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

D. Xu †, J. van der Voet † §, J.H. Waarsing ‡, E.H. Oei §, S. Klein §, M. Englund ||, F. Zhang ||, S. Bierma-Zeinstra † ‡, J. Runhaar † *

† Dept. of General Practice, Erasmus MC University Medical Center Rotterdam, the Netherlands
‡ Dept. of Orthopedics, Erasmus MC University Medical Center Rotterdam, the Netherlands
§ Dept. of Radiology & Nuclear Medicine, Erasmus MC University Medical Center Rotterdam, the Netherlands
|| Dept. of Clinical Sciences Lund, Orthopedics, Clinical Epidemiology Unit, Lund University, Sweden

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SUMMARY

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 (10), a cohort conducted on overweight women free of OA symptoms, both meniscus volume and meniscus extrusion were independently associated to incident radiographic knee OA[6]. 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,

* Address correspondence and reprint requests to: J. Runhaar, Department of General Practice, Erasmus MC University Medical Center Rotterdam, Room NA 1911 P. O. Box 2040, 3000 CA, Rotterdam, the Netherlands. Tel.: 31 (0)10-7044192.
E-mail address: j.runhaar@erasmusmc.nl (J. Runhaar).

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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[7]. However, most observations were based on cross-sectional data which could not evaluate the causal inference in this hypothesis[8]. 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[9].

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 (12).

Methods

Data from the PROOF study were used, details of which were described previously (ISRCTN42823086)[10]. 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) $\geq$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[11]. 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[12].

Semi-flexed posterior-anterior knee radiographs of both knees were acquired with the metatarsophalangeal protocol[13] at baseline and after 30 months and scored according to the Kellgren and Lawrence (K&L) criteria[14]. Incident radiographic knee OA was defined as K&L $\geq$ 2 at FU, with baseline K&L < 2. Medial knee alignment angle was also measured on radiographs for all knees[15].

Meniscus volume and extrusion determination

We quantified meniscus volume as described previously[16]. 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 (JR, PvdP) and one musculoskeletal radiologist (EO) 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[23] experiment on the atlas set of 25 MRI scans, comparing the automatic segmentations with the manual segmentations using the Dice Similarity Coefficient (DSC)[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

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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)	

%: valid percentage; SD: standard deviation; BMI: Body mass index; for continues variables (Age, Baseline BMI, Baseline medial meniscus width), N stands for numbers of observation; for categorical variables (Baseline self-report history of knee injury, Baseline cartilage defect), N stands for frequency.

Table I Demographic characteristics

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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 (23.0.0) 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 I. 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 1,343 ± 321 mm^3. The average baseline medial meniscus extrusion was 2.3 ± 1.2 mm (Table I). 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 1,350 ± 265 mm^3. The average FU medial meniscus extrusion was 2.6 ± 1.4 mm (Table II).

Repeatability

As previously described, reproducibility tests showed moderate agreement for KL grade ($\kappa = 0.6$) and good agreement for alignment ($\kappa = 0.7$) and minimal joint space width ($\kappa = 0.7$)[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].

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)[28] and the Root Mean Square Error of Approximation (RMSEA) = 0.067 (RMSEA<0.08: acceptable fit)[29]. For clarity reason, a simplified directed acyclic graph (DAG) was shown in Fig. 1 (see full DAG in Supplementary Fig. 1). All standardized adjusted regression estimates and corresponding *p*-values of the model are presented in Fig. 2 (full output presented in Supplementary Table 1).

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

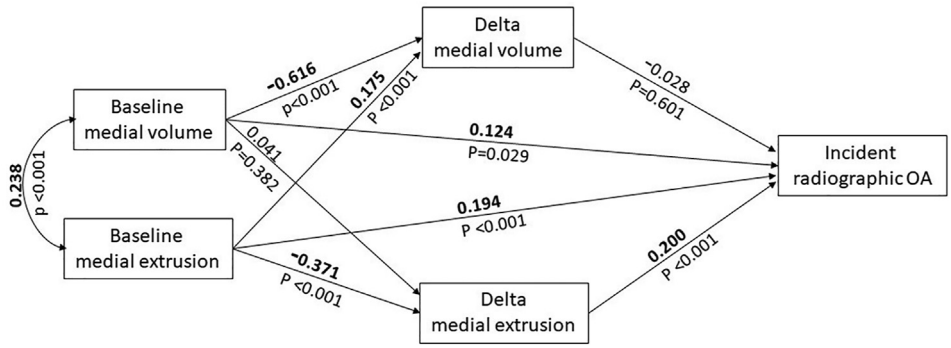

Fig. 1 **Simplified Structural Equation model to assess the interplay between baseline medial meniscus volume and extrusion, delta medial meniscus volume, and delta medial meniscus extrusion, and their associations with incident radiographic knee OA.** All estimates were adjusted for confounders (not 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.

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Characteristics variables	N (%)	Mean (SD)
Baseline medial meniscus volume (mm^3)	723	1,343 (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	1,350 (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)	

SD: standard deviation; KL: Kellgren & Lawrence; for continues variables (Baseline medial meniscus volume, Baseline medial meniscus extrusion, FU medial meniscus volume, FU medial meniscus extrusion), N stands for numbers of observation; for categorical variables (Baseline and FU KL grade), N stands for frequency.

Table II Baseline and follow-up characteristics

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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, $p < 0.001$].

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 4 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[9]. 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,

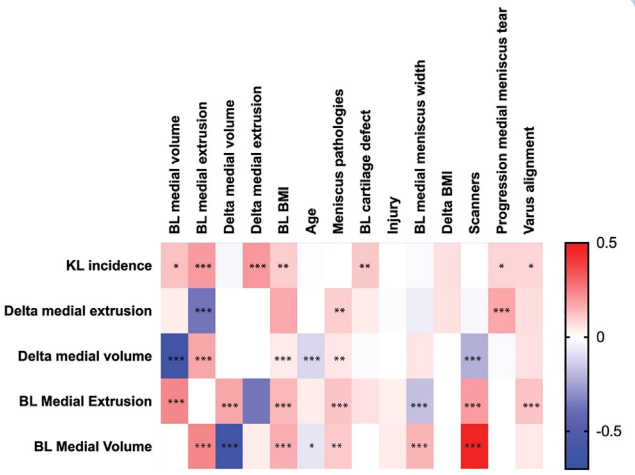

Fig. 2 **Standardized effects of full model.** All estimates were adjusted for confounders (not provided in the figure for clarity reasons), which included BL BMI at baseline, baseline medial meniscus body width, age, BL meniscus pathologies (excluding extrusion), BL cartilage defects,-self-reported 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, while the blue color means negative association. Darker color stands for stronger association. *$p < 0.05$, ***$p < 0.001$.

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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[7]. 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 30 months follow-up (Supplementary Fig. 4(a) and 4(b)). In addition, the model did not measure correlation between both side of knees within subject. However, the sensitivity analyses show no difference for main results (Supplementary materials Fig. 2 a and 2b). Finally, there were also some knees without MRI data at follow-up. According to the missing pattern (Supplementary Material Fig. 3) and 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).

Conclusions

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.

Contributions

D.X. contributed to data analysis, interpretation, writing of the manuscript and final approval of the article. J.V. contributed to revision of the article. F.Z. contributed to MRI data interpretation. M.E., S.K. and E.O contributed to the manuscript revision. S.K. in addition contributed to development of the automated meniscus segmentation method. J.R. and S.B. contributed to study design and final approval of the article.

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Competing interests

None declared.

Ethics approval

The PROOF study has been approved by the Medical Ethical Committee of Erasmus MC University Medical Center Rotterdam, the Netherlands.

Data availability statement

Data are available on reasonable request.

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Supplementary data

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