a PhD project investigating the role of the meniscus in the development of knee osteoarthritis, which he executed in parallel with his work as a trainee and radiologist and of which this thesis is the final result.

Jan is married with Marije Harkema since 2008, whom he knows since high school. Together they have four children: Mats (2013-2015), Julie (2015), Tieme (2017) and Amélie (2019). The family lives in Rotterdam.