Osteoarthritis and Cartilage xxx (xxxx) xxx–xxx

Osteoarthritis and Cartilage

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Factors associated with meniscus volume in knees free of degenerative features

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ARTICLE INFO

Article history:
Received 25 August 2022
Accepted 10 August 2023

Keywords:
Meniscus volume
Osteoarthritis
Epidemiology
MRI

SUMMARY

Objectives: To explore factors that were associated with meniscus volume in knees free of radiographic osteoarthritis (OA) features and symptoms of OA.
Methods: In the third Rotterdam Study cohort, clinical, radiographic, and magnetic resonance data were obtained at baseline (BL) and after 5 years of follow-up. Meniscus volumes and their change over time were calculated after semi-automatic segmentation on Magnetic Resonance Imaging. Knees with radiographic OA features (Kellgren and Lawrence > 0) or clinical diagnosis of OA (American College of Rheumatology) at BL were excluded. Ten OA risk factors were adjusted in the multivariable analysis (generalized estimating equations), treating two knees within subjects as repeated measurements.
Results: From 1065 knees (570 subjects), the average (standard deviation) age and Body mass index (BMI) of included subjects were 54.3 (3.7) years and 26.5 (4.4) kg/m^2. At BL, nine factors (varus alignment, higher BMI, meniscus pathologies, meniscus extrusion, cartilage lesions, injury, greater physical activity level, quadriceps muscle strength, and higher age) were significantly associated with greater meniscus volume. Five factors (injury, meniscus pathologies, meniscus extrusion, higher age, and change of BMI) were significantly associated with meniscus volume loss.
Conclusions: Modifiable factors (varus alignment, BMI, physical activity level, and quadriceps muscle strength) and non-modifiable factors (higher age, injury, meniscus pathologies, meniscus extrusion, and cartilage lesions) were all associated with meniscus volume or meniscus volume loss over time.

Introduction

Abnormalities in the meniscus, such as meniscus pathologies (e.g. meniscus tears and meniscus maceration) and extrusion, were previously identified as a strong risk factor for knee osteoarthritis (OA) development and OA progression.[1, 2] Using quantitative measurements on magnetic resonance imaging (MRI), some studies explored the role of (change in) meniscus size in OA development. Our previous research found that greater volume of the medial meniscus at baseline (BL) and greater meniscus volume loss over 2.5 years follow-up (FU) were strongly associated with incident radiographic knee OA, among overweight/obese, middle-aged women in the PROOF study.[3, 4] These results confirmed previous findings of altered meniscus body size during OA development[5] and together indicate that changes in meniscus volume could be considered as an OA risk factor.

Understanding the potential meniscus volume-related factors may be useful for understanding the natural history of OA in the knee and potential targets for OA prevention. Primary prevention targeting OA risk factors is believed to be most effective in a population free of structural and clinical knee OA. To prevent OA development with a focus on meniscus volume, the abnormalities in the meniscus volume must be prevented or reversed.[6] However, no interventions that directly target meniscus volume are available, other than partial meniscectomy, which is known to have detrimental effects and leads to OA development.[7] Therefore, it is important to explore potential factors related to meniscus volume. As the subjects in the PROOF study were at high risk of incident knee OA and

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https://doi.org/10.1016/j.joca.2023.08.003

therefore already presented with abnormalities in meniscus volume, it could be advocated to investigate meniscus-volume-related factors in a relatively low OA risk population.[8]

Currently, factors associated with meniscus volume are rarely reported.[9–13] A recent study[14] found that weight loss among OA subjects was associated with less progression of meniscus extrusion, but not with the change of meniscus size (i.e. meniscus width and height). As OA risk factors may interact, it could be hypothesized that some well-known OA factors, such as high Body mass index (BMI), menopause, and the lack of physical activity (PA)[15, 16] could be associated with meniscus volume as well. In addition, age, sex, malalignment, obesity, cartilage lesions, and trauma were also reported to be associated with meniscus pathologies (meniscus tear, degenerative lesion) and extrusion.[9–13] Therefore, these factors could also be related to meniscus volume and might be potential OA prevention targets.

In the present study, we aimed to explore the cross-sectional associations between several OA risk factors and meniscus volume. Also, we aimed to assess the association between these OA risk factors and the change of meniscus volume over 5 years. As mentioned, meniscus volume abnormality can already happen in the very early phase of knee OA. We, therefore, explored these associations in a low OA risk population, free of radiographic OA features (Kellgren and Lawrence (K&L) grade = 0) or clinical knee OA symptoms.

Methods

Subjects

An extension of the open population of the Rotterdam Study cohort, the third cohort, was initiated in 2006. Of these participants of the Rotterdam Study, all women aged between 45 and 60 years were invited to join a sub-study for investigation of early signs of knee OA.[17] All participants were interviewed at home or at the research center for BL demographics, including menopausal status and age. Participants were also invited to visit the research center for a physical examination, radiographs, and MRI of the knees. For the current research, knees without MRI records for meniscus volume, meniscus extrusion, or meniscus pathologies were excluded. Then, knees with radiographic signs of knee OA (K&L > 0) or clinical diagnosis of OA at BL, using the American College of Rheumatology-criteria, were excluded.

Clinical data

Body weight and height were collected at both BL and FU; BMI was calculated. Isometric quadriceps muscle strength was measured as maximal isometric contraction in a supine position, using a hand-held dynamometer, which is a previously validated method.[18] At BL, all participants filled in questions on self-reported knee injury over the past 6 years and activity level (Short QUestionnaire to ASsess Health-enhancing physical activity) to calculate total PA score in min/week.[19]

Radiographic data

Weight-bearing antero-posterior radiographs of both knees were taken at 70 kV, a focus of 1.8 mm^2, and focus-to-film distance of 120 cm, using High-Resolution G 35×43 cm film (Fujifilm Medical Systems, Stamford, CT, USA). Two independent readers who were blinded for any clinical or MRI data scored the radiographs using the K&L grading system.[20] The inter-rater agreement for the K&L score was 95%.[21] Contralateral knee radiographic OA status was defined as 0 if the contralateral knee K&L grade was 0, and as 1 if the contralateral knee K&L grade was > 0. Alignment was measured as the medial angle formed by the femur and tibia as described by Moreland et al.[22] and Brouwer et al.[23] Medial knee alignment angles were measured on the radiographs and defined as normal (182°–184°), valgus (> 184°), and varus (< 182°).

MRI data

We performed a multi-sequence MRI protocol on a 1.5T MRI scanner (General Electric Healthcare, Milwaukee, Wisconsin, USA). The knees of all participants were scanned using an 8-channel cardiac coil that allowed imaging of knees in one session without repositioning. The multi-sequence protocol contained a fast spin echo (FSE) proton-density/T2-weighted sequence, an FSE T2 weighted fat saturation sequence, a spoiled gradient echo sequence, and a fast imaging employing steady-state acquisition sequence. The total scanning time was 27 min for two knees. BL meniscus pathologies (e.g. meniscus tears, meniscus signal, meniscus maceration, and meniscus cyst), extrusion, and tibiofemoral joint cartilage lesion (either full or partial thickness lesion) were scored on magnetic resonance (MR) images using the MRI Osteoarthritis Knee Score (MOAKS).[24]

Medial and lateral menisci of both knees at BL and FU were segmented semi-automatically in the sagittal proton-density weighted MRI scan, using in-house developed software that is based on multi-atlas and appearance models.[25–27] The slice thickness of the sagittal FSE proton-density sequence was 3.2 mm. To optimize the method, 30 atlas knees were manually segmented using open source ITK-SNAP software,[28] and 5-fold cross-validation was used to select the weight parameter that is used to combine the multi-atlas and appearance components of the model. An independent test set of 40 knees which consisted of 10 right and 10 left knees at BL and 10 right and 10 left knees at FU was manually segmented as well and used to assess the model performance. Dice similarity coefficients for the medial and lateral meniscus were 0.82 (standard deviation (SD): 0.09) and 0.83 (0.06), respectively. Pearson correlation coefficients between automatically and manually measured volumes for the medial and lateral meniscus were 0.93 and 0.90, respectively. This validated model was applied to the MRI scans of the remaining subjects. An example of the intact meniscus and an example of the meniscus with tears were segmented and presented in Supplementary Fig. 1 and Fig. 2.

Statistical analysis

BL characteristics of the eligible participants were calculated. Before developing a multivariable logistic regression model, we evaluated multi-collinearity between potential factors by evaluating the variance inflation factor (VIF).[29] In this study, we deem VIF ≥2.5 as considerable collinearity.[29] For BL meniscus volume as an (continuous) outcome, the exposures in the Generalized Estimating Equation (GEE) model were BL menopausal status, history of injury, alignment (varus for medial meniscus volume, valgus for lateral meniscus volume), PA, age, BMI, quadriceps muscle strength, medial/lateral meniscus pathologies, medial/lateral meniscus extrusion, and medial/lateral cartilage lesions. For the change of meniscus volume as an (continuous) outcome, the exposures in the GEE model were identical to the BL model, with the addition of the change of BMI during FU. The change of BMI was calculated by subtracting FU BMI from BL BMI. To obtain an obvious coefficient size, we set the unit of PA as the original value divided by 1000 (kilo minutes/week). We also divided the maximum quadriceps strength (N) score by 10, which the unit is decanewton (daN). Meniscus extrusion was dichotomized into no (< 2 mm) and extrusion (≥2 mm).[24]

Characteristic variables	N knees (%)	Mean (SD)
Age at baseline (yr)	1065 (100)	54.3 (3.7)
BL BMI (kg/m^2)	1065 (100)	26.5 (4.4)
BL self-reported knee injury	107 (10.2)	
Knee varus alignment	588 (55.2)	
Knee valgus alignment	101 (9.5)	
BL postmenopausal	660 (62.6)	
#PA score (min/week)	1065 (100)	8.7 (4.6)
* Maximum quadriceps strength (daN)	1062 (99.7)	23.2 (4.7)
Meniscus pathologies medial	440 (41.3)	
Meniscus signal	367 (34.5)	
Meniscus tear	54 (5.1)	
Meniscus maceration	45 (4.2)	
Meniscus cyst	22 (2.1)	
Meniscus pathologies lateral	220 (20.7)	
Meniscus signal	166(15.6)	
Meniscus tear	30 (2.8)	
Meniscus maceration	41(3.8)	
Meniscus cyst	28 (2.6)	
Medial meniscus extrusion	586 (45.6)	
Lateral meniscus extrusion	35 (3.3)	
TFJ medial cartilage lesions	147 (13.8)	
TFJ lateral cartilage lesions	80 (7.5)	
BL medial meniscus volume (mm^3)	1065 (100)	1807 (367)
BL lateral meniscus volume (mm^3)	1065 (100)	1584 (313)

BL meniscus extrusion was defined as MOAKS grade ≥2; BL meniscus pathologies (e.g. meniscus signal, tears, maceration, and cyst) were scored on MR images using the MOAKS; BMI: Body mass index; #original value divided by 1000.
* original value divided by 10; TFJ: Tibiofemoral Joint.

Table 1 Osteoarthritis and Cartilage

Characteristics and features of the knee joint at BL.

Multivariable analysis (linear regression model with GEE) was performed (IBM SPSS 25.0.0.1), which treated two knees within subjects as repeated measurements and a p-value < 0.05 as statistically significant. As a sensitivity analysis, models were additionally adjusted for BL contralateral knee radiographic OA status.

Results

1065 knees (570 subjects) with K&L grade 0 and with MRI measures were available for analyses. The average (SD) of age and BMI were 54.3 (3.7) years and 26.5 (4.4) kg/m^2, respectively. The characteristics of selected participants are shown in Table 1. The average BL meniscal volume for the medial and lateral sides was 1807 (367) mm^3 and 1584 (313) mm^3, respectively (see Table 1). In the end, there were 1027 and 998 knees available for the cross-sectional and longitudinal models to be analyzed separately. There were no significant differences in the selected factors between included and excluded groups (data not shown).

There was no collinearity among independent variables (maximum VIF ≈ 1.6). All cross-sectional associations between selected factors and BL meniscus volume are shown in Fig. 1. Details of the effect sizes are also presented. Varus alignment (beta [95%CI]= 94.6 [48.2, 141]), a lower level of PA (beta= −6.3[−11.5, −1.2]), a higher age (beta=7.8[0.2, 15.4]), a higher BL BMI (beta = 23.5 [17.6, 29.4]), a higher quadriceps muscle strength (beta = 6.5 [0.9, 12.2]), medial meniscus pathologies (beta = 64.8 [17.2, 112.4]), medial meniscus extrusion (beta = 161.0 [112.9, 209]), and medial cartilage lesions (beta = −98.4 [−163.1, −33.8]) were associated with greater medial meniscus volume. Several factors were associated with a greater lateral meniscus volume: Injury (beta = 72.6 [5.3, 140.0]), higher age (beta = 8.8 [2.3, 15.4]), a higher BL BMI (beta = 24.6 [19.1; 30.0]), greater quadriceps muscle strength (beta = 9.0 [4.2, 13.8]), lateral meniscus pathologies (beta = 59.6 [4.9, 114.4]), and lateral cartilage lesions (beta = −108.3 [−200.9, −15.6]). Other factors were not significantly associated with BL meniscus volume.

The detailed results for the associations between all factors and the change of meniscus volume are also shown in Fig. 1. A history of knee injury (beta = 54.4 [14.1, 96.6]), BL BMI (beta=3.7 [1.5, 5.9]), medial meniscus pathologies (beta = 35.7 [16.9; 54.5]), and medial meniscus extrusion (beta = 22.0 [4.3, 39.7]) were associated with greater loss of medial meniscus volume. Postmenopausal status (beta = 19.2 [0.2, 38.2]), injury (beta = 39.4 [10.8, 67.9]), younger age (beta= −3.3 [−6.0, −0.6]), higher BL BMI (beta= 3.0 [1, 5.0]), greater loss of BMI (beta = 6.3 [1.2, 11.3]), lateral meniscus pathologies (beta= 55.5 [34.3, 76.7]), and lateral extrusion (beta= 53.0 [6.2, 99.7]) were associated with greater loss of lateral meniscus volume. The other selected factors were not significantly associated with the change of meniscus volume.

Contralateral knee radiographic OA status showed no association with meniscus volume, and the additional adjustment did not change the main results. Analysis with an additional exclusion of knees with radiographic OA at FU showed no changes in the main results. The details for sensitivity analysis are shown in the supplementary materials.

Discussion

This study explored the potential factors associated with meniscus volume in knees free of radiological features. We found that varus alignment, higher BMI, meniscus pathologies, meniscus extrusion, cartilage lesions, and a history of injury were significantly associated with greater meniscus volume or meniscus volume loss over time. Also, greater PA level, quadriceps muscle strength, and higher age were associated with greater BL meniscus volume or greater volume loss over time. However, because of the clinical interpretation, the magnitude of the change in the meniscus volume was only small.

Varus alignment and higher BL BMI, both local mechanical factors of OA,[30, 31] were associated with greater BL medial meniscus volume. Currently, this is the first report of the association between malalignment and meniscus volume. A higher BMI has been reported to be related to significantly greater meniscal width and length.[32] Knee malalignment and a high BMI have been associated with increased loading of the knee joint. Varus alignment could shift the load-bearing axis medial to knee center, creating a moment arm that increases forces across the medial compartment.[33] On the other hand, in valgus aligned knees, the medial compartment often continues to bear more load until more severe valgus is present,[34] which could explain the absence of an association between valgus alignment and lateral meniscus volume in the current study. Results were also supported by previous research that showed BMI was related to OA severity in those with varus alignment of the knees but not in those with valgus alignment of the knees.[35]

Other local mechanical factors could also indirectly contribute to the loading mechanism during OA development. Firstly, meniscus extrusion and pathologies were strongly associated with greater BL medial meniscus volume. The co-existence of these meniscus abnormalities could be explained as previously described[5, 8]; the meniscus is squeezed outside of the tibial compartment, known as meniscus extrusion, which could consequently lead to un-loading of the extruded meniscus and subsequent increasing of meniscus volume. The change of meniscus volume may be due to the instant effect which is different from the adaptive swelling caused by continuous high BMI loading. However, more research should be done to prove this hypothesis. Based on the finding from this study, the quantitative measurement for meniscus volume may potentially indicate meniscus pathologies which include meniscus signal, tears,

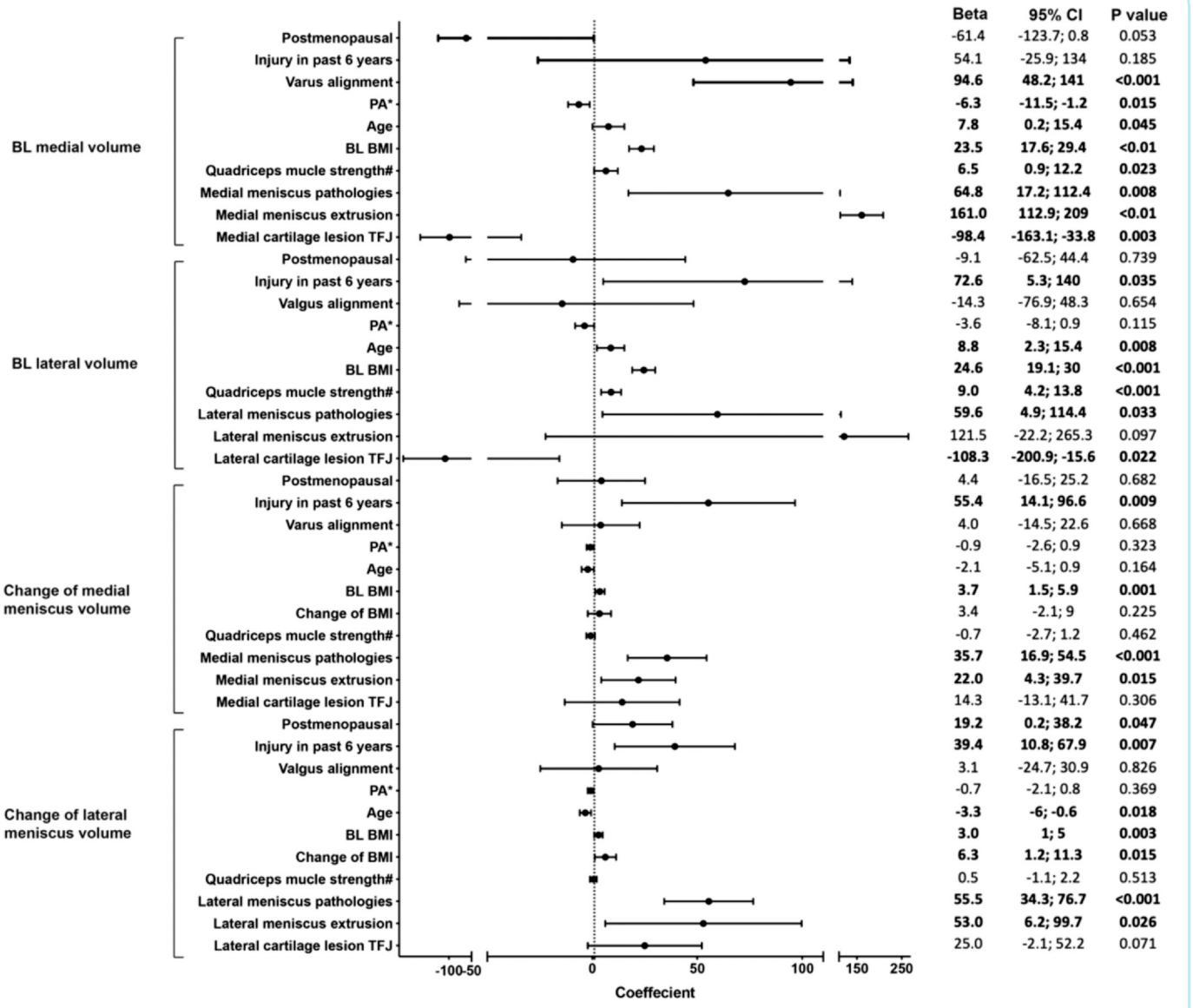

Fig. 1

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Factors associated with BL and change of meniscus volume. *: the unit was kilo minute/week; #: the unit was decanewton; BMI: body mass index; PA: physical activity; the reference for valgus alignment was neutral and varus alignment; the reference for varus alignment was neutral and valgus alignment; TFJ: Tibiofemoral Joint.

maceration, and cyst. More research should be done for the causal inference between each type of meniscus pathology (or morphology) and meniscus volume. Secondly, both tibiofemoral medial and lateral cartilage lesions were cross-sectionally associated with lower meniscus volume. Disturbance in the cartilage structure might be a reflection of a meniscus with lower volume that absorbs less shock when loading. Thirdly, lower PA levels or higher quadriceps strength were associated with greater meniscus volume at BL. However, these associations were weak. Currently, it is still unclear whether higher PA levels and greater quadriceps strength could play a protective role on knee structure during OA development,[36–40] due to the complex interplay between PA and quadriceps muscle strength.[41]

Some systemic factors were shown to be correlated to knee meniscus volume, but mainly in the lateral compartment. Age was associated with a higher risk of knee OA[42] and related to greater BL volume and greater volume loss over time in the lateral compartment. Similarly, postmenopausal status was also associated with greater loss of meniscus volume over time in the lateral compartment. The reason may be the decreasing estrogen levels, which leads to the weakening of the meniscal matrix and the laxity of the ligaments.[43] In addition, we also observed that the change in BMI was associated with the change of lateral meniscus volume. As obesity is related to systematic inflammation, greater BMI can also play as a systemic factor and may cause other knee structural changes such as knee cartilage defects and tibial bone enlargement,[44] which can lead to meniscus degeneration and volume loss over time.

This is the first study that explored a range of OA risk factors for their association with meniscus volume changes. A strength of this study is that we explored these associations in a population free of

structural and clinical knee OA. The high prevalence of meniscus pathologies indicated that minor changes in the meniscus such as meniscus signal could already be detected in the free disease phase. The main findings could contribute to a meniscal pathway for OA development that several factors such as increased loading (BMI, varus) and injury could lead to meniscus degeneration/micro-tearing (signal) and swelling (increased volume) and eventually macroscopic meniscus tearing and even maceration (volume loss), which accelerates cartilage loss/damage and OA. Secondly, the study found some modifiable factors which may give the implication for prevention of knee OA before the onset of the abnormities of the meniscus. To avoid great meniscus volume, promising research could focus on potential interventions such as reducing BMI, treating varus alignment, increasing the level of PA, and exercise intended for quadriceps muscle strengthening. Particularly, more studies should be done to prove the causal inference of these associations.

There were also some limitations to the current study. Firstly, we could not conclude causal effects from this cohort. Further causal analyses are warranted to confirm that the identified factors are indeed true interventional targets that could prevent the abnormality in meniscus volume. Secondly, five years FU is still relatively short for observation of OA structural changes in the selected population of middle-aged women free of radiographic features. A longer FU would be more sensitive to determine the association between these potential factors and meniscus volume. Thirdly, this was an explorative study and did not consider the multiple comparison correction. Therefore, in future research, external validation of our results should be evaluated. The multivariable analysis did not adjust the size of knee joint. However, the bias may not be significant, because there is no hypothetical causal effect of knee joint size on the selected potential predictors. Finally, some less obvious meniscus pathologies such as meniscus signal may cause bias in the measurement of segmented meniscus volume. However, this bias may not affect the association between other factors and meniscus volume, as meniscus pathology was adjusted for as a co-variant in the model.

Conclusion

Meniscus volume was cross-sectionally associated with load-related factors. Meniscus volume loss over time was mostly associated with systemic factors. As modifiable factors, varus alignment, higher BMI, lower PA level, and higher quadriceps muscle strength were associated with greater meniscus volume or meniscus volume loss over time. In particular, varus alignment and BMI were strongly associated with greater meniscus volume or meniscus volume loss in the long term. (Change in) Meniscus volume might provide explanatory pathways for other well-known OA risk factors, such as higher age, meniscus pathologies, meniscus extrusion, and cartilage lesions.

Funding

The China Scholarship Council (No. 201806380153).

Ethical approval

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

CRediT authorship contribution statement

Conception and design: (DX, JR, DS, SBZ), Rotterdam data obtaining and data cleaning: (DS), Meniscus segmentation: (JH, SK, EO), Analysis and interpretation of the data: (DX, JR), Drafting of the article: (DX), Critical revision of the article for important intellectual content: (DS, JR, JH, SK, EO, SBZ). Final approval of the article (DX, DS, JH, SK, EO, JR, SBZ).

Declaration of Competing Interest

None declared.

Acknowledgment

Part of the research has previously been accepted as an abstract and poster presentation at the Osteoarthritis Research Society International (OARSI) World Congress 2022.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.joca.2023.08.003.

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