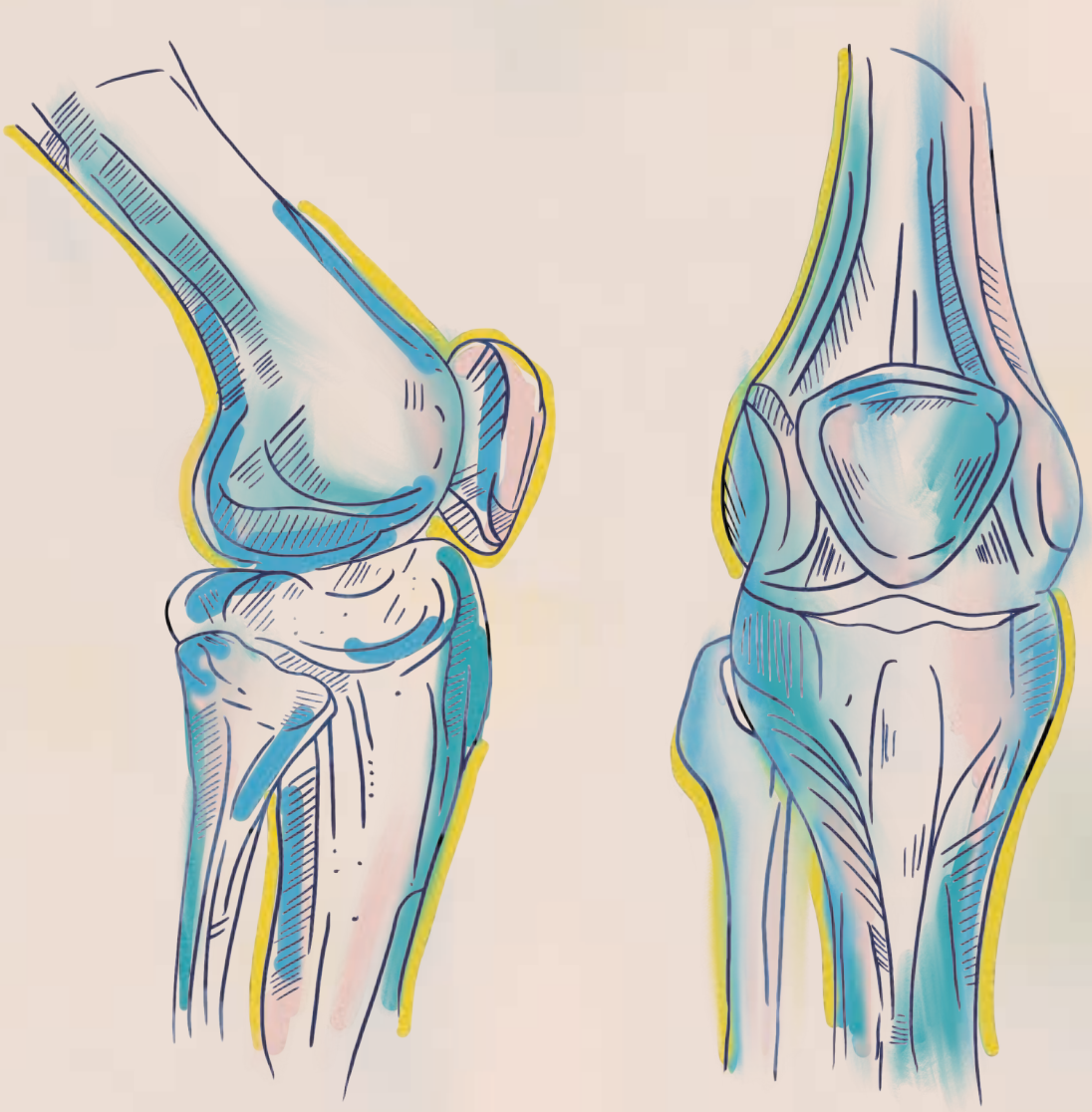
Patellofemoral pain and osteoarthritis

the role of shape and alignment



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Patellofemoral pain and osteoarthritis, the role of shape and alignment

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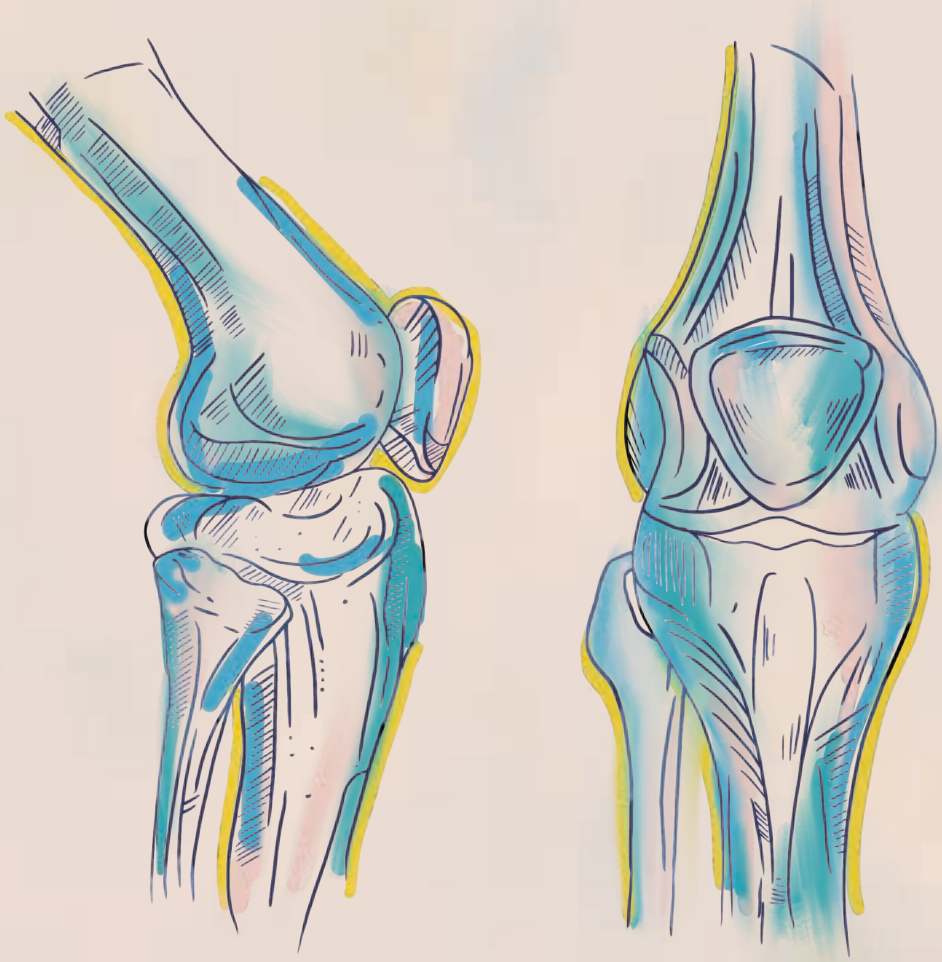
Contents



Chapter 1

General introduction

General introduction

Patellofemoral pain

Patellofemoral pain (PFP), commonly referred to as patellofemoral pain syndrome (PFPS) or anterior knee pain (AKP), is a common knee complaint in both active and sedentary individuals. PFP is characterized by pain behind the patella, often triggered by activity in the patellofemoral joint (i.e., running, squatting, stair climbing, cycling) or prolonged sitting[1]. Symptoms of PFP include crepitus, feeling of giving way, stiffness and sensations of swelling[2]. These symptoms often result in reduced physical activity, potentially reducing the quality of life and fitness of individuals with PFP[3]. Particularly interesting is the relatively high prevalence in adolescents and young adults compared to other musculoskeletal disabilities. Prevalence rates between 7-28% have been reported, with the highest prevalence in adolescent women[1,4].

Patellofemoral Osteoarthritis

Patellofemoral osteoarthritis (PFOA), a subdivision of knee osteoarthritis (OA), has very similar symptoms and characteristics as PFP. PFOA is also characterized by pain behind the patella, especially during stair walking, although not all patients with PFOA have these complaints. Young individuals with knee complaints are often diagnosed with PFP, while older patients are diagnosed with PFOA. This difference is partially due to age being one of the diagnostic criteria for knee OA[5]. Therefore, PFOA is more prevalent in older aged individuals compared to PFP, with again a higher prevalence in women[6].

Disease Continuum

Several key figures in the PFP and PFOA research fields have raised the hypothesis that PFP might be a precursor to PFOA[7–9]. The disease continuum hypothesis is supported by multiple factors. Firstly, there is an overlap in symptoms (*i.e.,* anterior knee pain, painful crepitus, pain with stair climbing, pain with prolonged sitting)[10–13]. Secondly, there is an overlap in biomechanical risk factors (*i.e.,* patellofemoral joint malalignment, patellofemoral joint maltracking and quadriceps dysfunction)[13–16]. Thirdly, there is an overlap in more general risk factors such as female sex[12,17]. However, direct associations between PFP and PFOA to support the disease continuum hypothesis have been elusive because of the lack of longitudinal data[7]. Moreover, structural abnormalities associated with the presence of PFOA on MRI have not been related to the presence of PFP[18]. Interestingly, some structural abnormalities related to OA are already seen in both young PFP patients but also in matched healthy controls. We hypothesize that because of the multifactorial nature of PFP there might be some specific subgroups in which structural abnormalities associated with PFOA are already present in young individuals with PFP[19]. These potential subgroups are of specific interest because of possible further research into the pathogenesis of PFP and insights in the possible disease continuum to PFOA.

Alignment and Shape

To gain a better insight in the possible continuum of PFP to PFOA we focused on alignment and shape in this thesis. Alignment and shape have been used quite interchangeably in the literature; I use this terminology as following. Alignment describes the relative position from one structure compared to another structure, for example, the Insall-Salvati ratio describes the relative position between the femur and the patella. Shape measures describe the shape of a single structure, such as the shape of the patella by itself or the sulcus depth on the femoral head.

While biomechanical factors influencing joint loading such as muscle strength and joint alignment have both been well documented[13,20], the association of joint shape with PFOA and especially PFP has been understudied. Furthermore, a bone shape model in which both PFOA and PFP subjects are represented, was missing from the literature. Because PFOA and PFP have overlapping biomechanical risk factors, and joint shape has been understudied in this population, we question ourselves whether joint shape might be a factor in the continuum of PFP and PFOA.

Statistical shape modelling

To investigate bone shape, we used statistical shape modeling (SSM), both in 2D and in 3D. SSM is a powerful and versatile method used in various fields such as computer vision, biology and medical imaging[21,22]. Essentially, SSM is a mathematical approach that enables us to analyze and understand the variability and patterns within the shapes of an object (*i.e.,* patella). SSM is a more powerful technique compared to traditional means of shape description, offering a statistical tool which allows quantification of shape variations within a population. SSM has been thoroughly used in research, showing cam impingement is related to osteoarthritis[23] and showing bone shape features related to PFOA[24].

Scope and outline of this thesis

The scope of this thesis is to better understand the role of biomechanical risk factors in PFP and PFOA. We therefore study several biomechanical risk factors and investigate if overlap exist in biomechanical risk factors between PFP and PFOA populations. In **Chapter 2**[16] we examine whether radiographic signs of OA are associated with patellofemoral joint alignment and in **Chapter 3**[25] we investigate the association between clinical symptoms and radiographic signs of OA, both in a young PFP population. In **Chapter 4**[26] we examine a possible association between both PFP, PFOA and 2D patellar shape. **Chapter 5** describes the association between 3D patellar shape and prevalence of PFP, in addition to the association of radiographic signs of OA. Lastly, **Chapter 6** shows associations between 3D patellar shape and PFOA[27].

References

1. Crossley KM, van Middelkoop M, Callaghan MJ, Collins NJ, Rathleff MS, Barton CJ. 2016 Patellofemoral pain consensus statement from the 4th International Patellofemoral Pain Research Retreat, Manchester. Part 1: Terminology, definitions, clinical examination, natural history, patellofemoral osteoarthritis and patient-reported outcome m. *Br J Sports Med*. Published online 2016:bjsports-2016-096268. doi:10.1136/bjsports-2016-096268

2. Thomeé R, Augustsson J, Karlsson J, Thomee R. Patellofemoral pain syndrome: a review of current issues. *Sport Med*. 1999;28(4):245-262.

3. Rathleff MS, Rathleff CR, Olesen JL, Rasmussen S, Roos EM. Is Knee Pain During Adolescence a Self-limiting Condition? Prognosis of Patellofemoral Pain and Other Types of Knee Pain. *Am J Sports Med*. 2016;44(5):1165-1171. doi:10.1177/0363546515622456

4. Smith BE, Selfe J, Thacker D, et al. Incidence and prevalence of patellofemoral pain: A systematic review and meta-analysis. *PLoS One*. 2018;13(1):1-18. doi:10.1371/journal.pone.0190892

5. Skou ST, Koes BW, Grønne DT, Young J, Roos EM. Comparison of three sets of clinical classification criteria for knee osteoarthritis: a cross-sectional study of 13,459 patients treated in primary care. *Osteoarthr Cartil*. 2020;28(2):167-172. doi:10.1016/j.joca.2019.09.003

6. Lankhorst NE, Damen J, Oei EH, et al. Incidence, prevalence, natural course and prognosis of patellofemoral osteoarthritis: the Cohort Hip and Cohort Knee study. *Osteoarthr Cartil*. 2017;25(5):647-653. doi:10.1016/j.joca.2016.12.006

7. Crossley KM. Is patellofemoral osteoarthritis a common sequela of patellofemoral pain? *Br J Sports Med*. 2014;48(6):409-410. doi:10.1136/bjsports-2014-093445

8. Witvrouw E, Callaghan MJ, Stefanik JJ, et al. Patellofemoral pain: consensus statement from the 3rd International Patellofemoral Pain Research Retreat held in Vancouver, September 2013. *Br J Sports Med*. 2014;48(1):411-414. doi:10.1136/bjsports-2014-093450

9. Utting MR, Davies G, Newman JH. Is anterior knee pain a predisposing factor to patellofemoral osteoarthritis? *Knee*. 2005;12(5):362-365. doi:10.1016/j.knee.2004.12.006

10. Schiphof D, Van Middelkoop M, De Klerk BM, et al. Crepitus is a first indication of patellofemoral osteoarthritis (and not of tibiofemoral osteoarthritis). *Osteoarthr Cartil*. 2014;22(5):631-638. doi:10.1016/j.joca.2014.02.008

11. Peat G, Duncan RC, Wood LR, Thomas E, Muller S. Clinical features of symptomatic patellofemoral joint osteoarthritis. *Arthritis Res Ther*. 2012;14(2):R63. doi:10.1186/ar3779

12. Lankhorst NE, A Bierma-Zeinstra SM, Middelkoop M van. Factors associated with patellofemoral pain syndrome: a systematic review. *Br J Sport Med*. 2013;47:193-206. doi:10.1136/bjsports-2011-090369

13. Mills K, Hunter DJ. Patellofemoral joint osteoarthritis: An individualised pathomechanical approach to management. *Best Pract Res Clin Rheumatol*. 2014;28(1):73-91. doi:10.1016/j.berh.2014.01.006

14. Sheehan FT, Derasari A, Fine KM, Brindle TJ, Alter KE. Q-angle and J-sign: Indicative of maltracking subgroups in patellofemoral pain. *Clin Orthop Relat Res*. 2010;468(1):266-275. doi:10.1007/s11999-009-0880-0

15. Sheehan FT, Derasari A, Brindle TJ, Alter KE. Understanding patellofemoral pain with maltracking in the presence of joint laxity: Complete 3D in vivo patellofemoral and tibiofemoral kinematics. *J Orthop Res*. 2009;27(5):561-570. doi:10.1002/jor.20783

16. Eijkenboom JFA, van der Heijden RA, de Kanter JLM, Oei EH, Bierma-Zeinstra SMA, van Middelkoop M. Patellofemoral alignment and geometry and early signs of osteoarthritis are associated in patellofemoral pain population. *Scand J Med Sci Sport*. 2020;30(5):885-893. doi:10.1111/sms.13641

17. van Middelkoop M, Bennell KL, Callaghan MJ, et al. International patellofemoral osteoarthritis consortium: Consensus statement on the diagnosis, burden, outcome measures, prognosis, risk factors and treatment. *Semin Arthritis Rheum*. Published online 2017:1-10. doi:10.1016/j.semarthrit.2017.09.009

18. van der Heijden RA, de Kanter JLM, Bierma-Zeinstra SMA, et al. Structural Abnormalities on Magnetic Resonance Imaging in Patients With Patellofemoral Pain: A Cross-sectional Case-Control Study. *Am J Sports Med*. 2016;44(9):2339-2346. doi:10.1177/0363546516646107

19. Selfe J, Janssen J, Callaghan M, et al. Are there three main subgroups within the patellofemoral pain population? A detailed characterisation study of 127 patients to help develop targeted intervention (TIPPs). *Br J Sports Med*. Published online 2016:bjsports-2015-094792. doi:10.1136/bjsports-2015-094792

20. van Middelkoop M, Macri EM, Eijkenboom JF, et al. Are Patellofemoral Joint Alignment and Shape Associated With Structural Magnetic Resonance Imaging Abnormalities and Symptoms Among People With Patellofemoral Pain? *Am J Sports Med*. 2018;46(13):3217-3226. doi:10.1177/0363546518801314

21. Cootes TF, Edwards GJ, Taylor CJ. Active appearance models. *IEEE Trans Pattern Anal Mach Intell*. 2001;23. doi:10.1109/34.927467

22. Cootes TF. Statistical Models of Appearance for Computer Vision. 2004;M(1):175-200. doi:10.1.1.58.1455

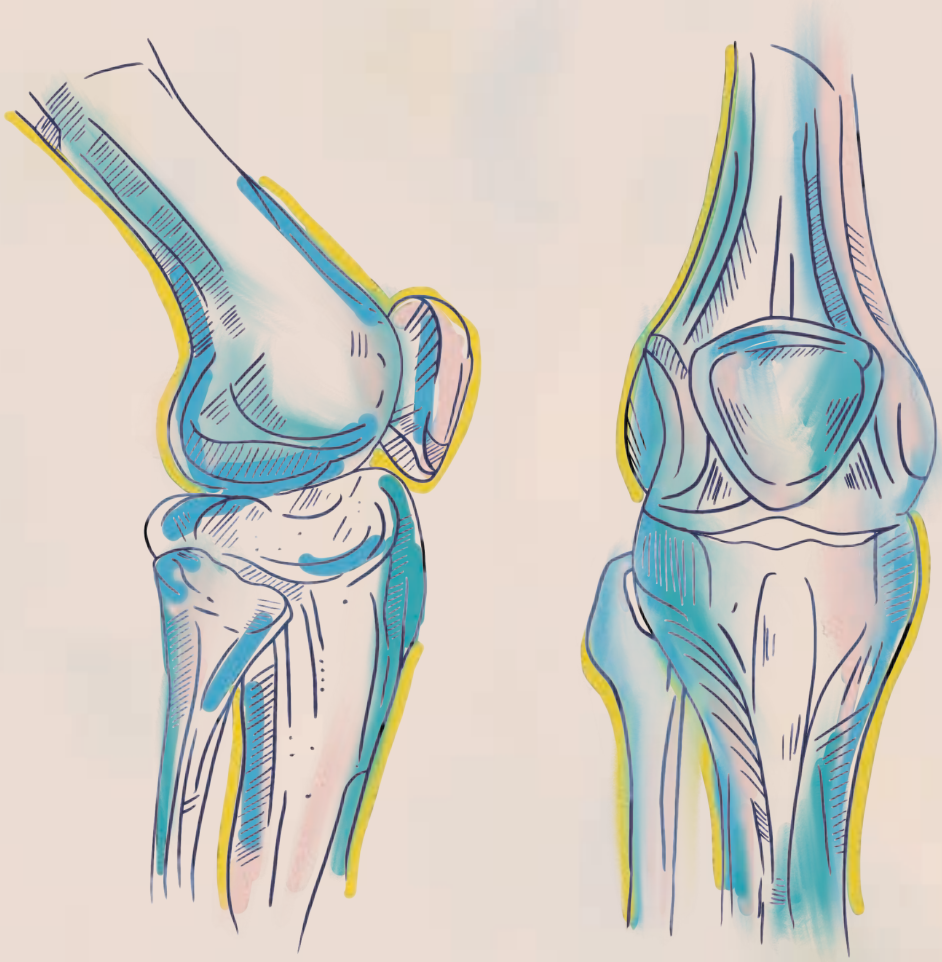
23. Agricola R, Heijboer MP, Bierma-Zeinstra SM a., Verhaar J a. N, Weinans H, Waarsing JH. Cam impingement causes osteoarthritis of the hip: a nationwide prospective cohort study (CHECK). *Ann Rheum Dis*. Published online 2012:918-923. doi:10.1136/annrheumdis-2012-201643

24. Liao TC, Jergas H, Tibrewala R, et al. Longitudinal analysis of the contribution of 3D patella and trochlear bone shape on patellofemoral joint osteoarthritic features. *J Orthop Res*. 2021;39(3):506-515. doi:10.1002/jor.24836

25. Eijkenboom JFA, Timmer ER, Van Heijden RAD, et al. Association between self-reported measures, physical examination, and early magnetic resonance imaging signs of osteoarthritis in patients with patellofemoral pain. *J Orthop Sports Phys Ther*. 2019;49(9):634-639. doi:10.2519/jospt.2019.8889

26. Eijkenboom JFA, Waarsing JH, Oei EHG, Bierma-Zeinstra SMA, Van Middelkoop M. Is patellofemoral pain a precursor to osteoarthritis? *Bone Jt Res*. 2018;7(9):541-547. doi:10.1302/2046-3758.79.BJR-2018-0112.R1

27. Eijkenboom JFA, Tümer N, Schiphof D, et al. 3D patellar shape is associated with radiological and clinical signs of patellofemoral osteoarthritis. *Osteoarthr Cartil*. 2023;31(4):534-542. doi:10.1016/j.joca.2022.12.008



Chapter 2

Patellofemoral alignment and geometry and early signs of osteoarthritis are associated in patellofemoral pain population

Joost J.F.A. Eijkenboom, Rianne A. van der Heijden, Janneke L.M. de Kanter, Edwin H.G. Oei, Sita M.A. Bierma-Zeinstra, Marienke van Middelkoop

Scand J Med Sci Sports. 2020 May;30(5):885-893

Abstract

Background: Patellofemoral pain (PFP) patients show increased prevalence of patellar malalignment. Structural and alignment abnormalities of the patellofemoral joint (PFJ) may play a role in development of PFP and patellofemoral osteoarthritis (PFOA).

Objectives: Evaluating associations of patellofemoral alignment and femoral geometry with bony and cartilaginous abnormalities in PFP patients and healthy control subjects.

Methods: Data from a case-control study were used (64 PFP subjects, 70 control subjects, 57% female, age 23.2(6.4)). Alignment and femoral geometry measures in the PFJ were determined using MRI. Structural abnormalities in the PFJ associated with OA (bone marrow lesions, osteophytes, minor cartilage defects and Hoffa synovitis), quantified cartilage composition (T1ρ relaxation times) in the PFJ and perfusion within the patellar bone were examined using different MRI techniques. Associations were analysed using regression analyses, adjusted for potential confounders.

Results: Lateral patellar tilt was negatively associated with presence of osteophytes on both patella (OR 0.91; 95%CI 0.84 to 0.98), anterior femur (OR 0.92; 95%CI 0.84 to 0.99) and minor cartilage defects on patella (OR 0.91; 95%CI 0.84 to 0.99). Patella alta was positively associated with presence of bone marrow lesions in the patella and minor cartilage defects (OR 48.33; 95%CI 4.27 to 547.30 and OR 17.51; 95%CI 1.17 to 262.57, respectively).

Patella alta and medial patellar translation were positively associated with T1ρ relaxation times within trochlear cartilage (β 5.2; 95%CI 0.77 to 9.58, and 0.36; 95%CI 0.08 to 0.64 respectively). None of the alignment and geometry measures was associated with bone perfusion.

Conclusion: Our study implies that associations between patellofemoral alignment and geometry and structural joint abnormalities linked to OA are already present in both PFP patients and healthy control subjects.

Introduction

Patellofemoral pain (PFP) is a common knee complaint, especially in active adolescents and runners[1]. Contrary to earlier beliefs, increasing evidence suggests that PFP is not a self-limiting disease[2,3]. Different treatment strategies are applied in the treatment of PFP, including strengthening exercises, taping and orthoses, but the reported effects are small to moderate[4–6]. In order to optimize treatment outcomes, there is need to elucidate the pathogenesis of PFP. There is overall consensus that the pathogenesis of PFP is multifactorial: numerous factors associated with PFP have been reported in literature, but the interaction between these proposed risk factors and the clinical entity of PFP remains unclear[7].

In a recent study several novel magnetic resonance imaging (MRI) techniques were applied to gain more insight in the etiology of PFP[8]. Although it was long believed that PFP was caused by chondromalacia[9], van der Heijden et al. showed that structural abnormalities (e.g. cartilage loss and osteophytes) seen on MRI are not associated with the presence of PFP[8,10]. Additionally, no differences in cartilage composition were seen between groups[11]. However, in another study, significantly higher T1ρ relaxation times in lateral patellar cartilage were found in a group of maltracking (e.g. patellar tilt present) PFP patients compared to healthy controls, indicating an impaired biochemical composition[12]. A recently published study showed that features of radiographic and MRI-defined patellofemoral osteoarthritis (PFOA) are evident in 20-30% of adults aged 26 to 50 years[13]. This suggests that particular subgroups in both patient and control groups appear to have structural abnormalities such as cartilage lesions and osteophytes in the patellofemoral joint (PFJ) and may be at increased risk to develop OA later in life. PFP as a predisposing factor for PFOA has been hypothesized in multiple studies but strong evidence is lacking[14–16]. This hypothesis is merely based on the converging risk factors of both diseases[17–19]. Malalignment and maltracking are risk factors found in both PFP and PFOA populations[20,21]. Macri et al. recently showed in a literature review that there is strong evidence for associations between trochlear morphology (sulcus angle and trochlear depth) and the presence of PFOA[20]. In PFP patients it has been shown that the distance between the tibial tuberosity and trochlear groove (TT-TG) were larger in a subgroup of extreme lateral maltracking patients which indicates an association between maltracking and joint geometry[22]. Other frequently reported measures of alignment, i.e. patella alta and patellar tilt, have been associated with the presence of PFP[23] but also with OA progression[24]. This suggests that malalignment is an important risk factor for both PFP and PFOA and that particular PFP patients might show early signs of OA development.

Considering that maltracking subgroups have previously been found within PFP populations[25] and maltracking has been associated with OA[20], it is hypothesized that malalignment in PFP is associated with structural damage in the PFJ. Therefore, the aim of the present study was to investigate the association between PFJ alignment and geometry measures, and structural changes in bone and cartilage in individuals with and without PFP.

Methods

Study Population

For current study purpose, data from a previously conducted case-control study were used in which subjects aged between 14 and 40 years with PFP and healthy control subjects were included[8,26]. PFP patients were included by their general practitioner, physiotherapist or sports physician if they were diagnosed with PFP based on the presence of at least three of the following symptoms: crepitus or pain while stair climbing, squatting, running, cycling, or sitting for a prolonged period with the knee flexed. A minimum symptom duration of two months to a maximum of two years was required for the PFP patients. Patients were excluded if they currently had a defined pathological knee condition of the affected knee, previous surgery or injury of the affected knee, or previous episodes of PFP more than two years ago or if onset of PFP occurred after trauma. After inclusion by the healthcare professional, the inclusion criteria were checked by the researcher (RA), who checked the presence of possible exclusion diagnoses such as tendinopathy and meniscal lesions. Sports team members, friends or colleagues of the PFP patients were included as control subjects, when possible matched for age, body mass index (BMI), sex and activity level. Control subjects were excluded on current or past PFP, traumatic injury or surgery on both knees or if they were first-grade family members of patients. Contraindications for contrast enhanced MRI and insufficient knowledge of the Dutch language were exclusion criteria for all participants. The medical ethics committee of the Erasmus MC approved this study (protocol MEC-2012-342), informed consent was accordingly obtained from all participants and the rights of the subjects were protected before measurements took place.

Measurements

All study subjects completed a questionnaire including questions on demographics (gender, age, BMI), sports participation (yes or no, before onset of pain and during study) and knee complaints (duration of the complaints, paint at rest and pain during activity using a numerical rating scale of 0-10 and function, measured with the Anterior Knee Pain Scale (AKPS) on a 0-100 scale). All subjects underwent 3 Tesla MRI (Discovery MR750, GE Healthcare) measurements using a dedicated 8-channel knee coil (Invivo Inc., Gainesville, USA). The most painful knee was chosen in patients, while a random knee was chosen if both were equally affected or in the case of control subjects.

MRI measurements included two 3D high resolution sequences (slice thickness 0.5 mm, 0mm interslice gap); routine sagittal spoiled gradient echo (SPGR) sequences and routine sagittal fat-saturated SPGR sequences. Furthermore, 3D fast spin echo (FSE) sagittal T1ρ mapping sequences were acquired (slice thickness 3 mm, no interslice gap). Due to ethical reasons, only the adult participants underwent dynamic contrast-enhanced (DCE) MRI, performed with a sagittal fat suppressed 3D SPGR sequence (slice thickness 5mm, no interslice gap) with a temporal resolution of 10 seconds and lasting for 35 phases after intravenous contrast administration (0.2 mmol/kg Magnevist (Bayer)). The exact MRI protocol parameters can be found in online appendix 1.

MRI Analysis

Patellar alignment and femoral geometry

Common alignment (Insall-Salvati ratio (ISR), patellar translation, patellar tilt) and femoral geometry (sulcus depth, sulcus angle, TT-TG) measures of the PF joint were performed, as advised by the stepwise systematic approach of Chhabra et al[27] (Table 1). The ISR was calculated by dividing patellar tendon length by the maximal diagonal length of the patella on the midline sagittal MRI image, a higher ratio indicates a higher riding patella (alta) and a lower ratio indicates a lower riding patella (baja). Patellar translation was measured as the distance between perpendicular lines drawn on an axial image from the medial edge of the patella through the most anterior point of the medial condyle. Positive values indicate lateral translation and negative values indicate medial translation. Patellar tilt was defined as the angle between two lines drawn along the bony lateral patellar facet and the tangent to the anterior femoral condyles at the level of the patellar midpoint. Positive values indicate tilt in the lateral direction whereas negative values indicate tilt in the medial direction. Sulcus depth was defined as the distance of the deepest area of the trochlear groove relative to the mean of the femoral condyle outsets and sulcus angle was defined as the angle between two lines from condyle outsets to the deepest area of the trochlear groove, measured on axial images. The TT-TG distance was defined as the maximum distance between two lines drawn perpendicular to the deepest area of the trochlear groove and the center of the patellar tendon insertion on the tibial tuberosity on axial images.

Table 1. Alignment and geometry measures

Alignment and shape measure	Definition	Positive direction	Negative direction
ISR	Patellar tendon length divided by maximal diagonal length of patella	High riding patella (alta)	Low riding patella (baja)
Patellar translation	Patella is translated in lateral or medial direction compared to trochlea	Patella is translated in lateral direction	Patella is translated in medial direction
Patellar tilt	The patella is not parallel with the condyle outsets	Lateral tilt (lateral side of patella is closer to trochlea)	Medial tilt (medial side of patella is closer to trochlea)
Sulcus depth	Depth of sulcus groove compared to femoral condyle outsets	-	-
Sulcus angle	Angle between the condyle outsets	-	-
TT-TG	Distance between tibial tuberosity and trochlear groove in the axial plane (requires multiple MRI slices)	-	-

ISR; Insall-Salvati ratio, TT-TG; tibial tuberosity trochlear groove distance

Structural abnormalities

The high resolution MRI and routine clinical MRI scans were used to score structural abnormalities within the PF joint, using the semi-quantitative magnetic resonance imaging osteoarthritis knee score (MOAKS). For the present study, MOAKS scores of the most prevalent[8] and relevant features were selected and dichotomized (0 = not present, ≥1 = present): Osteophytes on patella, osteophytes on anterior femur, bone marrow lesions (BMLs) in patella, BMLs in anterior femur, Hoffa synovitis and minor cartilage defects on patella (Figure 1). Hoffa synovitis was defined as high signal intensity of the superolateral part of the Hoffa fat pad, as described by Chhabra et al[27]. Minor cartilage defects were defined as high signal intensity, hypertrophy, fraying or fissuring of the cartilage. Alignment and geometry measurements and scoring of MOAKS features were performed by a senior resident (J.L.d.K) in radiology with musculoskeletal sub-specialization. All findings were verified by an experienced musculoskeletal radiologist (E.O). Both readers were blinded for participant status[8].

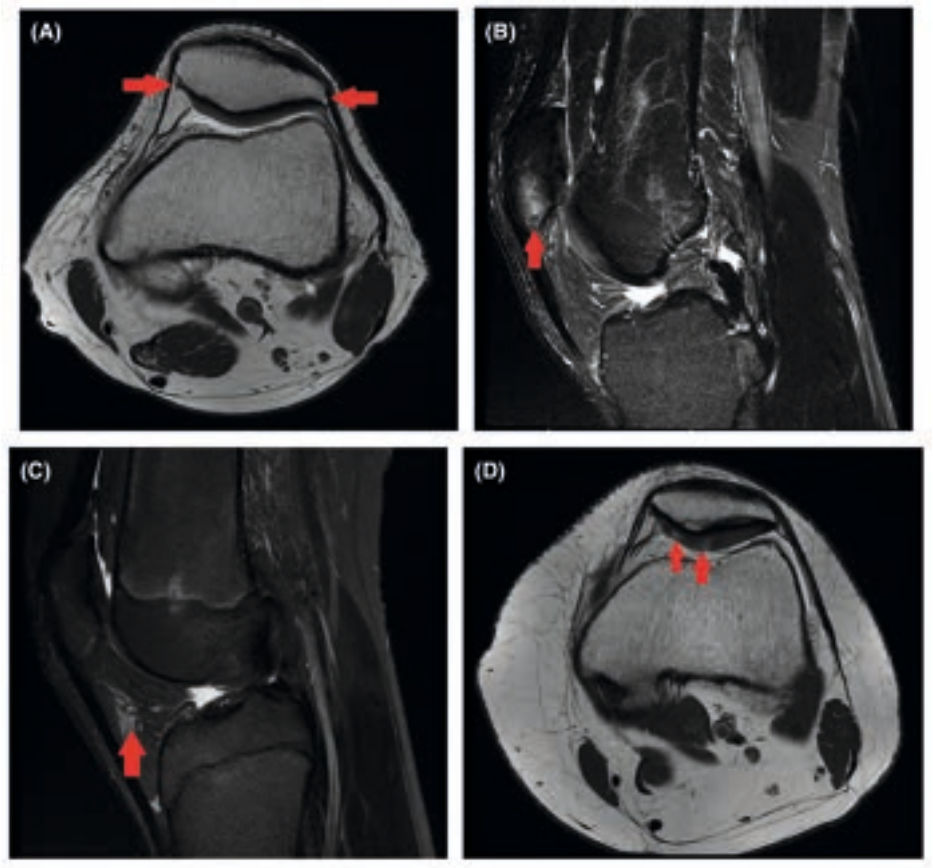
Cartilage composition and bone perfusion

T1ρ mapping MRI (3D fast spin echo sequence with 5 different spin lock times and a spin lock frequency of 500Hz) was used to quantitatively assess cartilage quality in which higher T1ρ relaxation time values are assumed to indicate less glycosaminoglycan[28]. Detailed methods have been described elsewhere[11]. For analyses, weighted mean relaxation times were obtained separately for femur and patellar cartilage. DCE-MRI scans were used to calculate Ktrans and Kep measures of blood perfusion in the patellar bone, as described by van der Heijden et al[29,30]. Weighted mean of Ktrans and Kep in the whole patella were calculated for analysis.

Statistical Analysis

Statistical analyses were performed in SPSS 21 (SPSS Inc, Chicago, USA). Descriptive statistics were used to describe subject characteristics, structural abnormalities, cartilage composition, perfusion parameters and alignment and geometry measures. Associations between alignment and geometry measures (independent variables) and cartilage composition, perfusion and structural abnormalities (dependent variables) were analyzed using multivariate linear and logistic regression techniques for each alignment or geometry measure separately, and adjustments were made for age, sex, BMI and the presence of PFP (case/control status). Linear regression results were presented by unstandardized regression coefficients (β) with 95% confidence intervals while logistic regression results were presented by odds ratios (OR) with 95% confidence intervals. Missing values were handled by performing complete case analysis.

Figure 1. Structural abnormalities



1a. Osteophytes on patella (axial proton density weighted MRI), **1b.** Bone marrow lesions in patella (sagittal T2 weighted fat saturated MRI) **1c.** Hoffa synovitis (sagittal T2 weighted fat saturated MRI), **1d.** Minor cartilage defects in patellar cartilage (axial proton density weighted MRI). Arrows highlight affected areas.

Results

The study population consisted of 76 females (56.7%) and 58 males (43.3%), with a mean age of 23.2 (6.4) years and BMI of 22.8 (3.4). Perfusion parameters were available for 35 PFP patients and 44 control subjects (adult subjects only), T1ρ relaxation times were available for 42 PFP patients and 50 control subjects (T1ρ sequence was unavailable at start of study) and structural abnormalities were available for all 64 PFP patients and 70 control subjects. Subject characteristics are presented in Table 2. Alignment and femoral geometry measures were available for all subjects (Table 3). No differences in alignment and femoral geometry measures were observed between groups.

Table 2. Characteristics of study participants.

	PFP n=64	**Control n=70**
Female gender (n (%))	35 (54.7)	41 (58.6)
Age (mean (SD))	23.4 (7.0)	23.1 (5.9)
BMI (mean (SD))	23.6 (3.8)	22.3 (3.0)
Presence of crepitation (n (%))	29 (45.3)	20 (29.0)
Sport participation		
During inclusion (n (%))	38 (40.6)	55 (78.6)
Before onset of pain (n (%))	48 (85.7)	N.A.
Pain in rest, NRS/10 (mean (SD))	3.9 (2.5)	N.A.
Pain during exercise, NRS/10 (mean (SD))	6.6 (2.2)	N.A.
AKPS score, 0-100 (mean (SD))	66.3 (11.6)	N.A.
Complaint duration, months (mean, (SD))	12.0 (7.1)	N.A.
Bilateral complains	33 (51.6)	N.A.
Patellar bone perfusion (Mean (SD))	n=35	n=44
Log Mean K_{trans} (min^{-1})	-1.89 (0.31)	-1.98 (0.29)
Log Mean K_{ep} (min^{-1})	-0.49 (0.22)	-0.58 (0.37)
Cartilage Composition (Mean (SD))	n=42	n=50
Mean T1ρ femur cartilage (ms)	661.6 (63.8)	659.8 (66.2)
Mean T1ρ patella cartilage (ms)	657.8 (83.7)	669.4 (55.1)
Structural abnormalities (n (%))	n=64	n=70
Osteophytes patella	45 (70.3)	42 (60.0)
Osteophytes anterior femur	12 (18.8)	9 (12.9)
BMLs patella	34 (53.1)	36 (51.4)
BMLs anterior femur	5 (7.8)	8 (11.4)
Meniscus extrusion	10 (15.6)	9 (12.9)
Hoffa synovitis	29 (45.3)	27 (38.6)
Minor cartilage defects patella	15 (23.4)	15 (21.4)

PFP; patellofemoral pain, BMI; body mass index, NRS; numerical pain scale, AKPS; anterior knee pain score, Ktrans; volume transfer constant from vascular space into tissue compartment, Kep; rate constant back from tissue compartment to vascular space, BMLs; bone marrow lesions

Table 3. PFJ alignment and geometry measures (Means (SD)) of patients and healthy control subjects.

	PFP n=64	**Control n=70**
ISR	1.2 (0.2)	1.2 (0.2)
Patellar translation †, mm	0.3 (2.6)	0.4 (2.3)
Patellar tilt †, ^{0}	8.3 (6.0)	10.1 (5.4)
Sulcus depth, mm	6.1 (1.0)	6.2 (1.0)
Sulcus Angle, ^{0}	137.3 (4.9)	136 (4.7)
TT-TG distance, mm	12.4 (4.4)	12.3 (4.2)

† Positive values are in lateral direction; negative values are in medial direction.
PFP; patellofemoral pain, TT-TG; tibial tuberosity trochlear groove distance, ISR; Insall-Salvati ratio

Table 4 presents the association between alignment and geometry measures and MRI outcomes. Lateral patellar tilt (^{0}) was negatively associated with the presence of osteophytes on both patella and anterior femur (OR 0.91; 95%CI 0.84 to 0.98 and OR 0.92; 95%CI 0.84 to 0.99, respectively) and minor cartilage defects on patella (OR 0.91; 95%CI 0.84 to 0.99). In addition, sulcus angle (^{0}) was negatively associated with the presence of Hoffa synovitis (OR 0.91; 95%CI 0.84 to 0.99) and lateral patellar tilt (^{0}) was positively associated with the presence of Hoffa synovitis (OR 1.08; 95%CI 1.01 to 1.16). ISR was positively associated with the presence of BMLs in the patella and minor cartilage defects on the patella (OR 48.33; 95%CI 4.27 to 547.30 and OR 17.51; 95%CI 1.17 to 262.57, respectively). Sulcus depth (mm) was negatively associated with presence of BMLs in the anterior femur (OR 0.45; 95%CI 0.22 to 0.93).

ISR was positively associated with T1ρ relaxation times of the trochlear cartilage (β 5.2; 95%CI 0.77 to 9.58) while lateral patellar translation was negatively associated with T1ρ relaxation times of the trochlear cartilage (β -0.36; 95%CI -0.64 to -0.08 respectively). None of the alignment or geometry measures were associated with bone perfusion.

Discussion

The purpose of this study was to evaluate the associations between PFJ alignment and femoral geometry measures, and changes in bone and cartilage associated with OA. The results demonstrate that, regardless of presence of PFP, several alignment and geometry measures already seem to be associated with cartilage and bone abnormalities at a young age. Patella alta, patellar tilt and trochlear geometry were associated with the presence of osteophytes and BMLs on both the anterior femur and patella, as well as Hoffa synovitis and minor cartilage defects on the patella. Additionally, patella alta and medial translation were associated with higher T1ρ relaxation times in the trochlear cartilage, indicating altered biochemical cartilage composition. In contrast to our hypotheses, no alignment or geometry measure was associated with bone perfusion.

Although our study provides no causality, one can speculate why some of these associations exist. Patella alta can result in a delayed engagement of the patella with the trochlea during flexion, and may therefore reduce contact area during early flexion[31]. The increase of shear stress as a result of reduction in contact area may result in bone marrow lesions and cartilage damage. Additionally, abnormal patellar positioning or sulcus geometry can also be hypothesized to reduce contact area in the PFJ during movement, resulting in higher shear stresses and structural damage.

Aberrant PFJ kinematics have previously been associated with malalignment[25] and abnormal joint geometry[32]. These abnormal kinematics are suggested to impact contact areas in the joint[33] and lead to increased joint stress in the PFJ[34], which in turn have been hypothesized to induce loss of cartilage and onset of BMLs[35] and structural damage[19].

Table 4. Associations between alignment and geometry measures and MRI outcome measures.

	ISR	Patellar translation† (mm)	patellar tilt† (^{0})	sulcus depth (mm)	sulcus angle (^{0})	patellar TT-TG (mm)
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Osteophytes patella	5.00 (0.43;57.80)	1.12 (0.95;1.32)	**0.91 (0.84;0.98)**	1.17 (0.76;1.78)	0.96 (0.89;1.04)	1.04 (0.95;1.14)
Osteophytes anterior femur	1.12 (0.06;19.57)	1.05 (0.87;1.27)	**0.92 (0.84;0.99)**	1.15 (0.68;1.95)	1.09 (0.98;1.22)	1.03 (0.92;1.15)
BMLs patella	**48.33 (4.27;547.30)**	0.91 (0.78;1.06)	0.97 (0.91;1.04)	0.88 (0.59;1.30)	1.07 (0.99;1.15)	1.05 (0.96;1.14)
BMLs anterior femur	3.89 (0.11;142.28)	0.95 (0.75;1.21)	0.99 (0.89;1.11)	**0.45 (0.22;0.93)**	1.06 (0.93;1.20)	1.02 (0.88;1.17)
Hoffa synovitis	1.47 (0.16;1.45)	0.90 (0.77;1.05)	**1.08 (1.01;1.16)**	1.04 (0.69;1.55)	**0.91 (0.84;0.99)**	1.02 (0.94;1.11)
Minor cartilage defects patella	**17.51 (1.17;262.57)**	1.11 (0.93;1.33)	**0.91 (0.84;0.99)**	0.93 (0.58;1.49)	1.06 (0.96;1.16)	1.04 (0.95;1.15)
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
T1ρ femur	**5.18 (0.77;9.58)**	**-0.36 (-0.64;-0.08)**	-0.04 (-0.16;0.08)	0.65 (-0.14;1.44)	0.01 (-0.14;0.17)	-0.02 (-0.19;0.14)
T1ρ patella	2.30 (-2.61;7.21)	-0.20 (-0.51;0.11)	-0.06 (-0.19;0.08)	0.04 (-0.83;0.92)	0.01 (-0.16;0.18)	-0.07 (-0.25;0.11)
Log mean Kep	-0.41 (-1.37;0.56)	0.04 (-0.02;0.09)	0.00 (-0.03;0.02)	-0.09 (-0.25;0.08)	0.01 (-0.03;0.04)	-0.02 (-0.05;0.02)
Log mean Ktrans	-0.24 (-0.69;0.20)	0.01 (-0.02;0.04)	0.00 (-0.01;0.01)	-0.01 (-0.09;0.06)	0.00 (-0.02;0.01)	0.01 (-0.02;0.01)

Odds ratios (95% CI) unless stated otherwise, adjusted for age, sex, BMI and presence of PFP. Significant associations in bold.
† Positive values are in lateral direction, negative values are in medial direction
PFP; patellofemoral pain, ISR; Insall-Salvati ratio, TT-TG; tibial tuberosity trochlear groove distance, Ktrans; volume transfer constant from vascular space into tissue compartment, Kep; rate constant back from tissue compartment to vascular space, BMLs; bone marrow lesions

The findings of this study support these theories, as we found multiple measures of alignment that correlate to the presence of BMLs, osteophytes and minor cartilage defects. Although there is limited evidence of presence of greater shear stresses in PFP patients[34], the association between malalignment, joint stresses and OA progression has been shown in knee valgus and varus patients[36]. Therefore, future research should investigate whether these alignment and shape measures in PFP patients indeed result in increased shear stresses in the PFJ and consequently result in early signs of OA. This in order to get a better insight in potential subgroups of PFP patients that are at high risk to develop OA at later age.

The associations between abnormal alignment and femoral geometry and the presence of structural abnormalities found in the present study, were equal in both PFP patients and healthy control subjects. Hence, there seems to be both PFP patients and healthy control subjects with particular bone alignment and geometry characteristics who have an increased prevalence of osteophytes, BMLs, Hoffa synovitis, minor patellar cartilage defects and deteriorated biochemical composition in femoral cartilage. This may indicate that a subgroup with specific alterations in alignment and bone geometry may be at greater risk to develop OA. It is so far unclear if these structural abnormalities will also result in definite OA. Further research into this young group with structural abnormalities could help understand the potential link between alignment and geometry and the development OA.

Many studies have already demonstrated an association between patellofemoral alignment and geometry and the presence of OA[19,20]. Those studies showed that patellar height, tilt and shallow trochleae were associated with a higher prevalence of BMLs and other signs of OA in the PF joint[19,20]. A flattened trochlea could increase the chance of a laterally displaced patella, causing damage in the PFJ[37]. Moreover, a recent multicenter study showed that patella alta is associated with worsening of structural features of PFOA[38]. It has been theorized that a higher riding patella increases the maximal patellofemoral contact force and contact pressure by increasing the flexion needed for PFJ contact[39]. While in the present study only a significant association with the presence of BMLs and minor cartilage defects on the patella was found, an identical trend was seen for all structural features assessed in this study. To further understand the influence of aberrant patellofemoral alignment and geometry on the later development of OA in a population with PFP, a longitudinal study with a long follow up is needed. While clinical implications have to be interpreted with caution, one could hypothesize that interventions influencing patellofemoral alignment, like bracing, could potentially prevent or delay the onset of OA in this subgroup.

A high riding or medially translated patella was associated with increased T1ρ relaxation times in femoral cartilage. The association between patella alta and the deterioration of the biochemical composition of cartilage may be explained by the increased contact forces in the PFJ, caused by patella alta[39]. This is in line with other studies which have described a loss of cartilage thickness associated with knee malalignment[40]. Wang et al. found higher

T1ρ values on the medial anterior femur in OA patients with knee varus[41]. We suspected lateral and medial patellar translation to have a greater association with lateral and medial trochlear cartilage T1ρ values respectively. However, additional explorative analyses in the current study with separate medial and lateral trochlear T1ρ relaxation times did not show a difference in the association with patellar translation between the lateral and medial compartment. Nonetheless, we did find a strong association between patella alta and impaired cartilage composition in the lateral trochlea.

No associations were found between patellar perfusion and alignment and geometry measures in our study. This indicates that the observed large perfusion variance between PFP patients in van der Heijden et al[30]. is probably not a result of differences in alignment or geometry measures between patients.

All conducted analyses were adjusted for age, sex, BMI and the presence of PFP (case/control status). These adjustments consistently revealed that a higher age results in a higher prevalence of osteophytes, independent of the alignment or geometry measure. This seems to be in line with literature on older OA subjects in which the prevalence of osteophytes, and consequently OA, increases with age[42]. Yet, we also found higher age is associated with a decrease in presence of BMLs. This seems to be in contrast with literature describing a higher prevalence in BMLs with increasing age[43]. Why BMLs in our study populations seems to decrease with age is unclear. These associations were found in the total study population, but remained present in the separate control and PFP study subgroups.

Strengths and Limitations

This is the first study investigating the associations between alignment and geometry in the PFJ and abnormalities in bone and cartilage associated with OA in a young population. For the analyses of the present study continuous measures of joint alignment and femoral geometry were used to preserve statistical power, whereas clinical cut-off values for normal and abnormal alignment and geometry measures have been proposed in literature[27]. We therefore exploratively tested these dichotomized variables in the current study and found similar directions of associations, although not all remained statistically significant, which is likely due to a loss of statistical power[44].

A relatively large number of statistical tests were used within our relatively small population, possibly causing false positive findings (Type 1 error). Additionally, the small number of participants used for analysis resulted in large confidence intervals for some of our analyses, limiting the precision of the association. Because a clear hypothesis was formed based on earlier literature showing associations between PFJ kinematics and structural abnormalities, we think that the study findings add unique information about the etiology of PFP and the value of joint kinematics and structural abnormalities.

No reliability data is available from the alignment, geometry and MOAKS measurements and we can therefore not exclude intra observer deviations in our data. However, all measurements were performed by experienced blinded radiologists.

Perspective

Our study showed no differences in alignment and femoral geometry measures between PFP and control groups. However, associations were found between alignment and geometry measures and structural joint abnormalities linked to OA in the PFJ in a young population, including PFP patients. This is in line with results found by Kang et all.[45] showing an increase in MRI abnormalities with changes in sulcus geometry. Since kinematics can be changed with noninvasive treatments like bracing[46] and training[47], one could potentially delay or prevent the onset of PFOA in young people with malalignment in the PFJ. Further prospective studies are needed to investigate the exact relation between malalignment and early OA in young populations.

References

1. Taunton JE, Ryan MB, Clement DB, McKenzie CD, Lloyd-Smith D R;, Zumbo BD. A retrospective case-control analysis of 2002 running injuries. *Br J Sports Med*. 2002;36(2):95-101. http://search.ebscohost.com/login.aspx?direct=true&db=cin20&AN=106963371&site=ehost-live%5Cnhttp://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed5&NEWS=N&AN=2002132668
2. Nimon G, Murray D, Sandow M, Goodfellow J. Natural history of anterior knee pain: a 14- to 20-year follow-up of nonoperative management. *J Pediatr Orthop*. 1998;18(1):118-122.
3. Lankhorst NE, van Middelkoop M, Crossley KM, et al. Factors that predict a poor outcome 5–8 years after the diagnosis of patellofemoral pain: a multicentre observational analysis. *Br J Sports Med*. 2016;50(14):881-886. doi:10.1136/bjsports-2015-094664
4. Swart NM, Van Linschoten R, Bierma-Zeinstra SMA, Van Middelkoop M. The additional effect of orthotic devices on exercise therapy for patients with patellofemoral pain syndrome: A systematic review. *Br J Sports Med*. 2012;46(8):570-577. doi:10.1136/bjsm.2010.080218
5. RA van der H, NE L, R van L, SMA B-Z, M van M. Exercise for treating patellofemoral pain syndrome (Review). *Cochrane Database Syst Rev*. 2015;(1):199. doi:10.1002/14651858.CD010387.pub2.www.cochranelibrary.com
6. Barton C, Balachandar V, Lack S, Morrissey D. Patellar taping for patellofemoral pain: A systematic review and meta-Analysis to evaluate clinical outcomes and biomechanical mechanisms. *Br J Sports Med*. 2014;48(6):417-424. doi:10.1136/bjsports-2013-092437
7. Powers CM, Witvrouw E, Davis IS, Crossley KM. Evidence-based framework for a pathomechanical model of patellofemoral pain: 2017 patellofemoral pain consensus statement from the 4th International Patellofemoral Pain Research Retreat, Manchester, UK: Part 3. *Br J Sports Med*. 2017;51(24):1713-1723. doi:10.1136/bjsports-2017-098717
8. van der Heijden RA, de Kanter JLM, Bierma-Zeinstra SMA, et al. Structural Abnormalities on Magnetic Resonance Imaging in Patients With Patellofemoral Pain: A Cross-sectional Case-Control Study. *Am J Sports Med*. 2016;44(9):2339-2346. doi:10.1177/0363546516646107
9. McConnell J. The management of chondromalacia: A long term solution. *Austrailian J Physiother*. 1986;32(4):215-223. doi:10.1016/S0004-9514(14)60654-1
10. Kannus P, Natri A, Paakkala T, Järvinen M. An outcome study of chronic patellofemoral pain syndrome. Seven-year follow-up of patients in a randomized, controlled trial. *J Bone Joint Surg Am*. 1999;81(3):355-363. Accessed January 8, 2018. http://www.ncbi.nlm.nih.gov/pubmed/10199273
11. van der Heijden RA, Oei EHG, Bron EE, et al. No Difference on Quantitative Magnetic Resonance Imaging in Patellofemoral Cartilage Composition Between Patients With Patellofemoral Pain and Healthy Controls. *Am J Sports Med*. 2016;44(5):1172-1178. doi:10.1177/0363546516632507
12. Thuillier DU, Souza RB, Wu S, Luke A, Li X, Feeley BT. T1ρ imaging demonstrates early changes in the lateral patella in patients with patellofemoral pain and maltracking. *Am J Sports Med*. 2013;41(8):1813-1818. doi:10.1177/0363546513495167
13. Collins NJ, Oei EHG, de Kanter JL, Vicenzino B, Crossley KM. Prevalence of Radiographic and Magnetic Resonance Imaging Features of Patellofemoral Osteoarthritis in Young and Middle-Aged Adults With Persistent Patellofemoral Pain. *Arthritis Care Res*. 2019;71(8):1068-1073. doi:10.1002/acr.23726
14. Crossley KM. Is patellofemoral osteoarthritis a common sequela of patellofemoral pain? *Br J Sports Med*. 2014;48(6):409-410. doi:10.1136/bjsports-2014-093445

15. Eijkenboom JFA, Waarsing JH, Oei EHG, Bierma-Zeinstra SMA, Van Middelkoop M. Is patellofemoral pain a precursor to osteoarthritis? *Bone Jt Res*. 2018;7(9):541-547. doi:10.1302/2046-3758.79.BJR-2018-0112.R1

16. Thomeé R, Augustsson J, Karlsson J, Thomee R. Patellofemoral pain syndrome: a review of current issues. *Sport Med*. 1999;28(4):245-262.

17. Lankhorst NE, Bierma-Zeinstra SMA, van Middelkoop M. Risk Factors for Patellofemoral Pain Syndrome: A Systematic Review. *J Orthop Sports Phys Ther*. 2012;42(2). doi:10.2519/jospt.2012.3803

18. Peat G, Duncan RC, Wood LR, Thomas E, Muller S. Clinical features of symptomatic patellofemoral joint osteoarthritis. *Arthritis Res Ther*. 2012;14(2):R63. doi:10.1186/ar3779

19. Mills K, Hunter DJ. Patellofemoral joint osteoarthritis: An individualised pathomechanical approach to management. *Best Pract Res Clin Rheumatol*. 2014;28(1):73-91. doi:10.1016/j.berh.2014.01.006

20. Macri EM, Stefanik J, Khan KK, Crossley KM. Is tibiofemoral or patellofemoral alignment or trochlear morphology associated with patellofemoral osteoarthritis? A systematic review. *Arthritis Care Res (Hoboken)*. 2016;68(10):1453-1470. doi:10.1002/acr.22842

21. Saikat P, Besier TF, Beaupre GS, Fredericson M, Delp SL, Gold GE. Patellar maltracking is prevalent among patellofemoral pain subjects with patella alta: an upright, weightbearing MRI study. 2014;31(3):448-457. doi:10.1002/jor.22256.Patellar

22. Carlson VR, Boden BP, Sheehan FT. Patellofemoral Kinematics and Tibial Tuberosity – Trochlear Groove Distances in Female Adolescents With Patellofemoral Pain. Published online 2016:1-8. doi:10.1177/0363546516679139

23. Kannus PA. Long patellar tendon: radiographic sign of patellofemoral pain syndrome--a prospective study. *Radiology*. 1992;185(3):859-863. doi:10.1148/radiology.185.3.1438776

24. Hunter D, Zhang Y, Niu J, et al. Patella malalignment, pain and patellofemoral progression: The Health ABC Study. *October*. 2008;28(30):4439-4448. doi:10.1037/a0013262.Open

25. Sheehan FT, Derasari A, Fine KM, Brindle TJ, Alter KE. Q-angle and J-sign: Indicative of maltracking subgroups in patellofemoral pain. *Clin Orthop Relat Res*. 2010;468(1):266-275. doi:10.1007/s11999-009-0880-0

26. van der Heijden RA, Rijndertse MM, Bierma-Zeinstra SMA, van Middelkoop M. Lower Pressure Pain Thresholds in Patellofemoral Pain Patients, Especially in Female Patients: A Cross-Sectional Case-Control Study. *Pain Med*. Published online 2017:1-9. doi:10.1093/pm/pnx059

27. Chhabra A, Subhawong TK, Carrino JA. A systematised MRI approach to evaluating the patellofemoral joint. *Skeletal Radiol*. 2011;40(4):375-387. doi:10.1007/s00256-010-0909-1.A

28. Oei EHG, van Tiel J, Robinson WH, Gold GE. Quantitative Radiologic Imaging Techniques for Articular Cartilage Composition: Toward Early Diagnosis and Development of Disease-Modifying Therapeutics for Osteoarthritis. 2012;100(2):130-134. doi:10.1002/acr.22316

29. Poot DHJ, van der Heijden RA, van Middelkoop M, Oei EHG, Klein S. Dynamic contrast-enhanced MRI of the patellar bone: How to quantify perfusion. *J Magn Reson Imaging*. 2018;47(3):848-858. doi:10.1002/jmri.25817

30. van der Heijden RA, Poot DHJ, Ekinci M, et al. Blood perfusion of patellar bone measured by dynamic contrast-enhanced MRI in patients with patellofemoral pain: A case-control study. *Journal of Magnetic Resonance Imaging*. http://linkinghub.elsevier.com/retrieve/pii/S1063458416005811. Published 2018.

31. Watson NA, Duchman KR, Grosland NM, Bollier MJ. Finite Element Analysis of Patella Alta. *Iowa Orthop J*. 2017;37:101-108.

32. Harbaugh CM, Wilson N a., Sheehan FT. Correlating femoral shape with patellar kinematics in patients with patellofemoral pain. *J Orthop Res*. 2010;28(7):865-872. doi:10.1002/jor.21101

33. Drew BT, Redmond AC, Smith TO, Penny F, Conaghan PG. Which patellofemoral joint imaging features are associated with patellofemoral pain? Systematic review and meta-analysis. *Osteoarthr Cartil*. 2016;24(2):224-236. doi:10.1016/j.joca.2015.09.004

34. Farrokhi S, Keyak JH, Powers CM. Individuals with patellofemoral pain exhibit greater patellofemoral joint stress: A finite element analysis study. *Osteoarthr Cartil*. 2011;19(3):287-294. doi:10.1016/j.joca.2010.12.001

35. Buckwalter JA, Anderson DD, Brown TD, Tochigi Y, Martin JA. The Roles of Mechanical Stresses in the Pathogenesis of Osteoarthritis: Implications for Treatment of Joint Injuries. *Cartilage*. 2013;4(4):286-294. doi:10.1177/1947603513495889

36. Cahue S, Dunlop D, Hayes K, Song J, Torres L, Sharma L. Varus-valgus alignment in the progression of patellofemoral osteoarthritis. *Arthritis Rheum*. 2004;50(7):2184-2190. doi:10.1002/art.20348

37. Stefanik JJ, Roemer FW, Zumwalt AC, et al. Association between measures of trochlear morphology and structural features of patellofemoral joint osteoarthritis on MRI: The MOST study. *J Orthop Res*. 2012;30(1):1-8. doi:10.1002/jor.21486

38. Stefanik JJ, Zhu Y, Zumwalt A, et al. The association between patella alta and the prevalence and worsening of structural features of patellofemoral joint osteoarthritis: The Multicenter Osteoarthritis Study. *Arthritis Care Res*. 2010;62(9):1258-1265. doi:10.1002/acr.20214

39. Luyckx T, Didden K, Vandenneucker H, Labey L, Innocenti B, Bellemans J. Is there a biomechanical explanation for anterior knee pain in patients with patella alta?: influence of patellar height on patellofemoral contact force, contact area and contact pressure. *J Bone Joint Surg Br*. 2009;91(3):344-350. doi:10.1302/0301-620X.91B3.21592

40. Moyer R, Wirth W, Eckstein F. LONGITUDINAL CHANGES IN MRI-BASED MEASURES OF FEMOROTIBIAL CARTILAGE THICKNESS AS A FUNCTION OF ALIGNMENT AND OBESITY Data from the OAI. *Arthritis Care Res (Hoboken)*. Published online 2016. doi:10.1002/acr.

41. Wang L, Vieira RL, Rybak LD, et al. Relationship between knee alignment and T1?? values of articular cartilage and menisci in patients with knee osteoarthritis. *Eur J Radiol*. 2013;82(11):1946-1952. doi:10.1016/j.ejrad.2013.05.010

42. Zhang W, McWilliams DF, Ingham SL, et al. Nottingham knee osteoarthritis risk prediction models. *Ann Rheum Dis*. 2011;70(9):1599-1604. doi:10.1136/ard.2011.149807

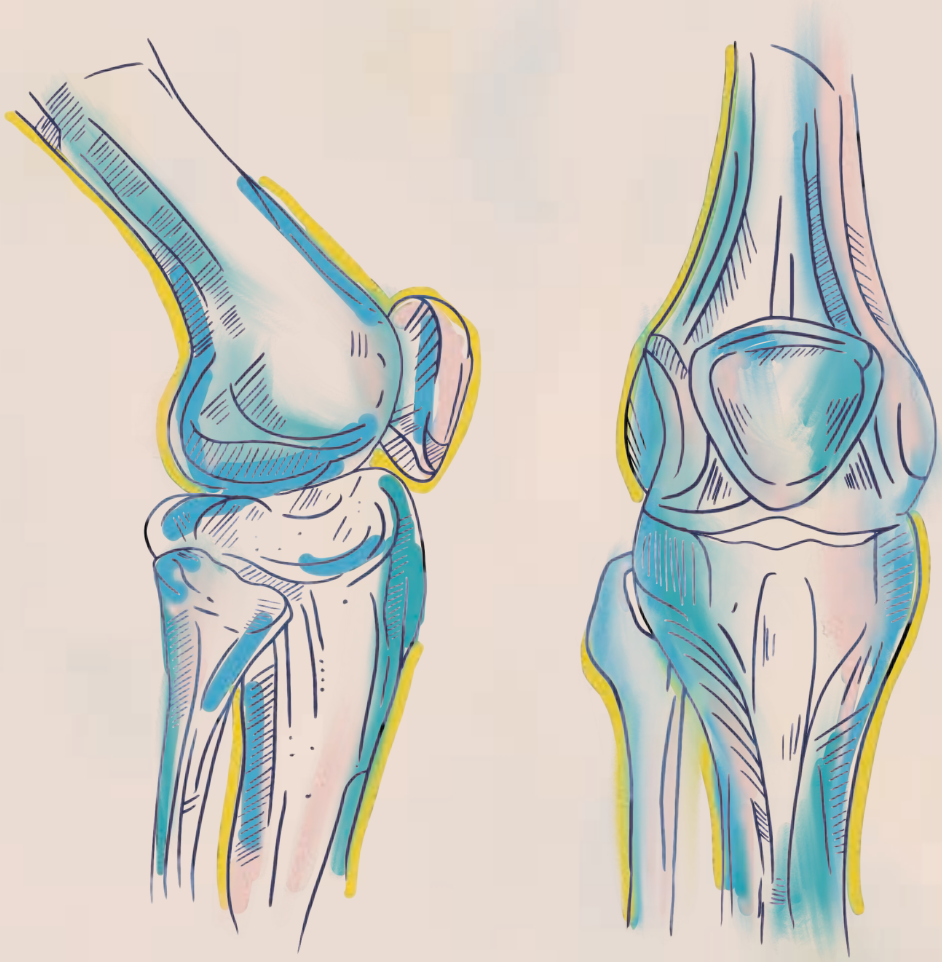
43. Antony B, Venn A, Cicuttini F, et al. Correlates of knee bone marrow lesions in younger adults. *Arthritis Res Ther*. Published online 2016:18-31. doi:10.1186/s13075-016-0938-9

44. Altman DG, Royston P. The cost of dichotomising continuous variables. *Br Med J*. 2006;332(7549):1080. doi:10.1136/bmj.332.7549.1080

45. Kang S, Park J, Kang S, Chang CB. MRI findings of young male soldiers with atraumatic anterior knee pain. Published online 2016:572-578. doi:10.1111/sms.12486

46. Callaghan MJ, Guney H, Reeves ND, et al. A knee brace alters patella position in patellofemoral osteoarthritis: a study using weight bearing magnetic resonance imaging. *Osteoarthr Cartil*. Published online 2016. doi:10.1016/j.joca.2016.07.003

47. Gretchen B. Salsich, Valentina Graci, PhD, and Dwayne E. Maxam P. The Effects of Movement Pattern Modification on Lower Extremity Kinematics and Pain in Females with Patellofemoral Pain. 2016;16(3):338-348. doi:10.1037/emo0000122.Do



Chapter 3

Association between self-reported measures, physical examination, and early MR imaging signs of osteoarthritis in patients with patellofemoral pain

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Abstract

Study design: Cross-sectional

Background: Structural abnormalities associated with osteoarthritis (OA) are found in some patients with patellofemoral pain (PFP).

Objectives: Investigate the association between early signs of OA on MRI and characteristics from self-reported measures and physical examination in patients with PFP.

Methods: Data of patients with PFP from a cross-sectional case-control study were used (N=64, 55% female, mean age 23.4(7.0)). Structural OA features (osteophytes, bone marrow lesions, cartilage defects, Hoffa synovitis, patellar tendon abnormalities) and quantitative T2 measurements of cartilage composition were extracted from MRI. Associations between characteristics from self-reported measures (pain in rest, pain during stair walking, knee function, duration of complaints, hours of sports participation), physical examination (crepitus, quadriceps strength) and early MRI signs of OA were analyzed.

Results: Symptom duration was associated with bone marrow lesions in the patella (OR 1.10; 95%CI [1.00-1.21]). Hours of sports participation per week was inversely associated with patellar tendon abnormalities on MRI (OR 0.75; 95%CI [0.59-0.97]). Crepitus and bilateral nature of the complaints were associated with small cartilage defects in the patellar cartilage (OR 11.95; 95%CI [2.25-63.61] and 7.62; 95%CI [1.08-53.75] respectively). No significant associations were found between clinical characteristics and cartilage T2 relaxation time.

Conclusion: Presence of crepitus, bilateral complaints, a long PFP symptom duration and reduced sport participation per week seem to be associated with early signs of OA in a young PFP population, which may represent a distinct subgroup of patients with PFP who have a high risk to develop PFOA.

Introduction

Patellofemoral pain (PFP) is a highly prevalent disorder; 12% of the patients who visit the general practitioner with knee pain are diagnosed with PFP[1] with a peak incidence at adolescent age. PFP is described as pain around or behind the patella associated with prolonged sitting, squatting, kneeling and stair climbing[2]. Contrary to earlier beliefs, PFP is not self-limiting and entails a personal and societal burden[3]. Multiple studies have been conducted to obtain more insight in this multifactorial condition, but the exact aetiology is still unknown.

It has been proposed in the literature that PFP is a risk factor for the development of patellofemoral osteoarthritis (PF OA)[4]. Therefore, changes in bone and cartilage associated with early osteoarthritis, such as osteophytes, bone marrow lesions, Hoffa synovitis and deteriorating cartilage composition have been proposed as potential pathophysiological factors of PFP[2,5,6]. In addition, T2 mapping can quantitatively measure the amount of water molecules in articular cartilage, and has been accepted as an early sign of OA[7,8] and could therefore play a role in understanding PFP pathophysiology.

A recent case-control study showed that a high prevalence of these early signs of OA are indeed apparent in patients with PFP[9]. However, these abnormalities were also seen in the healthy control population[9]. Nevertheless, it is still unknown whether the abnormalities seen on MRI in patients with PFP are related to clinical presentation and symptoms. It is of importance to investigate this potential association, since patients with early OA features may be prone to developing definitive OA in the patellofemoral joint at a later age. The identification of this subgroup, by means of self-reported measures and physical examination, could have clinical value in the education and early treatment of patients for preventing the development of OA later in life.

Several factors such as quadriceps weakness[10], crepitation[11], duration of complaints[12] and severity of knee pain[13] have previously been associated with a poor prognosis of PFP. We hypothesized that risk factors from self-reported measures and physical examination may also be associated with the early signs of OA seen in patients with PFP, and consequently with a poor prognosis of PFP. Although imaging outcome measures are not included in the routine clinical work-up of PFP[14] and early signs of OA on MRI are highly prevalent (90%) even in a population without knee pathologies[15], the identification of patient and clinical characteristics potentially associated with early signs of OA on MRI could help to identify a young population at risk of developing OA. Therefore, the aim of the present exploratory study was to investigate whether clinical characteristics from self-reported measures and physical examination are associated with early signs of OA seen on MRI in young patients with PFP.

Methods

Study Population

Data from patients with PFP collected in a previously conducted cross-sectional case-control study were used for the current study purpose[9]. Patients were recruited by physiotherapists, sport physicians and general practitioners. The diagnosis of PFP was based on presence of at least three of the following symptoms; crepitus or pain while stair climbing, squatting, running, cycling, or sitting for a prolonged period with the knee flexed[9]. Patients between 14 and 40 years old were included, with a minimum symptom duration of 2 months up to 2 years[9] to improve comparability with the literature[16]. Patients with previously diagnosed knee pathologies such as clinically-diagnosed Osgood-Schlatter and patella tendinopathy, surgery or injury, contraindication for MRI with contrast administration (not used for current study purpose) and insufficient knowledge of the Dutch language were excluded. An institutional review board approved this study (Medical Ethical Committee of the Erasmus MC, protocol MEC-2012- 342), informed consent was accordingly obtained from all participants and the rights of the subjects were protected before measurements took place.

Measurements

Clinical measurements included physical examination and self-reported measures assessed by questionnaires. The questionnaires included questions on demographics (sex, height, weight and age), sports participation (average hours of sports participation per week at the time of inclusion), duration of complaints and pain severity during activity in the past week (Numeric Rating Scale of Pain (NRS Pain[17]). Self-reported physical functioning was assessed with the Anterior Knee Pain Scale (AKPS[18]) and bilateral complaints were recorded (yes/no). The subscale "stairs" of the AKPS was dichotomized to make interpretation easier (difficulty / no difficulty). "Severe pain" during stair walking was defined as "pain both when ascending and descending" or "unable", while "no or slight pain" was defined as "no difficulty" or "slight pain when descending" as the answers. The standardized physical examination included presence of crepitus during squatting (yes/no), painful palpitation of the medial patellar compartment (yes/no), Clarke's compression test[19] and measurements of quadriceps strength[20]. Presence of crepitus was defined as a hearable grinding noise and/or palpable vibrations in the knee, detected by the hand of the investigator rested on the patella of the participant during loaded active flexion or extension of the knee. Quadriceps strength was measured three times using a handheld dynamometer[20] (MicroFET2; Fabrication Enterprises Inc, Elmsford, NY). The two highest values were used to determine the mean quadriceps strength per kilogram of bodyweight. The affected knee or randomly chosen knee if both knees were equally painful, were used for all questionnaires and measurements in this study.

A 3 Tesla MRI scanner (Discovery MR750, GE healthcare, Milwaukee, WI, USA) with a dedicated 8-channel knee coil (Invivo Inc.) was used with a protocol that included the

following pulse sequences; sagittal, axial, and coronal fast spin-echo proton density–weighted sequences with a slice thickness of 3 mm and sagittal and axial T2-weighted sequences with fat suppression with a slice thickness of 3 mm. The full MRI protocol can be found in online appendix 1.

MRI Analysis

The semi-quantitative magnetic resonance imaging osteoarthritis knee score (MOAKS[21]) tool was used to score OA features in the PF joint [22]. The MOAKS is a validated tool developed to study osteoarthritis. Additional patellofemoral joint features, possibly more applicable for this young population, were added: minor cartilage defects, (defined as high signal intensity, fraying or fissuring or hypertrophy of the cartilage) patellar tendon abnormalities (defined as thickening or high signal of the patellar tendon) and Hoffa synovitis (defined as high signal superolateral or moderate to severe edema of the Hoffa fat pad). These features were scored by a blinded senior resident in radiology with musculoskeletal sub-specialization and were later dichotomized to reduce the large numbers of MRI features (0 = not present, 1 = present) and in detail described by van der Heijden et al. (2016)[9] . All findings were confirmed by an experienced blinded musculoskeletal radiologist. For the current study purpose, the five most prevalent and relevant features with regard to PFP were used for the analysis (patellar osteophytes, bone marrow lesions in the patella, patellar tendon abnormalities (defined as tendon thickening or high signal tendon on MRI), minor patellar cartilage defects (high signal, hypertrophy and fraying) and Hoffa synovitis)[9]. The T2 mapping MRI sequence was used to quantify cartilage composition with higher T2 relaxation times indicating a deteriorated biochemical cartilage composition[23]. Weighted mean relaxation times were calculated separately for the anterior femur cartilage and patellar cartilage. Segmentations were performed by a blinded experienced observer, further details on T2 mapping methods can be found in van der Heijden et al. (2016)[22].

Statistical analysis

Statistical analyses were performed using SPSS, version 21 (SPSS Inc). Patients characteristics and prevalence of early signs of OA were described using descriptive statistics. Associations between self-reported measures, features from physical examination and early signs of OA were analyzed using linear (T2 relaxation times) and logistic regression (MOAKS features) models with adjustment for age, sex and BMI. The linear regression results were presented as unstandardized regression coefficients (β) and the logistic regression were presented as odds ratios, both with 95% confidence intervals. Missing values were handled by performing complete case analysis.

Results

Sixty-four patients with PFP were included between January 2013 and September 2014 (Table 1). The mean age was 23.4 years old and the mean BMI was 23.6 kg/m^2. There were 35 females. T2 relaxation times were available for 63 subjects (acquisition failed in 1 patient). Structural abnormalities on MRI were scored in all subjects.

Table 1. Characteristics of patients with PFP

	patients with PFP (n=64)
Female gender	35 (54.7)
Age (mean ± SD)	23.4 (7.0)
BMI (mean ± SD)	23.6 (3.8)
Pain during activity (NRS Pain, mean ± SD)	6.6 (2.2)
Anterior knee pain scale (mean ± SD)	66.3 (11.6)
Severe pain or unable to walk stairs	41 (64.1)
Sports participants at study inclusion	38 (59.4)
Hours of sports participation per week (mean ± SD)	2.4 (2.4)
Presence of crepitus	29 (45.3)
Positive Clarke compression test	14 (21.9)
Painful palpation, medial patellar facet	31 (48.4)
Quadriceps strength (N/Kg, mean ± SD)	3.67 (1.23)
Structural abnormalities (n (%))	
Osteophytes patella	45 (70.3)
BMLs patella	34 (53.1)
Minor cartilage defects	15 (23.4)
Patellar tendon abnormalities	24 (37.5)
Hoffa synovitis	37 (57.8)
Cartilage composition (ms, Mean (SD))	n=63
Mean T2 relaxation time femur cartilage	36.6 (2.5)
Mean T2 relaxation time patella cartilage	33.2 (2.8)

Data are reported as n (%) unless stated otherwise.
PFP, patellofemoral pain; SD, standard deviation; NRS, Numeric Rating Scale; N/Kg, Newton per Kilogram; BML, bone marrow lesions; ms, millisecond

Osteophytes on the patella were present in 70.3% of the patients with PFP and bone marrow lesions were seen in 53.1% of the patients. Hoffa synovitis was present in 54.7% of the patients. Less prevalent features included abnormalities of the patellar tendon (37.5%) and minor patellar cartilage defects (23.4%).

Table 2. Association between structural abnormalities seen on MRI and clinical characteristics (Odds Ratios, 95% CI).

	Osteophytes patella	BML patella	Minor Cartilage defects patella	Patellar tendon abnormalities	Hoffa synovitis
Pain and function					
Pain during activity (NRS Pain, 0-10)	1.04 (0.79;1.36)	1.13 (0.88;1.44)	1.01 (0.73;1.38)	1.04 (0.81;1.34)	1.05 (0.79;1.38)
Pain during walking stairs	0.33 (0.08;1.29)	0.86 (0.29;2.54)	0.87 (0.24;3.19)	0.45 (0.15;1.37)	0.69 (0.21;2.22)
Knee function (AKPS, 0-100)	1.04 (0.97;1.10)	0.96 (0.91;1.02)	1.02 (0.95;1.09)	0.99 (0.94;1.04)	1.01 (0.95;1.06)
Clinical Characteristics					
Duration of complaints (months)	0.96 (0.88;1.04)	**1.10 (1.00;1.21)**	1.06 (0.96;1.17)	1.06 (0.98;1.15)	0.95 (0.87;1.04)
Bilateral complaints	1.22 (0.34;4.39)	1.75 (0.52; 5.88)	**7.62 (1.08;53.75)**	0.29 (0.08; 1.06)	1.94 (0.53;7.06)
Presence of crepitus	1.74 (0.52;5.83)	1.36 (0.47;3.94)	**11.95 (2.25;63.61)**	1.20 (0.41;3.54)	0.38 (0.12;1.26)
Hours of sports participation per week	1.16 (0.90;1.50)	0.85 (0.69;1.06)	1.07 (0.82;1.39)	**0.75 (0.59;0.97)**	0.89 (0.71;1.12)
Quadriceps strength (N/Kg)	1.08 (0.62;1.88)	0.98 (0.61;1.60)	1.17 (0.63;2.16)	0.63 (0.36;1.10)	1.02 (0.61;1.70)

All analyses adjusted by BMI, age and sex. Statistically significant associations are presented in bold ($p<0.05$).
BML, Bone marrow lesions; NRS, Numeric Rating Scale; AKPS, Anterior Knee Pain Scale; N/Kg, Newton per Kilogram

Table 2 shows the associations between clinical characteristics and structural abnormalities on MRI. A longer duration of complaints was associated with the presence of bone marrow lesions in the patella (OR 1.10; 95%CI 1.00 to 1.21). Additionally, both the presence of crepitus (OR 11.95; 95%CI 2.25 to 63.61) and bilateral nature of the complaints (OR 7.62; 95%CI 1.08 to 53.75) were associated with minor cartilage defects in the patella. The pre-test probability for minor cartilage defects was 23.44%, while the post-test probability after presence of crepitus was 44.83% for minor cartilage defects, and the post-test probability after bilateral nature of complaints was 27.27% for minor cartilage defects. Finally, number of hours of sports participation per week was inversely associated with patellar tendon abnormalities (OR 0.75; 95%CI 0.59 to 0.97).

No associations were found between any of the clinical characteristics and T2 relaxation times (Table 3).

Table 3. The association between biochemical cartilage composition and clinical characteristics (B, 95% CI)

	T2 relaxation time anterior femur (ms) (n=63)	**T2 relaxation time patella (ms) (n=63)**
Pain and function		
Pain during activity (NRS pain, 0-10)	-0.11 (-0.40; 0.18)	-0.03 (-0.38; 0.33)
Pain during stair walking	-0.46 (-1.72 ;0.80)	0.22 (-1.34; 1.79)
AKPS (0-100)	0.02 (-0.04; 0.08)	0.05 (-0.03; 0.12)
Clinical characteristics		
Duration of complaints (months)	0.02 (-0.07; 0.11)	0.04 (-0.07; 0.15)
Bilateral complaints	0.37 (-1.00; 1.75)	-0.11 (-1.81; 1.59)
Presence of crepitus	0.67 (-0.56; 1.91)	0.72 (-0.80; 2.25)
Hours of sports participation per week	-0.13 (-0.37; 0.12)	-0.14 (-0.32; 0.30)
Quadriceps strength (N/Kg)	-0.27 (-0.84; 0.31)	-0.41 (-1.11; 0.30)

All analyses adjusted for BMI, age and sex. Statistically significant associations are presented in bold ($p<0.05$).
B, unstandardized regression coefficients; Ms, milliseconds; NRS, Numeric Rating Scale; AKPS, Anterior Knee Pain Scale; N/Kg, Newton per Kilogram

Discussion

The purpose of this study was to investigate the association between clinical characteristics from self-reported measures and physical examination and early signs of OA seen on MRI in patients with PFP. A longer symptom duration of PFP was associated with the prevalence of bone marrow lesions in the patella. An association was found between crepitus, bilateral complaints and the prevalence of minor cartilage defects on the patella. However, these associations had large confidence intervals that may be caused by the relatively small sample size. Biochemical cartilage composition was not associated with any of the clinical characteristics in our study.

Our results show that severity of pain and loss of function are not associated with early signs of OA in young patients with PFP. This indicates that even though there is a relatively high prevalence of early signs of OA, these signs do not seem to be responsible for the variation in pain severity, functional impairment or pain during stair walking within this group of patients with PFP. This is in line with earlier findings in OA research, where functional impairment and pain severity were rarely associated with synovitis and BMLs between patients with OA. However, variation in pain severity has been associated with both synovitis and bone marrow lesions in patients with OA and functional impairment has been associated with both synovitis and bone marrow lesions in patients with OA[24]. It would therefore be interesting to examine these associations in a longitudinal study following young patients with PFP and their possible progression to OA.

Quantitative MRI measures for changes in cartilage composition have recently been proposed as objective endpoints for early OA research[25] since changes in cartilage composition are present in the early OA disease process[26]. One of these measures, T2 relaxation times, has been suggested to be a sensitive imaging marker for quantitative monitoring of macro- molecules in early OA[27]. T2 measures have been reported to be significantly higher in patients with early OA compared to healthy controls[8]. Nevertheless, we earlier showed that no difference was present in composition of patellofemoral cartilage between patients with PFP and healthy control subjects[22]. In the current study we additionally show that no association seems to exist between cartilage composition and characteristics from self-reported pain and function and physical examination in this young PFP population. Since biochemical changes in cartilage are hypothesized to prelude cartilage damage in OA, and a strong association was found between minor cartilage defects and crepitus, it was expected to also find an association between T2 measures and crepitus. However, post hoc analysis revealed T2 was not associated with minor cartilage defects in our population.

An association between the presence of crepitus and minor cartilage defects on the patella was seen in our study. These findings are in line with the previously described strong association between the presence of crepitus and cartilage defects in patients with PF OA[28].

Additionally, crepitus has been associated with various other knee abnormalities (i.e. osteophytes, meniscal damage, cruciate pathology and medial collateral ligament pathology) on both X-ray and MRI in subjects with knee pain[29]. Since the prevalence of crepitus can be easily noted, it could be a convenient first indication of the onset of various radiological abnormalities within the knee. However, in the present young population the risk of such abnormalities for the individual patient with crepitus is still below 50%.

Bone marrow lesions have been reported to worsen patient prognosis in both inflammatory and non-inflammatory musculoskeletal conditions[30,31]. Our study shows a weak association between the presence of BMLs in the patella and a longer duration of complaints. This seems to be in line with Lankhorst et al[11] who found that a longer duration of complaints was associated with a poor prognosis of PFP subjects. The size and prevalence of BMLs have been shown to be associated with progression of disease[32] in addition to cartilage loss[33], risk of total joint replacement[34] and pain[35] in patients with OA. Our results imply that bone marrow lesions may also play a role in patient prognosis in patients with PFP.

Strengths and limitations

This is the first study investigating the association between early signs of OA on MRI and clinical characteristics and symptoms in a relatively young PFP population. Additionally, this study combined novel MRI techniques in a relatively large and young PFP population, adding great value to the current literature. However, a high number of statistical tests were used in this group of patients with PFP increasing the chances of false positive findings. Nonetheless, when applying a Bonferroni correction for multiple testing, our strongest association (crepitus and minor cartilage defects) would still be statistically significant ($p=0.004$) and shows a large effect size. To limit the number of statistical tests, only the five most prevalent and relevant structural abnormalities were analyzed in this study. This lead to the exclusion for analysis of structural abnormalities in a hypothetical important sub region in PFP, the trochlea[9]. However, post hoc analysis showed no significant associations between clinical characteristics and symptoms and the most prevalent trochlea feature (osteophytes, n=12).

Since structural abnormalities of the trochlea could not be taken into account due to low prevalence, the outcomes are only applicable to the patellar abnormalities. Moreover, only PFP patients with a symptom duration between 2 and 24 months were included and this may limit the generalizability of the findings to this specific group of patients. Due to the cross-sectional nature of our data, further research is needed to determine causality in the associations found.

Conclusion

The present study shows that pain severity and loss of function in PFP are not associated with early signs of OA. However, the presence of crepitus was strongly associated with minor cartilage defects on the patella. This could hypothetically be an important clinical risk factor within patients with PFP, indicating early cartilage damage. However, due to the cross-sectional nature of our data this needs further investigation in longitudinal studies.

References

1. Wood L, Muller S, Peat G. The epidemiology of patellofemoral disorders in adulthood: a review of routine general practice morbidity recording. *Prim Health Care Res Dev*. 2011;12(2011):157-164. doi:10.1017/S1463423610000460
2. Crossley KM, van Middelkoop M, Callaghan MJ, Collins NJ, Rathleff MS, Barton CJ. 2016 Patellofemoral pain consensus statement from the 4th International Patellofemoral Pain Research Retreat, Manchester. Part 1: Terminology, definitions, clinical examination, natural history, patellofemoral osteoarthritis and patient-reported outcome m. *Br J Sports Med*. Published online 2016:bjsports-2016-096268. doi:10.1136/bjsports-2016-096268
3. Rathleff MS, Rathleff CR, Olesen JL, Rasmussen S, Roos EM. Is Knee Pain During Adolescence a Self-limiting Condition? Prognosis of Patellofemoral Pain and Other Types of Knee Pain. *Am J Sports Med*. 2016;44(5):1165-1171. doi:10.1177/0363546515622456
4. Crossley KM. Is patellofemoral osteoarthritis a common sequela of patellofemoral pain? *Br J Sports Med*. 2014;48(6):409-410. doi:10.1136/bjsports-2014-093445
5. McConnell J. Running Injuries: The Infrapatellar Fat Pad and Plica Injuries. *Phys Med Rehabil Clin N Am*. 2016;27(1):79-89. doi:10.1016/j.pmr.2015.08.009
6. Fulkerson JP. The etiology of patellofemoral pain in young, active patients: a prospective study. *Clin Orthop Relat Res*. 1983;(179):129-133. Accessed December 11, 2017. http://www.ncbi.nlm.nih.gov/pubmed/6617004
7. Dunn TC, Lu Y, Jin H, Ries MD, Majumdar S. T2 Relaxation Time of Cartilage at MR Imaging: Comparison with Severity of Knee Osteoarthritis. *Radiology*. 2004;232(2):592-598. doi:10.1148/radiol.2322030976
8. Stahl R, Luke A, Li X, et al. T1rho, T2 and focal knee cartilage abnormalities in physically active and sedentary healthy subjects versus early OA patients—a 3.0-Tesla MRI study. *Eur Radiol*. 2009;19(1):132-143. doi:10.1007/s00330-008-1107-6
9. van der Heijden RA, de Kanter JLM, Bierma-Zeinstra SMA, et al. Structural Abnormalities on Magnetic Resonance Imaging in Patients With Patellofemoral Pain: A Cross-sectional Case-Control Study. *Am J Sports Med*. 2016;44(9):2339-2346. doi:10.1177/0363546516646107
10. Lankhorst NE, A Bierma-Zeinstra SM, Middelkoop M van. Factors associated with patellofemoral pain syndrome: a systematic review. *Br J Sport Med*. 2013;47:193-206. doi:10.1136/bjsports-2011-090369
11. Lankhorst NE, van Middelkoop M, Crossley KM, et al. Factors that predict a poor outcome 5–8 years after the diagnosis of patellofemoral pain: a multicentre observational analysis. *Br J Sports Med*. 2016;50(14):881-886. doi:10.1136/bjsports-2015-094664
12. Collins NJ, Bierma-Zeinstra SMA, Crossley KM, van Linschoten RL, Vicenzino B, van Middelkoop M. Prognostic factors for patellofemoral pain: a multicentre observational analysis. *Br J Sports Med*. 2013;47(4):227-233. doi:10.1136/bjsports-2012-091696
13. Collins NJ, Crossley KM, Darnell R, Vicenzino B. Predictors of short and long term outcome in patellofemoral pain syndrome: a prospective longitudinal study. *BMC Musculoskelet Disord*. 2010;11:11. doi:10.1186/1471-2474-11-11
14. Wang X, Oo WM, Linklater JM. What is the role of imaging in the clinical diagnosis of osteoarthritis and disease management? *Rheumatology*. 2018;(January):51-60. doi:10.1093/rheumatology/kex501
15. Guermazi A, Niu J, Hayashi D, et al. Prevalence of abnormalities in knees detected by MRI in adults without knee osteoarthritis: Population based observational study (Framingham Osteoarthritis Study). *BMJ*. 2012;345(7874):1-13. doi:10.1136/bmj.e5339

16. van Linschoten R, van Middelkoop M, Berger MY, et al. Supervised exercise therapy versus usual care for patellofemoral pain syndrome: an open label randomised controlled trial. *BMJ*. 2009;339:b4074. doi:10.1136/bmj.b4074

17. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF. *Arthritis Care Res*. 2011;63(SUPPL. 11):240-252. doi:10.1002/acr.20543

18. Kujala UM, Jaakkola LH, Koskinen SK, Taimela S, Hurme M, Nelimarkka O. Scoring of patellofemoral disorders. *Arthrosc J Arthrosc Relat Surg*. 1993;9(2):159-163. Accessed December 4, 2016. http://www.ncbi.nlm.nih.gov/pubmed/8461073

19. Nijs J, Van Geel C, Van Der Auwera C, Van De Velde B. Diagnostic value of five clinical tests in patellofemoral pain syndrome. *Man Ther*. 2006;11(1):69-77. doi:10.1016/j.math.2005.04.002

20. van der Heijden R, Vollebregt T, Bierma-Zeinstra S, van Middelkoop M. Strength and Pain Threshold Handheld Dynamometry Test Reliability in Patellofemoral Pain. *Int J Sports Med*. 2015;36(14):1201-1205. doi:10.1055/s-0035-1555855

21. Hunter DJ, Guermazi A, Lo GH, et al. Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score). *Osteoarthr Cartil*. 2011;19(8):990-1002. doi:10.1016/j.joca.2011.05.004

22. van der Heijden RA, Oei EHG, Bron EE, et al. No Difference on Quantitative Magnetic Resonance Imaging in Patellofemoral Cartilage Composition Between Patients With Patellofemoral Pain and Healthy Controls. *Am J Sports Med*. 2016;44(5):1172-1178. doi:10.1177/0363546516632507

23. Matzat SJ, van Tiel J, Gold GE, Oei EHG. Quantitative MRI techniques of cartilage composition. *Quant Imaging Med Surg*. 2013;3(3):162-174. doi:10.3978/j.issn.2223-4292.2013.06.04

24. Zhang Y, Nevitt M, Niu J, et al. Fluctuation of Knee Pain and Changes in Bone Marrow Lesions, Effusions and Synovitis on MRI: The MOST Study. *Arthritis Rheum*. 2011;63(3):1-13. doi:10.1002/art.30148.Fluctuation

25. Guermazi A, Alizai H, Crema MD, Trattnig S, Regatte RR, Roemer FW. Compositional MRI techniques for evaluation of cartilage degeneration in osteoarthritis. *Osteoarthr Cartil*. 2015;23(10):1639-1653. doi:10.1016/j.joca.2015.05.026

26. Lorenzo P, Bayliss MT, Heinegård D. Altered patterns and synthesis of extracellular matrix macromolecules in early osteoarthritis. *Matrix Biol*. 2004;23(6):381-391. doi:10.1016/j.matbio.2004.07.007

27. Regatte RR, Akella SVS, Lonner JH, Kneeland JB, Reddy R. T1?? mapping in human osteoarthritis (OA) cartilage: Comparison of T1?? with T2. *J Magn Reson Imaging*. 2006;23(4):547-553. doi:10.1002/jmri.20536

28. Schiphof D, Van Middelkoop M, De Klerk BM, et al. Crepitus is a first indication of patellofemoral osteoarthritis (and not of tibiofemoral osteoarthritis). *Osteoarthr Cartil*. 2014;22(5):631-638. doi:10.1016/j.joca.2014.02.008

29. Crema MD, Guermazi A, Sayre EC, et al. The association of magnetic resonance imaging (MRI)-detected structural pathology of the knee with crepitus in a population-based cohort with knee pain: The MoDEKO study. *Osteoarthr Cartil*. 2011;19(12):1429-1432. doi:10.1016/j.joca.2011.09.003

30. Starr AM, Wessely MA, Albastaki U, Pierre-Jerome C, Kettner NW. Bone marrow edema: Pathophysiology, differential diagnosis, and imaging. *Acta radiol*. 2008;49(7):771-786. doi:10.1080/02841850802161023

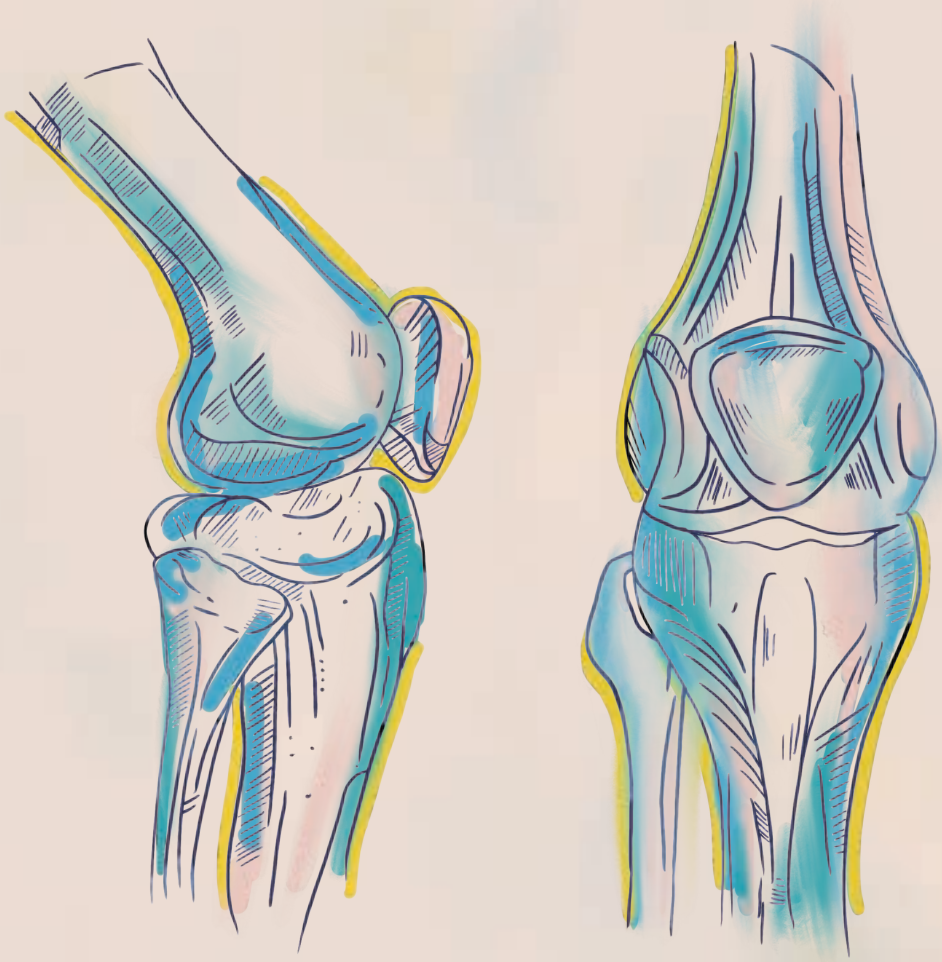
31. Eriksen EF, Ringe JD. Bone marrow lesions: A universal bone response to injury? *Rheumatol Int*. 2012;32(3):575-584. doi:10.1007/s00296-011-2141-2

32. Felson DT, Mclaughlin S, Goggins J, Lavalley MP, Gale ME. Bone Marrow Edema and Its Relation to Progression of Osteoarthritis. *Ann Intern Med*. 2003;139(12):330-336. doi:139/5_Part_1/330 [pii]

33. Roemer FW, Guermazi A, Javaid MK, et al. Change in MRI-detected subchondral bone marrow lesions is associated with cartilage loss: the MOST Study. A longitudinal multicentre study of knee osteoarthritis. *Ann Rheum Dis*. 2009;68(9):1461-1465. doi:10.1136/ard.2008.096834

34. Scher C, Craig J, Nelson F. Bone marrow edema in the knee in osteoarthrosis and association with total knee arthroplasty within a three-year follow-up. *Skeletal Radiol*. 2008;37(7):609-617. doi:10.1007/s00256-008-0504-x

35. Felson DT, Chaisson CE, Hill CL, et al. The Association of Bone Marrow Lesions with Pain in Knee Osteoarthritis. *Ann Intern Med*. 2001;134:541-549.



Chapter 4

Is patellofemoral pain a precursor to osteoarthritis?

Patellofemoral osteoarthritis and patellofemoral pain patients share aberrant patellar shape compared with healthy controls

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Abstract

Objectives: It has been hypothesized that patellofemoral pain, a common knee condition in adolescents and young adults, may be a precursor of degenerative joint changes and may ultimately lead to patellofemoral osteoarthritis. Since both conditions share several mechanical disease characteristics, such as altered contact area between the femur and patella and increased joint stress, we investigated whether these conditions share similar and different shape characteristics of the patella compared with normal controls.

Methods: This cross-sectional study compared three different study populations: 32 patellofemoral pain subjects (mean age, 32 years (22 to 45); 72% female); 56 isolated radiological patellofemoral osteoarthritis subjects (mean age, 54 years (44 to 58); 89% female); and 80 healthy control subjects (mean age, 52 years (44 to 58); 74% female). Measurements included questionnaires, and lateral and skyline radiographs of the knee. Two separate 30-point 2D statistical shape models of the patella were created from the lateral and skyline radiographs. A general linear model was used to test for differences in standardized shape modes (a specific shape variant of the patella) between patellofemoral osteoarthritis, patellofemoral pain, and controls, using Bonferroni correction and adjustment for body mass index and gender.

Results: Five shape modes showed statistically significant differences between groups: skyline modes 1 ($p < 0.001$), 8 ($p = 0.004$), and 10 ($p < 0.001$); and lateral modes 5 ($p = 0.002$) and 7 ($p = 0.002$). Skyline mode 8 and lateral mode 5 were similar for patellofemoral osteoarthritis and patellofemoral pain populations, while being statistically significant different from the control group.

Conclusion: Our results indicate that patellofemoral pain and patellofemoral osteoarthritis share similar shape characteristics, which are different from control subjects. These findings support the proposed continuum disease model of patellofemoral pain predisposing to the development of patellofemoral osteoarthritis.

Introduction

Patellofemoral pain (PFP) or anterior knee pain is a very common problem in young adults, particularly in women, characterized by pain behind and around the patella, often without clear aetiology[1]. Recent studies have suggested that PFP might predispose an individual to patellofemoral osteoarthritis (PFOA) later in life[2,3]. Patellofemoral osteoarthritis has not been investigated as frequently as tibiofemoral osteoarthritis (TFOA). However, the PFJ may be the first compartment affected in early knee osteoarthritis, which later affects both the patellofemoral and tibiofemoral compartments[4–6]. Moreover, a stronger association between pain and loss of function is seen in patients with isolated PFOA compared with those with isolated TFOA[4,7–9]. While no evidence of a causal relationship between PFP and PFOA has been shown[3,10], there are many overlapping disease characteristics that are associated with both PFP and PFOA, including patellar malalignment, quadriceps dysfunction, hip abductor dysfunction, painful crepitus with stair-climbing, and female gender[3,11–14].

One probable association that likely links PFP and PFOA is biomechanical dysfunction, since both PFP and PFOA are thought to be caused by alterations in patellofemoral joint mechanics[15,16]. Alterations in patellofemoral joint mechanics, such as malalignment, joint laxity, and muscular dysfunction, lead to pain and ultimately joint degeneration[11,17]. These changes may be produced by alterations in the contact area between patella and femur, resulting in increased joint contact stress and subsequent cartilage degeneration[16,18–21]. Thus, joint surface shape might influence contact areas and be associated with PFP and PFOA. The influence of joint shape on knee OA and PFP has been described individually, but similar shape patterns between these conditions have never been compared or investigated[22–26].

The influence of joint shape on knee OA has been described by Bredbenner et al[23], who found a greater width of the tibial plateau in anteroposterior (AP) and mediolateral (ML) direction in patients at risk of developing OA. This may be characterized as bone remodelling, one of the first signs of OA[27]. An increased ML width of both the femur and tibia is also seen in AP radiographs of patients with OA[24]. A recent study was able to predict the onset of knee OA, using a 3D bone shape model as the predictor[25]. Several bone shape variants have been described in PFP patients, as well as OA patients. Connolly et al[22] found, in a small study, that PFP patients had different contact areas with a higher prevalence of increased sagittal plane morphology ratios (patellar length/articular surface length) compared with healthy controls. Given the shared mechanical characteristics and the suggested link with joint shape, the aim of this study is to investigate possible similarities between the shape of the patella in PFOA and PFP patients using statistical shape modelling (SSM). Additionally, similarities in PFOA and PFP bone shape are compared with those of healthy control subjects. We hypothesize that there will be shape modes that show similarities between patients with PFP and PFOA, and differences compared with control subjects.

Patients and Methods

We undertook a retrospective case control study (level of evidence: III). We compared three groups: one group with a history of PFP (n = 32); one group with radiological PFOA (n = 56); and a healthy control group (n = 80). Subjects were selected from two different data sets: the baseline data from the Cohort Hip and Cohort Knee (CHECK) cohort[28]; and the five- to eight-year follow-up data of a randomized clinical trial (RCT) on the effectiveness of exercise therapy for PFP[29]. Informed consent was given by all subjects, and both studies were approved by the medical ethics committees of all participating centers; detailed descriptions of both study protocols can be found elsewhere[28,29]. From the CHECK study, the youngest subjects (up to 58 years at baseline) diagnosed with isolated radiological PFOA were selected. Additionally, we selected 80 control subjects in the same age range from the CHECK cohort without radiological knee OA, knee pain, or stiffness. Finally, we selected all PFP subjects with skyline and AP radiographs, aged between 22 and 47 years, from the follow-up data of the RCT. This group of PFP patients could be further subdivided into patients with a favourable recovery at follow-up ('completely recovered' or 'strongly recovered') and patients with an unfavourable recovery at follow-up ('slight improvement' to 'worse than ever'), measured on a seven-point Likert scale[29]. From both PFOA and PFP subjects, the most painful knee was selected for the analyses; from the control subjects, a knee was selected at random.

Measurements in both studies included questionnaires and radiographs. The questionnaires in both studies recorded demographics including: age; gender; education level (dichotomized into: high, "upper level high school, university"; and low, "elementary school, lower level high school, vocational college"); weight and height, from which body mass index (BMI) was calculated; bilateral symptoms (yes/no); and side of the most painful knee. Pain was assessed in both studies using pain at rest (11-point numerical rating scale (NRS))[30]. Also, pain, stiffness, and function were assessed with the Western Ontario and McMaster Universities Arthritis Index (WOMAC)[31] in the CHECK study, while WOMAC scores for the RCT study were calculated using the Knee Injury and Osteoarthritis Outcome Score (KOOS)[32]. The study population consisted of 56 subjects with PFOA (mean age, 54 years (44 to 58, SD 2.7); mean BMI, 29 (SD 5.1); 89% female), 32 PFP patients (mean age, 32 years (22 to 45, SD 8.5); mean BMI, 25 (SD 3.8); 72% female), and 80 control subjects (mean age, 52 years (44 to 58, SD 3.5); mean BMI, 25 (SD 3.6); 74% female). Characteristics are presented in table 1.

The radiological measurements for both studies consisted of semi-flexed weight-bearing AP radiographs, weight-bearing lateral radiographs, and skyline radiographs (30° and 45° knee flexion for CHECK and RCT study, respectively). Individual features of OA were scored according to the method of Altman et al[33]. The Kellgren and Lawrence (K&L) scores were recorded from the AP radiographs and used to exclude TFOA patients from all subject groups[34].

Table 1. Descriptive characteristics and radiographic findings of patients and controls

	Control (n = 80)	PFOA (n = 56)	PFP (n = 32)	p-value
Mean age, yrs (SD)	52.3 (3.5)	53.6 (2.7)	32.1 (8.5)	< 0.001*†‡
Gender, female	59 (73.8)	50 (89.3)	23 (71.9)	0.056*
Highly educated, yes	28 (35)	18 (32.1)	14 (43.8)	< 0.001*†‡
Mean BMI (kg/m2) (SD)	25.2 (3.6)	28.5 (5.1)	24.7 (3.8)	< 0.001*‡§
Bilateral complaints, yes	N/A	25 (44.6)	14 (43.8)	0.740¶
Side of most effected knee (right)	N/A	33 (58.9)	12 (37.5)	0.071¶
Mean NRS pain score (0 to 10) (SD)	N/A	3.7 (2.1)	1.6 (2.3)	< 0.001†**
Mean normalized WOMAC pain score (0 to 100) (SD)	20.4 (15.6)	25.6 (15.9)	45.8 (19.7)	< 0.001†**
Mean normalized WOMAC stiffness score (0 to 100) (SD)	28.9 (21.2)	35.9 (18.8)	21.5 (21.8)	0.002†**
Mean normalized WOMAC physical functioning score (0 to 100) (SD)	17.7 (13.8)	26.8 (17.4)	37.7 (17.3)	0.006†**
Kellgren and Lawrence score				< 0.001*†§
0 'none'	57 (71.3)	13 (23.2)	29 (90.6)	
1 'doubtful'	23 (28.7)	43 (76.8)	3 (9.4)	
>1 'minimal-severe'	0 (0)	0 (0)	0 (0)	
Osteophytes (lateral radiograph)				< 0.001*†§
None	63 (78.8)	5 (8.9)	28 (87.5)	
Doubtful	16 (20)	26 (46.4)	4 (12.5)	
Minimal	1 (1.3)	24 (42.9)	0 (0)	
Moderate	0 (0)	1 (1.8)	0 (0)	
Osteophytes (skyline radiograph)				< 0.001*†§
None	48 (60)	4 (7.1)	26 (81.3)	
Doubtful	25 (31.3)	11 (19.6)	6 (18.8)	
Minimal	4 (5)	37 (66.1)	0 (0)	
Moderate	0 (0)	2 (3.6)	0 (0)	
Joint space narrowing (skyline radiograph)				< 0.001*‡
None	73 (91.3)	35 (62.5)	30 (93.8)	
Doubtful	3 (3.8)	12 (21.4)	2 (6.3)	
Minimal	1 (1.3)	7 (12.5)	0 (0)	
Moderate	0 (0)	2 (3.6)	0 (0)	

Table 1. Descriptive characteristics and radiographic findings of patients and controls *(continued)*

	Control (n = 80)	PFOA (n = 56)	PFP (n = 32)	p-value
Sclerosis (skyline radiograph)				0.006*§
None	77 (85.6)	51 (91.1)	32 (100)	
Doubtful	0 (0)	5 (8.9)	0 (0)	
Minimal	0 (0)	0 (0)	0 (0)	
Moderate	0 (0)	0 (0)	0 (0)	

* One-way analysis of variance.
† Statistically significant difference between pFoA and pFp group.
‡ Statistically significant difference between control and pFp group.
§ Statistically significant difference between control and pFoA group.
¶ Chi-squared test.
** Unpaired Student's t-test.
PFOA, patellofemoral osteoarthritis; PFP, patellofemoral pain; N/A, not available; NRS, numerical rating scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

All individual features were scored by four different observers in the CHECK cohort. The interobserver reliability of K&L scoring in the CHECK cohort has been described previously, indicating fair to near perfect reliability (interobserver with trained reader prevalence bias adjusted κ score: 0.28 to 0.79)[35]. The radiographs of the PFP patients were scored by a trained medical student who was unaware of the context of the study and had established reliability (inter-observer with trained reader prevalence bias adjusted κ score: 0.61 to 0.75).

Radiological PFOA was defined according to the methods of Duncan et al[36] and Baker et al.[37] The presence of isolated PFOA was defined as a K&L score < 2 combined with: 1) an osteophytes grade ≥2 on skyline radiographs; 2) an osteophytes grade ≥2 on lateral radiographs; or 3) grade ≥2 joint space narrowing and grade ≥1 osteophytes on skyline radiographs.

Statistical shape models (SSM) were used to analyze the shape of the patella. A SSM quantitatively describes the complete variation in shape within a population by a set of statistically independent measures called modes. Each mode describes a specific shape variant of, in this case, the patella. The value of a mode for a specific patient indicates how strongly the shape variant, represented by the mode, is present in that patient. Therefore, if two patients had similar values for all the modes of variance, their patellae would be nearly identical. Two patients with vastly different values for all modes would have patellae, which look completely different. Even one different mode of variance can completely change the shape of a patella. Two separate SSMs were constructed from both the lateral and skyline radiographs. We limited the number of modes by restricting the SSMs to describe no more than 95% of the shape variation in our data set, as is customary in statistical shape modelling. Freely available active shape model software tools, described by Cootes

et al[38], were used to construct our SSMs. We used a 30-contour-point model to describe the patella in both models. These models were constructed by placing two points on distinct landmarks of the patella (the most lateral and medial corners on the skyline view, and the most superior and inferior corners for the lateral view) and semi-automatically placing the other points, at equal distance between these landmarks, using the active shape model within the software. After all points were applied to all subjects, the software used principal component analysis to transform the coordinates of the contour points into a smaller set of independent variables, the shape modes.

Statistical analysis

Descriptive statistics were used to describe the demographics, pain, and function of the subjects. Differences between the three study groups were tested using unpaired Student's *t*-tests (NRS, WOMAC scores), chi-squared tests (bilateral complaints, side of most affected knee), and one-way analysis of variance (ANOVA) (age, gender, education level, BMI, K&L scores, osteophytes, joint space narrowing, sclerosis), after confirming normal distributions. A general linear model with *post hoc* analysis, using Bonferroni correction for multiple testing, was used to assess the association between independent shape modes and group status (PFOA, PFP, or control), both with and without adjusting for gender and BMI[39]. Residuals followed a normal distribution (Shapiro–Wilk and QQ plots) and had homogeneous variance (Levene's test). Mean values for each group and mean differences between groups of standardized shape modes were reported for all statistically significant modes. Statistical significance was set at $p < 0.05$. Differences in modes associated with PFP between the PFP subgroups with a favourable recovery and unfavourable recovery at follow-up were tested using Student's *t*-test, also using a Bonferroni correction for multiple comparisons. Missing values were handled by performing complete case analysis, only using subjects who have no missing values in the analysis.

Results

Compared with PFOA patients, PFP patients were significantly younger ($p < 0.001$, one-way ANOVA), higher educated ($p < 0.001$, one-way ANOVA), had a lower BMI ($p < 0.001$, one-way ANOVA), less pain (NRS) ($p < 0.001$, unpaired Student's *t*-test) and higher WOMAC pain ($p < 0.001$, unpaired Student's *t*-test), stiffness ($p = 0.002$, unpaired Student's *t*-test), and function scores ($p = 0.006$, unpaired Student's *t*-test). A K&L score of 1 was seen in 28.7% of the control patients compared with 76.8% in the PFOA group and only 9.4% in the PFP group.

The skyline shape analysis consisted of 150 subjects (12 control and six PFOA cases from the CHECK data, 18 in total, were excluded due to poor quality of the radiograph) while the lateral shape analysis consisted of 156 subjects (ten control and two PFOA cases from the CHECK data, 12 in total, were excluded due to poor quality of the radiograph). The skyline model produced 12 modes of variance (Supplementary figure a), while the lateral model

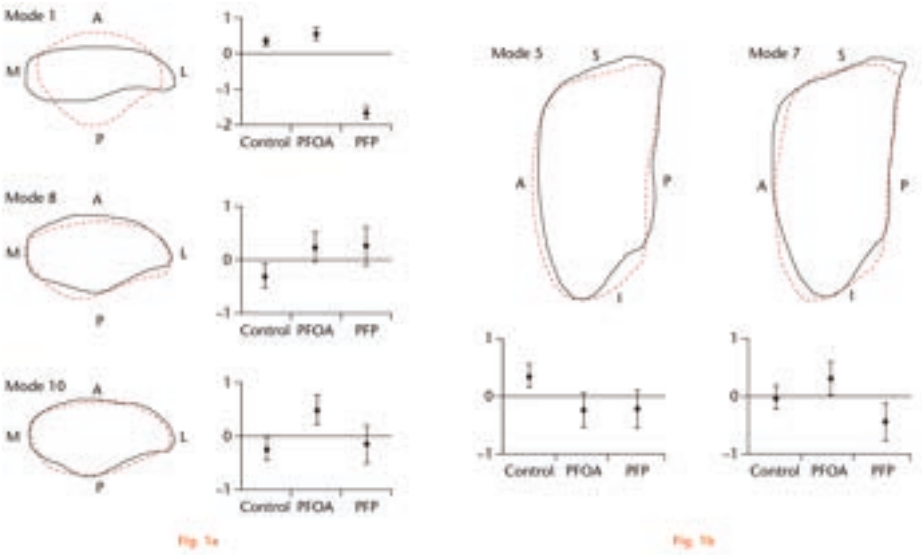
produced 17 modes of variance (Supplementary figure b). This resulted in a Bonferroni adjusted threshold for significance of 0.004 and 0.003, respectively.

Table 2. Mean values (and standard deviations) of standardized modes and p-values of group associations

	Control	PFOA	PFP	P-value	*Adjusted p-value
Skyline mode 1	0.33 (0.51)	0.54 (0.58)	-1.68 (0.47)	< 0.001	< 0.001
Skyline mode 2	0.18 (0.94)	-0.28 (1.14)	-0.15 (0.72)	0.031†	0.040†
Skyline mode 8	-0.30 (0.96)	0.24 (0.98)	0.26 (1.02)	0.004	0.006
Skyline mode 10	-0.24 (0.89)	0.48 (0.99)	-0.16 (0.98)	< 0.001	< 0.001
Lateral mode 4	0.09 (1.03)	-0.29 (0.90)	0.15 (0.91)	0.048†	0.053†
Lateral mode 5	0.33 (0.89)	-0.25 (1.09)	-0.22 (0.94)	0.002	0.003
Lateral mode 7	-0.02 (0.95)	0.32 (0.99)	-0.45 (0.98)	0.002	0.005

* A general linear model with Bonferroni correction was used to assess the association between independent shape modes and group status, both with and without adjusting for gender and body mass index.
† Considered as non-significant following bonferroni correction.

Figure 1.a) Skyline and **1.b)** lateral modes displayed as -2.5 (dashed red line) and +2.5 (solid black line) standard deviations for visualization purposes. Error bars show mean values of groups (2× standard error) for corresponding modes. Anterior (A), medial (M), lateral (L), posterior (P), superior (S), and inferior (I) locations are defined.



PFOA, patellofemoral osteoarthritis; PFP, patellofemoral pain.

The skyline shape model showed statistically significant associations between group status and modes 1, 8, and 10 (table 2, Fig. 1a). *Post hoc* analyses revealed statistically significant differences in skyline shape between all three subject groups within mode 1 (table 3). In addition, statistically significant differences were found between the control subjects and both PFOA and PFP subjects in mode 8. Mode 10 showed a statistical significant difference between the PFOA subjects compared with both control and PFP subjects. Adjustment for gender and BMI did not influence the strength of the three associations. Modes 1, 8, and 10 described a variance within the population of 43%, 1.9%, and 1.1%, respectively.

The lateral shape model showed statistically significant associations for group status and mode 5 and 7 (Fig. 1b). *Post hoc* analysis showed statistically significant differences in lateral patellar shape between control subjects and both PFOA and PFP subjects in mode 5 (table 3). In addition, *post hoc* analysis showed statistically significant differences in lateral patellar shape between PFOA and PFP subjects in mode 7. Adjustment for gender and BMI did not influence the strength of these associations. Mode 5 and 7 described a variance within the population of 8.5% and 4.0%, respectively. No significant differences ($p < 0.05$) were seen on any of the five statistically significant modes of the shape models between the subgroups of PFP patients with and without a favourable recovery.

Table 3. Post hoc analysis between groups (general linear models using pairwise comparisons)

	Variance explained (%)	P-value control vs PFP	P-value control vs PFOA	P-value PFP vs PFOA
Skyline Mode 1	43	**<0.001**	**0.047**	**<0.001**
Skyline Mode 8	1.9	**0.020**	**0.044**	1.000
Skyline Mode 10	1.1	1.000	**<0.001**	**0.008**
Lateral Mode 5	8.5	**0.022**	**0.012**	1.000
Lateral Mode 7	4.0	**0.096**	0.302	**0.004**

* Statistically significant

Discussion

Our study gave us the unique opportunity to study patellar bone shape in three distinct populations. Two shape variants were similar for both the PFOA and PFP groups and statistically different from the control group. The first shape variant indicates that both PFOA and PFP subjects have a more lateral positioned vertical ledge on the posterior side of the patella (Fig. 1, skyline mode 8, solid black line) compared with the healthy control group. Additionally, both PFOA and PFP subjects seem to have a rounder inferior-posterior articular area on their patella, increasing the articular surface area (Fig. 1, lateral mode 5, dashed red line) when compared with the control subjects. It has been suggested that this longer inferior-posterior area negatively affects the fit of the patella within the trochlear

groove, consequently leading to increased shear forces and joint stresses and finally leading to cartilage degeneration[11], while an increased articular surface area on the patella has been positively correlated with maltracking[26]. Therefore, the results seem to support the hypothesis that the initial onset of PFOA commences early in PFP patients, which might be a result of aberrant patellofemoral joint (PFJ) kinematics that are already present in younger PFP knees.

The associations found in skyline mode 1 and 10 are only correlated with either PFP or PFOA. Mode 1 suggests a large difference in bone shape, indicating that PFP patients have a more circular patella in the frontal plane, compared with control and PFOA subjects. However, this large difference may be a consequence of differences in knee flexion angle in the radiography protocol between the CHECK cohort and long-term RCT follow-up data. Skyline mode 10 suggests changes in vertical ledge depth and positioning similar to mode 8, but here only the PFOA subjects were different from the control group. The vertical ledge on the patella again seems to be located more laterally in PFOA subjects compared with control subjects, but also compared with PFP subjects. Lateral mode 7 suggests that subjects with PFP have a wider inferior patella compared with PFOA subjects, while at the same time being smaller and rounder on the superior side.

While our findings suggest that PFP and PFOA share similar patella shape variants, certain limitations should be acknowledged. First, we used data from two different studies and, consequently, slightly different radiography protocols. In particular, the difference in knee flexion angle between the cohort and RCT for the skyline radiographs might have had an effect on the projected 2D bone shape. This difference in projection angle appears to be captured in skyline mode 1. The other modes are unaffected by differences in projection angle since all modes are statistically independent as a result of their construction through Principal Component Analysis, which is part of the SSM.

Some of the shape differences found between our study populations might be explained by age differences. This is, however, inherent to our study, as we compared a condition that is more prevalent in a younger population (i.e. PFP) to a condition that affects a relatively older population (i.e. PFOA). Additionally, a disadvantage of shape modes is that it is not intuitively understood what these modes truly represent, since each mode is a composite of different correlated shape aspects. However, a mode might be used to derive a more intuitive geometrical marker, which can be measured directly and could be used in future studies as a prognostic or diagnostic biomarker. However, such a measure will only partly represent a shape mode and thus might not have the same associative strength of a shape mode.

Our study groups consisted largely of female patients, limiting the generalizability of our study in male populations. However, both OA[40] and PFP[41] are significantly more prevalent

in women, and therefore our population seems to be a good representation of the patient population as a whole.

Finally, we only modelled the shape of the patella, without considering the surface and effects of the femur. This limits generalizability of the results of our study to the patella only, and we are therefore not able to draw any conclusions as to the fit between the patella and the femoral trochlea. The fit between patella and trochlea is impossible to study in 2D radiographs, and the trochlear groove is not completely visible in the skyline radiographs. By only modelling the patella, we were able to detect very sensitive local or regional differences within the patella shape, which may be associated the PFP and PFOA.

In summary, we have demonstrated that some shape aspects, derived from radiograph-based 2D patellar bone shape modeling, are similar in subjects with PFP and PFOA, and differ from normal controls. These findings give support to the hypothesis that suggests altered patellofemoral joint kinematics leads to increase peak joint stress and pain in the young patient and may predispose to patellofemoral OA at a later life.

References

1. Rathleff MS, Skuldbøl SK, Rasch MNB, Roos EM, Rasmussen S, Olesen JL. Care-seeking behaviour of adolescents with knee pain: a population-based study among 504 adolescents. *BMC Musculoskelet Disord*. 2013;14:225. doi:10.1186/1471-2474-14-225
2. Thomeé R, Augustsson J, Karlsson J, Thomee R. Patellofemoral pain syndrome: a review of current issues. *Sport Med*. 1999;28(4):245-262.
3. Crossley KM. Is patellofemoral osteoarthritis a common sequela of patellofemoral pain? *Br J Sports Med*. 2014;48(6):409-410. doi:10.1136/bjsports-2014-093445
4. Duncan R, Peat G, Thomas E, Hay EM, Croft P. Incidence, progression and sequence of development of radiographic knee osteoarthritis in a symptomatic population. *Ann Rheum Dis*. 2011;70(11):1944-1948. doi:10.1136/ard.2011.151050
5. Stefanik JJ, Guermazi A, Roemer FW, et al. Changes in patellofemoral and tibiofemoral joint cartilage damage and bone marrow lesions over 7 years: The Multicenter Osteoarthritis Study. *Osteoarthr Cartil*. Published online 2016:1-7. doi:10.1016/j.joca.2016.01.981
6. van Middelkoop M, Bennell KL, Callaghan MJ, et al. International patellofemoral osteoarthritis consortium: Consensus statement on the diagnosis, burden, outcome measures, prognosis, risk factors and treatment. *Semin Arthritis Rheum*. Published online 2017:1-10. doi:10.1016/j.semarthrit.2017.09.009
7. Duncan R, Peat G, Thomas E, Wood L, Hay E, Croft P. Does isolated patellofemoral osteoarthritis matter? *Osteoarthr Cartil*. 2009;17(9):1151-1155. doi:10.1016/j.joca.2009.03.016
8. Stefanik JJ, Niu J, Gross KD, Roemer FW, Guermazi a., Felson DT. Using magnetic resonance imaging to determine the compartmental prevalence of knee joint structural damage. *Osteoarthr Cartil*. 2013;21(5):695-699. doi:10.1016/j.joca.2013.02.003
9. Hinman RS, Crossley KM. Patellofemoral joint osteoarthritis: An important subgroup of knee osteoarthritis. *Rheumatology*. 2007;46(May):1057-1062. doi:10.1093/rheumatology/kem114
10. Thomas MJ, Wood L, Selfe J, Peat G. Anterior knee pain in younger adults as a precursor to subsequent patellofemoral osteoarthritis: a systematic review. *BMC Musculoskelet Disord*. 2010;11:201. doi:10.1186/1471-2474-11-201
11. Mills K, Hunter DJ. Patellofemoral joint osteoarthritis: An individualised pathomechanical approach to management. *Best Pract Res Clin Rheumatol*. 2014;28(1):73-91. doi:10.1016/j.berh.2014.01.006
12. Lankhorst NE, Bierma-Zeinstra SMA, van Middelkoop M. Risk Factors for Patellofemoral Pain Syndrome: A Systematic Review. *J Orthop Sports Phys Ther*. 2012;42(2). doi:10.2519/jospt.2012.3803
13. Peat G, Duncan RC, Wood LR, Thomas E, Muller S. Clinical features of symptomatic patellofemoral joint osteoarthritis. *Arthritis Res Ther*. 2012;14(2):R63. doi:10.1186/ar3779
14. Kobayashi S, Pappas E, Fransen M, Refshauge K, Simic M. The prevalence of patellofemoral osteoarthritis: A systematic review. *Osteoarthr Cartil*. 2016;23(May):A189. doi:10.1016/j.joca.2015.02.968
15. Hunter D, Zhang Y, Niu J, et al. Patella malalignment, pain and patellofemoral progression: The Health ABC Study. *October*. 2008;28(30):4439-4448. doi:10.1037/a0013262.Open
16. Sheehan FT, Derasari A, Brindle TJ, Alter KE. Understanding patellofemoral pain with maltracking in the presence of joint laxity: Complete 3D in vivo patellofemoral and tibiofemoral kinematics. *J Orthop Res*. 2009;27(5):561-570. doi:10.1002/jor.20783
17. Fulkerson JP, Shea KP. Current concepts review: Disorder of patellofemoral alignment. *J Bone Jt Surg*. 1990;72A:1424-1429.

18. Teng H-L, MacLeod TD, Kumar D, Link TM, Majumdar S, Souza RB. Individuals with isolated patellofemoral joint osteoarthritis exhibit higher mechanical loading at the knee during the second half of the stance phase. *Clin Biomech*. Published online 2015. doi:10.1016/j.clinbiomech.2015.02.008

19. Herzog W, Diet S, Suter E, et al. Material and functional properties of articular cartilage and patellofemoral contact mechanics in an experimental model of osteoarthritis. *J Biomech*. 1998;31(12):1137-1145. doi:10.1016/S0021-9290(98)00136-5

20. Salsich GB, Perman WH. Patellofemoral joint contact area is influenced by tibiofemoral rotation alignment in individuals who have patellofemoral pain. *J Orthop Sports Phys Ther*. 2007;37(9):521-528. doi:10.2519/jospt.2007.37.9.521

21. Fitzpatrick CK, Baldwin M a., Laz PJ, FitzPatrick DP, L. Lerner A, Rullkoetter PJ. Development of a statistical shape model of the patellofemoral joint for investigating relationships between shape and function. *J Biomech*. 2011;44(13):2446-2452. doi:10.1016/j.jbiomech.2011.06.025

22. Connolly KD, Ronsky JL, Westover LM, Küpper JC, Frayne R. Differences in patellofemoral contact mechanics associated with patellofemoral pain syndrome. *J Biomech*. 2009;42(16):2802-2807. doi:10.1016/j.jbiomech.2009.07.028

23. Bredbenner TL, Eliason TD, Potter RS, Mason RL, Havill LM, Nicolella DP. Statistical shape modeling describes variation in tibia and femur surface geometry between Control and Incidence groups from the Osteoarthritis Initiative database. *J Biomech*. 2010;43(9):1780-1786. doi:10.1016/j.jbiomech.2010.02.015

24. Haverkamp DJ, Schiphof D, Bierma-Zeinstra SM, Weinans H, Waarsing JH. Variation in joint shape of osteoarthritic knees. *Arthritis Rheum*. 2011;63(11):3401-3407. doi:10.1002/art.30575

25. Neogi T, Bowes MA, Niu J, et al. Magnetic resonance imaging-based three-dimensional bone shape of the knee predicts onset of knee osteoarthritis: Data from the osteoarthritis initiative. *Arthritis Rheum*. 2013;65(8):2048-2058. doi:10.1002/art.37987

26. Harbaugh CM, Wilson N a., Sheehan FT. Correlating femoral shape with patellar kinematics in patients with patellofemoral pain. *J Orthop Res*. 2010;28(7):865-872. doi:10.1002/jor.21101

27. Burr DB, Gallant MA. Bone remodelling in osteoarthritis. *Nat Rev Rheumatol*. 2012;8(11):665-673. doi:10.1038/nrrheum.2012.130

28. Wesseling J, Boers M, Viergever MA, et al. Cohort Profile : Cohort Hip and Cohort Knee (CHECK) study. *Int J Epidemiol*. Published online 2014:1-9. doi:10.1093/ije/dyu177

29. Lankhorst NE, van Middelkoop M, Crossley KM, et al. Factors that predict a poor outcome 5–8 years after the diagnosis of patellofemoral pain: a multicentre observational analysis. *Br J Sports Med*. 2016;50(14):881-886. doi:10.1136/bjsports-2015-094664

30. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF. *Arthritis Care Res*. 2011;63(SUPPL. 11):240-252. doi:10.1002/acr.20543

31. Jinks C, Jordan K, Croft P. Measuring the population impact of knee pain and disability with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). *Pain*. 2002;100(1-2):55-64. doi:10.1016/S0304-3959(02)00239-7

32. Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health Qual Life Outcomes*. 2003;1(1):64. doi:10.1186/1477-7525-1-64

33. Altman RD, Gold GE. *Atlas of Individual Radiographic Features in Osteoarthritis, Revised*. Vol 15.; 2007. doi:10.1016/j.joca.2006.06.017

34. Kellgren JH, Lawrence JS. Radiological Assessment of Osteo-Arthrosis. *Ann Rheum Dis*. 1957;16(4):494-502. doi:10.1136/ard.16.4.494

35. Damen J, Schiphof D, Wolde S Ten, Cats HA, Bierma-Zeinstra SMA, Oei EHG. Inter-observer reliability for radiographic assessment of early osteoarthritis features: The CHECK (cohort hip and cohort knee) study. *Osteoarthr Cartil*. 2014;22(7):969-974. doi:10.1016/j.joca.2014.05.007

36. Duncan RC, Hay EM, Saklatvala J, Croft PR. Prevalence of radiographic osteoarthritis - It all depends on your point of view. *Rheumatology*. 2006;45(6):757-760. doi:10.1093/rheumatology/kei270

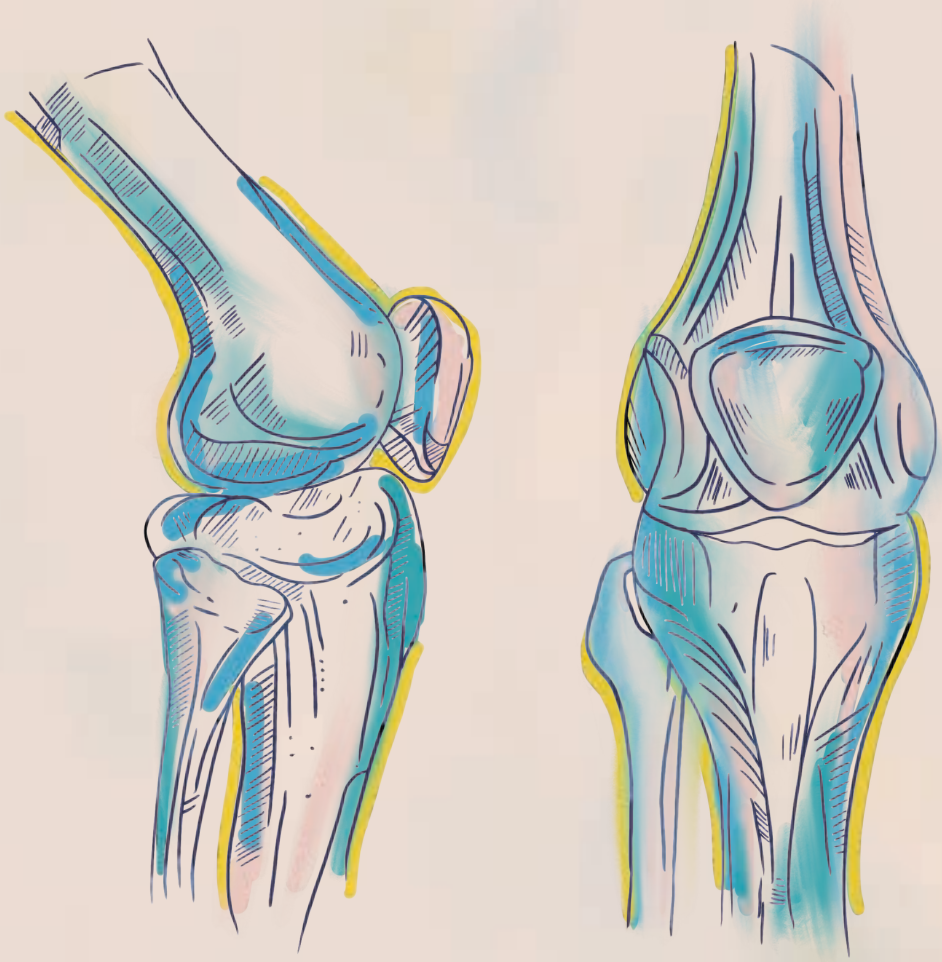
37. Baker KR, Xu L, Zhang Y, et al. Quadriceps weakness and its relationship to tibiofemoral and patellofemoral knee osteoarthritis in Chinese: the Beijing osteoarthritis study. *Arthritis Rheum*. 2004;50(6):1815-1821. doi:10.1002/art.20261

38. Cootes TF. Statistical Models of Appearance for Computer Vision. 2004;M(1):175-200. doi:10.1.1.58.1455

39. Bland JM, Altman DG. Multiple significance tests: the Bonferroni method. *BMJ*. 1995;310(6973):170. doi:10.1136/bmj.e509

40. O'Connor MI. Osteoarthritis of the Hip and Knee: Sex and Gender Differences. *Orthop Clin North Am*. 2006;37(4):559-568. doi:10.1016/j.ocl.2006.09.004

41. Boling M, Padua D, Marshall K, Guskiewicz K, Pyne S, Beutler A. Gender differences in the incidence and prevalence of patellofemoral pain syndrome. *Scand J Med Sci Sport*. 2010;20(5):725-730. doi:10.1111/j.1600-0838.2009.00996.x.Gender



Chapter 5

Patients with patellofemoral pain show different 3D patellar shape compared to healthy control participants.

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Abstract

Aims: The aim of the current study is to 1) quantitatively identify 3D patellar shape and evaluate whether significant differences in 3D shape factors exist between patients with patellofemoral pain and healthy controls; and 2) explore their potential association with the presence of structural abnormalities on the patella.

Methods: MRI from 62 patients with patellofemoral pain and 69 controls (mean age: 23.5 (7.1) and 23.1 (5.9) years) were acquired. 3D statistical patellar shape models were derived using semi-automatic segmentation to extract the patellar shape from the MRI. We scored bone structural abnormalities based on the MRI Osteoarthritis Knee Score. Using regression analysis, we determined associations between shape, group status and MRI Osteoarthritis Knee Score.

Results: 3D patellar shape was associated with patellofemoral pain. The lateral side and apex of the patella was more rounded in patients with patellofemoral pain, relative to controls (shape mode 16: odds Ratio 0,66 (95% CI 0,45-0,95). Patients with patellofemoral pain demonstrated a more diagonal, as compared to a horizontal, patellar base (shape mode 22: Odds ratio 1,56 (1,03-2,37)). 3D patellar shape was associated with the presence of patellar bone marrow lesions, anterior femoral osteophytes and bone marrow lesions, and Hoffa synovitis.

Conclusion: 3D patellar shape variations can statistically significantly be distinguished between patients with patellofemoral pain and healthy controls. In this young population, 3D patellar shape is already associated with the presence of structural abnormalities, which are linked to OA.

Introduction

Anatomical shape deviations and their relationship with disease and pathology has recently gained attention in the medical imaging research field[1–3]. The anatomical shape of bones and joints are essential to their function and it has been reported that shape abnormalities increase the risk of developing impairments and the severity of these impairments[4]. For instance, a cam lesion, which depicts an abnormal morphology of the femoral head and neck junction, is associated with femoroacetabular impingement. Furthermore, aberrant bone shape has been shown to predict development of structural abnormalities such as osteophytes and bone marrow lesions, linked to hip OA[5,6].

Recently, statistical shape modeling (SSM) techniques have become an important tool in bone research[7]. Unlike most 2D bone measures that rely on just 2 to 4 points to measure a single distance or angle, this technique allows us to quantify the complete three-dimensional (3D) bone shape, providing greater insights to the association between altered morphology and pathology[2]. SSMs of the knee have been previously used to evaluate whether the morphologies of the tibia and femur of individuals developing tibiofemoral knee OA are different from those who have had no signs of OA[1], whether bone shape could be used in the prediction of the onset of the tibiofemoral knee OA[8] and its progression[9] and whether certain bone shape variations of the knee are associated with the presence of radiographic tibiofemoral OA[10]. These studies have shown that bone shape is statistically significantly different between participants with and without tibiofemoral OA, and that bone shape may be a biomarker for knee tibiofemoral OA progression[9]. A biomarker for early OA detection or progression is essential in the search for successful (early) treatments of OA.

Since patellofemoral pain (PFP) has been suggested as a precursor to patellofemoral osteoarthritis (PFOA)[11] and knee OA commonly begins in the patellofemoral joint (PFJ)[12,13], 3D bone shape might also be a promising biomarker for patients with PFP. The contribution of a set of simple 2D geometric parameters (e.g., trochlear sulcus depth and Insall-Salvati ratio) to PFP has been previously investigated[14,15]. In literature, associations with the presence of PFP and morphology ratios of the patella, patella alta, patella tilt and maltracking have been described [16,17,18,19]. Nevertheless, these measures of bone shape are limited in their ability to describe overall patellar geometry. The newly emerging SSM techniques do have the ability to describe overall shape within a population of interest (e.g., individuals with and without PFP) using the relationship of independent patellar shapes (i.e. shape modes)[7].

Therefore, the aim of the current study is to quantitatively identify 3D shape variations in the patella, to evaluate whether significantly different shape factors exist between patients with PFP and healthy controls and to explore their potential association with the presence of structural abnormalities on the patella.

Patients and methods

Study Population

Data for the current study was derived from a previously completed case-control study. Data was collected from 134 participants (64 with PFP and 70 healthy controls)[20]. Participants were between 14 and 40 years old with 56% being females (Table 1). Patients with PFP were recruited via general practitioner, physical therapist or sport physician. Controls were recruited via sports team members and friends of the recruited patients with PFP. To be included in the PFP cohort, participants had to have crepitus or knee pain during at least 3 of the following activities: stair climbing, squatting, running, cycling, and sitting for a prolonged period with flexed knees. The minimum to maximum symptom duration for inclusion was 2 months to 2 years. The 2-year criteria focused the study on early onset PFP. Exclusion criteria were pathological knee conditions of the affected knee, previous episodes of PFP, previous surgery, injury or trauma leading to PFP in the affected knee. We excluded control participants if they had current or previous PFP, previous traumatic knee injuries, pathology of, or surgery on either knee. Additionally, first-grade family members of patients with PFP were not eligible to be a control participant. Both PFP and control participants were excluded if they had insufficient knowledge of the Dutch language to complete the questionnaires or contraindication evaluation forms for Magnetic Resonance Imaging (MRI) contrast. The medical ethics committee of the Erasmus medical center approved this study (MEC-2012-342). Informed consent was obtained at the start of inclusion from all participants.

Table 1. Characteristics of study participants.

	PFP n=62	Control n=69
Female sex (n (%))	34 (54.8)	41 (59.4)
Age, years (mean (SD))	23.5 (7.1)	23.1 (5.9)
BMI, kg/m^2 (mean (SD))	23.6 (3.7)	22.3 (3.0)
Presence of crepitation (n (%))	29 (46.8)	20 (28.9)
Sport participation		
At inclusion (n (%))	38 (61.3)	55 (79.7)
Before onset of pain (n (%))	47 (85.5)*	N.A.
Pain in rest, NRS/10 (mean (SD))	3.9 (2.4)	N.A.
Pain during exercise, NRS/10 (mean (SD))	6.5 (2.2)	N.A.
AKPS score, 0-100 (mean (SD))	66.7 (11.5)	N.A.
Complaint duration, months (mean, (SD))	11.8 (7.2)	N.A.
Bilateral complaints (n (%))	31 (50.0)	N.A.

* Data missing (n=7).
PFP; patellofemoral pain, BMI; body mass index, NRS; numerical pain scale, AKPS; anterior knee pain score.

Measurements

Questionnaires regarding demographics (gender, age, BMI) and knee complaints were completed by all participants. The latter included duration of complaints, pain at rest and during activity (measured using a numerical rating scale (NRS) of 1-10[21]), and function (measured using the Anterior Knee Pain Scale (AKPS) on a 0-100 scale[22]). MR images were acquitted using a 3 Tesla scanner (Discovery MR750, GE Healthcare, Milwaukee, WI, USA) with a dedicated eight-channel knee coil (Invivo Inc., Gainesville, USA). The MRI protocol was comprised of sagittal, axial, and coronal fast spin-echo proton density–weighted sequences (slice thickness of 3 mm) and sagittal, axial T2-weighted sequences with fat suppression (slice thickness of 3 mm). Furthermore, a 3D high-resolution sagittal with and without fat-saturated spoiled gradient-echo sequence was acquired with a slice thickness of 0.5 mm, repetition time of 17 ms, echo time of 5.4 ms, flip angle of 12, 288 3 192 matrix, and 15-cm field of view. Structural abnormalities associated with OA in the patellofemoral joint (bone marrow lesions, osteophytes, cartilage defects and Hoffa synovitis) were identified and recorded by a senior resident and radiologist with musculoskeletal sub specialization using the MRI OA Knee Score (MOAKS) assessment[23].

Statistical Shape Model of the Patella

Patellae were segmented from the MRI scans using a custom made semi-automatic recursive ray-tracing segmentation algorithm[24], which has been embedded in the software MIPAV (NIH, Bethesda, USA). The algorithm required a manual segmentation of the first, middle and final MRI slices on which the patella was visible and has a DICE similarity score of 96%[24]. The first author (*JE*), while blinded to participant cohort, visually checked and manually corrected the segmentations, when deemed necessary. 3D triangulated patellar surfaces (i.e., triangles with a maximum tangent edge size of 0.9 mm) were obtained using Geomagic (3D systems, North Carolina, USA).

A 3D SSM of the patella was built based on the triangulated bone segmentations. First, all participants' patellae were registered using an unbiased registration algorithm, which minimized differences in position, orientation and scaling among patellae[25]. Following the registration, corresponding points (n = 15924) across the registered patellae were automatically established[2,25]. The registration parameters (the scale parameter for the mixture of Gaussian, $\sigma = 0.6$; the number of points in the mean cloud, $n_m = 2000$; the trade-off parameter, $\lambda = 10\text{-}3$) were determined based on numerical experiments[2,25]. Finally, the main bone shape variations were extracted by performing principal component analysis on the covariance matrix of the corresponding points. To discard shape modes describing noise and preserve the ones describing patellar shape variations, parallel analysis was performed[26].

Statistical analyses

Logistic regression analyses, with adjustment for age, BMI and sex were performed to test the association between independent shape modes and group status (PFP versus controls). For the secondary outcomes, logistic regression analyses were performed to study the association between the presence of MOAKS features and the independent shape modes, adjusted for age, sex, BMI and group status. The MOAKS features included were patellar osteophytes, patellar bone marrow lesions (BML), patellar minor cartilage defects, anterior femoral osteophytes, anterior femoral BML and Hoffa synovitis. Results are expressed in odds ratios (ORs), with accompanying 95% confidence intervals (CIs). Significance was set at the 5% level. Differences in patient characteristics between groups were tested using student's t-tests. All statistical analyses were performed using SPSS using complete-case analysis (version 16.0, SPSS Inc., USA).

Results

The original study population included 134 participants[20]. However, some participants were excluded from this study due to low-quality MRI scans preventing us to segment their patellae (1 control participant and 1 PFP patient) and extremely aberrant patellar shape (patella bipartita, 1 PFP patient). Thus, the final cohort can be found in Table 1. Patients with PFP demonstrated higher BMI and lower sports participation at inclusion, relative to controls.

The first 25 shape modes (Figure 1) were retained for the logistic regression analyses. Shape variations described by shape modes 16 ($p = 0.025$; OR = 0.66 and CI = 0.45-0.95) and 22 ($p=0.036$; OR = 1.56 and CI = 1.03-2.37) showed significant associations with the presence of PFP (Table 2). Patellae of participants with PFP were positively deviated from the mean for mode 16. This translates in a more rounded shape at the patellar apex and lateral side in participants with PFP, while controls demonstrate a pointier patellar apex and lateral side (Figure 2, Online Appendix 1). Patellae of participants with PFP were negatively deviated from the mean for mode 22. This translates in a more diagonal patellar base in participants with PFP, while a more horizontal patellar base was observed in controls (Figure 2, Online Appendix 2). Modes 16 and 22 described 1.42% and 0.87% of total shape variation in the patella. Patellar shape at the extremes (i.e., 3 standard deviations away from the mean shape) of shape modes 16 and 22 deviated less than 1 mm from the mean patellar shape.

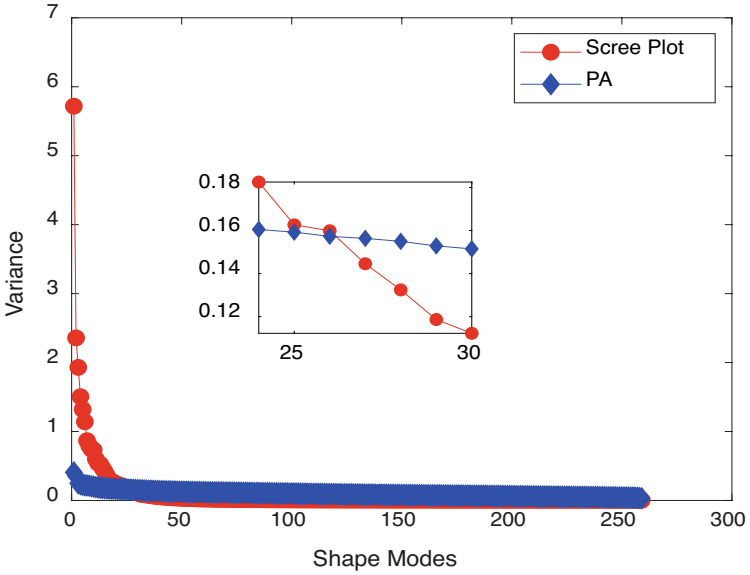
Table 2. Associations between group status (PFP patient and control participant) and patellar shape modes (OR with 95% CI).

	Crude associations	**Adjusted* associations**
Shape mode 1	0,88 (0,60-1,28)	0,89 (0,60-1,31)
Shape mode 2	1,13 (0,80-1,59)	1,23 (0,86-1,76)
Shape mode 3	0,96 (0,69-1,35)	0,99 (0,67-1,46)
Shape mode 4	1,03 (0,75-1,41)	0,97 (0,70-1,36)
Shape mode 5	1,11 (0,79-1,57)	1,06 (0,74-1,52)
Shape mode 6	0,96 (0,68-1,34)	0,89 (0,62-1,27)
Shape mode 7	1,19 (0,82-1,72)	1,16 (0,79-1,70)
Shape mode 8	1,20 (0,85-1,68)	1,23 (0,85-1,77)
Shape mode 9	1,14 (0,79-1,64)	1,24 (0,85-1,82)
Shape mode 10	0,97 (0,68-1,40)	1,04 (0,71-1,52)
Shape mode 11	0,87 (0,60-1,27)	0,90 (0,61-1,34)
Shape mode 12	0,96 (0,68-1,36)	0,92 (0,63-1,33)
Shape mode 13	1,12 (0,78-1,60)	1,14 (0,79-1,66)
Shape mode 14	0,72 (0,49-1,05)	0,75 (0,51-1,11)
Shape mode 15	0,94 (0,68-1,30)	0,92 (0,66-1,30)
Shape mode 16	**1,56 (1,09-2,23)**	**1,52 (1,06-2,20)**
Shape mode 17	1,14 (0,79-1,62)	1,17 (0,81-1,70)
Shape mode 18	0,97 (0,70-1,33)	0,86 (0,61-1,22)
Shape mode 19	1,14 (0,81-1,60)	1,07 (0,75-1,52)
Shape mode 20	0,75 (0,51-1,09)	0,72 (0,49-1,07)
Shape mode 21	0,99 (0,71-1,39)	0,93 (0,65-1,31)
Shape mode 22	**0,64 (0,42-0,96)**	**0,64 (0,42-0,97)**
Shape mode 23	1,15 (0,79-1,69)	1,17 (0,78-1,74)
Shape mode 24	0,85 (0,59-1,21)	0,82 (0,56-1,19)
Shape mode 25	1,16 (0,81-1,65)	1,18 (0,82-1,69)

Control = reference. *Adjusted for Age, BMI and Sex. Significant associations ($p<0.05$) in bold.

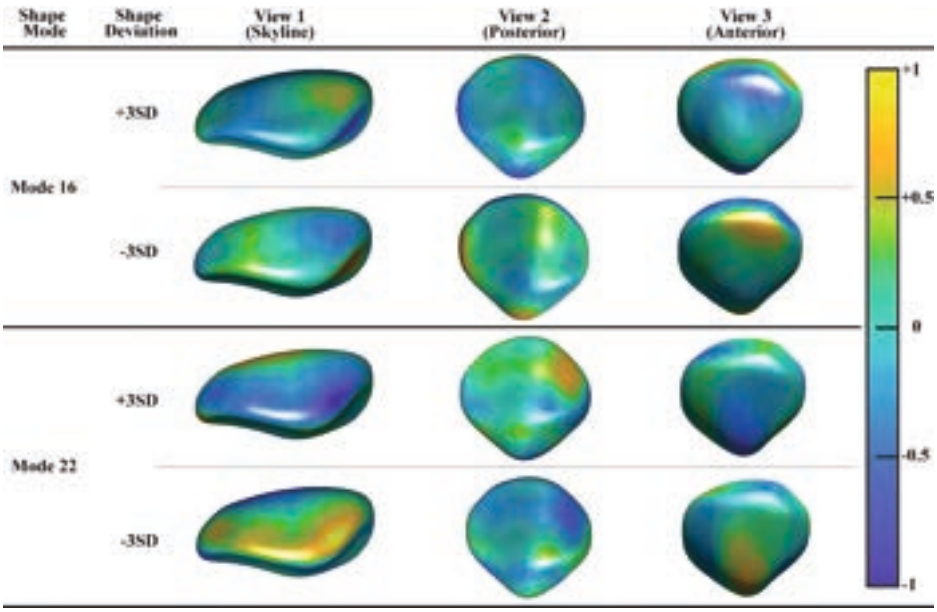
There were multiple associations between patellar shape modes and 5 out of our 6 tested MOAKS features (Table 3). Shape modes (1, 6, 9, 10, 12 and 23) had a statistically significant relationship with the presence of minor cartilage defects on the patella. Furthermore, mode 6 was associated with patellar BML, mode 9 was associated with anterior femoral osteophytes and mode 3 was associated with anterior femoral BML. Hoffa synovitis was associated with modes 5, 11, 12 and 24.

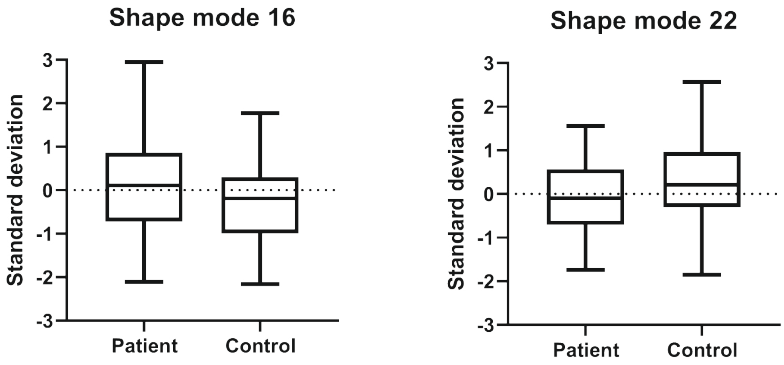
Figure 1. Parallel analysis



The scree pots with parallel analysis show the intersect between the observed data (red) and the simulated data (blue). All shape modes up to the intersection (25) were retained for statistical analysis.

Figure 2. Shape mode 16 and 22





Distance maps depict distances (in mm) between the patella at ±3SD along the shape modes 16 and 22, and the mean patellar shape. Boxplots show the distribution of patellar shape within the patient and control groups along the shape modes 16 (bottom left) and 22 (bottom right).

Discussion

We have advanced our clinically understanding of patellofemoral pain by demonstrating, for the first time, that 3D patellar shape variants are different in patients with PFP compared to controls, however the variance of these shape variants is low. Secondly, patellar shape variations in this young population are associated with the presence of structural abnormalities linked to OA.

In an earlier study using 2D SSMs, we showed that patients with PFP seem to have a more laterally positioned vertical ledge on the posterior side of their patella compared to healthy participants. Additionally, patients with PFP showed a more rounded inferior-posterior articular area on their patella when compared to healthy control participants[27]. However, we found a corresponding phenomenon in both studies, namely a rounder inferior-posterior articular area on the patella in PFP participants. Additionally, both studies seem to show a more pronounced crista on the posterior side of the patella in control participants.

Our results combined with previous studies on PFP suggests that bony shape and malalignment play a role in the aetiology of PFP. Patellar shape deviations have been related to sub-optimal patellofemoral joint, resulting in increased in patellofemoral joint pressure and shear stress during squats[28]. Although we did not investigate joint loading, our results suggest that pathological 3D shape contributes to PFP in adolescents and young adults by fostering joint incongruency and thus, altering joint loading. The deviation in the shape of the inferior-posterior side of the patella would naturally result in decreased patellar articular surface patients with PFP, increasing joint stress and peak forces[29].

Table 3. Associations between structural abnormalities and patellar shape modes (OR with 95% CI).

	Osteophytes patella	BML patella	Minor cartilage defects patella	Osteophytes femur anterior	BML femur anterior	Hoffa synovitis
Mode 1	0,81 (0,53-1,24)	0,67 (0,44-1,01)	**0,55 (0,33-0,92)**	0,96 (0,57-1,61)	0,91 (0,47-1,75)	0,79 (0,53-1,18)
Mode 2	0,73 (0,50-1,08)	0,86 (0,59-1,23)	0,93 (0,60-1,44)	0,93 (0,57-1,51)	1,28 (0,71-2,28)	1,03 (0,72-1,46)
Mode 3	1,43 (0,94-2,19)	0,88 (0,59-1,31)	0,90 (0,55-1,48)	1,20 (0,70-2,04)	**0,46 (0,22-0,95)**	1,31 (0,88-1,95)
Mode 4	0,98 (0,69-1,40)	1,14 (0,81-1,61)	1,21 (0,78-1,86)	0,97 (0,61-1,54)	1,14 (0,64-2,04)	1,05 (0,75-1,47)
Mode 5	1,44 (0,95-2,16)	1,18 (0,82-1,69)	1,06 (0,69-1,62)	0,90 (0,56-1,44)	1,13 (0,62-2,07)	**1,59 (1,08-2,35)**
Mode 6	1,10 (0,74-1,64)	**0,58 (0,39-0,86)**	**0,49 (0,30-0,81)**	1,07 (0,67-1,71)	1,09 (0,58-2,03)	0,76 (0,53-1,10)
Mode 7	1,22 (0,80-1,85)	1,09 (0,74-1,60)	1,19 (0,75-1,88)	1,41 (0,85-2,35)	0,57 (0,28-1,16)	1,49 (0,995-2,22)
Mode 8	1,16 (0,79-1,70)	0,98 (0,68-1,41)	1,31 (0,81-2,10)	0,95 (0,59-1,54)	0,88 (0,50-1,56)	0,99 (0,69-1,42)
Mode 9	0,80 (0,54-1,20)	0,84 (0,57-1,25)	**0,51 (0,29-0,90)**	**0,49 (0,27-0,90)**	0,86 (0,45-1,62)	1,07 (0,73-1,56)
Mode 10	1,06 (0,70-1,62)	0,76 (0,51-1,14)	**1,64 (1,00-2,68)**	1,20 (0,73-2,00)	1,46 (0,72-2,97)	1,33 (0,89-1,98)
Mode 11	1,45 (0,94-2,24)	1,22 (0,81-1,83)	0,84 (0,51-1,38)	1,17 (0,69-1,99)	0,78 (0,40-1,51)	**1,52 (1,01-2,29)**
Mode 12	1,02 (0,68-1,52)	1,01 (0,69-1,47)	**0,59 (0,36-0,97)**	1,23 (0,75-2,02)	1,36 (0,72-2,58)	**0,58 (0,39-0,88)**
Mode 13	1,00 (0,67-1,50)	0,90 (0,61-1,31)	1,03 (0,66-1,63)	1,02 (0,63-1,66)	1,08 (0,57-2,06)	0,93 (0,64-1,36)
Mode 14	1,27 (0,82-1,97)	1,05 (0,71-1,55)	0,67 (0,41-1,09)	0,71 (0,42-1,19)	1,19 (0,61-2,33)	0,97 (0,66-1,42)
Mode 15	0,98 (0,67-1,43)	1,06 (0,75-1,51)	1,05 (0,69-1,61)	1,09 (0,69-1,72)	1,06 (0,62-1,82)	1,09 (0,77-1,55)
Mode 16	0,93 (0,63-1,36)	0,99 (0,69-1,42)	1,18 (0,75-1,86)	0,92 (0,57-1,49)	0,82 (0,44-1,53)	1,07 (0,75-1,53)
Mode 17	0,92 (0,62-1,36)	0,88 (0,61-1,27)	1,24 (0,78-1,97)	0,88 (0,54-1,43)	1,16 (0,65-2,06)	0,91 (0,63-1,31)
Mode 18	0,82 (0,57-1,20)	1,00 (0,70-1,42)	1,04 (0,68-1,60)	1,08 (0,68-1,72)	1,59 (0,88-2,87)	0,74 (0,52-1,06)
Mode 19	0,81 (0,55-1,20)	0,99 (0,69-1,42)	1,01 (0,66-1,58)	0,71 (0,44-1,15)	1,08 (0,57-2,04)	0,87 (0,61-1,25)
Mode 20	1,03 (0,68-1,55)	1,25 (0,84-1,86)	1,30 (0,79-2,12)	1,26 (0,75-2,18)	1,12 (0,61-2,05)	1,06 (0,73-1,56)
Mode 21	1,23 (0,83-1,81)	0,99 (0,69-1,41)	0,93 (0,61-1,42)	0,87 (0,55-1,38)	0,99 (0,54-1,84)	0,76 (0,53-1,09)
Mode 22	1,11 (0,72-1,73)	1,15 (0,76-1,74)	1,18 (0,71-1,20)	0,82 (0,47-1,43)	0,98 (0,49-1,98)	0,78 (0,52-1,18)
Mode 23	1,46 (0,92-2,29)	1,05 (0,70-1,58)	**1,84 (1,11-3,04)**	1,21 (0,71-2,03)	1,50 (0,79-2,84)	1,13 (0,75-1,68)
Mode 24	0,80 (0,54-1,20)	0,99 (0,68-1,44)	1,12 (0,71-1,76)	0,65 (0,39-1,10)	0,86 (0,46-1,62)	**0,56 (0,37-0,85)**
Mode 25	0,79 (0,52-1,20)	1,21 (0,83-1,76)	1,17 (0,76-1,79)	1,07 (0,68-1,71)	1,06 (0,56-1,98)	1,10 (0,76-1,59)

*Adjusted for Age, BMI, Sex and group status. Significant associations ($p<0.05$) in bold.

While there have been multiple studies describing traditional measures of PFP shape and how they are altered in adolescents and young adults with PFP, a direct correlation between these shape measures and pain was not found[30,31]. A possible explanation may be that even though shape aberrations do increase joint stress and seem to be related with structural abnormalities, it may be too early in the disease process to experience pain from these early abnormalities.

PFP has been suggested as a precursor for PFOA. Structural abnormalities such as osteophytes, cartilage defects and bone marrow lesions are the hallmarks of structural OA. We show in the current study that the presence of these features is associated with particular bone shapes, however these bone shapes are not associated with the presence of PFP. future studies should investigate whether the shape modes associated with PFP, and moreover with the structural abnormalities, are also present in a PFOA population.

Strengths and Limitations

Our study is the first that investigated 3D patellar shape variations in a young PFP population and compared these with healthy control participants. Additionally, this is the first study that investigated associations between OA-related structural abnormalities and 3D patellar shape in a young PFP population. For all analyses, a relatively large sample of high-resolution MRI images were used.

However, several limitations should be addressed. First, semi-automatic segmentation can introduce human bias. On the other hand, manual evaluation of the automatic segmentation adds to the strength of this study. Automatic segmentation algorithms are imperfect and manual evaluation adds to the quality of the shape models. Furthermore we observed a strong association between bony shape and age, BMI and sex in explorative analysis, in line with literature[32,33], supporting the accuracy of the model.

Being the first study to use 3D SSM to study bone shape in PFP, we chose to focus our study by excluding the femoral model. However, congruence between the patellar and femoral articular surfaces likely plays a role in the distribution of joint pressure and shear stresses, since tibiofemoral congruence is hypothesized to effect load distribution in osteoarthritic knee[34].

Due to the explorative nature of this study, type 1 error was increased by the large number of statistical tests. However, to separate meaningful data from noise, parallel analysis was conducted on the 3D shape modes, prior to statistical analysis, which would reduce these errors.

Conclusions

In conclusion, we have shown that some bony shapes of the patella are associated with the presence of PFP. Mode 16 shows a rounder shape at the lateral side and apex of the patella

of patients with PFP compared to controls. Mode 22 shows a more diagonal base of the patella in patients with PFP compared to controls. Additionally, multiple bony shapes were associated with structural features of OA.

Acknowledgements and affiliations

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References

1. Bredbenner TL, Eliason TD, Potter RS, Mason RL, Havill LM, Nicolella DP. Statistical shape modeling describes variation in tibia and femur surface geometry between Control and Incidence groups from the Osteoarthritis Initiative database. *J Biomech*. 2010;43(9):1780-1786. doi:10.1016/j.jbiomech.2010.02.015
2. Tümer N, Blankevoort L, van de Giessen M, et al. Bone shape difference between control and osteochondral defect groups of the ankle joint. *Osteoarthr Cartil*. 2016;24(12):2108-2115. doi:10.1016/j.joca.2016.07.015
3. Pavlova A V., Saunders FR, Muthuri SG, et al. Statistical shape modelling of hip and lumbar spine morphology and their relationship in the MRC National Survey of Health and Development. *J Anat*. 2017;231(2):248-259. doi:10.1111/joa.12631
4. Harbaugh CM, Wilson N a., Sheehan FT. Correlating femoral shape with patellar kinematics in patients with patellofemoral pain. *J Orthop Res*. 2010;28(7):865-872. doi:10.1002/jor.21101
5. Agricola R, Heijboer MP, Bierma-Zeinstra SM a., Verhaar J a. N, Weinans H, Waarsing JH. Cam impingement causes osteoarthritis of the hip: a nationwide prospective cohort study (CHECK). *Ann Rheum Dis*. Published online 2012:918-923. doi:10.1136/annrheumdis-2012-201643
6. Castaño-Betancourt MC, Van Meurs JBJ, Bierma-Zeinstra S, et al. The contribution of hip geometry to the prediction of hip osteoarthritis. *Osteoarthr Cartil*. 2013;21(10):1530-1536. doi:10.1016/j.joca.2013.06.012
7. Sarkalkan N, Weinans H, Zadpoor AA. Statistical shape and appearance models of bones. *Bone*. 2014;60:129-140. doi:10.1016/j.bone.2013.12.006
8. Neogi T, Bowes MA, Niu J, et al. Magnetic resonance imaging-based three-dimensional bone shape of the knee predicts onset of knee osteoarthritis: Data from the osteoarthritis initiative. *Arthritis Rheum*. 2013;65(8):2048-2058. doi:10.1002/art.37987
9. Hunter D, Nevitt M, Lynch J, et al. Longitudinal validation of periarticular bone area and 3D shape as biomarkers for knee OA progression? Data from the FNIH OA Biomarkers Consortium. *Ann Rheum Dis*. Published online 2015:annrheumdis-2015-207602. doi:10.1136/annrheumdis-2015-207602
10. Haverkamp DJ, Schiphof D, Bierma-Zeinstra SM, Weinans H, Waarsing JH. Variation in joint shape of osteoarthritic knees. *Arthritis Rheum*. 2011;63(11):3401-3407. doi:10.1002/art.30575
11. Crossley KM. Is patellofemoral osteoarthritis a common sequela of patellofemoral pain? *Br J Sports Med*. 2014;48(6):409-410. doi:10.1136/bjsports-2014-093445
12. Stefanik JJ, Guermazi A, Roemer FW, et al. Changes in patellofemoral and tibiofemoral joint cartilage damage and bone marrow lesions over 7 years: The Multicenter Osteoarthritis Study. *Osteoarthr Cartil*. Published online 2016:1-7. doi:10.1016/j.joca.2016.01.981
13. Lankhorst NE, Damen J, Oei EH, et al. Incidence, prevalence, natural course and prognosis of patellofemoral osteoarthritis: the Cohort Hip and Cohort Knee study. *Osteoarthr Cartil*. 2017;25(5):647-653. doi:10.1016/j.joca.2016.12.006
14. Lankhorst NE, Bierma-Zeinstra SMA, van Middelkoop M. Risk Factors for Patellofemoral Pain Syndrome: A Systematic Review. *J Orthop Sports Phys Ther*. 2012;42(2). doi:10.2519/jospt.2012.3803
15. Drew BT, Redmond AC, Smith TO, Penny F, Conaghan PG. Which patellofemoral joint imaging features are associated with patellofemoral pain? Systematic review and meta-analysis. *Osteoarthr Cartil*. 2016;24(2):224-236. doi:10.1016/j.joca.2015.09.004
16. Connolly KD, Ronsky JL, Westover LM, Küpper JC, Frayne R. Differences in patellofemoral contact mechanics associated with patellofemoral pain syndrome. *J Biomech*. 2009;42(16):2802-2807. doi:10.1016/j.jbiomech.2009.07.028

17. Kannus PA. Long patellar tendon: radiographic sign of patellofemoral pain syndrome--a prospective study. *Radiology*. 1992;185(3):859-863. doi:10.1148/radiology.185.3.1438776

18. Saikat P, Besier TF, Beaupre GS, Fredericson M, Delp SL, Gold GE. Patellar maltracking is prevalent among patellofemoral pain subjects with patella alta: an upright, weightbearing MRI study. 2014;31(3):448-457. doi:10.1002/jor.22256.Patellar

19. van Middelkoop M, Macri EM, Eijkenboom JF, et al. Are Patellofemoral Joint Alignment and Shape Associated With Structural Magnetic Resonance Imaging Abnormalities and Symptoms Among People With Patellofemoral Pain? *Am J Sports Med*. 2018;46(13):3217-3226. doi:10.1177/0363546518801314

20. van der Heijden RA, de Kanter JLM, Bierma-Zeinstra SMA, et al. Structural Abnormalities on Magnetic Resonance Imaging in Patients With Patellofemoral Pain: A Cross-sectional Case-Control Study. *Am J Sports Med*. 2016;44(9):2339-2346. doi:10.1177/0363546516646107

21. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF. *Arthritis Care Res*. 2011;63(SUPPL. 11):240-252. doi:10.1002/acr.20543

22. Kujala UM, Jaakkola LH, Koskinen SK, Taimela S, Hurme M, Nelimarkka O. Scoring of patellofemoral disorders. *Arthrosc J Arthrosc Relat Surg*. 1993;9(2):159-163. Accessed December 4, 2016. http://www.ncbi.nlm.nih.gov/pubmed/8461073

23. Hunter DJ, Guermazi A, Lo GH, et al. Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score). *Osteoarthr Cartil*. 2011;19(8):990-1002. doi:10.1016/j.joca.2011.05.004

24. Cheng R, Jackson JN, McCreedy ES, et al. Patellar Segmentation from 3D Magnetic Resonance Images Using Guided Recursive Ray-tracing for Edge Pattern Detection. 2016;9788:1-9. doi:10.1117/12.2217232

25. van de Giessen M, Vos FM, Grimbergen CA, van Vliet LJ, Streekstra GJ. An efficient and robust algorithm for parallel groupwise registration of bone surfaces. In: *Lecture Notes in Computer Science (Including Subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics)*. Vol 7512 LNCS. Springer Verlag; 2012:164-171. doi:10.1007/978-3-642-33454-2_21

26. Tümer N, Arbabi V, Gielis WP, et al. Three-dimensional analysis of shape variations and symmetry of the fibula, tibia, calcaneus and talus. *J Anat*. 2019;234(1):132-144. doi:10.1111/joa.12900

27. Eijkenboom JFA, Waarsing JH, Oei EHG, Bierma-Zeinstra SMA, Van Middelkoop M. Is patellofemoral pain a precursor to osteoarthritis? *Bone Jt Res*. 2018;7(9):541-547. doi:10.1302/2046-3758.79.BJR-2018-0112.R1

28. Farrokhi S, Keyak JH, Powers CM. Individuals with patellofemoral pain exhibit greater patellofemoral joint stress: A finite element analysis study. *Osteoarthr Cartil*. 2011;19(3):287-294. doi:10.1016/j.joca.2010.12.001

29. Bartel DL, Davy DT, Keaveny TM. *Orthopaedic Biomechanics: Mechanics and Design in Musculoskeletal Systems*. Pearson; 2007. Accessed June 28, 2020. https://www.pearson.com/us/higher-education/program/Bartel-Orthopaedic-Biomechanics-Mechanics-and-Design-in-Musculoskeletal-Systems/PGM7396.html

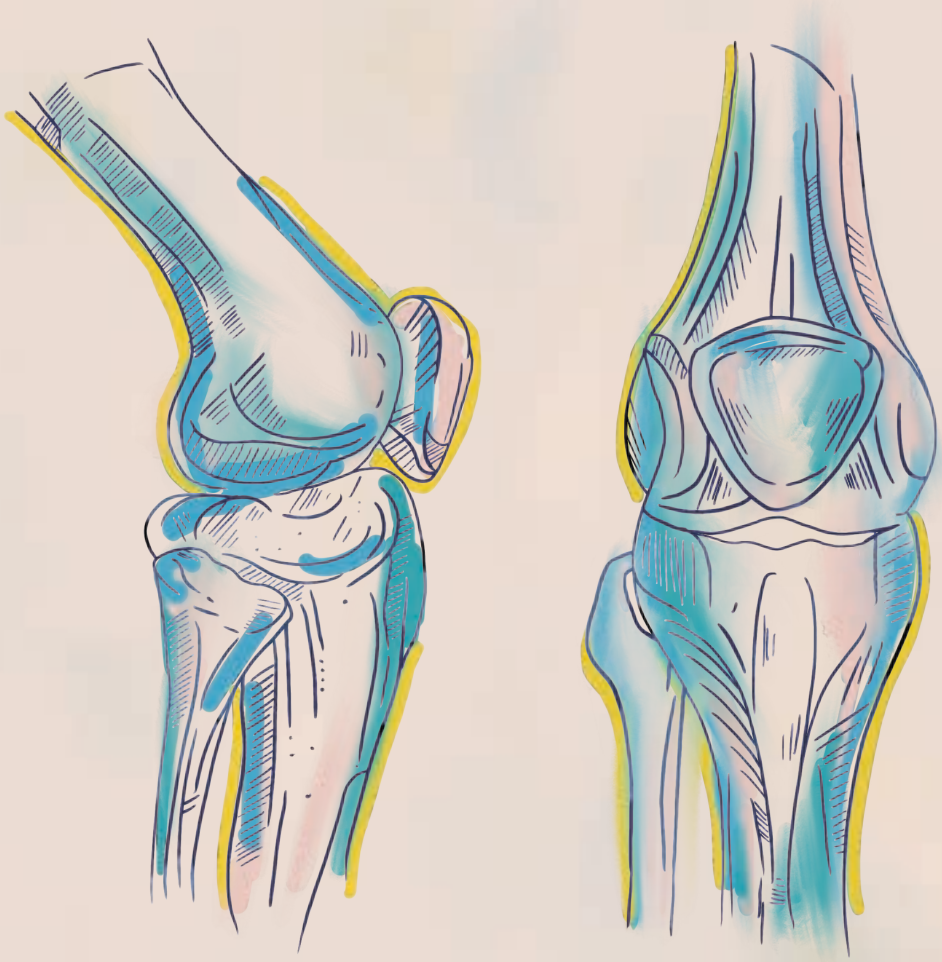
30. Fick CN, Grant C, Sheehan FT. Patellofemoral Pain in Adolescents: Understanding Patellofemoral Morphology and Its Relationship to Maltracking. *Am J Sports Med*. 2020;48(2):341-350. doi:10.1177/0363546519889347

31. Eijkenboom JFA, Timmer ER, Van Heijden RAD, et al. Association between self-reported measures, physical examination, and early magnetic resonance imaging signs of osteoarthritis in patients with patellofemoral pain. *J Orthop Sports Phys Ther*. 2019;49(9):634-639. doi:10.2519/jospt.2019.8889

32. Elkins JM, Simoens KJ, Callaghan JJ. Lower Extremity Geometry in Morbid Obesity—Considerations for Total Knee Arthroplasty. *J Arthroplasty*. 2018;33(10):3304-3312. doi:10.1016/j.arth.2018.03.060

33. Mahfouz M, Badawi A, Merkl B, et al. 3D statistical shape models of patella for sex classification. In: *Annual International Conference of the IEEE Engineering in Medicine and Biology - Proceedings*. ; 2006:3439-3445.

34. Hunter DJ, Sharma L, Skaife T. Alignment and osteoarthritis of the knee. *J Bone Jt Surg - Ser A*. 2009;91(SUPPL. 1):85-89. doi:10.2106/JBJS.H.01409



Chapter 6

3D patellar shape is associated with radiological and clinical signs of patellofemoral osteoarthritis

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Abstract

Objective: To examine the association between 3D patellar shape and 1) isolated magnetic resonance imaging (MRI)-based patellofemoral osteoarthritis (PFOA), 2) the morphological features of PFOA, and 3) the clinical symptoms of PFOA.

Design: MRI data from 66 women with isolated MRI-based PFOA and 66 age- and BMI-matched healthy women were selected from a cohort study. The patellae were manually segmented from MRI scans and used to create a 3D statistical shape model (SSM) of the patella. Structural abnormalities were semi-standardized scored on MRI using MRI osteoarthritis knee score (MOAKS). Regression analyses were applied to determine the associations between the shape parameters retrieved from the SSM, group status, clinical symptoms, and structural abnormalities.

Results: Four shape variants showed a statistically significant (<0.05) association with the group status. The mode responsible for most of the shape variations showed participants with PFOA possess a relatively thicker dorsal bump on the articular part of the patella, compared to patellae of control participants. Three of these variants showed an association with the presence of osteophytes and cartilage loss on the patella. Multiple associations were found between patellar shape and the clinical symptoms of PFOA.

Conclusions: Patellar shape is associated with the prevalence of MRI-based PFOA in women. Some shape variants were also associated with clinical symptoms. Interestingly, one particular shape variant associated with the presence of MRI-based PFOA was earlier shown to be associated with structural abnormalities associated with OA in a population aged under 40. This may suggest that patellar shape may be an early detectable risk factor for PFOA.

Introduction

Osteoarthritis (OA) is one of the most common causes for disability in elderly. Furthermore, the number of individuals affected by OA is suspected to increase further due to the overall increase of age and obesity in developed countries[1]. Knee OA is the most prevalent form of OA, with recent estimates as high as 22.9% in individuals aged 40 and over[2]. Absolute numbers are estimated at 654 million individuals worldwide[2]. Knee OA can be subdivided into patellofemoral OA (PFOA) and tibiofemoral OA (TFOA) and both can be present at the same time (complete knee OA). Although understudied, PFOA is a significant source of pain, joint stiffness, and functional limitation[3,4]. The prevalence of PFOA is high, with approximates of 50% of participants with MRI-based knee OA having the signs of PFOA to some degree[5]. Additionally, a recent study suggested knee OA most commonly starts in the patellofemoral joint[6], adding to the importance of more research into this subtype of OA.

While the exact aetiology of OA is not fully understood, joint biomechanics and the stresses generated in cartilage seem to play important roles in this regard[3]. Key factors in joint biomechanics, including joint loading[7,8], gait[9], and knee alignment[10] have been broadly studied and associated with the presence of OA. However, an important aspect of the patellofemoral joint (PFJ), namely 3D bone shape, has only recently been studied. 3D bone shape has the potential to extract more detailed shape features as to compared with 2D alignment measures. Moreover, clinical tools employing 3D shape assessment may offer diagnostic value by detecting individuals who are at an increased risk of disease commencement and progression. Multiple studies have connected bone shape in the tibiofemoral joint to OA progression[11], to total knee replacement[12], or to the MRI-based features associated with OA (BMLs[13] and Kellgren-Lawrence scores[14]). However, very little research has focused on bone shape in the patellofemoral joint. Liao et al. (2021) were the first assessing the correlation between 3D patellar shape features with longitudinal changes of PFOA[15]. They showed that subjects demonstrating worsening of PFJ lesions exhibited a patella with equally distributed facets and a lateral bump. Though the evidence is still minimal and a better understanding of patellar shape may add to the early detection of high-risk populations. Therefore, the purpose of this study is to examine the association between 3D patellar shape and isolated MRI-based PFOA in a larger population. Since not everyone with MRI-based OA has clinical symptoms, we additionally studied the clinical manifestations of PFOA and their associations with the shape variations in the patella.

Materials and methods

Study Population

For the current study, the baseline and follow-up (5 years) data of a subpopulation (RS-III-1) of the Rotterdam Study[16,17] were used. The Rotterdam study is a population-based cohort study in which the incidence and risk factors for chronic disabling diseases are investigated. The first 1116 women of RS-III-1, aged 45-60 years, were invited to participate in a sub-study investigating early signs of knee OA. Of these, 891 were included for the baseline measurements[18]. For the present study, we selected participants with isolated MRI-based patellofemoral osteoarthritis (iPFOA) at either baseline or follow-up. Participants with iPFOA were defined as patients having MRI-based PFOA while not having MRI-based tibiofemoral osteoarthritis (TFOA). Per patient with iPFOA, one matched control participant without PFOA and TFOA was included. One knee per subject was analyzed for the current study purpose. Matching was performed for known risk factors for knee OA, including age and BMI and additionally for knee side and time moment (baseline or follow-up) using case-control matching in SPSS with Fuzzy matching of 1 for BMI and 2 for age and random case order when drawing matches. The Medical Ethics committee of the Erasmus Medical Centre approved the study (MEC 02.1015) and all the participants provided written consent.

Measurements

Identical measurements were performed at baseline and follow-up, including questionnaires, patient history, physical examination and an MRI of both knees. The KOOS was used from the questionnaires to report on patient reported outcomes, including the subscales pain, symptoms, function in daily living (ADL), sport and quality of life (QoL). Potential risk factors for PFOA, including history of patellar pain, crepitation and BMI were extracted from the patient history and physical examination. The presence of crepitus was investigated and was defined as a hearable grinding noise and/or palpable vibrations in the knee during active flexion or extension, detected by the hand of the investigator rested on the patella of the participant. One KOOS question (pain, going up or down stairs) was dichotomized and was used as a measure for pain during walking stairs, as this is a known important clinical feature of patellofemoral pain: 0) none and mild 1) moderate, severe, and extreme.

MRIs were made using a 1.5T MRI scanner (Signa Excite 2, General Electric Healthcare, Milwaukee, US). The participants were scanned using an eight-channel cardiac coil. This way both knees could be scanned at once without the need to reposition the participant. The MRI sequences included a sagittal spoiled gradient echo sequence with a fat suppression: TR/TE 20.9/2.3, a flip angle of 35, a slice thickness of 1.6 mm, and a field of view of 15 cm^2.

Definition of iPFOA

MRI-based knee OA was scored for PFOA and TFOA for each knee separately, using the MRI osteoarthritis knee score (MOAKS)[19]. The MOAKS scoring was performed by a trained human movement scientist. Randomly picked knees (30 subjects) from the RS-III-1 cohort sample were also scored by a highly experienced musculoskeletal radiologist to determine inter-rater reliability (prevalence adjusted bias adjusted kappa (PABAK) 0.47-0.93, moderate to nearly perfect)[18].

PFOA was defined as having a definite osteophyte and partial or full thickness cartilage loss in the patella or the trochlea (anterior femur)[20]. TFOA was described as the presence of a definite osteophyte and full thickness cartilage loss, or one of these features and two of the following features[19]: (1) subchondral bone marrow lesions (BML) or cyst not associated with meniscal or ligamentous attachments, (2) meniscal subluxation, maceration, or degeneration (including a horizontal tear) or (3) partial thickness cartilage loss. After this scoring, each knee was classified into one of four categories: (1) iPFOA, (2) iTFOA, (3) complete knee OA, and (4) no knee OA.

Statistical Shape Model of the Patella

The same approach as described in a previous study[21] was followed to obtain 3D patellar bone surfaces based on MRIs. First, patellar bones were manually segmented from MRIs using MIPAV software (NIH, Bethesda, USA) while blinded for group status. The segmentations were performed by a researcher (J.E.) trained by a highly experienced musculoskeletal radiologist (E.O.). Second, 3D triangulated patellar surfaces (*i.e.*, triangles with a maximum tangent edge size of 0.9 mm) were created using Geomagic (3D systems, North Carolina, USA).

A 3D SSM of the patella was built based on the triangulated bone samples. First, all the participants' patellae were registered using an unbiased registration algorithm, which minimized the differences in the position, orientation, and scaling among the patellae[22]. Following the registration, the corresponding points (n = 15924) across the registered patellae were automatically established[22,23]. The registration parameters, including the scale parameter for the mixture of Gaussian, $\boldsymbol{\sigma}$ = 0.6, the number of points in the mean cloud, n_m = 2000, and the trade-off parameter, $\boldsymbol{\lambda} = 10^{-3}$, were determined based on numerical experiments[22,23]. Finally, the main bone shape variations were extracted by performing a principal component analysis on the covariance matrix of the data vectors consisting of the 3D coordinates of the corresponding points for each bone samples. To discard shape modes describing noise and preserve the ones describing patellar shape variations, a parallel analysis was performed[24]. This analysis is based on observed and simulated data[24], and the number of shape modes to be kept is found at their intersection.

Statistical analyses

Logistic regression analyses, with adjustment for age and BMI, were performed to test the association between the independent shape modes and group status (iPFOA versus matched controls). A *post-hoc* regression analysis was performed on shape modes associated with the presence of iPFOA to further investigate their relations with five possible structural abnormalities in the PFJ (*i.e.*, patellar osteophytes, patellar BML, patellar cartilage loss, anterior femoral osteophytes, and anterior femoral BML).

As secondary analyses, logistic regression analyses were performed to study the association between the clinical features (crepitus, history of patellar pain and pain during walking stairs) and shape modes, adjusted for age and BMI. Additionally, linear regression analyses were performed to study the association between short term pain and function (KOOS subscales) and patellar shape modes. Sensitivity analyses were performed with adjustment for group status (iPFOA or control participants) for shape modes where significant associations were found.

Results are expressed in odds ratios (ORs) or Beta's with the accompanying 95% confidence intervals (CIs). The differences in the patient characteristics between the groups were tested using the Student's *t*-tests and Pearson's chi-square test. All the statistical analyses were performed using SPSS (version 16.0, SPSS Inc., USA) and a p-value <0.05 was considered statistically significant.

Results

Our study included 132 women, 66 participants with iPFOA and 66 control participants with no knee OA (Table 1). As a result of participant matching, no differences between the groups were found in terms of age and BMI. Both groups were significantly different in terms of the presence of all MOAKS features, crepitation, and pain during walking stairs. Additionally, all iPFOA participants had lower KOOS scores as compared to their matched control participants.

Table 1. The characteristics of the study population.

	PFOA (n = 66)	**Control (n = 66)**	**p-value**
Age, years (mean (SD))	57.8 (3.85)	56.3 (3.88)	0.882*
BMI, kg/m^2 (mean (SD))	27.5 (4.35)	27.4 (4.41)	0.729*
Presence of MRI-based features (n (%))			
Osteophytes patella	42 (64%)	0 (0%)	<0.001º
Osteophytes anterior femur	40 (61%)	0 (0%)	<0.001º
BML patella	51 (78%)	26 (39%)	<0.001º
BML anterior femur	32 (49%)	13 (20%)	<0.001º

Table 1. The characteristics of the study population. *(continued)*

	PFOA (*n* = 66)	**Control (*n* = 66)**	**p-value**
Cartilage loss patella	59 (89%)	14 (21%)	<0.001º
Presence of clinical features (*n* (%))			
Crepitation	36 (56%)	30 (45%)	0.218º
History of patellar pain	25 (40%)	8 (13%)	<0.001º
Pain during walking stairs	22 (34%)	4 (6%)	<0.001º
KOOS subscales 0-100 (mean (SD))			
Pain	85.8 (17.0)	96.8 (10.4)	<0.001*
Symptoms	83.7 (18.0)	95.4 (8.4)	<0.001*
ADL	89.4 (15.5)	97.3 (9.5)	<0.001*
Sport	71.7 (31.6)	93.3 (18.2)	<0.001*
Quality of life	74.7 (24.9)	94.2 (12.4)	<0.001*

* student's t-test, º Pearson chi-square

The first 25 patellar shape modes were retained (Figure 1) and analyzed using logistic regression. The patellar shape variations described by modes 6 (OR 1.72, 95%CI 1.16-2.55), 13 (OR 1.65, 95%CI 1.12-2.44), 21 (OR 1.70, 95%CI 1.15-2.53), and 23 (OR 0.62, 95%CI 0.43-0.90) showed statistically significant associations with the presence of PFOA (Table 2). These modes described 4.5%, 2.1%, 0.9%, and 0.8% of the total shape variation in the patellar bone, respectively (3D files available in online appendix 3).

Table 2. The associations between the group status (participants with PFOA (n=66) and control participants (n=66) and patellar shape modes (OR with 95% CI).

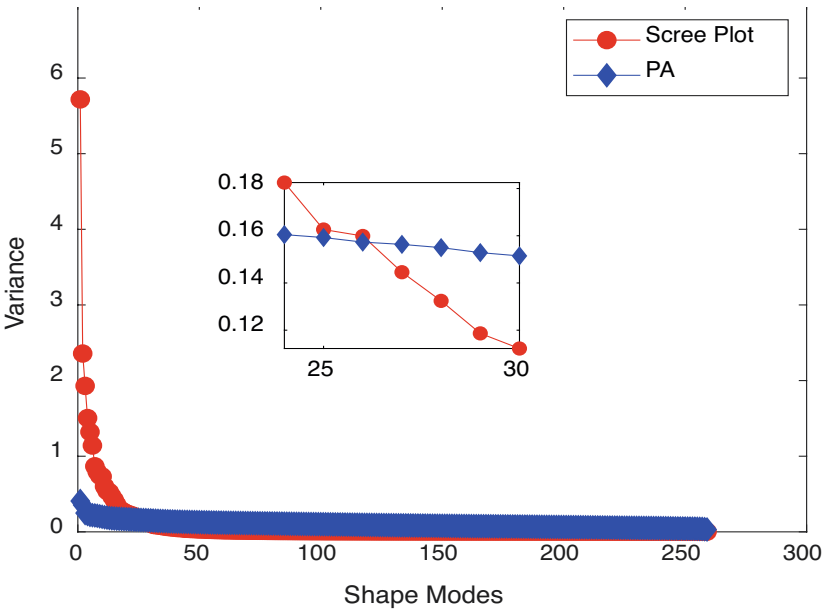
Shape Modes	**Crude OR**	**Adjusted* OR**
Mode 1	0.93 (0.63-1.36)	0.93 (0.62-1.38)
Mode 2	1.06 (0.73-1.52)	1.09 (0.75-1.58)
Mode 3	1.21 (0.84-1.74)	1.27 (0.87-1.83)
Mode 4	0.77 (0.53-1.13)	0.79 (0.53-1.17)
Mode 5	1.36 (0.95-1.95)	1.44 (0.99-2.10)
Mode 6	**0.58 (0.39-0.86) p=0.006**	**0.58 (0.39-0.87) p=0.008**
Mode 7	1.35 (0.96-1.91)	1.32 (0.93-1.88)
Mode 8	0.79 (0.54-1.15)	0.78 (0.53-1.15)
Mode 9	0.77 (0.55-1.08)	0.79 (0.55-1.13)
Mode 10	0.82 (0.58-1.14)	0.84 (0.60-1.19)
Mode 11	1.31 (0.92-1.87)	1.32 (0.92-1.90)
Mode 12	1.14 (0.81-1.61)	1.17 (0.82-1.68)

Table 2. The associations between the group status (participants with PFOA (n=66) and control participants (n=66) and patellar shape modes (OR with 95% CI). *(continued)*

Shape Modes	Crude OR	Adjusted* OR
Mode 13	0.70 (0.48-1.00) p=0.051	**0.61 (0.41-0.90) p=0.012**
Mode 14	0.88 (0.60-1.29)	0.90 (0.61-1.32)
Mode 15	1.40 (0.96-2.04)	1.40 (0.95-2.07)
Mode 16	1.03 (0.72-1.47)	1.05 (0.73-1.50)
Mode 17	0.78 (0.56-1.10)	0.75 (0.53-1.07)
Mode 18	0.81 (0.56-1.87)	0.82 (0.56-1.21)
Mode 19	1.08 (0.76-1.53)	1.03 (0.72-1.49)
Mode 20	0.92 (0.66-1.28)	0.80 (0.68-1.34)
Mode 21	**0.57 (0.39-0.85) p=0.005**	**0.59 (0.40-0.87) p=0.008**
Mode 22	0.94 (0.69-1.29)	0.90 (0.65-1.24)
Mode 23	1.61 (1.13-2.30) p=0.09	**1.61 (1.12-2.32) p=0.011**
Mode 24	0.92 (0.65-1.28)	0.88 (0.63-1.25)
Mode 25	1.14 (0.81-1.61)	1.12 (0.79-1.59)

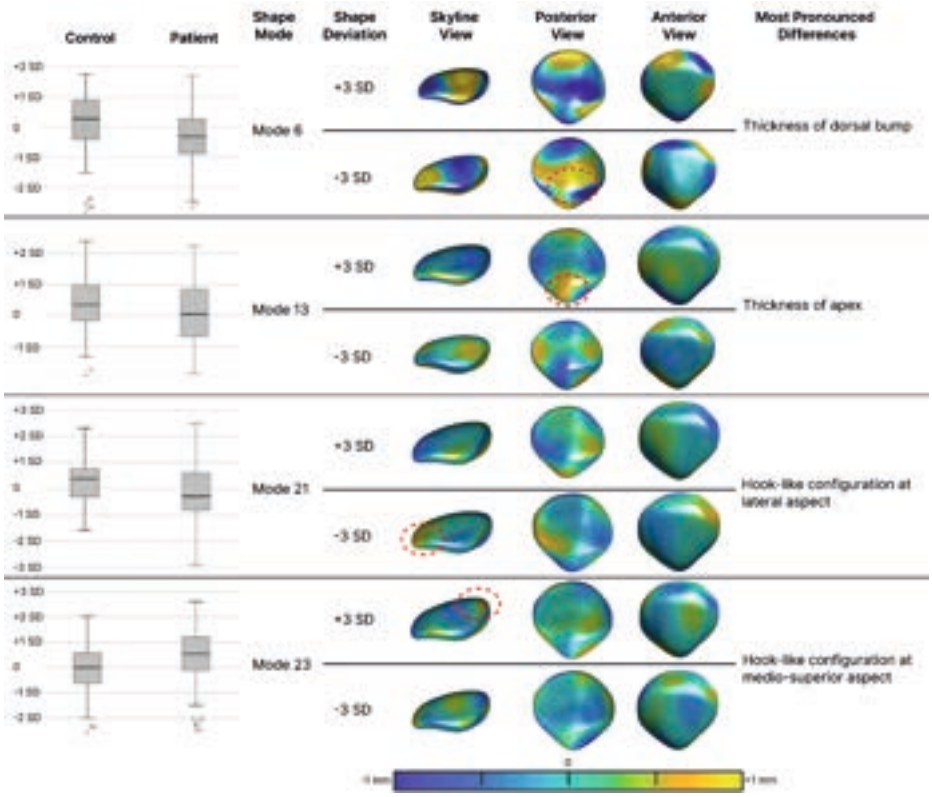
*Adjusted for age and BMI. Significant associations (p<0.05) are typed using a bold font.

Figure 1. Parallel analysis.



The observed data (red, scree plot) and the simulated data (blue, parallel analysis) insect at mode 25. Thus, all shape modes up to the intersection (25) were retained for statistical analysis.

Figure 2. The distributions and distance maps for the associated modes.



Distance maps in mm, yellow color indicates a positive distance from the mean shape while a blue color indicates a negative distance from the mean shape. Dotted line shows most pronounced differences in each shape mode.

For example, mode 6: In the boxplot we see that the population with PFOA more closely resembles a negative standard deviation. The extreme shapes in the negative direction (-3SD) show a thicker more pronounced (yellow) dorsal bump on at the articular part of the surface of the patella compared to the mean shape.

Shape mode 6 revealed mostly differences at the posterior aspect of the patella (Figure 2). The participants with PFOA seemed to possess a relatively more pronounced dorsal bump at the articular surface of the patella and a slightly shorter medial margin of the patella (Figure 2, mode 6, quartiles; -0.91, -0.30, 0.32). The control participants showed a less pronounced dorsal bump and a slightly longer medial margin of the patella (Figure 2, mode 6, quartiles; -0.40, 0.27, 0.91). The control subjects' patellae had, in general, a thicker apex (Figure 2, mode 13, quartiles; -0.18, 0.35, 0.99) as compared to those of the participants with PFOA (quartiles; -0.69, 0.04, 0.86). The hook-like configuration at the lateral aspect (Figure 2, mode 21, quartiles; -0.85, -0.28, 0.62) and the medio-superior aspect (Figure 2, mode 23, quartiles; -0.12, 0.54, 1.21) of the patella were more common in the participants with PFOA (control patient mode 21 quartiles; -0.30, 0.39, 0.78, mode 23 quartiles; -0.63, 0,00, 0.58).

Post-hoc analyses revealed that modes 6 and 13 were specifically associated with the presence of osteophytes, BMLs, and cartilage loss on the patella while mode 13 was additionally associated with BMLs on the femur (Table 3). Mode 21 was associated with both osteophytes on the anterior femur and cartilage loss on the patella. Mode 23 was only associated with osteophytes on the patella.

Table 3. The associations between the MOAKS features associated with presence of PFOA and the patellar shape modes (OR with 95% CI), n=132.

Shape Modes	Osteophytes patella (n=42)	Osteophytes anterior Femur (n=40)	BMLs patella (n=77)	BMLs anterior Femur (n=45)	Cartilage loss patella (n=73)
Mode 6	**0.55 (0.37-0.84) p=0.006**	0.68 (0.45-1.03)	**0.60 (0.40-0.90) p=0.012**	0.83 (0.56-1.22)	**0.49 (0.32-0.75) p<0.001**
Mode 13	**0.64 (0.43-0.97) p=0.033**	0.74 (0.49-1.11)	**0.68 (0.46-0.99) p=0.045**	**0.59 (0.39-0.90) p=0.014**	**0.64 (0.44-0.95) p=0.025**
Mode 21	0.71 (0.48-1.06)	**0.62 (0.41-0.94) p=0.025**	0.86 (0.60-1.24)	0.76 (0.51-1.11)	**0.62 (0.42-0.91) p=0.016**
Mode 23	**2.42 (1.53-3.84) p<0.001**	1.38 (0.95-2.02)	1.07 (0.77-1.50)	1.13 (0.80-1.61)	1.32 (0.94-1.87)

Adjusted for age and BMI. Significant associations (p<0.05) are typed using a bold font.

Shape variations described by modes 1, 6, 14, and 20 were linked to crepitus (Table 4). While modes 15 and 21 were associated with a history of patellar pain, modes 13 and 21 were associated with pain during walking stairs. *Post-hoc* analyses adjusted for the group status revealed that the associations between shape, crepitus, and the history of patellar pain remained largely unchanged, while the associations with pain during walking stairs was less pronounced and did not reach statistical significance (online appendix 1).

Table 4. The associations between the clinical features associated with presence of PFOA and the patellar shape modes (OR with 95% CI), n=132.

Shape Modes	Crepitus (n=66)	History of patellar pain (n=33)	Pain during walking stairs (n=26)
Mode 1	**0.63 (0.41-0.98) p=0.039**	0.69 (0.43-1.12)	0.86 (0.52-1.42)
Mode 2	1.08 (0.75-1.58)	1.28 (0.83-1.97)	1.34 (0.85-2.13)
Mode 3	1.12 (0.78-1.61)	1.04 (0.67-1.62)	0.95 (0.59-1.51)
Mode 4	1.11 (0.75-1.65)	0.87 (0.56-1.35)	0.84 (0.52-1.35)
Mode 5	1.14 (0.80-1.64)	1.26 (0.83-1.91)	1.12 (0.72-1.75)
Mode 6	**0.64 (0.43-0.95) p=0.026**	0.84 (0.55-1.28)	0.69 (0.43-1.08)
Mode 7	1.22 (0.85-1.75)	1.09 (0.74-1.60)	1.11 (0.73-1.70)
Mode 8	1.32 (0.90-1.95)	1.09 (0.70-1.70)	0.93 (0.58-1.48)
Mode 9	1.11 (0.78-1.57)	0.73 (0.48-1.11)	0.95 (0.61-1.46)
Mode 10	1.13 (0.81-1.58)	1.19 (0.81-1.76)	1.16 (0.76-1.77)
Mode 11	0.98 (0.69-1.39)	1.24 (0.82-1.89)	1.08 (0.69-1.67)
Mode 12	0.82 (0.57-1.12)	1.06 0.70-1.60)	1.21 (0.78-1.89)
Mode 13	0.96 (0.66-1.39)	0.70 (0.45-1.10)	**0.59 (0.36-0.97) p=0.036**
Mode 14	**1.60 (1.06-2.42) p=0.027**	0.93 (0.60-1.46)	0.72 (0.44-1.19)
Mode 15	1.00 (0.69-1.45)	**1.81 (1.12-2.93) p=0.015**	1.58 (0.96-2.61)
Mode 16	0.87 (0.60-1.25)	0.84 (0.55-1.28)	1.21 (0.77-1.90)
Mode 17	0.85 (0.60-1.20)	1.05 (0.71-1.55)	0.71 (0.45-1.10)
Mode 18	1.11 (0.75-1.64)	0.97 (0.62-1.50)	1.10 (0.69-1.77)
Mode 19	0.86 (0.60-1.24)	1.24 (0.82-1.88)	1.20 (0.77-1.89)
Mode 20	**0.61 (0.42-0.88) p=0.009**	1.09 (0.73-1.62)	1.04 (0.69-1.58)
Mode 21	0.87 (0.60-1.25)	**0.50 (0.32-0.80) p=0.004**	**0.55 (0.34-0.89) p=0.015**
Mode 22	0.80 (0.58-1.11)	0.88 (0.61-1.28)	1.22 (0.82-1.83)
Mode 23	0.98 (0.70-1.37)	1.21 (0.81-1.81)	1.44 (0.93-2.23)
Mode 24	1.09 (0.77-1.54)	0.81 (0.54-1.20)	0.99 (0.65-1.50)
Mode 25	0.87 (0.60-1.26)	1.11 (0.73-1.70)	0.88 (0.57-1.36)

Adjusted for Age and BMI. Significant associations (p<0.05) are typed using a bold font.

Finally, multiple associations were present between the patellar shape and KOOS subscales (Table 5). Mode 21 was associated with all KOOS subscales. Additionally, mode 1 was associated with the sport subscale, mode 2 was associated with the pain, ADL, and sport subscale, and mode 13 was associated with the pain and quality of life subscale. *Post-hoc* analyses adjusted for group status showed that these associations remained largely intact, as only one lost statistical significance (mode 13 and KOOS pain, online appendix 2).

Table 5. The associations between the KOOS subscales and patellar shape modes (Beta's with 95% CI).

Shape Modes	KOOS Pain	KOOS Symptoms	KOOS ADL	KOOS Sport	KOOS QoL
Mode 1	2.69 (-0.30;5.69)	2.80 (-0.20;5.80)	1.11 (-1.58;3.81)	**6.76 (1.26;12.26) p=0.016**	3.33 (-0.97;7.63)
Mode 2	**-3.34 (-6.14;-0.53) p=0.020**	-1.74 (-4.60;1.12)	**-2.61 (-5.12;-0.10) p=0.042**	**-5.47 (-10.67;-0.26) p=0.04**	-3.92 (-7.97;0.12)
Mode 3	-1.23 (-4.07;1.62)	-1.93 (-4.77;0.91)	-0.92 (-3.46;1.61)	-2.19 (-7.44;3.07)	-0.96 (-5.03;3.12)
Mode 4	0.77 (-2.18;3.71)	1.11 (-1.84;4.05)	0.42 (-2.21;3.04)	2.720 (-2.70;8.13)	-0.41 (-4.62;3.80)
Mode 5	-0.77 (-3.47;1.93)	-0.46 (-3.17;2.25)	-1.10 (-3.50;1.30)	-0.69 (-5.74;4.37)	-1.52 (-5.38;2.34)
Mode 6	1.01 (-1.77;3.80)	1.71 (-1.06;4.49)	1.01 (-1.46;3.49)	2.21 (-2.92;7.33)	3.04 (-0.90;6.98)
Mode 7	1.04 (-1.56;3.65)	-0.02 (-2.64;2.60)	0.31 (-2.01;2.64)	1.44 (-3.39;6.26)	0.50 (-3.23;4.23)
Mode 8	-0.53 (-3.41;2.34)	-1.80 (-4.66;1.07)	-0.44 (-3.00;2.12)	0.33 (-5.04;5.71)	-0.45 (-4.57;3.66)
Mode 9	-0.79 (-3.45;1.86)	-1.20 (-3.85;1.45)	-0.88 (-3.24;1.48)	-1.34 (-6.30;3.63)	-0.50 (-4.29;3.30)
Mode 10	-1.20 (-3.73;1.33)	-0.59 (-3.13;0.33)	-1.30 (-3.55;0.95)	0.21 (-4.48;4.90)	-1.89 (-5.50;1.72)
Mode 11	-0.68 (-3.31;1.94)	-1.88 (-4.49;0.72)	-0.69 (-3.03;1.64)	-4.02 (-8.81;0.77)	-2.01 (-5.74;1.72)
Mode 12	-0.79 (-3.47;1.89)	-1.34 (-4.02;1.34)	-1.48; (-3.85;0.90)	-4.17 (-9.10;0.76)	-1.98 (-5.80;1.84)
Mode 13	**3.01 (0.27;5.75) p=0.032**	2.42 (-1.34;5.18)	2.18 (-0.28;4.63)	4.84 (-0.27;9.94)	**4.47 (0.56;8.38) p=0.025**
Mode 14	1.74 (-1.18;4.65)	0.24 (-2.69;3.17)	1.82 (-0.76;4.41)	2.70 (-2.68;8.09)	1.51 (-2.66;5.69)
Mode 15	-1.97 (-4.78;0.84)	-1.30 (-4.13;1.53)	-1.51 (-4.02;0.99)	-0.33 (-5.59;4.94)	-3.31 (-7.31;0.69)
Mode 16	-1.07 (-3.80;1.66)	-0.15 (-2.89;2.59)	-1.03 (-3.46;1.40)	-3.37 (-8.40;1.67)	-0.67 (-4.57;3.24)
Mode 17	2.17 (-0.40;4.73)	1.47 (-1.11;4.06)	2.14 (-0.13;4.42)	2.89 (-1.87;7.64)	2.00 (-1.69;5.69)
Mode 18	-1.69 (-4.58;1.19)	-2.05 (-4.94;0.83)	-1.67 (-4.23;0.90)	-4.29 (-9.68;1.10)	-1.53 (-5.66;2.61)
Mode 19	0.32 (-2.41;3.06)	-0.44 (-3.18;2.30)	-0.65 (-3.08;1.79)	1.60 (-3.47;6.68)	0.61 (-3.31;4.52)
Mode 20	0.26 (-2.28;2.80)	0.51 (-2.03;3.05)	0.39 (-1.87;2.65)	0.99 (-3.70;5.67)	-0.04 (-3.66;3.59)
Mode 21	**3.85 (1.21;6.49) p=0.005**	**4.88 (2.29;7.47) p<0.001**	**3.49 (1.14;5.83) p=0.004**	**9.07 (4.24;13.89 p<0.001**	**6.95 (3.25;10.64) p<0.001**
Mode 22	-1.18 (-3.60;1.25)	-0.13 (-2.57;2.31)	-1.25 (-3.41;0.90)	-1.68 (-6.16;2.81)	-0.86 (-4.33;2.62)
Mode 23	-1.96 (-4.45;0.53)	-1.82 (-4.31;0.68)	-1.22 (-3.45;1.00)	-2.28 (-6.94;2.37)	-1.96 (-5.53;1.61)
Mode 24	-0.77 (-3.36;1.83)	0.65 (-1.95;3.25)	-0.84 (-3.15;1.47)	-1.93 (-6.74;2.89)	-1.86 (-5.56;1.84)
Mode 25	0.27 (-2.38;2.90)	0.26 (-2.40;2.91)	0.54 (-1.82;2.90)	-0.66 (-5.62;4.30)	0.65 (-3.13;4.44)

Adjusted for age and BMI. Significant associations (p<0.05) are typed using a bold font.

Discussion

We aimed to study whether patellar shape is associated with MRI-based OA in the patellofemoral joint. Four shape variants showed statistically significant differences between the participants with PFOA and control subjects. *Post-hoc* analyses showed that osteophytes and cartilage loss on the patella were the most prominent MOAKS features associated with these four shape variants. One shape variant, namely shape mode 21, showed clear associations with multiple clinical complaints associated with PFOA.

There has been extensive research on the association between knee alignment, trochlear morphology, and PFOA, which shows that there is strong evidence for an association between PFOA and patellar alignment[10]. Macri *et al.* (2019) showed that MRI-based PFOA is associated with anterior knee pain, suggesting that the MRI-based features of OA may contribute to localized symptoms[25]. More recent studies have additionally shown that patellofemoral frontal plane alignment is associated with patellar cartilage volume reduction[26] and osteophyte worsening in women[27]. Since 2D alignment and basic trochlear measures tell only a part of the story, more recent research has focused on 3D shape analysis in the knee[12,15]. These analyses have, for example, shown that the 3D femoral shape predicts total knee arthroplasty as a result of knee OA[12]. Furthermore, 3D patellar and trochlear bone shapes have been shown to be associated with the progression of MRI-based features of PFOA[15]. In this study, Liao *et al.* have shown that subjects with an increased level of the MRI-based degeneration of PFOA exhibit a patella with a lateral bump or hook, which seems to be in line with our findings as a longer lateral side of the patella was associated with PFOA (mode 21). However, while Liao *et al.* reported no associations between this lateral bump or hook and self-reported symptoms, we also found an association between this patellar shape and a history of patellar pain, pain during walking stairs, and all the subscales of the KOOS scoring system. This may indicate that a bump on the lateral, non-articular part of the patella influences joint biomechanics which may lead to the development of structural abnormalities and pain. Alternatively, lateral malalignment associated with OA might cause adaptation of the patella shape, with the lateral facet wrapping around the femoral condyle to form a hook. However, longitudinal data and validation in other datasets is required to investigate this association, and the direction of the association further, preferably including both the patellar and femoral parts of the patellofemoral joint.

While we found four shape variants associated with MRI-based PFOA, not all of these were associated with clinical symptoms and the explained variance was small. While shape mode 6 (responsible for 4.5% of the shape variations), was associated with structural PFOA features, it was only associated with crepitus in terms of clinical symptoms. On the other hand, the seemingly subtle shape variations in mode 21 (responsible for 0.9% shape variation) were found to be associated with almost all clinical symptoms. This may suggest that distinct patellar shapes are associated with specific MRI-based and clinical features in participants with MRI-based PFOA. It is unclear why this seemingly subtle

difference in shape has multiple clinical effects and therefore further validation in other study populations is mandatory.

The shape model applied in the current study was previously applied in a young population (14 to 40 years) showing symptoms of patellofemoral pain (PFP) and was compared to an age- and sex-matched control group (unpublished data) [28]. This provides us with the unique opportunity to compare the shape variations in the PFOA population as described in the current study with these found in this younger PFP population. This is of particular interest as it has been frequently suggested that PFP may be a precursor of PFOA, as they share multiple risk factors, including malalignment[29]. It is, therefore, particularly interesting to see that in both populations (*i.e.,* PFP and PFOA), shape mode 6 is associated with structural abnormalities[28], while showing no association with pain. The participants with PFOA who had a more pronounced dorsal bump suffered from a higher risk of bone marrow lesions, cartilage loss, and osteophytes on the patella compared to the control participants. Since the dorsal bump of the patella is one of the main articular surfaces in the patellofemoral joint, it can be hypothesized that this aberrant shape in this part of the patella may lead to an aberrant type of joint loading, which may consequently lead to bone and cartilage damage. Though, so far only suggestive since longitudinal evidence is lacking, this shape abnormality on the dorsal side of the patella could however potentially be an early risk factor for bone or cartilage damage on the patella. Future research should further investigate this potential association as this may add to the understanding of the possible continuum between PFP and PFOA, even if participants with this abnormality do not always experience pain.

Strengths and limitations

Our study is unique as it investigated the potential associations between the shape and both MRI-based and clinical features of PFOA in a large population study. However, some limitations need to be addressed.

First, the use of manual segmentation introduces human bias. To combat this bias, the segmentation was done by one person only, blinded for group status. Secondly, we focused on the shape of the patella alone. While we were able to show differences between the groups in terms of the patellar shape, it is important to note that the shape combination of the trochlea and patella is probably very important as well for joint loading. Future shape models in the patellofemoral joint should, therefore, focus on the combined bone shapes, taking the entire patellofemoral joint into account. Finally, before the SSM were build, we planned to use parallel analysis to determine the number of modes included in our statistical analyses. This resulted in a large number of shape modes, of which the variance was relatively low. Consequently, given the large number of tests, a type 1 statistical error may have occurred. However, our results were consistent across multiple comparisons, adding confidence to our results.

Conclusions

Some features of the patellar shape seem to be associated with the presence of MRI-based PFOA in middle-aged women, of which some variants were also associated with clinical symptoms. Further validation in other study populations is mandatory, given the relatively low percentage of explained variance, but also to confirm the association of one particular shape mode. This shape mode, mostly pronounced on the dorsal side of the patella, was earlier shown to be associated with structural abnormalities associated with OA in a population aged under 40.

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References

1. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. *Lancet (London, England)*. 2019;393(10182):1745-1759. doi:10.1016/S0140-6736(19)30417-9
2. Cui A, Li H, Wang D, Zhong J, Chen Y, Lu H. Global, regional prevalence, incidence and risk factors of knee osteoarthritis in population-based studies. *EClinicalMedicine*. 2020;29-30:100587. doi:10.1016/j.eclinm.2020.100587
3. van Middelkoop M, Bennell KL, Callaghan MJ, et al. International patellofemoral osteoarthritis consortium: Consensus statement on the diagnosis, burden, outcome measures, prognosis, risk factors and treatment. *Semin Arthritis Rheum*. Published online 2017:1-10. doi:10.1016/j.semarthrit.2017.09.009
4. Duncan R, Peat G, Thomas E, Wood L, Hay E, Croft P. Does isolated patellofemoral osteoarthritis matter? *Osteoarthr Cartil*. 2009;17(9):1151-1155. doi:10.1016/j.joca.2009.03.016
5. Kobayashi S, Pappas E, Fransen M, Refshauge K, Simic M. The prevalence of patellofemoral osteoarthritis: A systematic review. *Osteoarthr Cartil*. 2016;23(May):A189. doi:10.1016/j.joca.2015.02.968
6. Lankhorst NE, Damen J, Oei EH, et al. Incidence, prevalence, natural course and prognosis of patellofemoral osteoarthritis: the Cohort Hip and Cohort Knee study. *Osteoarthr Cartil*. 2017;25(5):647-653. doi:10.1016/j.joca.2016.12.006
7. Fok LA, Schache AG, Crossley KM, Lin Y-C, Pandy MG. Patellofemoral joint loading during stair ambulation in people with patellofemoral osteoarthritis. *Arthritis Rheum*. 2013;65(8):2059-2069. doi:10.1002/art.38025
8. Hart HF, Ackland DC, Pandy MG, Crossley KM. Quadriceps volumes are reduced in people with patellofemoral joint osteoarthritis. *Osteoarthr Cartil*. 2012;20(8):863-868. doi:10.1016/j.joca.2012.04.009
9. Teng HL, MacLeod TD, Link TM, Majumdar S, Souza RB. Higher knee flexion moment during the second half of the stance phase of gait is associated with the progression of osteoarthritis of the patellofemoral joint on magnetic resonance imaging. *J Orthop Sports Phys Ther*. 2015;45(9):656-664. doi:10.2519/jospt.2015.5859
10. Macri EM, Stefanik JJ, Khan KK, Crossley KM. Is Tibiofemoral or Patellofemoral Alignment or Trochlear Morphology Associated With Patellofemoral Osteoarthritis? A Systematic Review. *Arthritis Care Res*. 2016;68(10):1453-1470. doi:10.1002/acr.22842
11. Hunter D, Nevitt M, Lynch J, et al. Longitudinal validation of periarticular bone area and 3D shape as biomarkers for knee OA progression? Data from the FNIH OA Biomarkers Consortium. *Ann Rheum Dis*. Published online 2015:annrheumdis-2015-207602. doi:10.1136/annrheumdis-2015-207602
12. Barr AJ, Dube B, Hensor EMA, et al. The relationship between three-dimensional knee MRI bone shape and total knee replacement-A case control study: Data from the Osteoarthritis Initiative. *Rheumatol (United Kingdom)*. 2016;55(9):1585-1593. doi:10.1093/rheumatology/kew191
13. Dube B, Bowes MA, Hensor EMA, Barr A, Kingsbury SR, Conaghan PG. The relationship between two different measures of osteoarthritis bone pathology, bone marrow lesions and 3D bone shape: data from the Osteoarthritis Initiative. *Osteoarthr Cartil*. 2018;26(10):1333-1337. doi:10.1016/j.joca.2018.06.011
14. Bowes MA, Kacena K, Alabas OA, et al. Machine-learning, MRI bone shape and important clinical outcomes in osteoarthritis: Data from the Osteoarthritis Initiative. *Ann Rheum Dis*. 2021;80(4):502-508. doi:10.1136/annrheumdis-2020-217160

15. Liao TC, Jergas H, Tibrewala R, et al. Longitudinal analysis of the contribution of 3D patella and trochlear bone shape on patellofemoral joint osteoarthritic features. *J Orthop Res*. 2021;39(3):506-515. doi:10.1002/jor.24836

16. Hofman A, Van Duijn CM, Franco OH, et al. The Rotterdam Study: 2012 objectives and design update. *Eur J Epidemiol*. 2011;26(8):657-686. doi:10.1007/s10654-011-9610-5

17. Ikram MA, Brusselle G, Ghanbari M, et al. *Objectives , Design and Main Findings until 2020 from the Rotterdam Study*. Springer Netherlands; 2020. doi:10.1007/s10654-020-00640-5

18. Schiphof D, Oei EHG, Hofman A, Waarsing JH, Weinans H, Bierma-Zeinstra SMA. Sensitivity and associations with pain and body weight of an MRI definition of knee osteoarthritis compared with radiographic Kellgren and Lawrence criteria: A population-based study in middle-aged females. *Osteoarthr Cartil*. 2014;22(3):440-446. doi:10.1016/j.joca.2013.12.017

19. Hunter DJ, Guermazi A, Lo GH, et al. Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score). *Osteoarthr Cartil*. 2011;19(8):990-1002. doi:10.1016/j.joca.2011.05.004

20. Schiphof D, Van Middelkoop M, De Klerk BM, et al. Crepitus is a first indication of patellofemoral osteoarthritis (and not of tibiofemoral osteoarthritis). *Osteoarthr Cartil*. 2014;22(5):631-638. doi:10.1016/j.joca.2014.02.008

21. Cheng R, Jackson JN, McCreedy ES, et al. Patellar segmentation from 3D magnetic resonance images using guided recursive ray-tracing for edge pattern detection. In: *Medical Imaging 2016: Biomedical Applications in Molecular, Structural, and Functional Imaging*. Vol 9788. ; 2016:97880C. doi:10.1117/12.2217232

22. van de Giessen M, Vos FM, Grimbergen CA, van Vliet LJ, Streekstra GJ. An efficient and robust algorithm for parallel groupwise registration of bone surfaces. In: *Lecture Notes in Computer Science (Including Subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics)*. Vol 7512 LNCS. Springer Verlag; 2012:164-171. doi:10.1007/978-3-642-33454-2_21

23. Tümer N, Blankevoort L, van de Giessen M, et al. Bone shape difference between control and osteochondral defect groups of the ankle joint. *Osteoarthr Cartil*. 2016;24(12):2108-2115. doi:10.1016/j.joca.2016.07.015

24. Tümer N, Arbabi V, Gielis WP, et al. Three-dimensional analysis of shape variations and symmetry of the fibula, tibia, calcaneus and talus. *J Anat*. 2019;234(1):132-144. doi:10.1111/joa.12900

25. Macri EM, Neogi T, Tolstykh I, et al. Relation of Patellofemoral Joint Alignment, Morphology, and Radiographic Osteoarthritis to Frequent Anterior Knee Pain: Data from the Multicenter Osteoarthritis Study. *Arthritis Care Res*. 2020;72(8):1066-1073. doi:10.1002/acr.24004

26. Teichtahl AJ, Wluka AE, Cicuttini FM. Frontal plane knee alignment is associated with a longitudinal reduction in patella cartilage volume in people with knee osteoarthritis. *Osteoarthr Cartil*. 2008;16(7):851-854. doi:10.1016/j.joca.2007.12.002

27. Macri EM, Felson DT, Ziegler M, Cooke T, Guermazi A, Roemer F. The association of frontal plane alignment to MRI-defined worsening of patellofemoral osteoarthritis: The MOST study EM. *Osteoarthr Cartil*. 2019;27(3):459–467. doi:10.1016/j.joca.2018.11.004.The

28. Eijkenboom JJ, Tümer N, Waarsing EH, et al. Patellofemoral pain patients show differences in 3D patellar shape compared to healthy control subjects. In: *Osteoarthritis and Cartilage*. Vol 29. Elsevier; 2021:S336-S337. doi:10.1016/J.JOCA.2021.02.438

29. Crossley KM. Is patellofemoral osteoarthritis a common sequela of patellofemoral pain? *Br J Sports Med*. 2014;48(6):409-410. doi:10.1136/bjsports-2014-093445

Online Appendix 1. The associations between the clinical patellofemoral joint measures and the patellar shape modes, adjusted for the group status (OR with 95% CI).

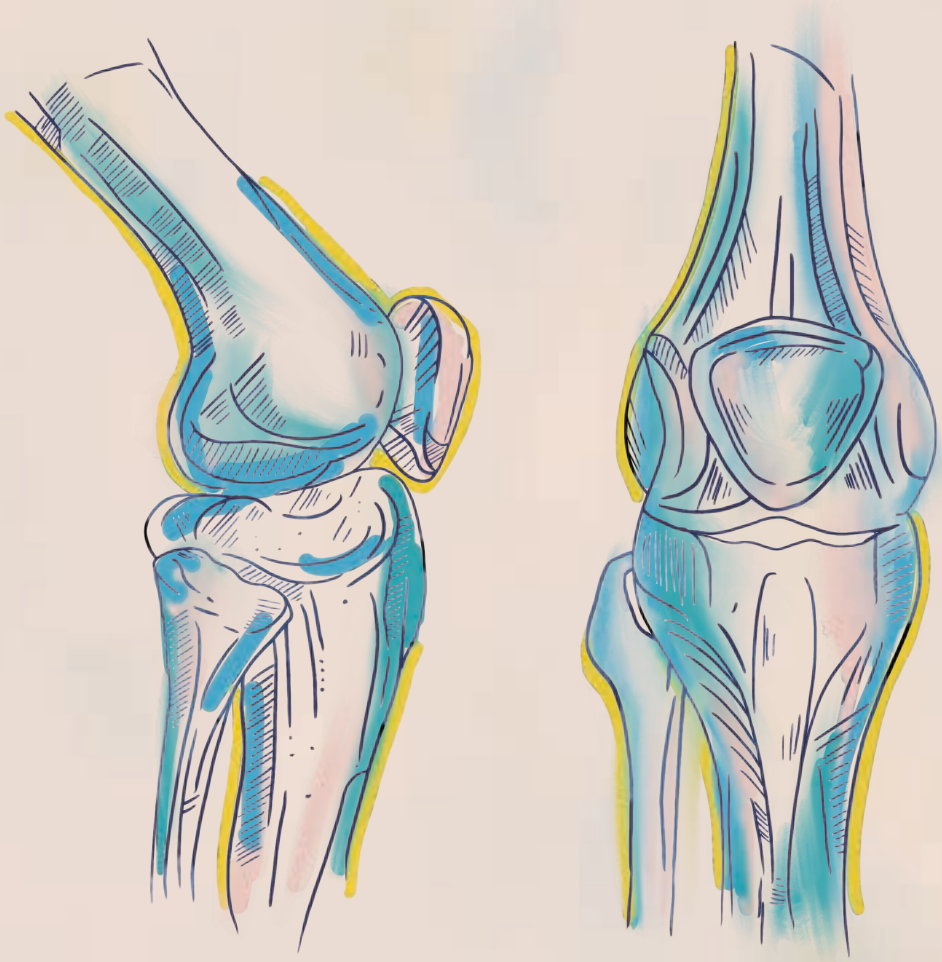
Shape Modes	Crepitus	History of patellar pain	KOOS walking stairs
Mode 1	**0.63 (0.41-0.98)**	-	-
Mode 6	0.68 (0.45-1.01)	-	-
Mode 13	-	-	0.69 (0.42-1.15)
Mode 14	**1.69 (1.10-2.60)**	-	-
Mode 15	-	**1.69 (1.02-2.79)**	-
Mode 20	**0.61 (0.42-0.89)**	-	-
Mode 21	-	**0.57 (0.35-0.916)**	0.65 (0.39-1.07)

Sensitivity analysis, resulting from statistically significant associations in Table 4, adjusted for the group status, age, and BMI. Significant associations (p<0.05) are typed using a bold font 9.

Online Appendix 2. The associations between the KOOS subscales and the patellar shape modes, adjusted for the group status (Beta's with 95% CI).

Shape Modes	KOOS Pain	KOOS Symptoms	KOOS ADL	KOOS Sport	KOOS QoL
Mode 1	-	-	-	**6.55 (1.47;11.63)**	-
Mode 2	**-3.21 (-5.84;-0.58)**	-	**-2.52 (-4.93;-0.11)**	**-5.20 (-10.01;-0.39)**	-
Mode 13	1.88 (-0.78;4.54)	-	-	-	2.52 (-1.17;6.20)
Mode 21	**2.67 (0.08;5.27)**	**3.65 (1.125;6.18)**	**2.67 (0.31;5.02)**	**6.85 (2.17;11.54)**	**4.96 (1.42;8.50)**

Sensitivity analysis, resulting from statistically significant associations in Table 5, adjusted for the group status, age, and BMI. Significant associations (p<0.05) are typed using a bold font.



Chapter 7

General Discussion

General discussion

Main findings

In this thesis we studied associations between joint alignment, joint shape, structural abnormalities in the knee joint, clinical characteristics and knee pain. We have shown that alignment in the patellofemoral joint (PFJ) is associated with structural abnormalities in bone and cartilage[1]. Patella alta, patellar tilt and the geometry of the trochlea were associated with structural abnormalities in a young population consisting of both participants with patellofemoral pain (PFP) and age, sex matched control participants. These abnormalities included bone marrow lesions (BML), osteophytes and (minor) cartilage lesions, which are common radiographic features of osteoarthritis (OA)[2]. While radiographic measures do not always translate into clinical symptoms, we have shown that these structural abnormalities are associated with some self-reported clinical characteristics of PFP[3]. In particular, bone marrow lesions, cartilage defects and patellar tendon abnormalities were associated with duration of complaints, bilateral nature of complaints and presence of crepitus in both control participants and participants with PFP.

In addition to the more traditional measures of alignment in the PFJ, as discussed above, we applied statistical shape modelling to study the association between patellar shape and the presence of PFP. We found associations between patellar shape and presence of PFP in both x-ray based 2D shape models[4] and in MRI based 3D shape models[5]. In 2D shape we found that participants with PFP had more equally distributed medial and lateral facets and a rounder inferior posterior patellar shape, compared to control participants without PFP. The 3D patellar shape model showed some small associations between shape and presence of PFP. Interestingly, one of these associations showed a similar result as found in our 2D study; a rounder, less pronounced lateral bump in participants with PFP. In addition to associations with presence of PFP, the 3D shape study revealed several shapes correlated with structural abnormalities on the PFJ.

The exact same 2D and 3D shape models used in a younger population with PFP, were also applied in a relatively older population with PFOA patients and matched controls. This gave us the ability to compare the results of these two populations. In the 2D shape study, presence of PFOA was also associated with patellar shape. Similar as the participants with PFP in the younger population, the participants with PFOA had more equally distributed medial and lateral facets and a rounder inferior posterior patellar shape, compared to control participants[4]. These 2D shape analyses may therefore support a possible connection between PFP and PFOA.

When assessing 3D shape models, multiple patellar shapes were associated with presence of radiographical PFOA. The strongest association between shape and PFOA was found in shape mode 6. In this shape variant, the participants with PFOA seemed to possess a relatively more pronounced dorsal bump at the articular surface of the patella and

a slightly shorter medial margin of the patella. The control participants showed a less pronounced dorsal bump and a slightly longer medial margin of the patella. This shape variant specifically showed associations with osteophytes, BMLs and cartilage loss on the patella in the older research population. Looking at the younger research population, we also found associations between shape mode 6 and BMLs and minor cartilage defects on the patella. This suggests that an increased dorsal bump and other shape difference apparent in this particular shape variant may predict the onset of early radiological signs of PFOA in a young population and may progress to established radiographic PFOA later in life.

Disease continuum

In 2010, Thomas et al. performed a systematic review to investigate the role of PFP as a precursor for PFOA[6]. At that time, they found seven retrospective studies that examined the association between PFP and PFOA. However, only one study had an ample group size and directly retrospectively studied the association between PFP and PFOA[7]. This study performed by Utting et al. (2005) found that patients who had undergone arthroplasty for isolated PFOA were far more likely to report a history of anterior knee pain in their adolescence and early adult years compared to patients who had undergone arthroplasty for isolated TFOA. Because of the retrospective nature of this study and lacking methodological quality of other studies, the authors of the systematic review were rightfully hesitant to draw firm conclusions about the potential disease continuum between PFP and PFOA.

In 2013, at the biyearly International Patellofemoral Research Retreat (iPFRR), the PFP-PFOA continuum was defined as a major topic of interest[8]. It was stated that although it is possible that there is a phenotype of PFP that goes on to develop PFOA, there is no evidence to support this view yet. One of the reasons that PFP and PFOA may be linked to each other is the fact that both share multiple risk factors[9]. A large part of these shared risk factors between PFP and PFOA are of biomechanical nature, and this thesis therefore focused further on hypotheses of biomechanical nature.

The development of PFOA has been commonly related to abnormal PF joint stress[9] and this abnormal PF joint and cartilage stress is also seen in individuals with PFP[10]. These increased stresses likely play a role in joint pathology by causing degradation of cartilage[11]. Abnormal PF joint stress has numerous contributing biomechanical factors such as BMI, muscle strength, joint alignment, joint shape and joint geometry[9]. Interestingly, although maybe not surprisingly, many of these factors related to joint stress, are also risk factors for both PFP and PFOA.

PFJ alignment is one of the risk factors commonly linked to both PFOA and PFP. Alignment measures such as patellar height (Insall-Salvati Ratio (ISR)), lateral patellar translation, patellar tilt and tibial tubercle to trochlear groove (TT-TG) distance are either broadly hypothesized or shown to be associated with both PFOA and PFP[9,12,13]. Our study in chapter 3 showed that patellar tilt and ISR are associated with minor cartilage defects and bone

marrow lesions in a young PFP population. This implies that joint alignment may play a crucial role in the development of morphological abnormalities in the PF joint, that are associated with PFOA. This was confirmed in a larger study sample where the presence of morphological abnormalities defined on MRI was related to a higher ISR (indicating patella alta), larger patellar tilt angle (indicating greater lateral tilt), and larger bisect offset (indicating greater lateral displacement) in people with PFP[14]. This implies that there might be a distinct subgroup of PFP patients that are more prone to develop PFOA later in life in which these abnormalities already develop early in life.

In addition to the factor 'joint alignment' and its associations with both PFOA and PFP, another biomechanical factor studied in this thesis is bone shape within the PFJ. It is important to note that joint alignment and bone shape likely interact with each other. Bone and joint shape are related to shear stress in the joint, and on its own turn correlate with joint alignment and kinematics[15]. This correlation can work in both directions. Bone adapts in reaction to sheer stress[16], especially at young age[17] and malalignment increases joint stress and may therefore influence bone shape. On the other hand, traditional measures of bone shape, such as sulcus angle can lead to malalignment[18]. One of our main hypotheses was that joint shape might be the missing link when searching for a connection between PFP and PFOA. We theorized that aberrant patellar shape at young age could lead to abnormal joint kinematics and increased shear stress, leading to joint pain (PFP). Overlapping, we theorized that this aberrant patellar shape and its effects on joint stress could start joint degeneration and ultimately PFOA. Using multiple different techniques some studies have linked bone shape to PFOA [19–21]. Though, one serious shortcoming of shape research lies in its interpretation. It is impossible to completely extract all details from the shape models, especially from the information presented in the manuscripts. Therefore, it is impossible to compare two separately made shape models.

To accurately study our hypothesis, we aimed to create combined SSMs, combining data from multiple previously conducted studies in both PFP and PFOA populations into one model. In chapter 4 we created a combined 2D shape model of the patella in a young PFP population and an older PFOA population. Moreover, in chapter 5 and 6 we created a combined 3D shape model of the patella in a young PFP population and a relatively older PFOA population. In the study where we applied 2D analyses we found two fairly strong shape modes associated with both the presence of PFOA and PFP, and therefore seemed to support our hypothesis. The first shape variant indicates both PFOA and PFP subjects have a more lateral positioned vertical ledge on the posterior side of the patella (skyline mode 8). The second shape variant indicates both PFOA and PFP subjects have a rounder inferior-posterior articular area of the patella (lateral mode 5). However, there was one large limitation in that study, namely the lack of control subjects in the PFP population. Therefore, we were unable to confirm whether differences between groups were a result of the PFP diagnosis or a result of other differences between populations or study designs. In our 3D shape model, we did find multiple patellar shape modes associated with both PFOA

and PFP separately. However, overlapping shape modes associated with both PFP and PFOA, as we hypothesized, were non-existent. We did however show that certain patellar shape characteristics were associated with features of OA in a young population, while this same patellar shape was associated with the presence of PFOA in the older population. As van der Heijden et al. earlier found no association between structural abnormalities in the PF joint and the presence of PFP[22], our findings do not seem to support our hypothesis on the PFP continuum model. Though our findings do suggest that particular patellar shapes might be important risk factors for the development of PFOA, independent of the presence of pain at a young age. Overall, I think we have not found enough evidence to support our hypothesis. However, we have only investigated the patellar shape and as noted above, the alignment and therefore complete articular joint shape might be crucial. Shape models combining multiple joints are complex, hard to interpret and therefore rarely applied[23]. Fitzpatrick et al.[15] developed a shape function model of the PF joint to quantify relationships between articular geometry, kinematics and contact mechanics. The application of such combined models in patient populations remains complex but seems promising and may help to get a better understanding on the etiology, development and risk factors of PFOA.

Future research and clinical implication

If we want to find a definitive answer whether bone shape is similarly aberrant in PFP and PFOA patients, further research is needed. The most powerful way to investigate this hypothesis, would be following a group of PFP patients and controls, over the course of decades, to see which PFP patients develop PFOA, and if this can be predicted by bone shape. It is important to include multiple shape measurements over time, since morphological changes connected to OA are associated with bone shape[24], and bone alterations are hypothesized to play an important role in OA development[25]. Furthermore, PFP subjects would preferably be classified in function based classification subcategories[26]; overuse, muscle performance deficits, movement coordination deficits and mobility impairments. It is plausible that the association between PFP and PFOA might only exist in some of these subcategories. If shear stress is indeed a contributing factor to both PFP and PFOA as discussed in the previous section of this discussion, an association between PFP, PFOA and bone shape is more likely in a subcategory of PFP patients with aberrant joint loading and shear stresses.

The value of this thesis is threefold. Clinically, if PFP indeed is a precursor of PFOA, one would be able to predict a possible onset of PFOA. When people get the diagnosis PFP, they could get additional education and be made aware of their increased chance to develop PFOA. People with PFP could have increased incentive to make life style changes and start preventive therapeutic measures such as physical therapy to reduce their BMI or improve alignment and posture. Since PFOA seems a common starting point of total knee OA[27], this could in theory greatly reduce OA burden.

Secondly, this thesis provides value showing that patellar bone shape is related to PFP, PFOA, clinical symptoms of knee impairment and radiographic signs of early OA. Since there is a possible biomechanical origin in the association between bone shape and PFOA, further research could also study the association between PFOA and patellar shape in particular phenotypes of OA[28] in which biomechanics play an important role. Bone shape could also be investigated as a phenotype of its own. Another interesting subgroup for shape analysis could be post traumatic OA, as it is known that this particular subgroup has a high risk to develop PFOA and show altered sagittal plane knee joint biomechanics during functional activities compared to healthy controls[29,30].

Third, if further research confirms our finding that patellar shape is associated with (early signs of) PFOA development, bone shape could be a useful clinical predictor for PFOA. Especially because technological advancements to make shape models feasible in a clinical setting are rapidly improving and soon within reach. Fully automatic segmentation of bones in the PFJ has already been applied by multiple research groups[31,32]. However, much research is needed before such a clinical implementation could be feasible and cost effective. We need to know more on the explained variance of such a shape model; what would be the number needed to screen to find one OA patient? Bone shape might only have a high percentage of explained variance in some particular subgroups, which has to be studied as discussed above. And if we can better predict the onset of PFOA, we need to get a better understanding in effective (preventive) therapies. In that perspective, preventive therapy in patients with anterior knee complaints might be promising in future in order to prevent the large predicted burden of OA and total knee arthroplasty[33].

References

1. Eijkenboom JFA, van der Heijden RA, de Kanter JLM, Oei EH, Bierma-Zeinstra SMA, van Middelkoop M. Patellofemoral alignment and geometry and early signs of osteoarthritis are associated in patellofemoral pain population. *Scand J Med Sci Sport*. 2020;30(5):885-893. doi:10.1111/sms.13641
2. Hunter DJ, Guermazi A, Lo GH, et al. Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score). *Osteoarthr Cartil*. 2011;19(8):990-1002. doi:10.1016/j.joca.2011.05.004
3. Eijkenboom JFA, Timmer ER, Van Heijden RAD, et al. Association between self-reported measures, physical examination, and early magnetic resonance imaging signs of osteoarthritis in patients with patellofemoral pain. *J Orthop Sports Phys Ther*. 2019;49(9):634-639. doi:10.2519/jospt.2019.8889
4. Eijkenboom JFA, Waarsing JH, Oei EHG, Bierma-Zeinstra SMA, Van Middelkoop M. Is patellofemoral pain a precursor to osteoarthritis? *Bone Jt Res*. 2018;7(9):541-547. doi:10.1302/2046-3758.79.BJR-2018-0112.R1
5. Eijkenboom JJ, Tümer N, Waarsing EH, et al. Patellofemoral pain patients show differences in 3D patellar shape compared to healthy control subjects. In: *Osteoarthritis and Cartilage*. Vol 29. Elsevier; 2021:S336-S337. doi:10.1016/J.JOCA.2021.02.438
6. Thomas MJ, Wood L, Selfe J, Peat G. Anterior knee pain in younger adults as a precursor to subsequent patellofemoral osteoarthritis: a systematic review. *BMC Musculoskelet Disord*. 2010;11:201. doi:10.1186/1471-2474-11-201
7. Utting MR, Davies G, Newman JH. Is anterior knee pain a predisposing factor to patellofemoral osteoarthritis? *Knee*. 2005;12(5):362-365. doi:10.1016/j.knee.2004.12.006
8. Witvrouw E, Callaghan MJ, Stefanik JJ, et al. Patellofemoral pain: consensus statement from the 3rd International Patellofemoral Pain Research Retreat held in Vancouver, September 2013. *Br J Sports Med*. 2014;48(1):411-414. doi:10.1136/bjsports-2014-093450
9. Mills K, Hunter DJ. Patellofemoral joint osteoarthritis: An individualised pathomechanical approach to management. *Best Pract Res Clin Rheumatol*. 2014;28(1):73-91. doi:10.1016/j.berh.2014.01.006
10. Farrokhi S, Keyak JH, Powers CM. Individuals with patellofemoral pain exhibit greater patellofemoral joint stress: A finite element analysis study. *Osteoarthr Cartil*. 2011;19(3):287-294. doi:10.1016/j.joca.2010.12.001
11. Li Y, Yuan Z, Yang H, Zhong H, Peng W, Xie R. Recent advances in understanding the role of cartilage lubrication in osteoarthritis. *Molecules*. 2021;26(20):1-19. doi:10.3390/molecules26206122
12. Macri EM, Stefanik J, Khan KK, Crossley KM. Is tibiofemoral or patellofemoral alignment or trochlear morphology associated with patellofemoral osteoarthritis? A systematic review. *Arthritis Care Res (Hoboken)*. 2016;68(10):1453-1470. doi:10.1002/acr.22842
13. Lankhorst NE, A Bierma-Zeinstra SM, Middelkoop M van. Factors associated with patellofemoral pain syndrome: a systematic review. *Br J Sport Med*. 2013;47:193-206. doi:10.1136/bjsports-2011-090369
14. van Middelkoop M, Macri EM, Eijkenboom JF, et al. Are Patellofemoral Joint Alignment and Shape Associated With Structural Magnetic Resonance Imaging Abnormalities and Symptoms Among People With Patellofemoral Pain? *Am J Sports Med*. 2018;46(13):3217-3226. doi:10.1177/0363546518801314
15. Fitzpatrick CK, Baldwin M a., Laz PJ, FitzPatrick DP, L. Lerner A, Rullkoetter PJ. Development of a statistical shape model of the patellofemoral joint for investigating relationships between shape and function. *J Biomech*. 2011;44(13):2446-2452. doi:10.1016/j.jbiomech.2011.06.025

16. Mukrimaa SS, Nurdyansyah, Fahyuni EF, et al. No 主観的健康感を中心とした在宅高齢者における 健康関連指標に関する共分散構造分析Title. *J Penelit Pendidik Guru Sekol Dasar*. 2016;6(August):128.

17. Tan VPS, Macdonald HM, Kim SJ, et al. Influence of physical activity on bone strength in children and adolescents: A systematic review and narrative synthesis. *J Bone Miner Res*. 2014;29(10):2161-2181. doi:10.1002/jbmr.2254

18. Chen J, Ye Z, Wu C, Zhang X, Zhao J, Xie G. Sulcus depth, congruence angle, Wiberg index, TT-TG distance, and CDI are strong predictors of recurrent patellar dislocation. *Knee Surgery, Sport Traumatol Arthrosc*. 2023;31(7):2906-2916. doi:10.1007/s00167-022-07245-3

19. Liao TC, Jergas H, Tibrewala R, et al. Longitudinal analysis of the contribution of 3D patella and trochlear bone shape on patellofemoral joint osteoarthritic features. *J Orthop Res*. 2021;39(3):506-515. doi:10.1002/jor.24836

20. Neogi T, Bowes MA, Niu J, et al. Magnetic resonance imaging-based three-dimensional bone shape of the knee predicts onset of knee osteoarthritis: Data from the osteoarthritis initiative. *Arthritis Rheum*. 2013;65(8):2048-2058. doi:10.1002/art.37987

21. Barr AJ, Dube B, Hensor EMA, et al. The relationship between three-dimensional knee MRI bone shape and total knee replacement-A case control study: Data from the Osteoarthritis Initiative. *Rheumatol (United Kingdom)*. 2016;55(9):1585-1593. doi:10.1093/rheumatology/kew191

22. van der Heijden RA, de Kanter JLM, Bierma-Zeinstra SMA, et al. Structural Abnormalities on Magnetic Resonance Imaging in Patients With Patellofemoral Pain: A Cross-sectional Case-Control Study. *Am J Sports Med*. 2016;44(9):2339-2346. doi:10.1177/0363546516646107

23. Cerveri P, Belfatto A, Manzotti A. Predicting Knee Joint Instability Using a Tibio-Femoral Statistical Shape Model. *Front Bioeng Biotechnol*. 2020;8(April):1-12. doi:10.3389/fbioe.2020.00253

24. Inamdar G, Pedoia V, Rossi-Devries J, et al. MR study of longitudinal variations in proximal femur 3D morphological shape and associations with cartilage health in hip osteoarthritis. *J Orthop Res*. 2019;37(1):161-170. doi:10.1002/jor.24147

25. Neogi T. Clinical significance of bone changes in osteoarthritis. *Ther Adv Musculoskelet Dis*. 2012;4(4):259-267. doi:10.1177/1759720X12437354

26. Willy RW, Hoglund LT, Barton CJ, et al. Patellofemoral pain clinical practice guidelines linked to the international classification of functioning, disability and health from the academy of orthopaedic physical therapy of the American physical therapy association. *J Orthop Sports PhysTher*.2019;49(9):CPG1-CPG95. doi:10.2519/JOSPT.2019.0302/ASSET/IMAGES/LARGE/JOSPT-CPG1-FIG171.JPEG

27. Lankhorst NE, Damen J, Oei EH, et al. Incidence, prevalence, natural course and prognosis of patellofemoral osteoarthritis: the Cohort Hip and Cohort Knee study. *Osteoarthr Cartil*. 2017;25(5):647-653. doi:10.1016/j.joca.2016.12.006

28. Mobasheri A, Saarakkala S, Finnilä M, Karsdal MA, Bay-Jensen AC, van Spil WE. Recent advances in understanding the phenotypes of osteoarthritis. *F1000Research*. 2019;8:1-11. doi:10.12688/f1000research.20575.1

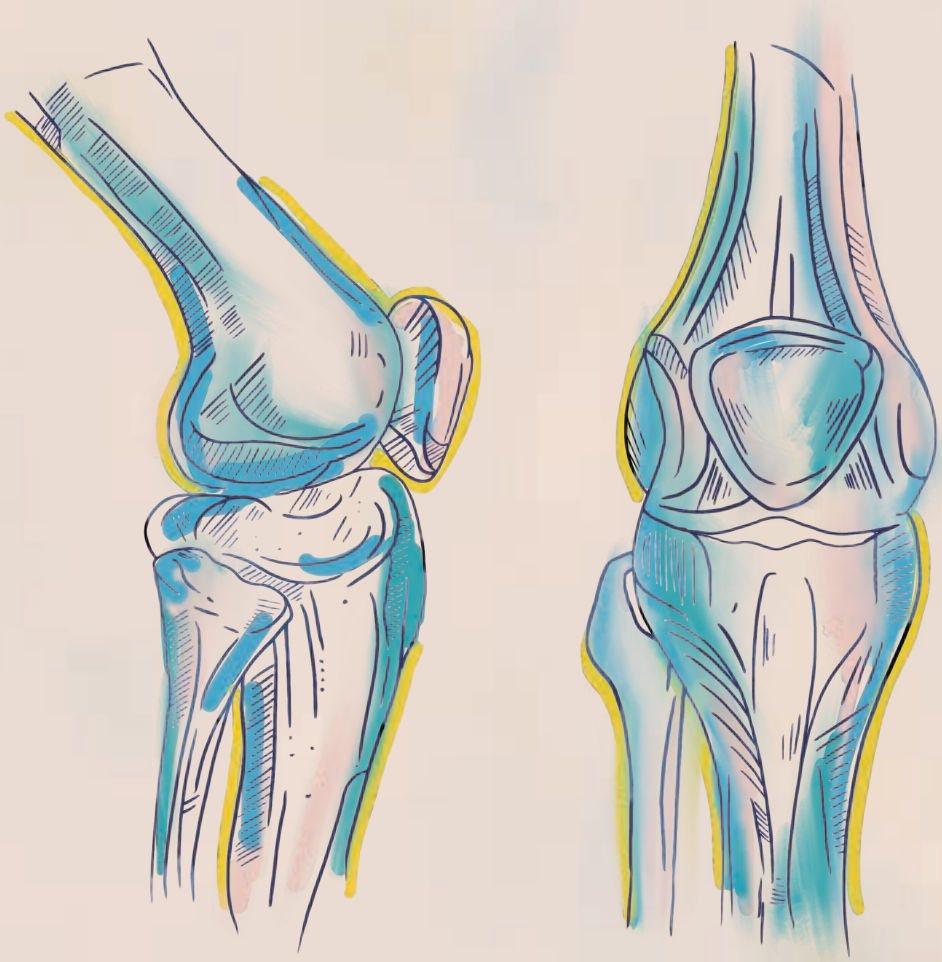
29. Johnston PT, McClelland JA, Webster KE. Lower Limb Biomechanics During Single-Leg Landings Following Anterior Cruciate Ligament Reconstruction: A Systematic Review and Meta-Analysis. *Sport Med*. 2018;48(9):2103-2126. doi:10.1007/s40279-018-0942-0

30. Hart HF, Culvenor AG, Collins NJ, et al. Knee kinematics and joint moments during gait following anterior cruciate ligament reconstruction: a systematic review and meta-analysis. *Br J Sports Med*. 2016;50(10):597 LP - 612. doi:10.1136/bjsports-2015-094797

31. Cheng R, Crouzier M, Hug F, et al. Automatic quadriceps and patellae segmentation of MRI with cascaded U2-Net and SASSNet deep learning model. *Med Phys*. 2022;49(1):443-460. doi:10.1002/mp.15335

32. Almajalid R, Zhang M, Shan J. Fully Automatic Knee Bone Detection and Segmentation on Three-Dimensional MRI. *Diagnostics*. 2022;12(1):1-16. doi:10.3390/diagnostics12010123

33. Culliford D, Maskell J, Judge A, Cooper C, Prieto-Alhambra D, Arden NK. Future projections of total hip and knee arthroplasty in the UK: Results from the UK Clinical Practice Research Datalink. *Osteoarthr Cartil*. 2015;23(4):594-600. doi:10.1016/j.joca.2014.12.022



Appendices

Summary

Patellofemoral pain (PFP) and patellofemoral osteoarthritis (PFOA) are two conditions affecting the knee joint. PFP is characterized by pain around or behind the patella and is most prevalent among adolescents. On the other hand, PFOA is a degenerative condition in the patellofemoral joint which leads to pain, stiffness, and reduced mobility. PFOA imposes a significant burden on individuals due to its association with chronic pain, diminished quality of life and increased need for therapeutic interventions. PFP has been hypothesized to predispose PFOA in later life.

In this thesis we aimed to get a better understanding of the association between the clinical and radiological measures and the signs of early osteoarthritis (OA). Additionally, we aimed to get a better understanding in the possible association between PFP and PFOA. The various studies and the accompanying results are summarized below.

In **chapter 2** we explored the prevalence of patellar malalignment among patients with PFP and its potential link to the development of PFP and PFOA. The primary objective was to examine the association between patellofemoral alignment, femoral geometry, and various bone and cartilage abnormalities in both PFP patients and healthy control subjects. We used data from a case-control study involving 64 subjects with PFP and 70 control subjects. Of these subjects 57% were female, with an average age of 23.2 years. We assessed the alignment and femoral geometry in the patellofemoral joint (PFJ) using magnetic resonance imaging (MRI). The MRI images were also used to examine structural abnormalities in the PFJ linked to OA, such as bone marrow lesions, osteophytes, minor cartilage defects, and Hoffa-synovitis. Additionally, we evaluated the cartilage composition in the PFJ and patellar bone perfusion through various MRI techniques. Associations between these measures were analyzed through regression analyses, taking into account potential confounding factors. The results revealed that lateral patellar tilt is negatively associated with the presence of osteophytes on both the patella and the anterior femur, as well as with minor cartilage defects on the patella. In addition, patella alta was found to be positively associated with the presence of bone marrow lesions in the patella and minor cartilage defects. Furthermore, patella alta and medial patellar translation showed a positive association with T1ρ relaxation times within trochlear cartilage, indicating altered biochemical cartilage composition. Interestingly, none of the alignment and geometry measures were linked to bone perfusion. In conclusion, our study indicates that the association between patellofemoral alignment and geometry and the structural abnormalities of the joint associated with OA, are present in both PFP patients and healthy control subjects.

In **chapter 3** we looked into the association between early signs of OA detected by MRI and various self-reported measures and physical examination characteristics in patients with PFP. We used data from 64 PFP patients which were selected from a previously published cross-sectional case-control study. 55% Of the subjects were female, with an average age of 23.4 years. Structural abnormalities such as osteophytes, bone marrow lesions,

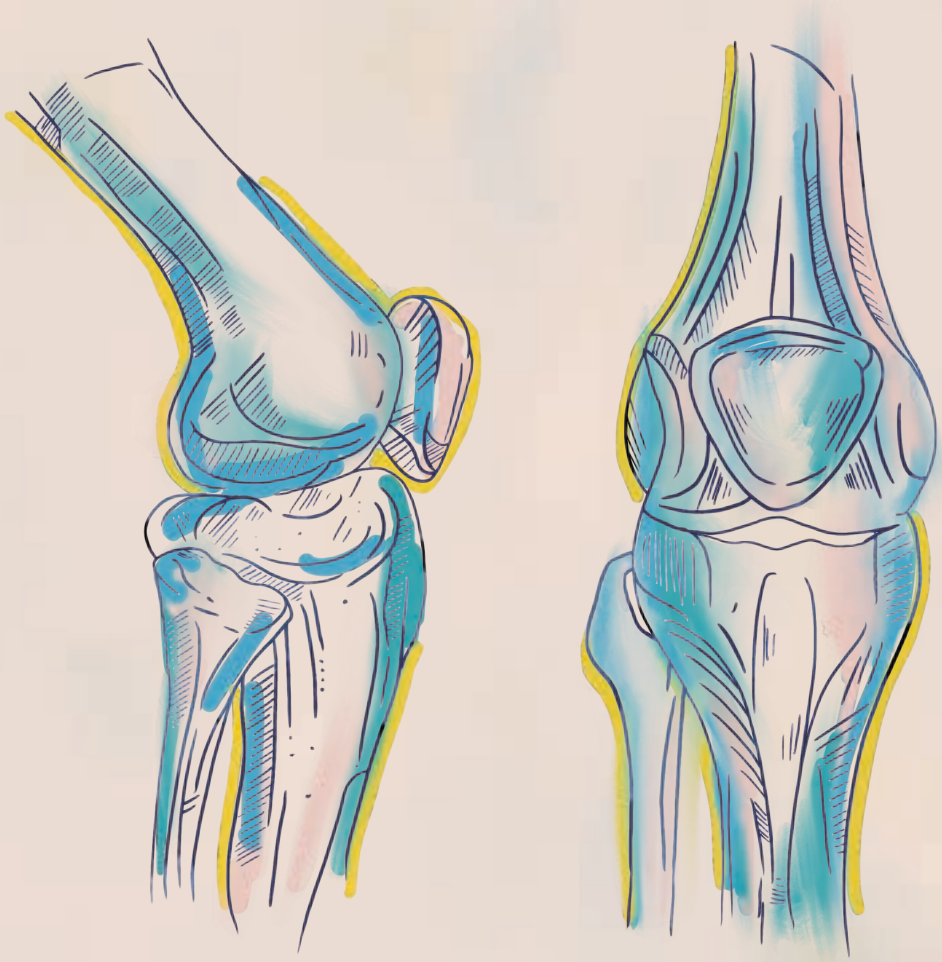
cartilage defects, Hoffa synovitis, and patellar tendon abnormalities were scored on MRI. Additionally, quantitative T2 measurements of cartilage composition were performed. Self-reported measures included pain at rest, pain during stair walking, knee function, duration of complaints, and weekly hours of sports participation. Physical examination factors like crepitus and quadriceps strength were also considered. Associations between these structural abnormalities and characteristics from self-reported measures and physical examination were analyzed using linear and logistic regression analysis. We found several associations. The duration of symptoms was associated to bone marrow lesions in the patella. The amount of weekly sports participation showed an inverse association with patellar tendon abnormalities. Moreover, the presence of crepitus and bilateral nature of complaints were both associated with minor patellar cartilage defects. However, the study found no significant connections between the clinical characteristics and cartilage T2 relaxation time. Overall, the study highlights the potential links between early MRI signs of OA and various self-reported and physical examination findings in patients with PFP.

In **chapter 4** we investigated the hypothesis that PFP might be precursor of degenerative joint changes leading to PFOA. Since PFP and PFOA share several mechanical characteristics, we studied whether subjects with these conditions also have similar patellar shape characteristics when compared to healthy control subjects. We compared three groups in this cross-sectional study: 32 subjects with PFP (average age 32 years, 72% female), 56 subjects with isolated radiological PFOA (average age 54 years, 89% female), and 80 healthy controls (average age 52 years, 74% female). We used lateral and skyline radiographs of the knee to create two separate 30-point two-dimensional statistical shape models of the patella. We then used a general linear model to compare shape modes among the PFOA, PFP, and control groups. This comparison was adjusted for body mass index and gender, and used a Bonferroni correction. The results showed that five shape modes had statistically significant differences between the groups. Specifically, skyline modes 1, 8, and 10, and lateral modes 5 and 7 differed notably among the groups. Notably, skyline mode 8 and lateral mode 5 were similar in both the PFOA and PFP groups, and significantly different from the control group. We concluded that PFP and PFOA share similar patellar shape characteristics, distinct from those of control subjects. This supports the theory of a disease continuum where PFP potentially predisposes to the development of PFOA.

The aim of **chapter 5** was to analyze the three-dimensional (3D) shape of the patella and determine if there are significant differences in shape between patients with PFP and healthy controls. Additionally, we wanted to investigate the possible association of patellar shape and the presence of structural abnormalities on the patella. MRI scans were used from a previously completed case-control study. We used MRI scans from 62 subjects with PFP (average age 23.5 years, 55% female) and 69 control subjects (average age 23.1 years, 59% female). We created 3D statistical models (SSM) of the patella using semi-automatic segmentation of the MRI scans. Structural abnormalities related to OA were assessed using the MRI Osteoarthritis Knee Score (MOAKS). Regression analysis was used

to explore the associations between the 3D shape of the patella, the status of being a patient or a control, and the scores on the MOAKS. We found significant associations between two 3D patellar shape modes and group status. Specifically, the lateral side and apex of the patella was more rounded in PFP patients compared to controls, as shown in shape mode 16 in this chapter. Furthermore, patients with PFP demonstrated a more diagonal, as compared to a horizontal, patellar base, as shown in shape mode 22 in this chapter. We also found an association between the 3D shape of the patella and the presence of patellar bone marrow lesions, anterior femoral osteophytes, bone marrow lesions, and Hoffa synovitis. In conclusion, the study successfully identified significant variations in 3D patellar shape between patients with PFP and healthy individuals. Notably, these variations in patellar shape are already associated with the presence of structural abnormalities linked to OA in this young population.

In **chapter 6** we explored the association between the 3D shape of the patella and three specific aspects: 1) the occurrence of MRI-based PFOA, 2) the morphological features characteristic of PFOA, and 3) the clinical symptoms associated with PFOA. For this study, 66 women diagnosed with isolated MRI-based PFOA and 66 healthy women matched in age and body mass index were selected from a cohort study. The patellae were manually segmented from the MRI scans and a 3D SSM of the patella was created. Structural abnormalities were scored using the MOAKS. Regression analyses were used to examine the association between the patellar shape group status, clinical symptoms, and structural abnormalities. The results showed four shape variants that had a statistically significant association with group status. The mode responsible for most of the shape variation indicated that participants with PFOA tend to have a thicker dorsal bump on the articular part of the patella compared to controls. Three of these shape variants were also associated with the presence of osteophytes and cartilage loss on the patella. Additionally, there were multiple associations identified between patellar shape and the clinical symptoms of PFOA. In conclusion, patellar shape shows associations with prevalence of MRI-based PFOA, structural abnormalities and clinical symptoms in women. Interestingly, one shape variant associated with MRI-based PFOA had previously been linked to structural abnormalities related to OA in individuals under 40. This may suggest that patellar shape may serve as an early detectable risk factor for the development of PFOA.



Appendices

Samenvatting

Patellofemorale pijn (PFP) en patellofemorale artrose (PFOA) zijn twee aandoeningen aan het kniegewricht. PFP wordt gekenmerkt door pijn rond of achter de knieschijf en komt het meest voor bij adolescenten. PFOA is een degeneratieve aandoening van het patellofemorale gewricht (PFG), wat leidt tot pijn, stijfheid en verminderde mobiliteit en komt het meest voor op oudere leeftijd. PFOA zorgt voor veel problemen doordat het gepaard gaat met chronische pijn, een verminderde kwaliteit van leven en een grote behoefte aan klinische ingrepen. Er wordt verondersteld dat PFP in latere levensjaren kan leiden tot PFOA.

In dit proefschrift hebben we ons gericht op een beter begrip van de associatie tussen klinische en radiologische gegevens en de tekenen van vroege artrose. Daarnaast hebben we onderzocht of er een mogelijke associatie bestaat tussen PFP en PFOA. De verschillende studies en bijbehorende resultaten worden hieronder samengevat.

In **hoofdstuk 2** hebben we de aanwezigheid van standsafwijkingen van de patella bij patiënten met PFP onderzocht en de mogelijke associatie met de ontwikkeling van PFOA. Het primaire doel was om de associatie tussen patellofemorale stand en geometrie en structule bot- en kraakbeenafwijkingen te onderzoeken bij zowel patiënten met PFP als gezonde personen. Er werden data van een case-control studie met 64 patiënten met PFP en 70 gezonde personen gebruikt. Hiervan was 57% vrouw, met een gemiddelde leeftijd van 23,2 jaar. We beoordeelden de stand (Insall-Salvati ratio, patellaire translatie, patellaire kanteling) en femorale geometrie (sulcusdiepte, sulcushoek, TT-TG afstand) in het PFG met behulp van MRI. De MRI-beelden werden ook gebruikt om structurele afwijkingen in het PFG te onderzoeken die verband houden met artrose, zoals beenmerglaesies, osteofyten, kleine kraakbeenafwijkingen en Hoffa-synovitis. Daarnaast werd de kraakbeensamenstelling in het PFG en de doorbloeding van het patellaire bot bepaald middels verschillende MRI-technieken. Associaties tussen stand- en geometrieparameters, structurele afwijkingen, kraakbeensamenstelling en doorbloeding werden geanalyseerd door middel van regressieanalyses, geadjusteerd voor mogelijke confounders. De resultaten toonden aan dat laterale patellaire kanteling (standsafwijking) negatief geassocieerd is met de aanwezigheid van osteofyten (structurele afwijking) op zowel de patella als de voorzijde van het femur, evenals met kleine kraakbeenafwijkingen op de patella. Bovendien bleek patella alta positief geassocieerd met de aanwezigheid van beenmerglaesies in de patella en kleine kraakbeenafwijkingen. Verder was er een positieve associatie tussen Insall-Salvati ratio, mediale patellaire translatie en kraakbeensamenstelling van het trochleair kraakbeen. Geen van de stand- en geometrieparameters waren geassocieerd met de doorbloeding van het bot. Concluderend suggereert deze studie dat een associatie tussen patellofemorale stand en geometrie en de structurele afwijkingen van het gewricht, aanwezig is bij zowel patiënten met PFP als gezonde personen.

In **hoofdstuk 3** werd de associatie tussen structurele kenmerken van artrose en zelfgerapporteerde pijn en functie bij patiënten met PFP onderzocht. Gegevens van 64 patiënten met PFP uit een eerder gepubliceerde cross-sectionele case-control studie zijn

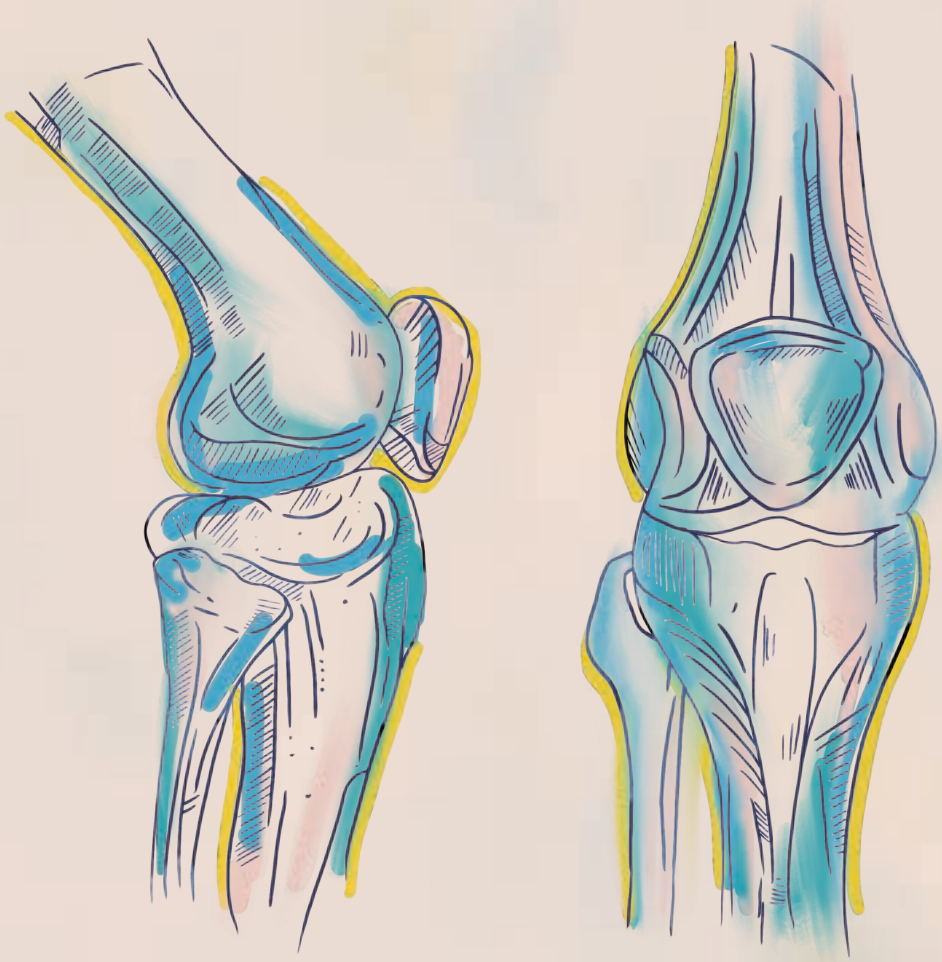
gebruikt. 55% Van de proefpersonen was vrouw, met een gemiddelde leeftijd van 23,4 jaar. Structurele afwijkingen zoals osteofyten, beenmerglaesies, kraakbeenafwijkingen, Hoffa-synovitis en patellaire peesafwijkingen werden gescoord op MRI. Daarnaast werden kwantitatieve T2-metingen van de kraakbeensamenstelling uitgevoerd. Zelfgerapporteerde gegevens omvatten pijn in rust, pijn tijdens traplopen, kniefunctie, duur van de klachten en wekelijkse uren sportdeelname. Ook werden fysieke onderzoeksfactoren zoals crepitus en quadricepskracht gemeten. Associaties tussen deze structurele afwijkingen en kenmerken uit zelfgerapporteerde gegevens en fysiek onderzoek werden geanalyseerd met behulp van lineaire en logistische regressieanalyse. We vonden verschillende associaties. De duur van de symptomen was geassocieerd met beenmerglaesies in de patella. Het aantal wekelijkse sporturen toonde een negatieve associatie met patellaire peesafwijkingen. Bovendien waren de aanwezigheid van crepitus en de bilaterale aard van klachten beide geassocieerd met kleine patellaire kraakbeenafwijkingen. Er werd geen verband gevonden tussen de klinische kenmerken en de T2-relaxatietijd van het kraakbeen. Over het geheel genomen benadrukt deze studie de potentiële verbanden tussen vroege MRI-tekenen van artrose en verschillende zelfgerapporteerde en fysieke onderzoeksbevindingen bij patiënten met PFP.

In **hoofdstuk 4** onderzochten we de hypothese dat PFP een voorloper kan zijn van degeneratieve gewrichtsveranderingen die leiden tot PFOA. Aangezien PFP en PFOA verschillende mechanische kenmerken delen, hebben we onderzocht of personen met deze aandoeningen een andere patalla vormen hebben in vergelijking met gezonde personen. We vergeleken drie groepen in deze cross-sectionele studie: 32 proefpersonen met PFP (gemiddelde leeftijd 32 jaar, 72% vrouw), 56 proefpersonen met geïsoleerde radiologische PFOA (gemiddelde leeftijd 54 jaar, 89% vrouw), en 80 gezonde personen (gemiddelde leeftijd 52 jaar, 74% vrouw). We gebruikten laterale en skyline-röntgenfoto's van de knie om twee aparte 30-punts tweedimensionale statistische vormmodellen van de patella te maken. Vervolgens pasten we een algemeen lineair model toe om vormmodi te vergelijken tussen de PFOA-, PFP- en controlegroepen. Deze vergelijking werd gecorrigeerd voor body mass index en geslacht, en een Bonferroni-correctie werd toegepast. De resultaten toonden aan dat vijf vormmodi statistisch significante verschillen vertoonden tussen de groepen. Opmerkelijk was dat twee skyline-modi vergelijkbaar waren in zowel de PFOA- als de PFP-groepen en significant verschilden van de controlegroep. We concludeerden dat PFP en PFOA vergelijkbare kenmerken aan de vorm van de patella delen, die verschillen van die van controle personen. Dit ondersteunt de theorie waarbij PFP mogelijk overgaat tot de ontwikkeling van PFOA.

Het doel van **hoofdstuk 5** was om de driedimensionale (3D) vorm van de patella te analyseren en te bepalen of er significante vormverschillen zijn tussen patiënten met PFP en gezonde personen. Daarnaast wilden we de mogelijke associatie tussen patellaire vorm en de aanwezigheid van structurele afwijkingen op de patella onderzoeken. We gebruikten MRI-scans uit een eerder afgeronde case-control studie van 62 personen met PFP (gemiddelde leeftijd 23,5 jaar, 55% vrouw) en 69 controle personen (gemiddelde

leeftijd 23,1 jaar, 59% vrouw). We creëerden 3D-statistische vormmodellen van de patella met behulp van semi-automatische segmentatie van de MRI-scans. Structurele afwijkingen gerelateerd aan artrose werden beoordeeld met behulp van de MRI Osteoarthritis Knee Score (MOAKS). Regressieanalyse werd gebruikt om de associaties tussen de 3D-vorm van de patella, de status van patiënt of controle en de scores op de MOAKS te onderzoeken. We vonden significante associaties tussen twee 3D-patellaire vormmodi en groepsstatus. Specifiek was de laterale zijde en de apex van de patella meer afgerond bij patiënten met PFP vergeleken met controle personen, zoals weergegeven in vormmodus 16 in dit hoofdstuk. Bovendien toonden patiënten met PFP een meer diagonale patellaire basis in plaats van een horizontale patellaire basis, zoals weergegeven in vormmodus 22 in dit hoofdstuk. We vonden ook een associatie tussen de 3D-vorm van de patella en de aanwezigheid van patellaire beenmerglaesies, osteofyten aan de voorkant van het femur, beenmerglaesies en Hoffa-synovitis. Concluderend heeft de studie met succes significante variaties in 3D-patellaire vorm geïdentificeerd tussen patiënten met PFP en gezonde individuen.

In **hoofdstuk 6** onderzochten we de associatie tussen de 3D-vorm van de patella en drie specifieke aspecten: 1) het voorkomen van MRI-gebaseerde PFOA, 2) de morfologische kenmerken die kenmerkend zijn voor PFOA, en 3) de klinische symptomen die samenhangen met PFOA. Voor deze studie werden 66 vrouwen met geïsoleerde MRI-gebaseerde PFOA en 66 gezonde vrouwen, gematcht op leeftijd en body mass index, geselecteerd uit een cohortstudie. De patellae werden handmatig gesegmenteerd uit de MRI-scans en 3D vormmodellen van de patellae werden gemaakt. Structurele afwijkingen werden gescoord met behulp van de MOAKS. Regressieanalyses werden gebruikt om de associatie tussen de patellaire vorm, groepsstatus, klinische symptomen en structurele afwijkingen te onderzoeken. De resultaten toonden vier vormvarianten die een statistisch significante associatie hadden met de groepsstatus. De vormmodus die de meeste variatie verklaarde, liet zien dat deelnemers met PFOA doorgaans een dikkere dorsale bult op het gewrichtsdeel van de patella hebben in vergelijking met controlepersonen. Drie vormvarianten waren ook geassocieerd met de aanwezigheid van osteofyten en kraakbeenverlies op de patella. Daarnaast werden er meerdere associaties geïdentificeerd tussen patellaire vorm en de klinische symptomen van PFOA. Concluderend vertoont de patellaire vorm associaties met de aanwezigheid van MRI-gebaseerde PFOA, structurele afwijkingen en klinische symptomen bij vrouwen. Interessant genoeg was een vormvariant die geassocieerd was met MRI-gebaseerde PFOA in deze studie, eerder geassocieerd aan structurele afwijkingen gerelateerd aan artrose bij individuen onder de 40 jaar. Dit kan suggereren dat de patellaire vorm kan dienen als een vroeg detecteerbare risicofactor voor de ontwikkeling van PFOA.



Appendices

Dankwoord

Het schrijven van een proefschrift was voor mij niet makkelijk. Zonder de mensen om mij heen was dit nooit gelukt. Jullie kennen me, ik ben niet lang van stof. Ik ga een aantal mensen specifiek bedanken, maar ben uiteraard iedereen dankbaar die mij heeft bijgestaan tijdens en buiten mijn promotietraject.

Allereerst wil ik alle deelnemers van wetenschappelijk onderzoek bedanken, zonder data geen onderzoek. Ik hoop dat in de huidige tijd genoeg mensen vertrouwen blijven houden in de wetenschap, zodat we als mensheid steeds een stap vooruit kunnen zetten.

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De gezelligheid op de afdeling liet mijn onderzoeksperiode voorbij vliegen, en zorgde voor plezier tijdens het werk en ook daarbuiten. Ik ben iedereen dankbaar die hieraan heeft bijgedragen.

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Rosemarijn, bedankt dat je het stokje hebt overgenomen. Ik vind het mooi om te zien dat een deel van mijn onderzoek voort leeft.

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Nazli, thank you for the help on my shape models. Even though you were very busy, you took the time to help me and explain every little detail.

Frances, Ruida and Jennifer. Thank you for the great collaboration and hospitality. My time in the NIH was eye opening, and your work ethic has inspired me to keep going.

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Thijs, grote broer. Jij stond altijd voor me klaar. Ik vind het knap hoe je de afgelopen jaren je eigen pad bepaald hebt. Dat heeft mij vertrouwen gegeven dat ik dat ook kan. Ik weet dat we het niet altijd overal over eens zullen worden, maar toch weet ik dat ik altijd bij je aan kan kloppen.

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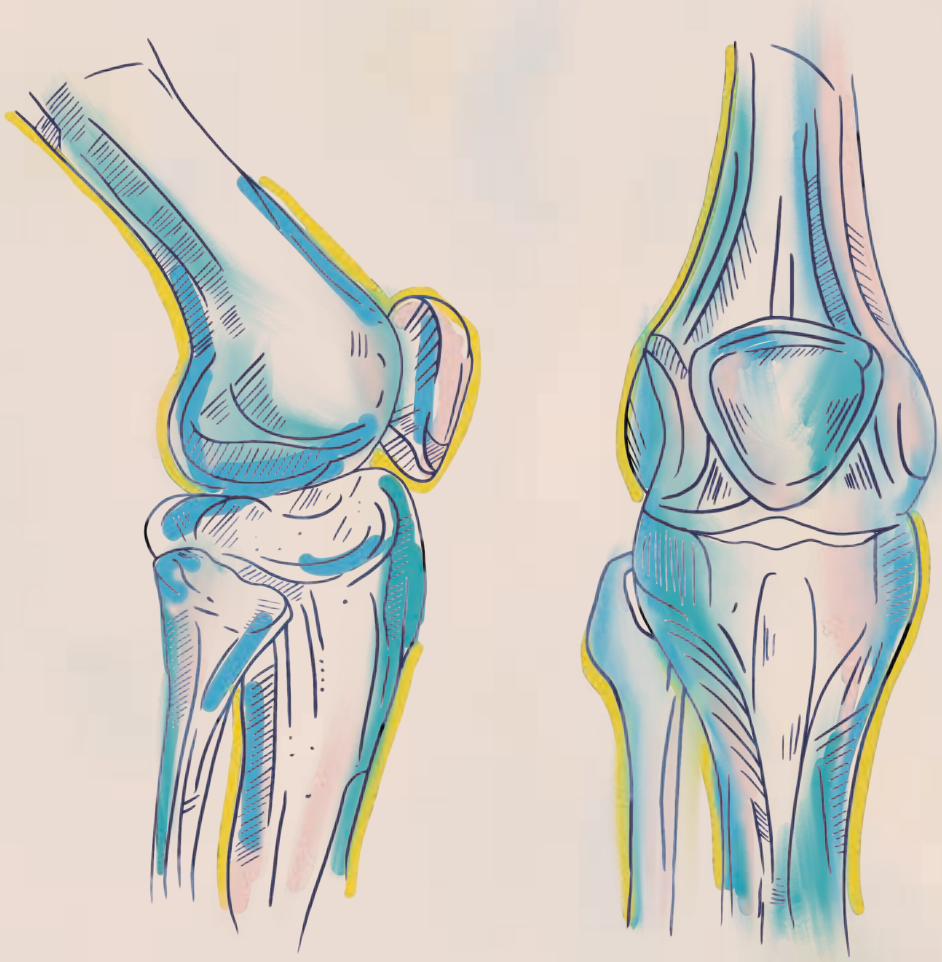


Appendices

Curriculum vitae

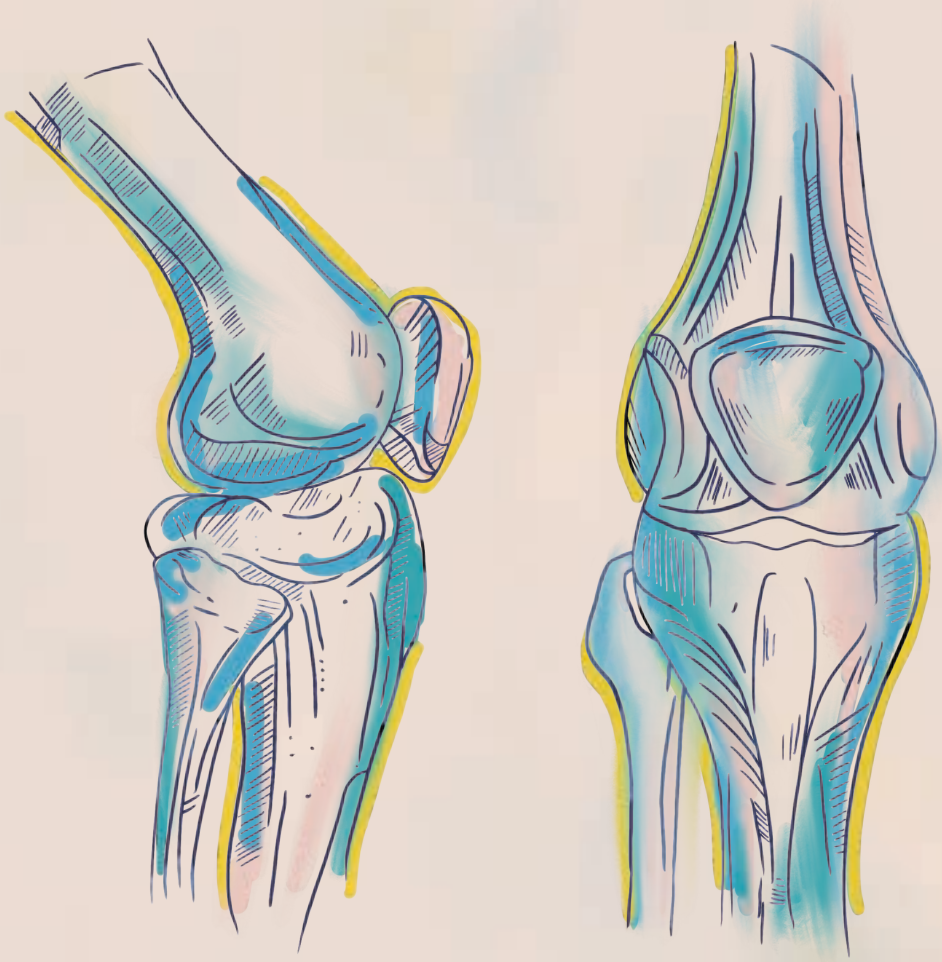
Joost Justus Franciscus Anna Eijkenboom is geboren op 6 januari 1988 in Geleen. Na het behalen van zijn VWO diploma aan het Trivianum in Sittard, begon hij met de bachelor Biomedische Wetenschappen aan de Radboud Universiteit in Nijmegen. Tijdens zijn bachelor heeft hij stage gelopen aan de Radboud Universiteit op de afdeling cognitieve neurowetenschappen. Vervolgens heeft hij voor de master Biomedische wetenschappen de specialistatie bewegingswetenschappen gekozen. Tijdens deze master heeft Joost onderzoek gedaan op de afdeling Fysiologie aan de Radboud Uniserviteit Nijmegen. Zijn afstudeerstage met focus op computer modulering vond plaats aan de afdeling Orthopedie. In 2014 slaagde hij voor zijn master Biomedische Wetenschappen.

In 2015 begon Joost aan zijn promotie onderzoek op de afdeling Huisartsgeneeskunde aan het Erasmus Medisch Centrum onder begeleiding van Prof. Sita Bierma-Zeinstra en dr. Marienke van Middelkoop. Tijdens zijn promotie heeft Joost onderzoek gedaan naar botvorm bij patellofemorale pijn en knie artrose. De resultaten van zijn promotie onderzoek staan beschreven in dit proefschrift. Tijdens zijn promotieonderzoek heeft Joost op zowel nationale als internationale congressen zijn onderzoeken gepresenteerd.

Na zijn promotie onderzoek is Joost aan het werk gegaan als product owner bij MiGuide, waar hij heeft bijgedragen aan een mobiele app voor diabetes patiënten. Daarna is Joost werkzaam geweest bij Linku als projectmanager waarbij zowel medische als niet-medische projecten in zijn portefeuille had.

Momenteel is Joost werkzaam als technical product owner bij BTCDirect, met als doel cryptovaluta toegankelijk te maken voor iedereen.

Joost woont in Oosterhout samen met zijn partner Rosalie en hun hond Loba.

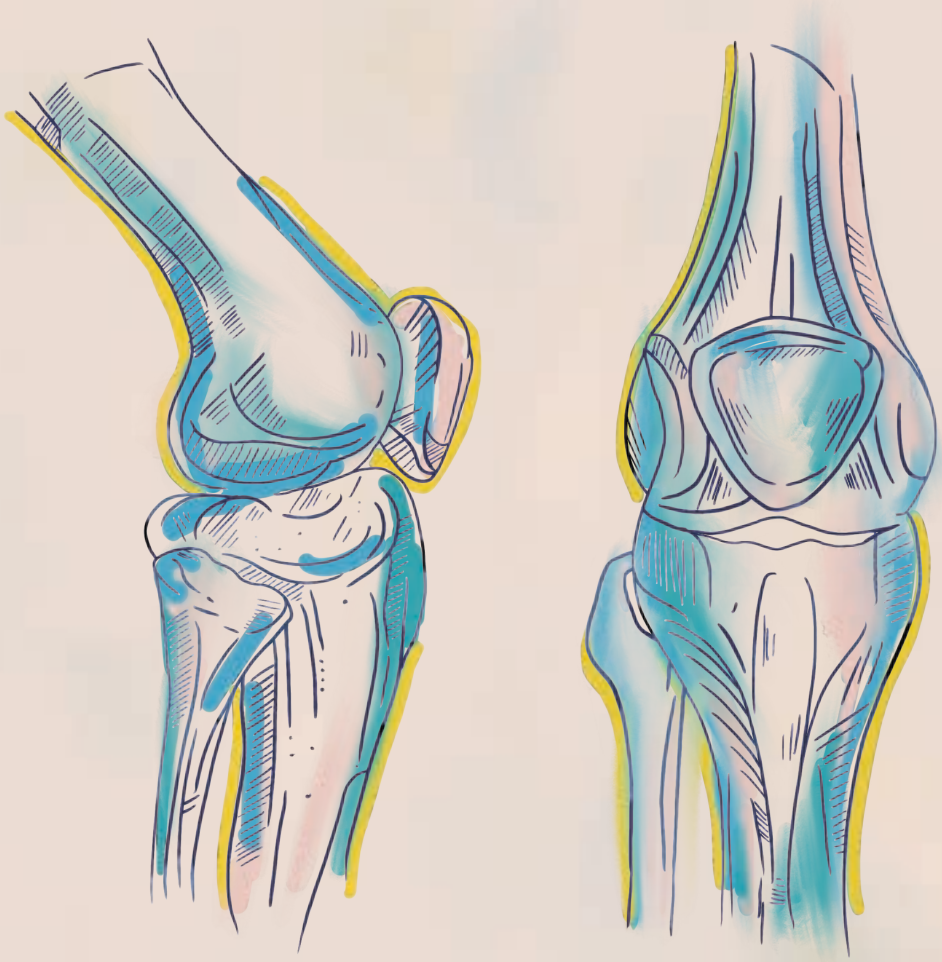


Appendices

PhD Portfolio

Erasmus MC Department: General Practice
PhD Period: 2015-2024
Promotor: Prof. dr. S.M.A. Bierma-Zeinstra
Co-promotor: Dr. M. van Middelkoop

	Year	Workload (ECTS)
Courses / training		
Research integrity	2016	0.3
Advanced Analysis of Prognosis Studies	2016	0.9
Effective writing and publishing scientific papers Maastricht	2016	3
Erasmus PHD day (3x)	2015-2018	1.5
Oral presentations		
PFP retreat Manchester, UK	2015	2
Scientific meeting dept gen practice (3x)	2015-2017	3
Dutch arthritis foundation visit Erasmus MC Rotterdam	2017	2
NHG wetenschapsdag Zeist	2017	2
Science day Orthopaedics Erasmus MC Rotterdam	2017	2
International Workshop on Osteoarthritis Imaging Rotterdam	2021	2
Poster presentations		
OARSI Amsterdam	2016	1
Scandinavian Sports Medicine Congress 2018 Copenhagen, Denmark (2 posters)	2018	2
OARSI Virtual meeting	2021	1
Teaching activities		
Supervision of master research project by medical student	2016	4
Critical reading for bachelor and master students	2017-2018	1
Conference participation		
NHG wetenschapsdag Rotterdam	2015	0.3
NHG wetenschapsdag Amsterdam	2016	0.3
Other		
International research visit, National Institute of Health, USA (4 wks)	2016	8
PFOA consensus meeting Rotterdam	2016	1



Appendices

List of publications

This thesis

Joost J.F.A. Eijkenboom, Rianne A. van der Heijden, Janneke L.M. de Kanter, Edwin H.G. Oei, Sita M.A. Bierma-Zeinstra, Marienke van Middelkoop. *Patellofemoral alignment and geometry and early signs of osteoarthritis are associated in patellofemoral pain population.*
Scand J Med Sci Sports. 2020 May;30(5):885-893

Joost J.F.A. Eijkenboom, Everlien R. Timmer, Rianne A. van der Heijden, Janneke L. de Kanter, Edwin H.G. Oei, Sita M.A. Bierma-Zeinstra, Marienke van Middelkoop. *Association between self-reported measures, physical examination, and early MR imaging signs of osteoarthritis in patients with patellofemoral pain.*
J Orthop Sports Phys Ther. 2019 Sep;49(9):634-639

Joost J.F.A. Eijkenboom, Jan H. Waarsing, Edwin H.G. Oei, Sita M.A. Bierma-Zeinstra, Marienke van Middelkoop. *Is patellofemoral pain a precursor to osteoarthritis? Patellofemoral osteoarthritis and patellofemoral pain patients share aberrant patellar shape compared with healthy controls.*
Bone Joint Res 2018;7:541–547

Joost J.F.A. Eijkenboom, Nazli Tümer, Dieuwke Schiphof, Edwin H.G. Oei , Amir A. Zadpoor, Sita M.A. Bierma-Zeinstra, Marienke van Middelkoop. *3D patellar shape is associated with radiological and clinical signs of patellofemoral osteoarthritis.*
Osteoarthritis Cartilage. 2023 Apr;31(4):534-542.

Other publications

Marienke van Middelkoop, Erin M. Macri, **Joost J.F.A. Eijkenboom**, Rianne A. van der Heijden, Kay M. Crossley, Sita M.A. Bierma-Zeinstra, Janneke L. de Kanter, Edwin H.G. Oei, Natalie J. Collins. *Are Patellofemoral Joint Alignment and Shape Associated With Structural Magnetic Resonance Imaging Abnormalities and Symptoms Among People With Patellofemoral Pain?*
Am J Sports Med. 2018 Nov;46(13):3217-3226.

Marienke van Middelkoop, Kim L. Bennell, Michael J. Callaghan, Natalie J. Collins, Philip G. Conaghan, Kay M. Crossley, **Joost J.F.A. Eijkenboom**, Rianne A. van der Heijden, Rana S. Hinman, David J. Hunter, Duncan E. Meuffels, Kathryn Mills, Edwin H.G. Oei, Jos Runhaar, Dieuwke Schiphof, Joshua J. Stefanik, Sita M.A. Bierma-Zeinstra. *International patellofemoral osteoarthritis consortium: Consensus statement on the diagnosis, burden, outcome measures, prognosis, risk factors and treatment.*
Semin Arthritis Rheum. 2018 Apr;47(5):666-675.

Joost J. F. A. Eijkenboom, Jos Runhaar. *Exploring the Results of a Pilot Study on the Combination of Exercise Therapy and Analgesics for the Treatment of Osteoarthritis Patients with Severe Pain: Comment on the Article by van Tunen et al.*
Arthritis Care Res (Hoboken). 2017 May;69(5):763.

H A de Ruiter, B van Gorp, **Joost J F A Eijkenboom.** *Comments on "Effects of high intensity resistance aquatic training on body composition and walking speed in women with mild knee osteoarthritis: a 4-month RCT with 12-month follow-up"*
Osteoarthritis Cartilage. 2017 Nov;25(11):e17-e18.