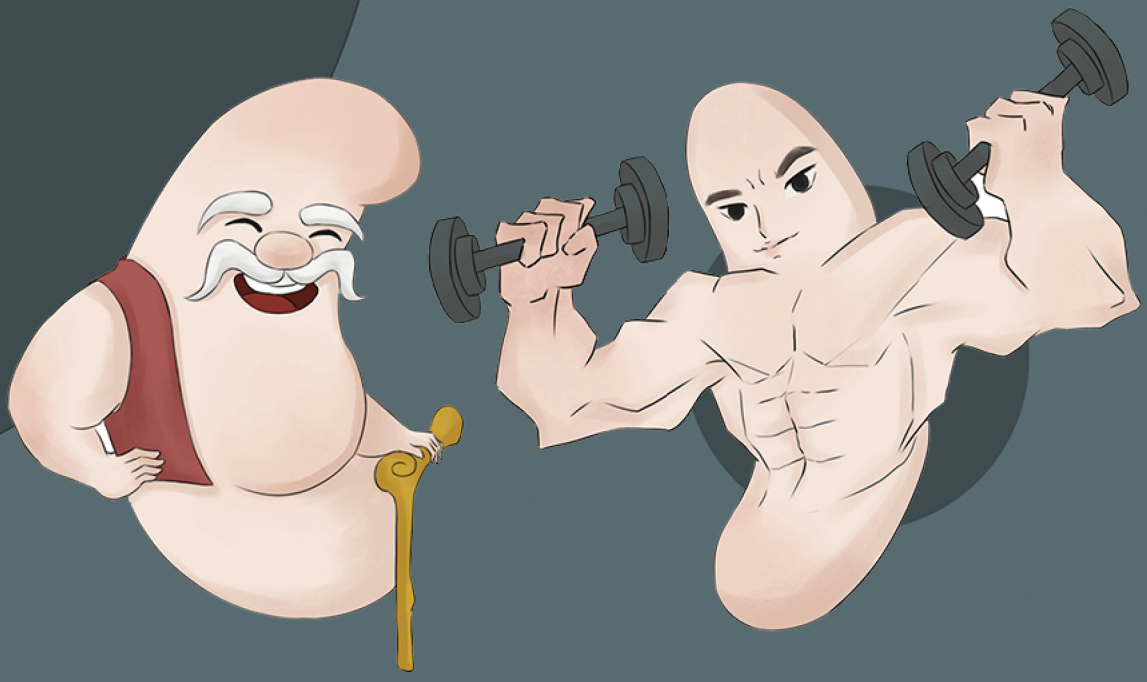
Structural Features of Early-stage OA:

keep your Menisci in Good Shape



Dawei Xu

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Structural Features of Early-stage OA: Keep your Menisci in Good Shape

Structurele kenmerken van vroege knieartrose: houd uw meniscus in vorm

Thesis

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by command of the rector magnificus

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MANUSCRIPTS THAT FORM THE BASIS OF THIS DISSERTATION

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Chapter 7. D. Xu, M. van Middelkoop, S. M. A. Bierma-Zeinstra, J. Runhaar. Physical activity and knee osteoarthritis features on MRI in individuals without osteoarthritis: a systematic review. Arthritis Care & Research. 2022; In press.

CHAPTER 1

General Introduction

EPIDEMIOLOGY OF KNEE OA

Osteoarthritis (OA) is a common disease that is estimated to affect more than 240 million patients worldwide, afflicting 10% of men and 18% of women aged 60 and older (1). The knee joint is the most common site of clinical osteoarthritis (2, 3). The prevalence and incidence of knee OA get reported differently based on the definition used, age, sex, and geographical area studied (4). A systematic review gave the global prevalence of 16.0% and incidence (203 per 10,000 person-years) of knee OA among individuals aged ≥15 (5). Data from the Netherlands in 2019 showed the prevalence of knee OA (based on ICPC disease code L90) as 5.1% for women and 3.0% for men. However, the codified knee OA may well be under-recorded and is approximately twice as high when supplemented with narrative data (6). In China, a meta-analysis found the overall pooled estimate of symptomatic knee OA prevalence was 14.6% (7). Spanish and UK general practice registry data has been used to report on the incidence of osteoarthritis in the general population (2, 8); The OA risk for knees among women increases rapidly (much more rapidly than in men) between the ages of 50 and 75 (2). Studies reported peaks in incidence generally around age 75 (16-17% for knee OA) (9).

OA is a painful and disabling disease that results in large socioeconomic costs (10). Knee osteoarthritis accounts for approximately 85% of the burden of osteoarthritis worldwide (11). In terms of disability burden, osteoarthritis and diabetes were responsible for the largest increases in years lived with disability at the global population level (11). Osteoarthritis accounted for 3.9% of years lived with disability worldwide in 2015, and by 2020 it had become the fourth leading cause of years lived with disability globally (12).

Early diagnosis and interventions in the early stage of knee OA are difficult due to the complexity and phenotypic heterogeneity of OA. Based on the criteria of the American College of Rheumatology (ACR), the current diagnosis of knee OA can usually be made by history and physical examination, including signs/symptoms of knee pain with stiffness, joint crepitus, and functional limitations, typical of a population aged above 50. Radiographically, OA was identified based on osteophytes and joint space narrowing, subchondral bone sclerosis, and cysts, and graded according to Kellgren and Lawrence (K&L) as grade II-IV (13, 14). However, the structural changes have already become irreversible by the time OA patients are identified by these radiographic criteria, which could explain why the efficiency of current treatments is limited. Identifying early OA changes and initiating interventions in OA risk populations are therefore needed.

MENISCUS CHANGES IN EARLY-STAGE KNEE OA

The knee menisci, of which the major components are water, collagen, and proteoglycans, maintain the long-term health of the knee joint. The most important component of the menisci is the collagen-proteoglycan meniscal matrix; the main functions of the menisci are load transmission to a large area of articular cartilage and shock absorption during dynamic movements (15, 16). In addition to lubrication, nutrition, and proprioception, the meniscus is also important for joint stabilization (17). The peripheral base of the meniscus is attached to the joint capsule and circumferential meniscal-matrix fibers form ligaments. Those ligaments attach the anterior and posterior horns of the menisci to the intercondylar part of the tibia. The attachment of the meniscus to the medial collateral ligament is firm, but the lateral attachment is more mobile. Owing to these anatomical differences, the medial and lateral menisci function differently as osteoarthritis progresses. In chapters 2 and 4, we will also show some different pathological roles between the medial and lateral meniscus during OA development.

Meniscus pathologies, which include meniscal tears (traumatic and degenerative), meniscus extrusion, and meniscal morphometrical abnormalities, play an important role in OA development. In the knees of both symptomatic and asymptomatic individuals, the prevalence of meniscus pathology was high (18-24). In patients with anterior cruciate ligament injuries, the presence of associated traumatic meniscus damage was the strongest predictor of the development of early joint cartilage matrix changes and long-term OA development (25, 26). Degenerative meniscal tears also act as key factors in the early-stage development of knee OA (27), although they are often not directly linked to knee pain (18). As well as the integrity of the meniscus, the position of the meniscus is also critical. Extrusion of the meniscal body was reported to be more frequent in OA knees compared to non-OA knees (28-30) and meniscal extrusion has been reported to be a risk factor for cartilage loss (30, 31), bone marrow lesions (32), and joint-space narrowing seen on conventional tibiofemoral radiographs (33, 34).

As osteoarthritis is a whole joint disease that involves almost all knee joint structures such as cartilage, subchondral bone, ligaments, capsule, synovium, and periarticular muscles (35), meniscus pathologies may interact with other structural changes. For the potential pathways based on these structural changes, several hypotheses still need to be examined. We will therefore test these hypotheses in Chapter 3 and explore the interplay between meniscal abnormalities and other intra-articular structural changes during OA progression.

IMAGING TECHNIQUES TO DETECT EARLY MENISCAL CHANGES

As an efficient and low-cost technique, radiography is a recommended imaging modality for assessing disease progression in OA research. Based on that, K&L grade systems are well-established, according to osteophyte formation, joint space narrowing, cyst formation, and subchondral sclerosis (36, 37). The progression of knee OA can be assessed by minimum joint space width narrowing (38, 39). However, these methods are flawed when considering structural changes in early-stage OA as they rely on the indirect assessment of the status of articular cartilage, which is prone to error (40). In addition, it is impossible to use radiography for monitoring other early structural changes, such as the morphology in synovium or meniscus pathologies, or for imaging the function or biochemistry of the cartilage before erosion.

The advantage of magnetic resonance imaging (MRI) is that it can image soft tissues within the joint. To measure the development of OA, cartilage morphology was one of the most reported MRI features (41). MRI semi-quantitative and quantitative scoring of knee OA have been performed for multi-feature joint assessment (42, 43). Semi-quantitative scoring methods subjectively grade for the severity of cartilage changes and also other joint structures, as introduced in the knee with the Whole Organ MRI Scoring (WORMS) system (44), which follows the principle of OA representing a failure of the joint as an 'organ'. In addition, quantitative analysis of cartilage with semi-automated separation of cartilage from subchondral bone and synovial fluid enables the recording of parameters such as cartilage volume, thickness, surface area, roughness, lesion size and depth, and areas of denuded subchondral bone. These assessments appear reliable and appropriate for cross-sectional and longitudinal studies (41, 45).

MRI is also a useful tool for visualizing and quantifying geometric parameters for the menisci. To detect meniscal degeneration or tears, patients are frequently referred to undergo MR scans of the knee before arthroscopic investigation (21). The 3D-segmentation MRI techniques allow researchers to clarify the effect of meniscal positioning, shape, and size on the development of OA and knee symptoms (46, 47) These techniques supplement the currently available semi-quantitative MRI scoring systems for the evaluation of knee OA, which incorporate semi-quantitative assessment of meniscal morphology and meniscal extrusion (44, 48-50) In addition, quantitative MRI techniques such as T2, T1, and T1ρ mapping provide spatially resolved measures of tissue structure or ultra-structure and composition beyond mere morphology (51, 52). In Chapter 2, we also apply some of these techniques to determine the association between meniscal volume and OA.

RISK FACTORS FOR MENISCUS PATHOLOGY

Identifying a target population for preventive measures is generally established by identifying its risk factors. A cluster of factors in the OA risk population has been identified by previous research. Advancing age, a history of injuries, meniscal lesions, malalignment, BMI >30 kg/m^2, and physiological knee laxity were considered as knee OA risk factors (53, 54). Moreover, genetic research revealed more than 80 genes related to OA pathogenesis, and some single-nucleotide polymorphism (e.g., the growth and differentiation factor 5 gene which is associated with the development of healthy bone and cartilage) (55, 56). These related factors could be generally classified as local and mechanical (misalignment, meniscus lesion etc.) and systemic factors (menopause, age, genetic loci etc.). In addition, some factors such as obesity can affect structures of the knee joint both systematically and mechanically.

Regarding the prevention of clinical and radiographic knee OA, the PROOF study was the first recorded randomized controlled trial (57). The trial originally aimed to evaluate the effect of a diet-and-exercise program and oral glucosamine in a population free of knee OA. Subjects in this high OA risk population were women aged 50 to 60 with a BMI ≥ 27 kg/m^2. The results from the selected population showed that the prevalence of meniscus tears was also high at 14.2% (58). Some results based on this indicate that meniscus extrusion was associated with incident knee OA. Therefore, the population in the PROOF study could be suitable to explore the role of meniscus abnormalities during OA progression.

In the prevention of meniscus abnormalities, there have been some studies on risk factors for meniscal pathologies (e.g., meniscus tear and extrusions). Meniscus pathology can be a result of not only acute knee trauma or surgery but also of both systemic effects and local biomechanical factors (59). A systematic review indicates that for degenerative meniscal tears, age (over 60), sex (being male), work-related kneeling and squatting, and climbing stairs (more than 30 flights) are risk factors for degenerative meniscal tears (60). Regarding the factors associated with meniscus extrusion, root and non-root tears are considered the most relevant (61-66). Other factors are knee misalignment and cartilage damage (67).

Factors that are related to meniscus morphometrics were rarely reported. There are some difficulties in the exploration of risk factors for meniscus abnormalities. Because some research indicated that asymptomatic patients could already have severe structural changes in knee joints (68), there are difficulties in using the OA risk population in a very early OA phase. The methods of classification will also help to understand the pathological mechanism of meniscus abnormalities during OA progression. In Chapter 4, we only included K&L grade = 0 and asymptomatic knees with a five-year follow-up. Whether some factors could become a potential target for the prevention of morphometric abnormalities will be explored in Chapter 5.

CONSERVATIVE TREATMENT FOR OA

The effect of surgical treatment has remained doubtful ever since surgical procedures on the meniscus were first reported (69). A systematic review with meta-analysis of high-quality literature provides relatively strong evidence that arthroscopic partial meniscectomy (APM) on degenerative meniscus tears did not improve functional activity or reduce pain compared with the results after conservative treatment or sham operation in knees with mild or no osteoarthritis (70). Previous research also showed that the risk of developing radiographic tibiofemoral OA was increased six-fold 21 years after total meniscectomy (71, 72).

According to the OARSI guideline (73), conservative treatments were recommended as the core treatment for the majority of knee OA patients. This included education, structured land-based exercise programs, dietary weight management in combination with exercise, and mind-body exercise. These non-surgical therapies were proved to also reduce symptoms such as knee pain among individuals with degenerative meniscal tears (74). Among these non-surgical therapies, the non-pharmacological approaches in particular are more likely to relieve symptoms and to delay or prevent functional decline (75). Many therapies could improve knee pain and function, such as increasing the level of exercises such as aerobic capacity, muscle strength, and endurance, and also facilitating weight loss (76-79).

In general, a hierarchy of management was recommended that consists of non-pharmacological modalities first, then drugs (i.e., NSAIDs and opioids etc.), and then surgery (80). However, physical exercise may have its limitations, as there is some evidence indicating that some types of physical activity (PA) could be potential risk factors during the development of knee joint structural changes (81-83). The latest review article showed that recreational activities and time spent in physical activity were not associated with incident knee OA outcomes (84). The safety should be tested in an earlier OA phase with more sensitive techniques such as MRI. Chapter 5 discusses the safety of PA.

Outline of the Thesis:

Meniscus hypertrophy was mentioned in some MRI scoring systems for meniscus pathologies. However, the association between meniscal volume and OA development was still unclear. In Chapter 2, we assess the association between meniscal volume, its change over time, and the development of knee OA after 30 months in overweight/obese women. Based on the main finding in Chapter 2 and other previous literature, abnormalities in meniscal volume and meniscus extrusion coexisted and may interact during OA development. In Chapter 3, we explore the interplay between medial meniscal volume and changes in it, meniscus extrusion, and radiographic OA development over 30 months of follow-up (FU). Currently, interventions targeting meniscal volume are still under debate. In Chapter 4, to identify some potential preventive

treatment targets through the meniscal volume abnormalities pathway, we aim to explore factors that were associated with meniscal volume in knees free of radiological features and symptoms. Abnormalities in meniscal volume might also be caused by genetic factors. Chapter 5 aims to assess the association between several selected OA risk SNPs and meniscal volume. Menopausal status is a well-recognized OA risk factor. Because all subjects in our study were female, the menopausal status is highly likely to have affected the development of meniscal pathologies. In Chapter 6, the aim is to examine the association between menopausal status and meniscus extrusion. Regarding knee function and pain management, higher physical activity (PA) was recommended for knee OA patients. However, the effect of PA on the knee joint structure is still unclear. In Chapter 7, we aim to systematically review all studies that evaluated the association between PA levels and OA features on MRI. To detect potential changes in a very early phase, we have only included subjects without knee OA.

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CHAPTER 2

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.

Keywords: Meniscal volume, Knee osteoarthritis, MRI

Key message:

1. Medial and lateral baseline volume were positively associated to K&L incidence, while medial and lateral delta-volume were negatively associated to K&L incidence.
2. Lateral meniscal baseline volume was associated to lateral JSN.

1. 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.

2. METHODS

For this study, data from the Prevention of knee Osteoarthritis in Overweight Females (PROOF) study (16) were used. Details regarding this study have been described previously (ISRCTN 42823086) [14]. 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.

2.1 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 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.

2.2 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 (21) at baseline and after 30 months and scored according to the K&L criteria (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).

2.3 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.

2.4 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.

2.5 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 (27) experiment on the atlas set of 25 MRI scans, comparing the automatic segmentations with the manual segmentations using the Dice Similarity Coefficient (DSC)(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.

3. RESULTS

3.1 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.

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 Heberdens's node in at least one hand. K&L: Kellgren and Lawrence.

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.

3.2 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).

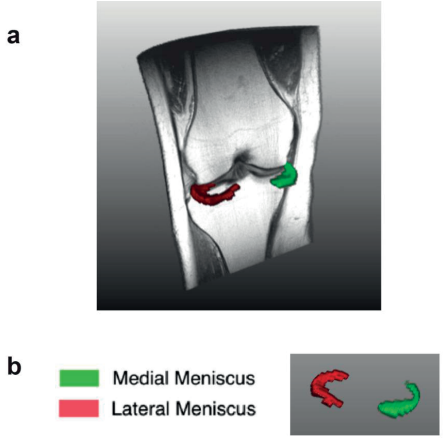


Figure 1 Example of meniscus segmentation
a: 3D overview of one left knee and coronal view of meniscus segmentation. b: 3D view of meniscus from segmentation (green: medial meniscus; red: lateral meniscus).

3.3 Baseline meniscal volume and knee OA development

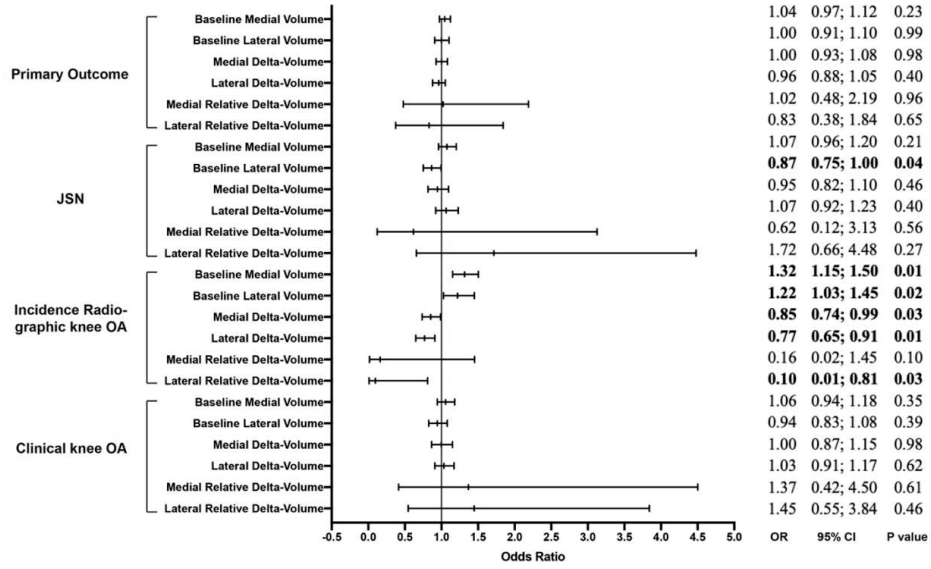
Baseline medial and lateral volume were not significantly associated to the primary outcome (odds ratio (OR) 1.04, 95% confidence interval (CI) 0.97-1.12 and OR 1.000, 95% CI 0.91-1.10). Lateral meniscal volume (not medial) was significantly associated to lateral JSN (OR 0.87, 95% CI 0.75-1.00). Baseline 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).

3.4 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).

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

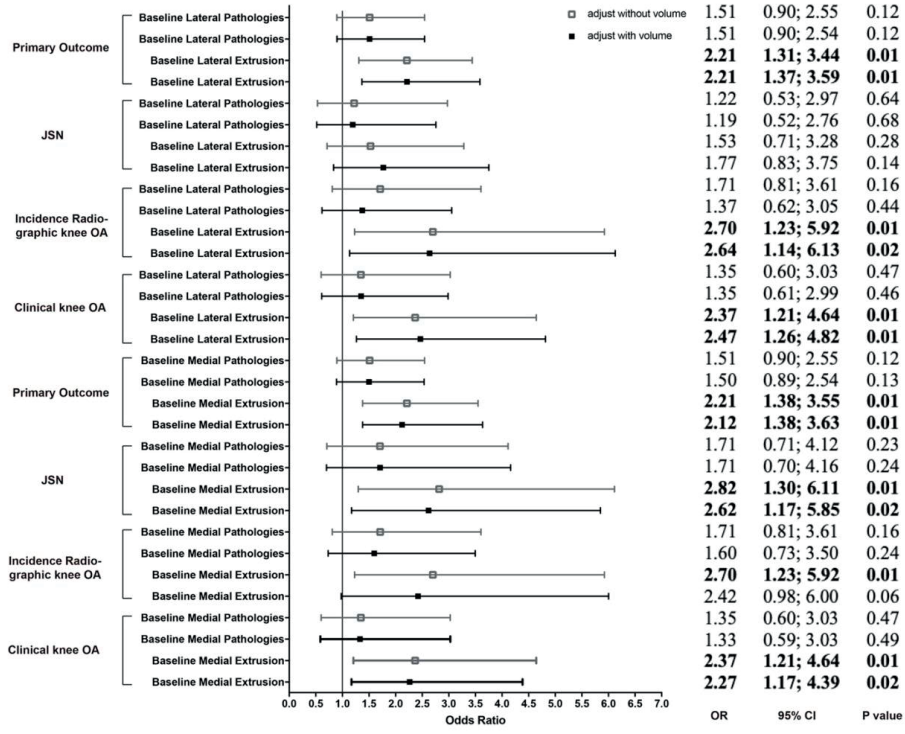


All odds ratios are adjusted for meniscal volume, BMI, age, knee injury and knee alignment, postmenopausal status, Heberden's nodes, meniscal pathologies, extrusion, osteophytes and cartilage defects at baseline. OR=odds ratio, 95% CI = 95% confidence interval, JSN medial (lateral) = medial (lateral) 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.

3.5 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 (see 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, 95% CI = 95% confidence interval, JSN medial (lateral) = medial (lateral) joint space narrowing. Hollow square: adjusted without meniscal volume; Solid square: adjusted with meniscal volu

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, Andrea *et al.* reported larger meniscal volume in the lateral meniscus body in knee OA subjects (13) and Wolfgang *et al.* found that menisci were thicker in OA knees and had a larger meniscal volume when compared to non-OA knees (8). 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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Contributions

DX contributed to data analysis, interpretation, writing of the manuscript and final approval of the article. JV contributed to revision of the article. MH, SK and EO contributed to analysis of MRIs and critical revision of the article in methods part. FW contributed to the primary analysis of the data and interpretation. SBZ contributed to the conception and design of the study including funding obtain and revision of the article. JR contributed to the conception and design of the study, including data collection, analysis, results interpretation and critical revision of the article.

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

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Data availability statement: Data are available on reasonable request.

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CHAPTER 3

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.

Key words: Meniscus volume; meniscus extrusion; knee osteoarthritis; MRI

1. 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, 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).

2. METHODS

Data from the PRevention of knee Osteoarthritis in Overweight Females (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).

2.1 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 [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.

2.2 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 ≥ 2 at FU, with baseline K&L < 2. Medial knee alignment angle was also measured on radiographs for all knees[15].

2.2.1 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.

2.2.2 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.

2.3 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

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].

3. 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)

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)	

%: 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.

3.1 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].

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)	

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.

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].

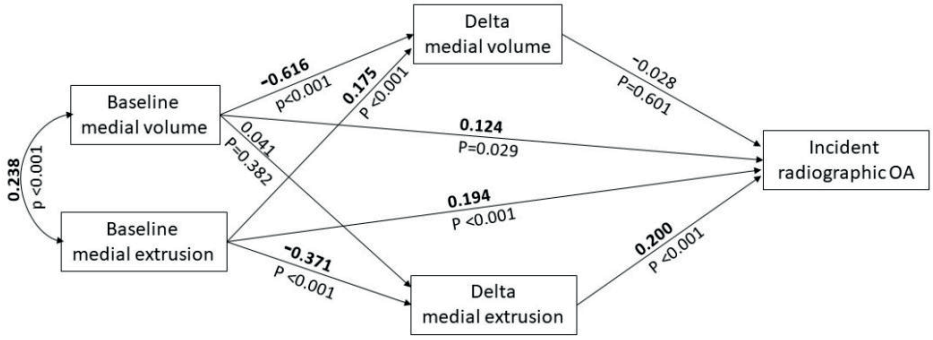
3.2 SEM model

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 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).

3.2.1 Effect of baseline medial meniscus volume on incident radiographic OA

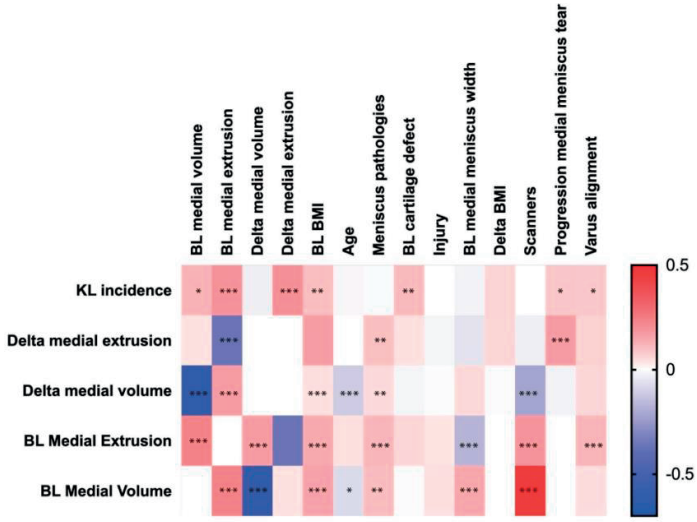
The direct effect of larger baseline medial meniscus volume on the incidence of radiographic knee OA was positive and with statistically significance [Estimate=0.124, p=0.029]. There was no statistically significant indirect effect of baseline medial meniscus volume on incident OA through delta medial 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 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].

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.

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, while the blue color means negative association. Darker color stands for stronger association. *p<0.05, *** p<0.001.

3.2.2 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].

4. 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, 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 be-

ing 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 Figure 4a and 4b). 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 Figure 2 a 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).

5. 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.

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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.

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.

Other acknowledgments: Part of the research has previously been accepted as abstract and poster presentation at the Osteoarthritis Research Society International (OARSI) World Congress 2020 and International Society of Osteoarthritis Imaging (IWOAI) conference 2020. The authors would like to acknowledge Dr. Nils Mattias Hansson, who contributed to meniscus volume segmentation, and Peter van der Plas for his efforts in the semi-quantitative scoring of the MRIs.

Supplementary Table 1. Regression weights between structural variables

			Estimate	Standard weight	S.E.	C.R.	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
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	***

Supplementary Table 1. Regression weights between structural variables (*continued*)

			Estimate	Standard weight	S.E.	C.R.	P
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	***

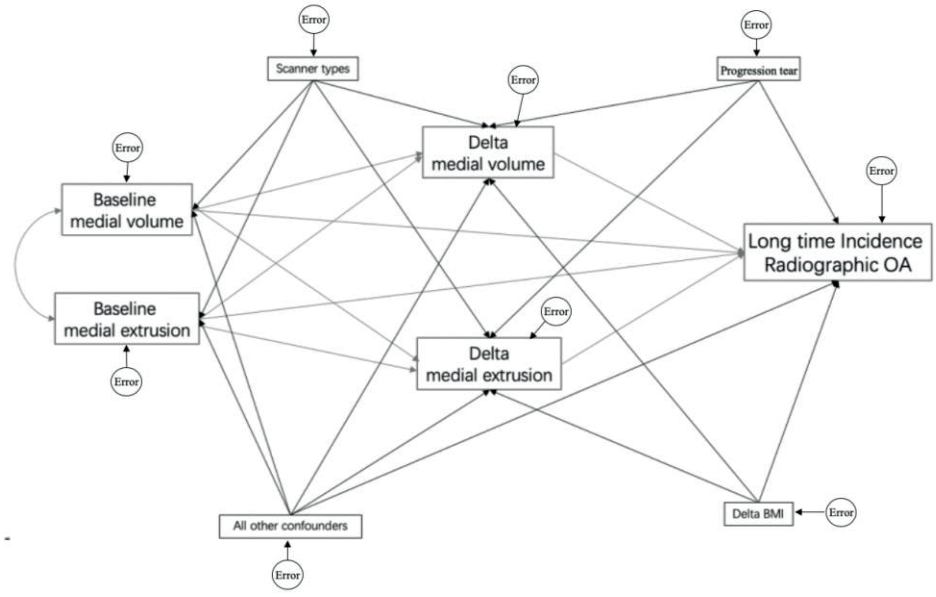
S.E.: standard error, C.R.: critical ratio, ***: P< 0.001

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: Kellegren & 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.

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

Figure 2 a. Full data analysis.

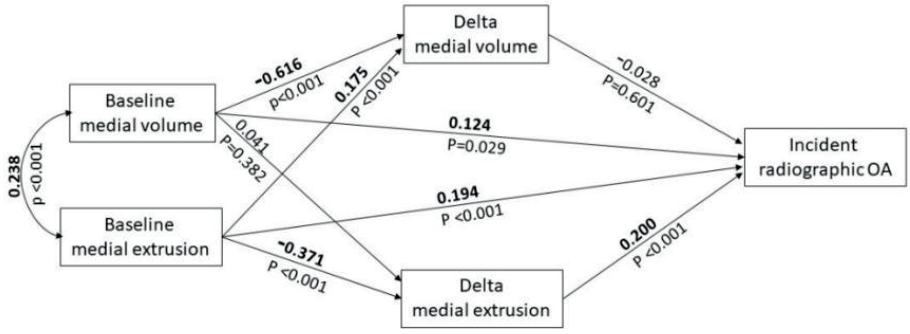


Figure 2 b. Right knee sub-data

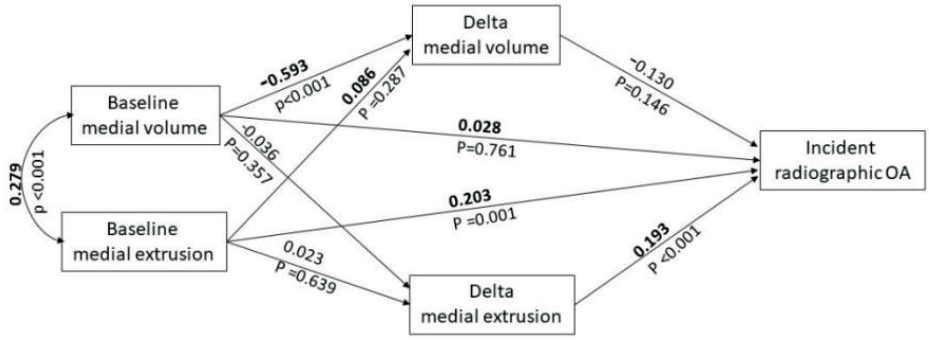
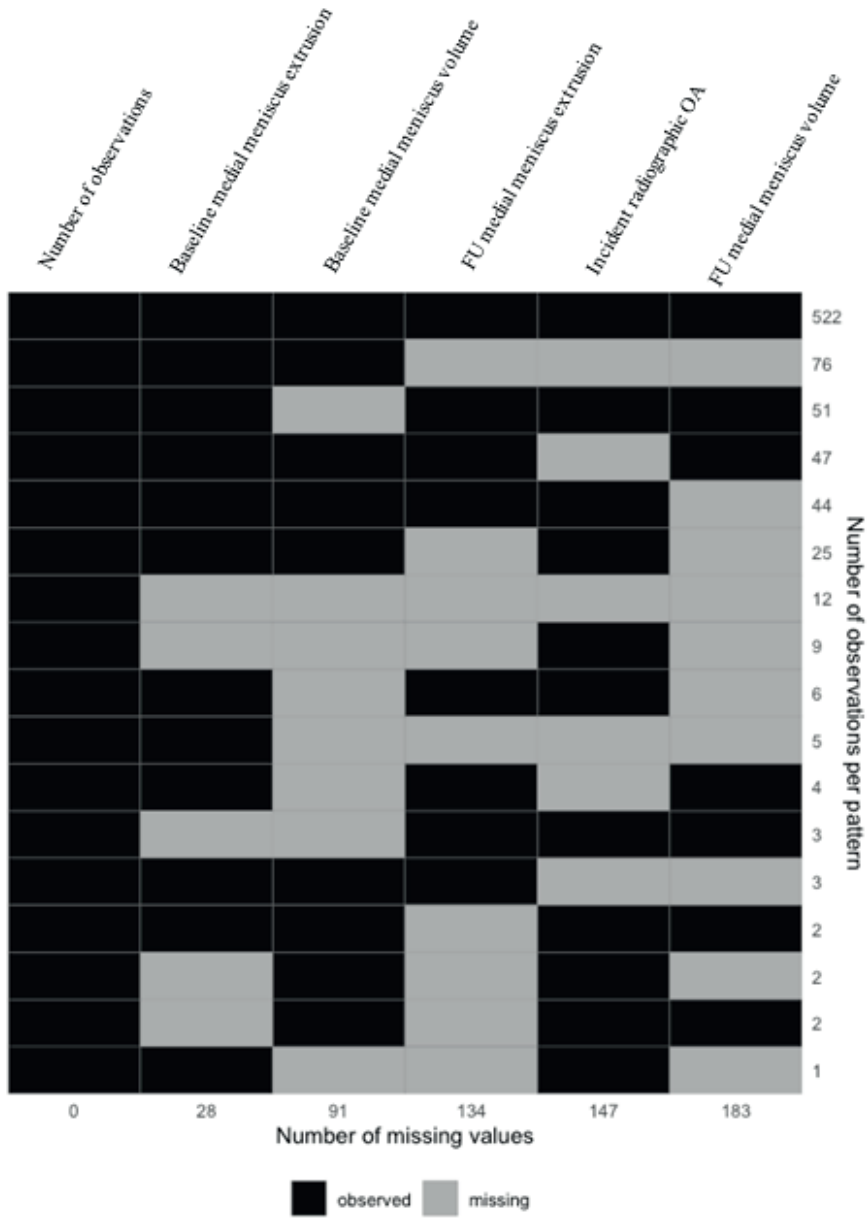


Figure 2a and 2b: the full data analysis and right knee sub-data analysis generate similar results overall. The major difference for the right knee sub-data, we observe baseline medial extrusion had opposite direct effect on delta medial extrusion. Because, this effect was without significance, the indirect 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 side 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. Scatter plot of meniscus volume and extrusion.

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

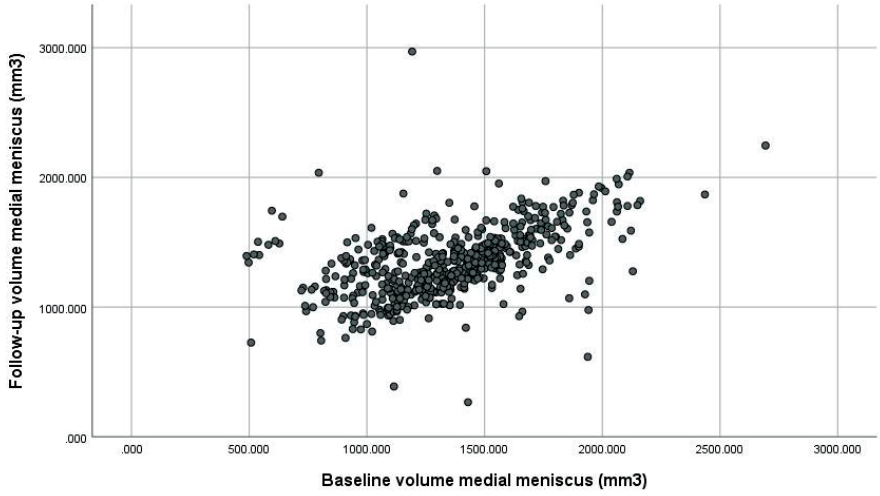
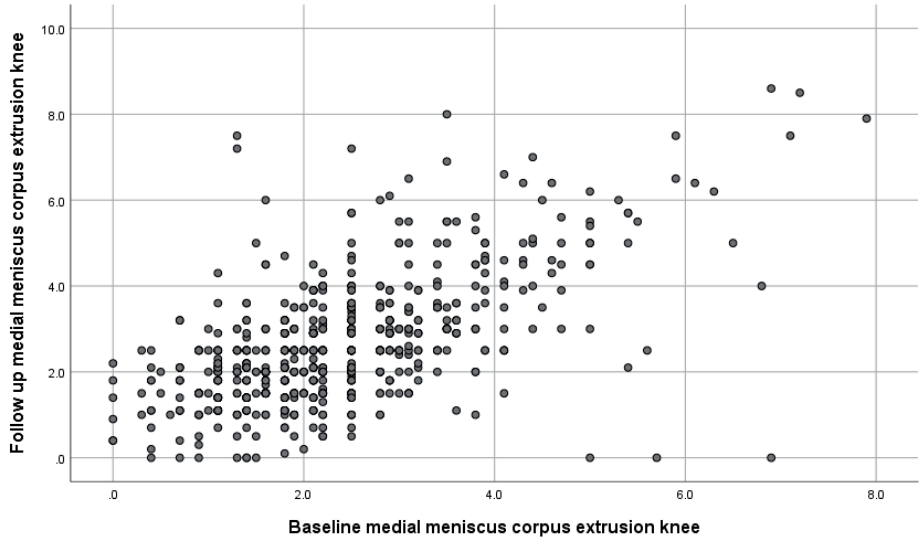


Figure 4 b. Scatter of follow-up medial meniscus extrusion versus baseline medial meniscus extrusion.



As shown in Figure 4a and Figure 4b, both medial meniscus volume and medial meniscus extrusion had substantial changes during 30 months follow-up.

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CHAPTER 7

Physical activity and knee osteoarthritis features on mri in individuals without osteoarthritis: a systematic review

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ABSTRACT

Purpose: To systematically review all studies that evaluated the association between physical activity (PA) levels and knee osteoarthritis (OA) features on MRI in non-OA subjects.

Methods: Inclusion criteria for prospective studies: 1. Non-OA subjects. 2. Average age: 35-80 years. 2. Any self-reported / objective PA. 3. Eligible MRI outcomes: OA-related measures of intra-articular knee joint structures. Exclusion: Evaluations of instant associations, which measured transient structural changes after PA.

Results: Two RCT studies and 16 observational studies were included. One out of eleven studies found PA was harmfully related to cartilage volume or thickness, but four studies found a significant protective association. Four out of ten studies found that PA was harmfully related to cartilage defects, while others showed no significant associations. Two out of three studies reported a significantly increased cartilage T2 value in individuals with more PA. All three studies reported no significant association between PA and BMLs. Two studies assessed the association between PA and meniscus pathology, of which only occupational PA involving knee bending was associated with a greater risk of progression.

Conclusions: Within the little evidence available, PA was not associated with the presence and progression of OA MRI features among non-OA subjects.

Keywords: Knee osteoarthritis, Physical activity, Magnetic resonance imaging, Epidemiology.

Key messages:

- Data on the effects of physical activity and the presence or progression of OA MRI features among non-OA subjects is sparse and highly diverse.
- Especially data on the presence or progression of bone marrow lesions and meniscus pathology is lacking
- No strong evidence was found for the presence nor the absence of an association between PA and the presence or progression of OA MRI features among non-OA subjects

1. INTRODUCTION:

As a modifiable behavior, physical activity (PA) is one of the highly recommended public health and clinical management interventions for secondary and tertiary prevention of osteoarthritis (OA).(1-3) Among OA risk patients, previous studies reported that PA had no,(4, 5) or protective effects against joint degeneration.(6, 7) However, in terms of the safety of physical activity for the primary prevention or early onset of OA, there are few studies and the findings to date are conflicting.(8)

There is a concern that some weight-bearing PAs may increase the risk of knee OA development.(9-11) However, it may take years to observe radiographic OA or symptomatic OA among individuals free of signs and symptoms. Even before the onset of symptomatic, structural changes are already developing, including the presence of bone marrow lesions (BMLs), cartilage loss, and changes in the meniscus. Therefore, detecting early structural changes in the knee among the non-OA population could be meaningful to judge the safety of PA.

Several studies used magnetic resonance imaging (MRI) to capture OA features, such as cartilage defects and meniscal pathologies, in the early stage of OA. Cartilage abnormalities, such as reductions in cartilage volume and thickness, may be associated with knee pain and joint space narrowing.(12-14) Knee cartilage defects play an important role in early knee OA, which could result in increased cartilage breakdown and lead to decreased cartilage volume and joint space narrowing.(15) Also, cartilage T2 relaxation time mapping is used to detect early articular cartilage degeneration,(16) with higher cartilage T2 values being associated with the development of radiographic knee OA.(17) By using MRI, several studies found both meniscus extrusion and greater meniscus volume were risk factors for early progress of OA.(18, 19) Thus, the MRI may be a sensitive and promising technique to detect potential structural changes caused by PA(20).

This study will, by systematically reviewing all studies, evaluate the association between PA and early knee OA features on MRI, among subjects free of knee OA.

2. METHODS:

The protocol has been registered in the International Prospective Register of Systematic Reviews database (PROSPERO: CRD42020218996). The searches were conducted of electronic databases (MEDLINE ALL Ovid, Embase, Web of Science Core Collection, CINAHL EBSCOhost and Cochrane CENTRAL register of Trials) from their earliest date until 29 of October in 2020. The Medial Subject Heading (MeSH) was shown in the supplementary materials.

2.1 Selection criteria:

Primary research of any study design: Controlled trials, prospective, retrospective study, cross-sectional study. There was no limitation on language.

One reviewer (DX) conducted title and abstract screening for all citations, meanwhile, either of three reviewers (JR, MVM, SBZ) independently also screened the citations for verification. Then, all researchers conducted screening for full-text articles based on the PICO (Population, Intervention, Comparison, and Outcome) below.

Population/Participant:

Subjects without radiographic knee OA (Kellgren and Lawrence grades <2), and with no or minimal, non-chronic knee symptoms (joint pain, aching, and/or stiffness) at baseline. 'Reported subjects' mean age should be between 35-80 years. There was no limitation on sex or other potential risk OA factors.

Intervention:

All types of PA: Self-reported PA (questionnaire) or any objective measurement, with no limitation on minimum duration.

Compared with (Placebo): No exposure of PA or lower level of PA (e.g. varying level of PA).

Outcome of interest: All cross-sectional and longitudinal measures of meniscus, cartilage, BML, osteophytes, and effusion/synovitis on knee MRI. We excluded the outcomes that are currently not well recognized as typical OA features. (21, 22) (e.g. patella bone volume and subchondral bone volume) Studies that measured MRI features immediately after PA were also excluded.

2.2 Data extraction (selection and coding)

Data extraction was carried out by one reviewer (DX) and independently verified by the second reviewer (JR). All reviewers made a final agreement on selected information and data.

Information was extracted on: a) study title, authors, publication year, country, and study design; b) participants, including total number and key baseline characteristics (age, population description, BMI, percentage of female); c) physical activity type, recording method (questionnaire/objective measurement), intensity, session frequency, duration of exposure and score range; d) knee joint MRI outcome data at baseline and follow-up; e) adjusted odds ratios or any association co-efficient for development and/or progression to MRI features for varying levels of PA; f) confounders used in the analyses.

2.3 Data synthesis

Due to the substantial heterogeneity within studies a narrative synthesis was conducted. Moreover, results were analyzed with a focus on the direction of the association (harmful/protective/no) of PA with MRI features, rather than on the magnitude of the association. The synthesis included collating and summarizing outcomes from separate MRI OA features and knee joint sub-locations (i.e. tibia, femur and patella, for both medial, and lateral compartments). Within each MRI outcome sub-location, types of physical activity and their associations with outcomes were summarized.

Risk of bias (RoB) assessment

The studies selected for inclusion in this systematic review were evaluated by two researchers (DX and JR) to avoid any discrepancies. Cochrane Collaboration's RoB Tool for randomized controlled trials was accepted as a standard tool.(23) The risk of bias in non-randomized studies-of interventions (ROBINS-I) for observational studies.(24) All RoB graphs were generated by a free access tool from McGuinness, LA et al.(25)

3. RESULTS:

There were 2322 articles retrieved from the databases. After the records were screened by title and abstract, a total of 107 articles were selected for further screening. In the end, 18 studies met the inclusion criteria (see Supplementary Figure 1 for reasons of exclusion), which included two RCTs (26, 27) and sixteen observational studies.(28-43) The mean age of selected studies ranged from 35 to 57.8 years. The characteristics of selected studies are summarized in Supplementary table 1.

RoB assessment

One RCT showed a low level of risk bias, while the other showed bias with 'some concerns'. Fourteen observational studies had a moderate-risk of bias and two a serious risk of bias. All details of sub-domains are shown in Supplementary Figure 2, 3.

Impact of PA on the cartilage volume and thickness

One RCT study and ten observational studies described the association between PA and cartilage volume or thickness. In the RCT, subjects were randomized over endurance training, strength training, or a control group. Among the ten observational studies, of which several explored multiple exposures, the exposures varied between a 'composite score of the amount of PA' (n=2), 'light PA' (n=2), 'vigourous PA' (n=7), 'PA to improve aerobic capacity' (n=1), and 'occupational activities involving knee bending' (n=11). See supplementary table 6 for an overview of all exposures.

One of ten observational studies found that more frequent PA was significantly associated with greater loss or lower current cartilage volume or thickness. In contrast, three observational studies found greater PA was significantly associated with less loss or higher current cartilage volume. One observational study found that more frequent PA was significantly associated with lower cartilage loss in high baseline cartilage volume, but greater cartilage volume loss in low baseline cartilage volume. Five observational studies and the RCT study found PA was not associated with any outcome of cartilage volume. All detailed results are shown in Supplementary table 2.

Impact of PA on the cartilage defects

One RCT study and nine observational studies measured the effect of PA on cartilage defects. The exposure in the RCT study was randomly assigned 'unilateral high-impact exercise' and outcomes were compared to the contralateral leg. Among the nine observational studies, the exposures varied between 'light PA' (n=1), 'vigorous PA' (n=8), and 'occupational PA involving knee bending' (n=9). See supplementary table 6 for an overview of all exposures.

Among nine observational studies, four studies found a significant association between PA and cartilage defects. All four studies showed PA was associated with a greater risk of cartilage defects. The RCT study and five observational studies found PA was not associated with any outcome of cartilage defects. The details are shown in Supplementary table 3.

Impact of PA on cartilage T2 values

One RCT study and two observational studies measured the association between PA and cartilage T2 values. The RCT study measured 12 sub-locations, but in none of them, a significant T2 difference between the 'unilateral high-impact exercise' leg and the contralateral leg. Among the two observational studies, exposures were 'occupational PA involving knee bending' (n=1) and 'a 'categorical measure of intensity of PA' (n=2). See supplementary table 6 for an overview of all exposures.

One observational study did not show any significant association between PA and T2 values. The other observational study found more frequent vigorous PA was related to a significantly higher T2 value. It also showed that 'Occupational PA involving knee bending' was associtated with significantly higher T2 value. Details were shown in Supplementary table 4.

Impact of PA on BML

One RCT and two observational studies assessed the association between PA and BML. The RCT did not observe an association between randomly assigned 'unilateral high impact exercise' and the change of BML over 6 months, compared to the contralateral knee.(27) In one observational study, 'Vigorous PA' was assessed twice and was not associated with the presence of

bone marrow lesions.(37) One cross-sectional study also did not found an association between participation in marathons and BML grade.(43) Details were shown in Supplementary table 5 and 6.

Impact of PA on meniscus pathologies

Two observational studies reported on the association between PA and meniscus pathologies. One study found more frequent 'occupational PA involving knee bending' was associated with a greater risk of progression overall and medial meniscus score.(30) However, this study did not observe an association between 'occupational PA involving knee bending' and meniscal lesions nor meniscus tears in a cross-sectional design. One cohort study found PA ('composite score of amount of PA') was not associated with meniscus extrusion in an OA risk population.(28) Details were shown in Supplementary table 5and 6.

4. DISCUSSION

To assess the impact of physical activity level on MRI OA features among non-OA populations, this systematic review summarized the evidence of 2 RCTs and 16 observational studies. The finding of this review indicated that in most cases, PA was not associated with MRI OA features. Most studies reported on the association between PA and cartilage. However, these associations were generally conflicting. Similar to radiographic findings in some studies, (44-46) the diverse effects of PA could be due to, amongst others, the different outcome measures, (47) populations, and study designs. Moreover, there was little evidence on the association between PA and BMLs or meniscal pathologies.

The results indicated that both light and vigorous PA might be important for maintenance for cartilage thickness/volume, but also could lead to cartilage volume loss over time. The inconsistency in results may be explained by cartilage volume being affected by many confounding factors. The study from Teichtahl A. et al. suggested an interaction between baseline cartilage volume and PA, which indicates that the protective role of PA might be dependent on the cartilage condition.(48) In addition, previous research indicated that cartilage swelling appears to precede volume loss during early OA.(49, 50) Among all selected studies, the condition of cartilage prior to initiating PA was unknown. Although cartilage loss is one of the major characters of OA progression, it will take years to observe an obvious change of cartilage volume/thickness. Most of the selected studies were cross-sectional design or with short period follow-up, which could further explain the inconsistent results.

Although there were some possible concerns that PA, especially vigorous PA, was related to the presence and/or progression of cartilage defects, more than half of the selected studies showed

no association between PA and cartilage defects. Cartilage injury may be of various etiologies, including acute traumatic injuries, early post-traumatic degenerative changes. Abnormal forces across the knee joint can also lead to cartilage damage and subsequent degeneration. Vigorous PA may cause cartilage injuries, which consequently increases the risk of OA progression. However, based on the current literature, we could not conclude that any specific PA type was associated with cartilage defects. This finding is supported by a recently published review, which reported that no new cartilage lesions were observed after running.(51)

Only one study reported that light or vigorous PA was associated with cartilage T2 values: From a compositional perspective, light PA could be protective to cartilage, while the vigorous PA might be detrimental to cartilage. T2 relaxation time measurements in the knee are sensitive to initial cartilage degeneration and reflect the histological changes of the cartilage matrix, particularly affecting water and collagen content as well as tissue anisotropy.(52-54) Furthermore, T2 changes could predict the onset of radiographic OA,(17) because the compositional measures enable early detection of changes in cartilage composition.(51) If the vigorous PA causes cartilage damage, the change of cartilage content could be detected by T2 at a very early phase. Nevertheless, owing to the very low number of studies available in the literature, the direct association between PA and the change of cartilage T2 values is still debatable.

Since one of only two available studies found that more frequent PA was associated with the progression of meniscus pathologies over 3 years, there is still a lack of evidence for the association between PA and meniscus pathologies. Previous research indicated that among mild to moderate OA patients, PA and dietary interventions that reduced their BMI were associated with less meniscus extrusion progression.(55) Overall, the number of available studies was too low, to draw strong conclusions.

To our knowledge, this is the first systematic review of the evidence that the association between and MRI OA features among non-OA subjects. We also included observational studies to obtain more information. There were some limitations of this review. Firstly, there were only 2 RCT studies included. The number of observational studies was also low which means the results remain inconclusive. Secondly, some eligible studies included participants with potential structural changes visible on MRI only at baseline, which may be confounding the association between PA and following structural changes. However, obtaining evidence for the association between PA and structural features of OA among non-symptomatic/non-OA diagnosed individuals, irrespective of the presence of OA MRI features might be more appreciated for clinical practice, as it is not feasible nor advised to screen for OA MRI features when prescribing PA for individuals without a diagnosis of knee OA. Thirdly, from this study, we could not indicate a threshold for safe levels of PA. Because the exposure of most included studies combined several types of PA, we were not able to present any results for specific types of PA. Fourthly, in

some studies, the sample size might have been too small to find significant associations. Finally, many studies were from the same country or the same population. Although the population characteristics showed some differences, it is still highly possible that these studies include the same population, which may limit generalizability.

4. CONCLUSION:

Within the sparse and diverse evidence available, no strong evidence was found for the presence nor the absence of an association between PA and the presence or progression of OA MRI features among non-OA subjects. Therefore, more research is required before PA in general and also specific forms of PA can be deemed safe for knee joint structures.

Competing interests: All authors have no conflicts of interest to disclose.

Contribution:

- Conception and design (JR, DX, MVM, SBZ)
- Screening of abstracts and full text (JR, DX, MVM, SBZ)
- Analysis and interpretation of the data (DX, JR)
- Drafting of the article (DX)
- Critical revision of the article for important intellectual content (JR, MVM, SBZ)
- Final approval of the article (DX, JR, MVM, SBZ)

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Ethical approval information: None

Data sharing statement: None

MEDICAL SUBJECT HEADING (MESH)

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('nuclear magnetic resonance imaging'/exp OR 'nuclear magnetic resonance'/exp OR ' nuclear magnetic resonance scanner'/exp OR (((magnet* OR imaging*) NEAR/3 resonance*) OR mri OR ((nmr OR mr) NEAR/3 (mapping OR imaging))):Ab,ti) AND ('knee'/exp OR 'patella'/de OR 'patellofemoral joint'/de OR 'tibiofemoral joint'/de OR 'knee osteoarthritis'/de OR 'knee meniscus'/de OR (knee OR knees OR patell* OR intrapatella* OR tibiofemor* OR menisc*):Ab,ti) AND ('physical activity'/exp OR 'sport'/exp OR exercise/exp OR 'muscle strength'/de OR kinematics/de OR (((physical* OR dynamic) NEAR/3 activ*) OR exercise OR sport* OR running OR cycling OR swimming* OR jumping OR jump OR isokinetic* OR gait OR walking OR walk OR ((resistance OR strength) NEAR/3 training*) OR (weight NEAR/3 (bear* OR lift*)) OR loading OR weightbear* OR weightlift* OR power-lift* OR powerlift* OR (muscle NEAR/3 (training OR strength)) OR flexion OR kinematic* OR athlet* OR runner* OR (leg NEAR/3 (squat OR swing)) OR chain-task*):ab,ti) AND ('normal human'/de OR 'volunteer'/de OR ((normal-human*) OR healthy* OR ((normal) NEXT/6 (adult* OR human* OR person* OR individual* OR Men OR women OR female OR male OR knee OR knees OR subjects OR individuals OR volunteer* OR control* OR athlete* OR runner* OR joint* OR participant*)) OR (free NEAR/3 symptom*) OR early-stage* OR (mild NEAR/6 (oa OR koa OR osteoarthrit*)) OR (kellgren NEAR/3 lawrence NEAR/3 (1 OR 0)) OR pre-oa OR pre-koa OR early-oa OR early-koa OR non-symptom*):ab,ti) NOT ([animals]/lim NOT [humans]/lim)

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(Magnetic Resonance Spectroscopy / OR Magnetic Resonance Imaging / OR (((magnet* OR imaging*) ADJ3 resonance*) OR mri OR ((nmr OR mr) ADJ3 (mapping OR imaging))).ab,ti.) AND (Knee/ OR Knee Joint / OR Patella / OR Patellofemoral Joint / OR Osteoarthritis, Knee / OR (knee OR knees OR patell* OR intrapatella* OR tibiofemor* OR menisc*).ab,ti.) AND (exp Sports / OR exp Exercise / OR Muscle Strength / OR (((physical* OR dynamic) ADJ3 activ*) OR exercise OR sport* OR running OR cycling OR swimming* OR jumping OR jump OR isokinetic* OR gait OR walking OR walk OR ((resistance OR strength) ADJ3 training*) OR (weight ADJ3 (bear* OR lift*)) OR loading OR weightbear* OR weightlift* OR power-lift* OR powerlift* OR (muscle ADJ3 (training OR strength)) OR flexion OR kinematic* OR athlet* OR runner* OR (leg ADJ3 (squat OR swing)) OR chain-task*).ab,ti.) AND (Healthy Volunteers / OR ((normal-human*) OR ((healthy* OR normal) ADJ6 (adult* OR human* OR person* OR individual* OR Men OR women OR female OR male OR knee OR knees OR subjects OR individuals OR volunteer* OR control* OR athlete* OR runner* OR joint* OR participant*)) OR (free ADJ3 symptom*) OR early-stage* OR (mild ADJ6 (oa OR koa OR osteoarthrit*)) OR (kellgren ADJ3 lawrence ADJ3 (1 OR 0)) OR pre-oa OR pre-koa OR early-oa OR early-koa OR non-symptom*).ab,ti.) NOT (exp animals/ NOT humans/)

Supplementary table 1 Study characteristics: Summary of included studies

Author, year	Population description	Country	Study design	Age (mean ± SD) years	Total sample (percentage of female)	BMI (mean ± SD) kg/m^2
Cicuttni, F. 2002	Asymptomatic healthy	Australia	Cross-sectional	52.2 ± 10	166 (58%)	25.6 ± 5.9
Cotofana, S. 2010	Asymptomatic healthy	Australia	Cohort	51.4 ± 3.3	38 (100%)	26.7 ± 5.9
Hanna, F. 2005	Asymptomatic healthy men	Australia	Cohort	51.9 ± 12.8	28 (0%)	24.9 ± 2.9
Hanna, F. 2007	Asymptomatic healthy women	Australia	Cross-sectional	52.3 ± 6.6	176 (100%)	27.1 ± 5.5
Hanna, F. 2007	Asymptomatic healthy women	Australia	Cross-sectional	52.3 ± 6.6	176 (100%)	27.1 ± 5.5
Hartley, C. 2019	Postmenopausal women	United Kingdom	Randomized controlled trial	61.7 ± 4.3	35 (100%)	24.1 ± 3.4
Hovis, K.2011	OAI (OA risk sub-population)	United States	Cohort	50.7 ± 2.7	128 (55%)	23.7 ± 2.0
	OAI (non-OA sub-population)			50.0 ± 2.8	33 (76%)	23.1 ± 2.2
Lin, W. 2013	OAI	United States	Cohort	52.8 ± 4.0	205 (61%)	23.7 ± 2.1
Wijayaratne, S. P. 2008	OAI (OA risk male sub-population)	United States	Cohort	52.8 ± 6.8	148 (100%)	27.3 ± 5.7
Wang Y. 2006	Asymptomatic healthy	Australia	Cohort	55.8 ± 8.8	84 (68%)	25.7 ± 4.5
Virayavanich W. 2013	OAI (OA risk male sub-population)	United States	Cohort	50.8 ± 2.9	115 (52%)	24.1 ± 1.9
Teichtahl A. J. 2011	MCCS (Asymptomatic healthy sub-cohort)	Australia	Cohort	57.8 ± 5.1	271 (62%)	25.7 ± 4.1
Teichtahl A. J. 2009	MCCS (Asymptomatic healthy sub-cohort)	Australia	Cohort	57.8 ± 5.2	271 (62%)	25.7 ± 4.1
Teichtahl A. J. 2010	MCCS (Asymptomatic healthy sub-cohort)	Australia	Cohort	46.5 (9.1)	96 (100%)	34.1 (9.8)
Teichtahl A. J. 2016	Obese population	Australia	Cohort	45.7 (9.3)	197	34.1 (9.5)
Tina, L. 2007 (same to Teichtahl 2011 data)	MCCS (Asymptomatic healthy sub-cohort)	Australia	Cohort	58 (5.5)	186 (34%)	25.2 (3.8)
Frank, G. 1992	Asymptomatic healthy*	United States	Cross – sectional	35 for control, 40 for marathon runner	74 (55%) for contorl, 23 (65%) for marathon runner	NI
Zhang, F. 2017	Obese woman	The Netherlands	Cohort	55.7 (3.2)	395 (100%)	32.4 (4.3)

*: With exclusion criteria of non-OA; NI: No information

Supplementary table 2 Summary of included studies assessing the relationship of physical activity (PA) and cartilage volume/ thickness in individuals without knee OA.

Author, year	N; FU	Type of exposure	Cartilage volume outcome
Cicuttni, F. 2002	166; no	Self-reported total PA (walking, home activity, sport) Score range: 0-16	Current cartilage volume
Hanna, F. 2007 & Hanna, F. 2007	176; no	Self-reported PA (Light exercise: walking, light housework, slow bicycling, etc.) Yes/No	Current cartilage volume
		Self-reported PA (Strenuous physical activity : bicycling, brisk walking, jogging, aerobics, et al. to raise pulse rate and make breath faster) Yes/no	Current cartilage volume
		Self-reported PA (strenuous activity (bicycling, brisk walking, jogging, aerobics, etc. "to raise pulse rate and make breath go faster") Frequency categorized: No, 1-2, 3-5, 6-8, ≥9 days per 14 days	Current cartilage volume
Hanna, F. 2005	28; 24 months	Self-reported total activity (walking, home activity, sport) Score range: 0-16	Annual change of volume
Cotofana, S. 2010	38; 3 months	Randomly assigned PA: Training intervention (cycling ergometer), randomized to: - Endurance (EP), - strength (SP), - control (CP).	Change of volume Change of Cartilage thickness
Wijayaratne S. P. 2008	148; 24 months	Self-reported total PA ("Fortnightly exercise that promoted an increased heart and respiratory rate for at least 20 min"), Yes/no	Annual change of cartilage volume

Associations	Statistical significance	Adjustment for confounders
* Medial(ß): -0.035 (-0.062, -0.008); * lateral(ß): -0.04 (-0.08, 0.000)	**P = 0.01** **P = 0.05**	Age, BMI.
$(ß): -86.2 (-622.2, 450.0)	P=0.75	Age, body weight, Patella bone volume
* Medial(ß): 0.12 (0.02, 0.21), * Lateral(ß): 0.04 (-0.09, 0.16), $ (ß): -52.3 (-224.1, 120.1)	**P= 0.02,** P= 0.54, P= 0.55	Age, BMI, respective tibial plateau bone area Age, body weight, Patella bone volume
* Medial(ß): 0.03 (-0.002, 0.05), * Lateral(ß): 0.02 (-0.01, 0.06),	P= 0.07, P= 0.23	Age, BMI, respective tibial plateau bone area
* (ß): -25 (-116.7, 66.6)	P= 0.57	Age, BMI, baseline tibial cartilage volume, tibial plateou area.
$ EP Mean difference: - 22.6 ± 448, $ SP Mean difference: 3.7±592, $ CP Mean difference: -1.2±996, # EP Central Medial (Mean difference): -35.4± 119, # SP Central Medial (Mean difference): 11.3±189, # CP Central Medial (Mean difference): -39.3±149, # EP Posterior medial (Mean difference): -16.5± 408, # SP Posterior medial (Mean difference): 17.7±289, # CP Posterior medial (Mean difference): -118±267, * EP Medial (Mean difference): 11.4± 223 * SP Medial (Mean difference):11.6±281, * CP Medial (Mean difference):37.4±466,	NS between groups NS between groups NS between groups NS between groups	No
$ EP Mean difference: -3.5±199, $ SP Mean difference: 6.2±310, $ CP Mean difference:13.0±342, # EP Central Medial (Mean difference): -33.8±195, # SP Central Medial (Mean difference):-0.5±243, # CP Central Medial (Mean difference):-24.8±161, # EP Posterior medial (Mean difference): -204±245, # SP Posterior medial (Mean difference): -6.6±156, # CP Posterior medial (Mean difference):-40.0±392, *EP Medial (Mean difference): 7.7±93.6, *SP Medial (Mean difference): -19.9±218, *CP Medial (Mean difference): 29.2±276,	NS between groups NS between groups NS between groups NS between groups	
$ (ß): -17.43(-37.74, 2.88),	P= 0.09	Age, body height, weight, initial patella cartilage volume, patella bone volume

Supplementary table 2 Summary of included studies assessing the relationship of physical activity (PA) and cartilage volume/ thickness in individuals without knee OA. (*continued*)

Author, year	N; FU	Type of exposure	Cartilage volume outcome
Teichtahl, A. J. 2012 & 2009	271; 24 months	Self-reported vigorous PA (jogging, cycling, tennis, aerobic dance, skiing, etc.), Grade range: 0 (never participated), 1 (participated at one time point), 2 (participated at both time points)	Annual change of cartilage volume
		Self-reported PA: Weekly frequency of vigorous PA, Range: 0(never), 1(seldom), 2(sometimes), 3(often)	
Teichtahl, A. J. 2010	96; no	Self-reported PA (Heavy lifting/ bending/ squatting), Grade for frequency: 0(never), 1(occasionally), 2(frequently), 3(very frequently), 4(most of the day)	Current cartilage volume
		Self-reported PA (Knee bending), Grade for frequency: 0, 1, 2, 3, 4	
		Self-reported PA (Stair climbing), Grade for frequency: 0, 1, 2, 3, 4	
		Self-reported PA (Walking), Grade for frequency: 0, 1, 2, 3, 4	
		Self-reported PA (standing), Grade for frequency: 0, 1, 2, 3, 4	
Teichtahl, A. J. 2016	197; 12 months	Self-reported PA active (Performed 3 weight-bearing sports regularly in last 12 months and or all five occupational activities at least frequently to most of the day) Yes/No	Annual percentage change of cartilage volume
		Occupational activity (Number of activities being performed frequently to most of the day) 0 - 5	
		Heavy lifting, bending, squatting (≥frequently): Yes/No	
		Bending(≥frequently), Yes/No	

Associations	Statistical significance	Adjustment for confounders
* Medial(ß): - 0.1 (- 8.3, 8.3); *Lateral(ß): 5.4 (-3.3, 14.1); $ (ß): -23.8 (- 44.1, - 3.5)	P=0.99, P=0.22, **P=0.02**	Age, gender, BMI Age, sex, body mass index, and the respective baseline measure (presence of cartilage defects; yes/no).
$(ß): -9.8 (-20.7, -1.1)	P= 0.08	
*Medial(ß): -10 (-52,32) *Lateral(ß): -17 (-65, 31) $ (ß): -65 (-145, 15)	P= 0.64, P= 0.50, P= 0.11	Age, BMI, frontal plane knee alignment and respective compartmental radiographic joint space narrowing (yes/no), respective tibial bone size for the medial and lateral tibial cartilage volumes
*Medial(ß): -7 (-55, 40) *Lateral(ß): 12 (-42, 67) $ (ß): -83 (-174, 8)	P= 0.75 P= 0.66 P= 0.07	
*Medial(ß): -12 (-59, 36) *Lateral(ß): -18 (-71, 35) $(ß) -42 (-136, 52)	P= 0.63 P= 0.50 P= 0.38	
*Medial(ß): -4 (-59, 52) *Lateral(ß): 33 (-30, 97) $ (ß)-51 (-159, 56)	P= 0.90 P= 0.30 P= 0.35	
*Medial(ß): -11 (-68, 45); *Lateral(ß): 17 (-48, 81) $(ß) -57 (-166, 53)	P= 0.70 P= 0.61 P= 0.30	
Low baseline cartilage volume: *Medial(ß): 0.9 (0.1, 1.6); *Lateral(ß): 0.0 (-0.7, 0.8) High baseline cartilage volume: *Medial(ß): -0.2 (-1.0, 0.6); *Lateral(ß): 0.4 (-0.4, 1.2)	 **P= 0.02** P= 0.91 P=0.55 P=0.30	Age, gender, annual percentage weight change and baseline medial tibial plateau bone area
Low baseline cartilage volume: Medial(ß): 0.2 (0.0, 0.04), Lateral(ß): 0.0 (-0.2, 0.2) High baseline cartilage volume: *Medial(ß): -0.2 (-0.4, 0.0); *Lateral(ß): 0.1 (-0.2, 0.3)	 P=0.047 P= 0.94 **P= 0.04** P=0.60	
Low baseline cartilage volume: *Medial(ß): 0.4 (-0.3, 1.2); *Lateral(ß): -0.3 (-1.1, 0.4) High baseline cartilage volume: *Medial(ß): -0.8 (-1.6, 0.0); *Lateral(ß): 0.4 (-0.4, 1.2)	 P= 0.28 P= 0.34 P= 0.06 P= 0.37	
Low baseline cartilage volume: *Medial(ß): 0.6 (0.0, 1.3); *Lateral(ß): 0.1 (-0.5, 0.7) High baseline cartilage volume: *Medial(ß): -0.3 (-1.0, 0.5); *Lateral(ß): 0.6 (-0.1, 1.3)	 P= 0.06 P= 0.72 P= 0.48 P= 0.08	

Supplementary table 2 Summary of included studies assessing the relationship of physical activity (PA) and cartilage volume/ thickness in individuals without knee OA. (*continued*)

Author, year	N; FU	Type of exposure	Cartilage volume outcome
		Stairs(≥frequently), Yes/No	
		Standing(≥frequently), Yes/No	
		Walking(≥frequently), Yes/No	
		Recreational activity, Walk≥ 5 km week^{-1}, Yes/No	
		≥3 weight-bearing sports regularly in last 12 months, Yes/No	
Tina, L. 2007	186; no	Self-reported PA (Weekly frequency of vigorous PA undertaken for at least 20 minutes): Categorize as never, 1-2 times/week, at least 3 times/week.	Current cartilage volume
		Self-reported PA, Duration of regular vigorous PA at least 3 times a week (Jogging, swimming, cycling, singles, tennis, aerobics dance, skiing etc.), Categorize as never, 1-2 times/week, at least 3 times/week.	Current cartilage volume

Legends: N: Total sample size. Cartilage location: *Tibia, # Femur, $ Patella; Odds ratio: OR(95% CI); Mean difference: Mean(Standard deviation); In association column, if no indication of Beta or OR, the value was the outcome mean value; NS: No significance; All change of cartilage volume were present or transformed as: Baseline value – follow-up value, unless indicated otherwise. Annual changes were calculated by change of volume divided by follow-up time in years; Annual percentage loss: (Annual change/Baseline value)*100; The reference for categorical exposure variables were no expose or the lowest grade, unless indicated otherwise.

Associations	Statistical significance	Adjustment for confounders
Low baseline cartilage volume:		
*Medial(ß): 0.5 (-0.1, 1.2);	P= 0.11	
*Lateral(ß): 0.5 (-0.1, 1.2)	P= 0.08	
High baseline cartilage volume:	P= 0.14	
*Medial(ß): -0.5 (-1.2, 0.2);	P= 0.50	
*Lateral(ß): -0.2 (-0.9, 0.5)		
Low baseline cartilage volume:		
*Medial(ß): 0.3 (-0.4, 0.9);	P= 0.38	
*Lateral(ß): -0.3 (-0.8, 0.4)	P= 0.40	
High baseline cartilage volume:	P= 0.39	
*Medial(ß): -0.3 (-1.1, 0.4);	P= 0.99	
*Lateral(ß): 0.0 (-0.7, 0.7)		
Low baseline cartilage volume:		
*Medial(ß): 0.4 (-0.3, 1.0);	P= 0.16	
*Lateral(ß): 0.0 (0.0, 0.0)	P= 0.19	
High baseline cartilage volume:	**P= 0.03**	
*Medial(ß): - 0.8 (-1.5, -0.1);	P= 0.89	
*Lateral(ß): -0.1 (-0.8, 0.7)		
Low baseline cartilage volume:		
*Medial(ß): 0.7 (0.1, 1.3);	**P= 0.03**	
*Lateral(ß): 0.4 (-0.2, 1.0)	P= 0.14	
High baseline cartilage volume:	P= 0.80	
*Medial(ß): 0.1 (-0.6, 0.8);	P= 0.73	
*Lateral(ß): 0.1 (-0.6, 0.8)		
Low baseline cartilage volume:		
*Medial(ß): 0.8 (0.0, 1.5);	**P= 0.04**	
*Lateral(ß): 0.1 (-0.6, 0.9)	P= 0.71	
High baseline cartilage volume:	P= 0.82	
*Medial(ß): 0.1 (-0.8, 1.0);	P= 0.43	
*Lateral(ß): 0.3 (-0.5, 1.2)		
*OR: 115 (24, 206)	**P= 0.01**	Age, sex, baseline body mass index, and tibial bone area
*OR: 114 (48, 181)	**P= 0.001**	

Supplementary table 3 Summary of included studies assessing the relationship of physical activity and cartilage defects in individuals without OA.

Author, year	N; FU	Type of exposure	Cartilage defects outcome
Hanna, F. 2007 & Hanna, F. 2007	176; no	Self-reported PA (Light exercise: walking, light housework, slow bicycling,etc) Yes/No	Presence of cartilage defects
		Self-reported PA (Strenuous physical activity : bicycling, brisk walking, jogging, aerobics, et al. to raise pulse rate and make breath faster) Yes/no	
		Self-reported PA (strenuous activity (bicycling, brisk walking, jogging, aerobics, et al. to raise pulse rate and make breath faster) Frequency categorized: No, 1-2, 3-5, 6-8, ≥9 days per 14 days	
Hartley, C. 2019 ;	35; 6 months	Randomly assigned PA (Unilateral, high impact exercise): EL (Exercise leg) versus CL(Control leg)	Change of cartilage defects,
Hovis, K.2011	161; no	Self-reported PA: frequent knee bending activities in past 30 days, Yes/ No	Cartilage lesion: cartilage maximum grade (WORMS) Cartilage lesion: Cartilage grade> 1, %
Wang, Y. 2006	84; 24 months	Self-reported PA (Walking + activities at home + sporting activities), Score range: 0 – 12.	Change in cartilage defects
Virayavanich, W. 2013	115; 36 months	Self-report Physical activities (kneeling and squatting) No. of frequent knee bending activities involved: Range categorized: 0, 1, ≥ 2.	Baseline level of cartilage lesion: (WORMS ≥1) Baseline level of cartilage defects (WORMS≥2)
		Self-report Physical activities (kneeling and squatting) Frequent knee bending: Yes/No	Progression of cartilage grade

Association adjusted	Statistics significance	Adjustment for confounders
$ 0.32 (0.03, 4.05),	P= 0.38	Age, BMI, respective tibial cartilage volume
* Medial (OR): 1.24 (0.45-3.37); * Lateral (OR): 1.19 (0.93-1.52); $ 2.3 (0.9, 6.0)	P= 0.68 P= 0.69 P= 0.08	
* Medial(OR): 1.06 (0.80, 1.40); * Lateral(OR): 1.19 (0.93, 1.52) $ 2.3 (0.9, 6.0)	P= 0.70 P= 0.17 P= 0.08	
No detailed results were available: The McNemar test showed no significant differences between any of the sub-locations.	NS	No
OA risk population: No vs Yes: 1.11 ± 1.33 vs 2.35 ± 1.70 , No OA risk population: No vs Yes: 1.82 ± 1.14 vs 2.00 ± 1.84	**P <0.0001** P = 0.589	Sex, age BMI
OA risk population: No vs Yes: 32% vs 68% No OA risk population: No vs Yes: 64% vs 65%	**P< 0.0001** P=0.760	
* Medial(ß): 0.071(-0.029, 0.170); *Lateral(ß): 0.050(-0.052, 0.153); $(ß): 0.079 (0.009, 0.168)	P= 0.16 P= 0.33 P= 0.08	Age, gender, body mass index, physical activity, baseline bone size, and baseline cartilage defect score
0 to 1 (OR): 3.08 (1.01–9.35) 1 to ≥ 2 (OR): 4.28 (1.37–13.35)	Significant Significant **P=0.012 (trend)**	sex, age, body mass index, history of knee injury, and knee surgery
0 to 1 (OR): 1.33 (0.50–3.55) 1 to ≥ 2 (OR): 3.35 (1.23–9.06)	NS Significant **P=0.018 (trend)**	
Overall joint (OR) 4.12 (1.27, 13.36), #$(OR): 3.05 (0.81–17.21) *# Medial(OR): 2.51 (0.33–), *# Lateral(OR): 2.93 (0.34–140.19)	**P= 0.009,** P = 0.117 P = 0.415 P=0.567	

Supplementary table 3 Summary of included studies assessing the relationship of physical activity and cartilage defects in individuals without OA. (*continued*)

Author, year	N; FU	Type of exposure	Cartilage defects outcome
Teichtahl, A. J. 2012 & 2009	271; 24 months	Self-reported vigorous PA (jogging, cycling, tennis, aerobic dance, skiing, etc.), Grade range: 0 (never participated), 1 (participated at one time point), 2 (participated at both time points) Weekly frequency of vigorous PA, Range: 0(never), 1(seldom), 2(sometimes), 3(often)	Change of cartilage defects
Teichtahl, A. J. 2010	96; no	Self-reported PA (Heavy lifting/ bending/ squatting), Grade for frequency: 0 (never), 1(occasionally), 2 (frequently), 3 (very frequently), 4 (most of the day) Self-reported PA (Knee bending), Grade for frequency: 0, 1, 2, 3, 4 Self-reported PA (Stair climbing), Grade for frequency: 0, 1, 2, 3, 4 Self-reported PA (Walking), Grade for frequency: 0, 1, 2, 3, 4 Self-reported PA (standing), Grade for frequency: 0, 1, 2, 3, 4	Current grade of cartilage defects
Tina, L. 2007	186; no	Self-reported PA (Weekly frequency of vigorous PA undertaken for at least 20 minutes): Categorize as never, 1-2 times/week, at least 3 times/week. Self-reported PA, Duration of regular vigorous PA at least 3 times a week (Jogging, swimming, cycling, singles, tennis, aerobics dance, skiing et al.), Categorize as never, 1-2 times/week, at least 3 times/week.	Presence of cartilage defects

Legends: Cartilage location: *Tibiofemoral, # Femur, $ Patella; OR: Odds Ratio; BMI: Body mass index; WORMS: Whole-Organ Magnetic Resonance Imaging Score; PA = physical activity; Change of cartilage defects were presented or transformed as: Follow-up grades – Baseline grades; The reference for categorical exposure variables were non-expose or the lowest grade of PA, unless indicated otherwise .

Association adjusted	Statistics significance	Adjustment for confounders
*Medial (OR): 1.5 (1.0, 2.3), *Lateral (OR): 1.0 (0.7, 1.4); $ (OR): 0.4 (0.2, 1.1).	**P= 0.04** P= 0.81 P= 0.07	Age, gender, BMI Age, sex, body mass index, and the respective baseline measure (presence of cartilage defects; yes/no).
$(OR): 0.6 (0.4, 1.1)	P= 0.08	
*Medial (OR): 0.9 (0.5, 1.3); *Lateral (OR): 1.0 (0.5, 1.9); $ (OR) 1.8 (1.0, 3.1)	P= 0.44 P= 0.99 P= 0.04	age, BMI, frontal plane knee alignment and respective compartmental radiographic joint space narrowing (yes/no)
*Medial (OR): 0.8(0.5, 1.3); *Lateral (OR): 1.2 (0.6, 2.3); $ (OR): 1.8 (1.0, 3.1)	P= 0.43 P= 0.63 **P= 0.05**	
*Medial (OR): 1.0 (0.6, 1.6); *Lateral (OR): 0.9 (0.5, 1.8); $ (OR) 2.9 (1.4, 6.0)	P= 0.97 P= 0.84 **P<0.01**	
*Medial (OR): 0.7 (0.4, 1.2); *Lateral (OR): 0.8 (0.3, 2.0); $ (OR): 2.3(1.2, 4.4)	P= 0.22 P= 0.67 **P= 0.02**	
*Medial (OR): 0.6 (0.4, 1.1); *Lateral (OR): 0.6 (0.2, 1.9); $ (OR) 1.7 (0.9, 3.3)	P= 0.13 P= 0.39 P= 0.11	
*(OR): 1.0 (0.8, 1.4)	P= 0.8	Age, sex, tibial cartilage volume, and BMI
*(OR): 1.1 (0.8, 1.3)	P= 0.6	

Supplementary table 4 Summary of included studies assessing the relationship of physical activity and cartilage T2 value in individuals without OA.

Author, year	FU	Type of exposure	T2 outcomes
Hartley, C. 2019 (UK)	35; 6 months	Randomly assigned PA (Unilateral, high impact exercise): EL (Exercise leg) versus CL (Control leg)	Change of T2 relaxation times
Hovis, K.2011 (US, OAI incident cohort and normal cohort both)	161; no	Self-reported PA: PASE score (3 level: E1 sedentary such as book reading ,computer playing, E2 light exerciser like walking table tenis , E3 moderate to strenuous excerciser like running, basketball and tennis.) Self-reported PA: frequent knee bending activities in past 30 days was analysis. No vs Yes.	T2 values
Lin, W. 2013 (US, same data as Hovis, K. 2011)	205; 48 months	Self-reported PA: PASE , Levels by tertile: High, moderate, low	Change of T2

Legends: Cartilage location: *Tibial femor, # Femur, $ Patella; **: Significant threshold after Bonferroni correction for multiple comparisons P< 0.004; OR: Odds Ratio; BMI: Body mass index; Change of T2 were presented or transformed as: Follow-up grades – Baseline grades; The reference for categorical exposure variables were non-expose or the lowest grade of PA unless otherwise indicated. PASE: Physical Activity Scale for the Elderly.

Association adjusted	Statistics significance	Adjustment for confounders
#Lateral Posterior (EL vs CL): 0.9 (−6.3 to 8.1) vs 0.0 (−7.2 to 7.2), #Lateral Central(EL vs CL): 1.1 (−8.5 to 10.6) vs −0.7 (−11 to 9.6), #Lateral Anterior(EL vs CL): −0.6 (−13 to 11.8) vs −0.5 (−12.9 to 11.9), *Lateral Posterior(EL vs CL): 0.7 (−6.2 to 7.7) vs 0.8 (−6.2 to 7.9), *Lateral Central(EL vs CL): 0.9 (−5.6 to 7.4) vs 0.6 (−5.4 to 6.5), *Lateral Anterior(EL vs CL): −0.2 (−8.1 to 7.7) vs 0.3 (−7.4 to 8.0), #Medial Posterior (EL vs CL): 0.8 (−5.8 to 7.3) vs 1.2 (−6.8 to 9.2), #Medial Central (EL vs CL): 0.1 (−7.6 to 7.8) vs 0.0 (−9.2 to 9.1), #Medial Anterior (EL vs CL): 0.5 (−8.4 to 9.4) vs 0.9 (−5.4 to 7.2), *Medial Posterior (EL vs CL): −0.1 (−5.9 to 5.7) vs 0.8 (−8.9 to 10.5), *Medial Central (EL vs CL): −0.3 (−12.2 to 11.5) vs 2.5 (−5.4 to 10.3), *Medial Anterior (EL vs CL): 0.9 (−8.4 to 10.2) vs 1.6 (−5 to 8.2),	P= 0.387 P= 0.212 P= 0.959 P= 0.939 P=0.729 P= 0.620 P= 0.705 P= 0.879 P= 0.579 P= 0.296 P= 0.025 ** P= 0.398	No
OA risk population: E1 vs E2 vs E3: Tibio-femoral joint: 46.3 ± 3.0 vs 45.4 ± 2.1 vs 46.3 ± 2.5, #Medial: 50.3 ± 3.1 vs 50.0 ± 3.2 vs 51.1 ± 4.0, #Lateral: 49.0 ± 4.2 vs 48.1 ± 3.0 vs 49.0 ± 3.2, *Medial: 39.1 ± 3.7 vs 38.6 ± 2.5 vs 39.3 ± 2.8, *Lateral: 39.7 ± 3.4 vs 38.1 ± 3.0 vs 40.0 ± 3.1, $: 44.6 ± 4.4 vs 43.1 ± 3.5 vs 44.6 ± 3.7.	 **P= 0.021,** P=0.081, P=0.201, P= 0.368, **P= 0.004,** P= 0.142	Sex, age, and body mass index.
OA risk population: Tibiofemoral joint: 43.3 ± 2.7 vs 44.7 ± 2.4, *Medial: 37.8 ± 3.1 vs 39.4 ± 2.6, *Lateral: 38.8 ± 3.2 vs 39.4 ± 3.3, #Medial: 49.4 ± 3.7 vs 51.0 ± 3.5, #Lateral: 47.5 ± 3.5 vs 49.1 ± 3.3, $: 42.6 ± 3.5 vs 44.5 ± 3.8, No OA risk population: Tibiofemoral joint: 39.8 ± 2.0 vs 41.6 ± 2.8, *Medial: 32.5 ± 1.7 vs 35.4 ± 3.8, *Lateral: 35.5 ± 3.2 ±vs 36.1 ± 3.4, #Medial: 47.0 ± 3.8 vs 49.9 ± 3.4, #Lateral: 44.1 ± 2.6 vs 45.1 ± 3.4, $: 41.5 ± 4.5 vs 42.3 ± 5.4,	 **P= 0.002** **P= 0.007** P=0.247 P=0.004 **P= 0.005** **P=0.011,** **p=0.009,** **P=0.005,** P=0.282 **P=0.010** P=0.360 P=0.897	
#Lateral (least square mean): 2.68 (2.19–3.17) vs 2.20 (1.69–2.71) vs 2.43 (1.94–2.92) *Lateral(least square mean): 2.05 (1.44–2.66) vs 1.82 (1.23–2.41) vs 2.23 (1.60–2.86) #Medial(least square mean): 1.58 (1.09–2.07) vs 1.18 (0.69–1.67) vs 1.39 (0.88–1.90) * Medial(least square mean): 2.12 (1.57–2.67) vs 1.98 (1.43–2.53) vs 2.79 (2.24–3.34) $(least square mean): 3.56 (2.68–4.44) vs 3.10 (2.18–4.02) vs 4.10 (3.22–4.98)		No

Supplementary table 5 Summary of included studies assessing the relationship of physical activity with knee articular joint BML and meniscus pathologies in individuals without OA.

Author, year	FU	Type of exposure	Outcomes
Hartley, C. 2019 (UK)	35; 6 months	Randomly assigned PA (Unilateral, high impact exercise): EL (Exercise leg) versus CL(Control leg)	Change of BML
Tina, L. 2007	186; no	Self-reported PA (Weekly frequency of vigorous PA undertaken for at least 20 minutes): Categorize as never, 1-2 times/week, at least 3 times/week.	Presence of BML
		Self-reported PA, Duration of regular vigorous PA at least 3 times a week (Jogging, swimming, cycling, singles, tennis, aerobics dance, skiing et al.), Categorize as never, 1-2 times/week, at least 3 times/week.	
Frank, G. 1992	97; no	Group control (CP) and marathons runners group(EP).	BML Grade: 0, 1, 2, 3
Virayavanich, W. 2013	115; 3 years	Self-reported PA : Repetitive knee bending exposure	Meniscal lesion (tear or signal abnormality; WORMS ≥ 1) Meniscal tear (WORMS ≥ 2)
			Progression/ change of meniscus score
F Zhang et al. 2017	395; 2.5 years	Self-reported PA : SQUASH, per 1 SD	Medial meniscal extrusion(extruded >=3 mm)

Legends: *Tibial femor # Femur $ Patella; BMI: Body mass index, BML: Bone marrow lesions.

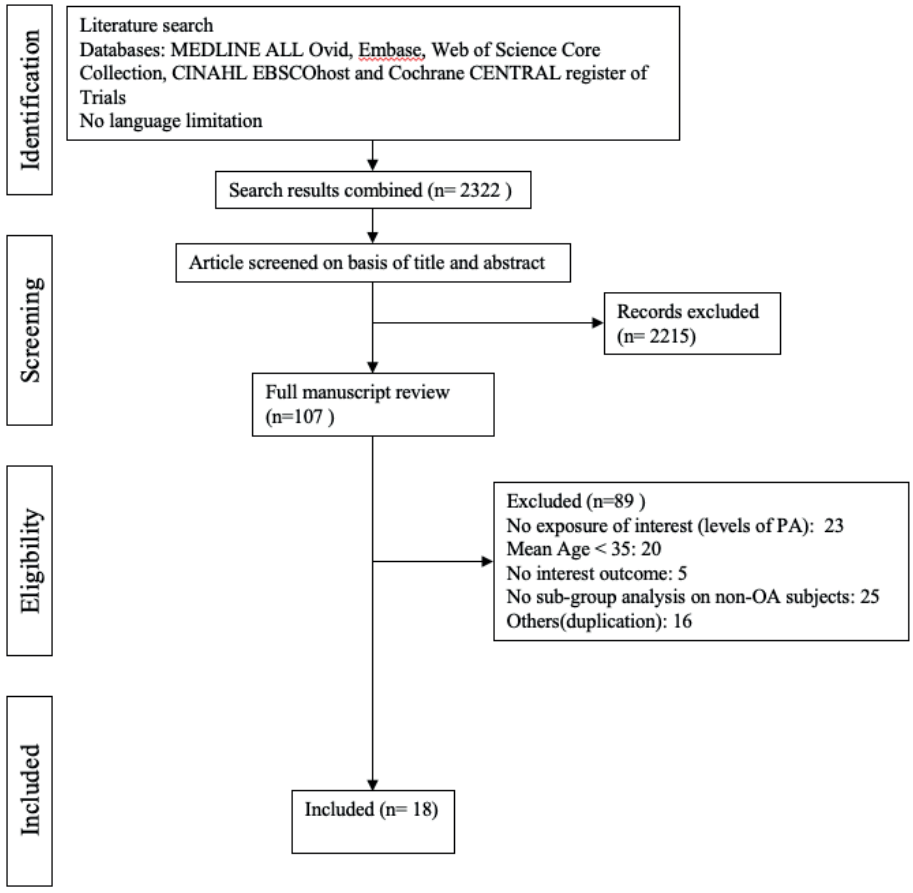
Association adjusted	Statistics significance	Adjustment for confounders
No detailed results were available: The McNemar test showed no significant differences between any of the sub-locations.	NS	No
*(OR): 0.9 (0.6, 1.4)	P = 0.6	Age, sex, tibial cartilage volume, and baseline BMI.
*(OR): 0.9 (0.6, 1.2)	P = 0.4	
CP : 72, 0, 1, 1 EP: 13, 2, 4, 4	No significant difference between groups	No
Overall meniscus OR: 0.78 (0.31, 1.96) Medial meniscus OR: 0.65 (0.26, 1.66) Lateral meniscus OR: 1.89 (0.57, 6.31) Overall meniscus OR: 1.12 (0.43, 2.93) Medial meniscus OR: 1.01 (0.36, 2.81) Lateral meniscus OR: 3.69 (0.43, 31.71)	P= 0.597 P= 0.369 P= 0.279 P= 0.820 P= 0.992 P= 0.171	Sex, age, body mass index, history of knee injury, and knee surgery
Overall meniscus OR: 4.34(1.16, 16.32) Medial meniscus OR: 7.38(1.06, 321.62) Lateral meniscus OR: 2.65 (0.51, 26.65)	**P= 0.015** **P= 0.040** P= 0.359	Sex, age, body mass index, history of knee injury, and knee surgery
Medial (ß): 0.05 (-0.05, 0.15) Lateral (ß): 0.00 (-0.12, 0.11)	P= 0.189 P= 0.382	tibia width

Supplementary table 6. Labels for physical activities in the eligible observational studies. Number represent frequency that each label was assessed against indicated outcome, including citations of the respective studies.

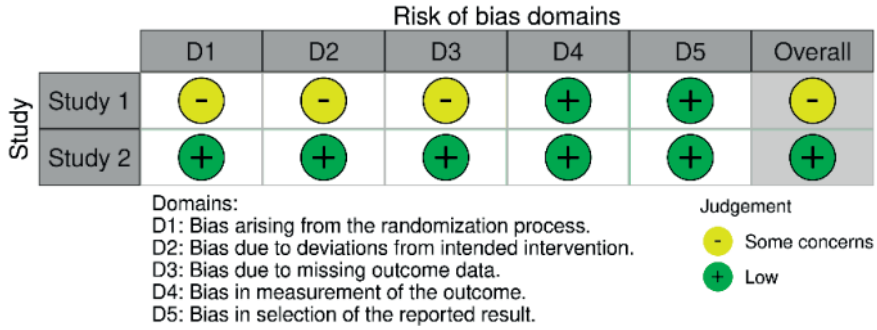
Label in cartilage volume/thickness	cartilage volume/ thickness	Cartilage defects	Cartilage T2-values	BML	Meniscus pathologies
A. Composite score of amount of PA	**2** [43][42]				**1** [29]
B. Light PA	**2**	**1**			
B1 Dichotomous measure of Light/ PA participation	[39]	[39]			
B2 Categorical frequency of Light/PA (c1)	[40]				
C. Vigorous PA	**7**	**8**		**2**	
C1. Dichotomous measure of strenuous/vigorous PA participation	[39][40]	[39]			
C2. Categorical measure of frequency of strenuous/vigorous PA	[33][36]* [38]*	[39][40] [36]*[33] [38]*		[38]*	
D. Dichotomous measure of PA to improve aerobic capacity	**1** [37]				
E. Occupational PA involving knee bending	**11**	**9**	**1**	**1**	**1**
E1. Categorical measure of the frequency of PA involving knee bending	[35]#	[31][35]^			
E2. Dichotomous measure of the frequency of PA involving knee bending	[49]^	[31][34]	[34]	[44]	[31]
E3. Composite measure of amount of PA involving knee bending		[41]			
F. Categorical measure of intensity of PA			**2** [32][34]		

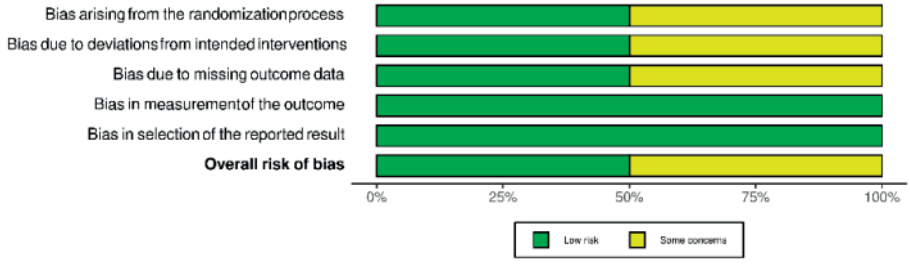
[nr.] is the reference number in the manuscript. PA: physical activity. BML: bone marrow lesions. *: exposure assessed twice. ^: exposure assessed 5 times. #: exposure assessed 6 times.

Supplementary Figure I Flow diagram of the systematic review literature search results

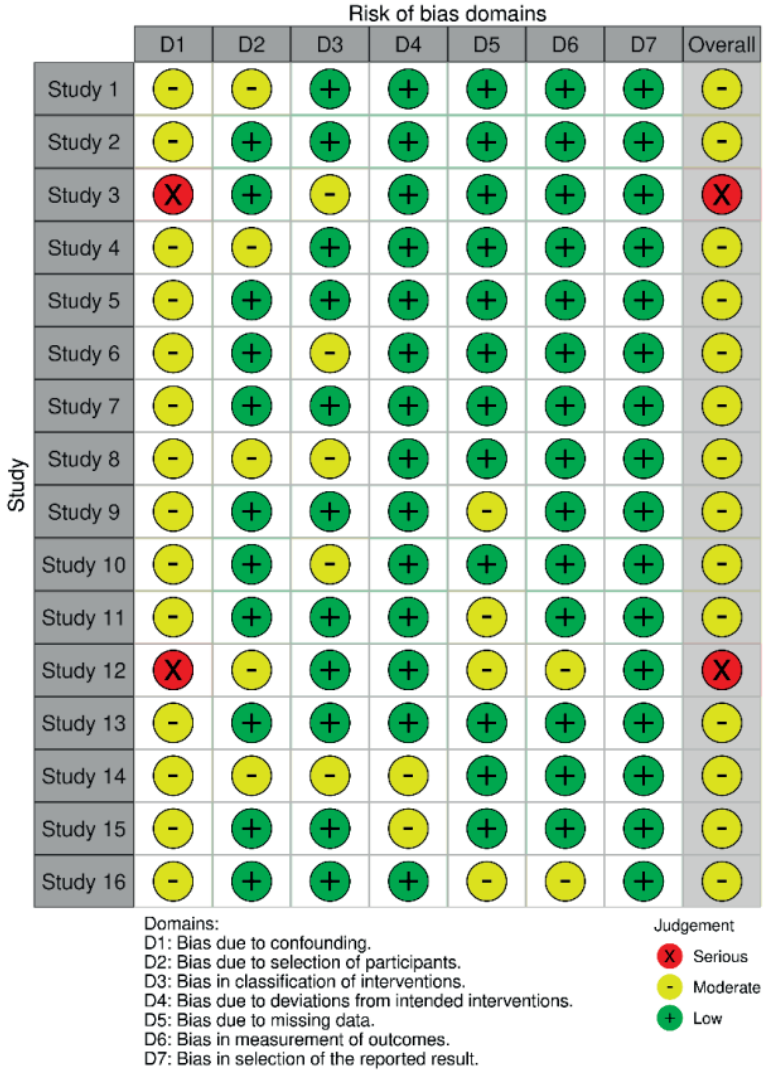


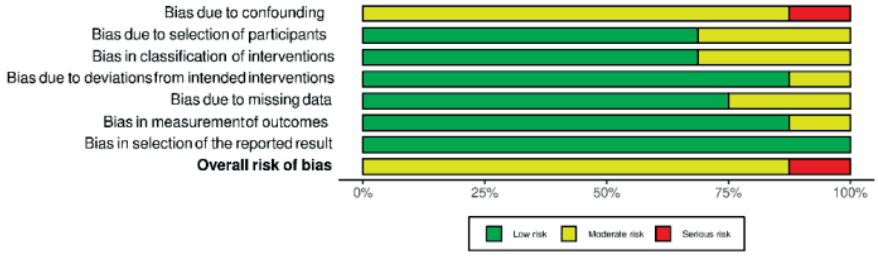
Supplementary Figure 2. Risk of Bias summary for RCTs.





Supplementary Figure 3 Risk of Bias summary for observational studies.





Cochrane CENTRAL register of Trials

((((magnet* OR imaging*) NEAR/3 resonance*) OR mri OR ((nmr OR mr) NEAR/3 (mapping OR imaging))):Ab,ti) AND ((knee OR knees OR patell* OR intrapatella* OR tibiofemor* OR menisc*):Ab,ti) AND ((((physical* OR dynamic) NEAR/3 activ*) OR exercise OR sport* OR running OR cycling OR swimming* OR jumping OR jump OR isokinetic* OR gait OR walking OR walk OR ((resistance OR strength) NEAR/3 training*) OR (weight NEAR/3 (bear* OR lift*)) OR loading OR weightbear* OR weightlift* OR power NEXT lift* OR powerlift* OR (muscle NEAR/3 (training OR strength)) OR flexion OR kinematic* OR athlet* OR runner* OR (leg NEAR/3 (squat OR swing)) OR chain NEXT task*):ab,ti) AND (((normal NEXT human*) OR ((healthy* OR normal) NEXT/6 (adult* OR human* OR person* OR individual* OR Men OR women OR female OR male OR knee OR knees OR subjects OR individuals OR volunteer* OR control* OR athlete* OR runner* OR joint* OR participant*)) OR (free NEAR/3 symptom*) OR early NEXT stage* OR (mild NEAR/6 (oa OR koa OR osteoarthrit*)) OR (kellgren NEAR/3 lawrence NEAR/3 (1 OR 0)) OR pre NEXT oa OR pre NEXT koa OR early NEXT oa OR early NEXT koa):ab,ti)

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TS=(((((magnet* OR imaging*) NEAR/2 resonance*) OR mri OR ((nmr OR mr) NEAR/2 (mapping OR imaging)))) AND ((knee OR knees OR patell* OR intrapatella* OR tibiofemor* OR menisc*)) AND ((((physical* OR dynamic) NEAR/2 activ*) OR exercise OR sport* OR running OR cycling OR swimming* OR jumping OR jump OR isokinetic* OR gait OR walking OR walk OR ((resistance OR strength) NEAR/2 training*) OR (weight NEAR/2 (bear* OR lift*)) OR loading OR weightbear* OR weightlift* OR power-lift* OR powerlift* OR (muscle NEAR/2 (training OR strength)) OR flexion OR kinematic* OR athlet* OR runner* OR (leg NEAR/2 (squat OR swing)) OR chain-task*)) AND ("normal human"/de OR "volunteer"/de OR ((normal-human*) OR ((healthy* OR normal) NEAR/5 (adult* OR human* OR person* OR individual* OR Men OR women OR female OR male OR knee OR knees OR subjects OR individuals OR volunteer* OR control* OR athlete* OR runner* OR joint* OR participant*)) OR (free NEAR/2 symptom*) OR early-stage* OR (mild NEAR/5 (oa OR koa OR osteoarthrit*)) OR (kellgren NEAR/2 lawrence NEAR/2 (1 OR 0)) OR pre-oa OR pre-koa OR early-oa OR early-koa OR non-symptom*)))

CINAHL EBSCOhost

(MH Magnetic Resonance Spectroscopy + OR MH Magnetic Resonance Imaging + OR TI (((magnet* OR imaging*) N2 resonance*) OR mri OR ((nmr OR mr) N2 (mapping OR imaging))) OR AB (((magnet* OR imaging*) N2 resonance*) OR mri OR ((nmr OR mr) N2 (mapping OR imaging)))) AND (Knee+ OR Knee Joint + OR Patella + OR Patellofemoral Joint + OR Osteoarthritis, Knee + OR TI (knee OR knees OR patell* OR intrapatella* OR tibiofemor* OR menisc*) OR AB (knee OR knees OR patell* OR intrapatella* OR tibiofemor* OR menisc*))

AND (MH Sports + OR MH Exercise + OR MH Muscle Strength OR TI (((physical* OR dynamic) N2 activ*) OR exercise OR sport* OR running OR cycling OR swimming* OR jumping OR jump OR isokinetic* OR gait OR walking OR walk OR ((resistance OR strength) N2 training*) OR (weight N2 (bear* OR lift*)) OR loading OR weightbear* OR weightlift* OR power-lift* OR powerlift* OR (muscle N2 (training OR strength)) OR flexion OR kinematic* OR athlet* OR runner* OR (leg N2 (squat OR swing)) OR chain-task*) OR AB (((physical* OR dynamic) N2 activ*) OR exercise OR sport* OR running OR cycling OR swimming* OR jumping OR jump OR isokinetic* OR gait OR walking OR walk OR ((resistance OR strength) N2 training*) OR (weight N2 (bear* OR lift*)) OR loading OR weightbear* OR weightlift* OR power-lift* OR powerlift* OR (muscle N2 (training OR strength)) OR flexion OR kinematic* OR athlet* OR runner* OR (leg N2 (squat OR swing)) OR chain-task*)) AND (TI((normal-human*) OR ((healthy* OR normal) N5 (adult* OR human* OR person* OR individual* OR Men OR women OR female OR male OR knee OR knees OR subjects OR individuals OR volunteer* OR control* OR athlete* OR runner* OR joint* OR participant*)) OR (free N2 symptom*) OR early-stage* OR (mild N5 (oa OR koa OR osteoarthrit*)) OR (kellgren N2 lawrence N2 (1 OR 0)) OR pre-oa OR pre-koa OR early-oa OR early-koa OR non-symptom*) OR AB ((normal-human*) OR ((healthy* OR normal) N5 (adult* OR human* OR person* OR individual* OR Men OR women OR female OR male OR knee OR knees OR subjects OR individuals OR volunteer* OR control* OR athlete* OR runner* OR joint* OR participant*)) OR (free N2 symptom*) OR early-stage* OR (mild N5 (oa OR koa OR osteoarthrit*)) OR (kellgren N2 lawrence N2 (1 OR 0)) OR pre-oa OR pre-koa OR early-oa OR early-koa OR non-symptom*)) NOT (MH animals+ NOT MH humans+)

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CHAPTER 8

General Discussion

Identifying early osteoarthritis (OA)-related structural changes and initiating interventions in OA risk populations is important in the prevention of OA. Meniscus pathologies play an important role in OA development (1, 2). To visualize and quantify geometric parameters for the menisci, 3D-segmentation magnetic resonance imaging (MRI) was used as a common tool (3, 4). Although there was evidence that greater meniscus size was related to the increased risk of OA development (5), the definition of this abnormality of the meniscus was still unclear. Previous research identified a cluster of factors that are related to meniscus pathologies (6, 7). However, the mechanism and clinical implication of the meniscus volume change were rarely addressed in previous research and were therefore studied in this thesis. With the work presented in this thesis, we have assessed the role of meniscus volume in OA development, studied the interaction between meniscus volume and other well-known meniscus pathologies, and have enriched our knowledge on the potential of OA prevention through targeting the meniscus, by exploring risk factors and the effects of potential preventive interventions. These studies led to some overall discussion points that will be considered in this general discussion chapter.

1. A UTILIZED BUT UNCLEAR NOTION: MENISCUS HYPERTROPHY

Comparison of Meniscal Volume in the Literature

In this thesis, we studied the impact of meniscal volume and meniscal volume change on osteoarthritis incidence and progression. It showed that the mean meniscal volume differed across the various study populations. In the high OA risk population of middle-aged overweight females (PROOF study data), the average baseline meniscal volume (medial and lateral) was 1355 ± 314 mm^3 and 1143 ± 256 mm^3, respectively (8). In the lower OA risk population of middle-aged females, which was reported from the general population (the Rotterdam cohort), we found the medial and lateral volumes were 1807 mm^3 and 1583 mm^3, respectively (Chapter 4). Compared to the Rotterdam cohort, subjects in the PROOF study had a higher prevalence of meniscus pathologies at baseline and a higher incidence of OA in the follow-up. We should not however conclude that the low OA risk population had greater meniscal volumes; these two studies also used different MRI machines, which could greatly affect the meniscal volume difference. (Chapter 3, Figure 2)

The adjacent structural findings in the knee may have a limited effect on meniscal volumes. In patients with chondromalacia patellae, the medial meniscal volume was 1928.9 ± 560.7 mm^3; the lateral volume was 1674.9 ± 504.8 mm^3 (9). The selected menisci were without abnormalities and did not show a great difference from the meniscal volume in the Rotterdam study. A within-person comparison in the Osteoarthritis Initiative (OAI) study showed that knees classified by joint space narrowing (JSN) did not show differences in meniscal volumes ((10) Figure 1) The

non-medial JSN group showed the medial volume was 2112 ± 871 mm^3 and the lateral volume was 2001 ± 602 mm^3. In the medial JSN group, the medial and lateral volumes were 1930 ± 747 mm^3 and 1964 ± 652 mm^3 respectively. The large standard deviations in the study may be due to the small sample size. Exceptionally, in the fresh-frozen human cadaver knees (11), the medial meniscal volume could be as high as 2927 ± 118 mm^3, while the lateral was 2801 ± 112 mm^3. The meniscus expansion may be related to reduced tension in adjacent structures such as muscle strength and ligament tightness in the cadaver knee, but there is no data on such effects.

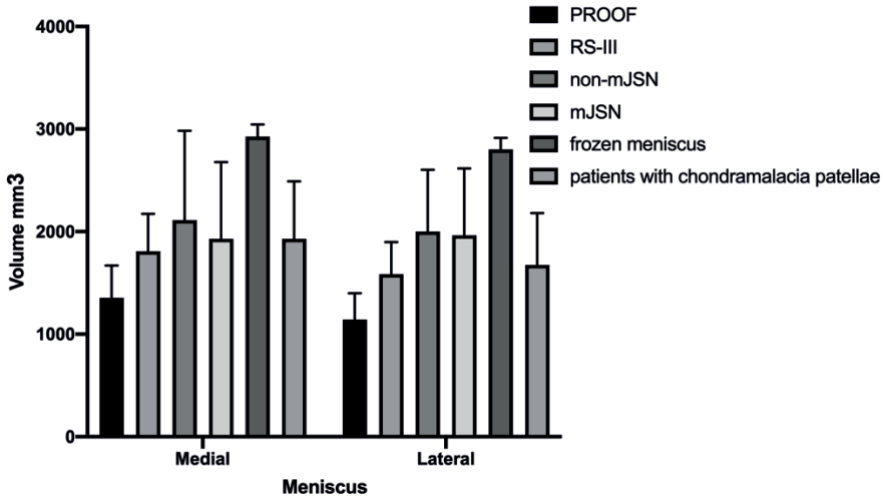
Female subjects generally have smaller meniscus sizes (width and length) than male subjects (12). Currently, no research reported on sex difference in meniscal volume; studies outside of this thesis, which include both male and female subjects, reported a different meniscal volume (Figure 1). The sex difference in volume may be due to the smaller biometrics of the knee joint in women and hormone modulation in middle age which could affect the morphometric features of the meniscus knee joints (13). Previous research indicated that decreasing estrogen levels may lead to an increased risk of OA after menopause (14). However, there was no direct evidence to support the idea that the sex hormone change could modify the meniscal volume. In Chapter 4, we found that a postmenopausal status was also associated with greater loss of meniscal volume over time in the lateral compartment but not with the baseline meniscal volume. In Chapter 6, we did not find an association between postmenopausal status and meniscus extrusion either. The results implied that the higher prevalence of meniscal extrusion may be explained by other mediating factors, such as meniscus tears and a higher BMI. The sex hormone may therefore not directly affect the meniscus size.

In general, the mean volume in current studies ranges from 1143 to 2112 mm^3 and can differ greatly across populations. Numerous factors could potentially have caused these differences. More details for meniscal volume-related factors and potential mechanisms were discussed in Chapter 4 and the following paragraphs. To compare absolute normal meniscal volume across the different populations, a method must be found to standardize the meniscal volume.

The Definition of Meniscus Hypertrophy from Previous Studies

Meniscus hypertrophy has been mentioned in a few previous publications. However, there is no agreement on the criteria for meniscus hypertrophy. According to the MOAKS score system (15), meniscus hypertrophy is defined as an increase in meniscal volume in a given sub-region when compared to normal. The criteria did not define normal meniscal volume, because the 'normal' meniscal volume could be so different. Jung *et al.* also mentioned meniscus hypertrophy after finding a high frequency of medial meniscus hypertrophy in persons with advanced varus knee OA (16, 17). The definition of hypertrophy in their work was still unclear. In 2003, they stated that "hypertrophy" was considered to be present when the height of the

Figure 1. The meniscal volume in published literature. PROOF: high OA risk population of middle-aged overweight females. RS-III: mid to old age women with a relatively low risk of OA; non-m JSN and m JSN knees were selected specifically to permit a between-knee, within-person comparison of painful knees in OAI sub-cohort; Frozen meniscus: fresh-frozen meniscus removed from acute injury from mid to old age subjects; Healthy meniscus from chondromalacia patellae patients were selected from the patient database of the University Hospitals of Pellenberg.



lateral meniscus was 2 mm greater than that of the medial meniscus, regardless of medial meniscus width, using reference values of the normal meniscus height, in which the lateral meniscus is normally smaller than the medial meniscus. In 2009, they stated "hypertrophy" was present when the medial meniscus height was >2 mm greater than that of the lateral meniscus, regardless of medial meniscus width, using reference values of normal meniscus size. They cited the same article which was used to establish standard diameters of the normal medial and lateral menisci in normal subjects by using MRI, but did not actually give a solution for defining meniscus hypertrophy (18). So a challenge still remains in finding the reference value for defining hypertrophy.

Defining a Standard for Meniscal Volume

Defining a normal meniscal volume could be difficult across different populations. For this reason, it is necessary first to standardize the meniscal volume by identifying a good reference value. Naturally, individuals will have different sizes of knee joints. The tibial plateau width depends on the size of the knee of the subject and could serve as a good reference value. The meniscal volume/tibial plateau width could be one option. Similarly, we also proposed using the area of the tibial plate surface which is a two-dimensional measurement. If we use meniscal volume divided by the tibial plateau area, it should be noted that the value is different from the average meniscal height. Because the meniscus does not fully cover the tibial plateau and

can sometimes also be extruded. To define lateral meniscus hypertrophy, previous research set medial meniscus size as a reference (18). However, whether the ratio of medial to lateral volume could be used for standardization remains doubtful. Specifically, the approach might not work when both menisci are affected. Finally, all proposed methods should be tested across different populations, as well as being based on different MRI modalities or segmentation methods from different research teams.

Finding a Cutoff for Meniscus Hypertrophy

Once the meniscal volume is standardized and becomes comparable among populations, setting the cutoff for meniscus hypertrophy becomes possible. Generally, there are two statistical approaches for determining a cutoff value (19): biomarker-oriented and outcome-oriented. The biomarker-oriented approach could split a continuous marker based on percentiles or the distribution of the biomarker. In contrast, the outcome-oriented approach selects the biomarker cutoff that takes into account the association between outcome and biomarker. The cutoff should be determined by the predictive value, which is more appealing for clinical use (20). The cutoff estimated by the outcome-oriented approach can be applied to predicting patient prognosis, while the biomarker-oriented approach may fail to select a cutoff related to the outcome. The outcome-oriented approach is therefore expected to provide a better cutoff value than the biomarker-oriented approach.

The primary step of the outcome-oriented approach is to find the relevant outcomes. Similar to deciding the 'pathological' meniscus extrusion, previous research selected some well-known outcomes, such as K&L grade, cartilage damage, and BMLs (21). For meniscus hypertrophy, one of the outcomes could be radiographic knee OA (K&L ≥2). Secondly, meniscus hypertrophy might be associated with meniscus degeneration. Meniscus lesions detected by the T2 value in MRI could therefore be another outcome. As cartilage composition changes and the cartilage loses its integrity during the process of OA, cartilage damage could be a third outcome. The difficulty in this could be that the structural changes will be less obvious in short term, especially for the low OA risk population. The solution could be an outcome named the SDC method (22), through which the smallest detectable change (SDC) in cartilage volume and thickness in previous studies has been determined, based on test-retest data (23, 24). In an OAI pilot study, the SDC thresholds for medial and lateral tibiofemoral compartment cartilage thickness loss were 102 μm and 92 μm, respectively (25). The SDC outcome method might give a good way of exploring the changes in meniscal volume and could give a more sensitive prediction of disease.

2. THE MECHANISM BEHIND MENISCAL VOLUME CHANGES

From the etiological perspective, the cause of meniscus hypertrophy is complicated. Firstly, in chapters 4 and 5, we found that both local and systematic factors were associated with meniscal volume. Among these, the most important factors were varus alignment and greater BMI, as the results indicated that local mechanistic factors show a dominant association with meniscal volume. Secondly, the hypertrophy in the medial and lateral menisci could be different. Previous research indicated that the medial compartment sustains more weight-bearing stress (26, 27). As we found the majority of local factors were associated with medial meniscal volume, the mechanical pathways may mainly contribute to the medial meniscus hypertrophy. For the lateral meniscus, hypertrophy may mainly be caused by systematic factors like age, post-menopausal status, GDF5, and COG5 SNPs. In addition, like other meniscus pathologies, the etiology of trauma could be the potential reason, as the results of Chapter 4 showed the history of knee injury and meniscus pathologies were associated with greater meniscal volume.

The Mechanism from Local Factors

In response to loading, the meniscal volume could change through many pathways (28). At first, we considered that the meniscus hypertrophy might be a reflection of the loading. In Chapter 3, our results also indicated that in the OA risk population, the meniscus extrusion could also cause meniscal volume to increase. The reason may be that the extruded meniscus partly moves outside of the joint margin and becomes hypertrophic without loading (2). Importantly, we only found that meniscus extrusion was cross-sectionally associated with greater meniscal volume, but not with long-term meniscal volume change. Therefore, in short term, meniscus hypertrophy could be an adaption of increased loading among the non-extruded meniscus. Meniscus hypertrophy might involve temporary swelling, which is possibly associated with the alteration of water content, because the actual water content of menisci is approximately 75%. Meanwhile, glycosaminoglycans (GAGs) hold water within menisci and are responsible for load distribution within the collagen matrix (29). Loading has been shown to temporarily increase the production of GAGs (29, 30), which could increase the hydrostatic and osmotic pressures. The extremely high negative charge present on these molecules attracts counter-ions, drawing water into the tissue (31). However, to prove this hypothesis, we need to analyze not only the change of water content of the knee meniscus, but also the GAG content in the meniscus.

In the long term, the abnormality in the meniscus could lead to meniscus degeneration, which is characterized as the breakdown of collagen fibers. However, whether the degenerated meniscus could cause a greater volume is not clear. Meniscus hypertrophy may share a similar mechanism to meniscus degeneration, as there are studies indicating that meniscus degeneration may be related to more water content (32, 33). However, there are no studies that mentioned this

higher water content as meniscus hypertrophy. Although roughly 70% of the dry weight of the meniscus is collagen (34), the results remain conflicting regarding changes in the content of collagen in menisci with degenerative conditions. Many studies indicated that the collagen fiber network could remain intact and functioning (35-37). It is thus doubtful whether collagen alteration is involved in meniscus hypertrophy. To better understand the interplay between meniscus hypertrophy and degeneration, it will be interesting to explore the association between meniscus hypertrophy and T2 value in the future.

Genetic Mechanism

Previous research concluded that approximately 30%-65% of the OA risk is determined by the genetic variants, which indicates that the meniscal volume could also be genetically determined (38, 39). In Chapter 5, we found both GDF5 and COG5 SNPs to be associated with meniscal volume. Although the GDF5 was widely reported as a genetic OA risk factor (40, 41, 42), there are still limited pathways that could explain the finding in this thesis. As a signaling molecule, GDF5 has been involved in the formation of almost all joint structures, as well as the pathological progression (43). In future experimental research, it will be interesting to explore the effect of GDF5 expression on the meniscus tissue in both biological function and pathological progression (i.e., proliferation and inflammation). Another potential link between GDF5 and meniscal volume is through GAG production. Kentaro *et al.* reported that GDF5 promoted the production of GAG (44), which may be related to greater meniscal volume. However, we found that GDF5 SNP was related to lower lateral meniscal volume. Therefore, whether the effect of GDF5 on meniscal volume could be mediated by the GAG pathway remains doubtful.

Currently, the role of COG5 in OA remains unknown, although it is convincingly associated with the risk of knee OA. COG5 was shown to play a role in cartilage metabolism (45). However, its role in the meniscus is rarely reported. Glycosaminoglycan (GAG) synthesis onto proteoglycan (PG) protein cores takes mostly place in the Golgi apparatus (46, 47). An intact COG complex is essential to normal Golgi structure and function. However, there is no existing evidence showing that COG5 could regulate the production of GAG. In future research, experiments involving the regulation of the GDF5and COG 5 in animal models may discover the causal relationship between these SNPs and meniscus size. Research which focuses on these genetic variants and their downstream products will be helpful to understand the hidden mechanism.

Interaction Between the Volume Change of Meniscus and Cartilage Abnormalities: Cause, Consequence or Co-occurring Features?

Abnormalities in both meniscus and cartilage can be observed in the very early phase of OA development (48, 49). It is very difficult to disentangle the causal relationship between changes in meniscus and cartilage. As meniscus and articulate cartilage have a close embryological and functional relationship (50, 51), dysfunction in the meniscus (pathologies) may lead to increased

biomechanical stress, and could subsequently cause cartilage loss and subchondral bone changes (2). Previous research reported that medial meniscus extrusion causes a decrease in coverage of the tibial plateau, which then leads to an increased load bearing of the cartilage (52, 53). However, in Chapter 3, we did not observe a significant association between greater meniscal volume and cartilage defects (54). The reason could be the cross-sectional design. To better understand the causal relationship between volume change in meniscus and cartilage, longitudinal change of cartilage with pre-existing meniscus hypertrophy is valuable.

Currently, no research reported that cartilage volume loss could cause an increase in meniscal volume. Previous research found that a degenerative meniscus tear is associated with pre-existing articular cartilage changes (49). Theoretically, the cartilage volume loss could cause meniscal volume change during OA development. Both cartilage and meniscus are present in the articular joint space (55), which means meniscus size might expand when cartilage volume is lost over time. Future research, which explores the hypothetical interaction between volume change in meniscus and cartilage volume should consider other local and systematic factors such as malalignment, change in BMI, joint inflammation, etc.

Greater Baseline Volume and Decrease of Volume over Time are both OA Risk Factors: Similarities to the Cartilage

In Chapter 2 we found greater meniscal volume and greater loss of volume over time were both related to higher OA risk. In Chapter 3, we found this greater meniscal volume was associated with greater meniscal volume loss over time. Previous research showed the change in cartilage volume had a similar pattern to the meniscal volume. The swelling of cartilage, in the form of increased volume (56), detected by MRI in early-stage OA, has been shown to correlate with depletion of proteoglycan matrix and cartilage volume loss (57). Early-stage OA is characterized by matrix changes, including a reduction in cellular and proteoglycan content and subsequent water retention and proteoglycan dilution (58). This depletion of the proteoglycan matrix has been closely related to the progression of the OA (56). Literature implied that the prior swelling of cartilage may be due to lower tensile stiffness of the collagen (59). The weakened collagen network is not able to counteract the swelling properties of proteoglycans or proteoglycan-water movement. To replace GAG in early-stage OA, the cartilage may also have the repair capacity known as hypertrophic repair (60, 61). Although the predominance of type I collagen distinguishes the menisci from the articular cartilage (62), the interaction between collagen degeneration and GAG increase could have a similar mechanism. The reason is that type I collagen fibers are radially and circumferentially orientated and could also provide resistance to tensile forces (63). However, as mentioned, these theories are hypothetical and need to be proved in histological measurement in the future.

Interestingly, one study indicated that the regression to the mean effect should be accounted for when evaluating the association between baseline cartilage volume and cartilage loss (64). Regression to the mean is a statistical phenomenon that can make a natural variation in repeated data look like a real change (65). It happens when unusually large or small measurements are followed by measurements that are closer to the mean. The research indicated that unusually high or low initial cartilage volume could be due to various pre-existing factors, such as cartilage random variation due to body size, sex, and co-pathologies (65). Potentially, this phenomenon could also be observed when exploring the association between greater BL meniscal volume and a decrease in volume over time. However, to test this assumption, sub-group analyses are needed in future studies. The cutoff for sub-group analysis could be mean BL meniscal volume.

3. THE POTENTIAL UTILITY OF MENISCUS HYPERTROPHY

Can we call Greater Meniscal Volume an OA Risk Factor, a Biomarker, or a Surrogate Outcome?

The main findings from Chapter 2 were based on an observational design study, which produced a preliminary identification of a greater meniscal volume as a risk factor for incident radiographic knee OA, independent from adjacent structural changes such as cartilage defects, meniscus pathologies, osteophytes, etc. (8). Chapter 4 indicated that meniscus hypertrophy may be partly due to other OA risk factors like high BMI and varus alignment. Therefore, meniscus hypertrophy may be deemed as an early sign of OA onset rather than a risk factor. Based on an approach for the classification of osteoarthritis biomarkers in 2006 (66), the meniscal volume could be deemed to be the prognostic marker for OA. As there was no evidence that the change in meniscal volume could be related to OA severity, it is not clear whether meniscal volume could be classified as a surrogate outcome (67).

There are some further steps to confirm meniscus hypertrophy is an early sign of OA. Firstly, generalizability should be tested in other populations. The results in this thesis are mainly based on female subjects. A similar finding was also reported independent of sex; the research in the mixed sub-cohort of OAI data reported that greater meniscus height was related to the subsequent progression of the OA-related structural changes (68). However, these findings were still based on Caucasian and high-risk OA populations. The generalizability might be tested in other non-high risk and especially different ethnic populations. Secondly, categorization of the meniscal volume is needed. The rationale for categorization is to obtain a clear abnormal volume boundary to either predict OA incidence or to evaluate the effectiveness of some preventative strategies in the early phase of knee OA. We offered potential solutions in the

previous section for identifying meniscus hypertrophy as an outcome-oriented method. (See the third paragraph in the discussion.)

What can we do with this 'Meniscus Hypertrophy'?

Similar to the role of "risk factor" in disease, this early sign of OA can be meaningful when it could answer questions from either risk stratification (prediction) or explanatory mechanisms (69). We discussed the potential mechanism behind meniscal volume change in the previous sections. Thus, the approach to identifying meniscus hypertrophy as an early sign of OA would be meaningful regarding the mechanism exploration for OA development. As we think meniscal volume is a non-modifiable factor, it might be unethical to predict OA by using meniscus hypertrophy when no well-accepted treatment is available yet. However, the prediction approach could be still meaningful to obtain a cutoff for hypertrophy. It is valuable to evaluate the improvement in OA prediction performance gained by adding meniscus hypertrophy as a new predictor. Similar to the quantitative measurement of cartilage volume, the meniscal volume could also serve as a clinical outcome for prevention strategies.

There are also some challenges to identifying meniscus hypertrophy as a clinical outcome by the prediction approach. Firstly, during the development of OA, the meniscus swelling condition may be temporary. In long term, the meniscal volume could diminish by 10% within 2 years of follow-up (70). The results from both the PROOF study and RS-III study also showed that the meniscal volume could decrease over time. Predicting OA risk with meniscus hypertrophy should consider this background of volume decrease. Secondly, there are still many uncertainties that the meniscus in each sub-location may change differently. Meniscus hypertrophy as measured by the global volume may therefore not give precise morphometric features with more complicated information. The statistic shape modeling was recently used to study the association between meniscus shape and incident OA (71). The technique showed promise for obtaining better prediction performance for knee OA. Thirdly, some previously suggested interventions in the prevention of OA might be harmful to meniscal volume, while others do seem to have potential. For example, our results from Chapter 4 found that quadriceps strength was known as an OA protective factor but positively associated with greater meniscal volume. On the other hand, as both greater PA levels and lower BMI were associated with greater meniscal volume, increased PA frequency and control of obesity should be encouraged in the prevention of both meniscus hypertrophy and OA incidence.

4. FINAL REMARKS

Firstly, this thesis explored early OA signs in the meniscus. There is still a long way to go for the early detection and prevention of knee OA. The main results indicated that the abnormalities

in meniscus size can be observed in the early phase of OA development and have the potential to become a prognostic marker for knee OA in the future. Secondly, this thesis explored the potential mechanism of meniscus hypertrophy mainly based on the epidemiology method. However, the fundamental mechanism of meniscus hypertrophy is almost hypothetical and needs further research to explore. Thirdly, in the prevention of OA, there is still some concern regarding the safety of some conservative strategies such as high levels of physical activities. As mentioned in the thesis, PA levels and BMI were both cross-sectionally associated with meniscal volume. More future work should focus on the longitudinal effect of these strategies on the meniscus.

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CHAPTER 9

Summary

Knee osteoarthritis (OA) is a common disease in the aging population and causes a great burden to society worldwide. Identifying early OA changes and initiating interventions in OA risk populations is important. Meniscus pathologies, which include meniscal tears, meniscus extrusion, and meniscal morphometrical abnormalities, play an important role in OA development. However, whether the meniscus volume is associated with incident OA is unknown. In Chapter 2, we assess the association between meniscal volume, its change over time, and the development of knee OA after 30 months in overweight/obese women. Data from the PRevention of knee Osteoarthritis in Overweight Females (PROOF) study was used. The main findings were that medial and lateral baseline (BL) and delta-volumes were not significantly associated with the primary outcome. Lateral meniscal BL volume was significantly associated with lateral joint space narrowing, while other measures were not. Medial and lateral BL volume were positively associated with incident radiographic knee OA, while medial and lateral delta-volume was negatively associated with incident radiographic knee OA. None of the meniscal measures were significantly associated with incident clinical OA. Chapter 2 concluded that larger BL meniscal volume and the decrease of meniscal volume over time were associated with the development of structural OA after 30 months in overweight and obese women.

Based on the main finding in Chapter 2 and other previous literature, abnormalities in meniscal volume and meniscus extrusion coexisted and may interact during OA development. In Chapter 3, we assume an interplay between (changes in) medial meniscus volume, meniscus extrusion and radiographic knee osteoarthritis (OA) development over 30 months of follow-up (FU). Based on PROOF data, the study found that the direct effects of both medial meniscus volume and extrusion at BL on incident OA were statistically significant. Additional indirect effects on incident radiographic OA through delta meniscus volume or delta meniscus extrusion were not statistically significant. The results indicated that BL medial meniscus volume and extrusion were associated with the 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.

Identifying a target population for preventive measures is generally established through identifying its risk factors. However, factors that are related to meniscus morphometrics were rarely reported. In Chapter 4, we explore factors that are associated with meniscus volume in knees free of radiographic OA features and symptoms of OA. In the third Rotterdam Study (RS-III) cohort, clinical, radiographic, and MR data were obtained at BL and after 5 years of follow-up. The study found that varus alignment, higher BMI, meniscus pathologies, meniscus extrusion, cartilage lesions, and injury were significantly associated with greater meniscus volume or meniscus volume loss over time. Also, greater physical activity level, quadriceps muscle strength, and higher age were associated with greater BL meniscus volume or greater volume loss over

time, but the magnitude of these effects was small based on clinical interpretation. Varus alignment, BMI, physical activity level, and quadriceps muscle strength are modifiable factors and could be targeted in the prevention of abnormity in meniscus volume. Those non-modifiable factors such as higher age, injury, meniscus pathologies, meniscus extrusion, and cartilage lesions could provide some mechanism pathway for OA development.

The cause of greater BL meniscal volume is not clear and genetic predisposition could play a role. In Chapter 5, we explore the association between selected single-nucleotide polymorphisms (SNPs) and the volumes of the lateral and medial meniscus. In the PROOF data, we investigated 4 SNPs known to have a relation to OA: DOT1L (rs12982744), COG5 (rs3815148), FTO (rs8044769) and GDF5 (rs78110303). We found that two SNPs were associated with decreased volume in the lateral meniscus, GDF5 (rs78110303) and COG5 (rs3815148). This finding offers a meniscal pathway to understanding why these SNPs are related to OA risk. We thought that the mechanism behind is interesting and needs further investigation in the future.

Decreased estrogen levels in postmenopausal women could alter the integrity of the menisci, leading to the weakening of the meniscal matrix. In Chapter 6, we use the RS-III cohort to evaluate the association between postmenopausal status and meniscus extrusion, a strong risk factor for OA development. In the unadjusted analysis, knees of postmenopausal women compared to premenopausal women showed a borderline significantly higher prevalence of meniscus extrusion at BL and FU. After adjustments, these associations became non-significant. Therefore, 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.

As there are concerns that a high degree of physical activity (PA) may be related to a higher risk of knee OA development, epidemiological studies have been undertaken to examine whether PA has effects on structural changes in the knee. Since the development of OA features on radiography usually takes years, several studies used MRI to capture OA features in the early onset of disease. In Chapter 7, we systematically review all studies that evaluated the association between PA levels and knee OA features on MRI in non-OA subjects. The systematic review analyzed two RCT studies and 16 observational studies. One out of eleven studies found PA was harmfully related to cartilage volume or thickness, but four studies found a significant protective association. Four out of ten studies found that PA was harmfully related to cartilage defects, while others showed no significant associations. Two out of three studies reported a significantly increased cartilage T2 value in individuals with more PA. All three studies reported no significant association between PA and BMLs. Two studies assessed the association between PA and meniscus pathology, of which only occupational PA involving knee bending was associated with a greater risk of progression. Although little evidence was available, the review

suggested that PA was not associated with the presence and progression of OA MRI features among non-OA subjects.

Chapter 8 gives a general discussion of the study results in this thesis. This part discussed the definition and potential utilities of meniscus hypertrophy. More importantly, the potential mechanism and clinical implication for meniscus volume change were discussed. With the findings in this thesis, we get a deeper insight into this meniscus pathology and OA development. The thesis provides new possibilities for the early diagnosis and prevention of knee OA.

CHAPTER 9

Samenvatting

Knieartrose is een veel voorkomende aandoening onder ouderen en levert wereldwijd een grote druk op op de samenleving. Het vroege herkennen van signalen van artrose en het initiëren van interventies in hoog-risicopopulaties is belangrijk. Pathologieën van de meniscus, waaronder meniscusscheuren, meniscus extrusie en vormafwijkingen van de meniscus, spelen een belangrijke rol bij de ontwikkeling van knieartrose. Het is echter niet bekend of het meniscusvolume geassocieerd is met incidentie van knieartrose. In Hoofdstuk 2 beoordelen we het verband tussen (de verandering van) meniscusvolume en de ontwikkeling van knieartrose na 30 maanden bij vrouwen met overgewicht/obesitas. Hiervoor werden gegevens van de 'PRevention of knee Osteoarthritis in Overweight Females (PROOF)' studie gebruikt. De belangrijkste bevindingen waren dat de baseline en de verandering in mediale en laterale meniscusvolumes niet significant geassocieerd waren met de primaire uitkomst. Lateraal meniscus volume op baseline was significant geassocieerd met vernauwing van de laterale gewrichtsspleet, terwijl andere metingen dat niet waren. Mediaal en lateraal volume op baseline waren positief geassocieerd met incidente radiologische knieartrose, terwijl de verandering in mediaal en lateraal volume negatief geassocieerd waren met de incidentie van radiologische knieartrose. Geen van de maten van meniscusvolume was significant geassocieerd met incidente klinische knieartrose. Hoofdstuk 2 concludeerde dat een groter baseline meniscusvolume en de afname van het meniscusvolume over de tijd geassocieerd waren met de ontwikkeling van structurele artrose na 30 maanden bij vrouwen met overgewicht en obesitas.

Gebaseerd op de belangrijkste bevinding uit Hoofdstuk 2 en de literatuur werd verondersteld dat afwijkingen in meniscusvolume en meniscus extrusie naast elkaar voor zouden kunnen komen en dat ze elkaar zouden kunnen versterken in het risico op het ontwikkelen van knieartrose. In Hoofdstuk 3 gaan we uit van een wisselwerking tussen (veranderingen in) mediaal meniscusvolume, meniscus extrusie en de ontwikkeling van radiologische knieartrose gedurende 30 maanden follow-up. Op basis van PROOF studie bleek dat de directe effecten van mediaal meniscusvolume en van extrusie bij baseline op incidente artrose statistisch significant waren. De indirecte effecten op incidente radiologische artrose via de verandering in meniscusvolume of de verandering in meniscus extrusie waren niet statistisch significant. De resultaten gaven aan dat baseline mediaal meniscusvolume en extrusie geassocieerd waren met de incidentie van radiologische knieartrose na 30 maanden bij vrouwen van middelbare leeftijd met overgewicht en obesitas, terwijl de veranderingen in deze factoren over de tijd niet extra bijdroegen. Om artrose van de knie te voorkomen moeten interventies mogelijk dus gericht zijn op het ontstaan van pathologieën van de meniscus, in plaats van op de progressie van deze pathologieën.

Het identificeren van een doelpopulatie voor preventieve maatregelen wordt over het algemeen gedaan via het identificeren van risicofactoren. Factoren die verband houden met volume veranderingen van de meniscus zijn echter zelden gerapporteerd. In Hoofdstuk 4 onderzoeken we factoren die verband houden met het volume van de meniscus in knieën zonder radiologische

artrose kenmerken en zonder symptomen van knieartrose. In het derde cohort van de Rotterdam Studie (RS-III) werden klinische, radiologische en MRI gegevens verkregen op baseline en na 5 jaar follow-up. Uit deze studie bleek dat een varus stand, hoger BMI, pathologieën van de meniscus, meniscus extrusie, kraakbeenlaesies en knie trauma significant geassocieerd waren met een groter meniscusvolume of afname van het meniscusvolume over de tijd. Ook werden meer lichamelijke activiteit, meer spierkracht van de quadriceps en een hogere leeftijd in verband gebracht met een groter meniscusvolume op baseline of een groter volumeverlies over de tijd, maar deze effecten waren slechts klein. Een varus stand, hoger BMI, meer lichamelijke activiteit en meer spierkracht van de quadriceps zijn beïnvloedbare factoren waarop behandelingen zich kunnen richten ter voorkoming van afwijkingen in het meniscusvolume. Die niet-beïnvloedbare factoren, zoals hogere leeftijd, knie trauma, pathologieën van de meniscus, meniscus extrusie en kraakbeenlaesies zouden mechanismes kunnen zijn die de associatie tussen meniscus volume en de ontwikkeling van knieartrose verklaren.

De oorzaak van een groter meniscusvolume is niet duidelijk en genetische aanleg zou een rol kunnen spelen. In Hoofdstuk 5 onderzoeken we de associatie tussen geselecteerde single-nucleotide polymorphisms (SNPs) en de volumes van de mediale en laterale meniscus. In de PROOF data hebben we vier SNPs onderzocht waarvan bekend is dat ze een relatie hebben met knieartrose: DOT1L (rs12982744), COG5 (rs3815148), FTO (rs8044769) en GDF5 (rs78110303). We ontdekten dat twee SNPs geassocieerd waren met een verminderd volume in de laterale meniscus, namelijk GDF5 (rs78110303) en COG5 (rs3815148). Deze bevinding biedt een mogelijk werkingsmechanisme waardoor deze SNPs gerelateerd zijn aan het ontwikkelen van knieartrose. Deze interessante nieuwe bevinding moet in de toekomst verder worden onderzocht.

Verlaagde oestrogeenspiegels bij postmenopauzale vrouwen kunnen de integriteit van de menisci veranderen, wat leidt tot verzwakking van de meniscusmatrix. In Hoofdstuk 6 gebruiken we het RS-III-cohort om de associatie tussen postmenopauzale status en meniscus extrusie, een sterke risicofactor voor knieartrose, te evalueren. De knieën van postmenopauzale vrouwen, in vergelijking met premenopauzale vrouwen, vertoonden een hogere prevalentie van meniscus extrusie op baseline en follow-up. Na correctie voor mogelijke confounders bleken deze associaties echter niet-significant. Daarom is er geen bewijs gevonden dat postmenopauzale vrouwen een verhoogd risico hebben op meniscus extrusie. Waarschijnlijk wordt de hogere prevalentie van meniscus extrusie bij postmenopauzale vrouwen verklaard door mediërende factoren, zoals meniscusscheuren en een hogere BMI.

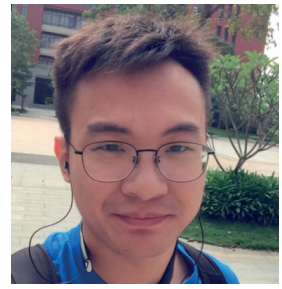
Aangezien er bezorgdheid bestaat dat een hoge mate van fysieke activiteit verband kan houden met een hoger risico op de ontwikkeling van knieartrose, zijn er epidemiologische onderzoeken uitgevoerd om te onderzoeken of fysieke activiteit effecten heeft op structurele veranderingen

in de knie. De ontwikkeling van artrosekenmerken op radiologie duurt echter jaren en daarom hebben verschillende onderzoeken MRI gebruikt om artrosekenmerken in een vroeg stadium van de ziekte te detecteren. In Hoofdstuk 7 bespreken we systematisch alle onderzoeken die de associatie tussen fysieke activiteit en kenmerken van knieartrose op MRI bij mensen zonder knieartrose bestudeerden. Eén van de elf onderzoeken naar kraakbeenvolume en kraakbeendikte vond dat fysieke activiteit een negatief effect had, maar vier onderzoeken vonden een significant beschermend verband. Vier van de tien studies vonden een negatief effect van fysieke activiteit op kraakbeendefecten, terwijl de andere studies geen significante effecten aantoonden. Twee van de drie studies toonden een significante toename in T2-waarde in meer fysiek actieve individuen. Alle drie beschikbare studies toonde geen associatie tussen fysieke activiteit en beenmerglaesies aan. Twee studies onderzochten de associatie tussen fysieke activiteit en meniscus pathologieën, waarin alleen werk-gerelateerde fysieke activiteit met kniebuigingen geassocieerd was met verergering van de afwijkingen. De systematische review concludeerde dat, hoewel er maar weinig bewijs beschikbaar was, fysieke activiteit niet geassocieerd is met de aanwezigheid en progressie van knieartrose kenmerken op MRI bij mensen zonder knieartrose.

Hoofdstuk 8 geeft een algemene discussie van de onderzoeksresultaten in dit proefschrift. Dit hoofdstuk bespreekt de definitie en mogelijke toepassingen van veranderingen in het meniscusvolume. Belangrijker nog, het mogelijke werkingsmechanisme en de klinische implicaties van verandering in het meniscusvolume worden besproken. Met de bevindingen in dit proefschrift wordt er een dieper inzicht verkregen in deze pathologie van de meniscus en de daarmee samenhangende ontwikkeling van knieartrose. Het proefschrift biedt nieuwe mogelijkheden voor vroege diagnose en mogelijke preventie van knieartrose.

APPENDICES

ABOUT THE AUTHOR



Dawei Xu was born on 27th Feb. of 1992 in Hengyang city, China. He graduated from the No.8 high school in Hengyang in 2010. After that, He finished his Bachelor's degree in Medicine at the University of South China for 5 years including a 1-year residency rotation at Second Xiangya hospital from Central South University. From 2015 to 2018, he finished his Master of Science program at Sun Yat-sen University (Guangzhou, China). He was doing research on the mechanism of rheumatoid arthritis disease and ischemic reperfusion injury in shock. During the years he was working as a researcher at Guangzhou Medical school and Weil critical care medicine institute (Guangzhou branch).

In 2018, he began his Ph.D. training in Rotterdam, the Netherlands. In ErasmusMC, he started his project which was supervised by prof. dr. Sita Bierma-Zeinstra and prof.dr. Jos Runhaar. The research was mainly focused on meniscus pathologies in OA development. In 2021, he obtained a Master of Science (MSc) degree in Clinical Epidemiology at the Netherlands Institute for Health Sciences (NIHES, Erasmus MC Rotterdam).

Dawei met his wife Xi in 2017, whom he married in 2020. They live in Hengyang, Changsha, Guangzhou, and Rotterdam. They have their baby at Cappella aand isslel and then give birth to the baby Maotang in Hengyang city in 2021. Now they have their new life in Guangzhou City.

LIST OF PUBLICATIONS

(https://www.researchgate.net/profile/Dawei-Xu-11)

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PHD PORTFOLIO

Name PhD student	Dawei Xu
Departments	General Practice
Research school	NIHES
PhD period	September 2018 – October 2022
Promotor	Prof. dr. S. M. A. Bierma-Zeinstra
Co-promotor	Dr. J. Runhaar

Activities	**Years**	**Workload (ECTS*)**
PHD training		
General courses		
Master of Science in Clinical Epidemiology, NIHES, Rotterdam	2019-2021	70
Course on Scientific Integrity, Erasmus MC, Rotterdam		0.3
Seminars/workshops/conferences		
Osteoarthritis Research Society International (OARSI) World Congress, Online (Poster)	2020	1
OARSI World Congress, Online (Oral)	2021	1
OARSI World Congress, Berlin (Poster)	2022	1
The International Workshop on Osteoarthritis Imaging (IWOAI) (Oral)	2019	1
IWOAI, Rotterdam	2021	1
Other activities		
Oral presentation in spreekkammer	2018-2021	
Oral presentation in ACE Bone & Joint meeting	2018-2021	

1 ECTS (European Credit Transfer System) is equal to workload of 28 hours.

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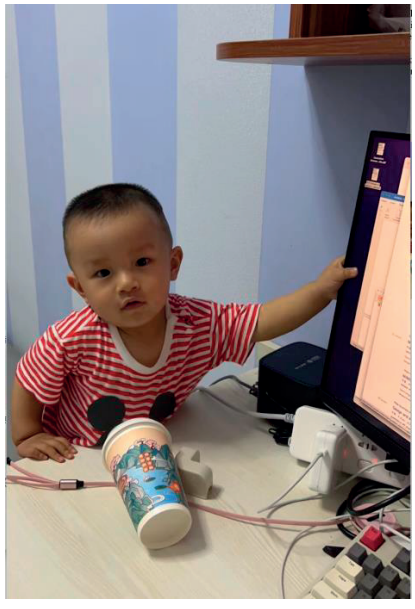

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Dawei Xu
Rotterdam & Guangzhou City
September, 2022

2023